Emerging nanomedicine applications and manufacturing: progress and challenges

Article

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Emerging Nanomedicine Applications and Manufacturing: Progress and Challenges

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The Academy of Pharmaceutical Sciences (APS)[1] and the British Society for Nanomedicine (BSNM)[2] organised a one-day session as part of the annual APS PharmSci conference, to discuss some of the latest developments in nanomedicine particularly in the areas of cancer, infection and targeting of the central nervous system (CNS). The primary objective of this meeting was to share and disseminate insights and experiences encountered in developing these novel medicines. Secondly, it aimed to define common challenges that the respective innovators and developers have faced, so that in the future efforts can be directed to resolving these by this growing and thriving community.

Developing a targeted therapeutic

Targeted drug delivery has been a goal of pharmaceutical companies for many years. The need to target specific cells, local or systemic, or tissues within the body is an ideal for numerous indications. The application of nanotechnology to this field has begun to address this targeted approach and been the subject of many articles in recent years with several reporting promising preclinical and clinical results. Throughout the conference a range of technological approaches to targeted delivery were discussed including polymeric nanoparticles, self-assembling micelles and liposomes.

A novel targeting approach has been taken by Dr Chris Scott (Queen's University Belfast) and his team, who reported that sialic acid-decorated nanoparticles were able to target sialic acid-binding immunoglobulin-like lectins (siglecs) to induce therapeutically useful effects on systemic and pulmonary inflammation in murine models.[3] Prof. Andreas Schätzlein (UCL & Nanomerics) presented work on Nanomerics' Molecular Envelope Technology (MET), where nanoparticles are engineered from biocompatible self-assembling polymers[4]. The team have shown that it is possible to encapsulate hydrophobic drugs and peptides, and in turn generate stable nanoparticles using MET. Most recently they have used MET to develop an orally active form of Amphotericin B (AmB). AmB is a polyene antibiotic, which is currently administered parenterally to treat fungal infections and Leishmaniasis[5]. Being able to deliver this antibiotic orally, would overcome the major adverse effects of parenteral delivery, which is infusion related toxicity. Other putative benefits of the

approach are aimed at limiting chronic toxicities such as nephrotoxicity and anaemia. Utilising industry standard models of visceral Leishmaniasis, candidiasis and aspergillosis in small animals, they have been able to show comparable efficacy to the current treatment of choice[6] – a parenteral liposomal AmB (AmBisome®). Furthermore, using industry standard models of the disease in small animals, results showed that this new formulation provided an improved selective bioavailability with efficient uptake by the gastrointestinal epithelia and transport to the lung, liver and spleen. Dr Marianne Ashford (AstraZeneca, AZ) discussed the collaboration between AZ and BIND Therapeutics, where together they are developing and scaling-up BIND's Accurins® for application in leukaemia and cancer. The aim here is to improve the therapeutic index of AZD2811, a potent selective inhibitor of the Aurora B kinase[7]. It was also noted that AZ has recently signed a license agreement with Starpharma around the use of its dendrimer drug delivery technology (DEP™)[8] in the development and commercialisation of an AZ compound.

These are just a couple of examples of the progress that is being made in the development of targeted therapeutics and it is apparent that these have shown sufficient efficacy in *in vitro* and initial animal models to warrant progression to the next stages of the development pathway. However, the discovery and proof of concept stages are only a part of the whole development process. Today researchers from industry and academia alike are facing developmental challenges as they progress their work through development to scale-up and into clinical practice.

Support for development

The process to take a therapeutic from discovery to clinic is challenging, long and expensive. This work tends to be undertaken by pharmaceutical companies and contract research organisations that have developed processes, know-how and have the necessary supply chains that meet quality assurance and regulatory standards. Throughout the discussion, regardless of the size of the company involved in these initial stages in development, it was apparent that it is difficult to source GMP compliant polymers to provide a viable supply chain and there is a shortage of suitable excipients, particularly for nucleic acid delivery. There is a need to educate and inform contract research and manufacturing organisations (CROs or CMOs) of the nanomaterials and formulations used in the design of nanomedicines in order that this gap can be filled. Given the willingness of many CROs and CMOs, it was suggested that most would rise to this challenge and would happily engage in this space.

Academics are now encouraged to deliver commercial and societal impact through their research, an increasing number are getting involved in development steps beyond the traditional proof-of-

concept stage, often referred to as technology readiness level (TRL) 3. Again, there was a consensus that there is a knowledge gap amongst many researchers about the requirements and processes that are required to take a therapeutic through further development stages. Dr Marianne Ashford explained that AZ and the University of Manchester have entered into a strategic collaboration called The North West Centre for Advanced Drug Delivery (NoWCADD) to help to bridge this gap and provide an arena through which knowledge transfer can occur between researchers and scientists from the different institutions. The primary aim of the centre is to translate promising drug delivery concepts into valued medicinal products for cancer and other serious diseases that include cardiovascular, metabolic, respiratory, inflammatory and autoimmune diseases. In addition, NoWCADD aims to support undergraduate learning within the Pharmacy School and inspire the next generation of pharmaceutical scientists. What sets this collaboration apart from other similar initiatives is that a lab scale manufacturing and characterisation capability for advanced drug delivery technologies is being established within the university. The initial phase of funding is for 5 years and it is anticipated that this will, with time, lead to collaborative relationships with other academic institutions and industrial partners. The NoWCADD (sites.pharmacy.manchester.ac.uk/nowcadd/) initiative was welcome news to many at the meeting and there was significant interest in its expansion plans and how other university groups might get involved.

