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Review

Engineering of pulmonary surfactant corona on inhaled nanoparticles to operate in the lung system

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ABSTRACT

Exposure of inhaled nanoparticles (NPs) to the deep lung tissue results in the adsorption of pulmonary surfactant (PSf) on the surface of NPs and the formation of a biomolecular corona. The adsorption of the peculiar phospholipids (PLs) and surfactant proteins (SPs) provides NPs with a new bio-identity, which likely changes their corresponding interactions with cells and other bio-systems. Exploring the interaction of NPs with the PSf film at the alveolar air-fluid interface can provide valuable insights into the role of biofluids in the cellular uptake of NPs and their nanotoxic effects. Wrapping biomembranes around NPs and the formation of lipoprotein corona regulate viscoelastic changes, NP insertion into the membrane, and cellular uptake of NPs. In this review, a concise overview has been presented on the engineering of PSf on inhaled NPs to operate in lung environment. First, the physiological barriers in the pulmonary delivery of NPs and approaches to regulating their pulmonary fate are introduced and rationalized. Next, a short description is given on the different sources used for exploring the interfacial performance of inhaled NPs in vitro. A discussion is then presented on SP corona formation on the surface of inhaled NPs, coronal proteome/lipidome in respiratory tract lining fluid (RTLF), regulation of NP aggregation and surfactant flow characteristics, PSf corona and its functional role in the cellular uptake of NPs, followed by explanations on the clinical correlations of PSf corona formation/inhibition on the surface of NPs. Finally, the challenges and future perspectives of the field have been discussed. This review can be harnessed to exploit PSf for the development of safe and bio-inspired pulmonary drug delivery strategies.

1. Introduction

The interaction of nanoparticles (NPs) with biological fluid at the nano-bio interface can alter their behavior and subsequent interaction with cells. This interaction applies to all nano-based platforms, regardless of their planned application or exposure route [1]. NPs show the potential to interact with different types of proteins in the blood and other extracellular fluids to form “protein corona”. The protein corona on the surface of NPs is classified as “hard” corona, which contains strongly interacted proteins, and “soft” corona, with loosely bound proteins [2,3]. Hard corona has a significant impact on the fate of NPs when they interact with cells [4,5], as well as NP-based pharmacokinetics, therapeutics, and diagnostics [6,7].

Several studies have looked into the interaction of proteins and complex fluids with different NPs, providing a physical explanation of the adsorption mode and associated kinetics [8,9]. However, most of these studies have focused on the formation of corona around NPs within plasma, with little attention paid to other biofluids. The respiratory tract, in particular, is known as one of the most likely routes for NP entry to the body. The physicochemical properties of NPs, as well as

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the breathing scenario, influence their deposition behavior in lungs. It has been demonstrated that large NPs (> 1 μm) are often deposited in the upper airways, whereas small NPs (100 nm to 1 μm) can enter the alveolar region [10,11]. Inhaled NPs with sizes of 100 nm have been found to accumulate in the alveoli [11,12], where they come into contact with interstitial fluid in lung. As a result, the translocation mechanisms are complex, and despite numerous efforts and substantial reports, these processes are not fully understood. Thus, both the potential pulmonary use of NPs, as drug delivery carriers and the associated nanosafety concerns necessitate conducting in-depth studies to examine the fate of NPs after deposition in the deep lung tissue and the interactions with respiratory tract lining fluid (RTLF) [13,14].

This distinct pulmonary surfactant (PSf) layer, a unique composition of lipids and proteins secreted by alveolar epithelial type II (ATII) cells, may result in the formation of a corona that differs significantly from the one that forms in the blood. While the composition of a plasma corona on the surface of NPs is well understood [15–18], little is known about how airborne NPs interact with the PSf as a highly complex fluid. As a result, several studies have focused on the interaction of NPs with sizes less than 100 nm and PSf to investigate the effect of PSf corona's molecular structure on NP translocation across the PSf layer. It has been demonstrated, for example, that the physicochemical properties of NPs control the formation of PSf corona and its translocation across PSf monolayers [14,19–21]. Furthermore, it has been expressed that the PSf component and the cell type play important roles in the cytotoxicity of NPs against lung cancer cells [22]. It was seen that silica (SiO_2) NPs at a specific dose (128 μg/mL) induced selective cytotoxicity against human bronchial epithelial (16HBE) cells derived from the higher cellular uptake of NPs and inhibition of the activities of ABC transporters in comparison with human lung epithelial (A549) cells [22]. Additionally, it was found that the incubation of SiO_2 NPs with dipalmitoyl phosphatidylcholine (DPPC) mitigated the stimulated cytotoxicity against 16HBE cells mediated by a significant decrease in the internalization of NPs [22].

Surfactant protein (SP) adsorption on the surfaces of NPs can, in fact, play an important role in NP uptake by alveolar macrophages (AMs), and this effect can be equalized or increased in the presence of lipids. Furthermore, both phospholipids (PLs) and SPs can adsorb onto NPs after inhalation, and NPs can change the lipidomic and proteomic profile of the PSf fluid [23–26]. Depending on the physiological properties of NPs, they can have varying affinities in their interactions with the surfactant layer and adsorbing different layers of PLs [14,19,24,27]. As a result, NP-PSf interaction can alter NP dissolution, stability, and cellular uptake [28], as well as PSf stability and lateral film organization [29,30].

Based on the great significance of NP-PSf interactions, several papers have recently reviewed the works conducted on revealing the mechanism(s) of such interplays. For example, a review on the pivotal role of PSf upon inhalation of NPs demonstrated that the inevitable interactions between NPs and PSf are a critical factor in determining the biological fate and behavior of NPs in lung tissue [31]. Also, Liu et al. discussed how the physicochemical features of NPs influence their fate and the physiological behavior of PSf [14]. Furthermore, Wang et al. discussed potential strategies for overcoming physiological barriers against pulmonary drug delivery (PDD) [32]. Huck et al. also reviewed several models based on native mucus in the context of PDD research and discussed the effect of tracheobronchial mucus composition and structure on its barrier features [33]. While these works greatly reflect some of the significant aspects of NP-PSf interactions, there still seems to be a need for a comprehensive understanding of the biophysical nature of PSf corona following interaction with NPs. In this review, we aimed to overview SP corona formation on the surface of inhaled NPs, coronal proteome/lipidome in RTLF, NP aggregation in relation to surfactant flow characteristics, and PSf corona as well as its effect on the cellular uptake of NPs.

2. Physiological barriers in pulmonary NP delivery

NP-mediated PDD is often hampered by two main challenges: 1) lung defenses comprised of airways and their mucosa (luminal defense mechanisms, epithelial cells, blood-derived cells of the mucosa), and alveolar spaces [27,34]; and 2) formation of PSf corona in alveolar regions due to presence of RTLF [35]. It has also been demonstrated that a small number of NPs can cross the pneumocyte layers and enter the systemic circulation [18]. Recently, Liu et al. overviewed the physicochemical properties of NPs influencing their fate in PDD, with a focus on NP clearance [27]. Additionally, Wang et al. reviewed the physiological barriers in NP-mediated PDD [32]. The readers are referred to these works for further information. In general, several major physiological barriers to inhaled NPs have already been reported, as summarized in Table 1.

3. Approaches to regulate the pulmonary fate of NPs

NP compatibility and tolerability offer potential opportunities for local NP-based PDD. Based on the physiological parameters of NPs, their retention time within the lungs could be regulated by a number of barriers, allowing them to stay for as short as a few minutes or for several weeks. Furthermore, the colloidal stability of NPs changes significantly after interaction with these barriers, which could result in the activation of clearance mechanisms. In other words, the type of binding interaction between PSf and NPs has the potential to influence the NP fate and its clearance in vivo. This type of data could be useful for the advancement of nanotherapeutics that target tumor sites, viruses, infections, and AMs. Several approaches have been reported to overcome these different barriers to develop a potential drug delivery system for NP-mediated pulmonary disorders (Table 2).

