UKICRS

NEWSLETTER 2015

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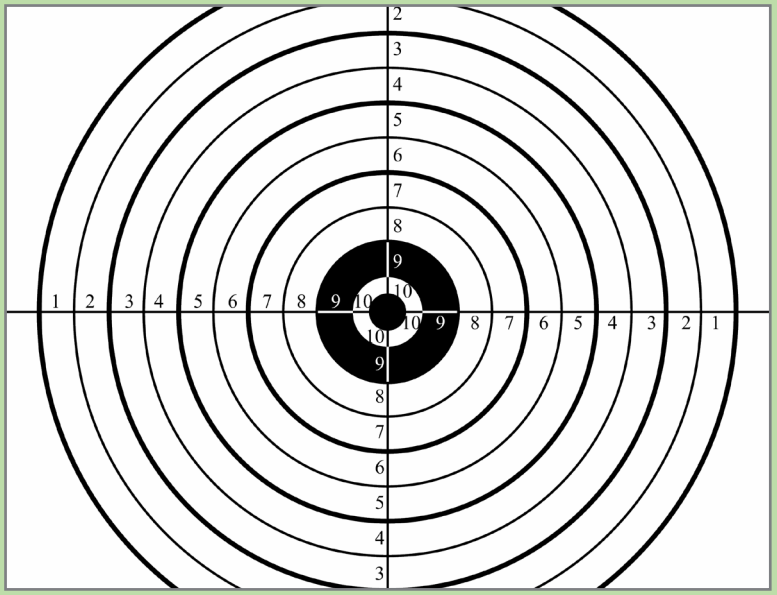
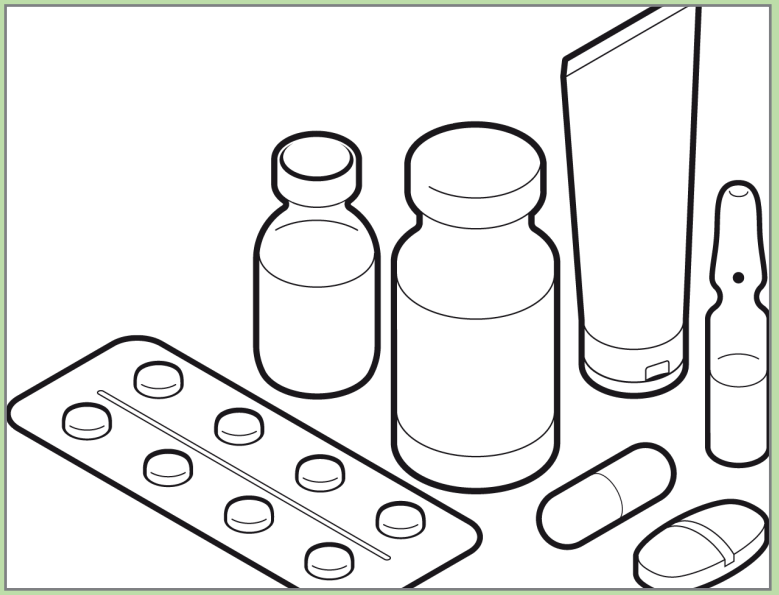
WHEN A DRUG BECOMES ORPHAN | BECOMING AN ENGAGING SCIENTIST | MORE THAN MEETS THE EYE | AND MORE!





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A WORD from THE CHAIR

Dear UKICRS members and friends,

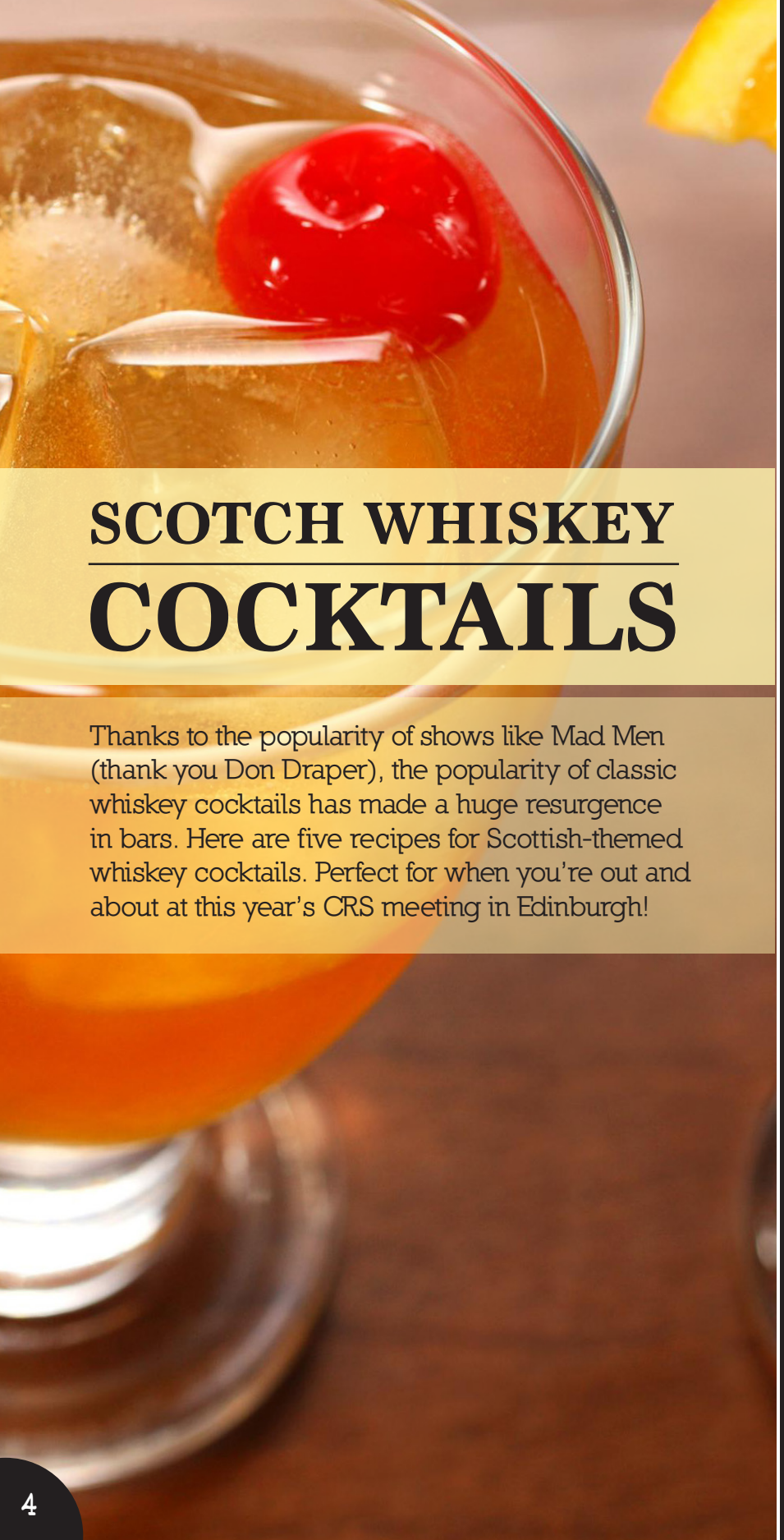
Welcome to 2015 UKICRS Newsletter! As always, we work hard to bring you a vibrant read and this year's edition is packed to the gills with interesting articles and insights to keep you up-to-date. Many thanks to Karl Malcolm and the newsletter team for their hard work. We trust you will enjoy the read.

It has been another great year at UKICRS, the highlight being our annual symposium held at the University of Nottingham. With more that 150 delegates in attendance, including several members of the CRS board, this was our biggest ever symposium. In addition to our two excellent keynote speakers, - Dr. Francesca Greco (University of Reading, UK and Prof. Ben Boyd (Monash University, Australia) - we continued in the spirit of past symposia with a clear focus on postgraduate student presentations. What's clear is that our symposium has become a must-attend event for the younger generation of drug delivery and formulation scientists. For the first time, we extended our programme to include two pre-meeting workshops (Early Researcher Forum & Horizon 2020) on the morning of Thursday 16 April, from which we have received very positive feedback. A big 'thank you' to all those involved in our symposium, especially Maria Marlow and Laura Mason, for organizing a hugely successful meeting.

During the last twelve months we have continued to support the younger drug delivery community. I was delighted that we were able to continue our annual essay prize that was first introduced in 2012. Many congratulations to the three winners, whose essays are incuded here. We also announced a new summer studentship, awarded to Zhiyuan Kok at the University of Nottingham.

As the host chapter, UKICRS are delighted that the Controlled Release Society's Annual Meeting & Exposition is returning to the UK this year (26-29 July 2015). UKICRS have recently funded ten registration fees for postgraduate students to attend. Also, conscious that a significant number of our membership would be in Edinburgh late July, it seemed entirely appropriate that we get together to celebrate and support the main CRS event. To this end, in conjunction with Encap Drug Delivery, we have planned a very special social event on Sunday 26 July. For those who have already signed up, you're in for a very special evening!

Finally, a big 'thank you' to all our sponsors and members. Your continued interest, support, participation and kind words mean we never grow tired of working on your behalf. If you are not a member yet, may I strongly encourage you to join (ukicrs.org). I promise we won't bombard you with emails, we'll take the time to email you a personal copy of the Newsletter, and, best of all, membership is completely free!



SCOTCH WHISKEY COCKTAILS

Thanks to the popularity of shows like Mad Men (thank you Don Draper), the popularity of classic whiskey cocktails has made a huge resurgence in bars. Here are five recipes for Scottish-themed whiskey cocktails. Perfect for when you're out and about at this year's CRS meeting in Edinburgh!

Highland Sling

2 oz Scotch whiskey blend
1/2 tsp sugar
1 slice of lemon
Juice of lemon

Celtic Twilight

1 oz Scotch Whiskey
1 oz Baileys Irish cream
1 oz Frangelico hazelnut liqueur

Aberdeen Angus

2 oz Scotch whiskey
1 oz Drambuie
1 tbsp honey
2 tbsp lime juice.

Dundee Dream

2 oz Scotch whiskey
1/2 oz sweet sherry
1/2 oz mandarin juice
1 oz lime juice
2 oz Canadian dry.

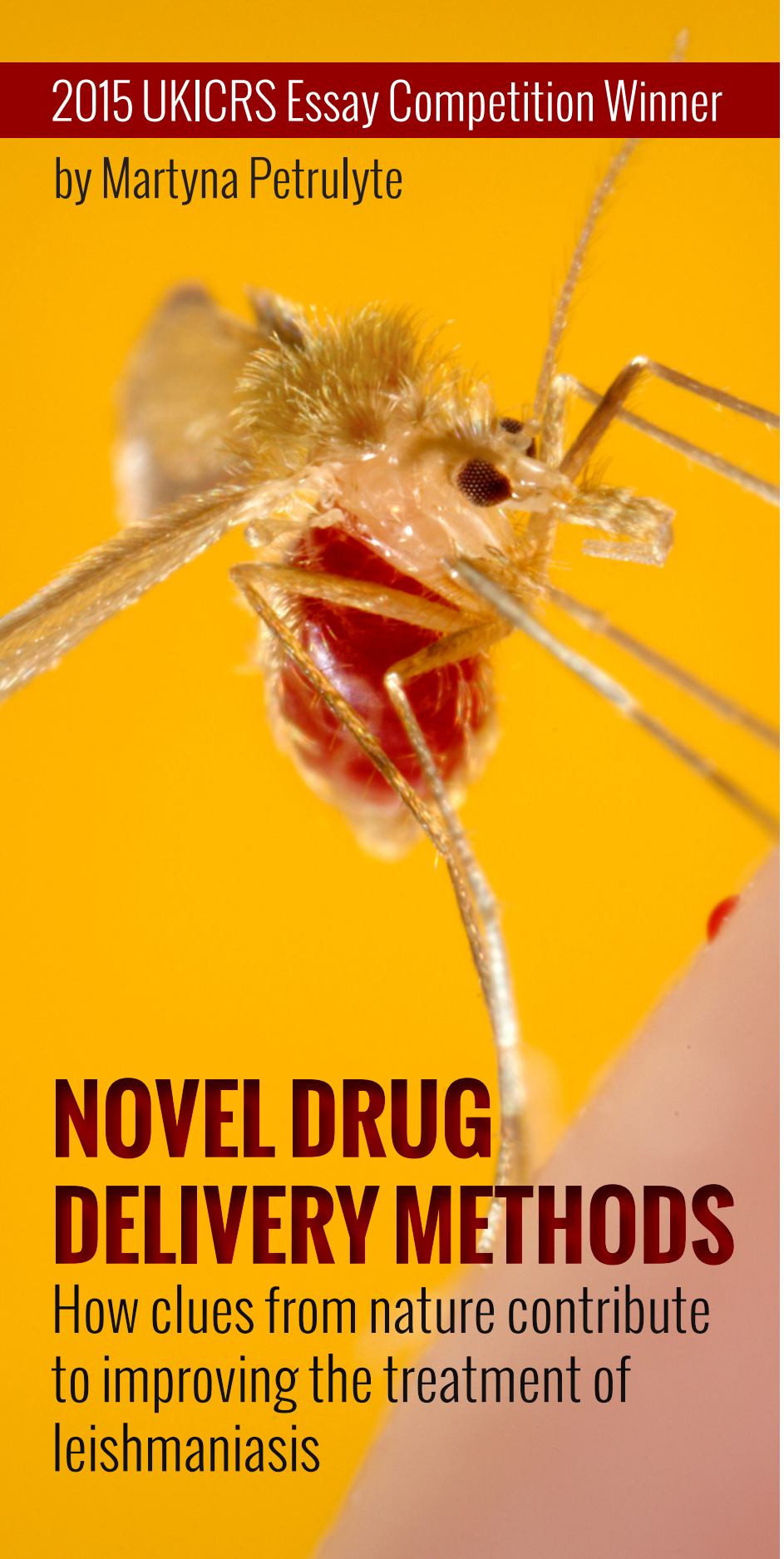
Loch Ness Mystery

3/4 oz Scotch whiskey
1/4 oz apricot brandy
1 dash orange Curaçao liqueur
2 oz grapefruit juice
1 slice of lime.

All served on ice, except the Aberdeen Angus where you light the Drambuie first for 30 sec and then add to a mug containing the whiskey, honey and lime.

2015 UKICRS Essay Competition Winner

by Martyna Petrulyte



NOVEL DRUG DELIVERY METHODS

How clues from nature contribute to improving the treatment of leishmaniasis

They thrive securely protected by an impenetrable fence. They do not feel the need to wonder how to get from point A to point B as they have loyal chauffeurs. They do not need to cook because a delivery man dressed in red provides them with food 24 hours a day, 7 days a week. They do not take out the trash or clean the place they live in as others do it for them. And the only thing that day in day out spins in their minds is an unquenchable desire to reproduce. No, this description is not about a rich careless lad, surrounded by many lackeys and maids, who does nothing but sleeps, eats and satisfies his sexual desires. Strange as it may sound but all of this is true for leishmanias: small, intracellular protozoan parasites that cause a devastating disease leishmaniasis which poses a health hazard for thousands of people in Asia, Africa, south of Europe, Central and South America[1].

Named as the Black Fever in endemic regions, leishmaniasis can manifest in a few forms. Cutaneous leishmaniasis causes skin ulceration characterized by a varied spectrum of red sores which heal very slowly and disappear only after months or even years, leaving disfiguring scars. A more life-threatening form is visceral leishmaniasis which impairs the function of several internal organs, including spleen, liver, and bone marrow. Unfortunately, without appropriate treatment the fatality rate can reach up to 100% within few years. Lastly, the rare form of mucosal leishmaniasis mainly destroys mucous membranes of the nasal, oral and throat cavities.

Currently, there are approximately 310 million people at risk of contracting leishmaniasis and the numbers are predicted to increase mainly because of their loyal chauffeurs, the sandflies, the majority of which belong to the subfamily Phlebotominae[2]. These tiny insects take up leishmania protozoa with blood from infected animals and during the subsequent bites pass them on to healthy individuals, disseminating the disease at incredible rates. Once inside the circulatory system, these parasites breach the cell membrane of macrophages, the essential immune cells in the body responsible for phagocytosis. Protected by the impenetrable fence formed by their own membrane as well as the membrane of macrophages, leishmanias are resistant to many drug delivery systems currently used in practice. Not only must the drug cross several membranes, but it also has to find infected macrophages in the first place, owing to leishmania's whimsical preference to populate different organs: spleen, lymph nodes, liver, bone marrow or skin.

Currently used chemotherapeutic agents targeted against leishmaniasis include stibogluconate, N- methylglucantime, pentamidine, or amphotericin B, all of which are administered intravenously[3]. This means that the patient must be hospitalized and since the medications mainly have a short half-life and quick clearance rate, the course of treatment is relatively long. Since a protracted stay in hospital may significantly affect patient's family and work, abandonment of treatment prior to completion of the entire course often occurs. This leads to the emergence of drug-resistant strains of leishmania which are unresponsive to previously effective medications. Therefore, scientists are now trying to get more knowledge about the native properties of leishmanias in the hope of developing more efficient drug delivery systems directed against specific aspects

of this parasitic infection. In the past few decades, an incalculable number of studies using leishmanias have shed light on the molecular basis of pathogenesis perfectly crafted by natural selection and this in turn has led to the development of new drug delivery systems.

Since macrophages are naturally prone to taking up various foreign substances due to a high number of specific membrane receptors, scientists devised a strategy to administer medications in such a form that the infected macrophages which reside in the liver and spleen would instinctively take up the highest concentration of encapsulated drugs, resulting in more efficient treatment of this parasitic infection. Stability, reduced organ toxicity and prolonged activity are those properties that led to the development of liposomes in order to enhance the targeting of medications for the treatment of leishmaniasis. Owing to thousands of unique receptor molecules on the surface of macrophages, they are able to distinguish between self and non-self molecules and this in turn makes them efficient at clearing vesicular drug carriers, including liposomes, from the blood following parenteral administration[4]. The liposomes are tiny vesicles made of several concentric lipid bilayers with aqueous media inside. Because they are biodegradable and non-immunogenic, liposomes offer a stable, long-lasting and highly selective drug delivery method[5]. A study published in 2011 revealed that antileishmanial agent-containing liposomes are at least 10-fold more effective than free drugs. The cytotoxicity analysis also showed that liposomes with the drug inside were two to three times more noxious towards macrophages than the free drug. Moreover, in order to kill all (100%) of leishmanias hidden inside the immunity cells the concentration of the drug was at least 40-fold lower when a drug was administered in liposomal form than with the free drug. Lastly, analysis of the specimens of leishmanias with fluorescence microscope showed the increased uptake of labelled liposomes in infected macrophages after brief incubation times in comparison to the non-liposomal drug[6]. This in turn reduces the amount of drug to be delivered (thus leading to lower costs) as well as the drug toxicity to non-target tissues (which may help diminish severe effects associated with non-specificity). Therefore, this data strongly supports the rationale for using drugs incorporated into liposomes as drug carriers rather than non-liposomal drugs against leishmania-infected macrophages.

Not only do the natural ferocious feeding habits of macrophages dictate the potential ways to deliver drugs into infected cells, but the knowledge of the inherent anatomy of the host, especially of those tissues targeted by leishmania, may also contribute to the development of more specific drug delivery methods. An in vivo study with mice showed that intraperitoneal injections of a free drug or a drug encapsulated in liposomes notably diminished the parasite loads in the liver by 43% and 55%, respectively, compared with untreated control group. If a drug was administered subcutaneously, the highest concentrations were found in lymph nodes around the site of injection. Similarly, after the intravenous injection, the parasite loads in the livers were not significantly reduced when compared with the control[7], possibly because non-target organs absorbed some of the drug. The probable explanation for high concentrations of the drug in the liver only after intraperitoneal injection might be the anatomical distribution of vessels, particularly the portal vein system which forces the transport of all blood from the intraperitoneal organs to enter the liver first, bypassing all other organs, and only then come back to the heart. Therefore, not only the carrier but also the route of administration exerts a significant impact on the treatment efficacy of leishmaniasis. However, because the disease mainly affects people living in developing countries where there is a shortage of well- qualified doctors and nurses and where the poor sanitation gives various infectious agents the ideal opportunity to spread uncontrollably, such questions as who is going to assure the aseptic intraperitoneal delivery of medications or who will control the appropriate disposal of used needles should be considered prior to incorporating this drug delivery methods into treatment guidelines.

