PHARMACOLOGY MATTERS

BRITISH PHARMACOLOGICAL SOCIETY

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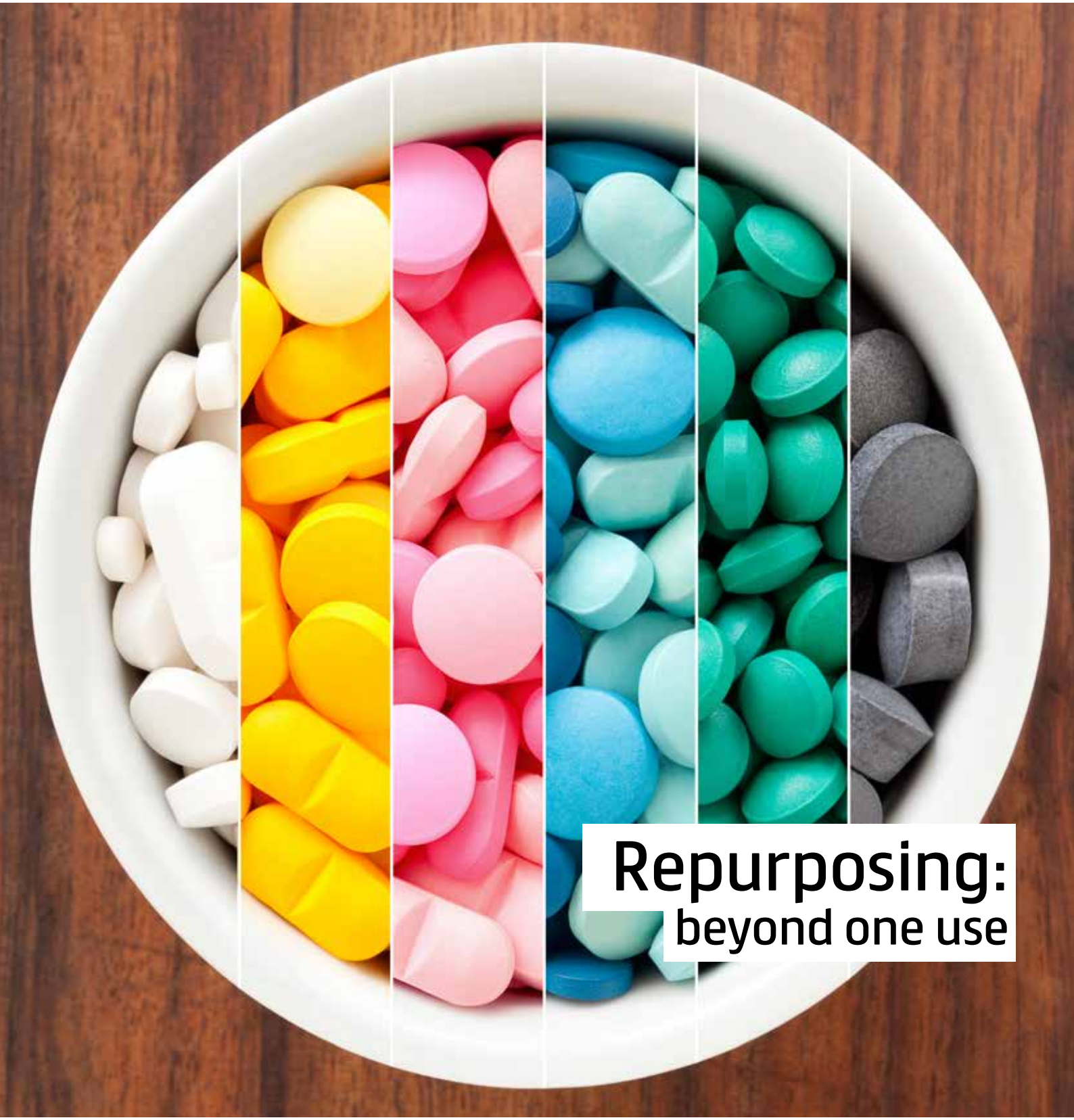

Repurposing: beyond one use

Drug repurposing | Alemtuzumab in multiple sclerosis | EU referendum

BRITISH PHARMACOLOGICAL SOCIETY

TODAY'S SCIENCE TOMORROW'S MEDICINES

Last chance to register

INTERNATIONAL NARCOTICS RESEARCH CONFERENCE (INRC)

10–14 July
Bath Assembly Rooms, Bath, UK

The International Narcotics Research Conference, founded in 1974, is an organisation whose purpose is to run an annual scientific meeting on the topic of opioid research bringing together scientists from around the world to discuss aspects of opioid research ranging from genetic and molecular to *in vivo* studies.

For more information about attending or presenting please contact **meetings@bps.ac.uk** or visit **www.bps.ac.uk**.

Editorial

Felicity N.E. Gavins
Editor-in-Chief, Pharmacology Matters

In this latest edition of *Pharmacology Matters*, the theme is one of 'repurposing in pharmacology' – this idea that a drug has more than one use has many advantages, including reducing R&D time, increasing success rate and reducing cost. David Cavalla from Numedicus Limited tells us more.

We have the latest news from Jono, who discusses one of the Society's major projects at present, that being *Focus on Pharmacology*. This will be familiar to many of you, but in this edition of *Pharmacology Matters*, Jono unveils the true meaning of this major endeavour.

Following this, Katharine Steer tells us a lovely story about one of the successes of the *Putting UK Pharmacology on the Map* Society initiatives, involving the James Black Foundation laboratory, which has now been transformed into the Judith Kerr primary school.

We all have an opinion regarding whether we want to be a part of Europe or not. It is hard to escape the media frenzy regarding the topic, particularly as we are only a few weeks away before we cast our vote. Even for me, although I am based across the pond in the USA, there is a great fascination as to whether the UK will leave. In the very enlightening article by Chinara Rustamova, David Webb, Stephen Hill, Robin Plevin and Iain Greenwood, we are provided with a breakdown of unbiased evidence regarding this hot topic, and it is certainly food for thought.

Elliot Lilley, senior scientific officer at the RSPCA, then discusses the issues surrounding the fact that although many journals have endorsed the ARRIVE guidelines few have actually done anything to assure compliance. I am pleased to say that the *BJP* does not fall into that category.

Vedia Can writes about the latest news from the Young Pharmacologists, and we have an article from Artysha Tailor, a student at King's College London, about her exciting venture of setting up a society called 'ThinkMental'. We also have an Ambassador update from Anne Leaver, Steve Tucker and Kayley Scott regarding a super event that was organized by Ambassadors from both Aberdeen and Edinburgh to promote understanding of drug development and therapy.

This is followed by an article written by Zoya Georgieva and Alasdair Coles, in which they discuss alemtuzumab (the humanized monoclonal antibody against CD52) as a positive treatment for multiple sclerosis.

Finally Barbara McDermott and Talja Dempster provide our regular meetings updates, and we also have the initial details about our annual meeting in December.

We hope that you enjoy this latest packed edition of *Pharmacology Matters*!

Best Wishes,

Felicity

Contents

Your BPS

Jono Brüün
Chief Executive

I wanted to take this opportunity to discuss one of our major projects at the moment – *Focus on Pharmacology*. I have mentioned *Focus* a few times previously in this column, or you may have heard about it if you attended *Pharmacology 2015*. There has been a great deal of work going into this project and I wanted to 'lift the curtain' to give you a glimpse into just some of what is going on.

Focus is a multi-faceted programme of work that is intended to help us understand the impact that pharmacology makes in the UK, and ensure that its underpinning knowledge and skills are supported – now and into the future. The project represents an ambitious new phase of the Society's investment in pharmacology as a responsive, integrated and proactive discipline. This is no easy feat – we are undertaking a number of different projects to help us gauge this. This has led to a number of collaborations and the opportunity to hear from hundreds of people within the pharmacology community.

Focus naturally divides into two themes: one focusing on the value of pharmacology in society and the other on education. Within the value strand, we're currently evaluating the impact of pharmacological research case studies using the Research Excellence Framework (**www.ref.ac.uk/**).

This allows us to look at the cross-collaboration among various disciplines, as well as the impact that each of these studies has had within society.

Our goals in education are clear, but complex. We are working to try to better understand the way in which pharmacology is taught in a modern academic framework; to bring the pharmacology teaching community together; to help ensure our students have more opportunity to create impact and to provide services that support the teaching of pharmacology, mapped to an understanding of the skills needs of industry and other potential employers.

To begin to address these objectives, we have undertaken a large scale and consultative review of the pharmacology curriculum. In September 2015, we held a higher education workshop where professionals in pharmacology teaching shared what they believed to be the core knowledge, skills and attitudes in undergraduate pharmacology education. These were then developed into the first statements, which were then scored by a group of individuals working across the pharmacological spectrum (our Expert Group), using the Delphi process. On 24 June, we will be holding another core curriculum implementation workshop to examine these results, explore the challenges in delivery, and work out how to frame the final curriculum. From then until the launch of the curriculum, we will be working out how the Society could best support institutions to deliver it. The findings of this project will also feed into a review of the Diploma for Advanced Pharmacology.

Linked to our review of skills needs and curricula, is a comprehensive review of the Integrative Pharmacology Fund (IPF), a £22 million fund for developing education, training and research using *in vivo* methods. The funding provided by the IPF for these initiatives and projects has now ended. Our project aims to evaluate the impact of these considerable investments. Last month, we held a workshop to discuss the interim report that we've developed so far.

We still need your help to understand the spread of pharmacology in the UK, and we would greatly value your input on two surveys we're conducting at the moment. You can participate on both surveys on **www.focus.ac.uk**. Information gathered from the first survey will help us to identify the UK pharmacology teaching community and pharmacology modules in broader life sciences degrees. The other survey results will help us to develop educational support for educators and users alike, so if you would value additional teaching resources in pharmacology, please let us know.

If you'd like more information about *Focus* or would like to share your views or any information you think may be relevant, please don't hesitate to contact Dr Anna Zecharia, Head of Education, Training & Policy, on **anna.zecharia@bps.ac.uk** or visit **www.bps.ac.uk/focus**.

This is just a glimpse at the work we've been doing to understand and support pharmacology teaching in the UK. After spending months examining evidence and researching, we will be looking at how we can use our understanding to better direct the strategy of the Society. I hope to be updating you many more times in the coming months (and years) as the results of all of this work bear fruit.

Back to school for a former pharmacology lab

Katharine Steer, Head of Communications & Membership

Some readers may recall that the site of the James Black Foundation laboratory was commemorated as part of the British Pharmacological Society's 'Putting UK Pharmacology on the Map' initiative in 2013.[1]

Sir James joined the Society in 1961 and was later elected as an honorary member in 1988 – the same year that he won the Nobel Prize with Gertrude Elion and George Hitchings for their discoveries of important principles for drug treatment. He was knighted in 1981 and awarded the UK's highest honour, the Order of Merit, by the Queen in 2000.

Sir James spent the early part of his career in industry: he invented the first beta-blocker (propranolol, launched 1964) while working at ICI (now AstraZeneca) and the first selective histamine H2 antagonist for the treatment of stomach ulcers (cimetidine, launched 1975) at Smith, Kline & French (now GSK). His research and discoveries reflected his deep fascination for receptor theory as the bedrock of pharmacology and drug discovery.

By 1984 Sir James joined King's College London (KCL), and in 1988 he founded the James Black Foundation, a group of scientists engaged in new drug research, supported in part by Johnson & Johnson. The group was primarily concerned with the development of drugs that inhibit gastrin, a hormone that may play a role in causing stomach cancer.

A laboratory building on Half Moon Lane in South London (between North Dulwich and Herne Hill train stations) was already well-known for KCL plant science research and was selected as the home of the James Black Foundation.

Fast-forward to the present and, while Sir James sadly died in 2010, the site continues its link with 'discovery' and 'development': as a new primary school.

The laboratory building in 2013, before it was transformed into a primary school.

The Judith Kerr Primary School is a bilingual English/German primary state school (the first in the country) and its intended focus will be language and science. The school reached out to the KCL pharmacology department, who kindly introduced the Society. The school is named after German-born British author and illustrator Judith Kerr, best known for her *Mog* series of books and (a personal favourite from my childhood) *The Tiger Who Came To Tea*. Judith is an official Patron for the school, and parts of the building are now decorated with her beautiful illustrations.

I'm pleased to report that the school is equally proud of its pharmacological connections and the role these could play in engaging pupils in science at an early age. An application has been submitted for an English Heritage 'blue plaque' to promote Sir James Black's history with the site. The Society is contributing a banner and materials to form the basis of a display about Sir James Black and his achievements. Members from KCL are also planning visits to the school to engage pupils in different aspects of pharmacology.

I was invited to attend the Grand Opening of the school at the end of the school day on 23 March 2016, along with Professor Rona MacKie (Lady Black, Sir James' widow). Headteacher Claire Eskelson welcomed invited guests, pupils, parents and supporters to celebrate the transformation of the building after some significant renovations. The pupils marked the occasion with an enthusiastic choral performance in the playground, and provided guests with tours of the school. I am grateful to Arlo, John and Emile from Years 3 & 4 for giving me a whistle-stop tour of their classrooms, including dedicated rooms for art and chess lessons (my guides were particularly keen to share their current rankings in the school's ongoing chess tournament!).

A pupil cuts the ribbon to officially open the Judith Kerr Primary School.

References

1. British Pharmacological Society. Putting UK Pharmacology on the Map. Available online: https://www.bps.ac.uk/about/about-pharmacology/putting-uk-pharmacology-on-the-map - insert short link if possible. Last accessed: 27 April 2016.

BRITISH PHARMACOLOGICAL SOCIETY

TODAY'S SCIENCE TOMORROW'S MEDICINES

Save the date

PHARMACOLOGY 2016

13–15 December
The Queen Elizabeth II Conference Centre, London

For more information about attending or presenting please contact **meetings@bps.ac.uk** or visit **www.bps.ac.uk**.

The British Pharmacological Society is delighted to announce initial details for our annual meeting, Pharmacology 2016. The latest research from across the whole spectrum of pharmacology will be the focus for plenary lectures, oral communications and poster sessions. There will also be invaluable opportunities for participants to network with pharmacologists from the UK, Europe and overseas.

