

## Commentary

S. Moein Moghimi\*, Peter P. Wibroe, Linping Wu and Z. Shadi Farhangrazi

# Insidious pathogen-mimicking properties of nanoparticles in triggering the lectin pathway of the complement system

**Abstract:** The lectin pathway of the complement system is an integral component of the innate immune system recognizing pathogens through patterns of sugar moieties displayed on their surfaces and neutralizing them through an antibody-independent reaction cascade. Many engineered nanoparticles incite complement through the lectin pathway, but these nanoparticles inherently do not express surface-exposed sugars. However, the projected polymeric surface architecture of nanoparticles may transiently resemble structural motifs of peptidoglycan constituents of pathogens and trigger the lectin pathway. We discuss these issues in relation to nanomedicine design and immune safety.

**Keywords:** drug delivery; infusion-related reactions; innate immunity; nanoparticles; nanomedicine; polymers.

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## Nanoparticles and the complement system

Many functional particles (e.g., iron oxide nanocrystals, gold nanoparticles, carbon nanotubes, graphene) and drug carriers (e.g., liposomes, polymeric nanospheres,

oil-in-water emulsions, polymeric micelles) exhibit an array of ‘pathogen-mimicking’ properties, which arises from a combination of their nanoscale size and aspect ratio, morphology and surface display of repetitive epitopes (e.g., clusters of functional groups, surface projected polymers), making them susceptible for interception by the body’s defences (1). The complement system is a key component of the innate immunity, which can be triggered by a wide repertoire of invading particles (including pathogens) (2). Accordingly, the complement system provides critical immunoprotective and immunoregulatory functions comprising opsonization, lytic and inflammatory processes (e.g., chemotaxis and leukocyte activation) (2). There are three established pathways of complement activation: classical, lectin and alternative pathways (2). Each pathway is triggered differently, but they converge to generate the same set of effector molecules (2, 3).

Complement activation and fixation has been a central point for efficient clearance of nanoparticles and drug carriers by phagocytic cells (4, 5). On the other hand, inadvertent complement activation may initiate adverse reactions and this has been noted following infusion of many therapeutic agents including antibody, polymeric, micellar- and particulate-based formulations into human subjects (6–8). The exact role and contribution of the complement system in infusion-related reactions is not clear, but liberation of complement bioactive products (e.g., C3a, C5a and C5b-9) can potentially modulate the function of a variety of immune cells (e.g., macrophages, monocytes, polymorphonuclear cells, platelets, mast cells) and vascular endothelial cells either directly or in cross-talk with pattern-recognition receptors (e.g., Toll-like receptors 2, 4 and 9) to account for some of the observed adverse events (6, 7). Furthermore, complement activation is also of serious concern for successful development of intravenous anti-cancer nanomedicine initiatives (9, 10). Indeed, recent studies have indicated that intratumoral accumulation of complement activating long-circulating nanoparticles in immunocompetent mice can accelerate tumor

**\*Corresponding author: S. Moein Moghimi**, Nanomedicine Research Group and Centre for Pharmaceutical Nanotechnology and Nanotoxicology, Department of Pharmacy and NanoScience Centre, University of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen Ø, Denmark, E-mail: moien.moghimi@sund.ku.dk

**Peter P. Wibroe and Linping Wu:** Nanomedicine Research Group and Centre for Pharmaceutical Nanotechnology and Nanotoxicology, Department of Pharmacy and NanoScience Centre, University of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen Ø, Denmark

**Z. Shadi Farhangrazi:** Biotrends International, Denver Technological Center, Greenwood Village, CO, USA

growth through C5a liberation (9), presumably through recruitment of regulatory T cells (resulting in deregulation or suppression of CD8<sup>+</sup> cytotoxic T cell activity), immunosuppressive monocytes and alternatively activated macrophages into malignant tumors as well as increasing tumor angiogenesis (9–11). Therefore, understanding of nanomaterial properties that incite complement is a prerequisite for design and engineering of immunologically safer nanomedicine and biomedical devices.