"Come forth into
the light of things,
let Nature be your Teacher."
William Wordsworth

Liposomal drug administration via intravenous or intraperitoneal injections does not sound like a groundbreaking scientific milestone such as the sequencing of the human genome in 2003, but a tattoo- mediated liposomal drug delivery system genuinely sounds as a different method outside of what is considered convention. Intravenous or intraperitoneal injections mainly target visceral leishmanias which affect internal organs, but the gold standard for treating cutaneous leishmanias currently is painful intralesional injections with anti-leishmanial drugs. By mimicking the natural act of a bite by the sandfly, scientists used the tattoo device to deliver drug-liposome complexes directly around the site of lesion produced by the parasite. During five days of the experiment, parasite-infected mice were treated with two tattooing sessions a day, each of which consisted of twelve 2-second administrations, for a total of 12000 punctures distributed equally around the edges of the sore. For comparison reasons two concomitant tests were carried out using different routes of drug administration, one involving intraperitoneal liposomal injections and another utilizing the topical route in which the encapsulated medication was applied directly on the lesion as an ointment. The latter drug delivery method showed a decrease from 26.9 to 7.4 mm^2. Clinically more significant results were achieved after intraperitoneal injections which resulted in a lesion size of 3.6 mm^2 on day 28 indicating that systemic administration of the anti-parasitic drug is more efficient than local treatment. Contrary to the systemic or topical drug administration, the tattooing led to virtually complete reduction of lesion size with a mean value of 0.4 mm^2. Although the results are promising, scientists are still concerned about the effective dose needed for such a drug delivery method as well as about the fate of liposomal vesicles following the tattooing session. Nevertheless, this technique seems to reduce the toxicity of the therapeutic agent as well as increase the efficacy of the drug in reducing the severity of

leishmaniasis.

Endemic in the tropics and affecting mostly people from lower socioeconomic backgrounds, this devastating parasitic infection is bound to become more widespread if immediate measures are not taken by financial and public sectors. The ongoing research by scientific groups worldwide yields brand new insights into specific remedy delivery methods for leishmaniasis and provides hope that one day the disease will be eradicated. By imitating the natural mode of transmission by sandflies researchers developed the tattoo-mediated delivery system, by delving into the anatomy of circulatory system of a host it was discovered that intraperitoneal drug administration is more selective for infected macrophages lodged in the liver and spleen and finally by luring infected voracious macrophages with appealing liposome-encapsulated anti-parasitic medications, researchers succeeded in prolonging the half-life of a drug as well as diminished the risk of adverse side effects. As William Wordsworth once said: 'Come forth into the light of things, let Nature be your teacher', we should keep our eyes open at the clues that nature left for us because only then we will be able to develop powerful therapeutic drug delivery methods and reduce morbidity and mortality rates of leishmaniasis.

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2015 UKICRS Essay Competition 2nd Prize

by Paul Brack

EXOSOMES

From dustbins to drug deliverers

Everyone who has taken a medicine will be familiar with the notion of side effects. These range from mildly annoying headaches to more serious effects, such as permanent loss of bodily functions and even death. What causes these side effects? Surely the drugs we take are carefully designed to only target the disease they are designed to treat? Unfortunately, our bodies are so comprehensively interlinked that it is incredibly difficult to send a drug to one particular set of cells without inadvertently giving it to a load more as well, no matter how careful we are. These unintended interactions result in side effects. Current methods of drug delivery are a bit like using a hand grenade instead of a bowling ball to take down the pins in a bowling alley; most certainly effective at doing the job, but rather heavy handed, to say the least.

Nature is much more precise than this. To continue the bowling analogy, nature can bowl with a ping pong ball and still manage to take down all the pins by hitting the first one in just the right spot. Our body's in-built delivery systems efficiently transport molecules to the exact place where they are needed, with minimal harm to their surroundings. In recent years, scientists have sought to hijack these systems to deliver drugs without side effects. By seeking to learn from and work with the body, researchers hope to be able to not only improve current treatments, but also treat diseases which are currently largely untreatable. One of the most exciting systems to emerge in recent years is exosomes.

A BRIEF HISTORY OF EXOSOMES

Exosomes are membrane bound vesicles, or in other words, blobs of watery liquid trapped in skins of fatty molecules (the same sort of phospholipid bilayer which makes up the membrane of all cells). The watery liquid part of the exosome is taken from the parent cell, and so contains a selection of what happened to be floating around in it at the time the exosome was made. Exosomes are then released by the cell, and can whizz off all around the body.

For a good few years after the discovery of exosomes 30 year ago, it was thought that their role was simply that of a dustbin into which unwanted bits of the cell were placed to be discarded. In much the same way that you don't go to the biggest theme park in the world and look at the bins, scientists thought the body had more interesting things to offer and didn't pay much attention to the poor exosomes. However, in 1996, researchers who had kept looking at the bins discovered that exosomes were doing rather more important things than removing waste. They found that certain immune cells secreted exosomes, and more importantly that the molecules bound up in them were essential for the immune response (the way your body recognises and defends itself bacteria, viruses and other harmful substances). It all got even more exciting in 1998 when it was found that dendritic cells (part of the immune system) in mice secreted exosomes containing molecules which could trigger an antitumour response.

Suddenly, it was apparent that exosomes were actually playing active and essential roles in intercellular communication. Further research showed that this was not necessarily a good thing. Exosomes can also transport pathogens between cells, and have, for example, been found to play a role in the spreading of several types of cancer, as well as transporting proteins called prions responsible for mad

cow disease. Nevertheless, these demonstrations of the ability of exosomes to transport large molecules over long distances in the body made researchers sit up and take notice. What if, instead of developing our own complicated techniques, we learned from nature to use the body's natural delivery vans, exosomes, to take drugs to their targets?

THE BODY'S DELIVERY VAN

How can exosomes be used to deliver drugs? First, we have to get hold of them. Fortunately, exosomes are easily found in urine and saliva, amongst other bodily secretions. However, we need to take exosomes from the right cells. In particular, we need to ensure that the cells from which they are taken do not stimulate the immune system otherwise they might trigger inflammation when they are administered to the patient. Another way to ensure there is no immune response is to take the exosomes from the person to whom you will be giving them. The exosomes must also be stable whilst travelling around the body in blood vessels.

Once suitable exosomes have been identified and extracted, they are then filled with a 'therapeutic cargo', or, in layperson's terms, a drug. Most studies up to now have loaded exosomes with small interfering RNAs (siRNAs), micro RNAs (miRNAs) and proteins, all of which are difficult to administer by more conventional drug delivery methods due to their instability (for the RNAs) in the blood and large size (proteins). Putting them inside an exosome allows them to get around the body unhindered. As siRNAs and proteins are particularly important components of treatments targeted at individual genes, many of which are now being developed for diseases such as Alzheimer's and various cancers, it is essential to find a viable way to transport them to the relevant part of the body without causing side effects. Exosomes offer this.

Exosomes can be loaded in several different ways. One of the simplest methods is called electroporation, and involves applying an electrical field to a suspension of exosomes and the cargo of choice. This creates pores in the membrane of the exosomes, and allows the cargo to move inside them. Once the exosomes have been loaded, they are ready to be administered to the patient. Again, this can happen in a number of ways, but the most common is by injection into a vein (hence the aforementioned requirement that exosomes must be stable in the blood). Once the loaded exosomes are inside the patient, they make their way to part of the body to which they have been targeted to tackle their disease. This targeting can either be done by making use of the natural affinity of a particular exosome for a certain cell, or by artificially adding appropriate targeting proteins to the exosomes after they have been taken out of the patient. Thus, exosomes are essentially 'Trojan horses', smuggling proteins and RNA into parts of the body where they would not otherwise be able to go. Self-derived exosomes (i.e. those taken from the person who is being treated) also have the advantage of not triggering any unwanted responses from the immune system leading to side effects. In the last few years, their utility as drug delivery vehicles in a range of conditions has been demonstrated in several diseases.

EXOSOMES IN THE BRAIN

As we live longer, diseases of the brain such as Alzheimer's and Parkinson's disease are becoming more common, affecting millions of people across the globe. One of the difficulties in treating such diseases is delivering drugs across the blood-brain barrier (BBB), a highly selective barrier which protects the brain from infection by preventing the entry of bacteria while letting oxygen through. However, the BBB also blocks the vast majority of drugs, and thus, in order to treat diseases of the brain, we need to find an effective way to transport medicines through it.

Nature can bowl with a ping pong ball and still manage to take down all the pins by hitting the first one in just the right spot.

Exosomes could be the answer. They play a major part in the development of Alzheimer's disease by transporting certain proteins which trigger it into the brain. However, this ability of exosomes to pass back and forth through the blood-brain barrier can be put to good use. In 2011, a team at the University of Oxford found that they could turn off a gene (BACE1) which is involved in Alzheimer's disease in a group of mice by using exosomes to deliver genetic code to their brains. To do this, they first extracted exosomes from mouse dendritic cells. These were then connected to proteins from the rabies virus which selectively target receptors in brain cells in order to make the exosomes target the brain, and then the exosomes were filled with genetic code in the form of siRNA. When the exosomes were injected back into the mice, a 60% reduction in the activity of BACE1 was observed, which would lead to a slowing of the progress of Alzheimer's. The team had successfully used the mice's own natural delivery system to selectively deliver genetic code to a gene in the brain which would otherwise have been inaccessible.

Exosomes are also known to be involved in other diseases of the brain, including multiple sclerosis, Parkinson's disease and Huntingdon's disease, and thus represent a highly promising solution to the knotty problem of getting drugs across the blood-brain barrier to treat these conditions.

EXOSOMES IN CANCER

Several exosome based therapies for cancer are already in clinical trials. Here, the exosomes act as vaccines, stimulating the immune system to produce an antitumour response. In one trial, a group of melanoma patients were treated with their own dendritic cell-derived exosomes which had been extracted and loaded with peptides known to generate an antitumour response. No toxicity was observed. Another trial using exosomes to treat the same cell type in non-small

cell lung cancer showed substantial slowing of disease progression. Both of these successes rely on the ability of the exosome to transport protein molecules to the exact cell type where they can do their damage.

CHALLENGES OF USING EXOSOMES

As exciting as the possibility of using exosomes in drug delivery is, there are some major challenges to be overcome. The first is that there is little understanding of how exactly exosomes cross natural barriers such as the blood-brain barrier. This makes it difficult to know which proteins should be added to an exosome to target it to a particular part of the body, or to identify which exosome type ought to be used to target a disease.

Another issue is that certain exosomes are involved in the spreading of diseases. It is critical to be aware of any naturally occurring cargo present in the exosomes that are extracted from patients in order to prevent the inadvertent spread of a disease alongside the drug when the loaded exosomes are administered. Even if the naturally occurring cargo of the exosomes has no link to a disease, it is still important to be aware of the exact biological function it fulfils, and also what the effect would be of introducing unusually large amounts of an exosome to a particular tissue in the body. As ever in drug delivery, it is critical to understand the role of any targeted cells in the functioning of the whole organism.

A further problem is that of isolating the exosomes. Current methods such as ultracentrifugation give a mixture of different types of exosomes, as well as other small vesicles and macromolecules. A more selective system is required. Alternatively, synthetic mimics of exosomes could be produced, avoiding the isolation problem completely. However, here there is the danger that if the mimics are not perfect copies they may be rejected by the immune systems of the patients to whom the drugs are given, rendering them useless.

THE FUTURE?

The recent explosion of interest in using exosomes in drug delivery is a great lesson in how researchers can learn from and work with nature to make medicine more effective. Exosomes have the potential to revolutionise medicine by providing a safe and effective method of delivering drugs to specifically targeted parts of the body across otherwise closed biological barriers. If the technological barriers to their deployment can be overcome, exosomes, once derided as the body's dustbins, will soon occupy a somewhat loftier status in the minds of drug delivery professionals and patients worldwide.

Paul Brack is a PhD student in the School of Chemistry at the University of Loughborough, UK. His project is focused on the generation of hydrogen for portable proton exchange membrane (PEM) fuel cells.

2015 UKICRS Essay Competition 3rd Prize

by Bethanie Ayerst

THE SWEET SIDE OF SCIENCE

Using sugars to improve drug delivery

Sugars can help improve the delivery of drugs. Yes, that's right, sugars! Amazing? Yes, but before you stick a painkiller into your favourite chocolate bar, hoping to cure your hangover in record time, we need to clarify the types of sugars that could be used. We are talking about much more complex sugars, sugars known as glycosaminoglycans. And although these glycosaminoglycans don't sound as appetizing as the sugars you are used to, I promise you, by the end of this article you will appreciate them just as much as your favourite chocolate bar.

When your body gets injured, a special group of biological molecules called growth factors promote the repair of that damaged tissue. These growth factors are found naturally in the body and help the healing process by enabling surviving cells to communicate with each other and their surroundings, and by encouraging new cells to enter the injury site and develop into the mature tissue needed. The regenerative properties of these magic molecules have been of great interest to scientists for their use as drugs to help encourage tissue repair, for example heart or bone repair.

However, so far the use of growth factors to promote tissue repair has come with little commercial or therapeutic success. Despite their obvious potential, the main problem is that when delivered into the body, growth factors have a tendency to escape from the injury site and migrate to other parts of the body, where they may actually cause more damage than benefit. For example, the use of growth factors involved in bone repair could lead to the formation of bone in non-bony tissues. In addition, many growth factors are degraded easily, meaning that you need large quantities to get anywhere near the desired outcome in the body. On top of this, many growth factors are extremely expensive to produce outside of the body for use as treatments. Accurate growth factor delivery, localization and efficacy are therefore vital hurdles to overcome if these molecules are going to be used successfully as drugs. Could sugars be the answer?

Complex sugars called glycosaminoglycans are found abundantly throughout nature and are vital for a wide range of biological processes, including, but not limited to, immune response and directing stem cells to become mature cell types such as heart or skin cells. Naturally, glycosaminoglycans coat and surround the cells in our body, being a major component of the extracellular matrix (the term given to the supportive environment that surrounds cells). In fact, like us, our cells are happy when surrounded by an environment full of sugar! Within this environment, the sugar glycosaminoglycans are able to capture, protect and display growth factors to our cells, helping to increase their stability, localisation

and activity.

Although glycosaminoglycans are all made up of the same essential building blocks, they can be linked and decorated in a variety of ways, producing numerous different structures. This is clever, because these different sugar structures then have preference to stick to and localize certain growth factors over others. This helps to stop the build-up of growth factors in places they are not needed and instead helps to attract them to where they are required. Complex modifications can occur on the sugars resulting in different signals and messages being transmitted between cells and their environment, as the body's requirements change. By understanding, and mimicking the environment in which growth factors naturally reside and act within the body, scientists are making huge improvements, and the therapeutic potential of growth factors is now becoming much more promising.

Natural glycosaminoglycan sugars can be isolated from a variety of sources, are commercially available, and are relatively inexpensive. However, when isolated natural glycosaminoglycans consist of a diverse range of sugar chains, making structure-function relationships hard to decipher. The mixture of large, structurally complex glycosaminoglycans are also a worry for clinical translation, due to the possible off-target effects that they may have within the body, for example attracting the wrong type of growth factor. This would lead to the same problems as when growth factors are delivered to the site of injury and migrate to other areas of the body causing an unwanted response, instead this time round the unspecific sugar chains may attract growth factors that are not needed to the injury site, again possibly doing more harm than benefit.

However, recently, scientists have demonstrated a quick and effective method for isolating and purifying a subset of glycosaminoglycan chains (from a natural source containing numerous glycosaminoglycans) with specific attraction for a particular growth factor. This relies on a method called affinity chromatography, whereby a biochemical mixture (in this case a commercially available diverse mixture of glycosaminoglycan chains) is separated according to a strong specific interaction (in this case between a chosen growth factor and certain glycosaminoglycan chains from within that mixture).

Using this method, scientists have begun isolating and purifying sugars that are able to bind to, and improve the activity of certain growth factors. For example, sugar chains with a specific attraction for vascular endothelial growth factor (VEGF), an important growth factor involved in the formation of blood vessels, has been isolated. Studies showed, that the when delivered with VEGF, the isolated sugar was able to improve blood vessel production from heart cells, compared to the delivery of VEGF alone. Importantly, and impressively, when delivered into chicks at the early stages of development, the sugar was able to promote the formation of blood vessels without the addition of any VEGF, indicating that the sugar alone could attract the body's own VEGF to the site of injury and promote repair. These results suggest that as well as stabilizing, localizing and improving the activity of growth factors, sugars may also be used to reduce, or completely negate the use of costly and problematic growth factors as drugs in tissue repair strategies. Instead, the sugar alone, may be just as effective for use as a drug to promote tissue repair.

For years, the study of complex glycosaminoglycan sugars (glycomics), has been unfairly hidden in the background of biomedical research, over shadowed by more popular, better understood, and well-funded areas of research such as genomics and proteomics. However, with advancements over the past decade or so, glycomics has steadily proved itself as a big player in the game too. New technologies allowing us to study and better understand the composition, and production of sugars, means that we are now starting to understand the full potential of these once forgotten molecules in cellular processes, and they are now starting to provide scientists with new and exciting opportunities to advance biomedical research.

Now becoming a 'hot topic' in scientific research, glycomics is helping to improve our understanding of biological recognition, and leading to improved therapeutic approaches, not only in the areas of drug delivery and tissue regeneration, but across the whole field of biomedical research.

It's been a long time coming, but we think that's pretty sweet indeed! Sweeter than your favourite chocolate bar anyway, that's for sure!

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by Stephanie Sloan & Jessica-May Fletcher

A WEE TASTE OF EDINBURGH

Those visiting Edinburgh are certain to enjoy the diverse relationship the city plays host to where centuries of captivating history meet a vibrant, cosmopolitan buzz. Edinburgh truly does come alive after dark and with a substantial range of pubs, from quant and intimate to live and electric, the city can cater for every taste.

The Grassmarket is a favourite spot for Edinburgh nightlife. The cobbled streets termed the 'Grassmarket' as it was once where local farmers brought their produce to barter with and sell. It is also famously known to be the location of one of the main gallows of the city where crowds would gather in their masses to witness public executions. With stunning views of the castle, impressive architecture and popular drinking venues it is a regular go to for students, tourists and locals alike. 'The Last Drop' is a traditional pub found immediately next to the scene of 18th century public hangings and is alleged to be haunted by the spirit of a young medieval girl with sightings taking place both deep in the cellar and in the bar area. With it's excellent ales and Scottish whiskies it is a great recommendation for anyone looking for a charming pub to relax and soak up some Scottish history. The Last Drop is only one of many pubs in this area, with many offering live music performances.

A short walk from the historic Grassmarket, you'll find possibly Edinburgh's most famous location – The Royal Mile. Running directly through the city's Old Town, from the iconic Edinburgh Castle down to The Palace of Holyroodhouse, Her Majesty The Queen's official residence in Scotland, The Mile offers many attractions both night and day. Whether you think it's 'tartan trash' or symbolic to Scotland's heritage, you are sure to find all things tartan, many the bagpiper and most likely bump into Nessie on The Mile. If you are lucky enough to visit Edinburgh during the annual Edinburgh Fringe Festival then The Royal Mile should be your go to spot for soaking up the atmosphere as street performers of all varieties entertain the crowds.

A well-loved pub just a short walk from The Royal Mile is Whistlebinkies. Open late every night and a very popular choice for those looking for live music with up to six different live bands playing every night offering a variety of Indie to Rock and Roll. You are sure to have a great night in Whistlebinkies but do come early if you prefer a seat!

Situated at the other side of Princes Street – Edinburgh's shopping district sits George Street. Contrasting to the quaint architecture of the Old Town, George

Street is home to delicious eateries, stylish bars and designer shops. The Dome is a well-established, first choice venue for delicious cocktails and fantastic place to meet friends. A stunning venue with an excellent reputation for quality service, if you are looking for a relaxed evening in a classy venue then The Dome is a great choice.