Symposia

Cardiovascular & Respiratory Pharmacology

- From bench to bedside: Targeting the pathophysiological responses of ischemia-reperfusion injuries
- BSCR embedded symposium: Targeting cardiovascular GPCRs using biased agonism
- Nanomedicine in pharmacology

Drug Discovery, Development & Evaluation and Toxicology

- Organ-on-a-Chip technology - the future of physiological profiling?
- Clinical application of systems pharmacology models
- Clinical pharmacology, pharmacokinetics and pharmacogenetics in pregnancy (C4P)

Integrative Systems Pharmacology

- The long reach of the bowel: Translating microbiome science into therapeutics for systemic human diseases
- Study, development and rationale use of immunopharmacological agents
- Immuno-Oncology: From bench to bedside
- Translation to therapeutics: Resolution of inflammation

Molecular & Cellular Pharmacology

- Non-traditional/orphan GPCRS as novel therapeutic targets
- Biochemical strategies in drug discovery and targeting
- Anti-tumour pharmacology and traditional Chinese medicine

Neuropharmacology

- Uses and challenges for human pharmacology studies to understand CNS diseases
- Fatty acid amides (aka lipoamines) beyond cannabinoids
- Recent developments in research of melatonin and its potential therapeutics application

1,081
participants welcomed last year

97%
of survey respondents were satisfied or more than satisfied with the scientific programme in 2015

48
countries were represented in 2015

Dates for your diary

Registration opens: 24 June

Abstract submission deadline: 9 September

Bursary application deadline: 9 September

Early bird registration deadline: 9 September

Exhibition & Sponsorship

By having exhibition space or sponsorship package at Pharmacology 2016 you will be reaching an audience of approximately 1,000 scientists. This well-regarded conference provides an informal yet professional environment in which to highlight your products and services.

For further information about how you can support Pharmacology 2016, please email **meetings@bps.ac.uk** or visit **www.bps.ac.uk/pharmacology2016**.

Drug repurposing to enable accelerated access to new therapies

David Cavalla, Numedicus Limited
with support from **Rick Thompson** (Findacure)

Drug repurposing, or the identification of secondary uses for existing drugs, is a term first used a few years after the establishment of NICE (the National Institute for Health and Care Excellence). In recent years, drug repurposing has become increasingly adopted by charities and some small biotech companies as a means to accelerate access and increase productivity in the pharmaceutical Research and Development (R&D) sector.

The advantages of this strategy are clear: it reduces drug discovery time by two-thirds, increases chance of developmental success by 250% and reduces cost of R&D for new medicines by five-sixths. We know from experience that it is common for medicines to have multiple uses and now believe that over 90% of existing drugs can be repurposed, in some cases more than once. Aspirin is a salient example: it was first used for pain, then as an antithrombotic and has recently been found to have important potential cancer preventative properties. It is an impressive array of uses for this common drug that has taken over a century to identify, but in the case of its use in cancer, has still not reached regulatory approval.

Drug repurposing holds huge future promise, particularly in the area of rare and orphan diseases, of which there are about 8,000, and only around 200 of these diseases have an approved pharmaceutical therapy. (An orphan disease is defined as one with a prevalence of less than 200,000 in the USA.) Moreover, although the numbers of patients affected by an individual rare disease is low, when added together a large number of patients are affected: 3.5 million in the UK, and 350 million worldwide.

Unfortunately, despite the advantages, there is a notable hesitancy among some pharmaceutical companies to pursue this strategy because of the unclear commercial position of drug repurposed treatments. Marketing departments are concerned that the new use of a compound which has competing generic alternatives cannot command the prices necessary to return the R&D investment – even though that investment is much less than would be required to commercialise an entirely new drug. To be clear, if the generic drug can substitute for the branded repurposed medicine – since, despite the possibility of method-of-use patent protection, such patents are often difficult to enforce – then any money spent in bringing the repurposed product to market is a wasted investment.

So, despite the advantages to the patient and to the medicines available to our health service, mainstream pharmaceutical research is often unpersuaded that this approach is commercially attractive. An alternative framework of incentives is therefore necessary to encourage the pharmaceutical industry to invest in drug repurposing, or an entirely new model of drug development and payment must be devised to facilitate the involvement of the charitable sector and promote patient-led research.

On 6–7 November 2015, I attended the annual conference of the Action Duchenne charity. One of the key points of debate was the status of ataluren, an expensive new product for Duchenne Muscular Dystrophy which is currently being considered for reimbursement by NICE.*

The subject raises substantial ire among people with Duchenne and their families, even though it is not a cure and is not the only highly priced product likely to be reviewed for this condition in the future. Yet at the same conference we heard about the potential for repurposed developments like sildenafil citrate, tamoxifen and metformin, cheap alternatives that are based on small molecule generic products. These latter research programmes are still of unproven utility, and would not conform to the standards of safety and efficacy required for widespread use. They are taken forward with public funds or charitable support, and in consequence are much slower to come to the market. Just like the above example of aspirin, development of alternative uses for generic products can take decades and formal regulatory approval may never be fully accomplished.

Used with kind permission from Action Duchenne

I have considered this problem deeply since I have worked in drug repurposing for as long as the strategy has had a name. I recently wrote a book called *Off-Label Prescribing: Justifying Unapproved Medicine*[1], where I proposed that there should be two levels of pricing for repurposed products to be imposed at the point of prescription and reimbursement, and operated for some years as an incentive to the repurposing innovator. In the era of electronic prescribing, this dual pricing arrangement is not difficult to implement. Moreover, it is a proposal that dovetails with the founding principle of NICE, that therapeutic indication and reimbursement are intertwined. Since the book was published, a very similar proposal was made by Prof Ben Roin, a policy strategist at Harvard/MIT, with respect to the US system of medicines.[2]

This simple change, linking prescription to condition on an electronic platform with a dual pricing structure, strengthens the value of mode-of-use patents for the pharmaceutical industry, thus promoting commercial investment into repurposing research. Of course, such a scheme would leave the pricing of the repurposed drugs in the hands of the commercial entities, but rigorous licencing and health technology appraisal processes would help to improve patient safety, and allow some control of pricing in the UK market.

Without changes to encourage commercial investment in repurposing, more creative models for both funding and licencing of drugs will have to be explored, with the aim of promoting patient driven research. Such routes could be particularly useful for rare diseases, where small markets drive up drug prices in those rare cases where development is seen. The Social Impact Bond model being piloted by the UK charity Findacure has clear potential in this area. Here, the charity secures funding to run phase II clinical trials of generic drugs repurposed for rare diseases that have a high cost of care to the NHS. Successful trials lead to off-label prescription in the NHS, and reduce the healthcare cost of patients. The NHS then pays a proportion of their savings back to the charity as a success payment, which is used to repay their investors, and develop further treatments. Here, funds for generic repurposing are leveraged from the savings made to the NHS, rather than commercial sales. Ideally, the treatment of the wider UK population, subsequent to successful phase II trials, would be carefully monitored and then fed into a dataset used for conditional approval, and ultimately licencing of the drug. This scheme, though promising, struggles to secure public sector investment in the current funding climate.

Lastly, what happens if nothing is done? There are clear dangers if a balanced framework of incentives for drug repurposing cannot be put in place, because in its absence, pharmaceutical research will be slanted towards high-priced products that are effectively unaffordable. The problem is that, under the current system, the interests of pharmaceutical companies are not aligned with those of patients and payers (such as the NHS): the need to make a profit takes companies towards difficult and lengthy research that can command a high price rather than easier and quicker research that might be unprofitable.

Without change, I see a future therapeutic landscape populated with a multiplicity of highly priced pharmaceutical research products that stretch the NHS budget to breaking point, and an increasingly disgruntled UK public that cannot comprehend why access to innovative products is denied. This is a lose-lose scenario for both governments and taxpayers alike. But particularly for the sake of patients, and especially for those with the thousands of rare conditions currently lacking any therapy, inaction is not an option.

About the author

David has 30 years' experience in various senior scientific and commercial roles within the pharmaceutical industry. He is currently involved with a number of biotech companies at board level. Previously he was founder and CEO of Arachnova Ltd, a company focused on therapeutic switching; previous affiliations include Glaxo Group Research Ltd and Napp Research Centre.

He is author of *Modern Strategy for Pharmaceutical R&D – Towards the Virtual Research Centre*, and *Off-Label Prescribing: Justifying Unapproved Medicine*. David frequently contributes articles on pharmaceutical strategy and is on the editorial board of *Drug Discovery Today*. He is author/inventor of more than 70 published papers and patents.

Note

*Recommended by NICE on 16 April 2016 in connection with a Managed Access Agreement (MAA) with NHS England for ambulatory patients older than 5 years old.

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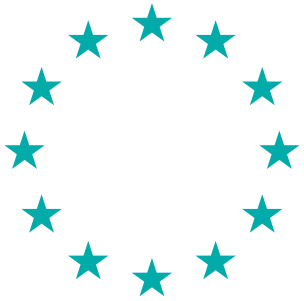
1. Off-label Prescribing: Justifying Unapproved Medicine. David Cavalla. ISBN: 978-1-118-9120 7-2. 216 pages. March 2015, Wiley-Blackwell.
2. Roin, B. Solving the Problem of New Uses http://dash.harvard.edu/bitstream/handle/1/11189865/Solving%20the%20Problem%20of%20New%20Uses%20.pdf Oct 13, 2015.

Europe – the final countdown to the referendum

Chinara Rustamova, Education, Training & Policy Officer
David Webb, President
Stephen Hill, President Elect
Robin Plevin, Honorary Treasurer
Iain Greenwood, Vice President – Policy & Public Engagement



In February 2016, the Prime Minister announced that voters in the United Kingdom (UK) would be given the chance to vote in a referendum on membership of the European Union (EU) to take place on 23 June. The British Pharmacological Society's Education, Training & Policy team set to work reviewing the available literature and other evidence about the impact of the vote across the breadth of pharmacology as a discipline and on our members based in the UK and EU. It was agreed that it would be helpful to provide members with a balanced summary of this work that would share sources of interest. The summary was carefully developed with input and approval from our Trustees, and as some of you will have seen, a final version was recently published on our website (www.bps.ac.uk/europe) in time for the final weeks of the campaign.

Our experience of the drafting this paper was enlightening: we uncovered information about aspects of the relationship between the UK and EU that we hadn't known before. We felt very keenly the responsibility for trying to produce a breakdown of evidence that didn't actively favour either the 'leave' or 'remain' campaigns, as the debate had already become heated and partisan. We hope members appreciate the hardwork.

The British Pharmacological Society is a charity with a mission to promote and advance the whole spectrum of pharmacology. Founded in 1931, the Society now represents over 3,500 members working across academia, industry, regulatory agencies and the health services, and many of whom are medically qualified. Clinical pharmacology is the only medical specialty in the NHS focusing on the safe, effective and economic use of medicines. The Society supports good prescribing in the UK, most recently notably by developing the Prescribing Safety Assessment with the Medical Schools Council and is interested in:

- Promoting and advancing high quality science, especially pharmacology and clinical pharmacology.
- Supporting students and academics in research, as well as the UK university system.
- Supporting UK industrial pharmaceutical discovery and development, and underpinning the role pharmacology and clinical pharmacology has to play in that environment.

Given that, the Society outlines in the following four sections the areas of the broader pharmacological landscape connected with Europe in a wide range of ways.

1. People: collaboration and mobility

When examining the possible effects of the UK leaving the EU, it is worth considering the value and impact of collaboration in the current 'ecosystem' of scientific discovery.

The UK is undeniably an international leader in scientific research – punching well above its weight. The UK represents only 1% of the world's population, but produces 16% of the world's most highly-cited articles from only 4.1% of the world's researchers. These researchers are highly collaborative, placing the country in a central position to be able to build a network of collaborative partnerships. For example, scientific papers that are co-authored with international researchers have a greater citation impact, than those articles that are not[1]. More than 60% of the UK's internationally co-authored papers are written alongside EU partners[2].

Countries displaying high levels of research collaboration characteristically have high levels of researcher mobility, both of which are associated with high research quality[3]. UK researchers are highly collaborative and mobile across the world[4]. In addition, EU funding mechanisms create opportunities for collaboration. By way of an example, the Marie Skłodowska-Curie Actions enable researchers, from PhD candidates to highly experienced researchers, to work in various countries, sectors and

disciplines across Europe[5]. The budget for this programme is €6.16 billion in the period to 2020[6].

Elsewhere, it is possible to see other examples of pan-European collaboration and mobility in support of UK and EU scientific discovery:

- The UK Government provides student loans and maintenance funding for EU students as a statutory obligation[7].
- The university sector contributes over £73 billion annually to the UK economy[8].
- EU nationals make up 15% of the UK-based academic workforce and EU students make up 5% of students in the UK[9].
- At 21%, science disciplines have a higher proportion of EU staff in comparison with 13% across other subjects[10].
- In 2013/2014, EU government bodies funded 8.5% of UK academic staff on fixed-term contracts and other EU sources, 2.1%[11].

And, a little closer to home, examples of relationship with EU can be seen in the British Pharmacological Society's own membership. Of the Society's 800+ members (typically 20% of total membership) based outside of the UK at the start of 2016, around 40% were based in EU countries, and of this group 5% were UK 'ex-pat' pharmacologists living and working in the EU. In addition, of the Society's members based in the UK, 10% are EU nationals.

Question:

How might Brexit affect researcher mobility and high quality science?

