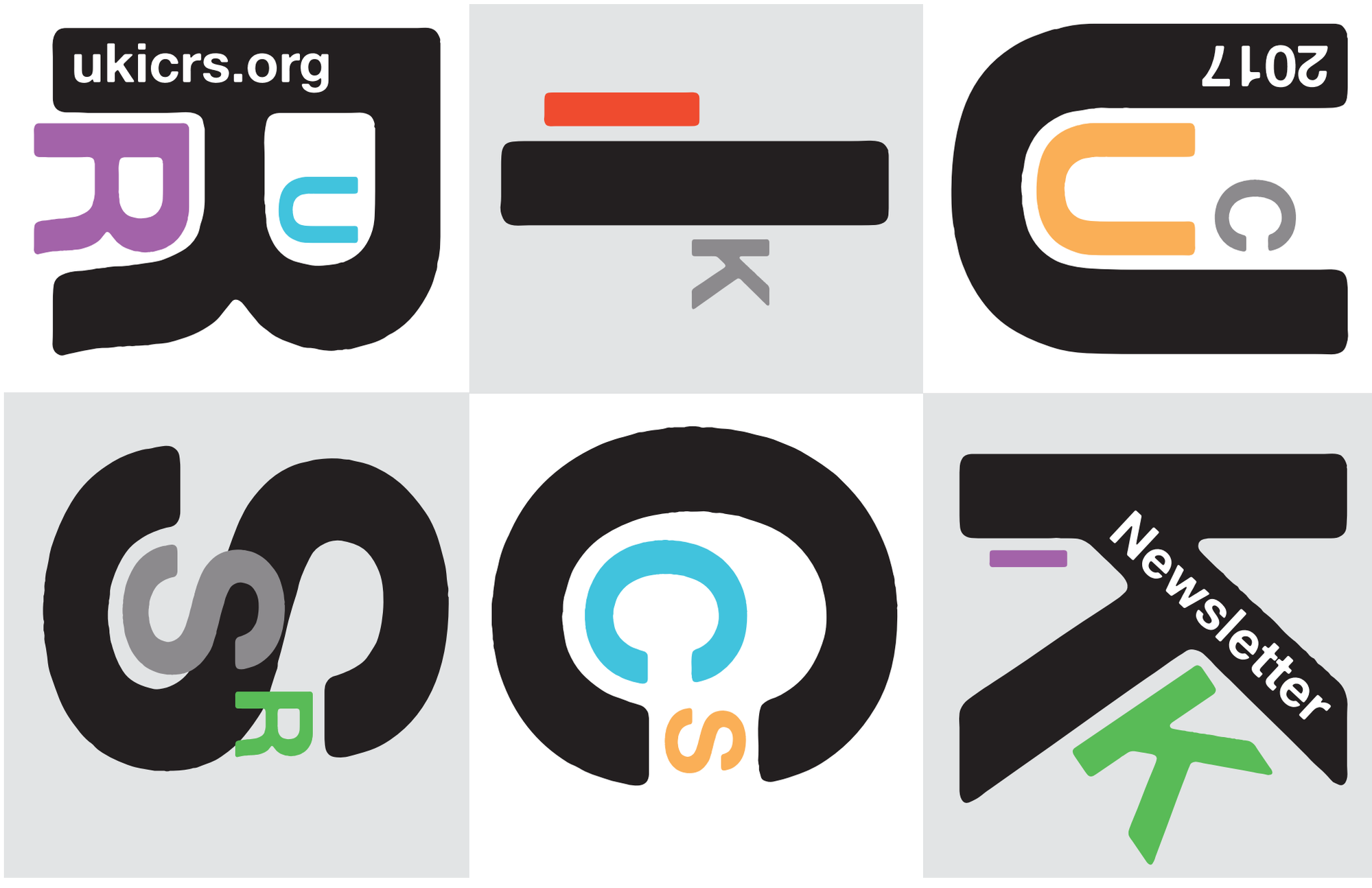

United Kingdom and Ireland Controlled Release Society

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ABOUT

UKICRS is the leading national organisation in the United Kingdom and Ireland for the promotion and advancement of the science of controlled release and drug delivery technology.

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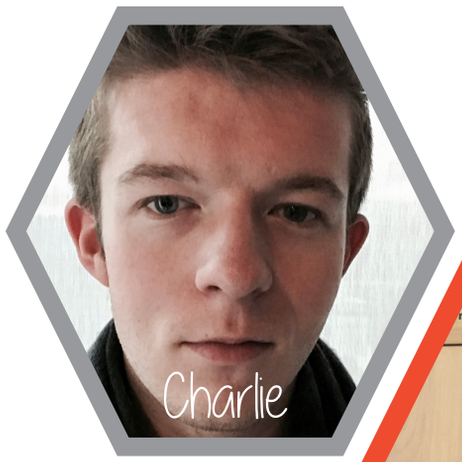

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SYMPOSIUM 2016 Review

Swapnil Khadke, Carla B. Roces, and Peter Stone
Aston University, United Kingdom

The UKICRS Symposium 2016 was held on the 21 and 22 April 2016 in Cardiff School of Pharmacy and Pharmaceutical Sciences, which is in the Redwood Building, Cardiff University. The symposium was aimed at those working in the working in the fields of pharmaceutical science and controlled release. As always, the symposium offered a wide range of opportunities for both young and established scientists to present their latest research and network with others from academia and industry. Following on from the success of last year's symposium in Nottingham, the UKICRS committee decided once again to run an extended two-day programme. The meeting kicked off with a Graduate Careers Event, an Ethical Debate and the Industrial Exposition. The Graduate Careers Event had over 80 attendees with Dan Palmer (Midatech Pharma) and Marie McGrath (GSK) providing insight and advice about careers in the pharmaceutical industry and how postgraduates can best maximise their future prospects. Emma Lane (Cardiff University) discussed ethics in science and how we as researchers have an obligation to be informed about the ethics of our direct actions and of those we are associated with.

UKICRS is always passionate about cultivating relationships with companies in the UK and Ireland working in the pharmaceutical sector. In the afternoon, we welcomed our industrial exhibitors, including Sirius, Biopharma Process Systems, Spraybase, Merrow Scientific, Stable Micro Systems and Buchi, who showcased their products and technologies through a series of short talks, exhibitions and demonstrations. The symposium dinner took place on Thursday evening at Zero Degrees, Cardiff, where delegates enjoyed excellent food and networking within the delights of a microbrewery.

The scientific programme for the second day included two keynote speakers, 11 talks from postgraduate students and postdoctoral researchers, and 68 poster presentations, with 118 delegates in total. Sion Coulman (Cardiff University) introduced the first keynote speaker Arto Urtti from the Centre for Drug Research at the University of Helsinki. The keynote lecture outlined ocular pharmacokinetic models as tools in drug delivery design. Arto also discussed the delivery of small and large molecules in the retina and remarked the importance of choosing a good animal model for ocular delivery, such as the rabbit model. The keynote lecture was followed by two short presentations: Sam Tarassoli (University College London, UK) describing novel polyglutamate-based indocyanine green nanoparticles for photothermal cancer therapy and Samuel Bizley (The Royal Veterinary College, UK) speaking about the study of the structural and barrier properties of equine skin for the deep tissue delivery of pharmaceuticals in equine therapy.

After the first session there was a coffee break with some delicious Welsh cakes! The second session consisted of three further short lectures chaired by Katie Ryan (University College Cork, Ireland). Affiong Lyire

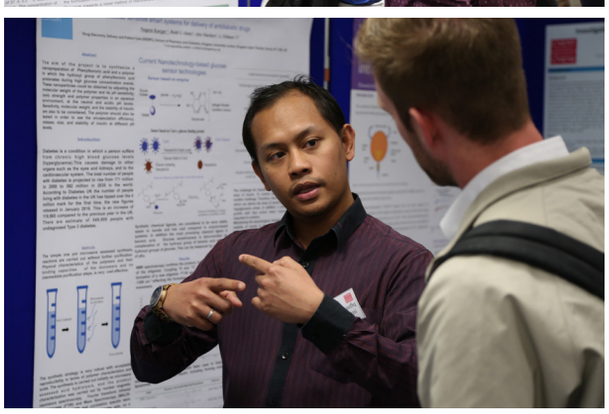
(Aston University, UK) spoke about the effect of basic and acidic amino acids on the physicochemical and biological properties of insulin in order to provide alternative safe and effective excipients that enhance buccal insulin delivery. Hope Roberts-Dalton (Cardiff University, UK) discussed the use of thiol-based labelling of prostate-derived exosomes for analysis of cellular uptake and intracellular trafficking. The final talk before the poster session and lunch break was delivered by Ali Athab Al-kinami (Kingston University London, UK) who talked about the antioxidant activity of HPMC-coated cerium oxide nanoparticles for cataract prophylaxis.

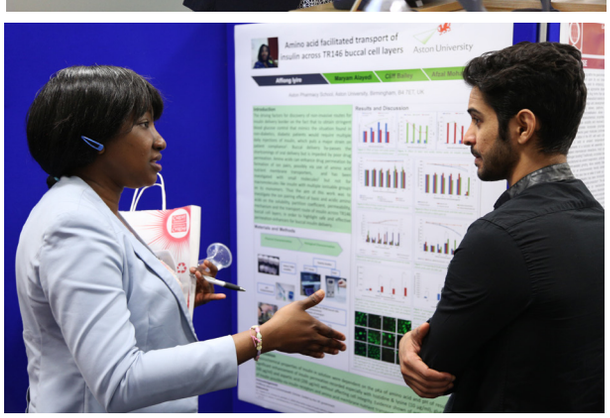
Following a packed poster session and lunch, the afternoon session was opened by Virginia Acha (Association of the British Pharmaceutical Industry), who discussed the history, current trends and future outlook of biosimilars of complex protein based drugs within the UK market. She was followed by Edward Mansfield (University of Reading), who spoke about how using different forms of a poly (2-oxazoline) coat affects the rate of nanoparticle diffusion through the mucosal layer. Ivan Hall Barrientos (University of Strathclyde) described the steps behind fabricating and characterising drug-loaded electrospun polymeric nanofibers for controlled release in hernia repair. David Walsh (Royal College of Surgeons in Ireland, Ireland) examined the controlled delivery of DNA from tissue engineered collagen scaffolds using non-viral star-shaped polypeptides.

The final session of the meeting was composed of three talks. Sarah Mallen (University of Limerick, Ireland) gave a presentation on oral delivery of nisin via mesoporous silica matrices. John Pollard (Aston University) spoke on utilisation of an in vitro high-throughput screening assay in the development of orally disintegrating tablets with enhanced delivery capability. Daire O'Donnell (Dublin City University, Ireland) evaluated the physicochemical characterisation tools that can aid oral drug delivery technology optimisation.

The meeting was concluded by Dimitrios Lamprou (University of Stathclyde), who announced the winners of the best talk and poster awards. The prizes for best oral presentation were awarded to David Walsh and Ivan Hall Barrientos, while the award for the best poster was awarded to Swapnil Khadke (Aston University) and the runners up were Hosam Al-Deen Abu Awwad (University of Nottingham) and Aboie Omulu (University College London).

Thank you to all delegates, sponsors, and speakers for your contribution to the symposium.





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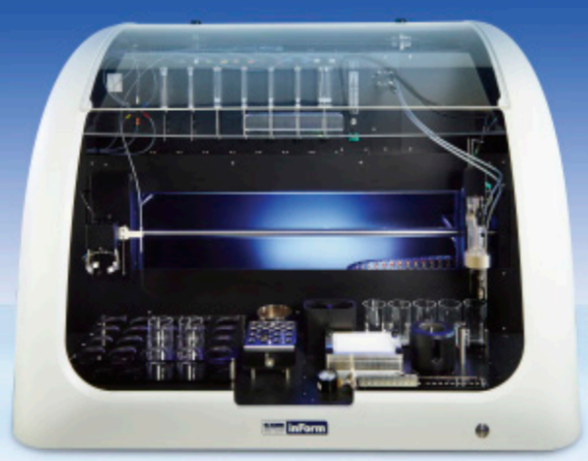

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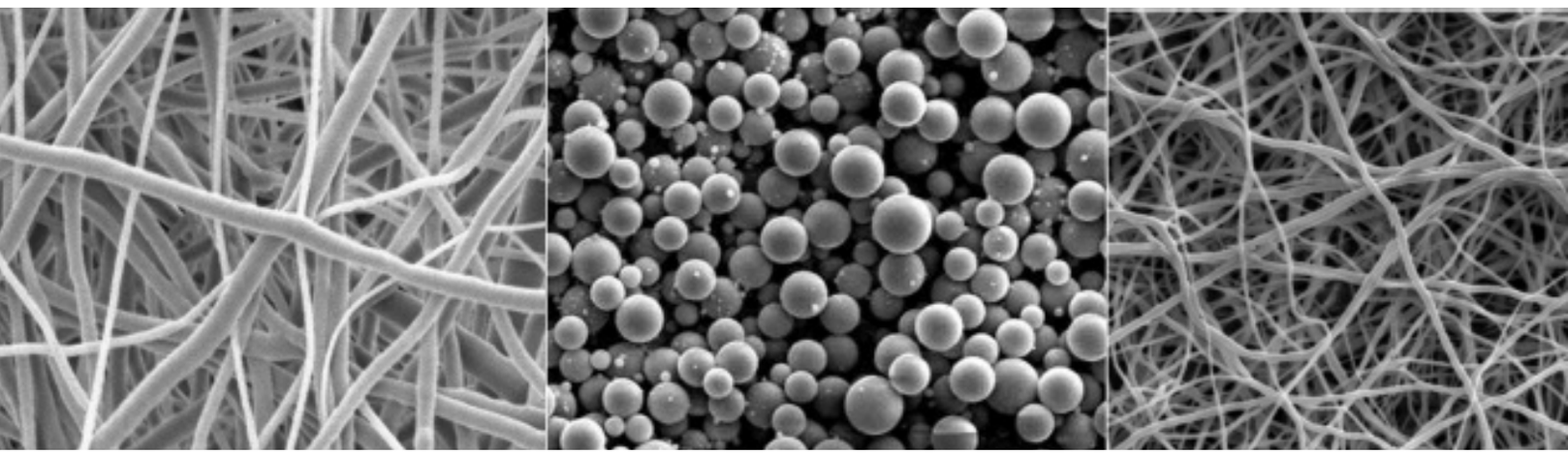

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"Doctor, please cure my disease for 55p"

BY MARTYNA PETRULYTE

1ST PRIZE: UKICRS ESSAY COMPETITION 2016

Back in August 1897 German scientists for the first time synthesized an innocuous-looking white pill which soon became an indispensable part of lives of many people worldwide. No other medication is used by a greater number of consumers globally than aspirin, an over-the-counter drug that is used to reduce fever and relieve various pains and aches. Costing only 55p in Boots, aspirin has a good reputation in treating diverse conditions that has been supported by a long history of use. Interestingly, this old analgesic has recently regained interest from pharmaceutical companies as it has been shown to be useful for curing some of the deadliest diseases of the 21st century: cancer, cardiovascular diseases (CVD), and even dementia.