4. Different sources used for studying the interfacial performance of inhaled NPs in vitro

BAL is the most common method employed to collect the RTLFs derived from the distal lung, which is an invasive and cost-expensive procedure. However, some other procedures such as exhaled breath condensate and bronchoscopic microsampling have been used to address the main concern raised by BAL, discussed in detail in a previous study [68]. Also, compositional differences were reported along the different respiratory passages, including nasal, tracheobronchial, and bronchoalveolar airways. Generally, it has been shown that the major components of the RTLFs are mucus gel layer, low molecular weight antioxidants (urea, ascorbate, glutathione, α-tocopherol), proteins [albumin, transferrin, immunoglobulins (A, G, M), lysozyme, α − 2-macroglobulin, α 1-antitrypsin, Clara cell secretory protein], surfactants [SP (A, B, C and D), lipids].

Although the human sample is considered a potential source as they contain all of the lipid and protein patterns, they suffer from several disadvantages, including tedious, costly, and time-consuming purification procedures, interindividual flexibility, and the presence of contaminated samples [68]. Therefore, exploring the cellular interactions of inhaled NPs in vitro by using a medium with sufficient supplements is crucial. Gambles solution has long been used as a simulated epithelial lung fluid, which mainly contains inorganic salts, where later on several modifications were applied to develop the solubility of drugs [69] as well as mimicking the acidic lysozyme environment, and particle ingestion by AMs [70] However, mixtures lacking saturated lipids and SP, which represent low interfacial performance, are not clinically capable of developing stable RTLF. The addition of DPPC (0.02% 50 w/v) may modulate the wettability, dispersity and dissolution of NPs. The solubility of the NPs can be changed under increasing lipid and SP concentrations. Therefore, use of an artificial surfactant (Survanta) with the composition of phospholipids (25 mg/mL), triglycerides (0.5–1.75 mg/mL), free fatty acids (1.4–3.5

Table 1
The physiological barriers to inhaled NPs [32,36].

Barrier	Composition	Structural organization	Function
Mucous	Water (≥95%), mucin glycoproteins, inorganic salts, lipids, proteins, Immune cells, nucleic acids, and filamentous-actin	Mucin glycoproteins	Formation of a negative charge, viscoelastic properties, wrapping and NP clearance
		Salts and pH	Mucus homeostasis, controlling the physiology of mucins, reducing the interaction of positively charged NPs with mucins, Regulation of viscoelastic properties of mucus
		Lipids and surfactant	Lipid: wettability, viscosity and stabilization of airway. Surfactant: first renewable barrier against NPs and reducing the surface tension; NP clearance through increasing the velocity of the mucociliary escalator
		Proteins	Antimicrobial, inflammatory, antiproteolytic, and antioxidant peptides along with enzymes
		Immune cells, nucleic acids and filamentous-actin	Regulation of immune reaction, mucus rheology, and viscosity
Innate defense functions	Macrophages, dendritic cells (DCs) and neutrophils	Macrophages	In bronchial tree and alveolar region regulate the clearance and digestion of NPs
		DCs	Along with macrophages triggering the immune response
Pulmonary surfactant	Lipid-protein system	Lipids and surfactant proteins	The formation of biomolecular surfactant corona around NPs to modulate the fate of inhaled NPs
Other physiological barriers	Inflammatory cytokines, cilia, extracellular matrix (ECM), biofilm	Inflammatory cytokines	Stimulated the immune reaction and endocytosis process.
		Cilia	NP clearance
		Extracellular matrix (ECM)	Formation of tissue desmoplasia as barrier to PDD
		Biofilm	As a barrier to PDD

mg/mL), protein (<1.0 mg/mL) was used for drug solubilization, revealing that the utilization of this surfactant as a commercial bovine lung fluid could regulate particle solubilization [71]. Therefore, several sources such as mucus, porcine surfactant, and bovine surfactant have been used to mimic the RTLF (Fig. 1).

Huck et al. examined the cytotoxic effects of SiO_2 NPs against macrophage-like THP-1 cells in vitro and found no discernible difference between native porcine and clinical Alveofact [72]. They then concluded that RTLF containing essential PLs and SPs appear to be an appropriate mixture for investigating the interaction of inhaled NPs with cells. It appears that a standardized fluid should be supplemented with several PLs, including DPPC, POPC, and POPG, as well as essential lung SPs. Thus, recombinant or synthetic proteins could be developed and used as promising alternatives to establish contaminant-free and cost-effective production of RTLF [73–75].

5. Surfactant proteins (SPs)

Because the lung is considered a potential target for the administration of several active pharmaceutical NPs through the airway, the interaction with PSf can affect the engineered NP's bio-behavior and applications. Thus, determining the in vivo fate of NPs after pulmonary administration, examining the effect of NP's physiological parameters on AM uptake as well as the inflammatory and lung clearance responses, and investigating the interactions between NPs and major SPs can provide useful information about the fate of NPs in vivo. It has been evidenced that in alveolar spaces, PSf corona formation is an inevitable phenomenon due to the presence of RTLF. This fluid contains plasma proteins and surfactant lipids [85–90% (*w*/w) PLs and 10–15% (w/w) of SP] [Fig. 2a(i)] [76–81].

Due to the unique structure of SPs with multiple domains [Fig. 2a(ii)] and different variants, they exhibit multiple structures with varying functions and stabilities, where amino acid 85 plays a significant role in the oligomerization pattern [78,82]. SP-A1 induces the formation of larger oligomers due to the presence of cysteine, in addition to the formation of dimers and hexamers like SP-A2 [83]. SP-A and SP-D show comparable characteristic structures through trimeric interaction of monomers as the oligomer structure of SP-A is derived from an octadecamer with six trimeric subunits in a flower bouquet-mimic architecture, whereas SP-D displays a cruciform morphology with 12 subunits configured in four trimeric subunits [84]. SP-B is a homodimer with three intramolecular S-S bonds per monomer and an additional S-S bond that stabilizes the dimeric structure [85,86]. SP-C is a specific SP with a short lipopeptide with two palmitoylated -SH at N-terminal [86,87]. Post-modification of SPs remarkably changes their oligomerization pattern and electrophoretic mobility [78]. Furthermore, arginine-85 has been unveiled to increase AM phagocytosis and trypsin digestion [88,89].

5.1. Formation of surfactant protein (SP) corona on the surface of inhaled NPs

SPs play a key role in the fate of NPs in PDD. Hydrophilic SP-A and SP-D are more abundant than hydrophobic SP-B and SP-C [79]. Studies have displayed that, in addition to playing a critical role in the regulation of the alveolar microenvironment and lung host defense [78], SPs, particularly SP-A and SP-D, can also play a role in NP-mediated PDD because interactions between NPs and SPs can alter NP biodistribution [79]. SP-B and SP-C could also regulate the dynamics of interfacial surfactant interactions, lipid transfer, membrane permeability/fusion processes, and homeostasis [90,91]. Some other proteins can interact with NPs in bronchoalveolar lavage fluid (BALF) and form a hard corona that can perform a variety of functions ranging from innate immunity to structural/cell trafficking (Fig. 2b)[92]. These proteins include serum albumin, apolipoprotein A, actin, cytoplasmic 1, α-1-antitrypsin, complement C3/C4, Ig α/γ-1 chain C region, Ig κ chain C region, hemoglobin, ubiquitin-60S ribosomal protein L40, annexin A2, napsin-A, BPI fold-containing family B member 1, α-enolase, polymeric immunoglobulin receptor, programmed cell death 6-interacting protein, lysozyme C, CD59 glycoprotein, and carcinoma-associated proteins.

