Biochemical and Biophysical Research Communications 468 (2015) 435–441

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Review

Perspective: Dendrimer drugs for infection and inflammation

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ARTICLE INFO

Article history:
Received 26 June 2015
Accepted 7 July 2015
Available online 10 July 2015

Keywords:
Dendrimer drugs
Infection
Inflammation

ABSTRACT

Biologists are dissecting complex biological pathways at breath taking speed. It is opening up new opportunities for the therapeutic evaluation of novel dendrimer drugs. This review focuses on studies of small dendrimers decorated with sulfate, phosphonate, N-acetyl-cysteine, glucosamine and mannose in animal model studies of infection and inflammation. It highlights those animal model studies which have demonstrated the most promising dendrimer drug constructs as potential new medicines. The issues relating to their analytical chemistry that are slowing the progress of dendrimer drugs into the clinic are highlighted. It should be possible to solve these with additional analytical expertise because it is small dendrimers with only 16–32 peripheral groups that make for the best infection and inflammation related medicines. Public-private partnerships are now needed to progress these dendrimer drugs into proof-of-concept clinical trials.

1. Introduction

Next generation drug development in oncology has been set alight by biological advances in immuno-oncology [1,2]. The breath taking speed at which complex biological pathways have been dissected by biologists across a spectrum of diseases means that their therapeutic manipulation with novel drugs becomes possible. The serious intent to make new medicines has accelerated small biotech growth. Big pharma has started taking these companies seriously [3].

Several novel biomaterial based products (i.e. not small molecules) have a realistic prospect of becoming clinically useful nanomedicines in the next decade. The key driver has been our better and deeper understanding of the immuno-biology of cancer, and of how we could therapeutically manipulate the host immune responses involved. Prospecting is promising for investors and the financial return likely to be large and sustained [4].

In contrast, the promise that was offered by linear polymers and dendrimers for manipulating biological responses in infection and inflammation has not translated into new medicines. Advances remain restricted to the academic community whose important translational insights have not led to the emergence of significant commercial and industrial traction. Detailed and expensive *in-vivo* animal model studies of disease have been few and far between. When they have been undertaken, the results are surprising, and remarkable, in terms of therapeutic efficacy seen. Publication in high profile multidisciplinary journals is testament to the interest generated. However, progress of optimised macromolecules into clinical trials has been almost absent.

2. Multiple academic chemistry platforms

There are several reasons that could explain the slow progress of dendrimer drugs into the clinic. Significant progress in the dendrimer field has been almost entirely driven by synthetic organic chemists in academia with an interest in polymeric structures. For years, their primary interest has been to make incrementally larger dendrimers with increasingly simpler synthetic chemistry processes [5,6]. However, their success, usually with their own chemistry platform, has not been paralleled by similar progress in the analytical chemistry techniques required to transform these molecules into pharmaceutical grade drugs; i.e. a reproducibility of manufacturing methodology and level of chemical characterisation robust enough for the drug regulatory authorities (FDA/EMA) to award them the status of an Investigational New Drug (IND) that can progress to a clinical trial.

The result is that many interesting dendrimer drugs have become stuck at this stage of development. The experiences of Brechbiel [7] and Baker [8–10] are representative examples; Baker conjugated folic acid to a generation 5 PAMAM dendrimer in order to target the cancer cells folate receptor and deliver methotrexate in a cell specific manner. However, (i) inefficiencies in the complex synthesis, (ii) inconsistencies in the amount of folic acid and methotrexate attached to the dendrimer, and (iii) a limited understanding of the dendrimer drug's properties halted its further clinical development. A more complete understanding of the

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http://dx.doi.org/10.1016/j.bbrc.2015.07.033
0006-291X/

interactions between the synthetic polymer and the target biological system was necessary. In both cases [7–10], the need for an intravenous route of administration of these dendrimer drugs further complicated their development into new medicines.

From the FDAs perspective, the issues as they relate to nanoparticles and nanoparticular drug delivery systems have been discussed by Hamburg [11] and Narang [12]. A particular challenge for dendrimer drugs remains the subject of active academic analytical research into producing reliable and reproducible mass spec data [13–16].