Consideration should be given to:

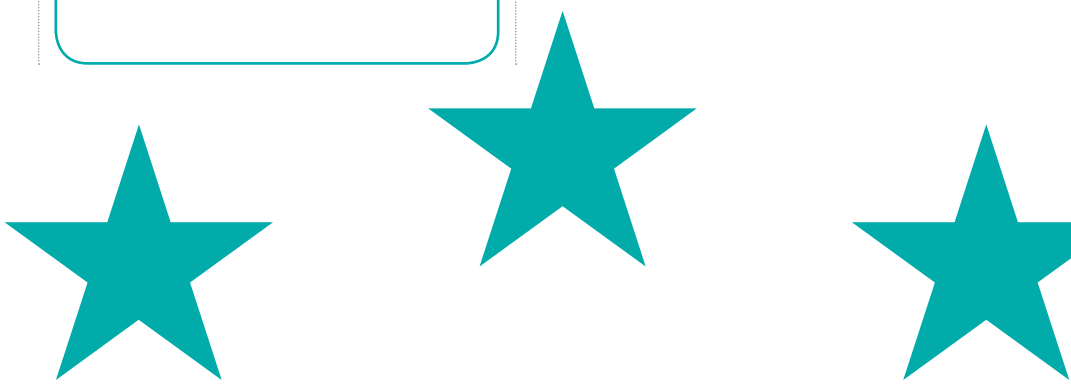
- Whether or not the UK will benefit from not having to provide students loans and maintenance funding for EU students.
- Whether or not fewer EU students might register at UK universities, if categorised as overseas students at higher fees[12], and what the resultant impact might be on the university sector that contributes over £73 billion annually to the UK economy[13].
- Whether or not there will be an impact on the number of partnerships and highly-cited research projects which are reliant on EU researcher mobility, especially where sustainable funding mechanisms have created opportunities for partnerships.
- The impact of restrictions on mobility on all sectors, including non-academic staff in academia and pharmaceutical industry.
- Whether or not researcher mobility and collaborations that might be built outside of the EU (for example with institutions and individuals in the US) would be enough to sustain and develop the UK research base, should there be a reduction in EU collaborations.

2. Funding

In 2007–2013, the UK contributed €78 billion to the EU of which €5.4 billion was indicated as being for the EU'S Research and Development (R&D) budget. During the same period, the UK received €48 billion, of which €8.8 billion was for research, development and innovation[14]. In other words, the UK received €1 billion per year on average which approximated to 15% of the national science budget during the same period[15]. Overall, the UK won 16% of research funding from the recent European Framework Programme (FP7) with only 12.7% of the EU-28 population[16]. While this funding stream is enormously valuable to the sector, some researchers and members of the Society report significant challenges in access to funding, in particular the complexity of application procedures – so called 'red tape' – which slows funding and grant applications down.

European Research Area and Horizon 2020

The European Commission launched the European Research Area (ERA) in 2000 to coordinate research and innovation activities in the EU. ERA initiatives are delivered through periodic framework programmes[17]. Meanwhile Horizon 2020 is the largest ever EU research programme, aiming to allocate €74.8 billion for research and innovation from 2014 to 2020[18]. The European Research Council allocates funding on behalf of Horizon 2020, and UK universities are expected to receive approximately £2 billion in the first two years of the programme[19].



Question:

In order to sustain science funding at current levels, and to remain competitive with our European counterparts, the UK Government would need to consider matching lost research income (which approximated to 15% of the national science budget during the period of 2007-2013), in the event of leaving the EU[20]. What might the impact be for pharmacology?

In the event of leaving the EU, there may be two major risks for UK pharmacology in relation to EU funding withdrawal, and the future of the European Medicines Agency (EMA). The 24 Russell Group universities, a number of which teach pharmacology, receive around £400 million of EU funding a year, which makes about 11% of their research income[21]. Losing access to EU research funding may affect not only these but a number of other universities, organisations and bodies receiving EU research funding. It seems uncertain as to whether the UK will be able to stay in the ERA or retain its association with Horizon 2020 and influence the direction or focus of future programmes.

Partnerships: Joint Programming Initiatives (JPIs)

JPIs are public-public research partnerships between ERA countries. Common research agendas are agreed by participating countries to implement jointly. There are currently ten JPIs and the UK participates in all of these joint programmes[22]. Two of these programmes have a pharmacological aspect:

- Alzheimer's and other Neurodegenerative Diseases
- Antimicrobial Resistance- The Microbial Challenge - An Emerging Threat to Human Health

In addition, one of the four programmes initially proposed under Horizon 2020 has a pharmacological angle:

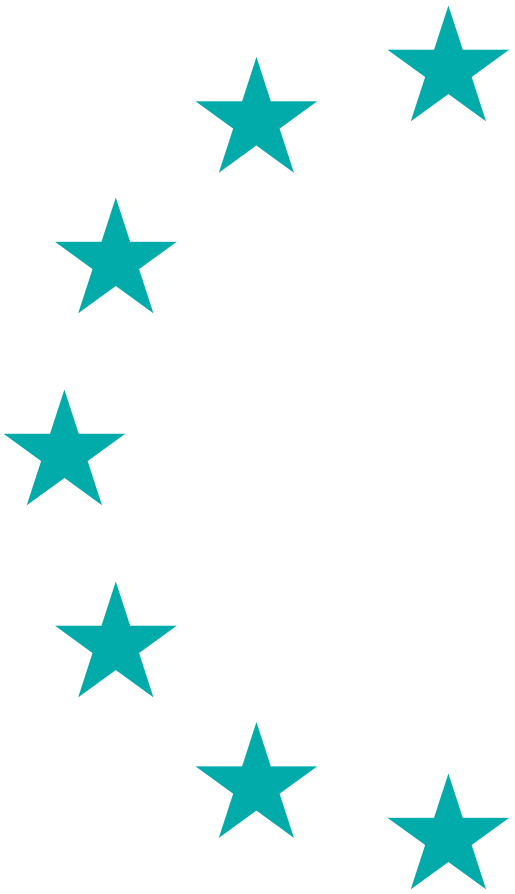
- **European and Developing Countries Clinical Trials Partnership 2 (EDCTP2):** EDCTP is a partnership between 14 African and 14 European countries that aims to support "collaborative research that accelerates the clinical development of new or improved interventions to prevent or treat HIV/AIDS, tuberculosis, malaria and neglected infectious diseases in sub-Saharan Africa"[23]. The UK is one of the 14 European countries. The European Union will allocate up to €683 million for the ten-year programme (2014–2024), to be matched by contributions from the European Participating States.

Partnerships: Joint Technology Initiatives (JTIs)

JTIs are public-private research partnerships between industry and EU member states. The current JTIs are active in a number of areas of strategic importance for the EU[24]. The largest public-private initiative has a pharmacological and pharmaceutical angle:

- **Innovative Medicines Initiative 2 (IMI2):** IMI2 is a joint undertaking between the European Union and the European pharmaceutical industry represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA). The partnership supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe[25]. It has a €3.3 billion budget for the period of 2014–2024[26] (half of the budget comes from Horizon 2020, €1.425 billion committed by EFPIA companies and up to €213 million by other life science industries or organisations).

During the first phase of the programme (2008–2013), IMI1 had a budget of €2 billion, half of which came from the EU's Seventh Framework Programme for research (FP7), and half of which came from EFPIA companies. It currently has over 50 projects focusing on varying topics including broader challenges in drug development like drug and vaccine safety, knowledge management, the sustainability of chemical drug production, the use of stem cells for drug discovery, drug behaviour in the body, the creation of a European platform to discover novel medicines, and antimicrobial resistance[27]. For example, CHEM 21, a €26.4 million project, brings together six pharmaceutical companies, 13 universities and four small to medium enterprises from across Europe with the aim to develop sustainable biological and chemical alternatives to finite materials. The project is led by The University of Manchester and GlaxoSmithKline and includes Pfizer, the Universities of Durham, York and Leeds and UK-based small to medium enterprises among other European participants[28].



Question:

Would the UK be able to continue taking part in JPIs, e.g. EDCTP2 and JTIs, e.g. IMI2? How would those who were excluded from research cooperation be supported?

The UK is currently taking part in most joint initiatives. The level of impact from leaving the EU would be different for each project and programme. For example, Norway participates in EDCTP2 and UK may well be able to negotiate its continued participation and contribution along similar lines.

Some projects, however, e.g. CHEM21 led by The University of Manchester and the GlaxoSmithKline, could be significantly affected. Since 2014, Swiss participants are no longer eligible for research funding from the EU and are funded by the Swiss Secretariat for Education, Research and Innovation (SERI). In addition, the Federal Council directly supports those who have been excluded from research cooperation[29].

3. Regulation

The UK is subject to EU legislation that has an impact on a number of pharmacology-relevant areas, e.g. pharmaceuticals, the working hours of doctors, Clinical Trials Directive, Directive 2010/63/EU on the protection of animals used for scientific purposes, and others. In return, the UK contributes to wider EU law in a variety of ways. For example, the Academy of Medical Sciences contributed to and led pan-European statements on research regulation and EU Research and Innovation strategy, and recently the Clinical Trials and Data Protection Regulations[30]. The Medicines and Healthcare products Regulatory Agency (MHRA) is a leading contributor to EU law and is respected internationally as one of the leading regulatory authorities for medicines and medical devices[31].

Clinical Trials Regulation

All clinical trials implemented in the EU are required to be conducted in accordance with the Clinical Trials Directive 2001/20/EC until the new Clinical Trials Regulation (CTR) EU No 536/2014 becomes applicable sometime after 28 May 2016. The UK had played a significant role in influencing the improvements to the clinical trials regulation[32]. The EMA was commissioned to establish an EU portal and database as a single entry point for submission of data and information relating to clinical trials required by the Regulation[33]. The House of Lords' Science and Technology Select Committee's report "EU membership and UK Science"[34] notes that clinical trials regulations were "highlighted as causing UK business and research to be disadvantaged compared to competitors outside the EU" by the UK science community. However, the development of the new clinical trials regulation is seen as a considerable improvement.

Directive 2010/63/EU on the Protection of Animals Used for Scientific Purposes

Directive 2010/63/EU governs animal research in the EU. Revising the earlier Directive 86/609/EEC, it was adopted on 22 September 2010 and is based on the principle of the three Rs, to replace, reduce and refine the use of animals used for research[35]. Article 2 of the Directive outlines that member states can maintain stricter provisions aimed at ensuring more extensive protection of animals which were in force on 9 November 2010[36]. Recently, the European Commission had started an infringement process against Italy concerning the overly stringent transposition of the Directive, as stricter provisions were not in force in the country before this date[37]. In the UK, revised legislation transposing the new Directive came into force on 1 January 2013[38]. The House of Lords' Science and Technology Select Committee's report "EU membership and UK Science" highlights the UK's involvement in the development of the framework.

European Medicines Agency (EMA)

Located in London, the EMA is responsible for the scientific evaluation, supervision and safety monitoring of medicines developed by pharmaceutical companies for use in the EU (since 1995)[39]. It is the largest EU body in the United Kingdom with a full-time staff of more than 600 people. British experts were leaders or co-leaders in examining 27 new drug applications in 2014[40].

Question:

In the event of Brexit, how would the Government tackle the regulatory infrastructure changes, particularly in relation to EMA?

A number of industry officials believe that the EMA would relocate from London to another member state in the event of Brexit[41]. The Swedish pharmaceutical association expressed interest in making Sweden the new host country for the EMA as a major boost for the country's entire life sciences field[42]. In case of relocation, UK could still continue its relationship with EMA and benefit from centralised marketing authorisations as Iceland, Lichtenstein and Norway are included for the latter. Otherwise, pharmaceutical companies will need to apply for marketing authorisations separately to the MHRA for every medicine they would like to supply in the UK[43]. Overall, the status of the MHRA would change and the organisation would potentially grow. Simultaneously, the MHRA would lose some of its ability to influence regulations due to the withdrawal from the EU platform.

The Unified Patent Court (UPC)

The agreement to create a unified patent court was signed by 25 EU Member States on 19 February 2013[44]. According to the agreement, the UPC will comprise of Court of First Instance, a Court of Appeal and a Registry. The Court of First Instance will be composed of a central division in Paris with two sections in London and Munich and local and regional divisions. The London section will be responsible for "Human necessities" and "Chemistry, metallurgy"[45]. There is a concern that the section of the Unified Patent Court will have to relocate from London before it even opens[46].

The European Strategy Forum on Research Infrastructures (ESFRI)

The ESFRI is a multi-disciplinary forum to support a coherent and strategy-led approach to policy-making on Research Infrastructure (RIs) in Europe and to facilitate initiatives leading to the better use and development of RIs[47]. All EU Member States are represented by two delegates on ESFRI including a number of Associated Nations. The current Chair of ESFRI is Professor John Womersley, the Chief Executive of the UK's Science and Technology Facilities Council[48]. The following landmarks that are pharmacology-relevant (health and food section) were identified in ESFRI Strategy Report on RIs (2016):

- **BBMRI ERIC** - Biobanking and BioMolecular resources Research Infrastructure
- **EATRIS ERIC** - European Advanced Translational Research Infrastructure in Medicine
- **ECRIN ERIC** - European Clinical Research Infrastructure Network
- **ELIXIR** - A distributed infrastructure for life-science information
- **INFRAFRONTIER** - European Research Infrastructure for the generation, phenotyping, archiving and distribution of mouse disease models
- **INSTRUCT** - Integrated Structural Biology Infrastructure

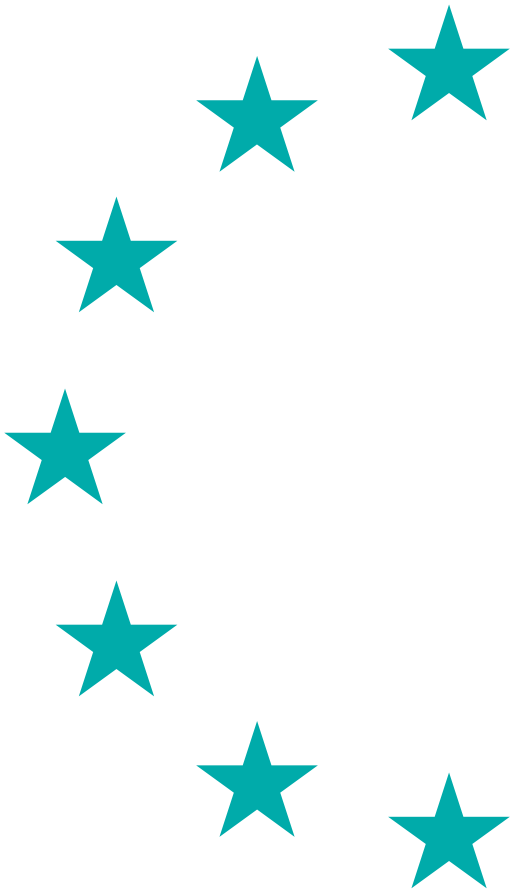
The UK takes part in BBMRI ERIC and INFRAFRONTIER and hosts the headquarters of ELIXIR (Hinxton) and INSTRUCT (Oxford). In addition, the UK hosts the headquarters of the Infrastructure for Systems Biology Europe (ISBE), the ESFRI Project in London (Imperial College London)[49]. As for ESFRI itself, which was setup as an informal forum in 2002[50], Norway and Switzerland participate in the forum and host the headquarters of projects. Given that, the UK is also likely to be able to continue its participation.