In the mid-eighties, new potential use of aspirin became widely accepted as many experiments have shown its ability to significantly reduce heart attacks. The underlying mechanism of this effect is that aspirin irreversibly inhibits platelet adhesion within the vessels by acetylating an enzyme called cyclooxygenase-1, which catalyzes the production of thromboxane A2, a powerful stimulant of platelet aggregation (Toth et al., 2013). Thus by inhibiting platelet stickiness, aspirin could be clinically used in treating ischaemic diseases characterized by thrombus formation. A large collaborative meta-analysis involving 135,000 patients in 2002 revealed that aspirin with doses of 75–150 mg daily taken up by survivors of myocardial infarction, stroke, transient ischemic attack, and angina decreased the chances of subsequent vascular events by 25% (Antithrombotic Trialists' Collaboration, 2002). Moreover, the Physicians' Health Study, which recruited over 22,071 healthy male physicians, uncovered the clinically significant benefits of daily aspirin intake in decreasing the risk of a first myocardial infarction by 44% (Steering Committee of the Physicians' Health Study Research Group, 1989). Thus, in addition to being antipyretic and analgesic, aspirin may decrease the incidence of the number one cause of death globally, cardiovascular diseases. Needless to say, any disease that is characterized by abnormal clotting process might be a potential candidate for aspirin treatment. However, long-term use of aspirin was indicated as a major cause of gastric bleeding and the proposal to take the drug prophylactically was challenged by recent meta-analysis which pinpointed to the risk of gastrointestinal hemorrhaging being higher than the actual protective action (Sutcliffe et al., 2013). Nevertheless, the impact of specific dose regimens each chosen for individual patients should be tested in order to critically evaluate the variability in response to the drug, an approach called personalized medicine which is now beginning to gain great interest.

A recent announcement of the prospective clinical trial in Australia involving 15,000 people aged over 70 hit the headlines and sparked countless scientific debates over whether aspirin can also be used to delay onset of Alzheimer's disease, the most common type of dementia which affects approximately 46.8 million people worldwide (World Alzheimer Report, 2015). Although reduced quality of life and considerable burden for caregivers as well as for economy instigated many studies to unravel the pathogenesis of Alzheimer's disease, however, now cure is available to date. A Swedish study which aimed to assess whether high-dose or low-dose aspirin may ward off Alzheimer's dementia in individuals over 80 years of

age has shown that women who were taking 75–160 mg of aspirin every day declined less on the Mini Mental State Examination (MMSE) which was used to assess cognitive functions (Nilsson et al., 2003). The underlying causes of neuroprotective effects of aspirin are unknown, however, it is believed that reduced aggregation of platelets in the brain following low-dose aspirin intake improves the cerebral blood flow (Ridker et al., 1996). Furthermore, aspirin is able to convert cyclooxygenase-2 into a form that produces two new anti-inflammatory neuroprotective docosanoids from docosahexaenoic acid (DHA) called lipoxins (Takano et al., 1998) as well as resolvins and NPD1 (Serhan et al., 2004). Intriguingly, the amount of NPD1 is diminished in the CA1 region of the hippocampus of Alzheimer's patients (Marcheselli et al., 2010) and therefore potentiation of NPD1 with aspirin might be a new therapeutic approach. It was also shown that NPD1 enhances the survival of neurons in the brain by suppressing apoptosis and production of β-A plaques which are abnormal proteins that cause neurotoxicity in Alzheimer's disease. Thus, by reducing endothelial inflammation and increasing levels of neuroprotective agents, aspirin may be a prophylactic daily drug for people over 65 who have the greatest risk of developing Alzheimer's disease.

A more surprising novel use of aspirin is its potential to reduce cancer incidence and mortality. A search for a drug for cancer treatment has been long and marked by significant scientific discoveries and unprecedented medical advancements but no cure has been found yet. Many clinicians and scientists, therefore, are aiming to prevent the development of cancer in the first place and suppress transformation of normal cells into cancerous cells. Cui et al. (2014) reported that prophylactic intake of high-dose aspirin was closely linked to decreased risk of developing pancreatic cancer. In addition, aspirin might be able to decrease the incidence of colorectal cancer. A study involving 662,424 men and women showed that the use of aspirin no less than 16 times per month was correlated with a 40% decreased risk of developing colon cancer over a 6-year period (Thun et al., 1991). An updated results of this study later showed a significantly reduced risk of colorectal neoplasia in people who took at least 325 mg of aspirin for at least 5 years as compared with nonusers (Jacobs et al., 2007). Moreover, not only prophylactic but also post-diagnosis use of aspirin might increase survival rates. Analysis of 830 individuals who were diagnosed with stage III colorectal cancer showed that patients who took aspirin consistently after diagnosis had a significantly reduced (48%) risk of recurrence and death from disease as compared to nonusers (Fuchs et al., 2005). What is emerging from long-term studies of aspirin and cancer is that the length of aspirin intake positively correlates with decreased chances of developing cancer. During a period of 24 years 79,439 women were followed and their use of aspirin was evaluated (Chan et al., 2007). From this cohort, 9477 deaths – of which 4469 were caused by cancer – were recorded at the end of the study. Compared with women who never took aspirin on a regular basis, women who used aspirin for more than 20 years were at lower risk of developing breast and lung cancer. However, a small advantage of aspirin with regards to cancer-related mortality was not observed until after at least 10 years of constant aspirin use. Although precise mechanism of aspirin's anti-neoplastic effects remains to be determined, several theories have been put forward to explain how aspirin can inhibit tumorigenesis. Aspirin might induce apoptosis pathway by upregulating p38 mitogen activated protein kinase (Schwenger et al., 1997). In addition, overexpression of cyclooxygenase-2 (COX-2) occurs in 80% of colonic tumors and this is closely related with proliferative activity of tumor and its metastatic capacity (Zhang et al., 2002). By inhibiting not only COX-1 but also COX- 2, aspirin may impede rapid proliferation of tumor cells. What is more, aspirin might inhibit the transcription factor nuclear factor-kappa B (NF-kappaβ) which is essential for regulating expression of many genes associated with tumour formation and inflammation, for example, interleukin-1, interleukin-6, and adhesion molecules (Kopp et al., 1994). Surprisingly, NF-kappaβ is known to have an important role in the control of HIV-1 gene expression by its ability to bind to the HIV long terminal repeat and induce the transcription of integrated HIV genome, leading to chronic and invariably fatal AIDS infection (Pande et al., 2003). A randomized controlled trial in Nigeria failed to show an increase in CD4+ cell count (post-treatment count was 293 cells/mL compared to the pre-therapy count of 257 cells/mL) after the treatment of HIV patients with selenium and aspirin (Durosinmi et al., 2008). However, mean body weight was increased after treatment which is of great benefit to debilitated HIV-positive patients. Larger studies involving more patients over prolonged time periods are needed to more reliably evaluate the aspirin's potential to ward off HIV.

Considering a wide spectrum of ailments that could be possibly treated, a cheap, easily manufactured and relatively safe pill with its anti-dementia, anti-platelet, anti-tumour, and even possibly anti-HIV effects may thus be soon hailed as a panacea for all ills. It is still too early to conclude that 55p is really all what is needed to ward off major killers of our century, but we are getting close.

References

Antithrombotic Trialists' Collaboration. (2002) Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high-risk patients. BMJ, 324:71–86.

Chan, A.T., Manson, J.E., Feskanich, D., et al., (2007) Long-term aspirin use and mortality in women. Arch Intern Med, 167(6):562-72.

Cui, X.J., He, Q., Zhang, J.M., et al., (2014) High-dose aspirin consumption contributes to decreased risk for pancreatic cancer in a systematic review and meta-analysis. Pancreas, 43(1):135-40.

Durosinmi, M.A., Armistead, H., Akinola, N.O., et al., (2008)

Selenium and aspirin in people living with HIV and AIDS in Nigeria. Niger Postgrad Med J, 15(4):215-8.

Fuchs, C., Meyerhardt, J.A., Heseltine, D.L., et al. (2005) Influence of regular aspirin use on survival for patients with stage III colon cancer: findings from Intergroup trial CALGB 89803. Journal of Clinical Oncology, 23(16S):3530.

Jacobs, E.J., Thun, M.J., Bain, E.B., et al., (2007) A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. J Natl Cancer Inst., 99(8):608-15.

Kopp, E., Ghosh, S. (1994) Inhibition of NF-kappa β by sodium salicylate and aspirin. Science, 265(5174):956-9.

Marcheselli, V.L., Mukherjee, P.K., Arita, M., et al., (2010) Neuroprotectin D1/protectin D1 stereoselective and specific binding with human retinal pigment epithelial cells and neutrophils. Prostaglandins Leukot. Essent. Fatty Acids, 82 (1), pp. 27–34.

Pande, V., Ramos, M.J. (2003) Nuclear factor kappa β: a potential target for anti-HIV chemotherapy. Curr Med Chem, 10(16):1603-15.

Pomponi, M.F., Gambassi, G., Pomponi, M., et al., (2011) Why docosahexaenoic acid and aspirin supplementation could be useful in women as a primary prevention therapy against Alzheimer's disease? Ageing Res Rev, 10(1):124-31.

Ridker, P.M., Hennekens, C.H., Tofler, G.H., et al., (1996) Anti-platelet effects of 100 mg alternate day oral aspirin: a randomized, double-blind, placebo-controlled trial of regular and enteric coated formulations in men and women. J Cardiovasc Risk, 3(2):209-12.

Serhan, C.N., Arita, M., Hong, S., et al., (2004) Resolvins, docosatrienes, and neuroprotectins, novel omega-3- derived mediators, and their endogenous aspirin-triggered epimers. Lipids, 39 (11), pp. 1125–1132.

Steering Committee of the Physicians' Health Study Research Group. (1989) Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med, 321:129–135.

Schwenger, P., Bellosta, P., Vietor, I., et al., (1997) Sodium salicylate induces apoptosis via p38 mitogen-activated protein kinase but inhibits tumor necrosis factor-induced c-Jun N-terminal kinase/stress-activated protein kinase activation. Proc Natl Acad Sci U S A, 94(7):2869-73.

Sutcliffe, P., Connock, M., Gurung, T., et al. (2013) Aspirin for prophylactic use in the primary prevention of cardiovascular disease and cancer: a systematic review and overview of reviews. Health Technol Assess, 17(43).

Takano, T., Clish, C.B., Gronert, K., et al., (1998) Neutrophil-mediated changes in vascular permeability are inhibited by topical application of aspirin-triggered 15-epi-lipoxin A4 and novel lipoxin B4 stable analogues. J. Clin. Invest, 101(4), pp. 819–826.

Toth, L., Muszbek, L., Komaromi, I. (2013) Mechanism of the irreversible inhibition of human cyclooxygenase-1 by aspirin as predicted by QM/MM calculations. Journal of Molecular Graphics and Modelling, 40, pp. 99–109.

Thun, M.J., Namboodiri, M.M., Heath, C.W. Jr. (1991) Aspirin use and reduced risk of fatal colon cancer. N Engl J Med, 325(23):1593-6.
World Alzheimer Report, 2015. Retrieved from https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf.

Zhang H, Sun XF. (2002) Overexpression of cyclooxygenase-2 correlates with advanced stages of colorectal cancer. Am J Gastroenterol, 97(4):1037-41

ABOUT THE AUTHOR

Maria is a third year Biomedical sciences (Anatomy) student at the University of Aberdeen, UK. After her studies, she plans to apply to apply for Medicine. As a new-generation biomedical student and a current employee of NHS Grampian, she believes that physicians with strong research backgrounds are a great asset in hospital settings.

To improve her research skills, Maria undertook two summer internships. In the Institute of Medical Sciences in Aberdeen, she experienced cutting edge research under the supervision of Prof. Peter Teismann on a project asking 'Are animals with an extended lifespan due to Nrf2 mediated enhanced antioxidant response less prone to develop Parkinson's disease?' As a participant of the Kupcinet-Getz Program at the Weizmann Institute in Israel under the supervision of Dr. Lilach Gilboa, she investigated how Stat and ERK signalling cooperate to control cellular extensions of escort cells in Drosophila ovaries.

Maria is also a teacher at the National Students' Academy where she teaches biochemistry/biology subjects to Lithuanian high school students distantly. Also, she runs the blog biolympiads.blogspot.com where she shares knowledge with students from all over the world.

UKICRS

Travel Award 2016

Congratulations to Siuyan Chen, a PhD student from Imperial College London, for winning the UKICRS's 2016 CRS Travel Award. Siuyan used the £1000 award to support her attendance in July at the 43rd Annual Meeting & Exposition of the Controlled Release Society in Seattle. Here, Siuyan provides us with her thoughts on her time at the conference.

"I was very honoured to receive the UKICRS Travel Prize 2016, as it allowed me to attend the 43rd Annual Meeting of Controlled Release Society in Seattle, US from 16-20 July 2016. This experience was invaluable to me, giving me the opportunity to participate in a leading scientific event attended by over 1,200 delegates from a wide research area.

I learnt about new developments in the integration of imaging and drug delivery, development of nanocarriers from nature, new applications and opportunities for gene delivery, and technologies to overcome biological barriers. My own research focuses on smart liposomes for efficient drug delivery to combat cancer, and attending such a conference whose scope is closely related to my research area is of great important to my future work. It helps me understand the new "hot" research topics in this area, such as exosomes and 3D printing in drug delivery applications. I also received useful feedback on the poster I presented. The suggestions from experts were beneficial to my future work and publication. In addition, I had the opportunity to talk to industry and discuss potential collaborations. Several pharmaceutical companies (Luye Pharma Group Ltd., Alnylam pharmaceuticals, etc.) were interested in the patent that we recently applied for, about novel delivery technology using modified peptide. Attending this conference provided me with face-to-face opportunities to connect with world renowned scholars and to become known in the academic circle; this is crucial for my career development. I would like to take this opportunity to thank the United Kingdom & Ireland Controlled Release Society for providing generous funding to support my attendance at this conference."

Siyuan Chen

PhD Candidate
Chemical Engineering Department
Imperial College London

New insights into old drugs: Printing the future

BY SADAF TAHERI

2ND PRIZE: UKICRS ESSAY COMPETITION 2016

It is no secret that the population is ageing. The concept of being 'super old' is no longer a myth, told only in fairy tales and biblical stories. In fact, in 2012 it was reported that close to half a million people over the age of 90 were living in England and Wales[1], corresponding to just under 1% of the population. This is largely a consequence of advances in modern medicine. Sadly, while the symptoms of old age may be prevented or masked through good quality healthcare, there is ultimately no cure. Spend an hour in your local pharmacy and you will quickly realise that the majority of the patients are over the age of 65. It's estimated that 40% of people in this age group (65 and over) have at least one limiting longstanding illness[2]. Generally speaking, these patients don't leave the pharmacy with a neat little paper bag containing one or two items. Many patients in this age group require large bags, full of medicine, to maintain their quality of life for the upcoming months. It is not uncommon for 6 to 10 different tablets to be seen on one person's prescription. More often than not, the tablets take substantially the same form - around, white tablet. However, each tablet will be accompanied by a different set of rules for the patient to follow. Individuals suffering from multimorbidities are not only dealing with their illnesses, but they are also up against a minefield of confusing and unforgiving dose instructions. Needless to say, this leads to confusion, poor adherence and dosing errors. The need for patient friendly, personalised medicine is apparent.