If you are looking for a quirky hang out offering something a little different and a great clientele then Treacle is perfect. Situated on Broughton Street only a short walk from the prestigious George Street you'll find Treacle, an extremely popular choice for students and a comfortable, modern bar. The cocktails are spectacular, offering delicious alternatives to your standard mojito and excellent bar staff keen to offer their own suggestions. A personal favourite for a few drinks before a night out, Treacle is a definite recommendation for a chilled out drink in a great venue.

No matter where you decide to visit, eat or drink whilst your stay in Edinburgh, you are sure to find something to suit your needs and enjoy the Scottish culture. A piece of Scotland that I must personally recommend exploring during a visit is Scotland's world famous whiskeys. Whisky is both an interesting and key aspect of our Scottish culture and brings visitors from all over the world to Scotland's capital city. What makes Scottish whisky so special and sought after above those produced in other countries is that it is the only whisky that can legally be marketed and sold as Scotch. A fantastic thing about whiskey is the abundance of different flavours and types of whisky, a dram to suit every individual. Distilleries, both big and small can be found right across Scotland, each belonging to a specific area. These areas are Speyside, Highland, Lowland, Campbeltown and Islay. Due to the highlands being such a large region, these whiskies have a greater variation in flavour and can be anything from a light, fruity malt to a full bodied, peaty whisky. Islay is a beautiful, scenic island on the west coast of Scotland and is home to 8 distilleries. Islay whiskies are renowned for their intense smoky flavours. A perfect example of this is Laphroaig quarter cask. During the prohibition of alcohol in America in the 1900's Laphroaig whisky was the only whisky allowed to be sold as it was considered a medicinal spirit. Islay is also home to the most heavily peated whisky in the world – Bruichladdich Distillery's Octomore. What makes Bruichladdich along with other Scottish coastal distilleries so special is that their whisky is matured by the sea. As the whisky matures, the casks 'breathe' in the rich sea air and this fantastic saltiness comes across in the finished product.

CRS REGISTRATION AWARDS

Congratulations to the ten postgraduate students and UKICRS members who received registration awards from UKICRS for attendance at this year's CRS Annual Meeting & Exposition in Edinburgh. The competition required applicants to write an original article on a topic relating to their postgraduate education or some aspect of pharmaceutical research. Several aticles are included in this edition of the UKICRS newsletter.

Farah Arikat (Cardiff University)

Enrica Calo (University of Reading)

Francesca Citossi (University of Nottingham)

Frazer Crofts (Aston University)

Rachel Donaghey (University of Strathclyde)

Olivia Kemp (University of Strathclyde)

Maryam Malekigorji (Keele University)

Sameer Joshi (Aston University)

Nichola Starr (University of Nottingham)

Peter Stone (Aston University)

In order for the admissions staff of our college to get to know you, the applicant, better, we ask that you answer the following question: Are there any significant experiences you have had, or accomplishments you have realized, that have helped to define you as a person?

I am a dynamic figure, often seen scaling walls and crushing ice. I have been known to remodel train stations on my lunch breaks, making them more efficient in the area of heat retention. I translate ethnic slurs for Cuban refugees, I write award-winning operas, I manage time efficiently. Occasionally, I tread water for three days in a row.

I woo women with my sensuous and godlike trombone playing, I can pilot bicycles up severe inclines with unflagging speed, and I cook Thirty-Minute Brownies in twenty minutes. I am an expert in stucco, a veteran in love, and an outlaw in Peru.

Using only a hoe and a large glass of water, I once single-handedly defended a small village in the Amazon Basin from a horde of ferocious army ants. I play bluegrass cello, I was scouted by the Mets, I am the subject of numerous documentaries. When I'm bored, I build large suspension bridges in my yard. I enjoy urban hang gliding. On Wednesdays, after school, I repair electrical appliances free of charge.

I am an abstract artist, a concrete analyst, and a ruthless bookie. Critics worldwide swoon over my original line of corduroy evening wear. I don't perspire. I am a private citizen, yet I receive fan mail. I have been caller number nine and have won the weekend passes. Last summer I toured New Jersey with a traveling centrifugal-force demonstration. I bat 400. My deft floral arrangements have earned me fame in international botany circles. Children trust me.

I can hurl tennis rackets at small moving objects with deadly accuracy. I once read Paradise Lost, Moby Dick, and David Copperfield in one day and still had time to refurbish an entire dining room that evening. I know the exact location of every food item in the supermarket. I have performed several covert operations for the CIA. I sleep once a week; when I do sleep, I sleep in a chair. While on vacation in Canada, I successfully negotiated with a group of terrorists who had seized a small bakery. The laws of physics do not apply to me.

I balance, I weave, I dodge, I frolic, and my bills are all paid. On weekends, to let off steam, I participate in full-contact origami. Years ago I discovered the meaning of life but forgot to write it down. I have made extraordinary four course meals using only a mouli and a toaster oven. I breed prizewinning clams. I have won bullfights in San Juan, cliff-diving competitions in Sri Lanka, and spelling bees at the Kremlin. I have played Hamlet, I have performed open-heart surgery, and I have spoken with Elvis.

But ... I have not yet gone to college.

MUSINGS OF A SPLIT PHD STUDENT

Farah Arikat

1st year PhD student
Cardiff School of Pharmacy and Pharmaceutical Sciences
& Cardiff School of Medicine
Cardiff University, UK

One week into my PhD and I was already being told the importance of starting to write my thesis and the ins and outs of a viva – what had I let myself in for! My memory was strenuously tested, being introduced to so many new people and attempting to remember their names (occasionally miserably failing, I have to admit), particularly since I am split between two schools: Pharmacy and Medicine.

Next on the list was lab meetings. I quickly found out I was part of three different research groups – "the microneedle group", "the skin group" and "the diabetes group", which meant attendance at three different lab meetings. Trying to remember which one was which was somewhat baffling, to say the least! During my interview I remember bragging, "I am the right candidate because I have a degree in Pharmacy, so I already know about drug delivery through the skin and I already know about immunology – I can get right into it." I also recall the interviewers grinning and realised why as I sat in my first meeting in which immunology was being discussed. It was like listening to a different language, where the words are made up of letters and numbers – CD44, IL-10, HLA, GAD65, CXCR3. What did it all mean? How did the different aspects of immunology and drug delivery fit together? What was my project even about? The solution was simple – I had to read. As time went by, these letters and numbers started making sense and the initial cloud of confusion was finally lifting.

Working in two internationally renowned labs (drug delivery and immunology) doesn't come without its perks. First, I have lots of supervisors - five to be precise. Whenever I'm in need of help or guidance, I can pick the brains of five highly skilled and knowledgeable top academics who bring along with them experienced and accomplished post-doctoral researchers and PhD students, what most people call your mentors in your first year as a PhD student, but what I call your "guardian angels"- and they don't even know it. They don't just teach you the lab techniques, they impart on you the most useful and relevant pearls of wisdom you could gain as they have only recently finished their PhDs and can fully empathise.

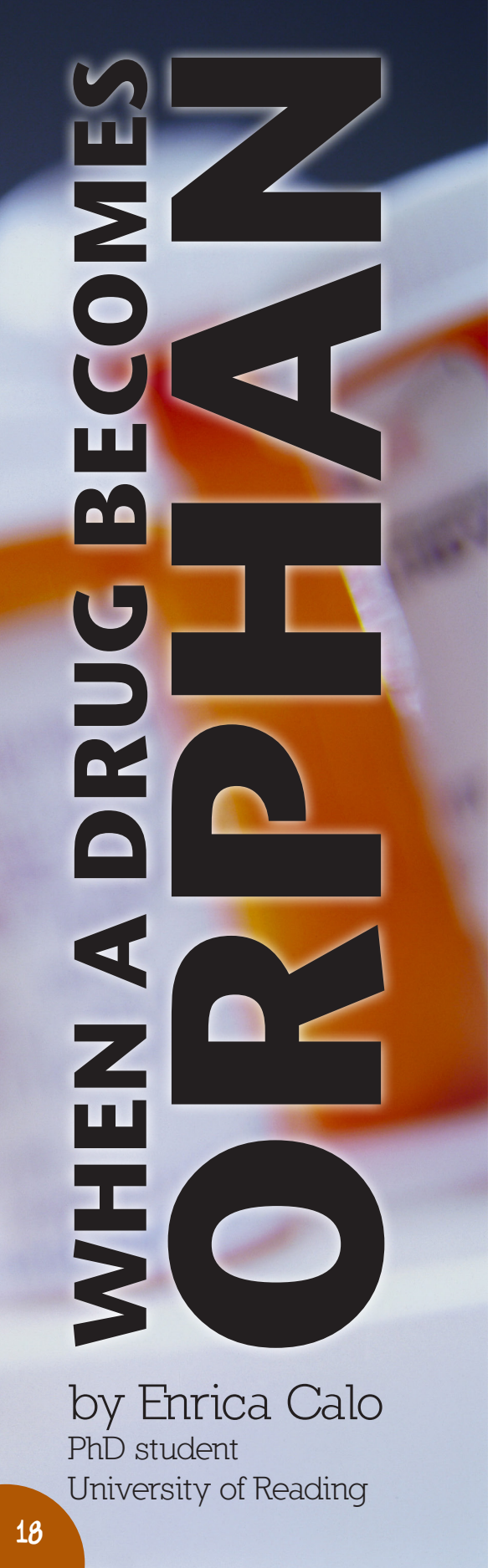
Working in two fields means two lots of reading, understanding and writing. However, it also means learning and becoming competent in a plethora of lab techniques such as HPLC, flow cytometry, cell culture, microscopy, drug formulation and drug delivery device characterisation. In the long-term this means becoming a multidisciplinary expert, something that will be indispensible in the ever more competitive job market.

Joining a gym was no longer on my agenda, as the half an hour walk (I say walk- I actually mean run to meetings) between the Schools of Pharmacy and Medicine means that I'm doing the recommended amount of daily exercise and then some!

Despite the advantages of having a split PhD, the downside is the added pressure juggling both sides of the work. However, time management, clear communication and knowing what you want to achieve will ensure your agenda is not in total disarray.

For me, a PhD is different to any other type of job or study. There is no clocking in or out, no register of attendance. It's down to you - your time and your research is your responsibility. But you should never feel alone or that you cannot ask for help. Like most things in life, it's a learning curve and you're allowed to make mistakes, as long as you take note of what went wrong, and get it right next time.

Needless to say, this PhD is turning out to be one of the most fulfilling, albeit challenging, experiences of my life and I eagerly look forward to seeing it through to the very end.



WHEN A DRUG BECOMES ORPHAN

by Enrica Calo
PhD student
University of Reading

'Rare' is not always a synonym for 'precious' as you would generally expect. For example, 'rare' is used to classify many diseases and conditions that affect small populations of people around the world. Well, 'small' if compared with the figures related to much more common pathologies such as lung cancer or diabetes.[1] In fact, we are talking about 300 million people.

More than 5000 diseases cannot currently be treated. Just to mention very few of them: Aase syndrome, Tourette syndrome, POEMS syndrome, Meleda disease, Nelson syndrome, Joubert syndrome, Familial adenomatosus polyposis (FAP), Linch syndrome or Sialidosis. The list seems dramatically endless and many of them start in childhood.[1]

The drugs that are developed to treat such rare diseases are labelled as 'orphan'. Sometimes drugs that are already used in the treatment of a common pathology could potentially have an 'orphan' indication[4], in other words they could be used for the treatment of a rare disease as well (i.e. thalidomide, an immunomodulatory agent with well-known teratogenic effect, was approved for the treatment of multiple myeloma). But what makes a drug 'orphan' is not just the relatively limited number of patients that would benefit from their launch or development, no. The problem is that their manufacturing would not be worth the profit that would come from them. Additionally, the legal context in which industry and research had to operate in the past to get a drug the designation of 'orphan' was very confusing and discouraging.

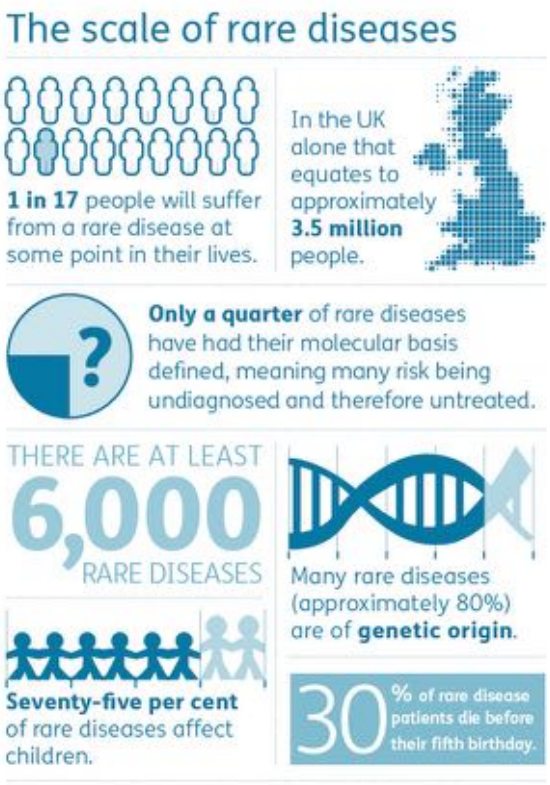
Since the 'Orphan Drug Act' (United States, 1983) things have changed a lot. With this act, new grants and contracts were offered from the US government to incentivise research and development of new drugs for rare diseases. The FDA was finally involved to help and organize the process of 'orphan drug status' designation approval through the Office of Orphan Product Development (OOPD)[4,5].

Europe had to wait a bit longer to see that something was effectively moving in the right direction. In fact, the 'Orphan Regulation' was first approved by the European Parliament on the 16th December 1999. One of the most relevant results of this was the establishment of the Committee for Orphan Medicinal Products (COMP). Since then, several regulations have been approved in Europe in order to make things clearer.

Now even the industry perspective seems to have changed: investing in orphan drugs means fewer competitors (or none), institutions' assistance during the process and quite interesting profit (they are among the priciest medicines you can find, some examples: Miglustat $128,000, Agalsidase beta $239,000 or Galsufase $441,000 per year).[7]
But what process exactly does a drug designed as 'orphan' go through? Well, the journey is arduous as usual: a 'pre-clinical' testing (lab and animal studies to make sure that a certain safety is met), Phase I, II and finally Phase III clinical trial. During Phase I the drug is for the first time administered to humans: healthy volunteers are given different doses of the treatment to establish its tolerability by the human body. Phase II trials start to actually investigate the effectiveness of the drug for specific pathological conditions (more than one hundred patients can take part) and which dosage works best. In Phase III patients are randomly administered the drug, a placebo or a different therapy ('a comparator'). This phase aims to collect all the information possible about effectiveness and safety of the treatment.
After the approval and registration of the drug, it has to pass the so-called 'post marketing studies' (or Phase IV trials). These tests are used to monitor the long-term efficacy and risks of the therapy approved and can take up to several years.[8] But what really makes the difference is the valuable help that come from incentives, tax reductions or exemptions and exclusivity on the market.

Last year, 17 drugs received the 'orphan' designation in Europe, much more than the number recommended in 2013. Many are the drugs that reached the market recently, such as Holoclar (February 2015) which is a stem-cell based treatment indicated for severe limbal stem-cell deficiency due to burns to the eye. These patients present damaged corneal epithelium and do not have sufficient limbal stem-cells (the limbus is represented by the edge of the cornea) that are supposed to regenerate it. With Holoclar therapy, patient's limbus cells are collected and grown in

Top selling orphan drugs	
Drug	Indication
Rituximab	Oncology
Ranibizumab	Ophthalmology
Somatropin	EPR, Metabolism
Lenalidomide	Oncology
Imatinib mesylate	Oncology
Filgrastim	Hematology
Glatiramer acetate	Multiple schlerosis
Recombinant Factor VIII	Hematology
Bosentan monohydrate	Cardiovascular
Bortezomib	Oncology



the lab in order to be used to repair the damage. Another recently marketed (January 2015) drug is Cerdelga (eliglustat) approved for the treatment of type-1 Gaucher disease (non-neuronopathic, in which the central nervous system is not affected). The patients affected by Gaucher disease present a deficiency of glucocerebrosidase, an enzyme that normally hydrolyses glucosylceramide, a fat that tends to accumulate in liver, spleen and bones. This typically causes bone pain and break, anaemia, fatigue, abnormal spleen and liver and bleeding tendency.[9-11]

Hopefully, the figures related to approved rare disease treatments will increase in the future thanks to the great work that research institutes and institutions are currently doing. And maybe all those patients will start feeling less orphan as well.

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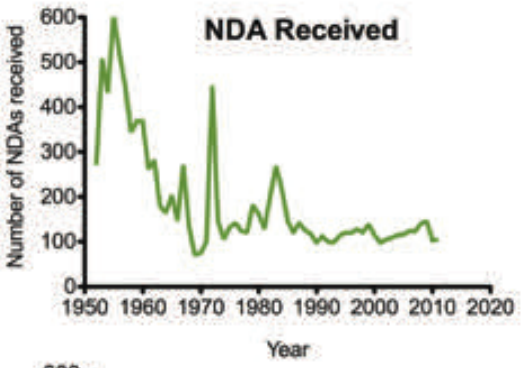
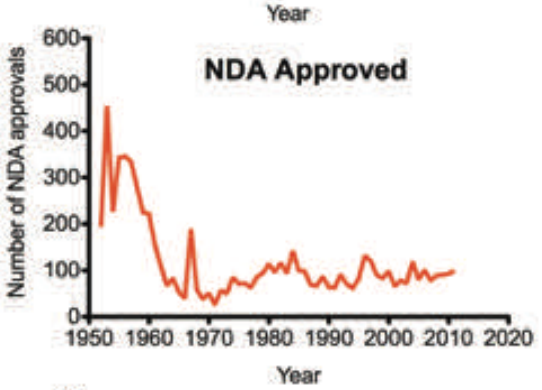
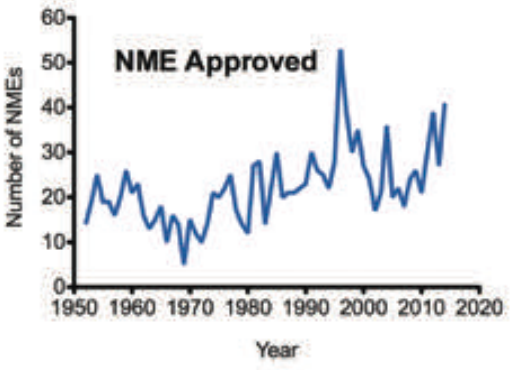
NDA – New drug applications
NME – New molecular entities







BECOMING AN ENGAGING SCIENTIST

by Rachel Donaghey (PhD student, University of Strathclyde, UK)

Postgraduate students at the University of Strathclyde (Glasgow, UK) are given the option to attend an innovative and exciting course which provides the tools essential for 'Becoming an Engaging Researcher' [1]. The course presents an opportunity to attend a variety of workshops with the aims of sharing research ideas within a specific discipline or by branching out into the wider community. The wide range of workshops include: utilising different forms of digital media to present research ideas, trying your hand at stand-up comedy with the amazing performers at Bright Club [2], or working with children, for example. The 'Engaging with Schools' workshop provides further information on the best way to begin working with young people and enables postgraduates to register as a STEM ambassador (Science, Technology, Engineering and Mathematics; http://www.stemnet.org.uk/). Security checks for protecting vulnerable groups are also required prior to working with children, however, costs are covered as part of the course [3].

The STEM network is an organisation which provides connections between schools, industries and academia with the aim of inspiring young people and their interest in science. Ambassadors of the STEM network have access to great support and resources such as lesson plans and activity ideas, while the network itself strives to assist its members in any way possible [4]. The only condition of becoming a STEM ambassador is that you contribute to a workshop at least once a year. Although participating in these activities can come at the cost of taking time out of the lab, the sense of satisfaction gained by being able to inspire even just one individual is priceless. As well as the feel-good factor, postgraduates can enjoy a change in scenery while taking on a new challenge which differs from the usual schedule of being a scientist.

STEM ambassadors receive a monthly newsletter describing the latest opportunities available within their chosen geographical areas. This newsletter enabled me to find out about a local STEM awareness day being held at my former high school. After sending a short email indicating my interest, the STEM network was able to arrange contact with the organisers at the school, who were then able to provide me with further information on how I could get involved. By specifically targeting the school in which I was taught, I was able to enhance the impact of my workshop by showing young students (~12 years old) that anything is possible (with a lot of hard work) and that they were all equally able to go into further education and conquer their own ambitions in life.