Prof. Steve Rannard (University of Liverpool & Vice Chair of the BSNM) also reported on the newly established Translation Advisory Board (TAB) (www.enatrans.eu/public/services/translation-advisory-board) that has been established as part of the EU ENATRANS project (Enabling NAnomedicine TRANSlation). The TAB constitutes a team of experts from across Europe that have been directly involved in nanomedicine development, translation and commercialisation. Together they will provide free of charge, non-binding and strategic advice to promote and guide projects, and support and define recommendations. It works via a stage-gate service that requires an application form to be submitted online; it is open to the European nanomedicine community at any stage of their development.

Scaling up

Moving from R&D to production scale always presents challenges. Some propose that by having an intermediate step, so-called pilot scale, would allow production of enough sample to supply the needs of ongoing clinical trials, whilst also demonstrating that materials and formulations can indeed be produced in larger quantities. Successfully achieving this intermediate step does not, however, ensure success at the larger industrial scale, but this does provide an important route for academics

to provide evidence that their novel chemistries can be scaled. To understand any changes that may occur to the critical nanomedicine components during the scale-up process, is one of the key challenges of the industry and there are companies who have developed expertise and know-how in this space. The outcome from this discussion was that researchers should be made aware of what is feasible and decision points used during industrial scale-up; this will allow progress through the earlier translational steps and definition of processes that are amenable to further development stages. The focus for researchers should remain on elucidating the mechanism of action and demonstrating clinical efficacy.

Characterisation and effective animal models

Prof. Jayne Lawrence, KCL, described work from her lab that explores self-assembling structures that employ the non-ionic surfactant dodecyldimethylamine-N-oxide to produce micelles. These structures have been explored from a formulation perspective in order to enhance the therapeutic index of prospective drug molecules. In order to understand, how these structures form and the effects of the varying concentrations and physical properties in their construction, Prof. Lawrence and her team utilise small-angle neutron scanning (SANS) as a key characterisation tool in their work. This technique is not widely used in the pharmaceutical industry, but in these experiments[9] and others[10] have shown that this technique provides valuable morphological information about the structures formed and the shape of the drug carrier; specifically highlighting how morphologies are affected with varying concentrations and physical conditions. Other techniques that were discussed included dynamic light scattering (DLS), flow cytometry and Izon Sciences' qNano Gold system. Whilst these are all effective techniques, which certainly add to the understanding of nanomedicine discovery and development, there was a general consensus that a lack of standardised characterisation techniques remains, particularly for bioanalytical assays and that standardisation would promote consistency and uniformity within this field.

Prof. Andrew Owen (University of Liverpool & Chair of the BSNM) informed delegates about the European Nanotechnology Characterisation Laboratory (EU-NCL) that was launched jn 2015. It has been funded by the European Commission's Horizon 2020 research and innovation programme and draws on expertise from eight core members (and fourteen satellite laboratories), including the US Nano-Characterisation Lab (NCL), which was established 10 years ago. The mission of EU-NCL is:

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- To provide a trans-disciplinary testing infrastructure covering a comprehensive set of preclinical assays (physical, chemical, *in-vitro* and *in-vivo* biological testing), allowing

researchers to fully characterise the biodistribution, metabolism, pharmacokinetics, safety profiles and immunological effects of their medicinal nano-products.

- To foster the use and deployment of standard operating procedures (SOPs), benchmark materials and quality management for the preclinical characterisation of medicinal nano-products.
- To promote inter-sector and interdisciplinary communication among key drivers of innovation, especially between developers and regulatory agencies.

It is anticipated that through this international collaborative approach, a defined set of measurements and characterisation processes can be established to support the development process for various nanomedicines. This may also avoid generalisations and assumptions about these formulations and materials, which can lead to either false expectations or unnecessary safety concerns[11]. Furthermore it will also help to address concerns over the effectiveness of some animal models. This was discussed particularly with respect to the enhanced permeation and retention (EPR) effect, which works well in mice and some humans, but generally this is a heterogeneous effect, in which many parameters (tumour type, size etc) seem to be playing a key role. By meeting the aims set out by this consortium, data sets will be able to be compared with confidence and aid regulation of safety, formulation, manufacture, and toxicology of these materials.

References:

1. The Academy of Pharmaceutical Sciences. www.apsgb.co.uk
2. British Society for Nanomedicine. www.BritishSocietyNanomedicine.org
3. Spence S, Greene MK, Fay F, Hams E, Saunders SP, Hamid U, Fitzgerald M, Beck J, Bains BK, Smyth P, Themistou E, Small DM, Schmid D, O'Kane CM, Fitzgerald DC,. Abdelghany SM, Johnston JA, Fallon PG, Burrows JF, McAuley DF, Kissenpfenni A, Scott CJ. *Sci. Transl. Med*. 7: 303ra140 (2015)
4. Nanomerics Ltd. www.nanomerics.com
5. Serrano DR, Ballesteros MP, Schätzlein AG, Torrado JJ, Uchegbu IF. *Pharmaceutical Nanotechnology* 1: 250-258 (2013)
6. Garrett NL, Moger J, Guarro J, Capilla J, Ballesteros MP, Schätzlein AG, Bolás F, Torrado JJ, Uchegbu IF, *Mol. Pharmaceutics* 12: 420–431 (2015)
7. BIND Therapeutics Inc. www.bindtherapeutics.com
8. Starpharma Holdings Ltd. www.starpharma.com
9. Lorenz CD, Hsieh CM, Dreiss CA, Lawrence MJ. *Langmuir*. 27: 546-5 (2011)
10. Ramzi A, Sutter M, Hennink WE and Jiskoot W. *J Pharm Sci*. 95: 1703-11 (2006)
11. Bitounis D, Ali-Boucetta H, Hong BH, Min D-H, Kostarelos K. *Adv. Mater*. 25: 2258-2268 (2013)