Introducing the poly-pill: essentially more than one drug within the same dosage form. There are currently many poly-pills on the market. These pills are commonly targeted at one disease state that requires a range of medicines to treat, for example diabetes or cardiovascular disease. They can also be described as fixed-dose combination therapies as they are fixed dose, immediate release delivery systems. The immediate release profile of these formulations is their major drawback, as controlled release is too difficult to achieve, which means that repeat dosing is required. Furthermore, for medicines to be personalised factors such as enzymatic functions of individuals must be considered. Physicians currently use age, size, race, kidney and liver functions while determining prescribed doses. In 2016, we have enough evidence to be able to confidently say that this is frankly not enough. For the poly-pill to be absolutely personalised, utilisation of new technologies is necessary.

In August 2015, Spritam® (the very first 3D printed drug) was approved by the Food and Drug Administration (FDA). The ground breaking news grabbed the attention of mainstream papers, who reported the development of a "new drug". Spritam® is in fact a very clever way of reintroducing levetricetam, an anti-epileptic drug that has been around since the 1990s.

The company responsible for Spritam®, Aprecia Pharmaceuticals, has developed a formulation method coined 'ZipDose® Technology'. The technology has facilitated the manufacturing of a highly porous, solid, orodispersible formulation of levetrictam. This formulation disintegrates rapidly (even at very large doses), and the foul taste of the medicine is also masked. The selling point of Spritam® is that it's "surprisingly easy to take" [3] i.e. a more convenient fashion of using high doses of levetrictam, but its novelty is that it is 3D printed.

So, what is 3D printing? The idea is actually relatively simple – a computer commanded robotic arm is used to deposit layer upon layer of a material to produce three dimensional objects. Making the 'ink/filament' is the difficult bit. The most common method of 3D printing is fused-deposition modelling (FDM), whereby a range of polymer filaments can be used and passed through a heated nozzle which causes the material to melt. The nozzle is capable of moving horizontally as well as vertically. In this manner the first layer of the object is printed. The build plate then lowers to allow for the next layer to be deposited. The printed objects can have any geometric shape and may even be hollow. By blending drug with polymer into a solid dispersion, pre-loaded dosage forms can be printed.

During a study at the University of Lancashire, ellipse shaped prednisolone tablets were 3D printed using FDM[4]. Prednisolone is a corticosteroid that is very commonly prescribed for the treatment of an array of inflammatory and allergic disorders including but not limited to asthma, eczema, inflammatory bowel disease and rheumatic diseases such as arthritis. The dosing regimen for corticosteroids is complex and varies widely from patient to patient, depending on the disorder that needs to be treated. A significant correlation was found between the theoretical volume and the mass of the tablets. This technology could be used in the development of fine-tuned tablets designed specifically for individual patient need.

Scientists at UCL School of Pharmacy have been using FDM printers coupled with hot-melt extrusion (HME) to print paracetamol tablets with five different geometric shapes. HME is a processing technique that has been used by the plastic industry since the 1930s. Today HME may also be regarded as an established technique used by pharmaceutical companies for development of drug delivery systems. Simply put, the process involves feeding the materials through a stationary, heated barrel containing a rotating screw which mixes the materials. It can be argued that by using HME to prepare filaments a higher percentage of drug can be incorporated into the dosage forms. The dissolution testing results of the printed tablets showed that the geometry had a significant effect on the release profile of the drug. They found that paracetamol release was dependent on the ratio between surface area and volume and not just surface area[5], giving the sphere and cube shaped tablets the fastest release rate. To move things forward the group has gone on to print caplets of the commonly available paracetamol and caffeine combination. Once more FDM was coupled with HME to impregnate a polymer with both active ingredients to create the filament. Although the possibility of printing caplets containing more than two active ingredients using this method is proposed, it has not yet been executed. It was found that printing the two ingredients in a layer by layer fashion allowed for immediate release of both drugs at a similar rate. Printing one active in the core of another however, created a lag time before the ingredient in the core was released. This result was achieved in both cases of paracetamol being the external layer and the core.[6]

Work carried out by The University of Nottingham has moved us one step closer to the tailor made 3D printed poly-pill. In the first of such studies, a 3D extrusion system was operated at room temperature to produce tablets containing three different active ingredients (captopril, nifedipine and glipizide). The pills demonstrated two different delivery systems. By using a wide range of polymers in a calculated blend, an osmotic pump section was printed for the captopril, while a controlled porosity membrane was printed for nifedipine and glipizide. Furthermore, all three drugs sat in their own compartments, preventing the possibility of any reactions between them[7]. Launched in the 1980s, captopril was the first angiotensin-converting-enzyme (ACE) inhibitor on the market. Although described as a great advance in cardiovascular medicine, captopril is now regarded as old fashioned and is very rarely used. This is largely due to its major shortfall compared to its offspring. Captopril has a short half-life (2 hr), whereas newer ACE inhibitors are used once daily. The work does not stop there; more recently poly-pills containing 5 different active ingredients have been printed by the same group. The tablets conveyed two defined release mechanisms - aspirin and hydrochlorothiazide were released immediately, while atenolol, ramipril and pravastatin were held within the so-called extended release compartment of the tablets[8]. Patients with cardiovascular disease often require

a form of this cocktail of anti-platelet, diuretic, beta blocker, ACE inhibitor and lipid regulating drug to maintain their level of health. Alterations in release profiles are of great importance. The diuretic which must be taken in the morning is released immediately while the pravastatin that has to be taken at night is retained.

With development of gene sequencing techniques such as Sanger and Nextgen sequencing, personalisation of medicine is no longer a thing of the past. Many pharmaceutical scientists have singled out 3D printing of delivery systems as the future of modern medicine. The ability to manufacture flexible delivery systems would benefit patients in a huge variety of ways. The technology offers the means of accurately altering the dose depending on the exact amount the patient requires. Imagine the dilemma consultants confront as they try to choose between risking overdosing the patient with poor kidney or liver function versus an unlicensed method of prescribing the right dose. This is why liquid drug delivery systems are often preferably used in geriatrics and paediatrics. Unfortunately, not every medicine is available in this format and liquid preparations are generally more expensive, more unstable or require a nurse to inject them. Visualise the struggle of the elderly patient with rheumatoid arthritis, who has to try and quarter the already tiny tablet in order to provide them with a lower dose. Picture the nervous young mother, worrying about the dose her child gets as they won't swallow the lot of the nasty tasting medicine. 3D printing has a possible solution for that too. Complete freedom in geometry means that children could have whatever shaped delivery system they desired, for example a favourite animal or fictional character. As discussed, 3D printing provides a viable method for the personalisation of medicines and greatly facilitates the development of sophisticated multi-drug delivery systems.

The elephant in the room, however, is the FDA and other regulatory bodies. Will they approve it? Technically, presenting old drugs in new formulations requires time-consuming clinical studies to occur before approval. However, there is no need to sweep multi-drug delivery systems or 3D printed medicine under the rug. Spritam® has after all been approved. Entresto™ has also been approved by both the FDA and the European Commission. Although not developed through 3D printing, Entresto™ is a combination of sacubitril (neprilysin inhibitor) and valsartan (angiotensin II receptor blocker), indicated for heart failure. What Norvatis has achieved with Entresto® is unique in a completely different way; a dual-acting pharmaceutical built as a supramolecular complex,[9] the first of its kind. As Alan Kay famously said "the best way to predict the future ... is to invent it". Such studies truly do give us new insights into old drugs. The research must continue.

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References

1. Points K. Statistical Bulletin Estimates of the Very Old (including and Wales. 2013:2002-12.
2. Age UK. Later life in the United Kingdom. 2014;(May):1-34. http://www.ageuk.org.uk/Documents/EN-GB/Factsheets/Later_Life_UK_factsheet.pdf?dtrk=true.
3. Spritam. Aprecia Pharmaceutical Company.
4. Skowyra J, Pietrzak K, Alhnan MA. Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing. Eur J Pharm Sci. 2015;68:11-17.
5. Goyanes A, Robles et al.,Effect of geometry on drug release from 3D printed tablets. Int J Pharm. 2015;494(2):657-63.
6. Goyanes A, Wang J, Buanz A, et al. 3D Printing of Medicines: Engineering Novel Oral Devices with Unique Design and Drug Release Characteristics. Mol Pharm. 2015;12(11):4077-4084.
7. Khaled SA, Burley JC, Alexander MR, et al., 3D printing of tablets containing multiple drugs with defined release profiles. Int J Pharm. 2015;494(2):643-650.
8. Khaled SA, Burley JC, et al., 3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles. J Control Release. 2015;217:308-314.
9. Feng L, Karpinski PH, Sutton P, et al. LCZ696: A dual-acting sodium supramolecular complex. Tetrahedron Lett. 2012; 53:275-76.

CONFERENCE REPORT

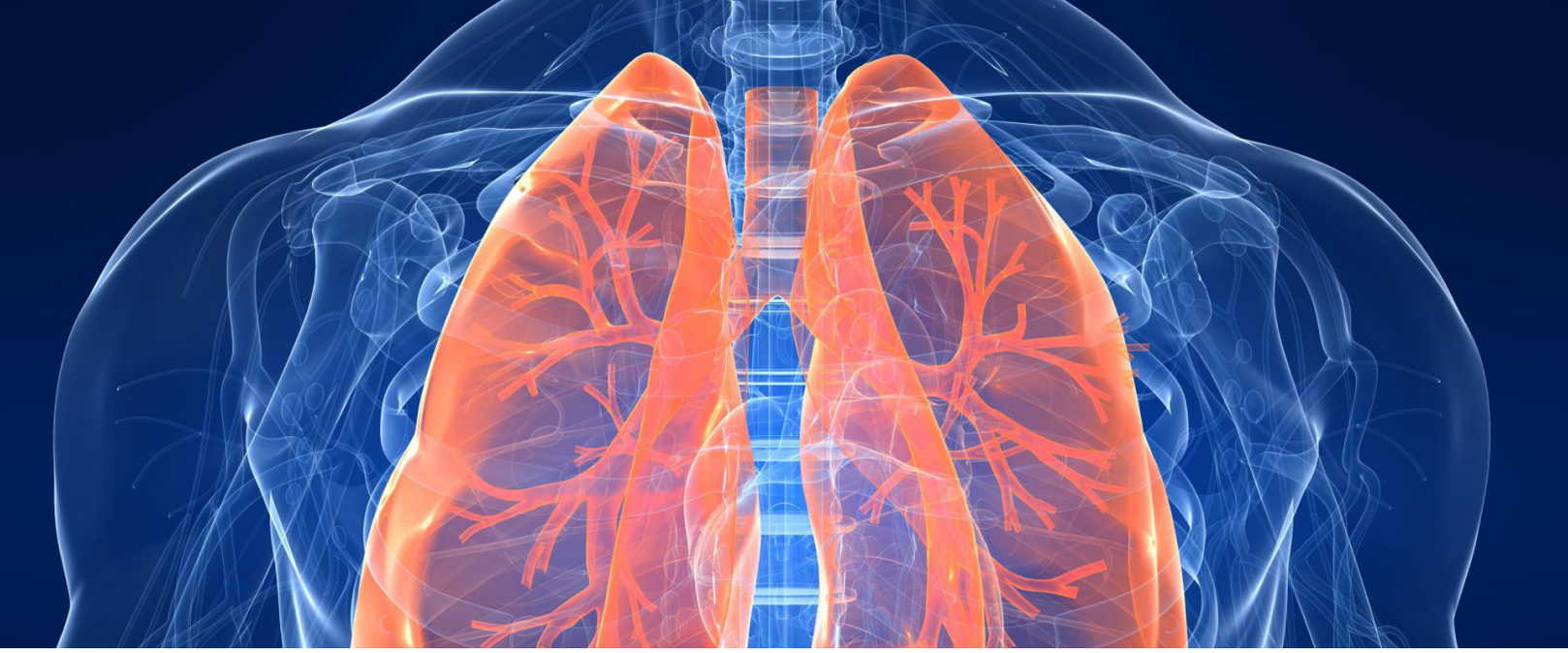
UKICRS sessions at 7th APS International PharmSci Conference 2016

The PharmSci 2016 conference took place 5–7 September 2016 in the newly-opened Technology & Innovation Centre at the University of Strathclyde, Glasgow. The theme of the conference was 'Pharmaceutical Sciences: Improving World Health'. UKICRS organised two engaging sessions highlighting some of the most current and emerging techniques and models used in research today.

"An experiment is a question which science poses to Nature, and a measurement is the recording of Nature's answer." (Max Planck). New discoveries and developments in drug delivery and therapeutics have been made possible not only by great scientists, but also through progression in the analytical tools at our disposal.

Session 1 (*Progressive experimental models in disease, drug discovery and regeneration)* took place on day 1 (Sept 5th 2016) and was chaired by Dr. Katie Ryan (University College Cork). The session involved speakers from academia and industry. Dr. Jens Kleem, (InSphero Switzerland) spoke about "Increasing biological relevance in vitro: From single microtissues to micro-physiological systems" and Dr. Lindsay Marshall (Aston University) gave an insightful talk on "Modelling human airways – from physiological features to pathological conditions". The final speaker in the session Dr. Maike Windbergs, (Helmholtz Institute for Pharmaceutical Research Saarland) explored the design and analytical evaluation of In vitro models of human skin wounds.

The second session (*Advanced analysis of drug delivery systems*) took place on Tuesday 6 September and was chaired by Dr. Maria Marlow, Nottingham University. Dr. Axel Zeitler (University of Cambridge) spoke about "Predicting Amorphous Stability and the Role of Secondary Dielectric Relaxations", whilst Prof. Arwyn Tomos Jones (University of Cardiff) discussed "Qualitative and quantitative confocal imaging to analyse endocytosis of plasma membrane targeting ligands and drug delivery vectors" and Prof. Phil Williams (University of Nottingham) Single molecule experiments in formulation development.



Theophylline: Increasing scientific and clinical evidence gives this old drug a new lease of life

MARIA MALAMATARI

JOINT 3RD PRIZE: UKICRS ESSAY COMPETITION 2016

Theophylline is a widely available and inexpensive methylxanthine, which belongs to the same chemical family as the common dietary xanthines, caffeine and theobromine. Theophylline and aminophylline (i.e. a mixture of theophylline and ethylenediamine in a 2:1 ratio, with higher aqueous solubility) have been used in the treatment of respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD) for more than 90 years. Theophylline's narrow therapeutic index and side effect profile, as well as the discovery of more potent and safer bronchodilators, caused it to fall out of favour with clinicians and patients. However, new insights into the molecular mechanism of action of theophylline, together with increasing clinical evidence suggests that it should be exploited as an anti-inflammatory agent rather than a bronchodilator. Theophylline may re-emerge as a combination formulation with inhaled corticosteroids in the management of chronic inflammatory diseases of the lungs.