Due to the presence of highly abundant plasma albumin in BALF, quantifying other low-abundance proteins, which play a key role in the formation of SP corona on NPs, using mass spectroscopy and downstream proteomic approaches is complicated and challenging. As a result, Kumar et al. depleted albumin from all reconstituted RTLF samples and investigated the formation of corona on two different NPs [92], SiO_2 NPs (200 nm) and poly(vinyl) acetate (PVAc) NPs (180 nm). SiO_2 NPs are widely used for the examination of SP corona [93,94] and the PVAc NPs are commonly used as a promising nanomedicine component [95]. It was discovered that the proteins involved in innate immunity constituted the majority of all SP corona components for bare NPs, followed by transport, lipid metabolism, structural/cell trafficking, complement, signaling, protease, tissue repair, and apoptosis proteins (Fig. 2b) [92]. Also, it was found that the compositions of SP corona

Table 2
Strategies for optimization of NP translocation via different barriers in the lung system.

Barrier	Strategy	Description	Types	Mechanism	Ref (s).
Mucus	Size of NPs	Pore size of the mucus can influence the penetration of NPs	Inorganic and organic NPs	Although small sized NPs (<340 nm) can penetrate mucus easily, larger-sized NPs can be mechanically penetrated	[37–39]
	Charge/ hydration layer	Anionic mucus prevents the adsorption (adhesive interaction) of naturally or anionic NPs	Polyethylene glycol (PEG)	PEGylating (2–5 kDa) of NPs may decrease the zeta potential and regulate the formation of hydration layer, which inhibits the interaction of NPs with physiological barriers	[40–44]
			Pluronic® F127 (F127)	Can manipulate the charge distribution and hydration shell due to presence of PEG to mitigate the interaction of NPs with mucus	[45–47]
			Fluorination	Fluorocarbon segments inhibited adsorption of mucin glycoproteins onto surface.	[48]
		Zwitterionic surface mimics the cellular PL membrane	Polydopamine	Polydopamine can facilitate mucus penetrability by mitigating interactions with anionic mucin fibers	[47]
	Pore size of mucin network	Increasing the average pore size of mucin by disulfide disruption	N-acetylcysteine (NAC)	NAC pretreatment as a reducing agent could regulate the elastic properties of airway mucus and enhance mucus penetrability mediated by a significant increase in the pore size of airway mucus	[49]
			-Thiol-carbohydrate structure (methyl 6-thio-6-deoxy-I-D-galactopyranoside) -Tris(2-carboxyethyl)phosphine	Perform comparable mechanism with NAC, however with higher stronger reducing property	[50,51]
		Increasing the pore size by interaction with peptide backbone and glycan structure	Alginate oligosaccharides	Interaction with both protein and glycan structures through involvement of hydrogen bonds reducing the mucin interlinking network	[52]
			Guluronate oligomers	Mitigated steric hindrance deduced primarily from lowering the mucin interlinking network	[53]
	DNA degradation	Increasing DNA degradation can result in improved mucus penetrability	Deoxyribonuclease (rhDNase dornase alfa, Pulmozyme®)	In a concentration-dependent manner result in DNA degradation and improved mucus penetrability	[54–56]
	Magnetic application	The magnetic field gradient could increase the mucus penetration of magnetic NPs.	Iron oxide NPs	The static magnetic field gradient should be much higher (295 T/m) than the regular one (10 T/m), which result in some serious adverse effects.	[57]
Macrophages	Size	Large NPs are prone to be phagocytosed by macrophages	Modified enzyme responsive-nano-in-microgel system	Increased lung deposition efficiency mediated by microgel and avoid MP uptake mediated by NPs	[58]
	Shape	non-spherical NPs can avoid macrophage uptake	Organic and inorganic NPs	Controlling high edge curvature regions could regulate MP-NP contact area and associated MP uptake efficiency of NPs	[59–61]
	Surface modification	The surface functionalization with hydrophilic moieties	Organic and inorganic NPs	PEGylation and modification of NP surface by neutral groups can modulate the macrophage uptake of NPs through regulation of surface protein corona.	[27]
	Surface charge	Biomimetic coating with Red blood cell (RBC) markers, platelet membrane coating, cancer cell membrane	Organic and inorganic NPs	CD44, and CD47 markers can result in MP scape property of NP through regulation of signal receptors mediated by lowering the surface charge of NPs	[32]
PSf	Size	It's not clearly determined the effect of size on the interaction of NPs with PSf	Organic and inorganic NPs	The interaction of NPs with different sized and PSf can occur through different mechanisms and the effect is not clear yet.	[62,63]
	Shape	The comparable dimension of NPs and PSf thickness can play a key role in the interaction of NPs and PSf	Organic and inorganic NPs	Rod-like NPs displayed the less contact with PSf relative to spherical ones. Also, based on the hydrophilicity or hydrophobicity of NPs, the main effect of shape is different	[20,64]
	Surface charge and grafting	Negatively-charged and positively charged NPs can interact differently with PS	Organic and inorganic NPs	Negatively-charged NPs interact with positively-charged SPs, whereas positively-charged NPs interact with negatively-charged lipids	[30,65, 66]
	Surface hydrophilicity	Translocation of NPs in PSs depends on surface hydrophilicity of NPs	Organic and inorganic NPs	Higher translocation of hydrophilic NPs in PS than hydrophobic ones, due to less favorable interaction of hydrophilic NPs with PSf	[19,67]

formed around SiO_2 NPs (200 nm) and PVAc NPs (180 nm) in RTLF were dominated by proteins with molecular mass < 70 kDa and isoelectric point of 7, regardless of NPs' zeta potential [92]. Furthermore, Clemments et al. demonstrated that the high surface curvature of small spherical SiO_2 NPs (70 nm) results in the potential interaction of smaller proteins with low molecular weights (<50 kDa) from biofluids [96]. Based on the comparison of the NP sizes in plasma, it can be concluded that larger-sized NPs may have a greater tendency to adsorb proteins with higher molecular weight. Since Kumar et al. used two different NPs with almost comparable size, one can expect that the distribution of the total mass of adsorbed SP corona is almost identical [92]. Particle size can influence the total amount of protein adsorbed on the surface of NPs as well as the SP corona composition. Other factors, such as NP shape, functional groups, and colloidal stability, may also play a key role in NP-protein interactions. In water, PBS, and biofluids, the zeta potential of NPs with different functional groups is always negative. For instance, it was disclosed that the zeta potential of citrate-coated gold NPs (AuNPs) in deionized (DI) water and BALF were -46.17 ± 2.17 and -14.25 ± 0.35, respectively. Further, albumin-coated AuNPs disposed a zeta potential of -46.9 ± 1.82 and -56.35 ± 3.32 in DI water and BALF, respectively. These results demonstrate that albumin-coated AuNPs were less likely to agglomerate in the presence of SP corona in comparison to the citrate counterparts [35,97]. Even for amine-modified polystyrene NPs with a size of 100 nm, the overall charge distribution was displayed to be negative [98]. Based on the comparable zeta potential of all NPs, it was discussed that any variation in the SP corona