THE CHALLENGE OF DEVELOPING A SUITABLE WORKSHOP

The STEM network offers a forum for ambassadors to share ideas and resources which can help when designing a workshop, however, developing one which is based

around your own specialist research area can prove more difficult. My challenge was to develop an activity which would give the children an insight into the field of nanotechnology. This was made possible by testing a principle at the more visible micron-level which would then enable students to discover how technology can be improved at the nanoscale. 'Small Science' was the theme of the workshop which involved the design of an experiment to illustrate how nanotechnology may be used to tackle the water crisis. The water crisis refers to the fact that even in the 21st century, millions of people lack the basic human right of access to safe, clean water [5]! After a brief explanation,

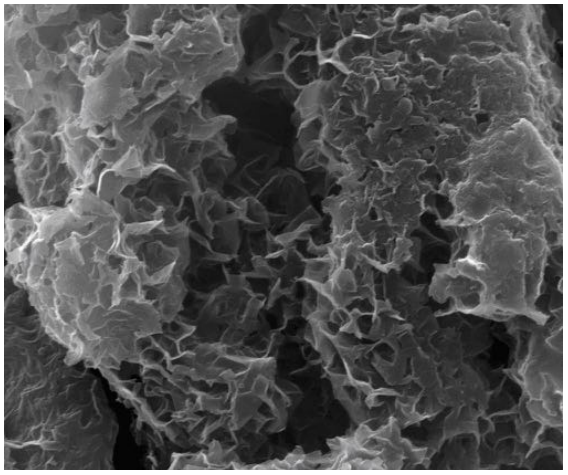


Figure 1: *Porous nature of activated carbon.*

students set up three columns containing filtration materials with different sized properties: gravel, sand and activated carbon. For the purpose of the experiment, activated carbon was termed 'micro-carbon', due to the presence of micrometre-sized channels which form in the carbon after the removal of hydrate groups (Figure 1).
Students were able to test each system by pouring a sample of water, previously collected from a 'contaminated' stream, to determine which system was best at removing contaminants from water (Figure 2). There are limitations of the experimental design because the sand occasionally

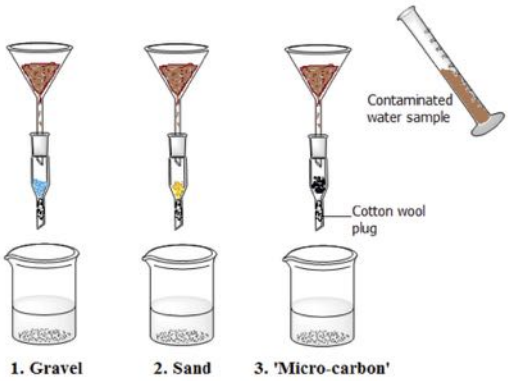


Figure 2: *Experimental design – efficiency of different materials to filter water.*

contaminates the water. However, the results help focus the group's discussion on ascertaining the features required to produce an effective water filter. Our results showed that gravel expressed an ability to trap large particles of dirt in order to achieve some degree of filtration, although smaller contaminants were able to pass through, while the micro-channels in the activated carbon were able to trap all visible contaminants so that the students obtained a clear sample after filtration. Upon explaining the theory of how decreasing particle size results in an increase in surface area (Figure 3), and that this in turn increases the contact of contaminants within the filters. Students could then contemplate how nanomaterials could be used to further improve filters for the removal of smaller materials such as microorganisms.

As well as participating in a fun and interactive workshop designed to engage young minds within the leading field of nanotechnology, the students were able to practically determine ways to overcome real life problems facing scientists today. This provides an insight to the relevance of the work of a scientist rather than attending a typical lesson on plant biology, for example. Students were also able to gain some practical experience in the use of the scientific method and discuss the importance of experimental design. As well as providing a number of benefits for the students, it is also possible to achieve personal goals such as breaking down common stereotypes, raising the profile of your research area and improving public awareness, as well as collaborating with others. As a result of my first engagement project, I was able to develop the following three skills:

1. Challenging the common perception

One of the most fundamental aspects of being a scientific researcher is contributing to knowledge within the scientific community.

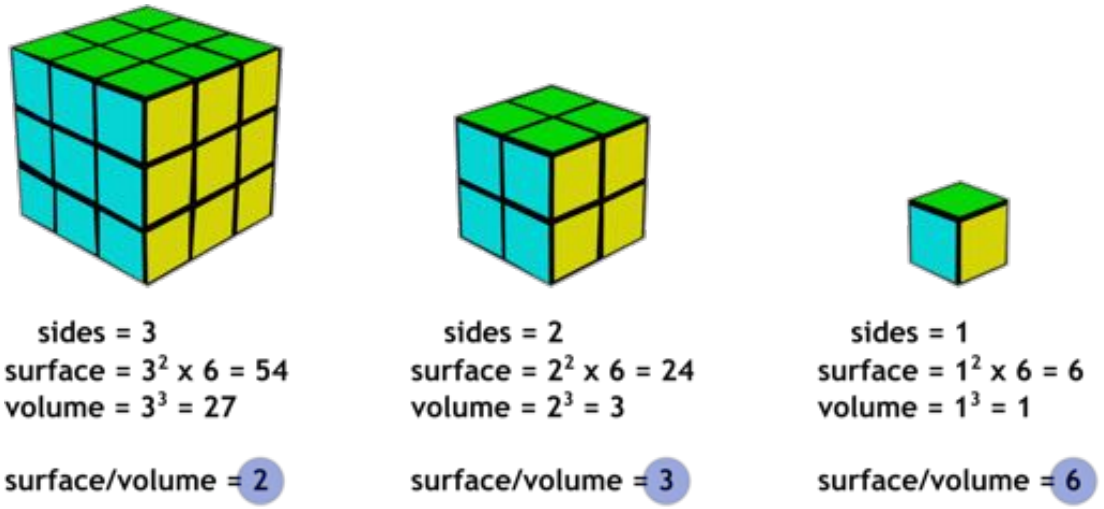


Figure 3: *The relationship between particle size and surface area*

However, it is becoming increasingly important to connect with society by reaching out to the general public, and rightly so! By breaking down the barriers between science and the public it is revealed that scientists are not solely older men with excessive facial hair and dreams of world domination, but they come in the form of regular people with a desire to make a difference in the world. We also exist in a time where media sensationalism is rife, particularly in relation to the advancement of nanomaterials. This can result in the skewing of important scientific facts which spark fears within the general public. However, this problem could be easily avoided if scientists engaged more frequently with the public.

2. Communication of your own research

There are also some selfish reasons for reaching out to the public. By undertaking a workshop for young people it becomes essential to develop an ability to explain your research in a simplified manner which is likely to be out-with your comfort zone. This is a challenging feat but in the end it becomes beneficial for the overall understanding and communication of your work. Having this quality becomes useful when attending multi-disciplinary conferences, for example, where you may be faced with explaining your research to a non-expert audience. In particular, engaging with children during your research can be a very rewarding experience as you possess the ability to inspire them to follow their own hopes and dreams.

3. Building connections and strengthening your professional network

Upon developing my workshop, I felt that it was important for me to give the students something in return, a small memento which would reinforce what they had learned throughout the day. After a quick internet search I came across the Nanooze magazine (Fig. 4), a wonderful resource targeted

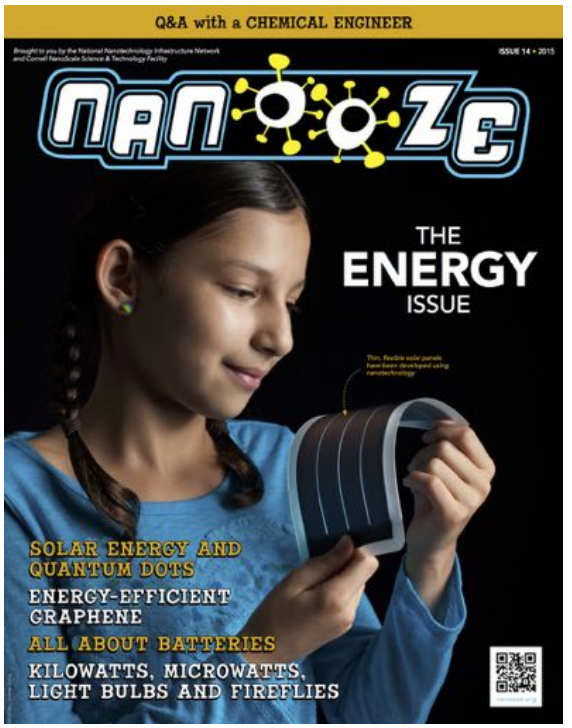


Figure 4: *The Nanooze magazine is published by Cornell University (US) and aims to explain all things nano to children.*

at children which takes a look at recent developments in nanotechnology [6]. Every issue of the magazine has a different theme, from nanomedicines to the unexpected properties of nanomaterials. Coincidently, scientists from Cornell whose research had featured in a UKICRS 2014 newsletter article are responsibly for the development of the Nanooze mag. It was a surprise to discover that they were also responsible for the development of the Nanooze magazine, which is distributed as a free resource to teachers within the US and is available to print from the website. I am deeply gratefully to Professor Carl Batt and Dr Lynn Rathbun who kindly shipped over copies of Nanooze magazine which enabled me to distribute copies to students and teachers at the school. As a result of this, my contribution was extended across the department and strong connections were made with the teachers. Consequently, I was invited to return to speak to some of the older students who were working on nanotechnology-related projects of their own.

PUBLIC ENGAGEMENT CAN LEAD TO OPPORTUNITIES YOU NEVER IMAGINED

There is a great deal of support available to begin your journey as an engaging scientist and working with children is just one method you can use to accomplish this. Sharing ideas with others opens up many opportunities for collaboration, developing new skills and enhancing creativity by providing a fresh and unique perspective on your own work. Becoming a STEM ambassador and subsequently working with children has provided me with the tools and confidence to go out into the general public and share my knowledge with others. After all, why would we be performing such great scientific research if we are unable to tell the rest of the world about it?

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3. Protecting Vulnerable Groups (PVG) scheme (http://www.pvgschemescotland.org)
4. Science, Technology, Engineering and Mathematics (STEM) Network (http://www.stemnet.org.uk/)
5. The WHO fact sheet on water health and safety(http://www.who.int/mediacentre/factsheets/fs391/en/)
6. The Nanooze magazine (http://nanooze.org/)

2015 SYMPOSIUM REVIEW

Maria Marlow
Laura Mason

This year's annual UKICRS Symposium (16–17 April 2015) was hosted by the University of Nottingham, with a specially extended programme. The symposium opened with two parallel workshops, one for our post-graduate students called the 'Early Researcher Forum' and an academic workshop focussing on UK and European research grants.

The Early Researcher Forum had over 70 attendees with Clare Jones (University of Nottingham Careers Service), Antony Williams (Royal Society of Chemistry), Arpan Desai (AstraZeneca) and Claire Madden-Smith (Juniper) speaking about how their careers have progressed and how postgraduates can best maximise their future prospects. A smaller group of about 10 academics attended the academic workshop.

In the afternoon, we welcomed our industrial exhibitors, including Stable Micro Systems, Surface Measurement Systems, SOTAX, Biopharma Systems, AstraZeneca and ISAC, who showcased their products and technologies through a series of short talks and exhibitions.

The scientific programme for the second day included 2 keynote speakers, 11 talks from postgraduate students and postdoctoral researchers, and 81 poster presentations, with a record 151 delegates in total. Dr Francesca Greco (University of Reading) kicked off the morning session with a keynote lecture about polymer-drug conjugates and how recent developments are offering potential for combination therapies and anti-angiogenic therapy.

The keynote lecture was followed by two short presentations from Laura Martinez-Marcos (University of Strathclyde), speaking about the use of hot-melt extrusion to enhance drug dissolution properties, and Nichola Starr (University of Nottingham) describing the use of TOF-SIMS to monitor compound permeation through human stratum corneum. After the coffee break, three further short presentations were delivered. Francesca Citossi (University of Nottingham) discussed the use of low molecular weight gelators for targeted cancer therapy, Sameer Joshi (Aston University) talked about the use of a liposomal drug delivery system enabling co-encapsulation of two anti-diabetic drugs, and Mariarosa Mazza (University of Manchester) described the

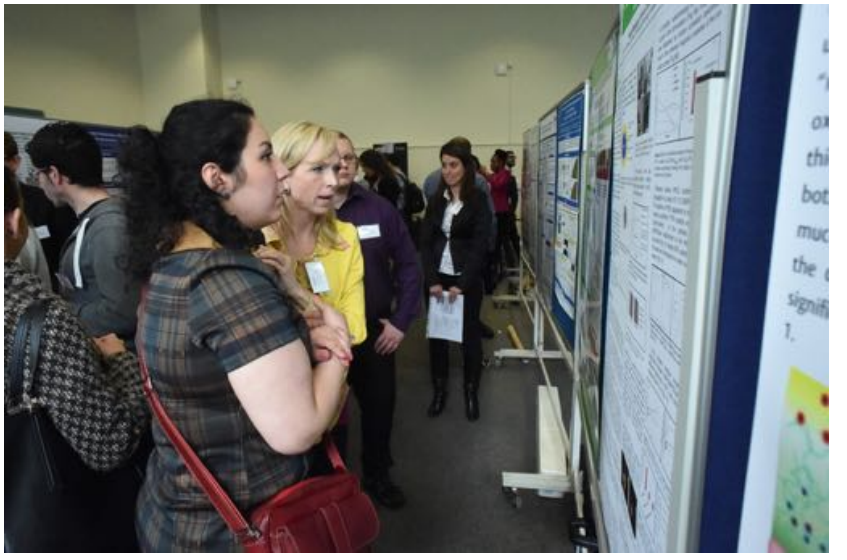
treatment of glioblastoma using peptide nanofiber vectors for siRNA.

Following a very busy poster session and lunch, the afternoon session was opened by Prof Ben Boyd (Monash University, Australia) who spoke about the digestion of lipid-based formulations. He highlighted how little we know about the digestion of everyday food products, such as milk, and discussed the implications and opportunities for the nanostructures formed during digestion. He was followed by PhD student Caroline Herron (Royal College of Surgeons in Ireland) who spoke about the development of a triggerable drug delivery system for use in critical limb ischaemia. Farah Arikat (Cardiff University) described the steps behind developing a microneedle delivery system for delivering antigen-specific immunotherapy. Riham El-Gogary (Ain Shams University, Egypt) spoke about using surfactants to coat PLGA nanoparticles enabling brain targeting of antioxidants.

After more coffee and posters, three talks closed out the final session of the meeting. Fraser Crofts (Aston University) gave a presentation on producing cationic liposomes by microfluidics. Ana Cadete (University of Santiago de Compostela, Spain) described the development of antibody-loaded hyaluronic acid nanocapsules for anticancer drug therapy. Daniel Margetson (Diurnal Ltd.) discussed the development and manufacture of Infacort, as a taste masked hydrocortisone product for the paediatric population.

The meeting was concluded by the UKICRS chair Professor Gavin Andrews (Queens University Belfast) who announced the prize winners for best oral and poster presentations. The prizes for best oral presentation were awarded to Caroline Herron (Royal College of Surgeons in Ireland) and Ana Cadete (University of Santiago de Compostela, Spain) while the prized for best posters were awarded to Emma Leire (University of Nottingham) and Zahraa Al-Ahmady (University of Manchester). Many congratulations to all the prize winners for their excellent presentations.

Thank you to all delegates, sponsors and speakers. We look forward to welcoming you all to Cardiff in 2016.



MORE THAN MEETS THE EYE

Peter Morrison

Senior Research & Development Chemist

Vista Optics Ltd., UK

The eye is an intricate and delicate organ that is relatively isolated from the rest of the body, its components are contained within tough membranes and further protection is provided with the 'blood-aqueous' and 'blood-retinal' barriers that prevent many solutes from entering the eye, ensuring the light transmitting pathways remain clear. Figure 1 shows the main ocular features.

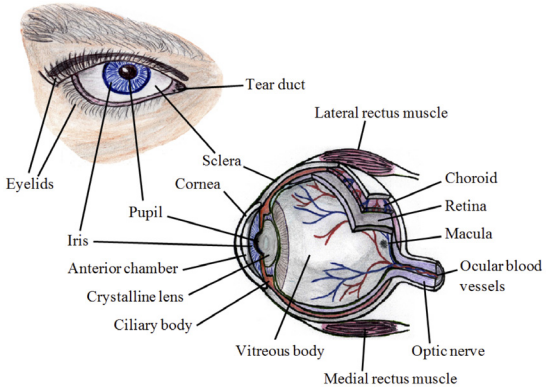


Figure 1. *Structures of the human eye.*

The cornea is a very efficient barrier to foreign compounds due to its multi-layered structure comprising of a lipophilic epithelium, which prevents ingress of aqueous substances. Directly under the epithelium is a homogeneous acellular layer, the Bowman's membrane. Next there is the stroma, a hydrophilic layer which makes up 90% the total cornea thickness, this structure is a highly resistant barrier to lipophilic compounds, however, aqueous solutions can readily diffuse through the layer. The next layer is another homogeneous acellular structure, the Descemet's membrane, a tough membrane that supports a single layer of endothelium cells which are important in maintaining the hydration balance of the cornea.[1,2] Figure 2 shows a micrograph of the layered structure of a bovine cornea; these features are typical of mammalian corneas. Historically, the human cornea is reported as having these five distinct layers common amongst many mammalian species. However, another thin and tough layer impervious to air was discovered in the human cornea and reported by Harminder Dua in 2013 and thus named 'Dua's layer'. It is a thin structure and resides between Descemet's membrane and the stroma.[3] This membrane could prove important during corneal transplant surgery by allowing the Descemet's membrane and endothelium to remain in place undisturbed during the procedure known as 'deep anterior lamellar keratoplasty'.

