BJP British Journal of Pharmacology

DOI:10.1111/bph.12820
www.brjpharmacol.org

Themed Section: Nanomedicine

EDITORIAL

Special issue of BJP on Nanomedicine

Correspondence
Andrew Owen, Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool L693GF, UK. E-mail: aowen@liverpool.ac.uk

Andrew Owen[1,2,3]

[1]*Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool L693GF, UK,* [2]*MRC Centre for Drug Safety Science, University of Liverpool, Liverpool L69 3GE, UK, and* [3]*Tandem Nano Ltd., Foundation Building, 765 Brownlow Hill, Liverpool L69 7ZX, UK*

LINKED ARTICLES
This article is part of a themed section on Nanomedicine. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2014.171.issue-17

Nanomedicine is an emerging field of life science that encompasses the application of nanotechnologies to drug delivery, diagnostics or regenerative medicine. The focus of this special issue of BJP is on drug delivery, targeting and safety of nanomedicines. While the relatively recent advent of technologies that allowed robust characterisation of the physical properties of nanomaterials has triggered an explosion of related publications, it is important to recognise that nanomaterials have medical applications dating back at least to the 1960s, when iron nanoparticles were first investigated as a therapy for anaemia (Marchasin and Wallerstein, 1964). Indeed, numerous other products (e.g. liposomes and polymer-conjugates) utilising materials measurable in the nano-scale have been successfully translated to approved medicines prior to the first Pubmed listing of the term 'nanomedicine' in 1999 (Weber, 1999). Since then, the number of publications relating to this search term has grown exponentially reaching over 1300 in 2013, and although dependant on the definition applied, there are now over 50 licensed products that are considered to be nanomedicines.

There have been numerous recent successes in applications for overcoming bioavailability issues or sustained release for orally administered drugs (Junghanns and Muller, 2008) and long-acting parenteral formats able to provide sustained therapeutic plasma exposure over a period of weeks to months (Boffito *et al.*, 2014; Owen, 2010). Moreover, the first aptamer-targeted polymeric nanoparticle medicine for the treatment of several cancers entered Phase III clinical trials in 2013 following very successful phase II data (Bertrand *et al.*, 2014). Multidisciplinary research is a prerequisite for nanotechnology to attain its true potential for optimising the pharmacological properties of medicines but traditionally, the field has been dominated by materials chemistry. Indeed, at the 2009 European Medicines Agency Expert Group Meeting on Nanomedicines, it was estimated that potentially 90% of materials being proposed were unsuitable for their proposed use. Further integration of life science research into the nanomedicine field is therefore of clear importance. With this in mind, the purpose of this special issue is to build on the success of the British Society for Nanomedicine (www.britishsocietynanomedicine.org) sponsored workshop at the Pharmacology 2013 meeting to further engage pharmacologists with this emerging field of medicine.

The first manuscript in this special issue was contributed by Dr Darren Moss and Dr Marco Siccardi from the University of Liverpool, UK (Moss and Siccardi, 2014). Their review provides an overview of the different types of materials chemistry-based nanotechnology that is being applied to improve the pharmacological properties of active pharmaceutical ingredients (APIs). The application of many current nanotechnologies aims to confer advantages for the pharmacokinetics and/or distribution of APIs, and the authors outline the current progress and gaps in knowledge when applying physiologically based pharmacokinetic (PBPK) modelling to estimate benefits or risks in the pre-clinical environment. PBPK modelling has gained much momentum in recent years and is now almost routinely integrated into drug development programmes for conventional medicines. When considering many nanomedicine candidates however, there are a considerably more diverse set of variables that need to be considered for accurate modelling. In many cases, the effect of the API physicochemical properties on pharmacokinetics and distribution may be, to varying degrees, overridden by the physical properties conferred by the nanotechnology (e.g.

size, surface charge, polydispersity, active moieties etc) and further understanding these effects is required.

The focus of the following articles in the special issue relates to current understanding of the safety of nanomedicines and current gold-standards for preclinical safety assessments. The first of these was contributed by members of the Nanosafety Research Group at Heriot Watt University, UK (Kermanizadeh *et al*., 2014). The effects of occupational, consumer and environment exposure to engineered nanoparticles are huge areas of toxicology research being conducted in parallel and often distinctly from nanomedicine development. However, there is potentially much to learn from the engineered nanotoxicology field that can be applied to the safety of nanomaterials used in medicine. Professor Vicki Stone at Herriot Watt University has contributed an enormous amount of research to understanding the effects of exposure to nanomaterials over the last decade. Their review outlines the current state of broader knowledge in regard to the effects of engineered nanomaterials on the liver and how route of administration can influence the observed responses. *In vitro* models that enable accurate prediction of *in vivo* responses are of clear value to accelerate development of safe nanomedicines, and the review summarises recent comparisons for hepatotoxicity in primary human cells and preclinical species.