4. Impact on the UK pharmaceutical industry

The pharmaceutical industry accounts for 20% of total expenditure on R&D implemented in UK businesses[51]. The sector brings a trade surplus of £3 billion per year[52] but it is safe to say there is some risk to the maintenance of that surplus, should UK vote to leave the EU. For example, the pharmaceutical labour force might be affected by restrictions on mobility, and participation of pharmaceutical companies, particularly small to medium enterprises in EU programmes, e.g. IMI2 would be restricted. In addition, the UK's access to the Small and Medium-sized Enterprises (SME) Instrument – a mechanism that allows EU to support growing businesses – would be under question. The budget for the SME Instrument for 2014–2020 is €3 billion (4% of Horizon 2020)[53].

Some changes would have a bigger impact on the pharmaceutical industry than on the UK pharmacological landscape. Pharmaceutical companies have invested to establish their European headquarters in the UK given the unrestricted access to the EU market. A number of companies based in Japan and USA had selected the UK as their European headquarters. This has contributed to the UK economy and generated job opportunities for UK nationals[54]. Leaving the EU might change the pharmaceutical landscape by prompting companies to relocate their headquarters[55]. HM Treasury has flagged that the benefits of the single market including access to wider market for pharmaceutical companies and their products would be at risk in the event of Brexit[56].

The chief executive of GlaxoSmithKline, Sir Andrew Witty, noted the benefits of having a Pan-European regulation at the World Economic Forum in Switzerland in January 2016[57]. Pharmaceutical executives believe that the level of fallout from Brexit will depend on whether UK stays part of the EMA. Switzerland, for example, has a separate drug approval process[58]. The UK could have a lesser priority in launch sequences of pharmaceutical companies if they were required to seek separate approvals in the UK[59]. In addition, UK pharmaceutical companies could seem less attractive because of tax incentives from business transactions in countries within the EU[60].



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Young Pharmacologists update: Representing Young Pharmacologists at Voice of the Future

Vedia Can, University of Westminster

Members of the Young Pharmacologists Advisory Group (Joanne Carter, Laura Ajram, Ross King and myself) attended the Voice of the Future (VOF) event on 1 March 2016 held in the Boothroyd Room at the House of Commons.

This prestigious event, hosted by the Royal Society of Biology in conjunction with the House of Commons Science & Technology Committee and other science organisations, gives young scientists and engineers the opportunity to quiz Members of Parliament and Ministers on science policy and current affairs in science and technology.

One of the goals of the Young Pharmacologists Advisory Group is to encourage students to study STEM-related subjects, in particular, pharmacology. However, we are aware that the number of students studying STEM-related subjects at higher education in the UK is reducing. I was fortunate enough for my question to be selected and answered by Jo Johnson MP, Minister for Universities and Science. I asked: "Do you think business should offer greater incentives for young people to study STEM subjects at university to help fill the shortfall of skills in the science and engineering sectors?" The response I received was very honest and reassuring. The Government is aware of the current initiatives set up by societies to encourage the development of skills for students studying STEM-related subjects, and they are keen to support businesses to ensure there are more apprenticeship vacancies and supportive measures available for skill development.

One of the highlights from this year's VOF was a video message from Major Tim Peake addressing MPs and Ministers, which was pre-recorded on the International Space Station. The British astronaut answered questions from Jo Johnson MP on experiments he is conducting in space and what more might be possible in the future. Major Peake described how his experiments often focus on understanding the body's ageing process and looking at ways to counter the negative effects of growing old. He emphasised that the future of scientific exploration lies in space. An example of a study that could be beneficial for asthma sufferers on planet Earth is the "Airway Monitoring" European project. This exciting and complex project investigates the changes of airway inflammation, and could provide us with key information that could help us combat the difficulties associated with asthma treatment and management.

Major Peake's positive energy and enthusiasm for science has definitely encouraged us all to pursue our dreams and address our questions on research and our future as scientists. His message was very inspirational and motivational for all attendees present at the VOF, which can be viewed on the following link: **https://www.youtube.com/watch?v=zY1brEl4nQY**

Personally, this event gave me the opportunity to learn more about science policy and how scientists can get involved with politics. I was able to gain a better understanding on how Parliament and the Government functions in the UK and the impact our government has on an international level. In addition, this event allowed scientists and engineers to gain a better insight into the career paths and opportunities available in politics or related disciplines. So, if you feel that a career change is what you need, why not try Science Policy?

You can find more information regarding the event on the Royal Society of Biology's website (www.rsb.org.uk/policy/policy-events/voice-of-the-future), and you can watch the entire event on this link: **http://www.bbc.co.uk/programmes/b054g39r**

Leading the way in raising publication standards

Elliot Lilley
Senior Scientific Officer, Royal Society for the Prevention of Cruelty to Animals

I've been a member of the Society for the best part of twenty years and throughout that time I've been a keen reader of the *British Journal of Pharmacology (BJP)*. Indeed, all of my results chapters of my PhD thesis were published in the journal as well as a number of abstracts from the many Society meetings I attended and presented at.

After obtaining my PhD, my contact with the journal was limited to reading articles and refereeing the occasional paper. During my 15 years in the pharmaceutical industry, publication was not always possible and I'm sad to say that I haven't published any original science in *BJP* since I finished my PhD.

After joining the RSPCA Research Animals Department in 2012, I was interested in the launch of the ARRIVE (Animal Research: Reporting of *In Vivo* Experiments) guidelines and proud to see that *BJP* was not only involved in the development of these important principles, but were one of the first journals to 'sign up' to their use. There is a growing literature that casts a poor light on the standard of reporting of pre-clinical research and ARRIVE offers a robust framework to try and address some of the issues that have been raised. However, in December 2012, I was reading the latest issue of the journal and noticed that, despite all papers that included animal data citing the ARRIVE guidelines, there was a distinct lack of adherence to the ARRIVE principles. I emailed a friend of mine who was also a senior editor to ask what process the journal had in place to monitor compliance with ARRIVE and was dismayed to find out that there was none.

I wrote to Ian McGrath (the then editor-in-chief) to express my concern and he asked me to submit a formal review of ten papers from recent issues. I focused on compliance with the twenty points outlined in the ARRIVE guidelines. None of the papers complied in full with the guidelines and some clear themes became apparent. No papers included an explanation for the group sizes used and power analysis was not mentioned. In most cases, it was impossible to follow the fate of each animal and in some papers animals seemed to disappear without explanation; figure legends frequently indicated a range of group sizes, again with no explanation.

I submitted my review and waited for a response. After a couple of

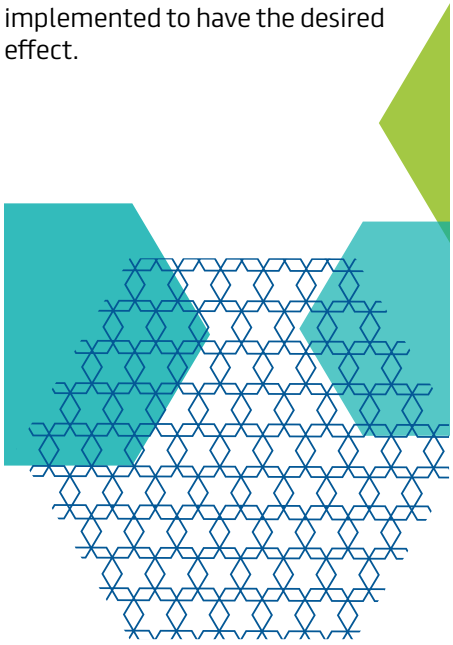
weeks Ian came back to me with a plan. He acknowledged the issue and asked me to become an editor of the journal and to contribute towards the development of a new system of submission and review. What happened next was a period of intense activity followed by some very long periods of waiting. It became apparent that after I sent anything to Ian, an intense period of discussion and deliberation took place that I (thankfully) was not privy to.

It was clear to me that the official ARRIVE checklist was going to be difficult to 'police' for any journal; authors were stating adherence, but the length and complexity of the checklist meant that the journal was failing to check this. What I had proposed to Ian was an overarching principle of 'full disclosure' accompanied with a modified ARRIVE checklist. Publications checklists like ARRIVE are very useful concepts that set out to encourage the inclusion of information critical for both the evaluation of quality and replication of the study, but if they are going to work, their principles must be taken into account during the planning and execution of the project. Trying to conform to the checklist at the point of submission to a journal is never going to be a feasible approach. We felt that a simplified ARRIVE checklist, that focused on the key issues of robust and transparent experimental design and ethical conduct of animal work, would be easier for authors, editors and referees to use. Ian also asked me to take on the role of 'animal ethics editor' to offer advice on animal welfare and ethics for senior editors whenever manuscripts raise concerns. While Ian and I had worked on the animal ethics part of the process, the policy on experimental design and analysis was led by Mike Curtis.

It took a while, but in mid-2015, the new process was launched with changes to the submission system and a series of editorials[1]. Since then, I have had a steady stream of 'animal ethics' referrals, about one per week, most of which can be dealt with by asking for clarification on a few methodological points.

Ian's term ended as editor-in-chief at the end of 2015 and Professor Amrita Ahluwalia has taken on the role. Under Amrita's excellent stewardship, the process has undergone further iterative change, taking into account feedback from authors. The latest 18-point checklist[2] is easy to follow and the revised author guidelines[3] make it clear what the journal expects. It combines the journal's requirements on animal ethics (and their transparent disclosure) with its requirements for improved standards of experimental design and analysis (the oversight of which is managed by the editor-in-chief).

I'm proud that *BJP* has taken the stance it has on this issue and welcomed the opportunity to play a part in the process. Many journals have endorsed ARRIVE, but few have done anything to ensure compliance; in this regard we are leading the way. These efforts should result in higher quality papers in our journal; papers that showcase robust and transparent experimental design and proper regard to the importance of good standards of animal welfare and ethics. Clearly this will only be achieved if everyone involved is committed to the process. Only time will tell if the new policies can be implemented to have the desired effect.



About the author

Elliot is a Senior Scientific Officer in the Research Animals Department of the Royal Society for the Prevention of Cruelty to Animals (RSPCA). Prior to joining the RSPCA, he spent 15 years as a pharmacologist in the pharmaceutical industry and has been a member of the British Pharmacological Society since 1994. He is an editor of the *British Journal of Pharmacology*, a former member of the the Society's Meetings Committee and a current member of the Animal Welfare and *In Vivo* Pharmacology (AWVIP) Sub- committee.

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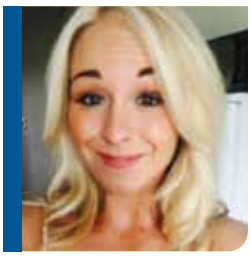
Moulding minds with jelly



Melissa McNaughton
Final year PhD student, University of Strathclyde

We all had a favourite teacher at school. For me, my biology teacher (Mr Cochrane) was the person who provided valuable advice at a time when I was struggling to decide which path to take when I left secondary school. I always knew that I wanted to go to university but I was unsure what I wanted to do. It was a close call between law and science. Mr Cochrane made learning biology truly exciting and really went the extra mile to get to know his students, so was naturally the person I looked to for advice when making this decision. He knew me well enough to know that I had a true passion and talent for biology which had developed and grown over five years of secondary school. His encouragement was enough to convince me to continue my education in science. Now, two and a half years into my PhD in biochemistry and cell biology at the University of Strathclyde, I am confident that I made the right decision. The reason I reflect on this period of my life is that it serves as a good example of the influence and impact that educators can have on the minds of the young and impressionable. In light of this, I developed a keen interest in STEM outreach to try and similarly touch the minds of young people, to engage them in the subject which I so passionately love. It was during my PhD that I volunteered to be the STEM ambassador for my research institute.

My role as a STEM ambassador at SIPBS involves coordinating and delivering STEM activities ranging from hosting summer laboratory projects for secondary school students to fun-filled afternoons of science for primary children. For the former, I have collaborated with the Nuffield

Melissa McNaughton, Professor Susan Pyne (SIPBS) and Aleena Khan. Nuffield Foundation STEM Inspire awards held at the Royal Society of Edinburgh in August 2014

Foundation on various occasions as a project provider for their STEM Inspire programme[1]. I felt particularly passionate about being a project provider on this programme, as it aims to provide gifted pupils from disadvantaged backgrounds with a mentor. This is an invaluable opportunity for the students and is one that I wish I had myself at that age. My remit in this role was to offer support and research experience to talented young individuals who were about to embark on their university career. Such projects give the student the opportunity to gain insight in to life as a scientist whilst acting as a stepping stone to studying a STEM subject at degree level.

In the 'fun-filled' category, creating and delivering one of these activities has been a particular highlight for me. 'Jelly cells' is an activity aimed at primary children (or anyone who likes sweets!).

I initially planned this activity as part of the Glasgow Science Festival[2], but after the success of the activity I now take it to local primary schools as part of my STEM outreach role. One of these schools was Lennox Primary in West Dunbartonshire. This activity provides the children with the opportunity to design their very own cells by adding sweets of various shapes and sizes (to represent intracellular organelles) to pre-set bowls of jelly. Although this activity took a bit of planning (Note: paper bowls will disintegrate when filled with hot jelly and spoil your freshly hoovered car mats!!) – three prototype bowls, fifty jellies and one risk assessment later, I was ready! It is always heartening to see the children engage in the activity whilst they eagerly volunteer to act as mitochondria, lysosomes and the all-important nucleus as I explain the role of each organelle.

In addition to designing their own cells, the children are encouraged to work in teams to discuss potential roles that their cell would perform in the body. Each team then presents their designer cells to the rest of the class. This is the most rewarding aspect of this activity. It's a great experience to witness the raw excitement the children display as they describe the fine details of their super-duper cell capabilities (from anti-aging to accelerated speed and eternal life).