3. Bigger dendrimers doesn't mean better medicines

The problem of turning dendrimers (and the same applies to linear polymers) into medicines has been compounded by the belief that making them bigger will make them better, and therapeutically more useful. In fact, this approach has primarily served to make the analytical chemistry challenges exponentially more difficult. It was done in the pursuit of two concepts. The first was that cavities within the dendrimer could be used to concentrate and carry small molecule drugs [17,18]. The second was that toxic anti-cancer drugs could be delivered and concentrated within tumours using the Enhanced Permeability and Retention (EPR) effect [19,20].

From the infection perspective, the hope has been to replicate and expand on the commercial success of liposomal-Amphotericin B (Ambisome) for treating invasive fungal infections. This has not proven to be the case because the cost of new drug delivery dendrimer platforms has not been commercially viable when compared to the low cost of the generic small molecule anti-infective drugs being delivered [21]. In this specific context, we have recently shown, in two *in vivo* mouse model systems, that very small MWt and very well characterised and low cost polymethacrylic acid of MWt 3.52 kDa can be used to effectively deliver amphotericin B to the site of infection for the cure of parasitic (cutaneous leishmaniasis) and fungal (invasive aspergillosis) infections [22,23]. Our approach has been progressed into a clinical trial of a cost-effective medicine (Anfoleish) for cutaneous leishmaniasis in South America by the Geneva based Drugs for Neglected Diseases Initiative (DNDi) [24,25].

At present, big pharma does not see this drug delivery area as a high value or high priority therapeutic opportunity. So, in my opinion, the future clinical development of dendrimer drugs is unlikely to be in either improved drug delivery or in enhancing the EPR effect for small molecule drugs.

4. Sulfate modified macromolecules for HIV

Crucially, this means that we should stop thinking about the core macromolecule and start thinking about the remarkable new biological properties of polyvalency that derive from decorating their surface with other molecules [26,27].

The first significant commercial player in this area decorated *all* of the surface amine groups of their dendrimer with sulfate groups. The idea was based upon our work which had shown that a partially sulfated linear dextrin polymer blocked HIV-1 infection *in vitro* and reduced the viral load in patients with late stage AIDS [28,29]. The molecular mechanism of action was blockade of the chemokine receptors CCR5 & CXCR4 which are required for viral entry into CD4+ cells after binding of HIV-1 envelope gp120 to human cell surface CD4 [30].

At that time, our greatest challenge related to the detailed analytical characterisation of a partially sulfated linear dextrin with a MWt of ~27 kDa. Starpharma adapted the idea into the *complete* sulfation of their dendrimer. SPL7013 was built from a divalent core, the benzhydrylamine amide of L-lysine with 4 layers of L-lysine added. A sodium 1-(carboxymethoxy) naphthalene-3,6-disulfonate group was attached to the peripheral 32 amines via amide linkers. Analytics used HPLC, LC/MS, capillary electrophoresis and electrospray mass spectrometry. A single peak with a MWt of 16,581 Da was claimed but this mass spec has not been published in either the academic or patent literature [31,32].

Starpharma should be commended for having achieved commercial success with this molecule as a topical vaginal virucide (VivaGel) with bioactivity against HIV and Herpes simplex virus [33,34]. This year, its product became commercially available as the coating on some condoms [35].

Two points are worth noting with regard to the successful commercial development of the SPL7013 dendrimer drug. Firstly, progression into accelerated FDA approved clinical trials was made possible by their claim that this was a single chemical entity which fulfilled all of the analytical chemical characteristics of a conventional *small* molecule drug rather than a macromolecular drug. This has set a very high analytical hurdle which no other dendrimer drug has managed to successfully jump in its progress to the clinic. It also contrasts with the opinion of almost all academic teams working in the dendrimer drug space who consider dendrimer drugs to be macromolecules. It is now important for a consensus to emerge on this matter; a lack of clarity amongst those working with dendrimer drugs means that the hurdle for obtaining FDA regulatory approval for clinical trial testing is very likely to remain too high for others to achieve. In this specific context, the recent analytical work of French groups to reliably and reproducibly define the precise MWt of their dendrimers (with all of the challenges that this involves) using mass spec based analytical techniques is to be highly commended [14,15,36].