The interaction between particulate matters and the complement system is complex and regulated by inter-related factors comprising morphology, dimension, chemical make up and surface characteristics (3). The majority of complement activation studies with medically relevant nanoparticles have been predominantly qualitative with limited focus on mechanistic aspects (1, 3). In case of the latter, attention has been mostly towards the classical and alternative pathways (3). Compelling evidence now suggest that many such nanoparticles insidiously incite complement through the lectin pathway, which involve carbohydrate recognition, but these nanoparticles natively do not express surface-exposed sugars (12–21).

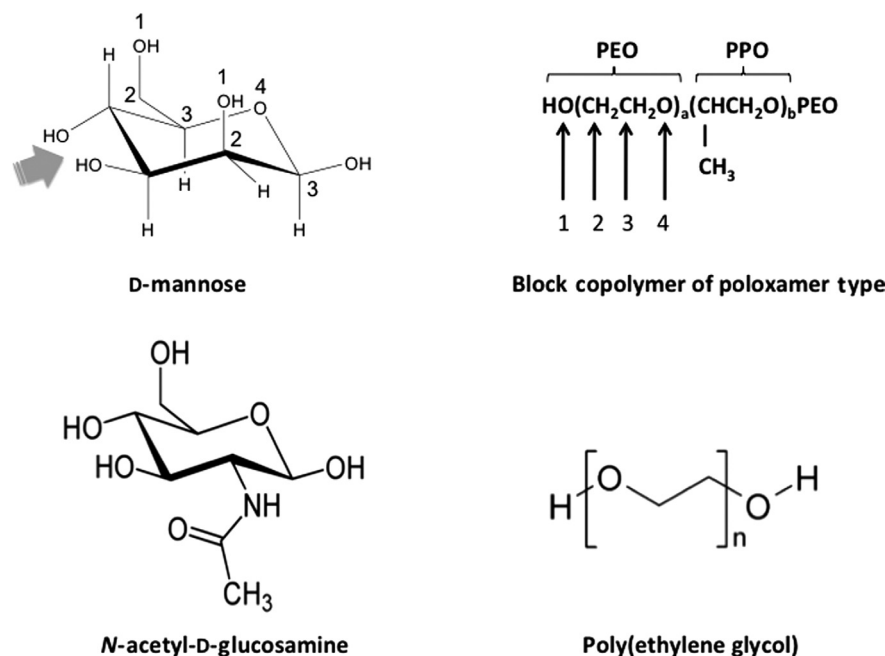
## The lectin pathway

In humans, five pattern recognition molecules are capable of initiating the lectin pathway (22, 23). These include mannose-binding lectin (MBL), ficolins of M, L and H classes, and collectin 11 (CL11 or CL-K1) all in association with a complex set of serine protease zymogens. To date, three serine proteases, namely MBL-associated serine protease (MASP) 1, 2 and 3 have been identified (22). In addition, two non-enzymatic fragments of the MASPs (MAp44 and MAp19) have been found in the recognition complexes (22). MBL binds carbohydrates with 3- and 4-hydroxyl groups in the pyranose ring (D-mannose and N-acetyl-D-glucosamine, GlcNAc) in a calcium-dependent manner (22). Serum L- and H-ficolin has a common binding specificity for GlcNAc. The M-ficolin is not a serum protein, but its mRNA is found in leukocytes and lung (22). CL11 has preference for L-fucose and D-mannose and binding is calcium-dependent, which resembles the specificity of mouse MBL-A (23). Binding of the lectin pathway recognition molecules to the corresponding surface-exposed carbohydrate ligands activates MASPs, although the exact molecular details are still poorly understood (22, 24). Typically, MASP2 cleaves the fourth and the second complement proteins (C4 and C2, respectively) to form the C3 convertase C4bC2a (22). In the absence of MASP2,

the lectin pathway is not functional as confirmed in both MASP2-depleted human serum and MASP2 knockout mouse (25, 26). A recent study (24), however, indicated that MASP2 activation strictly depends on MASP1, and inhibition of MASP1 prevents activation of MASP2. Furthermore, MASP1 was suggested to produce 60% of C2a responsible for C3 convertase formation (24). Accordingly, a new model of lectin pathway activation proposes that MASP1 when activated cleaves zymogen MASP2, where the active MASP2 then cleaves C4 and the associated C4b binds C2, which is then cleaved primarily by MASP1 and to lesser extent by MASP2 thus forming the C4bC2a complex (24). MASP1 is also able to cleave C3 directly, which results in activation of the alternative pathway (27). Others, based on a knockout mouse model, have also proposed a role for MASP1 and MASP3 in directly activating the alternative pathway factor D as well as limited factor B cleavage by MASP3 (28–30). However, there are ongoing debates on these findings (31, 32).