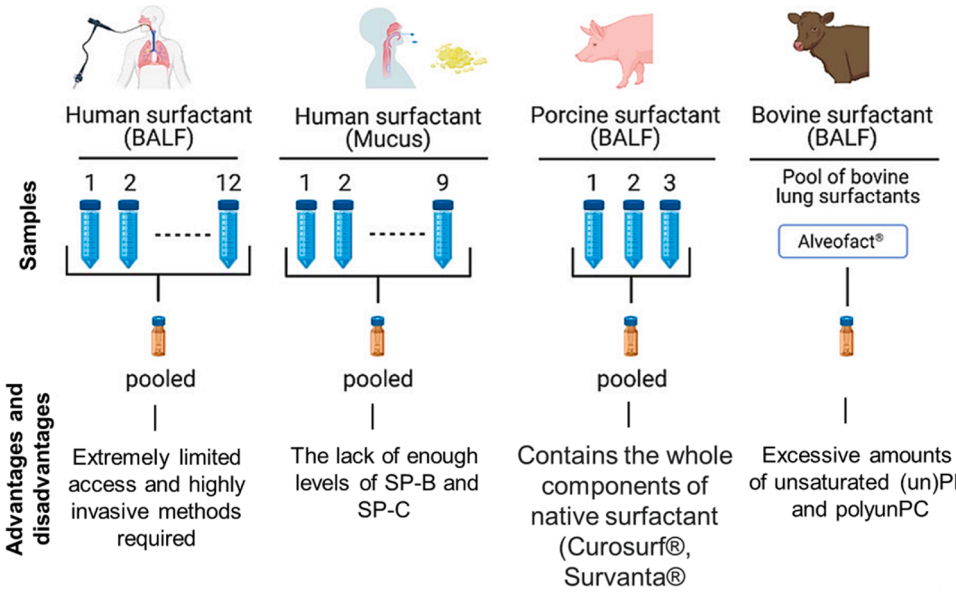

Fig. 1. Different sources used for studying the interfacial performance in lung tissue in vitro [72]. Reprinted under the terms of the CC-BY license [72]. Copyright 2021, Wiley Online Library.

between different species of polystyrene NPs could be due to the mode of colloidal stability, functional moieties, size, shape, and composition of NPs rather than surface charge. For example, although the composition of adsorbed SP corona formed on citrate- and albumin-coated AuNPs was comparable after BALF exposure [Fig. 2c(i)], the percentage of SP corona, concentration, and amount of SP corona per NP were significantly different for NPs of different composition (CeO_2, SiO_2-coated CeO_2, $BaSO_4$, and ZnO NPs) [Fig. 2c(ii)][35].

In general, the colloidal stability of NPs can be explained by the zeta potential value. A higher zeta potential value indicates that NPs have less agglomeration tendency. Different functional groups on NPs or interactions with proteins can alter the zeta potential value, colloidal stability, and physicochemical interactions at the nano-bio interfaces. For example, it was exhibited that coating magnetite and TiO_2 with SP-A [99] or $BaSO_4$ with albumin [35] enhances AM uptake, implying that the SP corona can play an important role in NP recognition, phagocytosis, and processing by AMs via changing the colloidal stability of NPs. Once NPs have been internalized by AMs, they can be cleared from the lungs at a rate that is heavily influenced by the composition of the SP corona [100]. In fact, the fast dissolution rate caused by NPs' high solubility can result in rapid uptake by AMs. It has been demonstrated, for example, that the SP corona with the high amount of albumin may increase the phagocytic activity of macrophages toward NPs [35,101, 102]. Other studies, however, presented that even with high levels of albumin in the SP corona of NPs, macrophage uptake was not significant [35,102]. The difference in NP clearance could be attributed to differences in NP dissolution rate in phagolysosomes [35], the folding state of adsorbed protein [102], cryptic epitopes [103], and conformation [104]. The amount of SP corona s adsorbed on NPs in BALF was found to be variable over time, especially for positively charged NPs, and the number of proteins per NP was large, indicating highly dynamic NP-protein binding kinetics [98].

A small number of proteins are thought to be responsible for a large portion of the SP corona [105]. As a result, the most abundant SP coronas could be preserved over time and across different particles, indicating that a small subset of proteins dominates SP corona formation [98]. Also, another important aspect of investigating the interaction of SP corona with NPs is to examine the composition of BALF to determine whether proteins adsorb in a concentration-dependent manner or through biophysical attraction. There was no direct correlation between the abundance of a specific protein in the SP corona and its concentration in BALF, implying that even low abundant proteins can be enriched on the surface of NPs via specific binding patterns [98,106, 107]. According to Vroman theory, high-affinity proteins, even in low abundance, can play a significant role in the formation of SP corona on NPs over time [108]. Furthermore, oligomerization of SPs and their associated large scale (around 40 nm in length) that is comparable to the size of NPs may result in some complicated analysis based on SP-NP interaction. It is surprising that a single functional domain of SPs, rather than the avidity of NPs' physicochemical properties, plays a key role in their binding characteristics.

6. Coronal proteome/lipidome in RTLF

The SP corona formed on the surface of NPs following exposure to lung tissue is unlikely to be similar to that found after incubation with plasma or blood [109] or cell culture medium [110]. However, performing a like-for-like comparison of the coronal proteome of NPs in different biofluids is often challenging. According to a review of the literature, SiO_2 NPs (200 nm) have been evaluated based on the composition of protein corona in two different biofluids, BALF [92] and plasma [111]. SP-A, albumin, complement C3/C4, and SP-B were manifested to be the most abundant proteins in the SiO_2 NP SP corona in the RTLF biofluid [92]. However, the SP corona composition in plasma was strikingly different from that found in the same NPs exposed to BALF, which was mostly covered by blood coagulation proteins [111]. Comparing the SP corona pattern on different NPs in BALF vs. plasma biofluids revealed that, while albumin can have a significant contribution to the SP corona composition in different biofluids, other specific proteins with a significant fingerprint in SP corona composition, such as SP-A/B/D, can have a remarkable effect on the NP's biological function (Fig. 3a) [112]. Furthermore, it has been demonstrated that the selective interaction of SPs controls the nearly identical lipid corona composition of different NPs [112]. For example, proteomic and lipidomic analyses of the NP corona in response to PSf interaction revealed that, while NPs with different hydrophilicity exhibit different SP corona patterns, they have comparable lipid composition [112]. Proteomic analysis revealed that several proteins, including SP-A, SP-D, and DMBT1, with high abundance in the SP corona of PEG-, PLGA-, and lipid-NP could mediate the formation of comparable lipid corona. Therefore, Raesch and coworkers claimed that the lipid-protein interactions can play a key role in the lipidomic profile of NPs in PS fluid and that some specific SP proteins