These interactive lessons, using role play as well as the lure of sweets, makes it easy to achieve the overall learning objective - to introduce the children to the building blocks of the body (cells) and give them a basic

Primary 3 and 4 children at Lennox Primary School engaged in Jelly Cell fun

understanding of how cells work. I hope that this activity is something that the children will remember and that they will take home a simple message: science is fun and it surrounds us every day!

Through the different activities that I have been actively engaged in, I have visited many schools and met some wonderful teachers who are committed to developing STEM initiatives as part of the curriculum they design for their pupils. One of those teachers, Mrs Crystal Thompson, has kindly provided her perspective on some of the activities she has been involved in organising in her role as STEM coordinator at Lennox Primary.

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About the author

Melissa received her BSc in Biochemistry and Pharmacology from the University of Strathclyde in Glasgow in 2013. Since then, she has undertaken a PhD in Biochemistry and Cell Biology at the Strathclyde Institute of Pharmacy and Biomedical Science (SIPBS), which she will complete in 2016. Melissa's research questions the role of a class of biologically active lipids in regulating senescence in cancer cells. She trained as a Science, Technology, Engineering and Mathematics (STEM) ambassador at the beginning of her PhD in 2013 and has since collaborated with the Nuffield Foundation, Glasgow Science Festival and the Carnegie Trust on various STEM outreach projects.

Setting futures in STEM

Crystal Ann Thompson
Primary 1/2 teacher and STEM coordinator at Lennox Primary, West Dunbartonshire

Scotland has a long history of scientific discovery. Children are fascinated by new discoveries and technologies and have a natural curiosity about the world around them. The biggest challenge when organising science and related activities in the primary school setting is to make sure that the activity is pitched at the right level. Communicating science to a lay audience has its own difficulties, but keeping children engaged in an activity when it is either too advanced or simply not challenging enough can spell disaster. There is no one-size-fits-all approach when it comes to developing a program of STEM-related activities that are suitable for primary 1–7 aged children (4–12 year olds). Each activity has to be finely tailored to match the children's level of understanding as well as taking into account the principles of curriculum design (challenge and enjoyment, breadth, progression, depth, personalisation and choice, coherence and relevance).

At Lennox, this involves working closely with the Principle Teacher, Jill Williams, and interacting with every teacher to identify key areas where STEM outreach would be of benefit to the day-to-day learning environment of the children in their class. We also engage with the children through our student committee to identify key areas that would be of interest to them. This dialogue really provides the ideas which I then take forward to seek out willing organisations (e.g. the British Pharmacological Society and Biochemical Society) to contribute towards the outreach in specific STEM subjects.

Lennox Primary was only established in August 2015 when two of the local schools merged but in this short time we have already managed to create links with some excellent organisations to help us deliver activities that cover a wide range of topics. One of these organisations is Generation Science[1] which has been actively involved in supporting activities: from 'Little Giants' where children examine differences in an insect's body compared to ours and learn how bees communicate with each other by dancing (primary 2/3) to holding interactive workshops related to generating green electricity (primary 5). Creating strong links with STEM ambassadors has also been tremendously important to the success of the STEM program at Lennox Primary. The school has also been working closely with The Environmental Trust (West Dunbartonshire). This organisation has been integral to the development of our outdoor learning environment. We have been extremely fortunate to have so many willing volunteers who work in STEM subject areas who have donated their time and resources to enhance our program. Children in primary 3 and 4 were recently treated to the Jelly Cell activity delivered by Melissa McNaughton. Primary 5 and 6 were then given the opportunity to learn more about climate change and its effects in Scotland as part of an activity delivered by Mr Fraser Ralston (STEM ambassador and Senior Operational Meteorologist and Transport Scotland Advisor). One of our recent visitors at Lennox was a graduate engineer at Atkins, Ms Lindsay Walter, who covered topics related to global warming and flood prevention with our primary 6 children. Our aim is to introduce our children to topics that they can relate to in their day-to-day lives that have obvious impact (i.e. health, disease, environment, renewable energy, communication, etc.).

Despite the generosity of volunteers, the costs associated with delivering diverse STEM activities can be quite considerable. Our parent council, 'Friends of Lennox', has done a wonderful job at hosting fundraising events to help support many of our extracurricular activities. In order to maintain our future activities and enhance our STEM program, we have been involved in several scientific outreach funding applications which have been led by Melissa McNaughton and others. If successful, then this will help to support our 'in-house' 2016–2017 STEM project 'Pond Life' which is centred on the establishment of a pond ecosystem within the grounds of the school.

In addition to interactive workshops (topics covering habitats, pond lifecycle, eutrophication), the aim of this project is to give the children the opportunity to conduct environmental enquiries and communicate their findings using a variety of tools from lab book to lab blog. The secondary, but equally important, aim of this activity is to establish a natural STEM activity that is literally built into the foundations of the school. The beauty of centring the project on the pond establishment is that it can take many years (over five years) to become fully developed. After this project is initiated, the plan is to create a learning framework that can be purposeful through the years that is driven and eventually maintained by the children over time. Peer learning

will be encouraged throughout to help confidence-building and promote interaction collaboration across the years. Our 'Pond Life' project was principally based on the interests of the children at the school. Listening to the children's ideas and identifying areas that they are keen to learn more about is really what drives me as STEM coordinator at Lennox Primary. They do all the hard work – I merely facilitate to get the experts on board to help bring their ideas to life.

Outreach activities sponsored by the British Pharmacological Society

The Society supports public engagement and outreach activities through its dedicated outreach funding scheme which offers up to £1,500 per project[2]. Four awards were given in 2015 which helped to support projects such as the Cambridge Hands-On Science (CHaOS) summer roadshow. The aim of the CHaOS roadshow was to travel to various schools and community centres and provide children aged 8–13 year old and their families with the opportunity to carry out hands-on experiments. Other ventures have proved diverse and collaborative (with other learned societies e.g. The Biochemical Society) and have included engaging events at science festivals across the length and breadth of the UK, establishing student-run laboratories in primary schools and the innovative online interactive *I'm a Scientist, Get Me Out Of Here: Pharmacology Zone*. A further round of funding applications is currently under consideration. Visit the Society's website for more information related to funding opportunities and to read more about the outreach projects that have been sponsored to date. **www.bps.ac.uk**

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About the author

Crystal Ann received her BSc Caledonian Degree by Negotiated Learning (Science) from Glasgow Caledonian University in 2006 and went on to receive her PDGE merit from Glasgow University in 2009. Since then, she has worked with West Dunbartonshire Council as a Primary School Teacher. In 2013, Crystal undertook the role of Science coordinator, with this role title latterly changing to STEM coordinator in 2015. In 2014, the role extended out with the school, to work in the learning community and beyond, with the introduction of the Scottish Schools Education Research Centre (SSERC) Mentor programme.

Going (Brazil) nuts about pharmacology and nanomedicine

Sophie Bradley, MRC Toxicology Unit, Leicester
André Luis Branco de Barros, Federal University of Minas Gerais, Brazil

All of the invited speakers and organisers of the Workshop on Drug Discovery and Nanomedicine at the Federal University of Rio Grande do Sul in Porto Alegre, Brazil. Taken 30th March 2016.

In March 2016, ten early career researchers were selected from the UK and Brazil to participate and present their research at a bilateral workshop on drug discovery and nanomedicine at the Federal University of Rio Grande do Sul in Porto Alegre, Brazil. This workshop, which was organised by Professor Adriana Raffin Pohlmann (Federal University of Rio Grande do Sul, Brazil) and Professor Nick Holliday (University of Nottingham, UK), was funded by the Newton Fund and the National Counsel of Technological and Scientific Development (CNPq).

The objectives of the workshop were to bring together early career researchers and provide the opportunity for them to form new collaborations and enhance their career opportunities. Here, Dr Sophie Bradley from the University of Leicester and Dr André Luis Branco de Barros from the Federal University of Minas Gerais, Brazil share their experience of the workshop, their research, and their hope for future collaborative ventures.

Dr Sophie Bradley:

Given the emphasis on drug discovery, the pharmacology-based aspects of the workshop were predominantly focused on G protein-coupled receptors (GPCRs) as potential therapeutic targets in a range of diseases, including metabolic diseases, cancers, cardiovascular diseases, inflammation and asthma. In addition to the selected speakers, three lectures were delivered by expert pharmacologists, Prof. Steven Charlton, Prof. Nick Holliday and Dr Liz Rosethorne from the University of Nottingham, who described basic principles in pharmacology and mechanisms of drug action. Over the course of the workshop, we also learnt about modern technologies being used to probe more complex aspects of receptor pharmacology, including bioluminescence resonance energy transfer biosensors and novel fluorescent imaging approaches.

These lectures were complemented by a series of presentations focusing on nanomedicine and the use of micro- and nanoparticles for therapeutics.

Of particular interest was the use of nanoparticles as carriers of therapeutics agents, for example, cytotoxic agents for cancer treatment and therapies for HIV and fungal infections. This really highlighted the potential for this type of approach in limiting side effects associated with standard anti-cancer drugs and overcoming issues with drug resistance.

I am coming to the end of my first post-doctoral position in Professor Andrew Tobin's laboratory at the University of Leicester, and am hoping to establish an independent research career within the next few years. My interests and expertise lie in the use of novel animal models to probe the physiological roles of GPCRs and to evaluate specific GPCRs as therapeutic targets in disease. The M1 muscarinic acetylcholine receptor (mAChR) is a highly attractive therapeutic target for improving cognitive decline in neurodegenerative diseases, such as Alzheimer's disease. We have used a novel mouse model of neurodegeneration to show that targeting the M1 muscarinic acetylcholine receptor may offer therapeutic potential in relieving symptoms of neurodegeneration, such as impairment in learning in memory, and also in modifying the progression of the disease. I presented some of this research during the workshop.

Seminars and lectures were followed by lively discussion sessions which promoted interaction between all of the speakers and audience. The social events in the evening were equally lively, particularly at Galpão Criolo in Porto Alegre where we experienced traditional Brazilian barbeque, live music, dancing and entertainment. The format of the workshop provided the perfect opportunity to engage with each of the early career researchers and discuss overlapping research interests.

In terms of future collaborations, I am really interested in using MRI to visualize misfolded protein accumulation in the brains of neurodegenerative mice, and how drugs that target GPCR may impact on these insoluble deposits. For this I hope to initiate collaboration with Javier Hernández-Gil (Imperial College London) who gave a really interesting presentation at the workshop on iron oxide nanoparticles and how they may be designed and used as a contrast agent for imaging purpose in addition to therapeutic agents.

André Luis Branco:

Nanotechnology is a field dedicated to the manipulation of atoms and molecules in order to construct new structures in a nanoscale range[1]. Since nanostructures show similar sizes as biological molecules, they can be engineered to exhibit several functions designed for biomedical applications[2]. Therefore, the term 'nanomedicine' comprises an area of medical science devoted to the use of nanoparticles for diagnosis, monitoring physical and pathologic process for therapy[3]. Over the last years, many studies have been reported in order to describe novel nanoparticle-based drug delivery systems. Administration of antitumor drugs-loaded nanocarriers typically yields high payload of drugs to the tumor when compared to conventional approaches. Furthermore, side effects may be reduced since nanoparticles can avoid some unspecific uptake in healthy tissues[4,5]. Recent advances in molecular imaging have driven the use of nanoparticles to visualise, characterise and measure biological process at molecular and cellular levels. Molecular imaging offers advantages over the traditional diagnostic imaging techniques since it provides functional imaging that enables the evaluation of chemical and biological process in the body, instead of just images of physical structures as given by traditional imaging approaches[6]. Due to the versatile nature of nanoparticles, many efforts have recently been made to merge diagnostic and therapeutic tools into a single particle, known as theranostics[7]. Therefore, the purpose of using theranostic nanoparticles is to diagnose and treat the diseases at their earliest stage, when the diseases are most likely curable.

Our group has been studying the use of radiolabeled nanoparticles as a theranostic nanoplatform for cancer. In this sense, we have been working on the design of functionalized radiolabeled pH-sensitive liposomes, loaded with several antitumor drugs, for breast cancer diagnosis and/or therapy. Another study conducted in our laboratory is based on use of nanostructured lipid carriers co-encapsulating, at least, two anticancer drugs. The *in vivo* results indicated high tumor uptake, which lead to a better treatment response.

From the nanomedicine perspective, several complementary studies were showcased at the Newton workshop. Dr Marcelo Bispo de Jesus (University of Campinas, Brazil) presented several interesting studies about cellular trafficking of nanostructures. The knowledge of the nanoparticle fate after reaching

The participants of the workshop enjoying a meal at Galpão Criolo, a traditional Brazilian Barbecue place.

a cell is extremely important to understand the molecular interactions of nanomaterials with diseased and healthy eukaryotic cells. Deeper works in this field might contribute to select the best nanoparticle to attain better *in vivo* outcomes.

The interactive nature of the workshop was of great benefit to all involved, from the selected speakers to the audience of students who attended to learn more about drug discovery and nanomedicine. For early career researchers, creating international collaborative networks is an essential process in career development. The quality of the presentations and discussions during this focused workshop pose new perspectives for the participants that might result in future collaborations.

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About the authors -

Sophie completed her PhD at the University of Leicester under the supervision of Prof. John Challiss, which was supported by a BBSRC CASE studentship with GlaxoSmithKline. During her PhD, Sophie characterised the pharmacological properties of novel allosteric modulators for the type 5 metabotropic glutamate receptor. Following completion of her PhD, Sophie moved to Prof. Andrew Tobin's laboratory at the MRC Toxicology Unit in Leicester, where she has been developing expertise in *in vivo* behavioural testing and novel imaging techniques to complement her background in molecular pharmacology.

André completed his PhD in 2012 from Federal University of Minas Gerais, Brazil. He completed his post-doctoral training from Center of Nuclear Technology Development, Brazil. André is now a Professor in the Faculty of Pharmacy, Federal University of Minas Gerais, Brazil. He is working on several projects which focus on the development of new radiopharmaceuticals and nanoplatforms for treatment and diagnosis of many diseases.