Secondly, the detailed clinical evaluation of the SPL7013 dendrimer drug had to rely upon substantive NIH/NIAID funding and upon university based investigators in the US (Starpharma is an Australian company) to take it through its clinical development. This suggests that the commercial and industrial appetite for investing the substantial funds required for taking dendrimer drugs through their clinical trials testing still remains low.

5. Phosphonate modified dendrimer drug for rheumatoid arthritis

A core arylaldehyde terminated dendrimer had *all* of its surface groups capped with phosphonic acid to give 16 phosphonate groups. It is not clear from the literature why the Poupot/Caminade group in France decided to take this particular approach but it seems that their academic interest was in: (i) phosphorus dendrimers *per se* as new chemical entities, and (ii) the pursuit of polyvalency as an important biological target. *In vitro*, the optimised molecule reduced monocyte activation (i.e. HLA-DR) and increased the multiplication of natural killer cells. Notably, dendrimer drugs with <16 phosphonate groups were much less bioactive [37,38].

In mouse models of rheumatoid arthritis, a fully capped azabisphosphonate dendrimer with 24 peripheral groups (rather than the 16 from their previous *in vitro* biological studies), was administered *intravenously*, once weekly, for 12 weeks. This led to a dose-dependent reduction in: (i) the pro-inflammatory cytokines TNF-α, IL-1β, IL-2, IL-6, IL-17 and IFN-γ from splenocytes; (ii) cartilage destruction; (iii) the bone erosion that characterises rheumatoid arthritis [39]. The anti-inflammatory cytokines IL-4 and IL-10 were increased. No off-target toxicity was seen. The primary cellular outcome was down-regulation of the pro-inflammatory cytokine response of monocytes. The precise molecular target of

this effect of the azabisphosphonate capped dendrimer remains to be defined [40]. This important animal model study has been the subject of a detailed review of the role of dendrimer drugs in rheumatoid arthritis and, potentially, other inflammatory arthritides [41]. The authors note that the Holy Grail is for an *orally* rather than an intravenously administered dendrimer drug.

The fully capped azabisphosphonate dendrimer was not toxic in nonhuman primates when injected intravenously at 10 mg/kg at weekly intervals for 4 weeks. Importantly, pro-inflammatory cytokines and anti-inflammatory cytokines were not altered in blood [42]. The authors acknowledge that ``dendrimers are very innovating nanomolecules with promising therapeutical applications, but far from the standards of the pharmaceutical industry''. To my knowledge, this phosphorus dendrimer drug has not been progressed into clinical trials testing in rheumatoid arthritis.

6. Some simple PAMAM dendrimers can inhibit inflammation

In 2009, Tomalia reported that PAMAM dendrimers with amine as well as hydroxyl surface groups exhibited significant anti-inflammatory activity in three different rat anti-inflammatory assay models [43]. This was dependent on three factors: (i) being a Generation 4 dendrimer with 64–128 peripheral groups; (ii) having an amine or hydroxyl surface functionality; and (3) the time elapsed after administration. Nitric oxide production and COX-1 & COX-2 synthesis were reduced. This contrasted with carboxylic acid terminated PAMAM dendrimers which had no anti-inflammatory activity.

In the case of amine terminated dendrimers taken generally, the interpretation of these results is complicated by the fact that they have an established toxicity for normal human and animal cell membranes which carboxylic acid terminated dendrimers do not have [44]. In addition, amine terminated dendrimers have antimicrobial activity which is greater for Gram negative bacteria (e.g. *Escherichia coli*) than Gram positive bacteria (e.g. *Staphylococcus aureus*) [45]. The molecular mechanism of action of this antimicrobial activity and cell surface toxicity is broadly based upon positively charged molecules punching holes in negatively charged bacterial and cell membranes to cause bacterial rupture and cell lysis respectively.