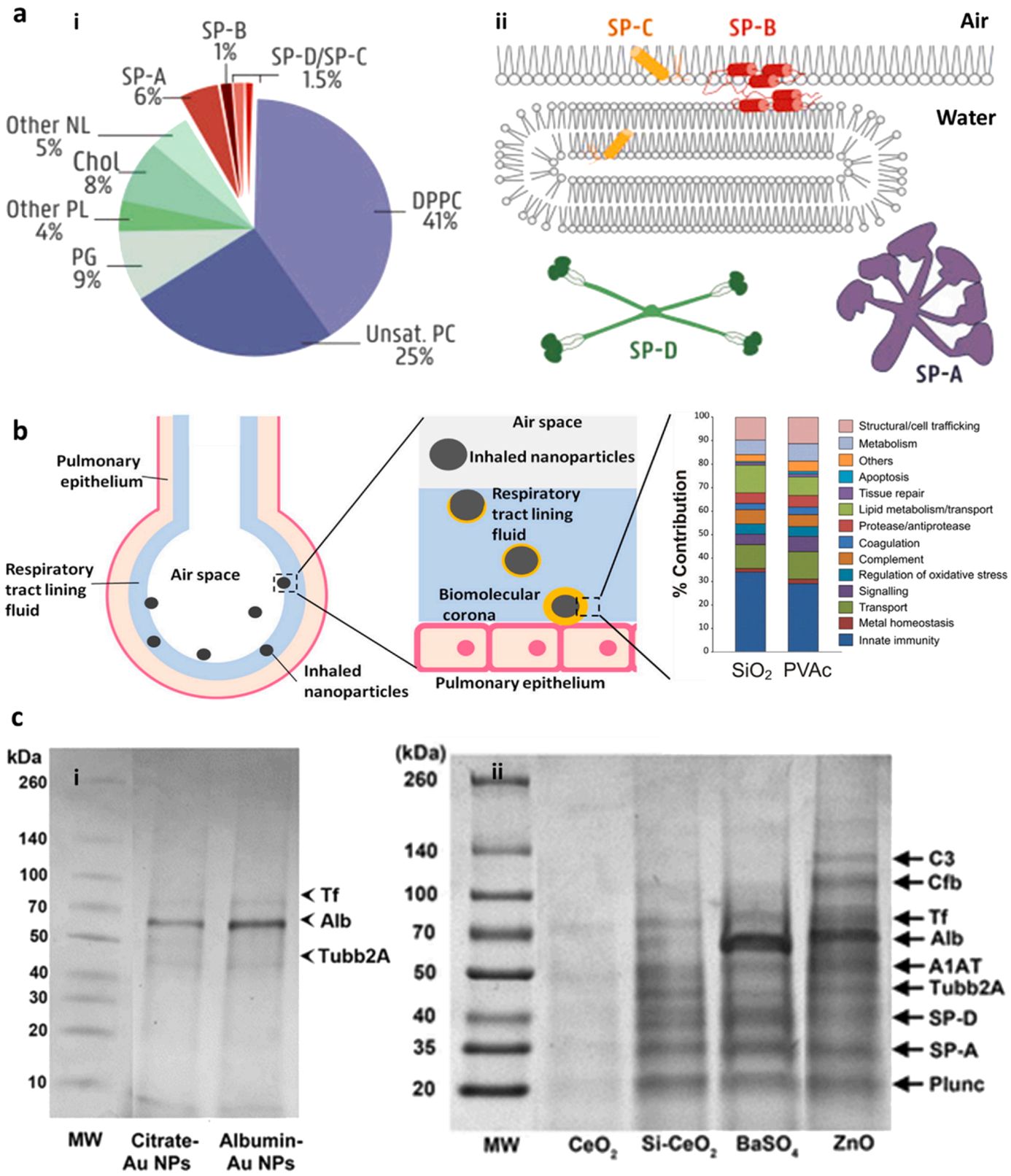

Fig. 2. (a) The lipid and protein composition of PSf (i) and the structural organization of SPs (ii) [79]. Copyright 2018, Elsevier. (b) Proteomic characterization of the hard PC around SiO_2 and poly(vinyl) acetate (PVAc) NPs with BALF [92]. Copyright 2016, Elsevier. (c) 1D gel electrophoresis of proteins eluted from AuNPs (i) and different NPs [35]. Reprinted under the terms of the CC-BY license [35]. Copyright 2017, Springer.
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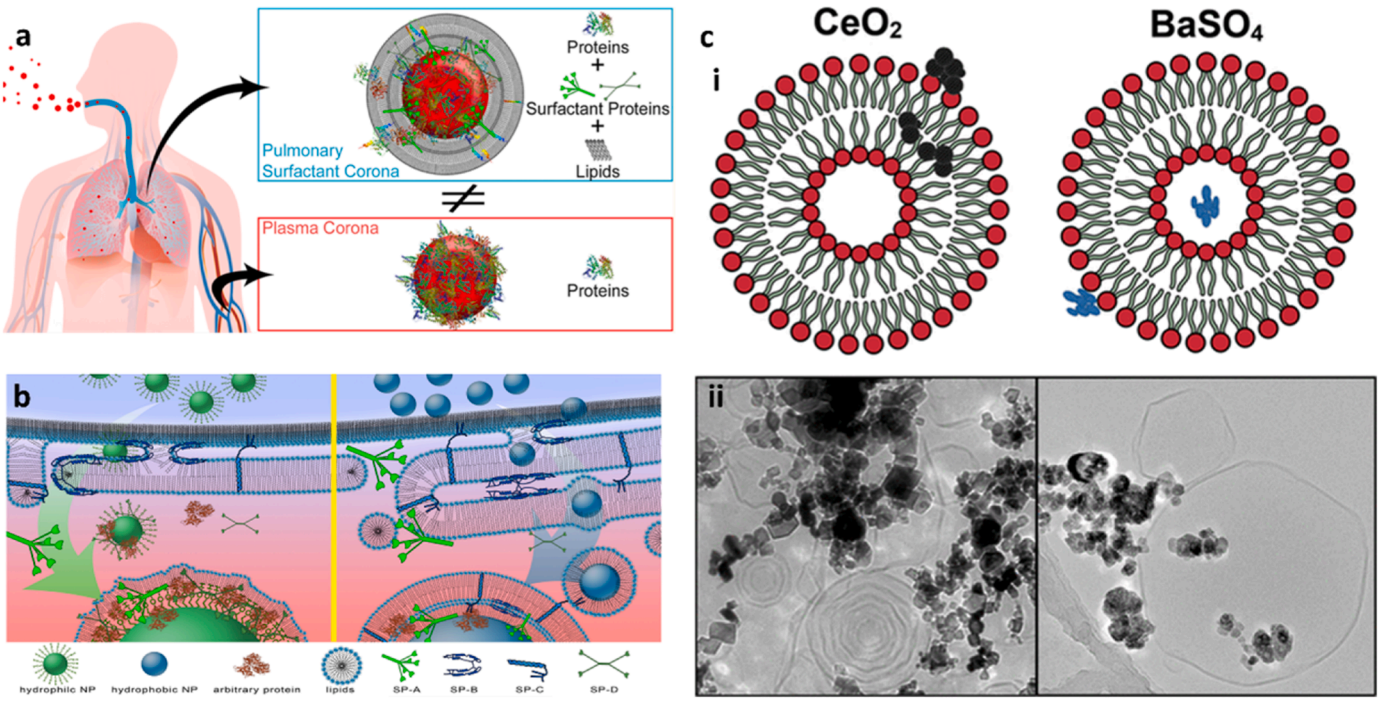

Fig. 3. (a) Different patterns of pulmonary surfactant (PSf) corona and plasma corona [112]. Copyright 2015, ACS. (b) Different interactions of hydrophobic and hydrophilic NPs with PS layer [112]. Copyright 2015, ACS. (c) Different interaction of NPs with different wettability with PLs, (i) Schematic representation, (ii) TEM images [113]. Copyright 208, ACS.
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with relatively high lipid and surface binding properties can manipulate the lipid pattern in coronas of multiple NPs [112].

The interaction of NPs with the PS layer differs, depending on their hydrophobic/hydrophilic nature. Opsonization of NPs by specific proteins, SP-A/SP-D/DMBT1, results in selective lipid binding mediated by these molecules in the case of hydrophilic NPs (PEG-NPs) [Fig. 3b(i)], whereas hydrophobic NPs (lipid-NPs) can directly interact with lipid layers and their associated proteins [Fig. 3b(ii)] [112]. Also, NP wettability could heavily affect NPs– PLs interactions, as hydrophobic NPs, CeO_2, showed the ability to accumulate inside lipid vesicles (LVs), whereas hydrophilic NPs, $BaSO_4$, interacted with the surface of LVs (Fig. 3c(i)) [113] determined by TEM analysis (Fig. 3c(ii)) [113].