Historical background

Theophylline was first extracted from tea leaves around 1888 by the German biochemist Albrecht Kossel. After a few years, different ways to chemically synthesise theophylline were discovered (e.g. Traube purine synthesis) making it an inexpensive compound primarily used as a diuretic [1]. In 1921, pharmacologists from Johns Hopkins University were the first to demonstrate that theophylline was a more effective bronchodilator than caffeine when tested in bronchial smooth muscle from pigs. A year later, the first study was published reporting that theophylline should be considered clinically for both acute and prophylactic treatment of asthma. However, theophylline did not receive further attention until 1937, when two clinical trials highlighted its value in the management of asthma. These studies together with numerous additional reports in the late 1930s opened the way for the approval of theophylline as an anti-asthmatic drug by the FDA in 1940 [2].

Theophylline became the mainstay of management of acute asthma exacerbations when it came into general use as it was more effective and safer than the available medications at the time (e.g. adrenaline, ephedrine, benzyl benzoate and asthma powders composed of potassium nitrate and stramonium leaves). Improved understanding of the pharmacodynamics and pharmacokinetics of theophylline together with the development of controlled-release drug delivery systems extended the use of the drug as a prophylactic agent for chronic asthma. However, nowadays due to the development of more effective therapies, such as the β2-agonists and the inhaled corticosteroids (ICS) and the rising concerns about the potential side effects of theophylline, the use of the drug in industrialised countries began to fall.

Current use of theophylline for the treatment of asthma and COPD

According to the Global Initiative for Asthma (GINA) stepwise approach to control symptoms and minimise risks in asthma, theophylline is classified as an alternative, less effective option to low-dose ICS (Step 2) and as an add-on treatment to low- or high-dose ICS

(Step 3 and 4) [3]. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), theophylline is a third-line bronchodilator after β2- agonists and anticholinergics and its use is recommended if the other two classes of drugs are unavailable or unaffordable [4].

Theophylline and aminophylline are both indicated for the treatment of chronic asthma and reversible airway obstruction [5]. Theophylline is formulated as controlled-release oral tablets and capsules and the typical adult dose ranges from 250–500 mg every 12 hr. Aminophylline can also be administered by intravenous infusion for severe acute asthma and severe acute exacerbation of COPD.

Due to its narrow therapeutic index (plasma concentration 10–20 mg L^{-1}), theophylline is an ideal candidate for controlled-release (CR) preparations. In this way, maintenance of optimal drug concentration and increased duration of therapeutic effect is achieved with minimised side effects. Moreover, less frequent administration (once or twice daily) facilitates patient adherence. However, CR preparations of theophylline should not be generically prescribed and patients should be maintained on the brand on which they have been stabilised [5]. This may be explained by the clinically significant differences in the extent and the rate of absorption observed among different commercially available CR formulations of theophylline.

Pharmacology of theophylline

Theophylline has a double action in the treatment of respiratory diseases: at high plasma concentrations, it acts as a bronchodilator while at lower plasma concentrations it exerts bronchoprotective properties [2]. The bronchodilation of airway smooth muscles caused by theophylline is mediated by two molecular mechanisms: phosphodiesterase (PDE) inhibition and adenosine receptor antagonism. Theophylline is a weak bronchodilator and a plasma concentration of 10–20 mg L^{-1} needs to be achieved for bronchodilation to occur. Unfortunately, at these high plasma concentrations and above, theophylline may also cause toxic effects such as nausea, vomiting, headaches, diuresis, cardiac arrhythmias and seizures. The side effects caused by theophylline are mediated by the same molecular mechanisms that are involved in bronchodilation [6].

Theophylline's non-selective PDE inhibition results in bronchodilation, but also adverse effects. Research has focused on discovery of highly selective PDE inhibitors for the treatment of respiratory diseases that will have greater efficacy but fewer side effects [7]. In July 2010, roflumilast (Daxas®; Nycomed) a PDE4 inhibitor with anti-inflammatory properties was approved in Europe as an add-on therapy for the maintenance treatment of severe COPD associated with chronic bronchitis [5].

It is accepted that airway inflammation plays a critical role in the pathogenesis of both asthma and COPD. In the past three decades, many clinical studies have suggested that theophylline has clinically relevant anti-inflammatory properties in asthmatic patients at plasma concentrations (≈ 5 mg L^{-1}), which do not present toxicity problems. The immunomodulatory effects of theophylline were observed even in patients already in treatment with ICS, indicating that ICS and theophylline mitigate inflammation through different molecular mechanisms, and thus combination therapy may have synergistic effects. Combining oral theophylline (250–375 mg/day) with a low dose of inhaled budesonide (400 mcg/day) was found to be equally effective as a high dose of budesonide (800 mcg/day^{-1}) for asthma control [8]. As a result, it was suggested that addition of low-dose theophylline to ICS may be preferable and cheaper than increasing the dose of inhaled corticosteroids. The molecular mechanisms behind the immunomodulatory effects of theophylline are mediated through adenosine receptor antagonism and histone deacetylase activity (HDAC). Theophylline is reported to increase directly the histone deacetylase enzymatic activity in epithelial cells and macrophages [9]. By increasing HDAC activity, theophylline inhibits the acetylation of core histones promoting repackaging of chromatin and thus it suppresses the expression of proinflammatory genes.

Low-dose theophylline restores corticosteroid resistance in chronic inflammatory diseases of the lungs

COPD is a chronic inflammatory disease of the lungs characterised by progressive airflow limitation that is poorly reversible. Macrophages play a pivotal role in the pathophysiology of COPD with a significant increase in their numbers in the lungs of COPD patients. The levels of inflammatory mediators such as interleukin-8 (IL-8) and TNF-alpha are also increased in the sputum of COPD patients [10]. The anti-inflammatory response of inhaled or oral corticosteroids is reduced in alveolar macrophages from COPD patients. This may be explained by a reduction in histone deacetylase activity (HDAC2) as a result of oxidative and nitrate stress in the macrophages of these patients. The reduced HDAC2 activity results in increased acetylation of the glycorticosteroid receptor which prevents it from inhibiting inflammation [11]. Theophylline was found to induce a sixfold increase in HDAC activity in macrophages of COPD patients and to enhance dexamethasone suppression of induced IL-8 [12].

The synergistic effect of theophylline with corticosteroids has also been reported in asthmatic smokers (worldwide one in four individuals with asthma still smokes!). A combination of low-dose theophylline (400 mg/day) and inhaled beclometasone (200 µg/day) significantly improved both lung function and asthma control in smoking asthma patients compared with each drug alone [13]. Reversal of corticosteroid resistance is recognised as a highly promising approach for emerging pharmacotherapies in COPD [11]. Therefore, co-administration of low-dose theophylline with ICS may become a common future treatment for chronic inflammatory lung diseases.

Delivery of theophylline to the lungs

Administration of theophylline by inhalation can be used as an approach to enhance local efficacy by delivering the drug to the site of action, while minimising side effects. Intratracheal administration of theophylline as a dry powder formulation to the airways of anaesthetised guinea pigs exhibited smooth

muscle relaxant and anti-inflammatory properties at very low doses (50–500 mcg) that would be predicted to have no systemic toxicity [14]. Recently, Pulmagen Therapeutics LLP carried out a phase II clinical trial assessing the effects of inhaled theophylline (ADC4022, 12.5 mg) co-administered with nebulised budesonide (1 mg twice daily) in patients with moderate to severe COPD. The results suggested that low-dose inhaled theophylline had the potential to reverse the anti-inflammatory effect of ICS in COPD patients [15]. In 2014, SkyePharma PLC became a partner in this project announcing the development of a fixed combination of low-dose theophylline (≈1% of recommended oral dose for bronchodilation effect) with the ICS fluticasone as a dry powder for inhalation [16]. The phase II efficacy and safety clinical trial carried out by the company is expected to conclude in 2017. As both theophylline and ICS are drugs with established pharmacological and toxicological profiles, the development risk and timelines are expected to be shorter compared to those for new chemical entities (10–15 years).

Conclusions

Since the first report on the clinical use of theophylline for asthma in 1922, its popularity as a treatment for the management of asthma and COPD increased and then declined. According to current guidelines, its use is now limited to add-on therapy for the management of asthma and COPD. However, new insights into the molecular mechanism of action of theophylline show that it has anti-inflammatory properties at low plasma concentration, such that toxicity is no longer a problem. Many clinical trials have demonstrated the ability of theophylline to restore the steroid resistance in patients with COPD and in this way to unlock the potential of ICS for the management of the disease. A formulation of low-dose theophylline with ICS that will be administered by a dry powder inhaler is currently in phase II clinical trials indicating the potential comeback of theophylline in our therapeutic armamentarium for treating chronic inflammatory diseases of the lungs.

References

1. Wettengel R. Theophylline - Past, present and future. Arzneim. Forsch. Drug Res. 1998;48:535–539.
2. Tilley SL. Methylxanthines in asthma. In: Fredholm BB, editor. Handbook of Experimental Pharmacology 200. Berlin: Springer; 2011. p. 439–456.
3. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2015. Available from: www.ginasthma.org
4. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016 (update). Available from: www.goldcopd.com
5. Joint Formulatory Committee. British National Formulary. 70 ed. London: BMJ Group, Pharmaceutical Press; 2015.
6. Barnes PJ. Theophylline. Pharmaceuticals. 2010;3:725–747.
7. Boswell-Smith V, Cazzola M, Page CP. Are phosphodiesterase 4 inhibitors just more theophylline? J. Allergy Clin. Immunol. 2006;117:1237–1243.
8. Evans DJ, Taylor DA, Zetterstrom O, et al. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. N. Engl. J. Med. 1997; 337:1412–1418.
9. Ito K, Lim S, Caramori G, et al. A molecular mechanism of action of theophylline: Induction of histone deacetylase activity to decrease inflammatory gene expression. Proc. Natl. Acad. Sci. USA. 2002;99:8921–8926.
10. Keatings VM, Collins PD, Scott DM, Barnes PJ. Differences in interleukin-8 and tumor necrosis factor-alpha in induced sputum from patients with chronic obstructive pulmonary disease or asthma. Am. J. Respir. Crit. Care Med. 1996;153:530–534.
11. Barnes PJ. Emerging pharmacotherapies for COPD. Chest. 2008; 134:1278–1286.
12. Cosio BG. Theophylline Restores Histone Deacetylase Activity and Steroid Responses in COPD Macrophages. J. Exp. Med. 2004;200:689–695.
13. Spears M, Donnelly I, Jolly L, et al. Effect of low-dose theophylline plus beclometasone on lung function in smokers with asthma: A pilot study. Eur. Respir. J. 2009;33:1010–1017.
14. Raeburn D, Woodman VR. Effect of Theophylline Administered Intratracheally as a Dry Powder Formulation on Bronchospasm and Airway Microvascular Leakage in the Anaesthetized Guinea-pig. Pulm. Pharmacol. 1994;7:243–249.
15. Oral and inhaled medicines for chronic lung disease. Pulmagen;2016. Available from: http://www.pulmagen.com/theocort.html [Last accessed 10 February 2016]
16. Addressing unmet needs in COPD: unlocking the potentila of ICS. SkyePharma; 2014. Available from: www.skyepharma.com/Doc/02_PDF/04_PRESENTATIONS_WEB CASTS/Skyepharma%20FTI%20Respiratory%20Meeting%2009- 09-14.pdf [Last accessed 10 February 2016].

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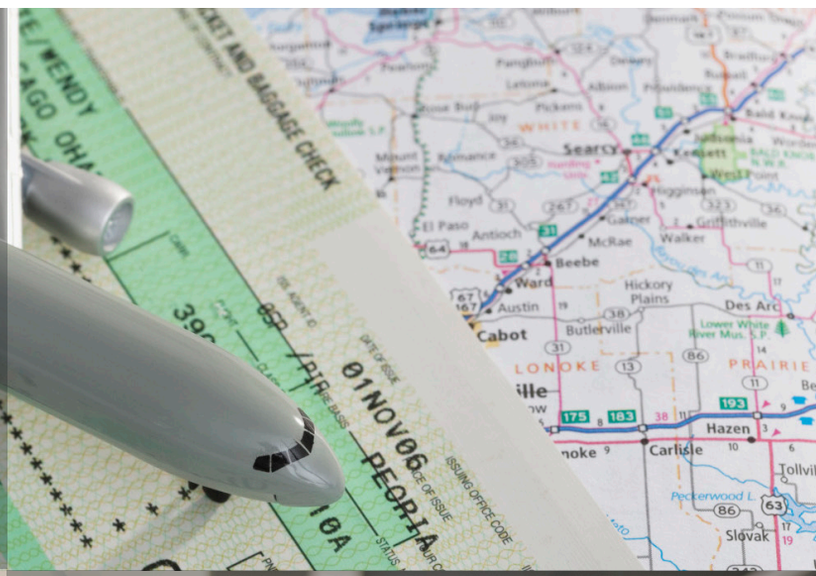

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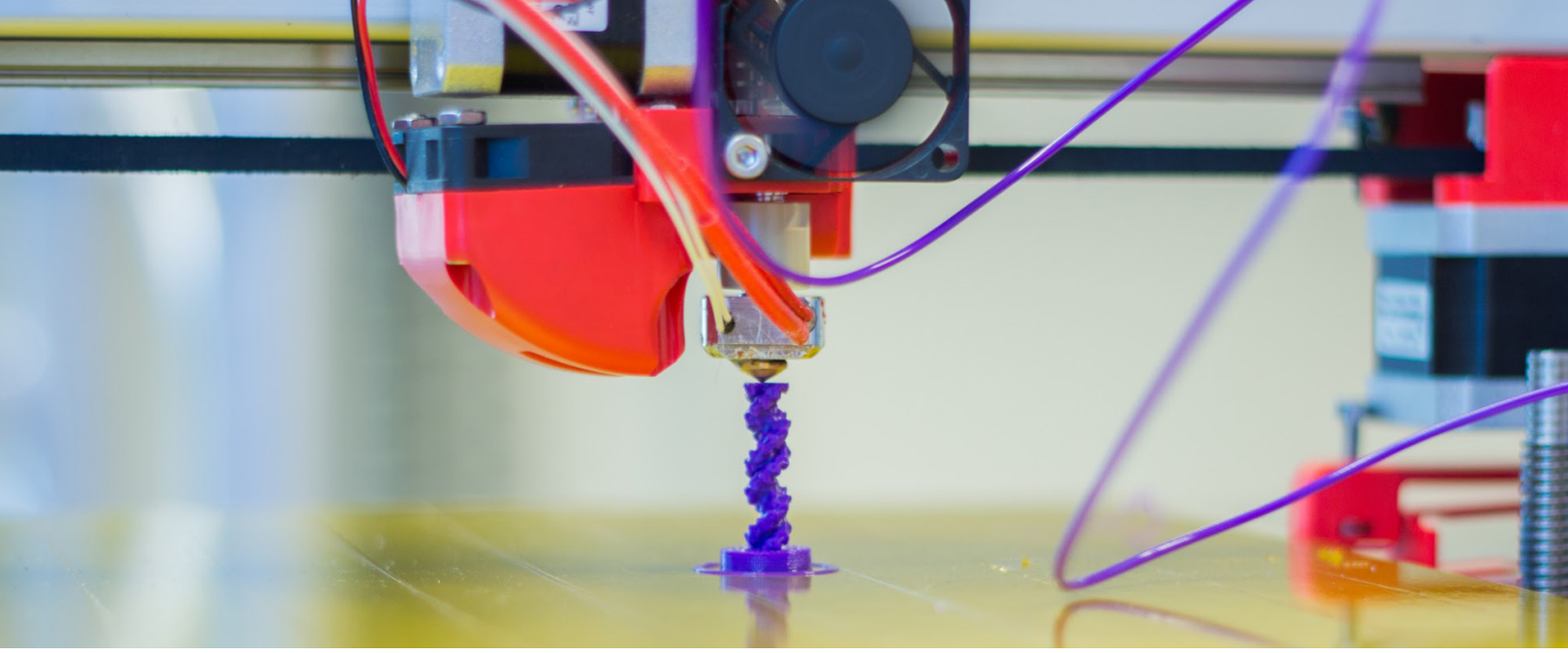

Additive Manufacture: The Key to a New Era of Personalised Medicines Manufacture

KATHERINE TRIFFITT

JOINT 3RD PRIZE: UKICRS ESSAY COMPETITION 2016

The concept of 'personalised medicine' is already making a significant impact in clinical practice, with a number of health specialities already adopting individualised treatment strategies. With respect to this, the future of medicine design will inevitably take into account patient genetic and proteomic factors, in combination with the prospect of formulating a wide-range of individualised medicines made available to the patient at the point of prescription.