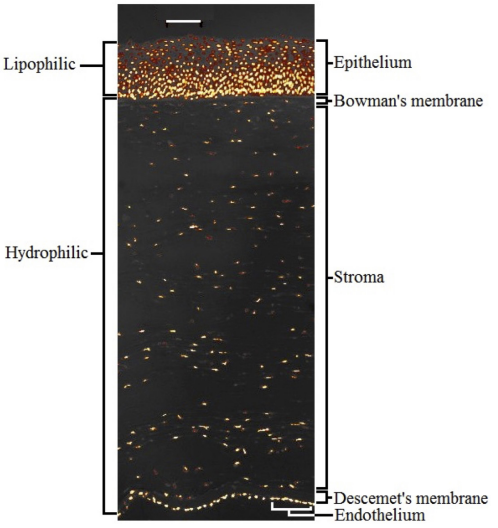


Figure 2. *Multi-layered structure of the cornea. Scale bar = 100 µm.*

Eye disorders can be classified as periocular (outside the eye) or intraocular (inside the eye). Periocular tissues include the surface areas of the sclera and cornea, the conjunctiva, inner eyelids and associated nasolacrimal mucosa. Intraocular structures can be subdivided into those of the anterior chamber and the posterior structures encasing the vitreous humour and retina. Periocular disorders are relatively easy to treat whilst intraocular disorders offer major challenges.[1,4,5]

There are three routes to deliver drugs in treating ocular disorders; topical, systemic and intraocular. Each has advantages and disadvantages. Intraocular drug delivery involves injection or implants directly into the eye. This method of drug delivery is not without risk and the procedure is undesired by many patients, but it offers a very efficient means to get drugs into the inaccessible structures within the main body of the eye. Intraocular injections have relatively short term efficacy in a timescale of weeks; however, implants can provide long term benefits for many years, and miniturisation of these drug delivery systems allows for less complicated implantation procedures.[6] Systemic drug delivery relies upon a relatively high concentration of the drug circulating in blood plasma in order to achieve a therapeutically effective dose within the eye.[6] This approach provides an inefficient strategy due to the blood-eye barriers preventing prevent drug from moving into the body of the eye. This method affects the body as a whole due to circulating systemic drug load, and undesired side effects can be experienced. Topically applied medication in the form of eye drops provide an intrinsic overdose followed by rapid elimination due to dilution and wash out by tears and nasolacrimal drainage mechanisms. Only a small amount, often much less than 1% of the instilled dose enters ocular tissue.[1,7-10]

Sustained and controlled release drug delivery systems

Maintaining a controlled release dose form at the target site could provide efficacious drug delivery and minimize or eliminate side effects due to systemic absorption by providing a sustained low dose at the intended site of action. Enhancing ocular retention of drugs by inclusion of viscosity enhancing compounds, for example cellulose derived polymers, is one strategy that can be used to keep the dose form at the eye's surface prolonging time for the drug to interact with ocular tissue. In situ gelling systems are more effective dosage forms that are applied as liquid drops for dose precision. They then transform to a gel under physiological conditions initiated by changes in temperature, pH or electrolyte composition of the tears. The drug formulation can include mucoadhesive components to aid

retention at mucosal membranes in the cul-de-sac behind the eyelids. These strategies aid drug retention by preventing non productive losses due to wash out and nasolacrimal drainage. Inclusion of drug loaded nanoparticles, which can be mucoadhesive, can provide a means of sustained release at the ocular surface.[1,4,7,11-13]

Ocular inserts are drug loaded devices that

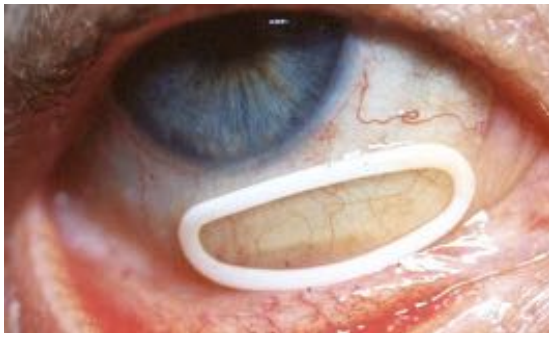


Figure 3. *OCUSERT® drug delivery system.[14]*

are placed in contact with the eye, usually in the upper or lower fornices. These devices can be erodible, non-erodible or soluble and they release their drug payload in different ways. For non-erodable devices their drug load slowly leaches out from the reservoir, they can be designed to deliver a precise amount of drug over a given period, after which they are removed and discarded. Figure 3 shows the OCUSERT® system designed to deliver pilocarpine over a 7-day period for the treatment of ocular hypertension,[14] and Figure 4 shows a recently developed system by Amorphex Therapeutics; the 'Topical Ophthalmic Drug Delivery Device' (TODDD). The device is currently in clinical trial and can delivery a drug or combinations of several drugs for up to three months.[15] Soluble and erodible ocular inserts release their drug payload from the matrices as they slowly dissolve or wear away due to the mechanical action of the eyelids, the advantage of this type of device is they don't need to be removed.

Figure 4. *Topical ophthalmic drug delivery device (TODDD).[15]*

Contact lenses and intraocular lenses as drug delivery systems

The idea of using contact lenses as drug delivery vehicles was first proposed by Otto Wichterle et al. around fifty years ago.[16] Since then much research and development has attempted to bring products to market. Even today there are no commercial products available, although off-label use of contact lens drug delivery vehicles has been attempted.[17] Hydrophilic and hydrophobic polymers are used to manufacture contact lenses and intraocular lenses and potentially both can be produced as drug delivery vehicles. Medicated contact lenses offer an attractive means to deliver drugs and this can be carried out in the long term by simple replacement of disposable lenses to allow for continued treatment.[18] In the case of intraocular lenses drug loading is provided during manufacture or prior to surgical implantation, therefore therapeutic action ends once the drug reservoir is depleted.

For contact lens drug delivery systems the simplest, but least effective means is to presoak hydrogel lenses in drug solution. Hydrogels are polymeric materials that are able to imbibe substantial amounts of water or drug solution. Figure 5 shows a typical hydrogel contact lens that could be used for this purpose. Using this system allows the drug to interact with ocular tissue longer than would be the case using eye drops, where they are quickly lost by wash out and nasolacrimal drainage. However, drug soaked hydrogel contact lenses only offer marginal benefits over other topical drug delivery methods due to the limited loading capacity of contact lenses for a drug solution, which is quickly depleted. Drug loading capacity of hydrogel contact lenses depends on factors such as; water content, lens geometry, drug solubility, molecular weight and the drugs affinity to bind with the polymer. Simple drug loading by presoaking / hydration of the contact lens in an aqueous drug solution offers a higher degree of bioavailability compared with eye drops, but the drug reservoir is quickly released, therefore sustained release is not achieved. Designing the lens to have a higher affinity to drugs can be gained by inclusion of monomers that can enhance drug / hydrogel affinity, for example, methacrylamide propyltrimethylammonium chloride, can provide drug binding sites in the polymer matrix and this can potentially allow for sustained drug release.[19] Nguyen et al. investigated silicone containing contact lens materials incorporating hyaluronic acid and they found that uptake of ciprofloxacin and dexamethasone phosphate solutions was enhanced compared to materials without hyaluronic acid, and drug release was achieved for more than seven days. They concluded that inclusion of hyaluronic acid with hydrogels could offer advantages when used to make contact lens drug delivery vehicles.[20] Alex Hui, 2012, reviewed recent developments including a number of techniques designed to provide controlled and sustained drug delivery from polymeric materials are summarised below.[21]

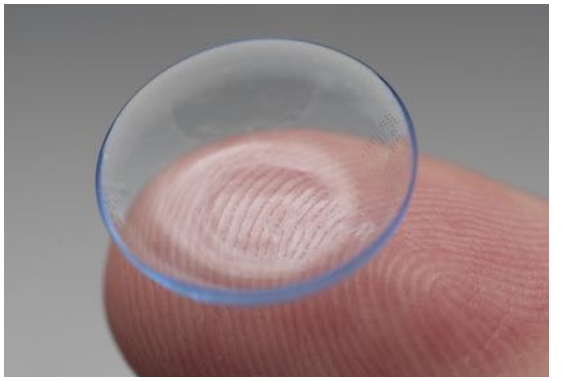


Figure 5. *Hydrogel contact lens suitable for drug delivery.*

- Molecular imprinting to provide the inclusion of cavities or an imprint at the lens surface during the polymerisation process – these regions have a high affinity for drugs and this serves to retard the diffusion of the loaded drug.[18,21] Alvarez-Lorenzo et al. reported higher drug loading and sustained release for at least 24 hr from molecular imprinted contact

lens materials they developed.[22]

- Drugs can be encapsulated into specifically designed polymer films and these can be sandwiched within the contact lens or attached to the lens as a surface coating.[18,20] Ciolino et al. developed a prototype contact lens system by coating ciprofloxacin loaded poly[lactic-co-glycolic acid] with polyhydroxyethyl methacrylate and these films were able to achieve sustained release for more than 4 weeks and they proposed that this could be used as an ocular drug delivery platform.[23]
- Diffusion barrier coatings added to the surface of drug loaded hydrogel contact lenses allow controlled drug release from within the hydrogel matrix.[21]
- Incorporation of micro / nanoparticles as drug carriers into the polymer formulation prior to polymerisation has been reported to enable contact lens drug delivery from days[24,25] to weeks[26,27], and the principle of this method is demonstrated in Figure 6.[28] First, drug molecules leach out from the particles and diffuse through the hydrogel polymer matrix, then move from the polymer into the tear film. The pre-lens tear film is subject to dilution, wash out and elimination, so adds little improvement to sustained drug delivery. However, the post lens tear film maintains intimate contact with the cornea surface and as the drug molecules move into the eye the drug load of the post lens tear film is replenished from the contact lens, maintaining a drug concentration at the cornea.

The above techniques minimise the burst release of drugs from contact lenses that is evident when using the simpler pre-soaking drug loading technique.

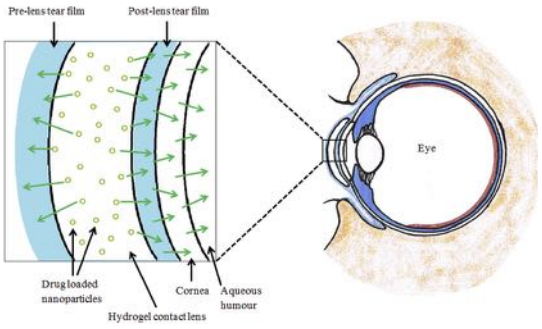


Figure 6. *Medicated contact lenses incorporating drug laden nanoparticles.[28]*

Figure 7. *A modern foldable intraocular lens.*

Medicated intraocular lenses

Intraocular lenses (IOLs) are used to replace the natural crystalline lens of cataract patients, or to correct refractive errors in people with healthy crystalline lenses. Intraocular lens replacement surgery is an invasive procedure, however, it is quick, effective and on the whole, a safe technique carried out in clinics around the world. The procedure requires insertion of instruments into the eye, whereupon the natural lens is emulsified (phacoemulsification) and extracted, then replaced with an IOL.[7] Early IOLs were rigid and required incisions up to ~12 mm, and rigid devices are still fitted in some parts of the world.[29] Modern IOL's are soft polymeric devices with shape memory that can be folded and placed into the eye using a purpose made injector through a small incision of ~2.2 mm, where it unfolds and assumes the designed shape, Figure 7. The surgeon manipulates the lens into place and the incision is self-closing (sutureless), this method induces much less trauma. It is a very cost effective method to help people suffering cataracts enjoy good visual health.[29]

Cataract surgery induces postoperative inflammation together with the risk of infection. Standard practice following intraocular surgery is to provide antibiotic and anti-inflammatory medication, and this is mostly provided topically using eye drops. Combining intraocular surgery and postoperative treatment in one procedure is appealing because it eliminates patient noncompliance and medication is placed exactly where it is required without having to pass through the ocular barriers. If IOLs can be designed to carry a drug payload this could provide the ideal means to treat post-surgery infection and inflammation. Drug loading can be achieved by pre-soaking a hydrophilic lens in a drug solution,[30] by loading the matrix during polymerization, by providing a drug loaded coating or by attaching drug depots to the IOL haptics.[31] Whichever method is chosen, an effective and non-toxic dose needs to be delivered over a sufficient time scale.[32] Gonzalez-Chomon et al. report a method that employs supercritical CO_2 to impregnate norfloxacin into IOLs made from acrylic hydrogels and they report that the IOLs were effectively loaded and were able to release the drug at an therapeutic level in a controlled manner sufficient to prevent fouling of the implanted IOL.[33,34] Drug delivery from depots that can be attached to the IOL's haptics provides a convenient means to provide controlled delivery of antibiotics post-surgery. These devices are biodegradable depots that can provide sustained medication in excess of four weeks.[35] It is in the author of this article's opinion that this technique can be exploited for delivery of other drugs, for example, anti-inflammatory medication.

Conclusions

In this brief article on ocular drug delivery, discussion first evaluated the complex anatomy of the eye placing a focus on the difficulties faced when treating ocular disorders due to the many clearance mechanisms. First there is dilution, wash out and rapid drainage that quickly reduces instilled drug bioavailability. Next, the barrier function of ocular membranes was considered with an emphasis on the need to prolong contact for effective drug penetration. Various strategies were considered to prolong the residence time of topically applied medication. Discussion then moved toward contact lenses as drug delivery devices and how they could provide sustained, low dose drug delivery directly to ocular tissue which could potentially eliminate systemic side effects. Much research has been carried out in this field but to date there is no commercial product on the market, however, some of the methods discussed have been employed 'off label'. Finally, intraocular lenses were considered for direct post-operative drug

delivery and this carries potential for future development.

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1. **Scottish actor Gerard Butler is a qualified dentist?**
2. **Scotland have qualified for nine Football world cups but have only played at eight.**
3. **The raincoat was invented by a Scot in 1824.**
4. **Queen Victoria smoked cigarettes when she was in Scotland to keep away midges.**
5. **The Scots invented bagpipes.**
6. **JD Salinger's 1951 novel 'Catcher in the Rye' has its title based on a Robert Burns poem.**
7. **Slains Castle in Aberdeenshire inspired the horror tale, 'Frankenstein' by Mary Shelley.**
8. **Kilmarnock Academy in Scotland is one of the few schools in the world to have educated two Nobel laureates.**
9. **In 1872, Scotland played England in the first international game of football. The result was 1-0 to Scotland.**
10. **Scotland has the biggest percentage of redheads in the world.**
11. **Which of the following are Scottish inventions?**
    - **Pedal bike**
    - **Plus and equal signs**
    - **Smallpox vaccination**
    - **Cure for leprosy**
    - **The ATM**
    - **Television**
    - **Logarithms**
12. **The actor Jason Statham competed for Scotland in diving team in the 1990 Commonwealth Games in Auckland.**

Smart iron oxide-gold nanoparticles for liver cancer treatment

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Hepatocellular cancer (HCC) is the sixth most prevalent type of cancer and the third leading cause of cancer-related death worldwide. It is also the most common form of primary liver cancer. To date, the only treatments for HCC are surgical intervention [1], transcatheter arterial tumour chemoembolization, drug-eluting bead embolization, radiofrequency ablation [2] and systemic chemotherapy with doxorubicin (Dox) and paclitaxel [3-4]. Recently, a slight increase in the median overall survival rate has been achieved by using multikinase inhibitor – sorafenib [5], but an effective therapy for HCC is still urgently required [6].

Failings in the apoptotic pathway can be associated with the onset of cancer, thus the activation of programmed cell death may be an ideal technique to control and decrease the tumour volume [7]. Many proteins contribute to the apoptosis process, which can be investigated in cancer treatment. Cytochrome c (Cyt c) is one of the proteins translocated from the mitochondria to the cytosol. After trigger by an apoptotic stimulus, Cyt c is released from the mitochondria, which facilitates the assembly of the apoptosome and finally initiates the activation of the caspase cascade [8]. This process can be utilised in practice through introducing Cyt c into tumour cells that can stimulate apoptosis and cause cell death. However, protein delivery is highly challenging and needs the application of precise drug delivery systems.

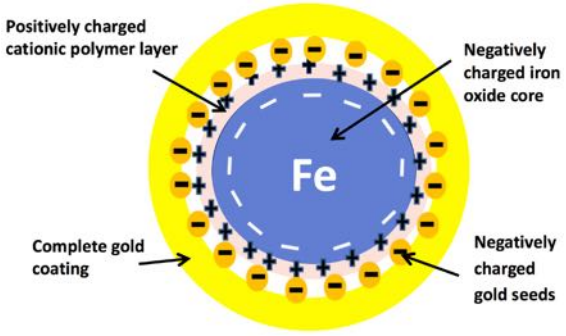

Figure 1. Schematic diagram of iron oxide-gold core-shell nanoparticle presenting electrostatic charges within each layer.

Previously researchers tried to introduce Cyt c into cells by applying biodegradable lipid nanoparticles (NPs) [9], mesoporous silica NPs [10], protein encapsulating NPs [11] and Cyt c based protein NPs [12]. Moreover, Cyt c has been previously investigated to conjugate with gold nanoparticles (AuNPs) [13].

Hybrid iron oxide-gold nanoparticles (HNPs) (Figure 1) consist of an iron oxide core coated by a rigid gold shell, which can undergo manipulation via external stimulus because of the inherent magnetic nature of the iron oxide core [14]. The multifunctional nature of these particles means they can be imaged by magnetic resonance imaging (MRI) due to the presence of iron core, whilst the biocompatible gold shell possesses drug carrier capability. As a result, these particles can be exploited as a precise therapy with decreased side effects.

Previously, HNPs have been demonstrated as effective carriers for the delivery of chemotherapeutic agents in pancreatic cancer cells [15]. In this study, the cytotoxic chemical, 6-thioguanine (6-TG) was conjugated directly onto the surface of HNPs by dative covalent linkage between the thiol (-SH) group present in the drug chemical structure and the gold surface. The IC50 value (half maximal cytotoxic concentration) for the treated human pancreatic adenocarcinoma cells (BxPC-3) with the novel formulation was reduced 10-fold in comparison with the free drug. Drug uptake investigations have revealed that after drug conjugation to the surface of HNPs, intracellular concentrations of 6-TG were increased compared with the free drug. These results emphasise the potential of HNPs to deliver chemotherapeutic cargo with enhanced cellular internalisation and higher drug efficiency [15].

The common concern in cancer chemotherapy is the systemic administration of various cytotoxic agents without tumour specificity as drug also affects healthy tissues. This results in various side effects, which may limit their therapeutic applications.

Cyt c is a protein with high molecular weight (12.7 kDa), which makes it hard to internalise into cells. This drug is fairly unstable, which means that it is an unfavourable candidate from a pharmaceutical delivery perspective

[16]. Due to its size, it has difficultly crossing the lipid bilayer of the cell membrane. Hence, an efficient drug delivery system to deliver Cyt c into the cytoplasm is required. By conjugation of the molecule onto the surface of the HNP a multifunctional particle is developed, which demonstrates drug delivery potentials as well as offering imaging capability due to the presence of iron oxide. Moreover, an external magnetic field can be applied to direct HNPs to a preferred area. This allows the

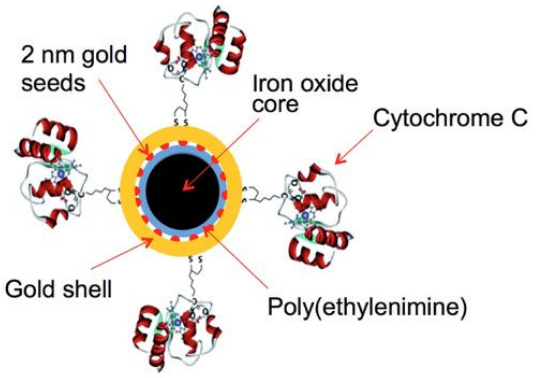

Figure 2. Schematic representation of hybrid Fe_3O_4-Au nanoparticle, in conjugation with cytochrome C.

particles to accumulate significantly more in the desired area, which highly decreases the systemic effects on normal tissues.

Cyt c as a pro-apoptotic protein can be administered to complement chemotherapeutic agents and thus increase their effect. The simultaneous administration of proapoptotic proteins with chemotherapeutic agents may induce tumour cell death with lower dose and thus reduces the severity of side effects.

In our study, we showed that the co-administration of the clinically used anticancer agent Dox with Cyt c conjugated onto HNPs (Figure 2). The novel formulations were evaluated in hepatocellular carcinoma cell line (HepG2) to show the additive pharmacological action and measure the alteration of IC_{50} value of Dox co-administered with conjugated Cyt c with HNPs (HNPc) in HepG2 cell line.

The particles were internalised by the HepG2 cells possibly through endocytosis. The levels of the Cyt c were monitored and the data showed that the hybrid formulations were internalised into HepG2 cells and gave significantly higher than the free drug. The intracellular concentration of Cyt c, released from hybrid formulations was threefold higher when conjugated to the HNP when compared to the free protein.

Dox alone induced a noticeable decrease in cell viability on HepG2 cells, as verified by MTT and tryptan blue cytotoxicity assays. Interestingly, when Dox was co-administered with HNP-c, there was a significant decrease in cell viability, determined by both cytotoxicity tests.

To conclude, this study shows the interesting potential of HNPs to act as drug carriers. By attaching Cyt c to the surface of HNP, this protein can enter to the HepG2 cell more easily, which was fairly impossible for the free drug. Moreover, combination of Dox with our novel formulation was considered ideal to be used as the results demonstrated a significant reduction of the IC_{50} of Dox in the combination with HNP-c. This combination is worth considering for HCC treatment as no effective chemotherapy is available for this type of cancer. Further research is ongoing in our laboratory to increase the efficacy and optimize the use of Cyt c nanoparticle drug delivery system.

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How are drugs named?

by Suzanne Koven

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One summer in college, when I couldn't think of what else to do, I held down three boring jobs, and took intensive Latin. Every morning we met in a blissfully air-conditioned classroom – that was the upside! – to conjugate and decline: a whole year of Latin in 6 weeks. I remember nothing I learned, of course. I'm reminded of the great Woody Allen line: "I took a speed-reading course and read War and Peace in twenty minutes. It involves Russia." I do remember one thing I learned, though, which is that manufacturers often turn to the classics when naming products – including medications.