7. Combining EPR with drug delivery

Kannan took this observation for the G4-PAMAM-OH terminated dendrimer as the starting point for their studies of inflammation. They *injected* this dendrimer directly into the *cervix* of a guinea pig model of chorioamnionitis to treat an *E. coli* induced infection of the uterus [46]. Treatment reduced the pro-inflammatory cytokines TNF-α, IL-1-β and IL-6 to normal levels in the placenta. It is important to note that the molecular mechanism of action of this hydroxyl terminated dendrimer's action was as an antibacterial because it inhibited the growth of *E. coli in vitro*. The authors proposed its use as a topical antibacterial agent.

When the same G4-PAMAM-OH dendrimer was *injected* directly into the *amniotic sac* of a fetus in a mouse model of intra-uterine inflammation (that was induced by infusion of bacterial lipopolysaccharide {LPS} into the uterus), the dendrimer accumulated in the blood vessels and parenchyma of the brain with uptake specifically into microglia (i.e. brain macrophages). The authors proposed that the injected intra-amniotic dendrimer was swallowed by the fetus *in utero* and then ingested via the gut; it was then distributed via the blood stream to the brain [47].

Kannan has gone on to show that the *intravenous* administration of the G4-PAMAM-OH dendrimer to newborn rabbits with *E. coli* endotoxin (i.e. synonymous with Lipid A) induced brain injury also resulted in the dendrimer's selective accumulation in activated brain microglia and astrocytes [48]. In my opinion, this is most likely to be an infection related example of the EPR effect on the blood brain barrier which, when inflamed, becomes permeable to macromolecules and leucocytes. They went on to attach N-acetyl-cysteine (NAC) to the periphery of this dendrimer because NAC has a long history of acting as a reactive oxygen species scavenger and inhibiting the expression of pro-inflammatory cytokines [49].

In other words, they chose to combine the EPR effect of the G4-PAMAM-OH dendrimer with an NAC drug delivery approach using a disulphide linker; high intracellular levels of glutathione would trigger the intracellular release of NAC from the dendrimer. On the basis of NMR studies and a widely distributed mass spec, they estimated a dendrimer surface loading of NAC of 19%. Brain injury was induced in newborn rabbits by injecting LPS *in utero*. *Intravenous* injection of the G4-PAMAM-NAC dendrimer to rabbits at 6 h after birth led to reduced brain injury on day 5 after birth [48].

Their most recent study was in a dog model of hypothermic circulatory arrest induced brain injury. They first confirmed the EPR effect of the G4-PAMAM-OH dendrimer in injured brain. As other studies had shown that pre-treatment with NAC was protective in animal models of cardiac arrest, they went on to investigate this too in their animal model. At 3 mg/kg and given *intravenously*, the G4-PAMAM-NAC dendrimer drug improved the neurological score at day 1 post injury but this benefit was not sustained at day 3 post injury [50]. The dose of dendrimer drug was chosen on the basis of their previous studies; the authors suggest that a higher dose may be required.

The absence of adverse effects with their dendrimer drug is likely due to the lower dose of NAC required to achieve neuroprotection because of the EPR effect; i.e. more NAC was delivered, concentrated and retained in the area of brain tissue injury where the local and higher concentration of glutathione accelerated the intracellular release of NAC.

8. Molecular modelling of dendrimer drugs

We had previously achieved considerable success in reducing the number of compounds that needed to be chemically synthesised (i.e. ~5) for detailed biological studies by taking a molecular modelling based approach to PEGylated proteins and peptides [51–54]. We have been equally successfully in applying this approach to PAMAM and triazine and PETIM dendrimers [55–61]. The approach works best for smaller rather than larger generation dendrimers.

This means that the translation of synthetic dendrimer chemistry into clinically useful bioactivity can be aided and accelerated by the use of computational modelling of 3-dimensional macromolecules with the target receptor of interest. The structural data generated from these molecular dynamics simulations also provides valuable biological insights. The subject has been discussed in detail in our papers [51–61] and in two recent reviews [62,63]. The power of this approach is considerable in providing important insights into parameters such as dendrimer size, shape, architecture, surface chemistry, and rigidity and flexibility. It enables the computer aided design of dendrimer drugs that can replicate the flexibility, cluster density, surface electrostatic charge and hydrophilicity of a synthetic ligand for a receptor [59]. The outcome is a much better basis on which to understand and predict the interaction of a dendrimer drug with a receptor.