The organiser of the workshop, Professor Adriana Raffin Pohlmann (centre) with Sophie Bradley (left) and another invited speaker from the University of Strathclyde, Margaret Cunningham (right).

How to set up a Society that Thinks Mental

Artysha Tailor
Student, King's College London

I was seven days away from my second year exams of dental school - I was racking up a maximum of three hours sleep per night over a period of two weeks, I couldn't work out why I had a continuous low grade headache, my brain was on overdrive trying to absorb the copious facts but I just couldn't retain anything. I was panicking; my heart was racing and I was faced with the possibility of failure.

I had come into a degree straight from school; I found school fairly easy, getting good grades throughout and never failing an exam. I had suddenly found myself at university, living away from home and feeling out of my depth. I had never experienced this sort of exam-induced anxiety and it was not helping me…and I was not helping it. However, a good friend, help from my parents and a mindfulness tape did help. They gave me back my sleep, reduced my anxiety, allowed me to understand and retain information again. I managed to get through my exams and was onto the next year with a better awareness of my own mental health.

I am sure this is a more common scenario than most would like to admit.

Prior to this, I knew the effects of mental illness quite well – from my early to late teens I had looked after a family member with a severe mental health problem. I observed, first hand, the devastating effects of others perceiving their mental illness as not being "a part of them" and instead being some sort of exogenous entity… and I watched the stigma that followed. As a result, I am more open and accepting of all mental health.

ThinkMental

This combination of experiences led me to investigate if there was a society at King's College London that was dedicated to mental health. There wasn't one and so, together with a friend who I met through our mutual passion, ThinkMental was born. It is dedicated to raising awareness and breaking down barriers of stigma towards mental health through informal support groups, educational talks, campaigning and many more activities.

There are a lot of things to think about when starting your own society but a good place to start is by considering what your aims are, how you will do it and where will you get the money from to set the society up? Getting advice from your student union (SU) is often useful. The rest, such as a name, logo and social media page will come in time and it's a good idea to reel in some favours from skilled colleagues around you to help with these.

In order to establish a society, you need a good team and you need to think carefully about a few things - who is going to be part of this team, where are you going to find them (your student union might be able to help), what are they going to do (don't forget you can have more than one person for a given role!) and what is their primary reason for wanting to help you? The last question is an important one because someone wanting to help solely for the sake of it looking good on his or her CV is unlikely to be a reliable team member. Try your best to find people with as much passion as you.

If your society can fit under the umbrella of your SU, which is normally done by ratification, it will help with a whole host of things such as online advertisement of events, funding and so on. Our ratification with the SU meant we could apply for funding of up to £1,000 towards our ThinkMental Health awareness week.

All female a cappella group, The Rolling Tones, singing at ThinkMental's Variety Show, by Artysha Tailor

Funding is really important when you're a new society. Without money it's hard to organise and advertise events; no student will be interested in a society that doesn't do anything! As well as approaching your SU for funding, try and obtain sponsorship from a company (they often ask for favours in return for their money, for example their logo at the bottom of event advertisements).

Ratification may also allow you to hire out and use SU and university spaces for free or for very little money. Use this to your advantage – you can hire out lecture theatres, classrooms, your SU bar and more. This year we used this to our advantage to hire out a student space to put on a Variety Show with music, dance and drama acts, for very little money.

Pop that Stigma campaign, by Artysha Tailor

This brings me on to another great tip – collaborate with other societies. One of the reasons why our Variety Show was so successful was because of collaborations with other societies, such as The Rolling Tones (seen in the picture on the left), Bhangra Society and Running a Mock Improv (a very talented improvisation group). These societies were well established with large followings and this allowed us to reach out to a larger audience, which we would have otherwise not been able to.

When coming up with ideas for events, try to think about who your audience will be. Mental health is a hard topic to engage students with and we generally have two types of events: one type where people will turn up because they're already interested and campaigns, where we go around trying to get people's neurons firing. For example, our tea and talk events, where we create an informal, non-discriminative environment for people to talk, tend to attract people that already have an interest. While our campaign events involve actively approaching students to try and create an open conversation about mental health. Two good examples are our "Pop that Stigma" and "Splash that Stigma" campaigns. Both are exercises which involve writing negative connotations of mental health on balloons and white t-shirts, respectively, and then symbolically popping the balloon or splashing coloured powder on the words. The aim of this process is to wipe out the negative associations and replace them with something positive.

Last but not least, publicising your society events is really important. Think about what sort of students you are likely to engage and target them, whether it is through social media, asking other societies to publicise your events, handing out and putting up flyers or getting an article about your society in a relevant university publication.

So, if you're thinking about setting up a society my best pieces of advice are: think carefully about what your aims are, who is going to be your committee,

Splashing out the stigma campaign, by Artysha Tailor

where you're going to get funding from and how you can tailor your events to the people you're likely to engage with. It's a broadening experience trying to set something up from scratch - you'll meet some incredible people and do some incredible things along the way.

How to Contact ThinkMental:

- **thinkmentalsoc@gmail.com**
- **www.facebook.com/thinkmentalsoc**

Get in touch if you'd like to know more or get involved!

It is coming to the end of the academic year now so things are winding down a little. However, we'll have events going on next year - like the ones that have already been mentioned plus more.

About the author

Artysha is a fourth year dental undergraduate at King's College London. It was during her intercalated Neuroscience that she, along with Chloe Cameron, founded the ThinkMental society and sat on the committee as Co-Presidents. During that year the society won the Best New Activity group award from their student union. Currently Artysha sits on the committee as the charities officer and also sits on the Dental Council committee as the Welfare Officer.

Ambassador Update: Innovative Chemistry in Drug Design and Pharmacology in the Public Eye

Anne Leaver University of Edinburgh, **Steve Tucker** University of Aberdeen and **Kayley Scott** University of Glasgow

There has been a lot of progress in anticancer drugs and medical imaging. The availability of new cancer treatments has increased, and the technology of imaging has allowed the detection of abnormal blood vessels and tissue, improving diagnosis and treatment. This has involved bringing new ideas from diverse fields of chemistry and biophysics into drug design and monitoring.

Innovations Biotechnology at the Edinburgh International Conference Centre focused on the biotechnology of drug discovery and new approaches to cancer research and imaging of the eye. Two early career scientists presented innovative research to a public audience of all ages and took part in discussion and networking sessions before and after the presentations.

The event was sponsored by the British Pharmacological Society, in order to promote understanding of drug development and therapy. It was organised as part of the the Society's Ambassador scheme, recently set up by the Society to widen access and promote pharmacology using a diversity of approaches including student societies, school and public outreach and networking. In this event, jointly organised by Edinburgh and Aberdeen Ambassadors, a new idea was trialled; student ambassadors and reporters from all over Scotland were invited to help run the event. In addition to meeting and greeting the public, student ambassadors and reporters were also able to learn from shadowing professional staff at the international conference centre. In the auditorium, student ambassadors and reporters were introduced and attendees were encouraged to discuss elements of their studies and ambitions with them, as well as the importance of biotechnology. The Society also handed out information about pharmacology careers and encouraged students to look into grants/prizes for basic research, as well as membership and work in clinical therapeutics. Of particular note was the efforts of the student ambassador from the University of Aberdeen (Denys Prociuk) and the student reporter from the University of Glasgow (Marzug Ungogo) who helped with setting up the event, and spent time welcoming the public to the British Pharmacological Society's stand.

The first speaker was Asier Unciti Broceta, from the Edinburgh Cancer Research Centre at the Western General Hospital. Asier recently won two prestigious awards. The first was a Healthcare Technology Challenge Award, to carry out work on palladium-

Dr Anne Leaver (BPS ambassador) chairs the BPS sponsored ecent in Edinburgh.

activated therapy, which involves converting inactive pro-drugs into anti-cancer agents within the tumour. Asier also received the Royal Society of Edinburgh's Patrick Neill medal for his work on biomedical technologies and innovative therapeutics. Asier has studied Medicinal Chemistry in Spain, Italy and the UK and has developed new areas of translational research. He joined the Chemistry department at Edinburgh, where he developed carriers which target specific cells, chemosensors, and bioactivity screens and, as the impact of these findings became apparent, later moved to the Edinburgh Cancer Research Centre. Asier also discussed kinase inhibitors, another important group of anti-cancer drugs which owe a lot to pioneering research led by Philip Cohen in Dundee.

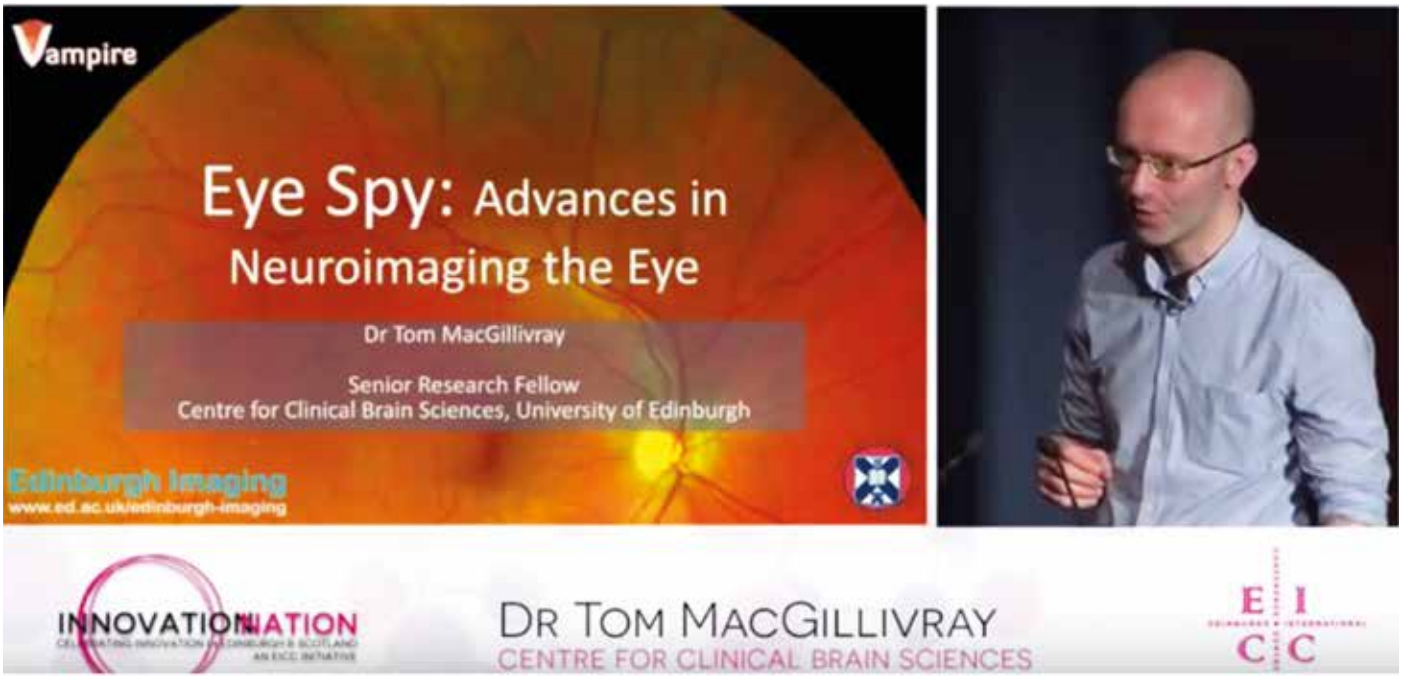
The next speaker, Dr Tom McGillivray from the Centre for Clinical Brain Sciences, talked about imaging of the eye and his role in project VAMPIRE (Vascular Assessment Measurement Platform for Imaging the REtina). Tom trained in Edinburgh as a biophysicist and is a member of Edinburgh Imaging, an Edinburgh and Dundee collaboration with domestic as well as international links. Work in his retinal imaging lab in the Edinburgh Royal Infirmary aims to identify disease and monitor the effectiveness of treatments. During his presentation, Tom discussed the potential of eye imaging for detecting cardiovascular disease, cancer, and neurodegeneration. Tom's particular interest is small blood vessels and microvascular disease. The shared blood supply between the brain and retina, and the influence of the kidneys on vascular function through renin-angiotensin mean that retinal imaging and angiography can act as biomarkers in MS, stroke, dementia and diabetes. These conditions are characterised by thinning of the retina and/or dying back of small blood vessels. The project aims to collect data on retinal structure and disease progression and link this data with prognosis and intervention. Thus retinal biomarkers may provide early warnings of disease and indicate response to therapy.

During the lectures, student reporter Kayley Scott referenced a quote from Dr MacGillvray's lecture: "empowering the high street optician to be screening for more than just eye health". She felt it really summed up the whole idea of Innovation, with science constantly driving us forward to new discoveries to help make life better for people.

Below are some quotes gathered by the Society's student reporter, Kayley Scott, during the Innovations Biotechnology and Drug Discovery networking event.

Kayley spoke to members of the public, asking what it was that brought them to the event. A high school delegate told Kayley "I want to keep learning and understanding science". A retired physicist & engineer: "I want to know what we can learn from animal cells and how we operate"; he was keen to explore "a different aspect of science" than what he had previously experienced.

Dr Asier Unciti Broceta begins his talk on novel approaches to cancer treatment.



Dr Tom MacGiilvray begins his talk on eye imaging.

Afterwards, Kayley was introduced to Andy, a 75-year-old man who attended Innovation Nation because the presentations are relevant to his life, after being diagnosed with cancer and eye problems. He told Kayley this attracts him to attend further research-led events in these fields and he believes events like these provide "a wealth of information" for the public.

Kayley spoke to Dr Broceta and Dr MacGillvray and asked them why they wanted to be involved in these public events.

Dr Broceta spoke about his home in Spain and his outreach to local high schools: "I visit high schools to show students that they can follow this pathway [into science] and do it too".

Dr MacGillvray told Kayley that he supports these public events by the British Pharmacological Society, as they provide people with "an exciting opportunity, meeting people you wouldn't normally communicate with" and that he feels it allows researchers to "cross disciplines and convey new research". He also told Kayley he believes it is important to invite the public to explore science and hopefully "inspire new participants" for studies.