My Latin teacher was a young instructor who mentioned that he was supplementing his meagre academic income by moonlighting with a marketing firm. His job was to use his knowledge of Latin and Greek to think up names for medications and other goods. "We want something like 'Xerox'!" he told us the marketing firm told him. "Like 'Xerox'!" (Xero is the Greek root meaning "dry"– xerostomia is the medical term for dry mouth – and so "Xerox" emphasized that this particular photocopy method didn't involve wet ink, as anyone old enough to remember those sticky purple mimeographed sheets they used to hand out in school will appreciate...)

But I digress. Every drug has at least three names. First, there's the chemical name, then there's the generic name, and then there is a brand name (sometimes more than one, if it's produced by more than one company). For example, a commonly used diuretic's chemical name is 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid, its generic name is furosemide and its brand name is Lasix.

Brand names and, to a lesser extent, generic names, are chosen with great care and often at great expense. Often, as I mentioned, Latin (or, less frequently, Greek) roots are chosen to enforce, even if only subliminally, our association with the drug. Some examples:

Paxil: an antidepressant and anti-anxiety drug (Pax=peace in Latin)

Lunesta: a sleeping medication (Luna=moon in Latin)

Viagra: a medication for erectile dysfunction (Vi[r]= man in Latin and Agra=field, usually farmed or fertile in Latin and Greek)

Fosamax: a drug for osteoporosis, or bone thinning (Os=bone Max=great in Latin)

Sometimes, drug names are chosen because of the meaning their sounds imply. For example, several drugs that regulate heart rhythm end in the suffix -olol (propranolol, atenolol, nadolol) – those two echoed syllables mimicking the beating heart. The letters "X," "Z," "N," "Q," and "K" connote cutting edge science, which the makers of Zantac, Nexium, and Protonix (all medicines for acid reflux) wish to convey. "S." "M," "V," "L" and "R" are "soft" letters, which the names of drugs for women are likely to include. Examples are Sarafem (for pre-menstrual syndrome) and Provera and Vivelle (hormone replacements). Many birth control pills employ these letters and sort of sound like women's first names: Junel, Alesse, Apri, Mircette, Yasmin, etc. Medications marketed to men are more likely to contain a "hard" sound like "T," "G," "K" or "X" – like Flomax for enlarged prostate or Levitra, for erectile dysfunction. An exception is Cialis, also for ED and with only soft syllables but with a meaningful classical root (cael=sky in Latin, also connoting "up" or "above," as in "ceiling."). Even when drugs have randomly chosen names, the companies that make them seek assistance. There's actually a website with a program, Drug-o-Matic , that generates names for pharmaceuticals.

But the frequent use of certain classical roots ("Pro," "Uni," "Vi," etc.) and of certain high tech sounding letters ("X" and "Z," especially) has led to the problem of drugs that sound alike and can be easily confused. Up to 15% of errors in drug administration are caused by the similarity of drug names, such as Celebrex (for arthritis) and Celexa (for depression) or Zocor (for high cholesterol) and Zoloft (for depression or anxiety) or Lamisil (an anti fungal) and Lamictal (an anticonvulsant and mood stabilizer). Many hospitals have initiated systems to flag such drugs.

So, it turns out that some of the effects drugs have on us occur even before we open the bottle – or so pharmaceutical companies would have it.

Formulation development of novel abuse deterrents

Jenifer Mains, Wei Tian, Alyn McNaughton and Stephen Brown

Illicit drug misuse remains a challenging public health problem, with approximately 8.2% of adults aged sixteen to fifty nine in England and Wales reporting use of an illicit drug within the last twelve months in 2013[1]. Prescription drug misuse, for non-medical reasons, can be difficult to prevent, with around 2.5% of people in the USA above the age of twelve reporting prescription drug misuse within the last month[2]. The supply of such medicines can vary, with reports of drug acquirement from a relative or friend, GP prescription, purchased from a drug dealer or purchased over the internet. Prescription drug abuse is not only confined to the use of opioids but extends to compounds such as amphetamines, benzodiazepines, barbiturates and hormonal compounds. As a result of this problem, research and development has moved towards the investigation and design of formulations of such compounds, which offer abuse deterrence properties in an attempt to reduce the incidence of prescription medicine misuse. This change in focus in development interests has led to the generation and publication of the FDA Abuse-Deterrent Opioids – Evaluation and Labelling Guidance for Industry[3]. The FDA regard prescription drug misuse as a public health crisis and have commented that they will encourage the development of opioid compounds which offer abuse deterrent properties. The guidance for industry currently focuses on opioid compounds only and details recommendations for the developmental programme study design. The suggested studies, to be performed prior to marketing, include laboratory based manipulation and extraction studies. In this instance the investigator should manipulate the formulation using methods typically available to abusers and using an understanding of the physicochemical properties of the active pharmaceutical ingredient (API), in order to demonstrate the abuse deterrent nature of the product. If successful, the investigator should then go on to characterise the pharmacokinetic (PK) performance of the product on administration via the intended route. Once the PK data is obtained, a clinical abuse study via a randomised, double blind, placebo controlled and positive controlled crossover study may be suggested. In this case experienced recreational drug abusers are the recommended user population to assess the abuse deterrence properties of the designed formulation.

Laboratory based manipulation and extraction studies should be based on the potential routes of abuse for the specific compound under investigation. The

abuse potential of a particular product is dependent on the physicochemical properties of the drug, the strength, dosage form type, formulation composition and known routes of misuse. Prescription medicines are typically abused through injection, insufflation or modification of the oral administration route. Liquid formulations of compounds liable to abuse can be directly injected and if the compound is not suitable for direct injection, the abuser can extract the API using solvents and inject the resultant solution. If injection is not desirable, formulations can also be abused through the nasal route. In this instance the formulation will be crushed until a desirable particle size is achieved and the resultant powder will be administered via the nasal cavity. As well as these commonly associated routes of drug misuse, dosage forms can also be abused through oral drug delivery. The effect of controlled or extended release formulations especially those utilising functional coating can, in some cases, be overcome by chewing or grinding the formulation prior to swallowing. In addition, extraction of API from extended release formulations, to ensure immediate release of the API (known as dose dumping) can be facilitated by solvent extraction prior to administration, or in some cases through co-administration will alcohol. The pharmacokinetic profile of the product can vary as a result of manipulation. As part of a development study characterisation tools like the abuse quotient of the product may be determined using PK data ; this is based on the theory that products with a short T_{max} and high C_{max} are more desirable to achieve a euphoric effect (Figure 1). If a formulation can prevent manipulation enabling dose dumping to generate short T_{max} and high C_{max} and maintain its target profile, it may be less liable to abuse. Based on the API physicochemical properties and routes of misuse, various laboratory investigations can be performed to characterise the abuse potential of the formulation. Commonly investigated in-vitro assessments can include assessment of particle size reduction using household tools, syringe-ability and inject-ability, using a small volume of water and assessing the mass ejected from a syringe equipped with a needle, vaporization, by heating the formulation to assess the concentration of drug available for inhalation and formulation dissolution, in the presence of ethanol[4].

The development of abuse deterrence formulations can be divided into two main strategies; chemical or physical design barriers to prevent API misuse. Chemical barriers include the use of antagonist/agonist combinations, aversive agents such as mucosal irritants or the use of a prodrug. Whereas, physical barriers form part of the formulation design and create a physical obstacle preventing dosage form manipulation to release the API.

An example of an antagonist/agonist combination to provide a chemical barrier includes the developed Elite technology, wherein an opioid antagonist, such as naloxone, is coated onto an inert pellet, with a non-releasing membrane surrounding the antagonist[5]. The therapeutic opioid agonist is then applied on top of this layer. Release of the antagonist will not occur on swallowing however, in the event of dosage form manipulation, by crushing, for attempted intravenous (IV) administration, the antagonist is released and diminishes the effect of the agonist. Following on from an antagonist means of abuse deterrence, compounds which induce a detrimental physical effect on the body have also been developed. Aversion® technologies include the use of an aversive agent within formulations in order to prevent abuse. In this case niacin, water soluble vitamin B3, is formulated into a nanoparticle for delivery with the API, at concentrations which cause no physical effect if the formulation is administrated within the recommended therapeutic dosing regimen[6]. If this medicinal product is administrated at greater levels than intended, the abuser will experience niacin induced flushing. Formulations with of this type with co-administration of an undesirable compound may require complex ethical considerations and may not be as suitable as other means of minimising abuse. Taking chemical means of abuse prevention one step further, an amphetamine prodrug has also been developed in an attempt to minimise abuse. In this instance amphetamine is covalently bound, to form the prodrug homoarginine amphetamine for enzymatic conversion to amphetamine in-situ[7]. It is claimed at high levels of administration, outside the therapeutic window of the API, the prodrug will be excreted intact. In addition, if the abuse attempts to administer this dosage form via an alternative route such as IV or intranasal administration, manipulation of the dosage form will not breakdown the prodrug to an appreciable extent and the abuser will not achieve the desired effect.

Physical barriers focus on modification of formulation composition in order to prevent misuse. Examples of this type of system include crush resistant tablets, tamper resistant beads and high viscosity formulation matrices. Crush resistant tablets have been developed using a polyethylene oxide (PEO) polymer matrix to deliver the opioid tapentadol over an extended release timeframe[8]. The matrix was designed in order to prevent the tablet being crushed to facilitate subsequent API extraction. The abuse deterrent nature of the formulation was assessed

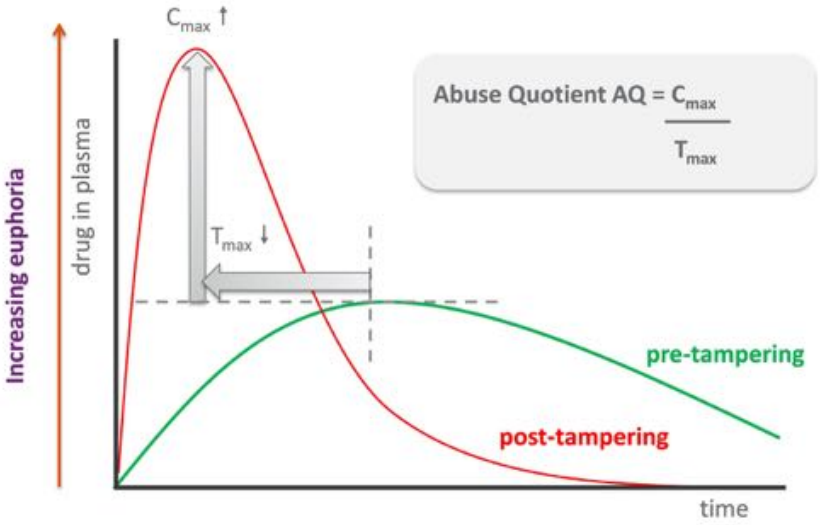

Figure 1. Change in drug profile with tampering and calculation of abuse quotient based on pharmacokinetic data.

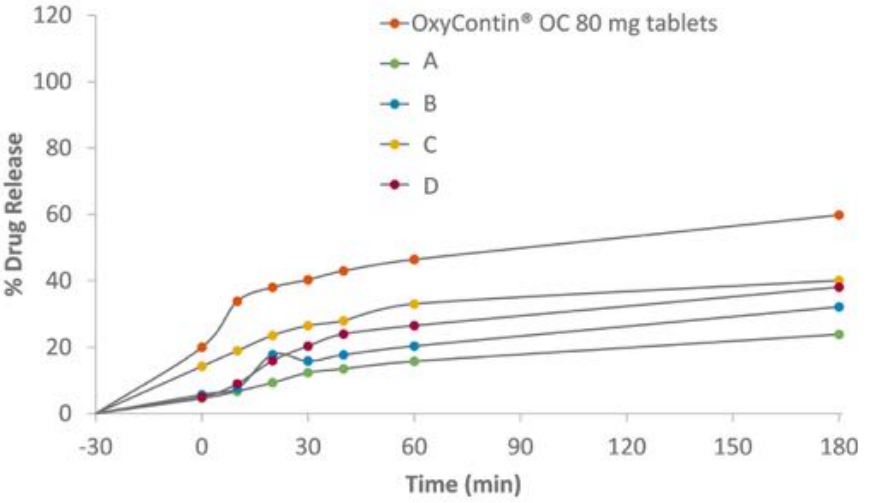

Figure 2. Release profiles of oxycodone for Intact dosage forms assessed following 30 min in acid, then 30 min in ethanol.

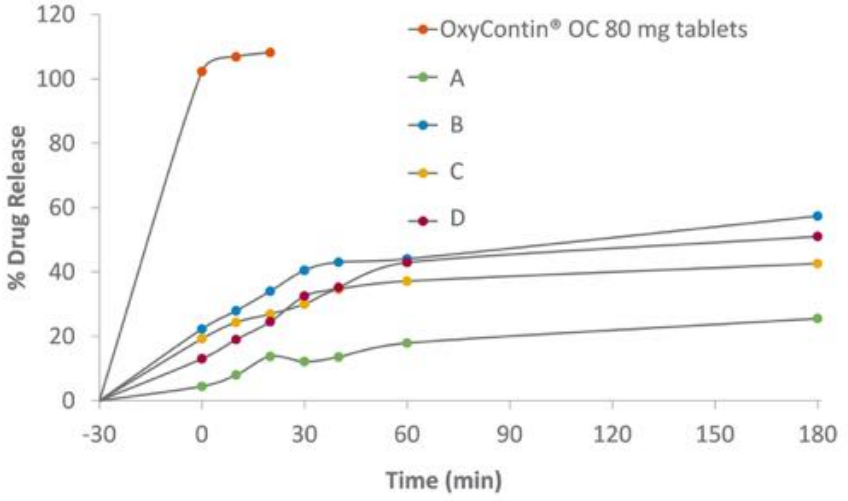

Figure 3. Release profiles of oxycodone for Intact dosage forms assessed following 30 min in acid, then 30 min in ethanol.

Table 1. Levorphanol pharmacokinetic crossover study of ER abuse deterrent formulations (A-D) vs. IR levorphanol. *Ratio to IR formulation (%)

PK Parameter	LFHC Test Formulations vs. Immediate Release RLD				
	IR Levorphanol	Formulation A	Formulation B	Formulation C	Formulation D
T_{max} (hr)	2.4	10.36	12.29	9.15	11.53
C_{max}*	100	40.89	29.97	32.01	26.66
AUC_{inf}*	100	99.27	92.98	86.99	82.16
% decrease in AQ from IR formulation		90.6	95.2	91.6	94.5

in-vitro and demonstrated that on physical breaking, capsules remained intact with slight deformation, although there was a slight increase in in vitro release recorded (30% within 30 min of assessment)[8]. Following on from this formulation type, tamper resistant microparticles (DETER®) have also been designed to minimise the abuse potential of APIs commonly prone to abuse. In this instance a salt of the API is formed with fatty acids, in order to increase the lipophilicity of the drug. The resultant drug is then combined with a water insoluble excipient to form a homogenous matrix[9]. The abuse potential of the API in this case, is limited by resistance to change in release profile to immediate release through physical particle size reduction and prevention of dose dumping. Similarly high viscosity excipient matrices with high melting points have been designed to prevent dosage form manipulation[10]. These formulations are highly viscous, therefore cannot be injected, are difficult to powder so cannot be snorted and are difficult to extract using solvent systems. The use of liquid filled hard capsule (LFHC) shells for delivery of these formulations enable these high viscosity materials to be filled at high temperature, where material flow is enabled. In addition, using this technology immediate release (IR) and extended release formulations (ER) can be developed. For in-vitro extraction assessments, four formulations designed using this technology

were filled into hard gelatin capsules and were assessed in comparison to Oxycontin OC 8 mg tablets. Each of the dosage forms were placed intact in 0.1N hydrochloric acid and agitated at 240 rpm in an orbital shaker for 30 min, followed by addition of 95% ethanol and continued agitation in the orbital shaker (Figure 2). This was then repeated for dosage forms following crushing prior to assessment (Figure 3). For the OxyContin® tablet formulation, crushing resulted in immediate extraction in ethanol, whereas extraction in ethanol was limited for the abuse deterrent formulations A, B, C and D following crushing of the capsules. Similarly this technology has been used to develop extended release formulations of levorphanol and these formulations have been compared to an IR levorphanol product in-vivo[11]. Four prototype abuse deterrent dosage forms of levorphanol ER (A, B, C and D) were tested in an analytically masked, fasted, single-dose five-way crossover bioavailability study vs. IR levorphanol. Fifteen healthy non-smoking subjects aged 18-45 were assigned to each treatment period, with a seven to fourteen day washout between treatments (Table 1). The developed formulations demonstrated prolonged T_{max} with reduced C_{max}, in comparison to the IR product, whilst maintaining drug exposure (AUC). This resulted in a decrease in abuse quotient (AQ) in the range of 90.6% to 95.2% in comparison to the IR product, across all four formulations investigated, making the formulations less desirable to a misuser.

On completion of a successful development program and demonstration of formulation efficacy and abuse deterrent properties, according to the FDA guidance, the ability of such formulations to reduce rates of abuse in society requires investigation post marketing. One such substance which has been formulated into an abuse deterrent formulation, and assessed for rates of abuse, is a formulation of oxycodone. Oxycodone extended release was reformulated in 2010, in order to reduce the abuse potential of this drug. Abuse patterns of the reformulated oxycodone were assessed in individuals deemed to have substance abuse problems, in comparison to the abuse of the original oxycodone formulation, not designed to deter abuse[12]. The oral abuse of the reformulated product was reported to be 41% lower than the original formulation, similarly the non-oral abuse of the reformulated product was 66% lower than for the original oxycodone formulation. This was confirmed in a second study where participants were interviews with regards to their levels of abuse of reformulated extended release oxycodone and the original extended release formulation. Abuse rates for both formulations via any route was characterised and for the original formulation was 74%, whereas the abuse deterrent formulation was reported as 33% [13]. Both studies demonstrate the ability to combat prescription drug abuse, by making dosage forms more challenging to abuse.

Prescription drug misuse remains a challenging public health problem. In order to reduce prescription drug misuse, the substances liable to misuse and the methods and route by which these substances are misused requires understanding. Formulation development can help to combat this problem, through the use of chemical and physical design strategies, to deter misuse of the medicinal product. Characterisation of the abuse deterrent nature of the developed formulations is required to assess the practicality of abusing the formulations and the prevalence of product abuse should be assessed post marketing, to demonstrate that there is a reduction in the rate of abuse with the abuse deterrent formulation when compared with the conventional product.

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That's about the size of it!

Since liposomes were first discovered back in the 60s, a race has been taking place to find the perfect method of reducing their size into the nanometre range and the ultimate holy grail of less than 100 nm. Four main strategies have been investigated; sonication (probe and bath), high shear mixing, extrusion and microfluidics. Each has their own strengths and weaknesses, and each has been shown to reduce the size of at least certain liposome formulations to the size required. Sonication, particularly probe, is seen as a simple, long-established method that is inexpensive. However, it is plagued with issues around contamination and lipid degradation. While bath sonication alleviates many of these issues, it can be slow and limited in its scope of lipids. Extrusion is a good solid method, with good polydispersity and an ability to really get the right size, but suffers with the higher transition temperature lipids, contamination and labour intensive, especially with the smaller extruders. High shear mixing has great scale-up capacity, and can be done relatively quickly, but is limited in the lipids it can reduce, and has never really taken off within the research community compared to the drug industry. Microfluidics has high scalability and has high throughput potential, but because of the bottom up method, the polydispersity of the liposomes can be greater, and there can be trace amounts of ethanol contamination. Each of these techniques has been used in research at one time or another and the number of papers reported for each strategy is presented in Fig. 1.