The article by Kermanizadeh *et al*. clearly outlines that certain aspects of the hepatic response to engineered nanomaterials involve mechanisms with an immunological basis. One clear focus of the Nanotechnology Characterization Laboratory (NCL) in Maryland USA, has been to understand the immunological consequences of exposure to nanotechnology products, who have been at the cutting edge of this research area. Dr Marina Dobrovolskaia is leading this research at NCL and along with her colleague Dr Ilinskaya have provided a more specific overview focusing on the consequences of immunosuppressive and anti-inflammatory properties of nanomaterials (Ilinskaya and Dobrovolskaia, 2014). The paper provides a balanced overview of unintentional immune interactions but also those with potential therapeutic benefit, which integrates current understanding of how nanomaterial physical properties influence immunological and inflammatory responses. A clear message from this manuscript is that while huge progress has already been made, there is a requirement for future research to more precisely define and rationalise structure-activity relationships across different nanomaterial types.

The final contribution to this special issue of BJP reviews the current state of global research efforts that aim to capitalise on the distinctive attributes of viruses that may enable them to be modified for use in drug delivery (van Kan-Davelaar *et al*., 2014). Dr Melissa Koay and colleagues at the University of Twente and Radboud University provide a balanced overview of progress being made to use viruses as nanocarriers in diseases such as cancer and infection. The article also describes information relating to the immune stimulation by these particles, and emerging work on safety considerations that need to be considered for further development. While clearly still in its infancy compared to some other nanomedicine technologies the unique properties of viruses certainly warrant further investigation towards targeted nanocarrier approaches.

In summary, nanomedicine encompasses a broad range of different fundamental objectives and material types. Progress is being made in a number of different areas with some approaches already validated for optimised pharmacological behaviour. The safety and toxicity of nanomaterials used for medical applications is currently the subject of intensive global research efforts. Nanotechnology has received negative publicity in recent years, but it is important to recognise that its utility was authenticated prior to the term being coined, and the overwhelming majority of applications being investigated within the pharmaceutical sector aim to improve the safety of medicines by decreasing dose or fine-tuning distribution. Although not specifically addressed within this special issue, regulation of nanomedicines is also being extensively discussed, a key question being whether existing assessments are sufficiently robust to detect potential safety issues during development, rather than whether safety issues exist. The global nanomedicine market has been estimated to reach ~100 billion US dollars by the end of 2014 (Morigi *et al*., 2012) and it is important to accelerate multidisciplinary research in the UK to ensure a competitive position in this persistently emerging area.

References

Bertrand N, Wu J, Xu X, Kamaly N, Farokhzad OC (2014). Cancer nanotechnology: the impact of passive and active targeting in the era of modern cancer biology. Adv Drug Deliv Rev 66: 2–25.

Boffito M, Jackson A, Owen A, Becker S (2014). New approaches to antiretroviral drug delivery: challenges and opportunities associated with the use of long-acting injectable agents. Drugs 74: 7–13.

Ilinskaya AN, Dobrovolskaia MA (2014). Immunosuppressive and anti-inflammatory properties of engineered nanomaterials. Br J Pharmacol 171: 3988–4000.

Junghanns JU, Muller RH (2008). Nanocrystal technology, drug delivery and clinical applications. Int J Nanomedicine 3: 295–309.

Kermanizadeh A, Gaiser BK, Johnston H, Brown DM, Stone V (2014). Toxicological impact of engineered nanomaterials on the liver – a review. Br J Pharmacol 171: 3980–3987.

Marchasin S, Wallerstein RO (1964). Treatment of Iron-Deficiency Anemia with Intraavenous Iron Dextran. Blood 23: 354–&.

Morigi V, Tocchio A, Bellavite Pellegrini C, Sakamoto JH, Arnone M, Tasciotti E (2012). Nanotechnology in medicine: from inception to market domination. J Drug Deliv 2012: 389485.

Moss DM, Siccardi M (2014). Optimising nanomedicine pharmacokinetics using physiologically based pharmacokinetics modelling. Br J Pharmacol 171: 3963–3979.

Owen RT (2010). Paliperidone palmitate injection: Its efficacy, safety and tolerability in schizophrenia. Drugs Today (Barc) 46: 463–471.

van Kan-Davelaar HE, van Hest JCM, Cornelissen JJLM, Koay MST (2014). Using viruses as nanomedicines. Br J Pharmacol 171: 4001–4009.

Weber DO (1999). Nanomedicine. Health Forum J 42: 32, 36–37.