## Examples of nanoparticle-mediated activation of lectin pathway

Nanoparticle surface camouflaging with materials such as poly(ethylene glycol)s, PEGs, and block copolymers of poloxamer and poloxamine series has long been shown to combat macrophage recognition and confer longevity in the blood (1, 33, 34). Although long believed that such strategies could suppress opsonization events in the blood (33, 34), recent studies have demonstrated that some of these engineered entities can, indeed, incite complement and depending on surface polymer configuration complement activation may proceed exclusively through the lectin pathway (12, 13, 17–19, 21). For example, alteration of poloxamine 908 copolymer architecture on polystyrene nanospheres of 220 nm in size from a flat to mushroom-brush configuration switched complement activation from the C1q-dependent classical pathway to a lectin pathway in human serum (12). This copolymer has repetitive recognition patterns of relative polarity and hydrophobicity, where the patterns may change with changes in surface density of the copolymer. Consequently, this may create new binding sites for complement recognition and shifts complement activation pathway from classical to lectin mode. Indeed, one intriguing aspect of PEG and block copolymers of poloxamer and poloxamine series is structural similarities between their terminal region and D-mannose/GlcNAc (Figure 1). In this respect, the surface projected poly(ethylene oxide) chains of the poloxamine



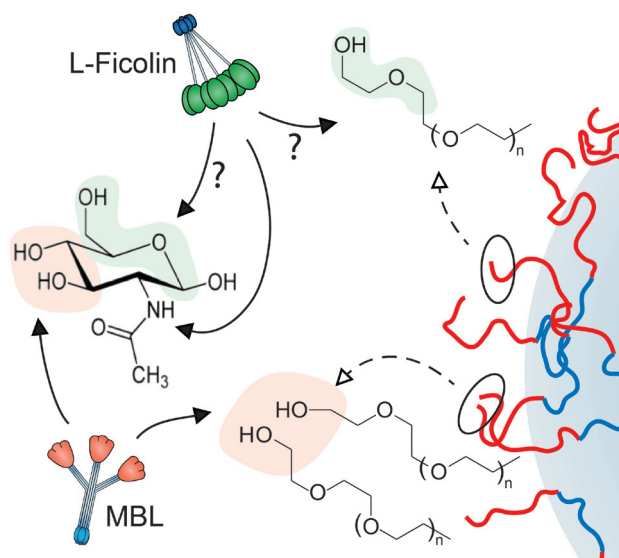
**Figure 1:** Structural similarities between D-mannose, N-acetyl-D-glucosamine and selected polymers used in nanoparticle engineering. Compare sequences numbered 1–4 between the sugars and polymers, which can be repeated in different ways on both sugars. The arrow indicates the MBL binding site (the equatorial OH groups) in D-mannose (arrow head). The binding sites for ficlins and collectin 11, however, remain unknown. PEO, polyethylene oxide; PPO, polypropylene oxide. The structure of poloxamines is not shown, but poloxamines are star-shaped copolymers comprising of four POP chains joined by a central ethylene diamine bridge, where each POP block is flanked at the other end by a POE chain.

908 in close proximity (as in mushroom-brush configuration) may form dynamic ‘pathogen-mimicking’ clusters transiently resembling structural motifs of the D-mannose/GlcNAc, which serves as a platform for MBL/ficolin/CL11 docking (Figure 2). Accordingly, it is not surprising to see that block copolymers in different forms (e.g., micelles, gels) also trigger lectin pathway in a size- and shape-independent manner (14).