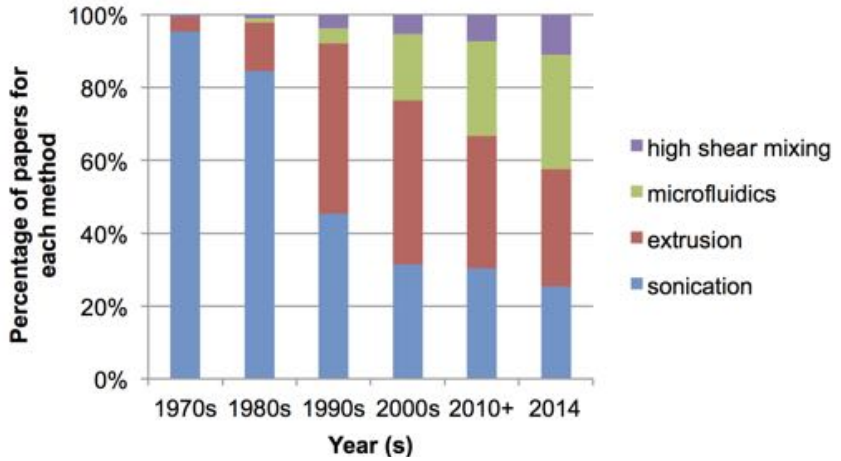

Figure 1: *The number of hits for each technique coupled with the word liposome and inputted into web of science for each decade since 1970.*

Back in the 1970s, the preferred technique was sonication. Shortly after, extrusion came along, offering greater benefits such as a better polydispersity and reduced degradation to the lipids. Then, in the 1990s, microfluidics entered the scene. Since then it has been a battle between these three techniques, each with their own merits and issues. High shear mixing has generally been used less, particularly within research, but is still an important part of the mix.

In 2014, 16 papers reported high shear mixing for preparation of liposomes, 37 sonication, 46 microfluidics, and 47 for extrusion. These numbers show us that it still really is a three horse race between microfluidics, extrusion and sonication. But how could this play out over the next few years? As the graph shows, there has been a steady decline in the number of papers using sonication and more recently, extrusion. Whether this decline continues is not certaint, but if it does, then it is certain that microfluidics will continue to grow in popularity. However, what is possible is that another technique may come along, like microfluidics did back in the 90s, and grow and take over. Could bath sonication possibly take over from probe as the go-to method for sonication of liposomes? Could methods be combined such as sonication and microfluidics to create even better liposomes? As more is done within the liposome formulation field, it is certain that current techniques will get better, new techniques will come along, and that liposome formulation will continue to be a force within the drug delivery system world.

by Peter Stone, Aston University


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Fixed dose combination drug products: are we entering a new era of drug cocktails?

Shu Li, Queens University Belfast

Non-communicable diseases (NCDs), also know as chronic diseases, are major causes of morbidity and mortality globally, responsible for 38 million (68%) of the world's 56 million deaths in 2012 alone[1–3]. A large proportion of deaths caused by NCDs are reported to occur before the age of 60, during the most productive period of life[4]. Cardiovascular diseases (CVD) are at the forefront, accounting for most NCD fatalities, with more than 2150 deaths attributable to CVD each day, an average of 1 death every 40 seconds in the United States[5], around 160,000 deaths each year in the UK or, 17.5 million people annually worldwide. Other major causes of mortality include cancers, chronic respiratory diseases and diabetes, responsible for 8.2, 4.0 and, 1.5 million deaths annually, respectively. Together with CVD, these four groups of conditions/diseases account for 82% of all NCD deaths.

The treatment of these illnesses often includes long-term polypharmacy with multiple agents prescribed simultaneously in complex regimens. During the course of such therapies, poor patient compliance is considered a significant issue in preventing successful treatment and management[6,7] In fact, it has been reported that patient adherence during chronic disease treatment is typically sub-optimal with only 50% of patients being compliant following year 1 of therapy, and this figure falls to merely 15% in year 2[8–10]. Failure to adhere to complex dosing regimes has been shown to lead to serious complications including development of drug resistance, occurrence of adverse health outcomes, worsening of disease, decreased quality of life, increased mortality rates, and in almost all cases, an increase in healthcare expenditure8. Undoubtedly, the cause of poor adherence is multifactorial, however it is well accepted that substantial improvements are achievable through reduction of pill burden and dosing frequency[11–13]. A fixed-dose combination (FDC) product is, to some extent, like a drug cocktail with two or more active pharmaceutical ingredients (API) formulated at certain respective fixed ratios in a single dosage. FDCs have been extensively used in almost all therapeutic areas for more than a half-century with many products commercially available. There is an abundance of literature demonstrating the benefit of using FDCs as an approach to simplify complex dosing regimens and hence increase patient adherence through reduced dosing burden[13–16]. The vast majority of marketed FDC products are administered orally, whilst other dosage forms including inhalation, vaginal and topical formulations also being available.

Since their conception, FDCs have had a turbulent ride wherein drug combinations have often been combined principally for marketing purposes and without sufficient evidence of improved clinical efficacy[17]. Interestingly, over the last decade there has been a renaissance of FDCs, principally driven by the poor compliance associated with the complex therapies required to manage the increasing number of patients suffering from chronic diseases. Whilst there still remains significant controversy surrounding the clinical advantage of FDCs, the majority of drug regulatory agencies are actively progressing FDCs and have established corresponding guidelines for industry. Moreover, FDCs also offer benefits such as improved sustainability of current pipelines, decreased sum of dispensing fees, and simplified logistics of distribution.

FDCs are complex drug delivery systems containing two or more drugs. Additionally these dosage forms may also contain different layers designed to provide a variety of drug release profiles. Consequently, formulation design and process development associated with FDCs may be more complicated and challenging than that for equivalent

single drug products. Several factors must be considered including drug-drug compatibility, drug excipient compatibility, disproportionate dose of drugs, requirement for different release kinetics, and oversized dosage forms as a result of high dose strength (>1000~1500mg)[14]. Undoubtedly all of these factors interrelate in a complex manner that will affect formulation design and choice of manufacturing method. For example, an artesunate/amodiaquine FDC, used in the treatment of malaria, shows incompatibility between the two active agents. In such cases, physically separated drug layers should be developed rather than a monolithic FDC[18]. With respect to oral drug delivery systems, suitable designs for such systems may include multi-layered tablets, compression-coated tablets, multiparticulates in capsules, combinations of coated and uncoated beads, and pellets of one drug placed within a powder of the second active[19]. For FDCs showing extreme disproportionate dose strength, i.e. a glimepiride/metformin combination (type II diabetes treatment) with a weight ratio of 3/500mg, an active film coating of the low dose agent and a core of the high dose agent may be optimal[20]. Development of different release kinetics may be easily achieved via physical separation of both drugs, embedding them in layers capable of providing different release profiles[21,22]. Traditional methods employed to manufacture the aforementioned formulations are rather complex with multiple staged operations such as granulation followed by compression using specifically designed multilayer tableting tools, or preparation of beads or pellets using extrusion spheronisation followed by layering using a coating process. By comparison, multilayer co-extrusion, a processing method commonly utilised in the polymer and food industry (i.e. plastic packaging, multi-layered tubing, chocolate core cereals and filled hard candy) with a single-step operation, may provide the needed paradigm shift in FDC manufacture. Moreover, by incorporating different active drugs into separated layers allows increased space for formulation design and accurate control over the release pattern of each individual drug.

It is, however, important to note that co-extruding pharmaceutical formulations is by no means an easy task, with issues principally relating to flow instability including interfacial instability, melt fracture and or layer heterogeneity. In fact, the technique is relatively new in relation to oral drug product manufacture in the pharmaceutical industry. Given that this is a non-ambient process, the likelihood of drug degradation or drug-drug interaction may also be increased. However, many articles have been published detailing potential solutions to such problems. Moreover, as a versatile technique capable of producing a wide range of differently structured layers in a solvent-free and continuous fashion, multilayer co-extrusion complies comfortably with the evolving view of pharmaceutical manufacture and is gaining increasing interest in the last decade with a number of studies published in developing co-extruded oral use FDCs[24–26]. With the potential of simplified manufacturing, expanded pipeline capacity and, improved dosage form versatility,HME co-extrusion now sits well positioned to provide a robust and convenient method for FDC product manufacture. As previously described chronic diseases including cardiovascular disease, retroviral infections, cancers, chronic respiratory diseases and diabetes are now primarily responsible for premature death, globally. The renaissance of 'Drug cocktails' represent a new and exciting era that may just provide a much-needed solution to a significant number of global health issues revolving around long-term therapies. These include inadequate prescription of medication, poor adherence to treatment, and expensive fees for multiple dispensing in polypharmacy. With 'easier to count and easier to take' FDC products, manufactured using new technologies that, that tackle global health issues, are rapidly gaining interest.

Shu Li is a postdoctoral research fellow supervised by Prof. Gavin Andrews in the Pharmaceutical Engineering Group at the School of Pharmacy, Queen's University Belfast. Shu Li is currently employed on a project aimed at developing fixed dose combinations using advanced engineering technologies.

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Neglecting the Stratum Corneum

The Need for Analytical Advancements to Monitor Skin Permeation

Nichola Starr

Transdermal delivery offers several key advantages over other administration routes such as oral and hypodermic injections. However, the number of approved drugs which utilise this technology is very limited, with less than 20 reaching the market by 2010 [1] Transdermal delivery offers the potential to avoid hepatic first pass metabolism and the GI tract, which are limiting factors for bioavailability and cause the failure of many potentially efficacious compounds. A transdermal patch allows administration of a continuous dose, avoiding the variations in plasma concentration associated with other dosage forms. In general, transdermal delivery systems are inexpensive, non-invasive and pain free, offering patients a convenient method of drug delivery that can be self-administered if needed, resulting in high patient compliance.

Technological advancements in transdermal drug delivery systems have seen this route of administration rapidly increase in popularity over the last two decades. First generation systems involve the use of a transdermal patch or particular topical formulation to drive the transport of drug compounds across the skin. Improvements in patch technology have seen an increase in these systems reaching the market. However, they are only successful for a narrow range of compounds with the correct properties. Second generation systems involve the inclusion of a skin permeation enhancer, which causes disruption to the stratum corneum structure, such as chemical enhancers and iontophoresis. The limitation to the wider use of these systems is that they can often result in skin irritation and damage to deeper living skin tissue. A third exciting generation of systems are now emerging which use advanced technologies, such as microneedles, to specifically target the stratum corneum, enhancing permeation whilst minimising adverse effects by localising barrier disruption. It is important to realise that the development of transdermal delivery systems hugely relies on comprehensive knowledge about stratum corneum permeation, yet the indus-

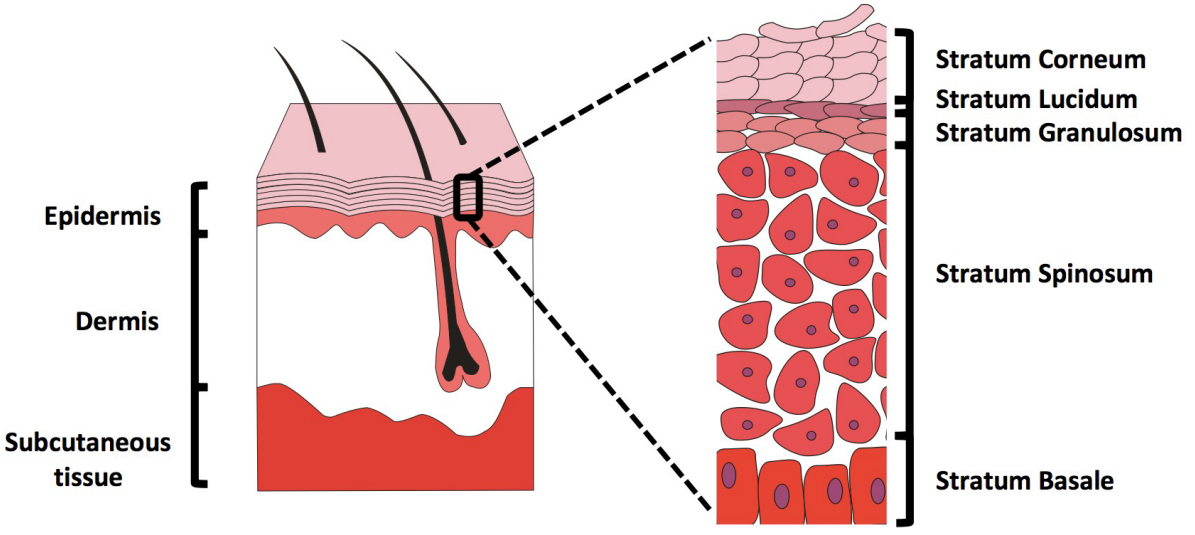

Figure 1. A schematic showing the three main layers of the skin and highlighting the five subsections of the epidermis.

Nichola Starr is a PhD student in the Department of Pharmacy, University of Nottingham

trial standard for monitoring skin permeation provides limited information on this [1,2,3].

THE EMERGENCE OF COSMECEUTICALS

Delivery of compounds through the stratum corneum is a problem which is now affecting the cosmetic industry as well as the pharmaceutical industry, with the emergence of "cosmeceutical" topical products. While this term is not recognised by the European or US regulatory bodies, it is being used by the cosmetic industry to describe certain products which claim to have positive physiological effects, such as retinoid based creams marketed as anti-wrinkle products. Topical cosmeceutical products, unlike pharmaceuticals, are not intended to be delivered to systemic circulation via the transdermal route, but instead should have a localised effect within the viable epidermis. These systems still, however, face the same challenges in order to pass the stratum corneum. More importantly, as they are still classed legally as cosmetic products they do not require the same regulation as pharmaceuticals and therefore their mechanism of action is less explored and often unknown. More detailed analysis regarding not only their mechanism of action but also their permeation profile and metabolism within the skin would allow for significant improvements in this class of products [4,5].

THE BODY FIGHTS BACK

As described above the potential of both transdermal delivery systems and topically applied cosmeceuticals is largely restricted by the efficiency of the main barrier to the body, the stratum corneum. This tissue provides a simple yet very effective barrier, consisting primarily of terminally differentiated keratinocytes, termed corneocytes, embedded in an intercellular lipid matrix.

Permeation across this tissue can occur via a transcellular, intercellular or follicular route. As hair follicles occupy less than 0.1% of the skin surface this is not a route commonly targeted. The transcellular pathway is the shortest route. However, it involves difficult penetration of the keratin containing corneocytes and multiple transfers between the lipophilic matrix and the more hydrophilic corneocyte cells, making this pathway unfavourable for most molecules. The intercellular is therefore the most preferred permeation pathway, yet this also presents problems. Due to the amphiphilic nature of the lipid matrix this pathway also contains both lipophilic and hydrophilic regions and, despite the stratum corneum being only 20 µm thick, the intercellular pathway is estimated to be around 500 µm in length. It is therefore not surprising that few molecules are able to easily penetrate this tissue [2,6,7].

Despite the stratum corneum proving to be the limiting factor for permeation, the industrial standard for testing potential topical products provides only basic information regarding permeation through this tissue. The Franz cell experiment monitors the concentration of a compound that has penetrated through ex vivo skin tissue which has typically been heat separated or dermatomed to a predetermined thickness. The concentration of permeated compound is determined by chromatographic mass spectrometry analysis, such as HPLC-MS. The stratum corneum is then removed using a tape stripping sampling method and the strips are pooled, dissolved and analysed by the same method to determine the concentration that has resided within the stratum corneum. Therefore, although this model can be used to determine the extent of permeation across the stratum corneum it provides no in depth analysis on an individual layer by layer basis.

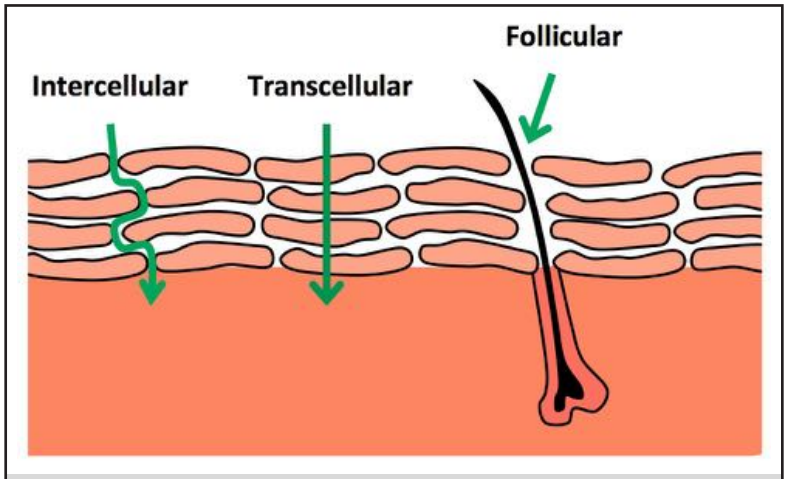

Figure 2. A schematic showing the three main permeation pathways through the stratum corneum.

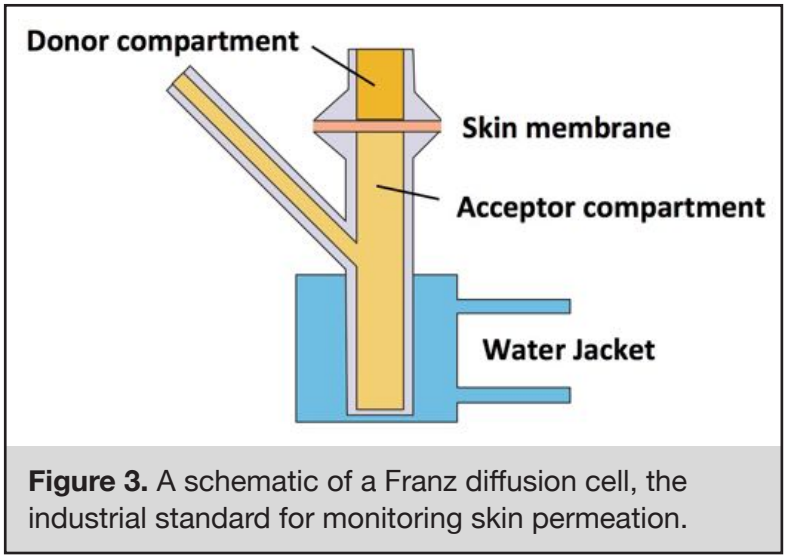

Figure 3. A schematic of a Franz diffusion cell, the industrial standard for monitoring skin permeation.

EMERGING ANALYTICAL TECHNIQUES

A great need therefore exists for the development of advanced analytical methods to monitor skin permeation on a more in-depth level, in

order to support a surge in both transdermal delivery system developments and modern cosmeceutical products. This has been recognised by several groups already, who have shown the potential use of various techniques to enable a more detailed analysis of drug permeation through the stratum corneum. Of particular importance are emerging techniques that have the potential to monitor this tissue in vivo. Confocal Raman spectroscopy is a popular technique and numerous groups have demonstrated its ability to conduct depth analysis in vivo directly from human volunteers. [8-12] Whereas others have instead combined the use of tape stripping with a surface analysis technique, showing initial data to support the use of techniques such as ToF-SIMS [13] (Time of Flight Secondary Ion Mass Spectrometry) and EDX [14] (Energy Dispersive X-ray). Tape stripping is a sampling method which can easily be applied to collect human stratum corneum in vivo, allowing layer by layer analysis when coupled with surface analysis.

CONCLUSION

It is apparent therefore that steps are being made towards the development of new analytical techniques to study permeation through this important tissue. However, these are still very recent and further advancement is needed in order to solidify their advantages over traditionally used methods and enable their widespread use.

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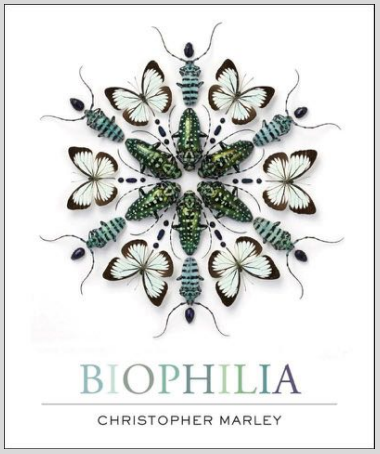
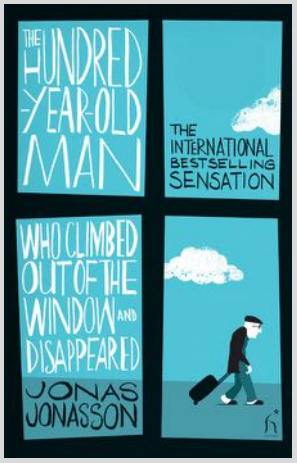
THE BOOK NOOK



Biophilia
by Christopher Marley

Biophilia means "love of nature." The word was invented by evolutionary biologist E.O. Wilson, who believes that biophilia is a deep human instinct. Artist Christopher Marley is a biophiliac, and his art expresses his passionate engagement with the beautiful forms of nature. Beginning with insects, and moving on to aquatic life, reptiles, birds, plants, and minerals, Marley has used his skills as a designer, taxidermist, and environmentally responsible collector to make images that produce strong, positive emotional responses in viewers. Marley has a brilliant eye for colour and pattern in animals, plants, and minerals, and he captures deep relationships between different natural objects. Marley's book will have strong appeal not only to nature lovers, but to designers, artists, craftspeople, and anyone looking for visual inspiration in the arts.