9. Dendrimer glucosamine blocks TLR4 in trauma & infection

Our dendrimer drug focus has been on the therapeutic manipulation of the pro-inflammatory cytokine response that is triggered by Toll Like Receptor (TLR) −4. This cell surface receptor plays a critical role in ensuring a prompt and efficient innate immune response to an acute threat. It is central to the innate immunity of pathogen associated molecular patterns because it allows macrophages and dendritic cells to distinguish self structures from pathogen associated non-self structures.

9.1. LPS & MD-2 & glucosamine

Lipopolysaccharide (LPS ~10 kDa) is the outer membrane glycolipid of Gram negative bacteria. It is composed of:- (a) the hydrophilic polysaccharide core; (b) the solvent exposed hydrophobic Lipid A; (c) the O-antigen. Only the Lipid A is required to induce pro-inflammatory cytokine responses. It is composed of a diphosphorylated β-1,6-linked D-glucosamine disaccharide linked via amide or ester bonds to 3-hydroxy fatty acids further substituted by nonhydroxylated 12–14 carbon fatty acid chains [64]. The cell surface interaction between LPS, TLR4 and MD-2 protein is central to the initiation of the pro-inflammatory cytokine response. The presence of a D-glucosamine disaccharide in Lipid A led us to choose to target MD-2 by decorating dendrimers with D-glucosamine.

The promiscuity of MD-2 is an important evolutionary feature and reflects the need for it to be able to recognize all of the diverse LPS structures synthesized by individual species of Gram negative bacteria, as well as the binding of those endogenous host derived ligands which can also act as alert signals for tissue injury. Importantly, this includes enzyme derived fragments of hyaluronan from injured extracellular matrix [65].

9.2. Hyaluronan

A major hallmark that alerts the host to the onset of tissue injury is a sudden increase in hyaluronan turnover in the extracellular matrix [66]. In its native form, hyaluronan exists as an inactive high MWt nonsulfated glycosaminoglycan polymer of ~2 million Da. It is made up of repeating disaccharide units of (beta, 1–4)-D-glucuronic acid-(beta, 1–3)-N-acetyl-D-glucosamine. Tissue injury initiates its rapid breakdown by local enzymes. The small MWt fragments generated consist of hyaluronan oligomers of 12–16 disaccharides with a MWt ~200 kDa. These fragments have all the features of a pathogen associated molecular pattern and they can trigger TLR4 on macrophages and dendritic cells in a receptor–ligand interaction that is identical to LPS [66,67]. When these hyaluronan oligomers of 12–16 disaccharides are compared to LPS, it is important to note that only high and localized concentrations of hyaluronan fragments at the site of tissue injury can trigger the TLR4 mediated pro-inflammatory cytokine response [68]. Irrespective of whether a pathogen or surgical trauma initiated the injury, successful repair of tissue requires a coordinated host response to limit the amount of structural damage. Resolution of the acute inflammatory response requires clearance of the hyaluronan fragments from the focal site of injury by further enzymatic degradation to small oligomers of ~28 kDa which have no biological activity.

Crucially, low level stimulation by pro-inflammatory cytokines is physiologically beneficial for dealing with infections because it enables co-stimulatory molecule (e.g. HLA-DR) activation and generation of the adaptive immune response. It is only when pro-inflammatory cytokine production becomes large that it becomes pathological, with septic shock and death as the eventual outcome.

9.3. PAMAM-DG and PETIM-DG

Having started our studies with a Generation 3.5 PAMAM dendrimer with 16 peripheral glucosamines of MWt 13.6 kDa, our integration of molecular modelling studies with biological experiments has led to a 75% reduction in the molecular weight of DG to 3.3 kDa, and an increase in its purity to 97%. We have coined the term `synthetic baby-bio (SBB) for such molecules [58]. Our molecular modelling studies went on to show that DG blocks pro-inflammatory cytokine production by interfering with the electrostatic binding of: (i) the 4′phosphate on the di-glucosamine of LPS to Ser118 on MD-2; (ii) LPS to Lys91 on MD-2; (iii) the subsequent binding of TLR4 to Tyr102 on MD-2 [58].