Computational studies have also been conducted to evaluate the transport of PL-wrapped NPs. Surface charges of NPs, in addition to wettability, can play an important role in the interaction of lipids with NPs. As a result, Mandal et al. demonstrated in a molecular dynamic

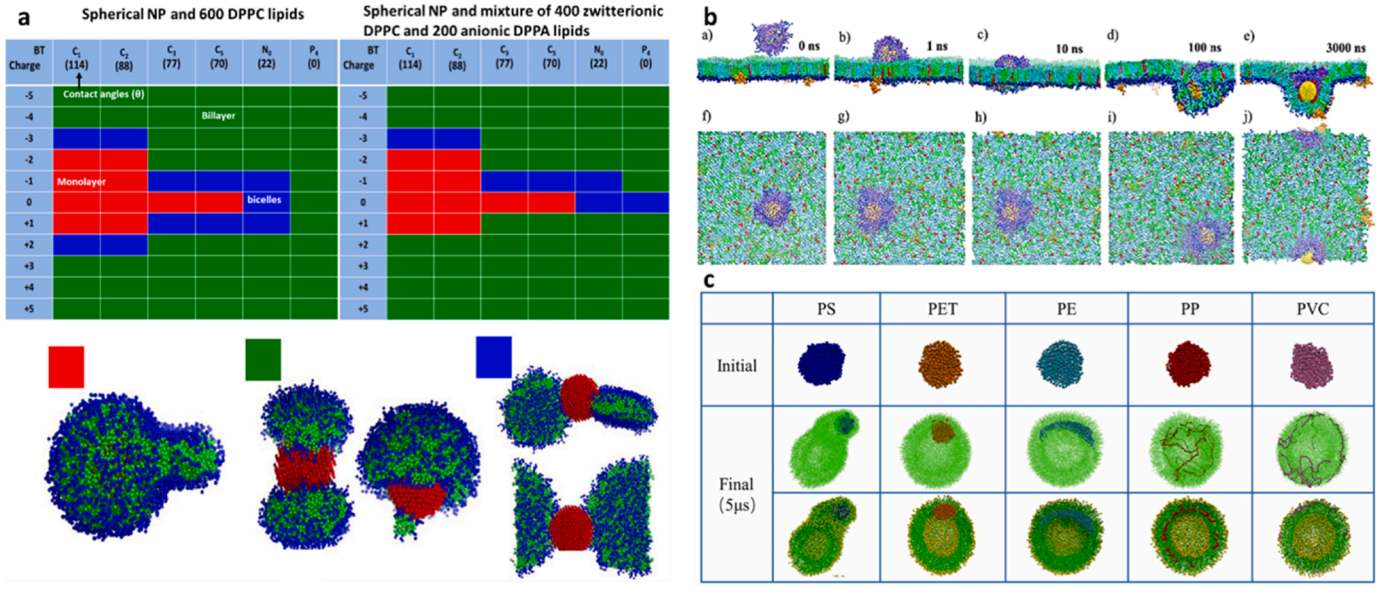

Fig. 4. (a) MD simulation of the effect of zeta potential and hydrophobicity on PL-NP corona formation [114]. Copyright 2018, Elsevier. (b) Time evolution of snapshots displaying Pl-AuNP permeation into the LS monolayer at, (a–e) side view and (f–j) top view [115]. Copyright 2021, ACS. (c) Initial and final snapshots of NP interactions with PSf along with cross-sectional view [119]. Copyright 2022, Elsevier.
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(MD) simulation study based on scoring the hydrophobicity and hydrophilicity of NPs with contact angles (θ) of 100° and 0°, respectively, that NPs with low surface charge density cannot form a bilayer unless their θ is less than 20° (Fig. 4a) [114]. For NPs having a $\theta > 20°$, a high surface charge density is required to cause the formation of bilayer coronas, while lipid monolayers form around less charged NPs with $\theta > 70°$, and bicelles (disk-like portions of a bilayer) are adsorbed to the surface of hydrophilic NPs ($20° < \theta < 70°$). However, the zeta potential of NPs was discovered to be less than 50 mV, indicating that NP hydrophobicity, rather than zeta potential, governs the formation of NP-lipid corona and relevant architecture. Moreover, it was shown that the PL-AuNPs are quickly attached to the surface of the monolayer, and some of the ligands are rearranged to facilitate hydrophobic-hydrophobic interactions and result in the formation of buckle (Fig. 4b), and the presence of PL along with SP peptide synergistically increases the level of cholesterol aggregation, which significantly changes the long-term properties of monolayers [115]. The surface tension of PSf is important in their interaction with NPs, and altering the lipid configuration or removing the proteins normally mediated by charged NPs will cause the interaction and penetration of NPs to influence the surface tension of the SFs [30]. While the interaction of low concentrations of charged NPs results in the depletion of lipids or SPs which has little effect on the surface tension of the SFs, the associated adverse effects become significant at high concentrations of NPs [30,116]. Furthermore, the infrequent removal of lipids by neutral NPs can be compensated by the prompt replacement of bulk lipids from the subphase [117]. The biophysical properties of the PSf can influence NP penetration through changes in lipid packing during breathing. As surface tension reduces (compression), the lipid chain shows highly ordered/closely packed lipid structures, preventing the translocation of NPs with similar charges to those of lipids across the monolayer. It has been manifested that surface tension changes the binding energy and energy cost of lipid tails with negatively-charged NPs. As the energy cost of repulsing the lipids at the biointerface increases at low surface tension, NPs cause probable lipid repulsion to the liquid phase, which stimulates film protrusion and probable collapse, as reported for hydrophobic NPs [118].

In general, PSf molecules spontaneously interact with NPs to form PSf corona, which normally results in NP dissolution and interferes with the typical biophysical performance of PSf. The NP size, molecular weight, and surface charge of polymer NPs can all play a role in the mechanism of LS adsorption and NP dissolution. Li et al., for example, demonstrated that regulating NP physiological parameters can modulate competitive interactions between NPs-NPs and NPs-PSf [119]. They used five different polymer NPs (Fig. 4c) and MD simulation studies disclosed that only polypropylene and polyvinyl chloride were dissolved by PSf [119]. This data contradicted previous findings that polystyrene NPs are easily dissolved by lipid bilayers [120], which could be attributed to NP self-assembly and cross-linking. Furthermore, polypropylene NPs were demonstrated to be well-dissolved in the vesicular membrane, whereas less hydrophobic polyvinyl chloride NPs interacted with the outer leaflet head group (Fig. 4c). Smaller-sized NPs (5 nm) have lower crosslinking properties and a higher facilitated dissolution rate than larger-sized NPs (10 nm) [119]. Moreover, NP dissolution along with vesicle formation was assessed by analysis of gyration radius and self-assembly energy. It was realized that only polypropylene and polyvinyl chloride NPs show a significant increase in the gyration radius over time along with having the highest interaction energy [119]. The length and shape of polymers in the case of polymer NPs have been reported to modulate the bending rigidity that manipulates the cross-linking performance, dissolution rate and corresponding interactions with different types of cancer and non-cancerous cells and tissue accumulation [30,119,121]. For further information regarding polymer rigidity and biomedical applications, readers are referred to the review paper reported by Kozlovskaya et al. [121].

Exploring the effect of NPs on the function of the PSf film can thus provide useful information about NP translocation. The interaction of NPs with PSf is most likely caused by NP adherence to the individual constituents of the PSf. Charged/hydrophobic NPs can interact with lipid heads/tails or deplete some proteins, causing film curvature and thus changing surface tension. However, the natural PSf structure and geometry are far more complex than the computational models. The natural PSf monolayer film coexists with multiple underlying multilayers, which may impede subsequent NP translocation due to NP interaction with the multilayer surface and/or aggregation. Furthermore, because the conformations of native SPs are more complex than those of mini-SPs in theoretical simulations, simulation studies cannot potentially model all of their characteristics. It is critical to create more advanced PSf models to investigate the functions of the various constituents in the NP-PSf interactions, which will require the use of much more dynamic computing software.