However promising this looks to the evolution of disease treatment, applying the concept of personalised medicine to the pharmaceutical industry presents a number of challenges. For example, production of drug doses tailored to individual needs may in the future require novel manufacturing technologies capable of producing small scale numbers of dosage forms1 available to the patient at the point of prescription presentation (i.e. community pharmacy). Current commercial medicines formulation technology only operates efficiently on a large scale[1], and therefore will only have limited future use in producing common dosage forms required in large percentage groups of the population. Manufacture therefore may move away from such industrial production, and instead towards in situ formulation of individually tailored unit dosage forms and drug combinations[2].

Additive manufacture is one promising area for development with regard to the manufacture of personalised medicines[1]. Since its initial development and utilisation as a production tool for rapid prototyping1 in the late 80's, early 90's[3], additive manufacture has been adopted in many industry settings as a novel and highly efficient means of development. Binder Jetting is one form of additive manufacture that follows the principle of binding solution deposition from a print head onto a powdered substrate layer to allow consolidation[1]. The desired object is subsequently built up in the same fashion, layer by layer. Such technology is now seen in a diverse number of manufacturing fields, including architecture, nanosytems, aerospace industry, fashion and biomedical research[2]. Medical researchers have also utilised additive manufacture to create bones and functional organs[4,5,6], bringing such potential in the medical field to light, with the pharmaceutical field potentially to follow.

Using associated desktop technology in a pharmaceutical care settings could potentially allow the production of personalised medicine guided by their respective prescription[7]. Possibilities include single blend tablets made of a specific drug and dose to suit individual need[7] (e.g. for drugs that present with a narrow therapeutic index such as warfarin), multi-layer tablets to provide combinatorial therapy of different strengths or release profiles of the same drug, or a combination of two or more separate drugs with the aim to reducing tablet load[7].

Fused-deposition modelling (FDM) is another recent approach in additive manufacture, in which an extruded polymer filament is softened by passing through a

heated printing tip[8]. Once deposited on the printers build plate, the polymer will harden and can then have subsequent polymer layer built on top in identical fashion to produce the desired 3D object.[8]

In order to manufacture a pharmaceutically relevant tablet via FDM, it is necessary to incorporate the drug of interest into a polymer filament in order for feeding into the print stock[1]. Such has traditionally been achieved via soaking of the polymer in alcoholic solutions containing the active drug[8]. Although relative success has been seen in drugs such as 4-aminosalicylic acid (4-ASA), 5-aminosalicylic acid (5-ASA)[9] and prednisolone,[10] the process relies upon passive diffusion and as such requires extended manufacture time, including additional drying steps with often only a low overall drug load achieved.[8] The use of hot melt extrusion is a far more feasible and proven effective alternative methodology. It can be described as a process by which raw materials (i.e. drug and excipients) are forced to mix in a rotating screw at elevated temperatures[2], and then converted into a product of uniform shape and density via extrusion through a die under defined conditions.[8,11] The use of hot melt extrusion to produce drug-loaded filaments required for additive manufacture has already been shown to be achievable for water-soluble filaments when producing oral formulations.[2,12] For example, Goyanes et al[2] successfully prepared both paracetamol and caffeine-loaded poly(vinyl) alcohol (PVA) filaments via a Noztec Pro hot melt extruder (Noztec, UK) at 180°. The attempt to incorporate higher drug loading percentages reduced filament quality (via possible polymer crystallinity alterations[2]) and thus additive manufacturing potential in this instance, however drug loading percentages above 10%w/w were subsequently achieved via the addition of plasticising excipients[2]. Alongside its success in the literature, hot melt extrusion offers further advantages in additive manufacture including (as previously mentioned) the possibility of working without solvents and thus avoiding the need for subsequent drying steps,[11,13] low cost, fast production and availability for continuous production.[11]

The nature hot melt extrusion dictates that both the excipients and more importantly the drug of interest are stable at high temperatures. Long residency time and high glass transition temperatures have often been described as potential drawbacks to the hot melt extrusion process[14], however there are a number of ways to overcome this limitation should the drug of interest be thermally unstable. One such example could be the formulation and subsequent production of drug salts (e.g. through the reaction of an acid drug with an amine to form an ionic salt) which are known to remain stable at high temperatures, or to co-crystallise the drug with a co-former that could potentially provide desired stability. There is a currently huge pharmaceutical interest in crystal engineering as a means to optimise chemical and physical drug properties such as solubility, hygroscopicity and dissolution rate.[15–17] Therefore, the consideration to also alter glass transition temperature may be reasonable. The use of co-crystal engineering in this sense however is only speculative, as there is currently no research to support the suggestion that addition of a second entity or co-former during the process would alter the glass transition of a specified drug. No conclusions therefore can be drawn regarding the use of co-crystallisation to provide thermally stable drug products for hot melt extrusion, however the process may be taken into consideration for future development in the area.

Once fed into the print stock, the drug-loaded polymer filament is ready for commencement of fused deposition modelling. It is at this point that associated print software is utilised to adjust parameters of the manufacture, which will subsequently lead to the production of desired dose forms. Printing parameters such as deposition rate, tip size, push-out, suck-back and path-speed have all been used successfully to alter and control tablet shape within satisfactory limits.[7] One specific parameter of interest in formulating tablets for individualised doses is infill percentage. In order to increase the mechanical strength of the desired tablet, a greater infill percentage would be selected which would raise the degree to which the printer will pack the void space with polymer.[1] This parameter can vary from 0% (empty) to 100% (solid) and therefore has the potential not only to modify the structure of the tablet (i.e. 0% infill will result in a hollow tablet), but in doing so also modify the physical properties of the resultant formulation, such as its dissolution profile.[1] For example, tablets with lower percentage infills demonstrated faster drug release in studies undertaken by Goyanes et al1 (i.e. 6 and 15 hr timeframes for complete drug release in 10% and 50% infill tablets, respectively). This study also demonstrated a linear relationship between infill percentage and tablet weight, suggesting that drug dose could be controlled via selection of appropriate infill percentage1. This has vast potential in the area of individualised medicine, where tablets could be manufactured at specific doses for an individual via calculation of the appropriate infill percentage.

The research field associated with global additive manufacturing is not only currently wide open, but is also gaining significant momentum, with many industrial sectors across the world participating in its development. Indeed, it is forecast to be a key enabler in high value manufacturing with a worldwide market estimation of £67 billion by 2020[3,18]. The UK is currently among the global leaders in both knowledge development and successful application of additive manufacturing technology[3], with considerable capacity for further research including the involvement of 81 organisations (24 universities and 57 companies) since 2007[3]. Significant public and private sector investments totalling approximately £90million has been placed within the UK to expand the Technology Readiness Level of additive manufacturing, with the Government Office for Science's Manufacturing

Foresight Report 2013 claiming “advances in technologies such as additive manufacture … will take place closer to the customer, with a much greater range of products becoming more personalised and tailored to specific needs”.[19] Within the pharmaceutical industry, GlaxoSmithKline Research & Development have expressed interest in exploring the use of additive manufacture in the production of oral solid dosage formulations, with the future intent to distribute cartridge-based printing machines in local pharmacies and hospitals in the hope of providing patients with customised medicines at the point of prescription3. Given the current literature and financial support for research, the future of pharmaceutical additive manufacture looks both exciting and incredibly promising. Goyanes et al[2] describe perfectly the concept that ‘theoretically, computer aided design could leave imagination and the resolution of technology as the only limits to the design and manufacture of complex, multifaceted tablets’. With such in mind, it is a fair assumption to make that additive manufacture indeed holds the key to a new era of medicines manufacture.

References

1. Goyanes, A., Buanz, A.B.A., Basit, A.W., Gaisford, S., (2014), Fused-filament 3D printing (3DP) for fabrication of tablets, International Journal of Pharmaceutics, 476:88-92
2. Goyanes, A., Wang, J., Buanz, A., Martinez-Pacheco, R., Telford, R., Gaisford, S., Basit, A.W., (2015), 3D Printing of Medicines: Engineering Novel Oral Devices with Unique Design and Drug Release Characteristics, Molecular Pharmaceutics, 12:4077-4084
3. AM National Strategy, Positioning Paper: The Case for Additive Manufacturing, March 2015, Available athttp://www.amnationalstrategy.uk/wp-content/uploads/2015/05/AM-Strategy-Positioning-Paper.pdf
4. Jones, N., (2012) Science in Three Dimensions: The Print Revolution, Nature, 487(7405):22-23
5. Mannoor, M.S., Jiang, Z., James, T., Kong, Y.L., Malatesta, K.A., Soboyejo, W.O., Verma, N., Gracias, D.H., McAlpine, M.c., (2013), 3D Printed Bionic Ears, Nano Letters, 13(6):2634-2639
6. Kolesky, D.B., Truby, R.L., Gladman, A.S., Busbee, T.A., Homan, K.A., Lewis, J.A., (2014), 3D bioprinting of vascularised heterogenous cell-laden tissue constructs, Advanced Materials, 26(19)3124-3130
7. Khaled, S.A., Burley, J.C., Alexander, M.R., Roberts, C.J., (2014), Desktop 3D printing of controlled release pharmaceutical bilayer tablets, International Journal of Pharmaceutics, 461:105-111
8. Goyanes, A., Chang, H., Sedough, D., Hatton, G.B., Wang, J., Buanz, A., Gaisford, S., Basit, A.W., (2015), Fabrication of controlled-release budesonise tablets via deasktop (FDM) 3D printing, International Journal of Pharmaceutics, (article in press) available at http://dx.doi.org/10.1016/j.ijpharm.2015.10.039
9. Goyanes, A., Buanz, A.B., Hatton, G.B., Gaisford, S., Basit, A.W., (2015) 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets, European Journal of Pharmaceutics and Biopharmaceutics, 89:157-162
10. Skowyra, J., Pietrzak, K., Alhnan, M.A., (2015) Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing, European Journal of Pharmaceutical Science, 68:11-17
11. Thiry, J., Krier, F., Evrard, (2015), A review of pharmaceutical extrusion: Critical process parameters and scaling-up, International Journal of Pharmaceutics, 479:227-240
12. Goyanes, A., Martinez, P.R., Buanz, A., Basit, A., Gaisford, S., (2015) Effect of geometry on drug release from 3D printed tablets, International Journal of Pharmaceutics, 494:657
13. Bruce, L.D., Shah, N.H., Waseem Malick, A., Infeld, M.H., McGinity, J.W., (2005), Properties of hot-melt extruded tablet formulations for the colonic delivery of 5-aminosalicylic acid, European Journal of Pharmaceutics and Biopharmaceutics, 59:85-97
14. Breitenbach, J., (2002), Melt extrusion: from process to drug delivery technology, European Journal of Pharmaceutics and Biopharmaceutics, 54:107-117
15. Chen, J.A., Li, S., Lu, T.B., (2014), Pharmaceutical Cocrystals of Ribavirin with Reduced Release Rates, Crystal Growth and Design, 14:6399-6408
16. Vishweshwar, P., McMahon, J.A., Bis, J.A., Zaworotko, M.J., (2006), Pharmaceutical Co-Crystals, Journal of Pharmaceutical Sciences, 95:499-516
17. Steed, J.W., (2012), The role of co-crystals in pharmaceutical design, Trends in Pharmacological Sciences, 34(3):185-193
18. Innovate UK (formerly TSB), (2012), Shaping our National Competency in Additive Manufacturing: A technology innovation needs analysis, Swindon: Innovate UK (formerly TSB)
19. Foresight, (2013), The Future of Manufacturing: A new era of opportunity and challenge for the UK, Summary Report, The Government Office for Science, London

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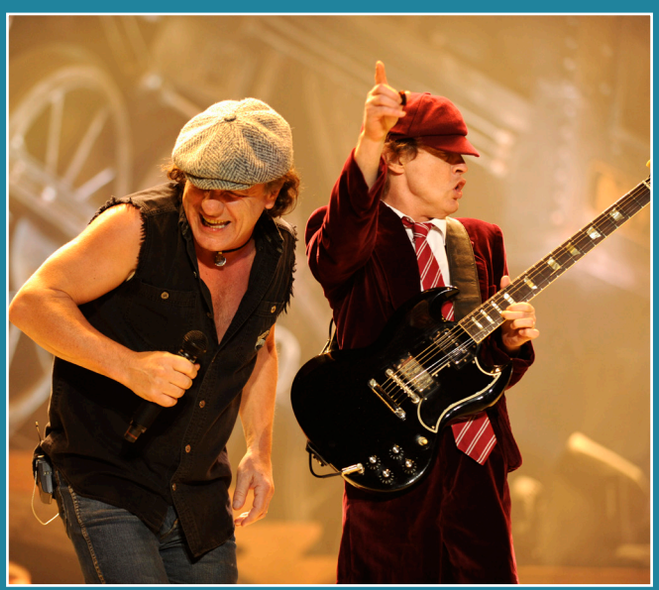
WEIRD ... BUT TRUE!

