DIRNANO

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Complement Benign Nanoparticles

The field of nanomedicine has witnessed remarkable advancements, with nanoparticles (NPs) emerging as promising carriers for drug delivery, imaging, and diagnostics. However, the interaction of NPs with the immune system remains a critical consideration. The intricate interplay between NPs and the immune system has garnered significant attention in the field of nanomedicine. Among the immune components, the complement system plays a pivotal role in non-specific host defence and homeostasis. The complement system consists of a series of proteins that interact in a cascade-like manner. Activation of the complement cascade can lead to opsonization of NPs, promoting their clearance by phagocytes. Additionally, excessive complement activation may trigger inflammatory reactions, compromising NP functionality (1).

Many surface engineering strategies have been developed to reduce complement activation, achieve longer circulation, and target specific action of NPs. The majority of the surface modification of NPs has been carried out by grafting non-ionic hydrophilic polymers and/or surfactants such as polyoxazolines, polybetaines (zwitterionic molecules) (2,3), polyglycerols, (4,5) and polysaccharides (chitosan, dextran and hyaluronic acid). Among these surface modification techniques, the best-studied technique includes the use of polyethylene glycol (PEG). The PEG chains have been grafted on the particle surface by either covalent conjugation through surface functional groups or covalent attachment of PEG derivatives for example poly (lactic acid) (PLA), poly (alkylcyanoacrylates), and poly (lactic *-co-* glycolic acid) (PLGA) (6,7) However, these approaches do not entirely abolish the immune reactions to nanoparticles (8,9). Therefore, refined surface engineering strategies are required to modulate the interaction of NPs with immune system and development of complement benign NPs could help to overcome the pro-inflammatory responses associated with uncontrolled activation of the complement system.

Nanoscale parameters influencing complement response.

Many nanoscale characteristics of NPs and/or immune systems influence

complement response.
These include –

Particle curvature - The curvature of NP surfaces significantly impacts complement interactions. Curved surfaces alter the accessibility of complement proteins, affecting their binding and activation. For instance, NPs with high curvature may enhance complement activation due to increased protein engagement (10).

Spacing arrangement and periodicity of surface ligands - The arrangement of ligands on NP surfaces influences complement responses. Multivalent engagement can occur when multiple ligands interact simultaneously with complement proteins.
Therefore, optimal spacing between ligands can enhance or inhibit complement activation. Periodic arrangements may lead to cooperative binding, affecting the conformational changes necessary for complement activation (11).

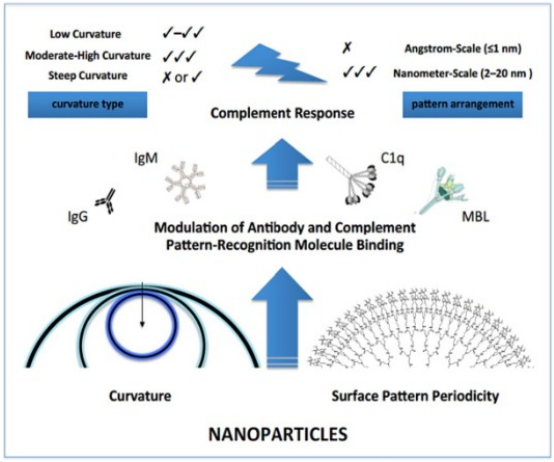

Figure 1: Schematic representation showing the role of particle curvature and surface pattern periodicity in complement response.

Antibodies - also play a crucial role in NP recognition by the immune system. NPs coated with antibodies can activate the complement cascade. The density and orientation of antibodies on NP surfaces impact complement engagement.

Complement pattern-recognition molecules - Proteins like C1q, mannose-binding lectin and ficolin have distinctive shapes with many binding sites that can recognize different spectrums of ligands and specific patterns on NP surfaces. Their binding triggers complement activation. The spatial arrangement of these molecules affects their ability to engage with NPs. Because the functional binding of complement pattern-recognition molecules to target epitopes is dependent on the ligand periodicity and their nanometer-scale spacing arrangement, entities that display surface patterns below the nanometer-scale spacing arrangement are therefore
expected to evade complement (11,12).

Therefore, understanding how nanoscale features influence complement responses is essential for designing safer and more effective NP-based therapies. This has been the focal point of study for ESR 4, who aims at developing NPs by polymer pairing approach and determining their influence on immune response. The study would help in recognising the implication of nanometer-and-armstrong scale parameters modulating NP interaction with complement proteins. Such understanding holds immense promise for example, we can obtain tunable complement responses that is by engineering NPs with specific surface characteristics, we can tailor the complement activation. We can unlock new possibilities for precision medicine, ultimately benefiting patients worldwide.

In summary, optimizing drug delivery systems involves a delicate balance between achieving efficient drug delivery and minimizing immune responses. By understanding complement interactions and employing smart design principles, we can enhance the success of targeted therapies.

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News from the DIRNANO consortium

Secondments:

1. Hajira Banu Haroon (ESR 4) has started her secondment at CIBIR, Rioja where she will be performing the biodistribution studies of polymeric nanoparticles under the guidance of Dr. Alfredo Martinez

2. Margarita Kislukhina (ESR11) Margarita, ESR11, is currently undertaking her second secondment at the University of La Rioja within Professor Francisco Corzana's laboratory. Additionally, she has the privilege of receiving training at the nearby partner organization, Fundación Rioja Salud, under the guidance of Dr. Alfredo Martínez. Research focuses on peptide synthesis, polymer development, and hybridoma culture aimed at producing targeted antibodies of high efficacy.

Presentations and Publications:

1. Hajira Banu Haroon (ESR 4) gave an oral presentation on her work at the 9th International Conference on Nanomedicine, Drug Delivery, and Tissue Engineering (NDDTE 2024), Imperial College London, UK.
Hajira's talk was titled "Macromolecular Pairing on Nanoparticle Surface Modulates Immune Response".

2. Cristina Fontecha Cuenca (ESR 03), Hajira Banu Haroon (ESR 4), Rita Ribeiro (ESR 08), Dr. Jutta Horejs-Hoeck, Prof. Moghimi, Dr. Tore Skotland, and Dr. Kristen Sandvig in collaboration with colleagues from Oslo University

Hospital, Norway has published an article titled "Preclinical Efficacy of Cabazitaxel Loaded Poly(2-alkyl cyanoacrylate) Nanoparticle Variants" in International Journal of Nanomedicine.

Awards and accolades:

Hajira Banu Haroon (ESR 4) received the "Best Paper Award" for her oral presentation at the 9th International Conference on Nanomedicine, Drug Delivery, and Tissue Engineering (NDDTE 2024), Imperial College London, UK. The work was developed in collaboration with Pedro M Veloso (ESR 2) at Prof. Papini's lab at the University of Padova.

Final Meeting:

The final meeting to mark the conclusion of the DIRNANO project will be held at the University of Salzburg from July 10th to 12th, 2024.

Stay tuned and follow all updates on our website and our LinkedIn page!

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