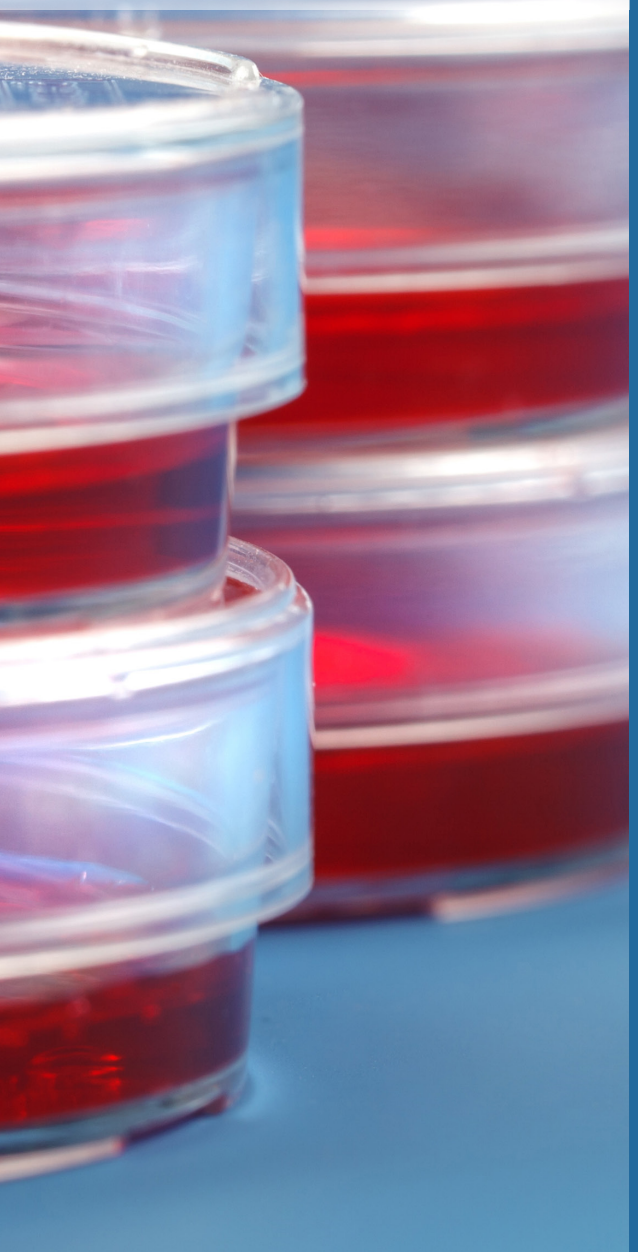


The 100 year old man who climbed out the window and disappeared
by Jonas Jonasson

It all starts on the one-hundredth birthday of Allan Karlsson. Sitting quietly in his room in an old people's home, he is waiting for the party he-never-wanted-anyway to begin. The mayor is going to be there. The press is going to be there. But, as it turns out, Allan is not ... Slowly but surely Allan climbs out of his bedroom window, into the flowerbed (in his slippers) and makes his getaway. And so begins his picaresque and unlikely journey involving criminals, several murders, a suitcase full of cash, and incompetent police. As his escapades unfold, we learn something of Allan's earlier life in which - remarkably - he helped to make the atom bomb, became friends with American presidents, Russian tyrants, and Chinese leaders, and was a participant behind the scenes in many key events of the twentieth century.

HYDROGELS

Smart biomaterials with multiple applications



by Francesca Citossi
University of Nottingham

Self-assembling low molecular weight hydrogels represent a fascinating group of smart biomaterials that gained an increasing success in the last decade because of several applications and advantages over the traditional polymeric-based hydrogels. Particularly, they are molecules with a molecular mass lower than 3000 Da, and can gel water in small amounts (0.1–5 wt%) by temperature, pH or enzyme-triggered methods. Self-assembly of these materials occurs via non-covalent physical forces, such as hydrogen bonds, van der Waals interactions and π-π stacking, to form structures such as fibres, tapes, rods and sheets in the nanometer range.[1]

Intense research has been recently carried out in different fields to mimic nature's ability to self-assemble into hierarchically and well-arranged functional materials. Amongst hydrogels' numerous applications, the most attractive ones involve their use as alternative 'smart' devices to the existing materials. Some examples include applications such as photoconductive materials, water purification agents, artificial scaffolds for cell adhesion/proliferation and drug delivery.

In the field of photoconductivity, perylene bisimides represent an interesting family of hydrogels with energy transfer properties (electron accepting). Their aromatic structure makes them ideal self-assembling molecules due to π-π stacking interactions that result in fibres formation, which allow the energy transfer through π-electron delocalisation. Roy et al. firstly described a perylene bisimides-amino acid conjugate which formed a pH-triggered hydrogel capable of photo-switching behaviour.[2] More recently, Zang et al. reported on the self-assembly of a water soluble perylene diimide compound into nanofibres. When exposed to vapours of an electron donor compound (a base), conductivity of hydrogels increased by two orders of magnitude, confirming their electron acceptor nature.[3] Adams and his group also found highly stable photoconductive perylene bisimides-based hydrogels. They reported on the correlation between the changes of hydrogel morphology and their photoconductive ability: the more organised the structure, the higher the photoconductivity.[4] All these results prove that these materials represent promising future hydrogel-based photodetectors and photovoltaics.

Another emerging application for hydrogels is as water purification agents. Banerjee et al. have been one of the first groups to describe the use of self-assembling Boc-protected tripeptides as absorbing agents for toxic organic dyes deriving, for example, from textile industrial wastes. Taking the advantage of the amphiphilic properties of these hydrogels, which combine a hydrophilic and a hydrophobic moiety, they demonstrated the gels ability to completely remove waste-water dyes, such as Rhodamine B, from aqueous solutions. Also, they managed to regenerate the original peptide hydrogels by changing the pH of the newly formed dye-hydrogels.[5] Hamley and Miravet also reported on the discovery of new hydrogels as water purification platforms. They synthesised compounds with two substituted aromatic groups linked by a urea or thiourea, which self-assemble in water at low concentrations by a pH-switch method. As in the previous study, they quantified the dye uptake (methylene blue). The results showed that all these hydrogels were able to absorb the dye from the aqueous solution.[6] More recently, Smith et al. reported on a new hydrogel, a dibenzylidene sorbitol derivative functionalised with a hydrazide, which proved to remove pollutant dyes, such as naphthol blue black. Results showed that this hydrogelator can absorb stoichiometric amounts of the dyes at different conditions of pH. Also, they managed to desorb the dyes from the hydrogels by changing the pH, thus proving the recycling properties of the gel.[7]

The field of tissue engineering represents another important hydrogel application. Indeed, this field has been extensively explored in the last 20 years as these materials can be used as 3D scaffolds for cells adhesion and proliferation. Almost all the examples of gels reported in the literature refer to peptide hydrogels because of their biocompatibility, easiness of

synthesis and mechanical properties. Most of the research focuses on peptide hydrogels as 3D scaffolds in tissue culture: Zhang, Stupp, Ulijn and Miller's groups are only few examples. Zhang et al pioneered these studies using long chain peptides (with 10 amino acids residues or more) for regenerative medicine and stem cell differentiation. For example, they developed a hydrogel peptide scaffold to encapsulate chondrocytes and showed the ability of these cells to differentially grow and synthesise extracellular matrix.[8] Stupp et al represent an important group that studies hydrogels applications in regenerative medicine. They used the self-assembling nanofibres obtained by the well-known adhesion ligand RGD (Arg-Gly-Asp) to produce 3D artificial matrices for cell signalling.[9] Very recently, they used self-assembling peptides to promote the proliferation and alignment of neurolemmocytes (Schwann cells) and demonstrated that these hydrogels can be a solution for treatment of peripheral nerve injuries.[10] Ulijn et al focused on the use of simple Fmoc-protected di- or tripeptide hydrogels as artificial extracellular matrices for dermal fibroblasts adhesion.[11] They also showed that substitution of the protecting group Fmoc with naphthalene or Cbz (benzyloxycarbonyl) on the dipeptide did not affect the ability of chondrocytes proliferation and adhesion.[12] Miller's group synthesised an octapeptide, based on the alternation of hydrophobic and hydrophilic amino acids, which showed self-assembling properties. They proved the hydrogel biocompatibility with bovine chondrocytes by evaluating cells viability, proliferation and collagen deposition under 2D and 3D cell cultures conditions for 21 days.[13] More recently, they introduced a new enzyme-trigged gelation method: a protease from Bacillus Thermoproteolyticus Rokko was used to produce a hydrogel in phosphate buffer based on the octapeptide previously reported. They developed a new method for encapsulating human fibroblasts in the hydrogel, showing proliferation of cells.[14]

In the last decade, self-assembling low molecular weight hydrogels also have emerged as alternative drug delivery platforms to the existing polymeric-based hydrogels. Indeed, they possess better properties in terms of drug loading, lack of toxicity and biodegradability compared to the traditional polymer systems. One of the most common strategies used for hydrogels as drug delivery systems is the chemical conjugation of a therapeutic compound via a covalent bond to a functional group that leads to formation of a self-assembling prodrug from which the active drug is released after hydrolysis or enzymatic degradation. From the most recent studies, examples of anti-inflammatory and anticancer hydrogels have been reported. Stupp et al. reported the synthesis of self-assembling naproxen-peptide conjugates, linked by an esterase sensitive linker, for controlled release of the anti-inflammatory drug. They proved that the hydrogel was able to release the active compound when incubated with an esterase enzyme, thus demonstrating the possible clinical applications for arthritis treatment.[15] Xu and Yang pioneered the synthesis of self-assembling paclitaxel prodrugs by conjugating the anticancer drug to different functional groups (e.g. peptides, folic acid): in all these cases, they showed a controlled release of paclitaxel from the hydrogel after incubation with phosphatase enzyme.[16] In one study, they also demonstrated the practical application of these gels in vivo, by locally injecting the gel in solid breast tumours: they showed the hydrogel's ability to inhibit tumour growth and prevent metastasis, thus proving the potential of therapeutic hydrogels for solid tumour treatment.[17]

All the examples reported above demonstrate the potential applications of this new emerging class of biomaterials and their properties in different fields, ranging from photoconductivity and water purification, to tissue engineering and drug delivery.

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Linking Industry and Academia in Teaching Pharmaceutical Development and Manufacture

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Linking Industry and Academia in Pharmaceutical Development and Manufacture (LIAT-Ph) is a two-year project funded by the Education, Audiovisual & Culture Executive Agency of the European Union under its Life Long Learning Programme - Knowledge Alliance.

The LIAT-Ph project commenced in September 2013 and seeks to address the learning needs of future industrial pharmacists (i.e. pharmacy students) and working industrial pharmacists, through the combined efforts of academia and pharmaceutical industry partners. Industrial pharmacists should be equipped to respond to the challenges of the rapidly changing environment in which they work; they should be capable of working as part of a multi-disciplinary team comprising pharmacists, chemists and engineers, as companies seek an increasingly more integrated approach to the product development cycle.

The consortium comprises five higher education institutions (HEIs) and seven pharmaceutical companies (of which six are small to medium enterprises – SMEs) and has specific expertise in the area of bio/pharmaceutical product development - this is the part of the drug product life cycle on which the LIAT-Ph project is focused.

In year one of the project, the LIAT-Ph consortium undertook a review of the undergraduate pharmacy curricula in the participant countries to determine what competencies are currently being achieved by graduate pharmacists and, if/where deficiencies exist in the current undergraduate curricula. Through a survey of industrialists we have identified which stage of education (undergraduate, postgraduate, continuing professional development) is most appropriate to develop various competencies relating to the industrial pharmacist. We have discussed how best to address the deficiencies which have been identified, and the HEIs have shared curricula details to facilitate the introduction of curricular changes. Industry partners have indicated willingness and enthusiasm to be involved in undergraduate teaching in different ways, e.g. face-to-face, e-learning, student placements.

PhD students pursuing PhDs in pharmaceutics and pharmaceutical technology are ideally positioned to enter the pharmaceutical industry in a variety of roles. The consortium has developed courses and structured training appropriate for such students to increase their employability within the industry. Furthermore, these structured intensive courses have provided an opportunity for up-skilling of academic staff involved in undergraduate and postgraduate teaching. Three intensive courses have been successfully delivered as part of the LIAT-Ph project, covering the topics of: "Biopharmaceuticals" (in Dublin), "Drug Product Development and Manufacture Within the QbD Concept" (in Belgrade) and "Advanced Solid Dosage Forms" (in Belfast).

Industrial placements for PhD students/academic staff are another component of the project. Two two-week student industrial placements have taken place thus far, with a further three placements to be completed before the end of the project timeframe. Placements have been extremely well received by both the students and industry partners involved.

As healthcare professionals, pharmacists in industry are obliged to undertake continuing professional development (CPD). The consortium is well placed to identify CPD needs of the industrial pharmacists and has identified a number of topics for CPD courses that match with the expertise of the consortium partners. A focus of the second year of the project is to develop short e-courses that can serve the dual purposes of providing CPD offerings to practising industrial pharmacists and taught components of structured PhD programmes within the partner universities. The consortium plans to have four or five such courses complete by the end of the project timeframe, in September 2015.

For more information on the LIAT-Ph consortium and project activities please see the website: www.liatph.com

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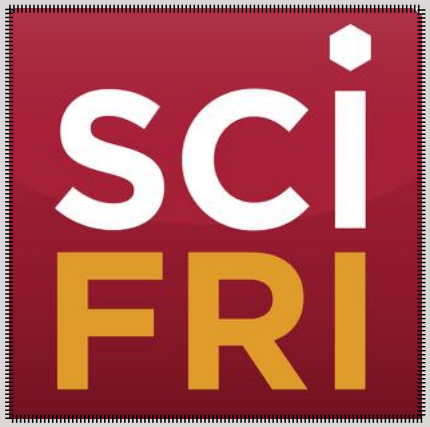

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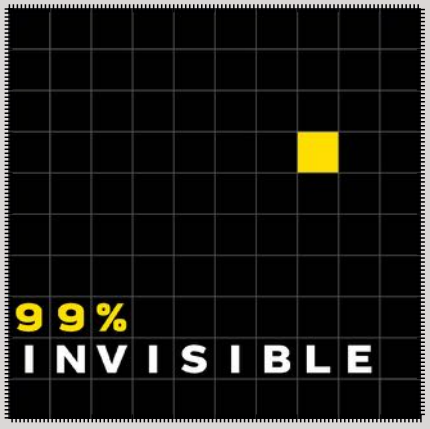

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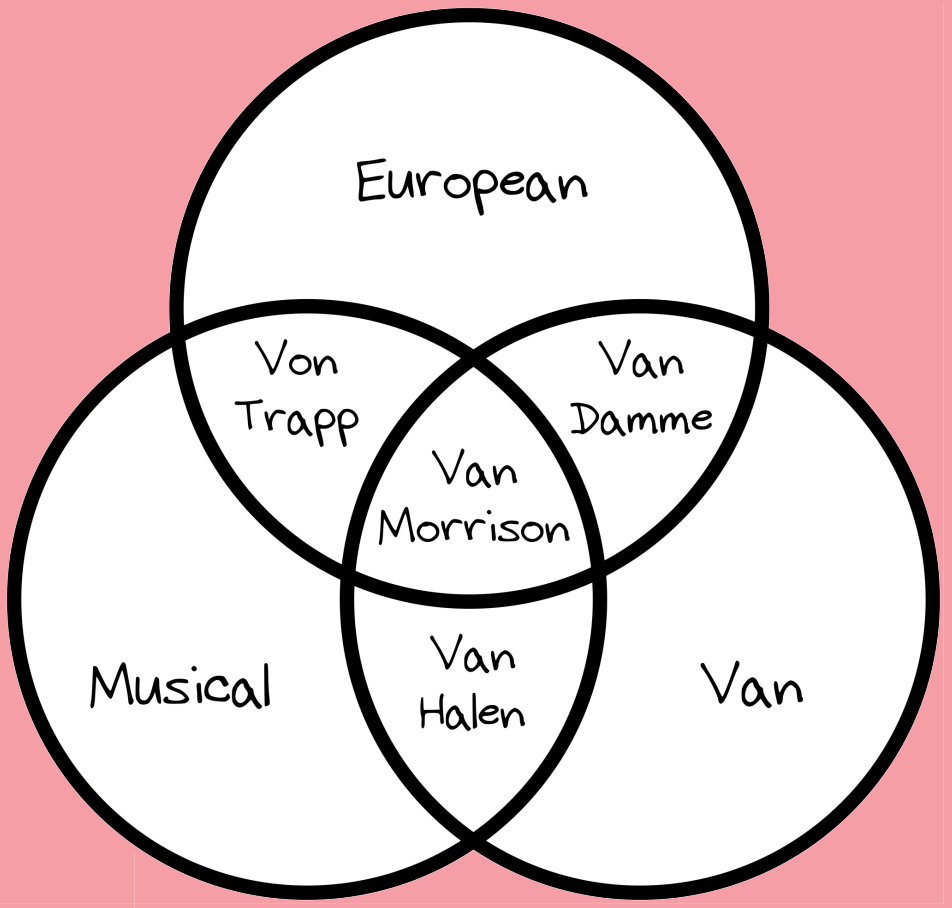

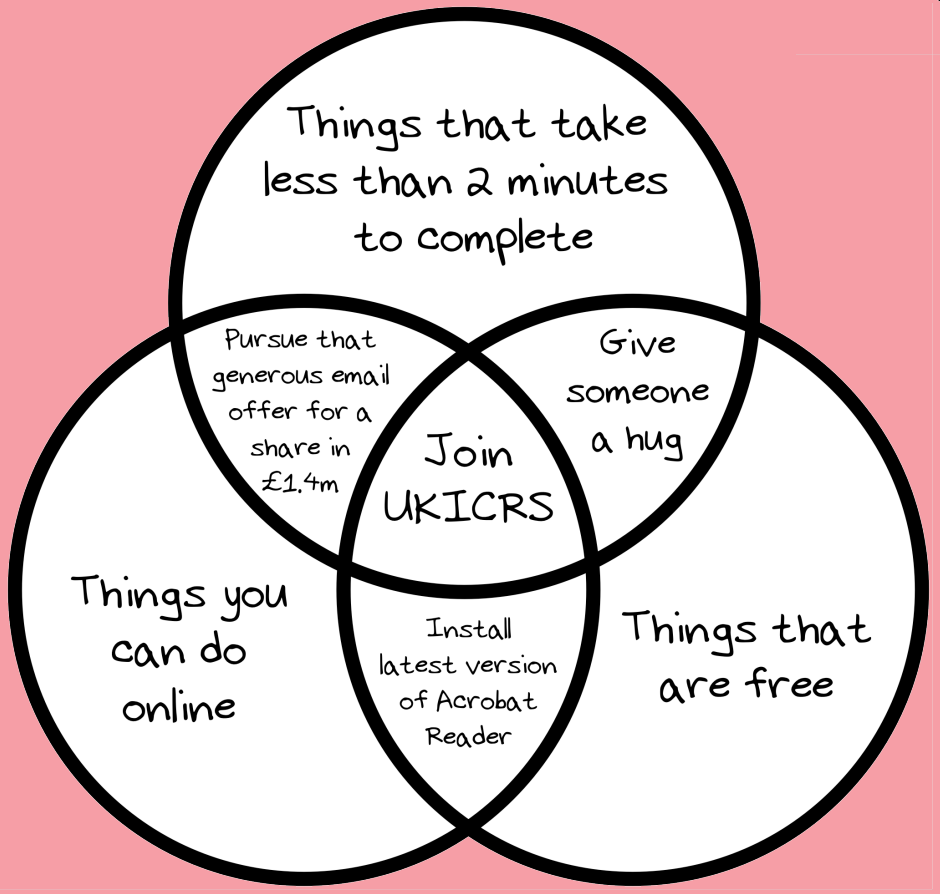

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