In general, theoretical studies show that moderate surface hydrophilicity and surface charge can facilitate NP translocation through the PSf film. However, even if the neutral NPs translocate across the PSf film without significant interaction or adhesion, they may still displace the lipids or SPs due to their apparent surface polarity. As a result, the PSf film can undergo surface curvature and collapse at low surface tension after NP translocation, which warrants further investigation.

7. Regulation of NP aggregation and surfactant flow characteristics

The main aspects of NP-PSf interaction have been reported to be SLBs, cellular uptake mediated by lipid vesicles, and the possible formation of aggregated species of NPs [122,123]. These interactions occur spontaneously and can be controlled by manipulating the NP dimension and surface chemistry [124–126]. Oikonomou et al., for example, demonstrated that dispersed negatively-charged cellulose nanocrystals with rod-shaped morphology (200 nm) can form strong electrostatic interactions with cationic surfactant, resulting in nanocrystal aggregation while the formed vesicles are intact (Fig. 5a) [127]. The development of intact vesicle deposition on solid support is a key factor in the advancement of active ingredient nanocarrier-based PDD systems. Based on this, the interaction of positively charged vesicles of ditallowethylester dimethylammonium chloride (DEEDMAC) with smooth (viscose) and rough (cotton) negatively charged cellulose fibers (Fig. 5b) was investigated [128]. Viscose fibers had greater vesicle deposition than cotton fibers, as evidenced by apparent zeta potential changes [Fig. 5b(i)] and fluorescence microscopy imaging [Fig. 5b(ii)] [128]. As a result, it was discovered that the NP roughness can play a significant role in the level of vesicle deposition and its integrity. Furthermore, it has been demonstrated that the interaction of positively charged NPs with negatively charged vesicles results in the formation of mixed aggregates with enhanced scattering (Job scattering plot, Is) [125]. However, SLB formation can mitigate the formation of aggregated species of NP-vesicles complex [125]. It has also been demonstrated that, in contrast to lipoprotein corona models or even NP wrapping, clinical PS vesicles retain their intact structure and Al_2O_3 NPs are trapped at their surface (Fig. 5c) [124], resulting in a sol-gel transition correlated with viscoelastic changes (Fig. 5d) [11]. Aggregation of NPs in the surfactant phase may change the interaction of NPs with lung cells. In other words, aggregation could mitigate the AMs and pneumocytes uptake of NPs by slowing the NP diffusion in the hypophase. As a result, it can be concluded that nanovehicle aggregation may alter the interfacial and bulk properties of PSf and interfere with lung function.

To modulate the aggregation process, wrapping the bilayers around NPs can be a potential strategy for manipulating the development of SLB-coated NPs. To achieve this, the membrane elasticity and bending energy are crucial factors that mediate the probability of SLB formation [125,129]. It has been evinced that the gel-to-fluid transition of Curosurf® occurs at $T_m = 29.5$ °C, implying that at physiological temperature, PLs provide a long-range structural disorder with an associated

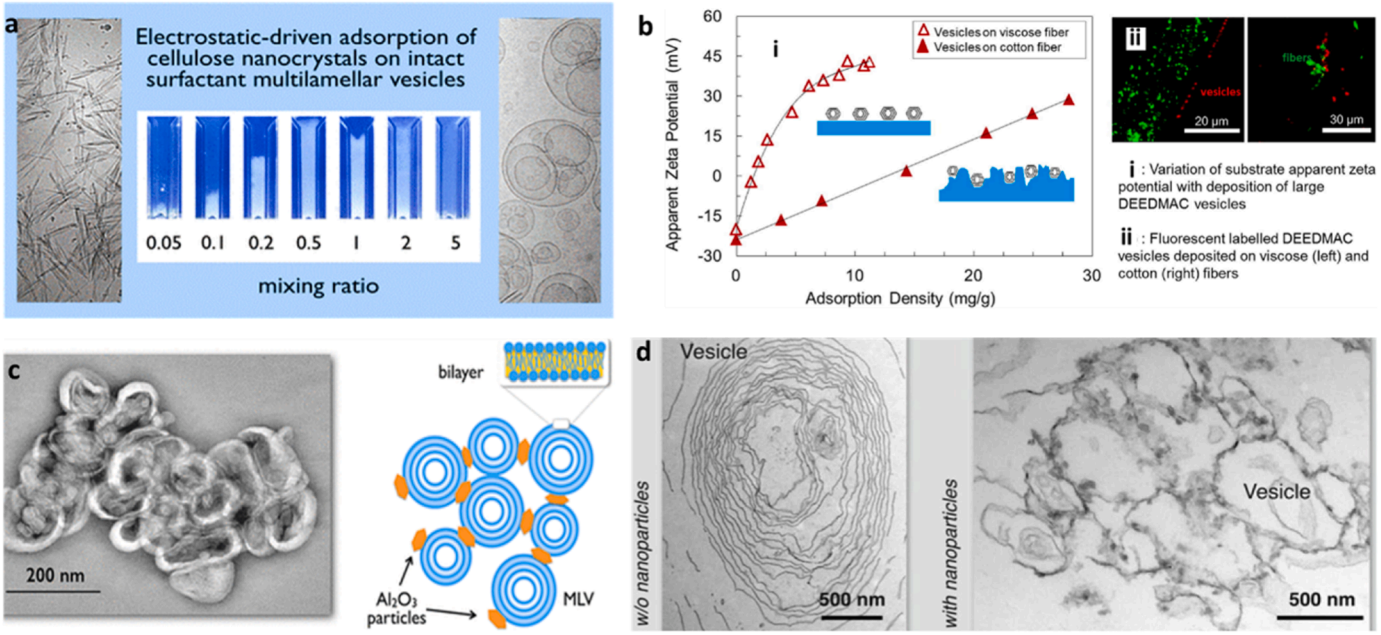

Fig. 5. (a) Exploring the interaction of dispersed negatively-charged cellulose nanocrystals (CNCs) with rod-shaped morphology with positively-charged surfactants results in the formation of intact vesicles and aggregated species [127]. (b) Deposition of positively-charged vesicles of ditallowethylester dimethylammonium chloride (DEDMAC) on smooth (viscose) and rough (cotton) negatively charged cellulose fibers were investigated evidenced by zeta potential measurement (i) and fluorescence imaging (ii) [128]. Copyright 2016, Elsevier. (c) Biophysicochemical interaction of a clinical PSf with Al_2O_3 NPs [124]. Copyright 2015, ACS. (d) Sol-gel transition stimulated by Al_2O_3 NPs in a model PSf [11]. Copyright 2022, Elsevier.
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decrease in membrane elasticity [125], which can result in the formation of SLB. In terms of NP colloidal stability, NP internalization into vesicles is charge and size-dependent. It has been demonstrated, for example, that cationic SiO_2 NPs with a size> 20 nm have a high enough adhesion energy to be internalized by vesicles [130]. It was also discovered that SLB-modified NPs can only enter the outer membrane layer of liposomes [130]. Other non-specific interactions causing the disintegration, aggregation, and deformation of multivesicular architectures have been reported following the interaction of titanium oxide NPs and PSf [131]. Also, cationic NPs such as modified SiO_2 NPs and Al_2O_3 NPs with a size of around 40 nm can change surfactant flow characteristics at very low concentrations [132]. It was found that SiO_2 NPs resulted in a reduction of viscosity and associated fluidification, whereas Al_2O_3 NPs stimulated a liquid-to-soft solid transition and increased viscosity evidenced by wire-based active microrheology technique. Therefore, the capability of NP with high percolation properties during cross-linking of the vesicular network can play a key role in the microrheology of a fluid [132]. Also, the concentration of PSf [133], the source of exogenous PSf [134], the size of NPs [135], and the charge [130] are all critical issues following exposure of NPs to PSf. As the population of hybrid colloids and the viscosity change, the viscoelastic properties of the fluid and the associated invagination can change.