Similar observations have been reported with carbon nanotubes coated with PEG-conjugated molecules or covalently functionalized with PEG, where gross surface polymer architectural changes not only triggered lectin pathway, but further modulated the mode of lectin pathway activation through binding of different lectin pathway initiating molecules (e.g., MBL vs. L-ficolin) (13).

Non-specific adsorption of heavily glycosylated plasma proteins such as apolipoprotein B-100 and certain classes of antibodies to surface engineered nanoparticles may further contribute to lectin pathway activation (12, 14, 34). On binding and conformational transformation, the glycosylated modules of these proteins may act as template for binding of lectin pathway initiators.

Dextran-coated super paramagnetic iron oxide nanoparticles also incite complement through lectin pathway



**Figure 2:** Possible mechanisms of nanoparticle-mediated activation of the complement lectin pathway. The right segment is a schematic representation of a polymer-coated nanoparticle. The dynamics of the terminal regions of surface projected polymers (e.g., poloxamers and poloxamines) in close proximity may transiently resemble structural motifs of N-acetyl-D-glucosamine/D-mannose recognizable by lectin pathway initiators (e.g., MBL, L-ficolin). See Figure 1 for polymer structures.

(21). In human sera, activation was MBL-dependent as well as proceeding directly through the alternative pathway. In mouse sera, activation was MBL-A/C dependent, but alternative pathway contributed via the amplification loop only (21). These observations highlight important differences and similarities in nanoparticle-mediated complement activation between humans and mice. Accordingly, complement activation and related adverse events studies in animals may not necessarily translate into a human system (10, 21).

## Outlook

Evolution has afforded complement system a powerful tool to combat pathogens through lectin pattern recognition. It is not surprising to see that man-made materials such as various polymers [e.g., PEG, poloxamers, poloxamines, poly(caprolactone), poly(glycolic acid), poly(lactic acid), poly(lactide-co-glycolide), polyoxazoline, chitosan] and drug delivery systems based on such polymers trigger lectin pathway. Indeed, many such entities share structural motifs with peptidoglycan constituents of the pathogens that incite complement through MBL, ficolin and collectin 11 binding, and therefore needs revisiting. For example, chitosan is composed of repeating units of D-glucosamine, together with residual GlcNAc units. A repertoire of glycosylated plasma proteins may further aid lectin pathway activation on nanoparticle binding and conformational changes and also warrants clarification (34). Protein fingerprinting and mass spectrometry studies, however, reveal little in terms of surface-dependent and fluid-phase complement cascade and the precise role of lectin pathway initiators in nanoparticle-mediated complement activation (35, 36), where qualitative analysis could be misleading (1). Future studies should examine nanoparticle-mediated lectin pathway activation of the human complement system more carefully through integrated approaches and ‘structure-activity’ mapping, which may lead to identification of structural motifs and geometrical arrangements that dock lectin pathway initiators. Collectively, these approaches may initiate better approaches for safer nanoparticle design and engineering (an ‘immune safe-by-redesign’ concept). Indeed, a recent study demonstrated that MBL-binding kinetics are critically dependent on structural characteristics on the nanometer scale, including the dimensions of polyvalent MBL oligomers as well as the mode of ligand presentation on surfaces (37). Future developments in microstamping may further aid mechanistic understanding of spatial and architectural arrangements of immobilized

polymers in controlling the binding kinetics of lectin pathway initiators. Through such studies and computational analysis it may be possible to simulate time-dependent nanoparticle surface changes in vivo (e.g., in the blood or on nanoparticle extravasation to interstitial spaces) that may subsequently shift complement activation from one pathway to another, thereby initiating delayed reactions. Finally, complement activation as whole seems to play an important role in nanomedicine-mediated infusion-related reactions and progression of cancer, but the exact contribution of the lectin pathway needs to be mapped out. Accordingly, we should be cautious in extrapolating the outcomes of animal studies to human safety pertaining intravenous nanomedicines and nanopharmaceuticals, since there are differences in complement activation processes between humans and other species and particularly in relation to lectin pathway activation.