Playing 'Thunderstruck' by AC/DC in a loudspeaker plasma reactor helps produce excellent ''Teflon-like'' controlled release coatings on porous silicon microparticles loaded with the anticancer drug camphothecin. Weird, but true! Apparently, the ''non-monotonic frequencies'' offered up by arguably the greatest rock'n'roll band of all time (IMHO) are just perfect for creating chaotic motion of the microparticles during the plasma polymerization step. It makes you think, though ... might 'You shook me all night long' have been an even better choice of song to rock those particles?!



Steven J.P. McInnes, Thomas D. Michl, Bahman Delalat, Sameer A. Al-Bataineh, Bryan R. Coad, Krasimir Vasilev, Hans J. Griesser, and Nicolas H. Voelcker. **''Thunderstruck'': Plasma-Polymer-Coated Porous Silicon Microparticles As a Controlled Drug Delivery System**. ACS Applied Materials & Interfaces, 2016, 8 (7), pp 4467–4476. DOI: 10.1021/acsami.5b12433

ETHICS IN SCIENCE

Dr Emma Lane, Neuropharmacologist (not ethicist), Cardiff University School of Pharmacy and Pharmaceutical Sciences.

Ethics is defined – by that fount of all knowledge, Wikipedia – as 'the branch of philosophy that involves systematising, defending and recommending concepts of right and wrong conduct'. It derives, apparently from Greek, as the words for habit or custom and indeed many scientists are well accustomed to dreading the question 'do we need to consider ethics?'. More often than not, if you need to ask the question, then yes you do. But we probably don't ask the question enough.

In an ever more complex scientific arena, we are never far from an ethical dilemma. Some ethical issues are more obvious, and have to be dealt with via formal processes, for example the use of human subjects and tissues in research and the use of animals. Others however, are around moral and professional issues. The first are imposed on us as descriptive ethics; what does society and the culture around us believe is morally correct? While the latter are prescriptive ethics; how should I behave as a researcher, what character traits should I cultivate?

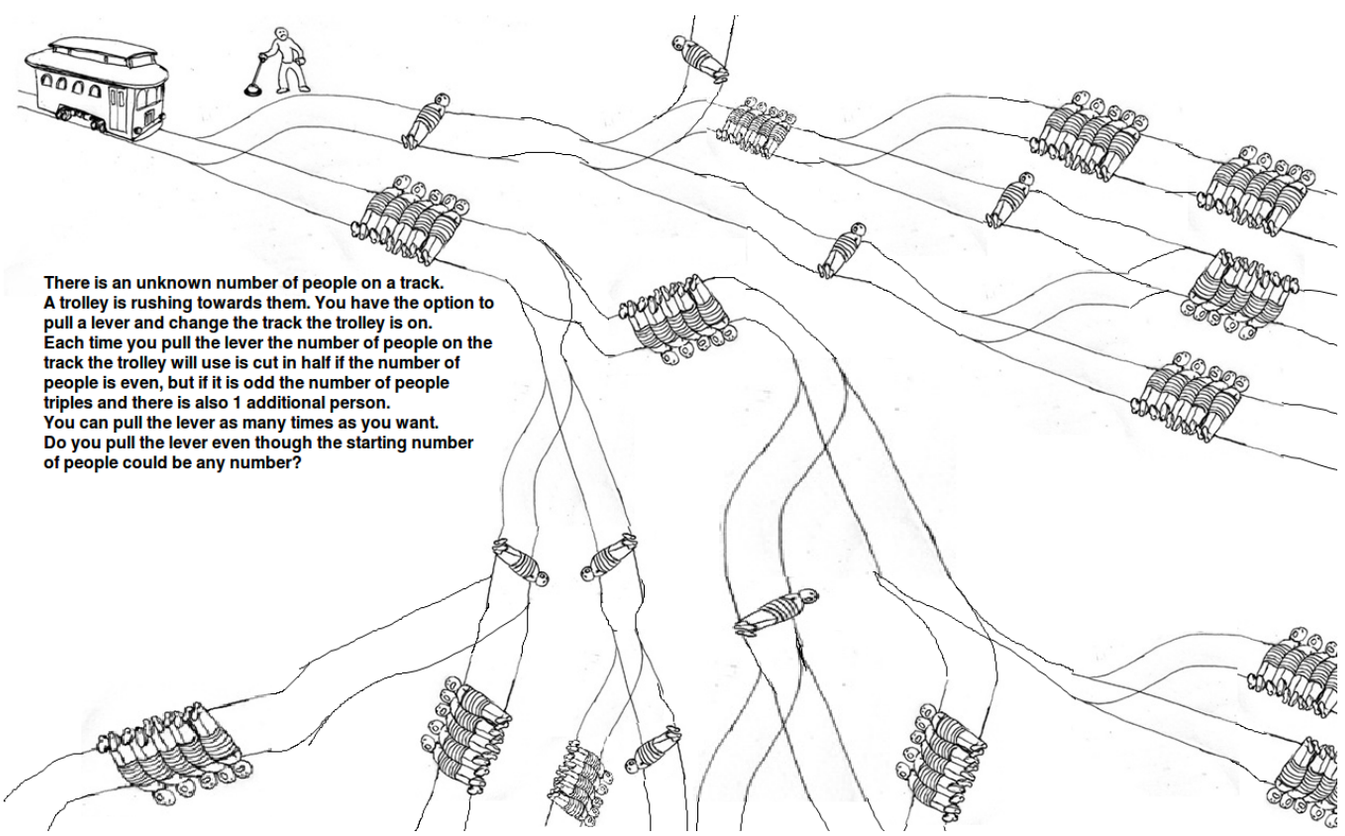
If we focus on the descriptive, and animal research in particular, the ethical debate has raged in the UK for centuries. With some of earliest legislation around cruelty to animals and the establishment of societies dedicated to the prevention of cruelty from the mid 1800s. We like to think of ourselves as a nation of animal lovers, only we do have a tendency to pick and choose the animals we love! Around 2.5 billion animals are killed in the UK on an annual basis for food, whilst our much adored pet cats are themselves responsible for the deaths of over 220 million small mammals and birds! This helps us contextualise the approximately 4 million animals per year used in research, and this is in fact less than the number of small animals killed in 1 week by your lovable moggy and their feline friends.

Until recently, as scientists we worked under the regulatory control of the UK Animals (Scientific Procedures Act) 1986 which introduced a system of licensing premises, projects and individuals to regulate the way in which animals were kept, what could be done to them and by whom. This has now been superseded by EU legislation, but unusually we in the UK were at an advantage and pre-existing rigorous processes have only been subject to minimal alterations

in real terms. The core principles enshrined in this legislation are the 3Rs, reduction, replacement and refinement. The ethical arguments around animal research are complex and diverse (and written about extensively by far more informed ethicists than me!) but can be made both to justify and decry animal research. Unfortunately, the system means that unless we are actively engaged in the animal work ourselves we are not compelled to consider the ethics. Collaboration is a fundamental part of scientific enquiry and progression but what is our ethical obligation to be fully informed about the procedures the animals have been subject too by collaborators, and the restrictions they work under?

Fundamentally, in most ethical situations we all have a choice about what we believe, and we all have a right to our own opinion, but importantly we also have an obligation to be informed about the ethics of our direct actions AND those that we are associated with. Ignorance, should never be an excuse.

Regardless of the type of research we are undertaking, if we consider the Wikipedia definition carefully (be honest, it's the one we'd all use if we had to look it up, whatever we tell the undergraduates!), consideration for the professional ethical issues we face as scientists should give us all pause for thought at some time in our careers. How do we want to behave as supervisors of PhD students, how do we behave towards peers, competitors, collaborators and support staff, how do we publish? The pressures on us all are to publish first, publish impactfully, publish with a good authorship position, etc, but we must not loose sight of our ethics in all of this. In order to do this we need to at least have considered what we would aspire to be as a scientist, author, collaborator or colleague in a perfect world. How many of us stop and think about that?



The figure above (taken from https://www.reddit.com/r/math/comments/4i3kho/collatz_trolley_problem/) shows a development of Collatz 'The Trolley Problem' as a series of ethical dilemmas which can parallel life in general but certainly a life in science.

A GUIDE TO GETTING A JOB IN THE PHARMA INDUSTRY

by Marie McGrath (GlaxoSmithKline)

As an employee and an employer at GSK, I thought I would share some hints and tips for getting a job in this Industry. In fact, many of my tips aren't specific to pharma and could help you to get a job anywhere!

What research experience or skills do I need for a job in drug delivery?
It is a tough and competitive world out there and so employers are looking for candidates that are first and foremost technically competent. Think about the job that you are applying for. If you are applying for a job in Drug Delivery and your most relevant expertise is in horticulture then you are probably going to fail at the application stage. Beyond this, if you have the technical expertise and competence that the job description demands then there are a number of other key skills that an employer will be looking for, which include:

- Technically agile – technologies and focus will change and evolve
- Problem solver
- Innovative
- Practical
- Translational – how to get the idea to the Patient: regulatory, cost, partners
- Can communicate new technology to a project team from a different scientific discipline

Work experience isn't essential but it definitely helps and demonstrates genuine passion for the subject area. Try to identify opportunities to gain experience in Industry, if that's where you want to be. This could be student placements, PhD or postdoctoral experience. Learning opportunities are different yet equally valuable at different size companies - align these with your expertise and values.

However, even if you possess all of these skills and experiences you won't make it very far unless you communicate it effectively. Invest time crafting your CV and application form and then prepare well for interviews. Below are some of my personal hints and tips:

Make sure you get the easy parts of the paperwork right!
It sounds obvious but spelling and grammar DO matter (proof reading is advised). Also use the word count - it's there for a reason! For your qualifications include your GCSEs, A Levels, Degree modules and ensure you include your grades. Note that some programmes require

specific subjects – make sure you have these. For the employment and work experience section start with the most recent and think about what's relevant i.e. responsibility, accountability, have you achieved an output, facilitated others or worked as part of a matrix team? Some things may not be relevant e.g. job shadowing and routine work with no responsibility. Extra Curricular activities and interests are important. They can show responsibility, drive, teamwork and proactivity amongst other important skills.

Tailor your CV and application to the Company and the Role.
It is not a one size fits all approach. Think about the values and interests of the company. You can normally glean this from websites - What are the company values? Do you align well with these and have experience that demonstrates how? What words are highlighted? Do they list competencies/ behaviours desired? What are the company's strategic areas for growth? Study the role and the potential career path. You will need a high level understanding of the role you are applying for as well as some future vision for the role. Don't be afraid to ask for clarifications before the interview to help you prepare – you should understand the role you are applying before you interview. Make sure you prepare your CV, application form and interview with the specific role in mind i.e. why do you want this?

When completing the application form look out for the clues in the question and carefully consider the language that you use. For example, remember that competencies are what you CAN do. For any questions related to competencies therefore focus on what you have already experienced / achieved. However strengths are what you ENJOY doing. The focus on these type of questions are the future and what you really want from your career. For example, when answering a question about "continuous improvement", competency in this area would be "...from feedback I learnt how to better engage my audience and get my ideas across" whereas a strength would be "...I love learning and receiving feedback on my performance will help me improve the way that I communicate my ideas"

When answering questions on an application form or for an interview be genuine and don't be afraid to give personal insights or opinion. Also use a variety of examples - do not rely solely on your PhD area of technical expertise and don't repeat yourself. Prepare situational examples both inside and outside of work environment. Be yourself and show how your expertise and interests can add value to another area. Describe how you work and engage with other people to deliver an objective and be clear about your role in the team. It can be helpful to try to base your answers on a structure eg. use the STAR technique to answer questions - Situation, Task, Action, Result.

When preparing, think about the questions the employer is likely to ask.
Examples of classic application form and interview question include:

- Why do you want to work for the company ?
- (When answering this focus on your motivation for the company, not the job.)
- What do you know about the company?
- What attracts you to the company?
- How has the company, or its employees inspired you?
- How the company can drive your career?

Your enthusiasm for Company values and purpose must radiate from your answer. However, don't just regurgitate the company website without explaining why you want to work there!

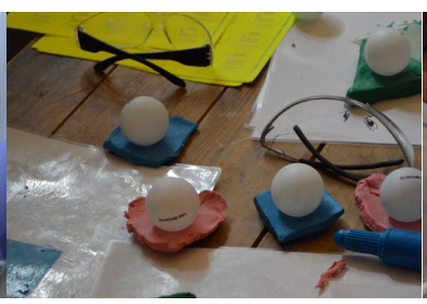
Talk about a leadership role or your proudest achievement in an extra curricular activity, interest or hobby.
Try not to talk about a job or an academic project! Provide your personal roles or achievements e.g. a prize, award, position of responsibility / leadership. Highlight how you managed multiple commitments, how you worked with /guided/ influenced/ listened to other people. What challenges did you overcome and how? Show energy, initiative and enthusiasm! Remember, you can mention multiple examples. Also use these types of questions as opportunities to exemplify some of the behaviours that the company value e.g. teamwork, communication, flexibility, building relationships, self-awareness.

So, overall, the key message is to prepare, perfect and persist. Good luck with the job hunting and maybe I will hear from some of you in the future!

SCIENCE IN THE PARK

Inspiring the next generation of pharmaceutical scientists






On the 19th March, I was part of a group of students and staff from the EPSRC sponsored Centre for Doctoral Training (CDT) in Advanced Therapeutics and Nanomedicines to showcase our science at the "Science in the Park event" in Nottingham. This event, organised by the British Science Association as part of British Science Week (http://nottsbsa.org), gives children the opportunity to learn more about a wide range of science in the historical and picturesque surroundings of Wollaton Park and Hall. This year 7000 visitors attended, attesting to the popularity of the event.

As a group, we took three different activities to represent the breadth of research within the CDT and the School of Pharmacy. The first was to show the visitors how tablets were made using a single punch hand press. While many of the visitors had taken tablets, few had ever seen them made before. We demonstrated different rates of release using a simple but visual dissolution experiment and effervescent vitamin tablets.

The second activity gave an insight into pharmacy in the past with extemporaneous formulation of creams. We explained how pharmacists in the past would make the majority of the medicines they dispensed and how that differs from the role of a pharmacist in the modern day. The children made their own hand creams with a range of colours and smells, which they labelled and took home as souvenirs.

The final activity was to demonstrate nanoparticles and the principle of targeted therapeutics. Plasticine and table-tennis balls acted as the drugs, with a 3D poster with corresponding shapes representing the human body. This helped the children to understand how targeting might work and why it can be so important. While the first two activities were very much led by us, the nature of this activity allow the children to experiment and work together.

It was fantastic to see so many children, and some of the parents, becoming enthusiastic about science. Kitted out with lab coats, safety specs and gloves, they certainly looked the part as the next generation of scientists. With so many visitors it was a very busy day, but definitely worth the effort that went in to organising the exhibits. Hopefully you are now inspired to organise your own event and take part in British science week.