9.4. Surgical trauma

With surgical trauma, DG inhibited hyaluronan-TLR4 cell surface mediated pro-inflammatory cytokine production from human macrophages and dendritic cells while allowing the activation and maturation of dendritic cells to occur [69]. The animal model used was that of an adult rabbit and glaucoma filtration surgery; the surgical intervention was precisely defined and the clinical outcome clear cut because it was blindness. In 2004, we showed that DG (given as a subconjunctival injection and an intraperitoneal injection {×3/week} for 30 days) increased the success rate of glaucoma filtration surgery (i.e. no blindness) from 30% to 80% in this clinically validated rabbit model of surgical scaring. Histology showed that the degree of tissue based inflammatory cell infiltration and abnormal collagen formation was minimal. The study proved that dendrimer drugs could be designed and synthesized to enable the therapeutic manipulation of the early and critical stages of the tissue repair and regeneration pathway.

9.5. Severe infectious diarrhoeas

The hurdle for showing a therapeutic benefit of DG in a very severe infectious disease was much higher. In an adult rabbit intestinal loop model of Shigellosis (i.e. infectious bloody diarrhoea), DG given locally into the gut prevented the pathogen induced and cytokine mediated injury to the gut wall that was associated with increased IL-6 and IL-8. Bacterial invasion of the gut wall was minimized (Fig. 1). No adverse immuno-modulatory effects or tissue toxicity was seen. It is important to note that DG has no conventional antibiotic like properties.

9.6. Nonhuman primate study of DG in severe infection

We have gone on to evaluate DG in *Shigella dysenteriae* Type 1 diarrhoea in nonhuman primates because this bacteria causes the most severe of all infectious diarrhoeas and colitis. Using cGMP grade PETIM-DG of 97% purity, a GLP study was performed that was funded by NIAID. We infected rhesus macaques orally with *S. dysenteriae* and also treated them *orally* (once daily) with DG. Antibiotics were not given for this life threatening infection. Six days later, the clinical score for diarrhoea, mucus and blood was lower as was neutrophil infiltration of the colon wall. Tissue fibrin thrombi were reduced and vasculitis did not occur. There was no tissue toxicity or adverse systemic immuno-modulatory effect. These results show that an oral TLR4 antagonist can ensure controlled resolution of the infection related inflammatory response and prevent neutrophil mediated gut wall necrosis in severe entero-invasive infections, even when an antibiotic is not given (paper submitted).

This means that small, well defined, cost-effective and orally delivered glycosylated dendrimers could become a useful new

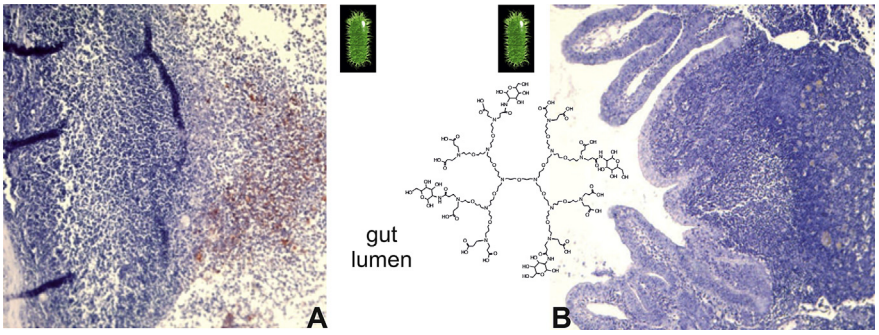

Fig. 1. DG prevents gut wall damage in severe infectious diarrhoeas. Gut immuno-histochemistry for *Shigella* LPS (brown stain) showed a large reduction in bacterial gut wall invasion in rabbits treated with PETIM-DG. (A) There is a lot of brown staining in the Peyer's patch (i.e. lymph node) whose surface epithelium has been destroyed by the *Shigella* infection. (B) With PETIM-DG treatment, there is very little brown staining in the Peyer's patch and the surface epithelium is intact. The blue counterstain is hematoxylin. The infecting *Shigella* bacteria are shown in green. For more experimental details see Ref. [60].

therapeutic addition for a spectrum of other infection induced and cytokine mediated inflammatory diarrhoeas.