Kayley feels we should continue hosting such events, as it is a fantastic way for the general public, researchers and young scientists to be involved with the ever changing world of science: "I feel that bringing wider understanding to people through these talks is vital to continue to inspire people to become engaged with research in new ways. Not only this, but the informal aspect is very welcoming and a fantastic way to network and share interests and hopefully meet some exciting people! I know I certainly did! Thank you again for involving me in this wonderful event and fantastic opportunity."

A video of the event is available online: **https://youtu.be/ZF0x2t_BkUw**

Upcoming British Pharmacological Society meetings and workshops

- **International Narcotics Research Conference (INRC) 2016**
  10 – 14 July 2016 | Bath
- **New Insights in Inflammation**
  27 July 2016 | London
- **Drug Discovery Workshop**
  6 – 7 September 2016 | Edinburgh
- **General and Advanced Receptor Theory Workshop**
  12 – 13 September 2016 | Liverpool
- **Pharmacological aspects of microvascular cell-cell signalling and CVS disease**
  21 – 22 September 2016 | Oxford
- **Pharmacokinetics and Pharmacodynamics Workshop**
  25 – 26 October 2016 | Birmingham
- **British Pharmacological Society's President's Lecture**
  17 November 2016 | London
- **Pharmacology 2016**
  13 – 15 December 2016 | London

To register your interest and for further information about any of these scientific meetings and workshops, please contact **meetings@bps.ac.uk** or visit **www.bps.ac.uk/news-events**

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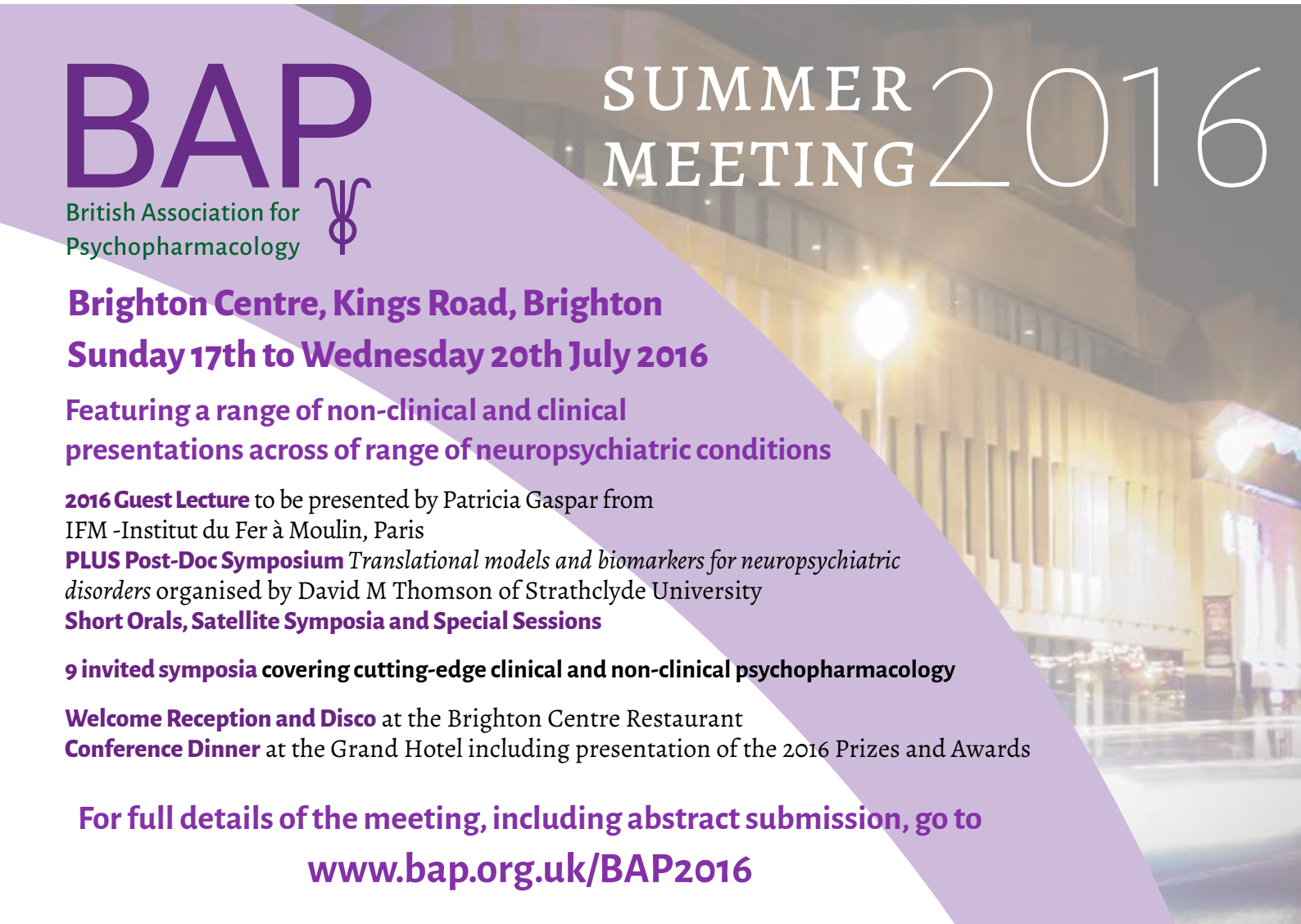


BAP
British Association for Psychopharmacology

SUMMER MEETING 2016

Brighton Centre, Kings Road, Brighton
Sunday 17th to Wednesday 20th July 2016

Featuring a range of non-clinical and clinical presentations across of range of neuropsychiatric conditions

2016 Guest Lecture to be presented by Patricia Gaspar from IFM -Institut du Fer à Moulin, Paris
PLUS Post-Doc Symposium *Translational models and biomarkers for neuropsychiatric disorders* organised by David M Thomson of Strathclyde University
Short Orals, Satellite Symposia and Special Sessions

9 invited symposia covering cutting-edge clinical and non-clinical psychopharmacology

Welcome Reception and Disco at the Brighton Centre Restaurant
Conference Dinner at the Grand Hotel including presentation of the 2016 Prizes and Awards

For full details of the meeting, including abstract submission, go to
www.bap.org.uk/BAP2016

Alemtuzumab in multiple sclerosis: a whistle-stop tour

Zoya Georgieva, Addenbrooke's Hospital, Cambridge
Alasdair Coles, Addenbrooke's Hospital, Cambridge

Multiple sclerosis (MS) is the most common cause of chronic neurological disability in young adults, affecting 1 in 1,000 in Western countries. In 85% of MS cases, episodes of inflammation (relapses) result in the loss of myelin around nerve fibres in the brain or spinal cord (demyelination), followed by complete (later- partial) recovery[1]. Repeated cycles of demyelination and imperfect repair cause accumulation of irreversible disability over time; in later stages disability progresses independently of relapses (secondary progressive MS, SPMS; figure 1).

Relapses have been treated with corticosteroid therapy for more than five decades but disease-modifying therapies (DMTs) are relatively recent advances. Interferon β and glatiramer have been mainstay DMTs since 1993. Only in the last 10 years have monoclonal antibody DMTs been ushered into the clinical spotlight.

Alemtuzumab is a humanised monoclonal antibody against CD52, a marker expressed on the surface of T-lymphocytes, B-lymphocytes and monocytes, but not on blood cell precursors. Within minutes of intravenous infusion, alemtuzumab results in a profound long-lasting reduction in blood lymphocyte counts (lymphopaenia)[2].

Alemtuzumab is given as a daily infusion for five days, then the lymphocyte pool is allowed to repopulate before a second cycle of three days' infusion a year later. Subsequent infusions are only given if there is a sign of disease activity (relapses or new MRI lesions).

Because of its high efficacy, alemtuzumab was licensed in the EU to treat active relapsing-remitting MS in 2013, and subsequently in the USA, Canada, Australia, Switzerland, Israel, Mexico, Argentina and Brazil; in April 2014 it was recommended by NICE. This is the culmination of more than three decades of research, but alemtuzumab did not start life as an MS drug (figure 2).

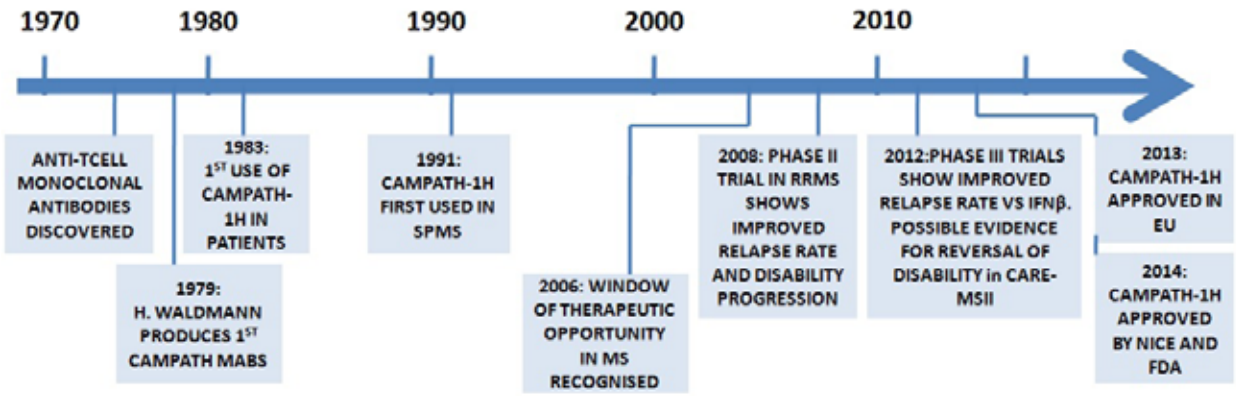
From bone marrow transplants to multiple sclerosis:

Graft-versus-host disease was a major impediment to bone marrow transplant, alongside graft rejection; both were known to be driven by T-cells in the donor bone marrow or recipient, respectively. In the 1970s, monoclonal antibody (Mab) technology made it possible to specifically target T-cells and clear them from the donor's marrow, or from the recipient's blood. A single inoculation of human T-cells in a rat created a family of Mabs, all targeting CD52. One of these antibodies, CAMPATH-1G, was especially stable and effective, and was initially used in patients with aggressive chronic lymphocytic leukaemia, a blood cancer. After a dramatic initial improvement, patients tended to stop responding to treatment, partly because their immune system would recognise the rat-derived Mab as 'foreign' and develop neutralising antibodies against it.

To overcome this limitation, CAMPATH-1G became the direct precursor of humanised CAMPATH-1H, now called alemtuzumab[3]. Alemtuzumab was initially used to treat blood cancers and vasculitis (inflammation of blood vessels); the rationale for using it in

Figure 1: Natural History of MS

Figure 2: Alemtuzumab research timeline



multiple sclerosis was likewise to clear the T-cells driving the disease.

Between 1991 and 1999, a total of 36 MS patients were treated with alemtuzumab[4,5], all with secondary progressive disease and MRI evidence of active inflammation. Despite a great reduction in relapses and new inflammation, 15 of 28 patients had an increase in disability. This was approximately equivalent to walking 100 m unaided at entry to the study and requiring crutches to walk 20 m at the end of follow-up. Patients with greater brain atrophy (reflecting nerve cell loss) were more likely to have progressive disability through worsening of existing symptoms. They also tended to have more inflammatory lesions before treatment.

To address this dissociation between progression of disability and suppression of inflammation, 22 patients with aggressive relapsing-remitting MS (RRMS) were treated with alemtuzumab. In this cohort there was 91% reduction in relapse rate and 16 of 22 patients experienced improvement in their disability over one year (the remaining patients except one were stable)[6].

This led to a paradigm shift in MS: accumulation of disability is determined by neuron loss, which is dependent on the inflammatory burden at earlier stages of disease, making early treatment crucial (figure 2). Subsequent alemtuzumab trials have all been in patients with early but active disease (at least two relapses in two years) and mild-to-moderate disability at entry.

Efficacy in early MS

A phase II randomised controlled trial (RCT) (CAMMS223) compared alemtuzumab to the most efficacious therapy at the time, interferon β-1a (IFNβ-1a), in 334 patients with moderate disability and disease duration of three years or less. Alemtuzumab reduced the accumulation of disability by 71% during 36 months of follow-up[7], an effect durable at five years of follow-up[8].

In phase III trials in treatment-naive (CARE-MSI)9 and previously treated patients (CARE-MSII)[10], alemtuzumab was superior to IFNβ-1a in reducing relapse rate (49% and 54% reduction, respectively). There was also evidence for reduced accumulation in disability from the CARE-MSII trial, but not in CARE-MSI. This possibly occurred because, purely by chance, a lower than expected proportion of the control group in CARE-MSI achieved the disability outcome, making a difference between the groups difficult to detect.