Intravesical Drug Delivery For Treatment of Bladder Cancer

Oluwadamilola Kolawole[1], Wing-Man Lau[1], Hugh Mostafid[2] & Vitaliy Khutoryanskiy[1]

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Introduction

Bladder physiology

The urinary bladder has two main functions, namely storing and voiding urine (Fig. 1). However, it also plays regulatory roles, preventing the influx of urine and toxic substances into systemic circulation.[1] Morphologically, the bladder appears almost spherical and its overall size is dependent on the volume of urine stored. Normally, it should accommodate between 400 and 600 mL urine and would not necessarily store such volume before sensation of urination is activated at about 150 to 300 mL urine capacity.[1] The myovesical plexus within the bladder wall produces particular signals when the bladder becomes engulfed with urine, while the detrusor muscles regulate the extent and frequency of urine voiding by responding to such sensations.[2]

Bladder cancer incidence and symptoms

In the developed countries, bladder cancer (BC) is ranked 4th in terms of cancer incidence rate in men, though women are less affected.[3] Non-muscle invasive BC (NMIBC) is the type confined to the urothelial wall which does not invade the muscular regions and is the most prevalent form of BC at first diagnosis, in about 70–80% patients.[3] Haematuria is one of the commonest symptoms (with 85% of patients experience this), other symptoms of BC include urinary urgency, and painful urination.[4]

Staging of bladder cancer

The transitional cell carcinomas (TCCs) constitute about 90% of BC cases; incidence rate of squamous

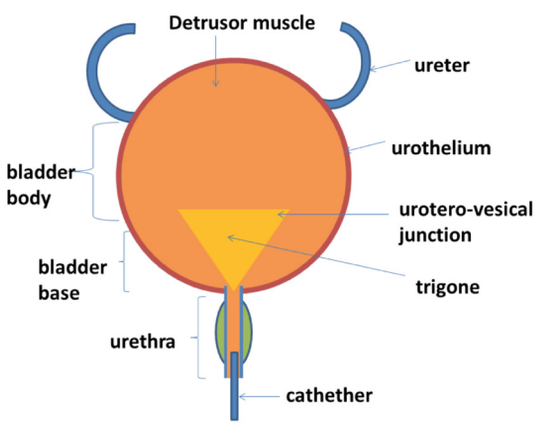

Figure 1. Schematic diagram of bladder showing intravesical drug delivery.

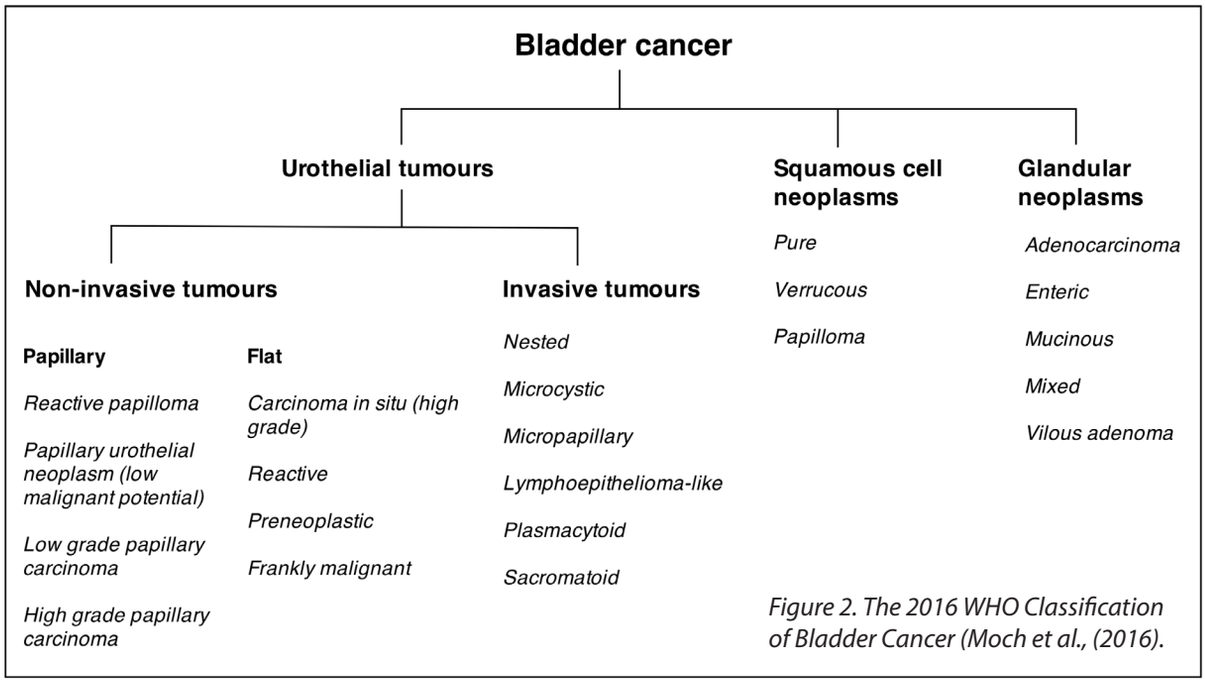

Figure 2. The 2016 WHO Classification of Bladder Cancer (Moch et al., (2016).

cell carcinomas (SCCs) are 3–7%, while the adenocarcinomas (ACs) cases are 2% in proportion.[5] Usually, the innermost portions of the bladder (transitional epithelial cells) are initially affected by most BC types. The nearby connective tissues and muscles become involved as the tumor progresses. Afterwards, the lymph nodes or pelvic organs are also affected. The metastatic stage arises when tumor cancer cells spread to distant organs such as lungs, liver and bone marrow.[5] Treatment of bladder cancer is dependent on the stage and severity of disease.[5] The World Health Organization provides a detailed clinical classification of BC shown in Fig. 2.[6]

The Tumor Node Metastasis system is used to classify BCs according to their degree of progression. From a broad point of analysis, it may be superficial, which is restricted to the Ta, T1 regions; BCs that have invaded the muscle are termed T2–T4; an aggressive superficial tumor with great ability to invade muscular regions is called carcinoma-in-situ (CIS).[1] The BCs are also classified based on their degree of differentiation, where G1 and G3 are the least and most malignant forms, respectively.[7] The tumor grade influences the ease at which the disease would progress as well as the possibility of recurrence post therapy.

Intravesical drug delivery

The clinical management of NMIBC requires transurethral resection of the tumor tissues followed by chemotherapy or immunotherapy to prevent implantation of residual malignant cells.[4] Tumor recurrence and progression to an invasive form after surgical resection of superficial tumor[7] provides rationale for the instillation of one or multiple therapeutic agents through a catheter, into the bladder post-surgery and this is termed intravesical drug delivery (IDD).[8]

The exploration of IDD for BC is necessitated due to the poorly vascularised nature of the urothelium that makes drug delivery via systemic administration unviable. Also, the oral route is equally not practicable because of drug exposure to the degradative effect of gastric acid and enzymes, results in poor drug bioavailability in the bladder.[1,9] Moreover, increase in drug dosage during conventional therapy with the aim of improving local drug concentration within the bladder will only lead to elevated adverse drug reactions and non-selective toxicity to healthy tissues.

Problems with intravesical drug delivery

The pharmacological advantage of IDD is limited by the urothelial barrier; remarkable drug dilution by the urine, and the drug wash-off tendency during the urine voiding phase.[10] This situation is particularly responsible for the recurrent episodes of BC post-surgery and adjunct therapy. Also, the urothelium while trying to carry out its storage and voiding roles also regulates the materials that are reabsorbed into the systemic circulation. Thus they limit the permeation of potentially beneficial chemotherapeutics and biologics for the BC therapy.[1]

Thus it is not sufficient to simply administer cytotoxic agent intravesically, there is the strong need for the careful design of formulations that would be able to circumvent the cellular and molecular limitations

Table 1. Some notable research work on intravesical formulations

Class	Agent	Carrier	Dosage form	Reference
In situ gelling system	Adriamycin	Poloxamer 407 (triblock copolymer), sodium hydrogen carbonate, HPMC, HSA	Floating hydrogel nanoparticle composite system	Lin et al., 2014
Mucoadhesive polymeric system	Doxorubicin	Copolymer of 2-(acetylthio)ethylacrylate and 2-hydroxyethylmethacrylate	Thiolated microgels	Cook et al., 2015
	Gemcitabine	Thiolated chitosan based NPs loaded chitosan gel or Poloxamer gel	Thiolated NPs-hydrogel composite	Senyigit et al., 2015
	Doxorubicin	β-cyclodextrin, mesoporous silica	Surface-modified nanoparticles	Zhang et al., 2014

that have been posed by the pathophysiology of the bladder in order to generate advanced drug delivery systems, with improved safety (target-specific); efficacy (cellular uptake, internalization and cytotoxicity) and sustained release (prolonged cytoadhesion) profile.

Approaches to improve the efficiency of intravesical drug delivery

IDD using advanced formulation strategy would provide site-specific delivery which ensures that therapeutic drug dose is available at target site for improved efficacy and therapeutic outcomes with minimal toxic effect.[1]

Some of the strategies that have been employed include improving the permeability of the bladder (using physical and chemical methods), use of nanocarriers, mucoadhesive carriers, polymeric hydrogels and thermal assisted chemotherapy.[1] However, the heat associated treatment has not been embraced beyond academic institutions because it is not patient friendly.[11] Also, properties of the drug like molecular weight (≤ 200 Da), water or lipid solubility, and aqueous / organic phases' partition coefficient (log P) of −0.4 to −0.2 or −7.5 to −8.0 are suitable for intravesical administration.[1] Thus limited number of drugs may be appropriate for IDD if not cleverly formulated.

Advanced formulations via intravesical route

Some of the recent IDD studies explore strategies such as mucoadhesive polymers, floating systems, and in situ gelling systems in order to improve the intravesical delivery of bladder cancer chemotherapeutics (Table 1).

In situ gelling systems

In situ gelling systems are polymeric aqueous solutions that are liquid with flowing tendency at room temperature and become gel at physiological environment in response to various stimuli such as pH, enzyme or temperature. Temperature is the commonly explored stimulus for such formulations.[1] Tyagi et al., 2004 identified this phenomenon in triblock copolymer (PEG-PLGA-PEG) based dispersions (30% w/v)[12] and this formulation was labelled with fluorescein (FITC) and evaluated in cystitis inflamed rat model. FITC expression in urine 24 h post instillation suggested its sustained release potential compared to free FITC that lost fluorescence after 8 h.[12] Misoprostol loaded hydrogel showed remarkable improvement in inflammatory tissue features compared to free drug. Cytotoxocity testing of hydrogel also suggested that the formulation has minimal toxicity on the urothelium.[12]

Composite Nanoparticle-Hydrogel (NP-H) delivery system with in situ gelation and bladder cavity floating features have also been designed to serve as a drug depot for gradual adriamycin (ADR) release as well as prevent urinary obstruction associated with the high viscosity of conventional hydrogels.[13] The safety of ADR has also been improved by formulating it as human serum albumin based NPs (103 nm) that are loaded into Poloxamer 407 (P407) and hydroxypropyl methyl cellulose based thermosensitive hydrogel.[13]

The P407 facilitated gelation while HPMC prolonged gel erosion which ensured sustained drug release. Sodium hydrogen carbonate made the ADR encapsulated NPs–H system (NP-ADR-H) floatable in urine environment by producing CO_2 in acidic medium; which binds onto hydrogel surface and prevents obstruction of the urinary tract.[13] HPMC ensures attachment of the NPs to the bladder wall

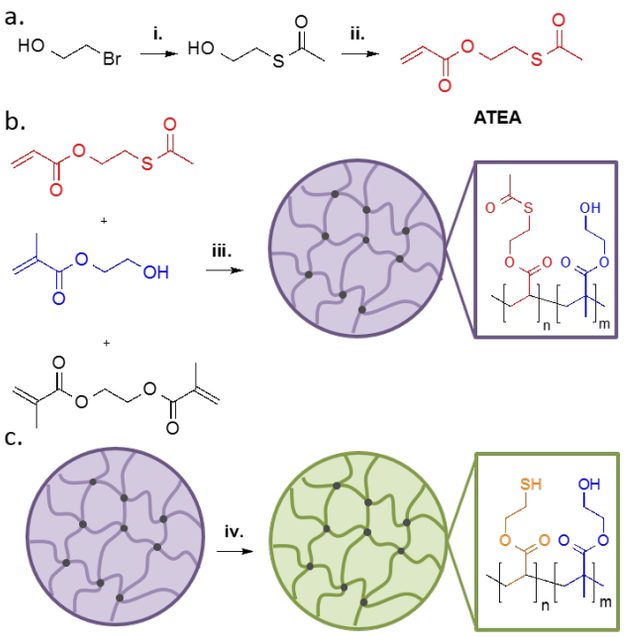

Figure 3. Synthetic route to ATEA, (a) protected thiomonomer. (b) Polymerisation to form ATEA: HEMA copolymer microgels, displaying the pendant functionalities present. (c) Deprotection of ATEA using sodium thiomethoxide to yield thiol-bearing microgels. (i) Potassium thioacetate, acetone, 24 h. (ii) Acryloyl chloride, trimethylamine, DCM, reflux, 24 h. (iii) Ammonium persulfate, ethylene glycol dimethacrylate, water, 70°C, 6 h. (iv) Sodium thiomethoxide, methanol, 30 min. This figure is reproduced from Cook et al., (2015). Published by The Royal Society of Chemistry.

in order to release drugs in a sustained pattern. NP-ADR-H had gelation time of 2 min when evaluated at 37°C, in comparison with other evaluated carriers (NP-ADR or non-floating hydrogel), forming gel in about 5 min.[13]

Mucoadhesive polymeric formulations

Some hydrophilic polymers such as chitosan are intrinsically mucoadhesive but functional groups such as thiols can be employed to chemically modify them in order to improve their mucoadhesion.[14] For example, functionalised cyclodextrin based silica NPs have been evaluated for their potential treatment of superficial bladder cancer.[8] Thiol-functionalised mesoporous silica NPs (MSNPs-CD-(NH_2)-SH) had superior adhesion to urothelium compared to amino- and hydroxyl-modified NPs (MSNPs-CD-(NH_2)-NH_2 and MSNPs-CD-(NH_2)-OH) during the mucin-NP interaction studies because covalent bonds and noncovalent bonds were formed respectively, with mucin.[8] Doxorubicin was released faster (63%) from MSNPs-CD-(NH_2)-SH under simulated urine conditions (pH 6.1) relative to PBS (pH 7.4) with drug release of about 13% after 48 h using porcine bladder tissues.[8] Also, MSNPs-CD-(NH_2)-SH showed a dose related cytotoxic activity on cancerous bladder cells with IC_{50} of 3.92 ± 1.06 µg mL^{-1} compared to free Dox (IC_{50} of 0.45 ± 0.05 µg mL^{-1}), which suggests a gradual and sustained drug release from thiolated silica NPs.[8] This has clinical implication of reducing the frequency of dosing as well as enhancing patient acceptability.[8]