10. Exploring nebulised macromolecules

Generation 3 and Generation 4 PAMAM dendrimers have been successfully used for the delivery of steroids to the lung as an additional treatment approach for asthma [70,71]. They were stable to nebulisation and the characteristics of the aerosol were influenced more by nebuliser design than by dendrimer generation. In my opinion, the field of linear polymers and dendrimers and nanoparticles has been inadequately explored and exploited with regard to the pulmonary route of administration. For example, we have recently shown that a very low MWt amphotericin B-polymethacrylic acid (PMA of 3.52 kDa) nanoparticle can be made simply and easily and also delivered safely via a nebuliser. In a mouse model of life threatening invasive pulmonary aspergillosis, it protected the lung from disease by killing $>99\%$ of the *Aspergillus fumigatus* and by reducing lung TNF-α by 90% [23]. Our study provides animal model based proof of concept that very small and cost-effective nanoparticles can be made simply and delivered safely and effectively to lung by the aerosol route in order to prevent life threatening invasive fungal infections.

The Caminade/Majoral group in France have also become interested in dendrimer drugs for the lung. They have made Generation 3 and Generation 4 poly(phosphorhydrazone) dendrimers and grafted them with 48 and 96 mannose groups respectively. The polydispersity was 1.17 and mass spec data was not provided.

In vitro, both mannodendrimers bound to the DC-SIGN receptor on dendritic cells and inhibited LPS-induced TNF-α, IL-6 and IL-8 [72]. In C57BL/6 and BALB/c mouse models of acute lung inflammation (induced by exposure to aerosolized LPS), they showed a $\sim$42% reduction in lung neutrophil recruitment at 18 h post exposure. Alveolar wall thickening (a histological indicator of persistent inflammation) did not occur. My reservation, from a clinical perspective, is that they had to *pre-treat* mice *orally* for *15 days* with the mannodendrimer to show the reduction in lung inflammatory cell infiltrate. The reason for this long period of pre-exposure prophylaxis to the G3 mannodendrimer was not discussed.

11. Optimal polyvalency is defined by 16–32 surface dendrimer groups

Taken together, these studies make it clear that multivalent supramolecular structures can be synthesised which allow for competitive multi-point attachment to important and powerful immunological receptors. Garcia-Vallejo et al. have also defined the optimal level of multivalency necessary to achieve internationalisation in dendritic cells [73]. They found that glycopeptide dendrimers carrying 16–32 glycan units (i.e. a Generation 3 dendrimer) were optimal. This size of core dendrimer facilitated DC-SIGN targeting and internalisation and led to a robust induction of both CD4 and CD8 T-cell responses. It suggests that relatively simple multivalent dendrimer based targeting systems could also be used for the effective and efficient delivery of antigenic peptides to dendritic cells.

12. My perspective on dendrimer drugs as medicines to market

Although therapeutic opportunities for dendrimer drugs *should* be plentiful in oncology as well as in infection and inflammation, progress into clinical trials has been rare. A consensus now needs to emerge amongst those working on dendrimer drugs as to how to progress them rapidly, safely and efficiently to beyond the academic laboratory. We can all see what has already been achieved by protein and antibody based drugs; I am certain that as much could be achieved with dendrimer drugs in advancing new treatment approaches for patients in modern medicine. In order for this to happen, what is now needed, more than anything else, is effective and co-ordinated leadership to lead the commercial charge for dendrimer drugs as marketable medicines. In 2015, this has also been highlighted by other investigators in the field [74].

Conflict of interest

Dr. Shaunak reports that he is the inventor of patent WO/2003/089010 and WO/2012/025745 which are owned by Imperial Innovations.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.bbrc.2015.07.033.

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