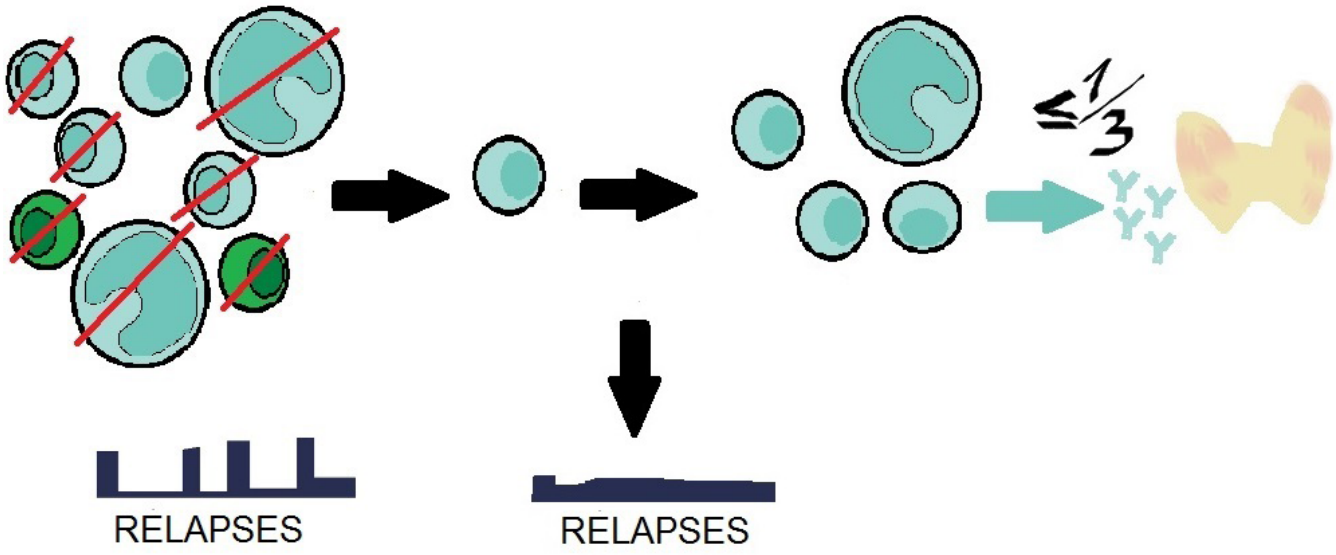
Interestingly, in CAMMS223 and CARE-MSII a significant number of alemtuzumab patients (but not controls) experienced improvement in their disability. To date, no treatment has been conclusively shown to reverse disability in MS, but the observed effect is plausible. T-cells repopulating the immune system after alemtuzumab may secrete factors that support the survival of nerve cells and oligodendrocyte precursor cells (which give rise to myelin-producing cells, needed for repair)[11]. There are now two active trials investigating MRI measures of remyelination following alemtuzumab (ClinicalTrials.gov NCT01307332, NCT01395316).

Follow-up studies (ten years for CAMMS223 and five years for the CARE-MS studies) indicate that roughly half of patients need only the initial two cycles of therapy for disease control over five years; a third need one additional cycle of treatment, 20% have two re-treatments and 10% need five cycles in total. Most patients have stable or improved disability at 5–10 years after first treatment.

The immune system after alemtuzumab

The mechanism of action of alemtuzumab is incompletely understood, but it would be simplistic to suggest it is purely an immunosuppressant.

Figure 3: The immune system after alemtuzumab



Firstly, treated patients typically do not suffer serious infections although mild-to-moderate respiratory, urinary and herpetic infections are common. Patients remain able to mount an immune response to a range of vaccines as demonstrated in a small case-control series[12]. Additionally, no cases of progressive multifocal leukoencephalopathy (a usually fatal disease caused by JC virus in immunosuppressed individuals) have been reported in MS patients receiving alemtuzumab.

Secondly, treatment efficacy lasts beyond the period of most profound lymphopaenia[13] and the repopulating immune system after treatment is altered. Repopulating T-cells tend to come either from expansion of residual cells in blood or new cells generated in the thymus; these have different properties. For unclear reasons, patients who develop autoimmunity after alemtuzumab have defective thymic function and instead repopulate via peripheral expansion.[14]

Adverse effects

Up to a third of patients treated with alemtuzumab develop novel autoimmunity[5], usually affecting the thyroid gland (figure 3). Idiopathic thrombocytopaenia (a bleeding tendency due to low blood platelets, in 2% of treated patients) and glomerulonephritis (inflammation of the kidney, in 0.1% patients) have also been reported. However, re-emergence of the original autoimmune condition (MS) is uncommon. Predicting novel autoimmunity is difficult: IL-21 is a known marker, whose use is currently precluded by the lack of a suitable detection kit[15]. The risk is instead managed by regular monitoring of blood tests to detect emerging autoimmune disease early on.

Additionally, most alemtuzumab recipients experience a post-infusion syndrome (fever, labile blood pressure, wheeze, rash), and a transient worsening of their existing neurological deficits. Current treatment regimens control these symptoms using steroids, antihistamines and inhalers.

A balancing act

With the increasing availability of potent immunomodulatory therapies for MS, clinicians and patients now face choices: which agent, when, at what risk? No head-to-head trials exist between the newer DMTs (natalizimab, fingolimod and alemtuzumab). However, a Cochrane review has estimated that over 24 months, alemtuzumab is superior at reducing relapses (by 54% versus placebo), followed by natalizumab (44%) and fingolimod (28%). Alemtuzumab came second in reducing accumulation of irreversible disability (65%)[6].

The Association of British Neurologists recently classified DMTs as drugs of moderate efficacy (category 1) and drugs of high efficacy (category 2, to which alemtuzumab belongs). One treatment approach is 'escalation therapy': using category one therapies early and reserving category two drugs for later stages. This is in contrast to 'induction therapy' where a potent DMT is used first to control early disease. The two approaches have pros and cons, comprehensively reviewed elsewhere[17]. The alemtuzumab trials leading to its approval were in patients with early moderately active disease and its license reflects this, allowing both escalation and induction strategies. The decision remains in the hands of the clinician and patient.

A patient's perspective

This story would be incomplete without considering the perspective of the patients who have received alemtuzumab treatment. In preparing

the manuscript, we came across the online diary of one such patient. His story is best rendered in his own words and can be found here: http://www.davidscampathstory.org/experience.html.

Conclusion

Alemtuzumab is an exciting addition to the range of treatments for multiple sclerosis. A few days of infusion can suppress disease activity, and allow endogenous repair, over many years. This comes at a cost, the most prominent being the risk of autoimmune disease for five years after each cycle of treatment; this requires careful monitoring by patient and neurologist. The next chapter will likely see a return to the bench side to elucidate its mechanisms of action, and to exploit its potential in studying human autoimmunity.

About the authors:

Alasdair is Professor of Neuroimmunology in the Department of Clinical Neurosciences at Addenbrooke's Hospital, Cambridge. He led the first investigator-led trial of alemtuzumab and was the UK chief investigator for the phase II and III trials. His research since 1994 with Alastair Compston led to licensing alemtuzumab in multiple sclerosis.

Zoya is an academic clinical fellow at Addenbrooke's Hospital, Cambridge. She is interested in neuroimmunology, specifically MS, to which she was first introduced by Prof Coles during her foundation medical training. She is currently supervised by Dr Joanne Jones (Cambridge), studying the mechanisms of autoimmunity in lymphopaenia

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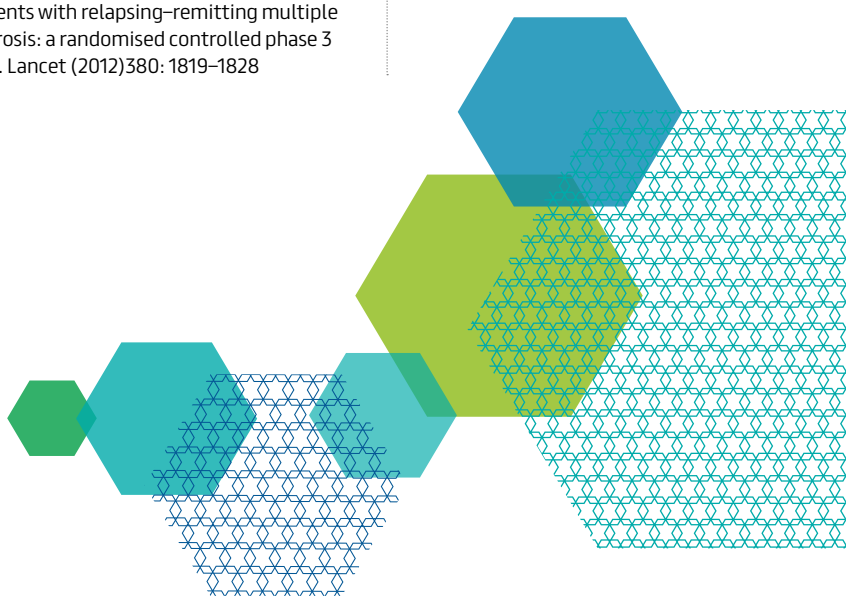


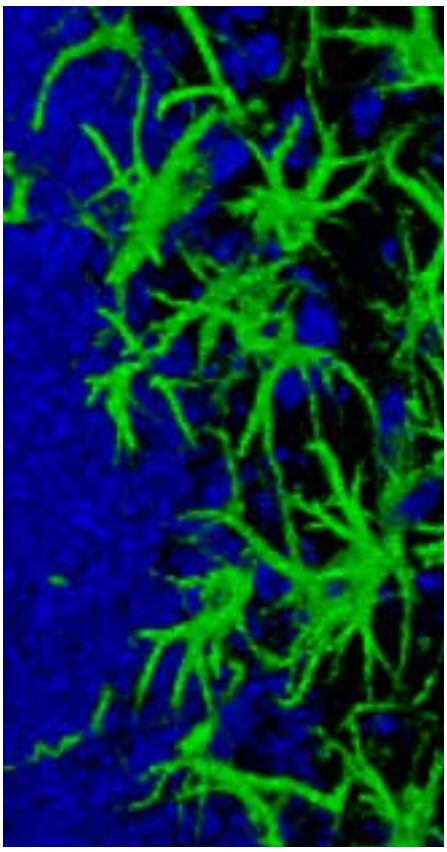
Meetings update

Barbara McDermott, Vice President – Meetings
Talja Dempster, Head of Meetings & Events

Past meetings & events

6th Focused Meeting on Cell Signalling

The British Pharmacological Society's 6th Focused Meeting on Cell Signalling took place on 18–19 April 2016 at the University of Leicester. The conference was attended by 178 delegates drawn primarily from the UK, but also with attendees from across Europe (France, Germany, The Netherlands, Belgium, Sweden, Switzerland and Malta), as well as from further afield (Australia, Canada and USA). 84 abstracts were presented in the form of oral communications and posters and the feedback survey had a satisfaction rate of 98.7%.



Upcoming meetings & events

International Narcotics Research Conference

10–14 July 2016, Assembly Rooms, Bath

The International Narcotics Research Conference's purpose is to bring together scientists from around the world to discuss aspects of opioid research ranging from genetic and molecular to *in vivo* studies. Previous meetings have been held throughout the world and the Society is delighted to be hosting the 2016 meeting.

The programme for the upcoming INRC meeting is available on our website. There will be a full programme of science from Monday–Thursday including plenary lectures, symposia on opioid receptor structure, receptor regulation and crosstalk, neuronal plasticity, pain, craving and addiction, emotional disorders, and the immune system, as well as poster sessions.

Please visit **www.bps.ac.uk/inrc** for more information and to register to attend.

New Insights in Inflammation

27 July 2016, University of East London, London

This meeting concentrates on the latest concepts in inflammation, centring on the cutting edge research being carried out by young scientists. Themes such as innate immune cells, inflammation and degenerative diseases, the resolution of inflammation, and metabolomics will be welcomed. The meeting is deliberately left wide in order to enable early career researchers to present their work in a series of oral communication and poster sessions dedicated to them. It celebrates the 50th Anniversary of Pharmacology at the University of East London, where inflammation and immunity has been a core research topic since the pioneering work of Dr GB West in the histamine era.

Please check the Society's website **www.bps.ac.uk** for more information and to register to attend.

Delegates at the 6th Focused Meeting on Cell Signalling

Pharmacology 2016 symposia announced

13–15 December 2016, QEII Conference Centre, London

Pharmacology 2016 will welcome members from the American Society for Pharmacology and Experimental Therapeutics (ASPET), the American Society for Clinical Pharmacology and Therapeutics (ASCPT) and the Chinese Pharmacological Society (CPS).

The symposia for the meeting have been announced, as follows:

Cardiovascular and Respiratory Pharmacology

- From bench to bedside: Targeting the pathophysiological responses of ischemia-reperfusion injuries
- Targeting cardiovascular GPCRs using biased agonism
- Nanomedicine in pharmacology

Neuropharmacology

- Uses and challenges for human pharmacology studies to understand CNS diseases
- Fatty acid amides (aka lipoamines) beyond cannabinoids
- Recent developments in research of melatonin and its potential therapeutics application

Integrative Systems Pharmacology

- The long reach of the bowel: Translating microbiome science into therapeutics for systemic human diseases
- Study, development and rationale use of immunopharmacological agents
- Immuno-oncology: From bench to bedside

Molecular and Cellular Pharmacology

- Non-traditional/orphan GPCRs as novel therapeutic targets
- Biochemical strategies in drug discovery and targeting
- Anti-tumour pharmacology and traditional Chinese medicine
- Translation to therapeutics: Resolution of inflammation

Drug Discovery, Development and Evaluation and Toxicology

- Organ-on-a-chip technology - the future of physiological profiling?
- Clinical application of systems pharmacology models
- Clinical pharmacology, pharmacokinetics and pharmacogenetics in pregnancy (C4P)

Vice President – Meetings role applications

In June, the Society will be inviting applications for a number of leadership roles on Council. The participation of members in this way ensures that Council is able to achieve the Society's mission to promote and advance the discipline of pharmacology in all its forms, and to establish and deliver our strategic aims. These posts will be filled by election later this year, with elected candidates taking office on 1 January 2017.

The role of Vice President – Meetings is to direct and guide the scientific meetings programme of the Society to serve the needs of the membership. This includes working with the Meetings Committee to recommend an annual programme of meetings, taking into consideration the strategy and direction given by Council. Annual budgets, which include the provision of bursaries, are agreed with the Finance Committee.

To register your interest and receive more information on the Vice President – Meetings role, please contact the Society's Finance & Commercial Director, Mike Poole (mike.poole@bps.ac.uk).

BRITISH PHARMACOLOGICAL SOCIETY

TODAY'S SCIENCE TOMORROW'S MEDICINES

Register & submit your research

PHARMACOLOGICAL ASPECTS OF MICROVASCULAR CELL-CELL SIGNALLING AND CVS DISEASE

21–22 September 2016
Oxford, UK

There has been a dramatic increase in our understanding of cell signalling over the last five years, with key papers indicating the importance of endothelial cell projections as signalling microdomains, which appear subject to disruption by cardiovascular disease. This focused meeting will provide a forum for scientists working in vascular biology, with a particular interest in identifying novel therapeutic targets in endothelial cell dysfunction that is a feature of cardiovascular disease.

Deadlines for your diary:

Abstract submission: 10 August

Early registration: 26 August

Bursaries (available for members of the British Pharmacological Society): 10 August

For further information about attending or presenting at this meeting, please email **meetings@bps.ac.uk** or visit **www.bps.ac.uk/cvs.**