Cook et al., polymerised thiol-bearing monomer such as 2-(acetylthio)ethylacrylate (ATEA) with 2-hydroxyethylmethacrylate (HEMA) using ethylene glycol dimethacrylate (Fig. 3) to generate thiolated microgels (635–977 nm in diameter), chemically cross-linked thermoresponsive polymer network with high encapsulation efficiency (75–86%), colloidal stability (negative zeta potential), excellent bladder mucoadhesion as well as sustained drug release (over 300 min).[15]

Also, the retention of drug loaded microgels on the bladder tissues can be modulated by variation of the molar proportions of both monomers to generate microgels with desirable thiol content. For example, microgels with the greatest and least degree of thiolation was achieved with 80 mol% and 30 mol% ATEA, respectively.[15] The former resisted wash off by artificial urine during ex vivo porcine bladder mucosa studies compared with the latter. This may be associated with greater amount of thiol groups forming covalent disulphide bridges with the cysteine-rich regions of urothelial mucins and mucosal adherence was independent of surface charge or polarity of carrier. Doxorubicin was taken up into the microgel matrix during formulation and drug loading greater than the therapeutic doses of doxorubicin (1 mg mL^{-1}; 30–100 mL solution) may be achievable with 30 mol% and 80 mol% ATEA / HEMA based microgels (2.5 mg mL^{-1} versus 2.7 mg mL^{-1}).[15]

Senyigit et al., (2015) showed that thiolated chitosan based NPs loaded into 2% chitosan gel (CH-TGA NPs/CH gel) were more resistant to dilution by artificial urine compared to NPs dispersed in poloxamer gel (CH-TGA NPs / Plx gel) at 37°C.[16] During bioadhesion test using bovine bladder mucosa, CH-TGA NPs/CH gel also had improved bioadhesive properties compared to Plx gel based carrier after incorporation with Tyrode solution (1.003 ± 0.048 N.mm vs 0.378 ± 0.022 N.mm), amounting to a 51% and 80% reduction in bioadhesive properties, respectively.[16] In vitro Gemtacibine HCl (Gem-HCl) release studies also show that the rate of drug release following dispersal of NPs into CH-gel and Plx gel decreased by a magnitude of 1.5 and 2.6, respectively as well as release rate of 33.4% ± 5.0% vs 19.6 ± 1.6% in 4 h.[16] Ex vivo studies also showed that greater percentage of drug permeated the bladder mucosa for the CH-gel based carrier than that of Plx-gel (33.16 ± 5.11% vs 18.78 ± 1.97%). Thus CH-TGA NPs/CH gel may be a potential intravesical delivery

system for Gem- HCl in order to improve efficacy and drug residence time within the bladder.[16]

Conclusion

The intravesical route has been identified as the most viable means of improving drug delivery for BC management especially at the early stages. This is as a result of the limitations of the oral and systemic therapies such as poor bioavailability and adverse events. However, the IVDD also has disadvantages like drug dilution by urine and wash off during micturition due to conventional formulations made of simple solution of the chemotherapeutic agent being readily prone to elimination. Moreover, the urothelial barrier limits permeation of potentially useful therapeutic agents for BC treatment. This results in frequent dosing or retention of catheter within the urethral tract, which may lead to bladder irritation and infection. Drug carriers that would explore combination of delivery strategies would be desirable in order to prevent BC recurrence and progression.

References

1. GuhaSarkar, S.; Banerjee, R. Intravesical Drug Delivery: Challenges, Current Status, Opportunities and Novel Strategies. J. Control. Release 2010, 148 (2), 147–159.
2. Khandelwal, P.; Abraham, S. N.; Apodaca, G. Cell Biology and Physiology of the Uroepithelium. Am. J. Physiol. Renal Physiol. 2009, 297 (6), F1477–F1501.
3. Torre, L. A.; Bray, F.; Siegel, R. L.; Ferlay, J.; Lortet-tieulent, J.; Jemal, A. Global Cancer Statistics, 2012. CA a cancer J. Clin. 2015, 65 (2), 87–108.
4. Kaufman, D. S.; Shipley, W. U.; Feldman, A. S. Bladder Cancer. Lancet 2009, 374 (9685), 239–249.
5. Sharma, P. Cancer Immunology - Bladder Cancer http://twww.cancerresearch.org/cancer-immunotherapy/impacting-all-cancers/bladder-cancer (accessed Nov 2, 2015).
6. Moch, H.; Cubilla, A. L.; Humphrey, P. A.; Reuter, V. E.; Ulbright, T. M. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs—Part A: Renal, Penile, and Testicular Tumours. Eur. Urol. 2016, 1–14.
7. van Rhijn, B. W. G.; Burger, M.; Lotan, Y.; Solsona, E.; Stief, C. G.; Sylvester, R. J.; Witjes, J. A.; Zlotta, A. R. Recurrence and Progression of Disease in Non-Muscle-Invasive Bladder Cancer: From Epidemiology to Treatment Strategy. Eur. Urol. 2009, 56 (3), 430–442.
8. Zhang, Q.; Neoh, K. G.; Xu, L.; Lu, S.; Kang, E. T.; Mahendran, R.; Chiong, E. Functionalized Mesoporous Silica Nanoparticles with Mucoadhesive and Sustained Drug Release Properties for Potential Bladder Cancer Therapy. Langmuir 2014, 30 (21), 6151–6161.
9. Elstad, N. L.; Fowers, K. D. OncoGel (ReGel/paclitaxel)--Clinical Applications for a Novel Paclitaxel Delivery System. Adv. Drug Deliv. Rev. 2009, 61 (10), 785–794.
10. Lee, H.; Cima, M. J. An Intravesical Device for the Sustained Delivery of Lidocaine to the Bladder. J. Control. Release 2011, 149 (2), 133–139.
11. Barocas, D. a.; Globe, D. R.; Colayco, D. C.; Onyenwenyi, A.; Bruno, A. S.; Bramley, T. J.; Spear, R. J. Surveillance and Treatment of Non-Muscle-Invasive Bladder Cancer in the USA. Adv. Urol. 2012, 2012, 19–24.
12. Tyagi, P.; Li, Z.; Chancellor, M.; De Groat, W. C.; Yoshimura, N.; Huang, L. Sustained Intravesical Drug Delivery Using Thermosensitive Hydrogel. Pharm. Res. 2004, 21 (5), 832–837.
13. Lin, T.; Wu, J.; Zhao, X.; Lian, H.; Yuan, A.; Tang, X.; Zhao, S.; Guo, H.; Hu, Y. In Situ Floating Hydrogel for Intravesical Delivery of Adriamycin without Blocking Urinary Tract. J. Pharm. Sci. 2014, 103, 927–936.
14. Barthelmes J, Dunnhaupt S, Unterhofer S, Perera G, S. W.; Bernkop-Schnurch, A.. Thiolated Particles as Effective Intravesical Drug Delivery Systems for Treatment of Bladder-Related Diseases. Nanomedicine (Lond). 2013, 8 (1), 65–75.
15. Cook, M. T.; Schmidt, S. A.; Lee, E.; Samprasit, W.; Opanasopit, P.; Khutoryanskiy, V. V. Synthesis of Mucoadhesive Thiol-Bearing Microgels from 2-(acetylthio)ethylacrylate and 2-Hydroxyethylmethacrylate: Novel Drug Delivery Systems for Chemotherapeutic Agents to the Bladder. J. Mater. Chem. B 2015, 3 (32), 6599–6604.
16. Senyigiti ZA, Karavana SY, Ilem-Ozdemir D, Caliskan C, Waldner C, Sen S, Bernkop-Schnurch A, B. E. Design and Evaluation of an Intravesical Delivery System for Superficial Bladder Cancer : Preparation of Gemcitabine HCl-Loaded Chitosan – Thioglycolic Acid Nanoparticles and Comparison of Chitosan / Poloxamer Gels as Carriers. Int. J. Nanomedicine 2015, 10, 6493–6507.


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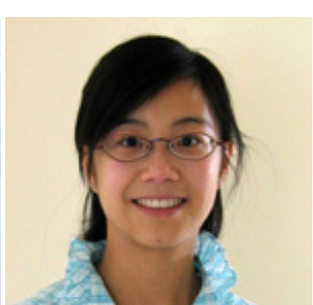
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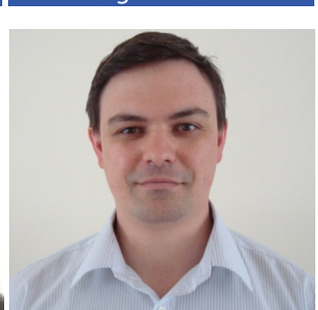
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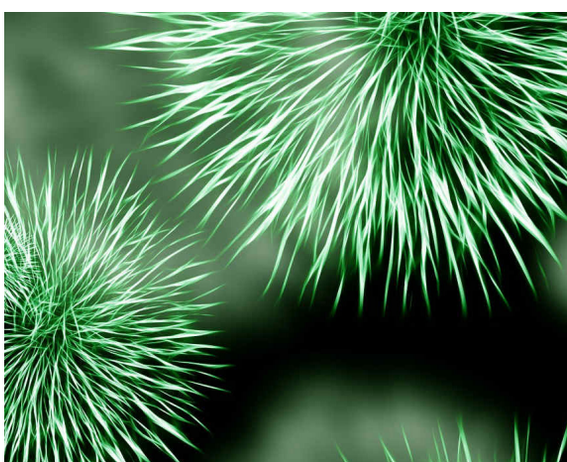

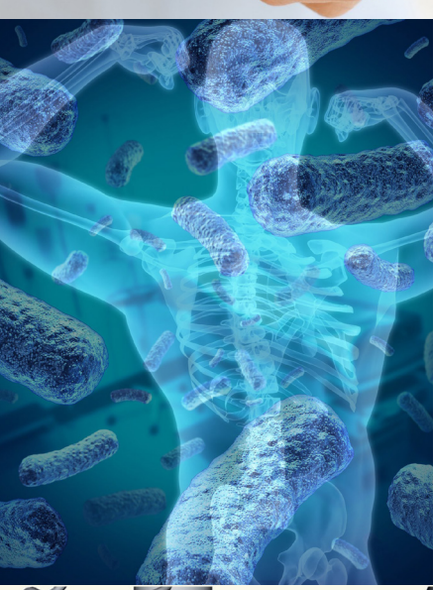

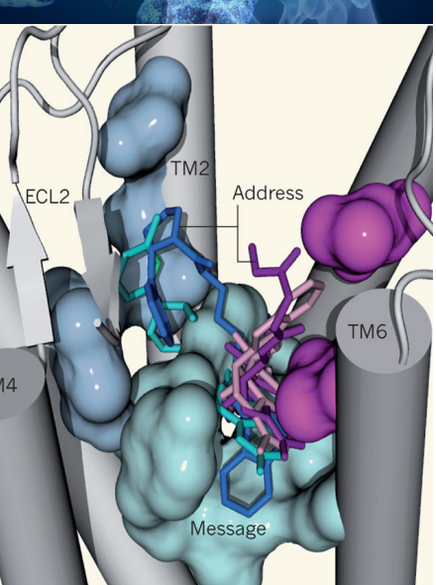

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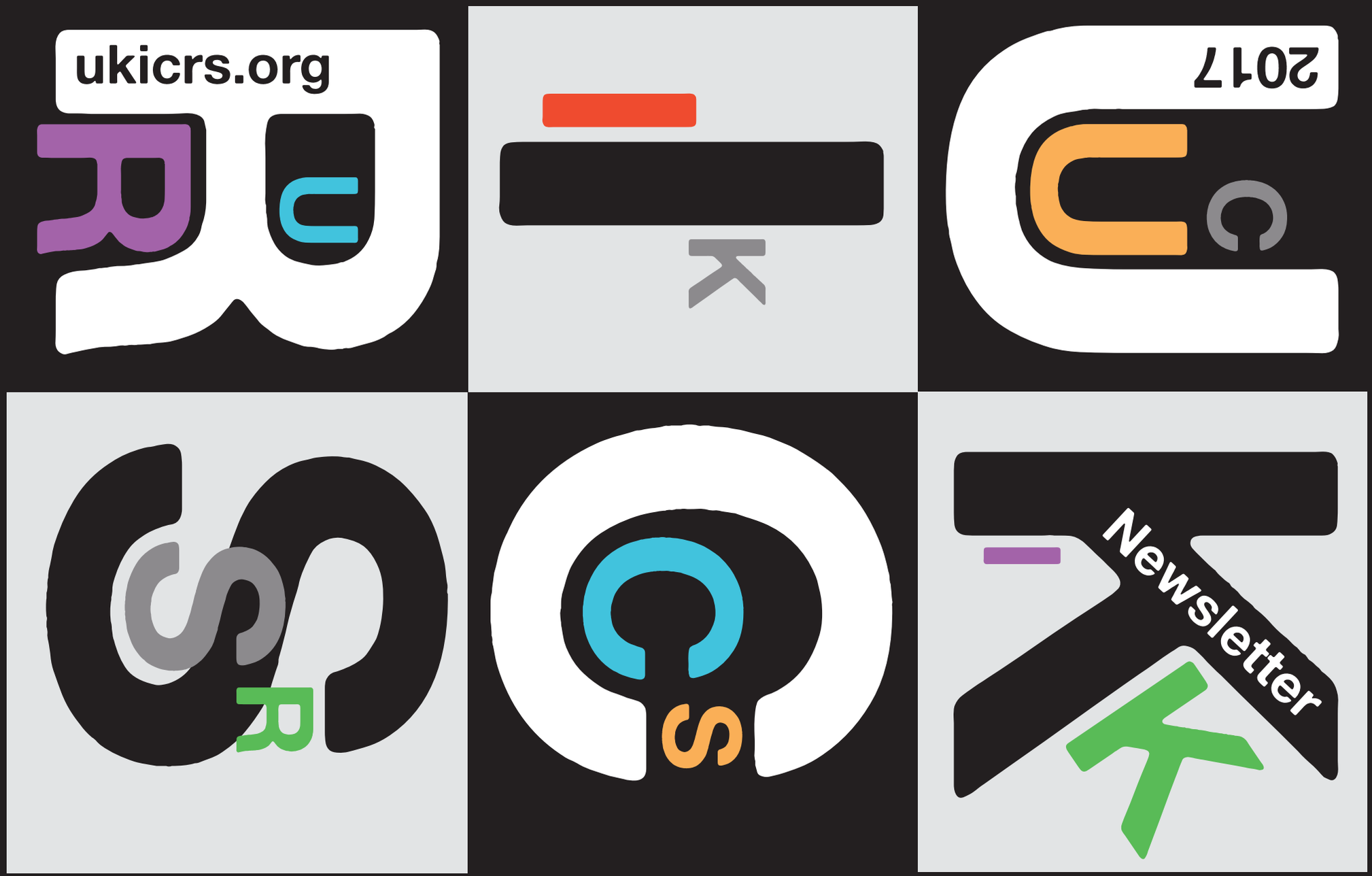

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