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## Bionotes



### S. Moein Moghimi

Nanomedicine Research Group and Centre for Pharmaceutical Nanotechnology and Nanotoxicology, Department of Pharmacy and NanoScience Centre, University of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen Ø, Denmark  
moien.moghimi@sund.ku.dk

S. Moein Moghimi read Biochemistry at the University of Manchester (UK) and in 1989 earned his PhD in Biochemistry (Liposome Immunobiology) from Charing Cross Hospital Medical School (Imperial College, University of London). He is currently based at the University of Copenhagen (Denmark) where he serves as Professor of Nanomedicine at the Department of Pharmacy, Professor of Pharmaceutical Nanotechnology at the NanoScience Centre, and Director of the Centre for Pharmaceutical Nanotechnology and Nanotoxicology. He is also a full member and affiliate professor at the Department of Translational Imaging, Houston Methodist Research Institute (Weill Cornell Medical College), Houston Methodist Hospital Systems, Houston, Texas (USA), adjunct professor at the Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado-Denver Medical Center (USA), visiting professor at University of Padova (Italy) and the elected Fellow of the Institute of Nanotechnology (UK). Earlier, he served as the Honorary Professor of Nanomedicine at the Multidisciplinary Research Center, Shantou University (China). Before joining Copenhagen, Moein was Senior Lecturer in Biopharmacy and Molecular Pharmaceutics at the School of Pharmacy, University of Brighton (UK) and The University Research Fellow in Advanced Drug Delivery Systems at the Department of Pharmaceutical Sciences, University of Nottingham (UK). His research activities are focused on pharmaceutical nanoscience and fundamental nanomedicine and nanosafety. Moein is the Associate Editor of *Nanomedicine: Nanotechnology, Biology and Medicine* and the *Journal of Biomedical Nanotechnology* and further serves on the editorial board of several peer-reviewed international journals, including *Advanced Drug Delivery Reviews*, *Nanomedicine-UK*, *Journal of Liposome Research* and *Molecular and Cellular Therapies*.

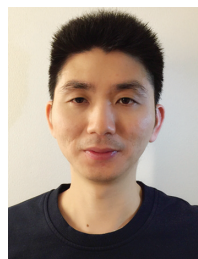


### Peter P. Wibroe

Nanomedicine Research Group and Centre for Pharmaceutical Nanotechnology and Nanotoxicology, Department of Pharmacy and NanoScience Centre, University of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen Ø, Denmark

Peter P. Wibroe has a solid background at the interface of nanotechnology and pharmaceutical sciences. Peter is dedicating his research to the intriguing interplay between the physicochemical

properties of synthetic nanoparticles and biological systems, with a special focus on the complement system. Peter is currently enrolled as a PhD student in the Nanomedicine Group led by Professor Moghimi, where he is developing immune-safe and efficient drug delivery vehicles based on understanding of the molecular mechanisms by which nanoparticle surface presentation modulates complement recognition and responses. In this respect, Peter has already published several papers and reviews about the complement system and the underlying mechanisms of material recognition.



### Liping Wu

Nanomedicine Research Group and Centre for Pharmaceutical Nanotechnology and Nanotoxicology, Department of Pharmacy and NanoScience Centre, University of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen Ø, Denmark

Liping WU obtained a Master's degree in Biomaterials from Shantou University (China) in 2008. He began his PhD studies under the direction of Professor Moghimi at the University of Copenhagen and obtained his PhD in Nanomedicine in 2014. Currently he is a senior postdoctoral scientist in the same group, focusing on design and engineering of immune-safe advanced biomaterials and drug delivery systems for specific targeting through an interdisciplinary approach.



### Z. Shadi Farhangrazi

Biotrends International, Denver Technological Center, Greenwood Village, CO, USA

Z. Shadi Farhangrazi, PhD, MS, MBA is a biochemist, neuroscientist, infectious diseases expert, strategist, entrepreneur, and an expert in the area of innovation and entrepreneurship. She is the Founder, President and Managing Partner of management consulting firm Biotrends International. Farhangrazi is also a faculty member at Daniels College of Business, and University College, University of Denver. She has been teaching workshops and classes on entrepreneurship, innovation, strategy and non-profit management and has worked with multinational companies, SMEs, non-profit organizations and governmental organizations internationally. She has an active interest in nanomedicine innovation and translation.