8. Pulmonary surfactant (PSf) corona and its functional role in the cellular uptake of NPs

NP-mediated PDD or inhalation toxicology must be investigated primarily from the perspective of the formation of NP-biomolecular (protein and lipid) corona found in RTLF [92]. Furthermore, because the physiological properties of nanomaterials can play an important role in their interaction with biomolecules and associated corona formation in lung, NPs can be artificially manipulated to potentially avoid biomolecular corona formation through various strategies such as surface chemistry modification, stealth technology, and pre-coating with specific biomolecules to achieve potential targeting effects in vivo [128, 136,137]. Furthermore, NPs in each biofluid behave differently, resulting in different macrophage immune responses. By manipulating the surface of NPs as well as their composition, the proteome and lipidome profiles of NPs can be controlled to regulate innate immunity and phagocytosis. As a result, for inhaled NPs, the formation of lipid corona should be evaluated in addition to manipulation of SP corona based on albumin and SPs, as the interaction of proteins and lipids in the corona regulates AM uptake of NP. It was discovered, for example, that the SP-A interaction can significantly influence the uptake of NPs by AMs, and this behavior was influenced by lipids [138]. Also, after being exposed to SP-D, AM uptake of single-walled carbon nanotubes increased significantly [23], which was further enhanced with PL [139]. Furthermore, it has been discovered that accelerated AM uptake of NPs mediated by DPPC modification can be delayed by PEG modification (Fig. 6a) [140]. As a result, it is possible to conclude that NP clearance can be controlled by adjusting the coating composition and interacting with PLs [141]. As a result, the data on corona formation in plasma could not be expanded to predict downstream pulmonary behaviors to inhaled NPs due to the presence of lipids and different types of proteins. Furthermore, due to differences in the protein composition of serum and BALF, the time frame for the formation of a stable corona on the surface of NPs in these biofluids can differ. For example, it was discovered that a stable hard corona can be formed between 0.5 and 2 min [15,142] or 5–15 min [92, 98] following NP exposure in serum or BALF, respectively.

In some cases, the formation of a biomolecular corona on the surface of inhaled NPs is frequently regarded as a major challenge for drug delivery applications. According to recent studies, the physicochemical properties of the PSf corona influence the cell interaction of inhaled NPs [136]. It has been demonstrated, for example, that several parameters such as lipoprotein corona deformation, corona density, and ligand-receptor binding affinity can influence NP endocytosis. It has been demonstrated that lipid corona deformation improves the interaction of coating ligands with associated receptors, and that lipid corona

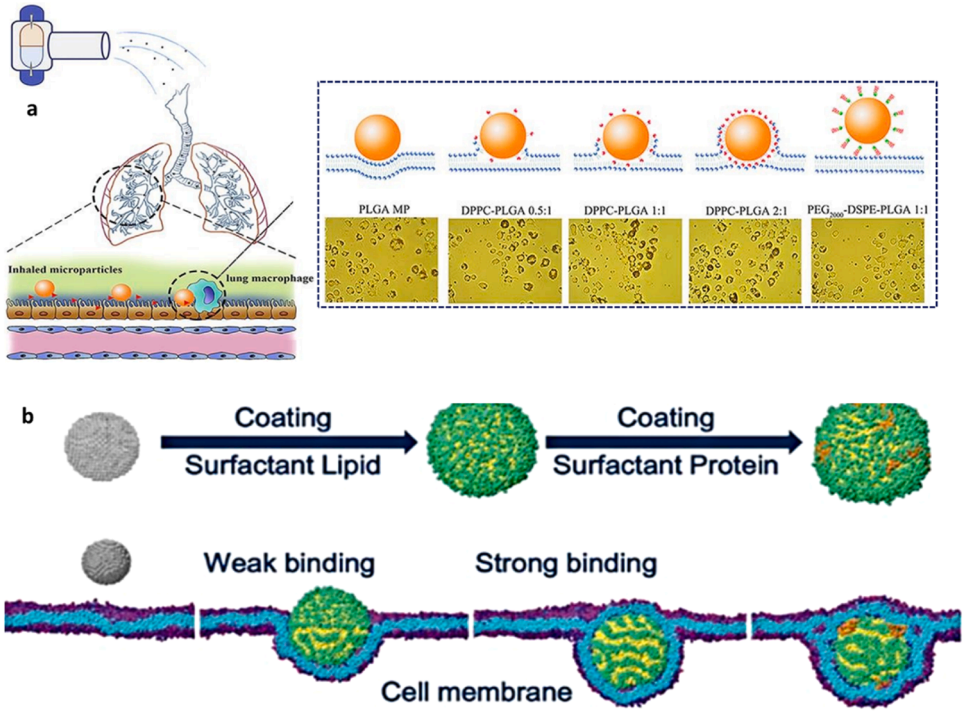

Fig. 6. (a) PL-functionalized poly(lactide-co-glycolide) micro-based particles for changing the interaction with AMs [140]. Copyright 2019, Elsevier. (b) The endocytosis process and efficiency mainly rely on the density of the coating surfactant lipids at the surface of NPs [136]. Copyright 2018, ACS.
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density manipulates the quantity of exposed ligands as well as the wettability of NPs, influencing endocytosis kinetics based on specific and nonspecific bindings. Furthermore, SPs associated with lipid coronas can influence the endocytosis process and NP efficiency (Fig. 6b) [136]. However, the uptake of NPs by AMs is strongly influenced by lipid corona and to be only slightly affected by hydrophilic SPs [14,23,138]. It has been demonstrated that the engulfment potency is primarily determined by the NP coverage ratio based on lipid density. A more effective way to increase NP uptake by cells such as AMs is to coat them with biomolecules rather than surfactant lipids that can anchor to membranes (increase adhesion energy) [136]. Therefore, the cellular uptake of NPs appears to be significantly reduced in high surfactant lipid coverage due to exposure of hydrophobic tails to water, diminishing hydrophobicity and reducing membrane lipid extraction. In general, deposition of lipid layers and vesicles on the surface of NPs causes the formation of either supported lipid bilayers (SLB) or supported vesicular layers (SVLs), depending on several factors such as the gel-to-fluid transition, NP type, NP roughness, and surface coverage [128]. Although vesicle disintegration on the surface of some NPs may not be a desirable phenomenon in the development of vesicle-based drug delivery platforms, the SLB can be used to manipulate NP cellular uptake. It has been demonstrated, for example, that SLB-SiO_2 NPs (40 nm) reduce the cytotoxicity and rate of cellular uptake in A549 malignant epithelial cells [122]. It was discovered that membrane damage and NP accumulation/aggregation in the cytoplasm, as well as their localization, are heavily SLB-dependent [122]. It was then demonstrated that SLBs have a significant influence on cellular interactions and associated functions, potentially introducing a new approach to NP coating. As a result, it can be claimed that the fate of NPs in the alveolar region, whether they translocate through the epithelial cell layer or are internalized by AMs, is determined by their potential interaction with the PSf [32,138,143]. This knowledge has led to the investigation of the NP-PSf interaction and its functional role in the cellular uptake of NPs and the development of PDD systems.

9. Clinical correlation

The lung organ is prone to PDD mediated by inhalation, intranasal or intra-tracheal administration routes [144,145]. Indeed, PDD allows for potential lung targeting, which has several advantages over other administration methods [146]. As a result, compounds with therapeutic potential can be directly targeted into the lungs with relatively homogeneous distribution and several notable advantages such as avoiding first-pass metabolism as well as having a rapid onset of action, a high local accumulated dose, and fewer significant side effects [147]. NP formulations have demonstrated a number of advantages over traditional dosage forms, including facilitated dissolution, drug protection, and the potential for PDD [148,149]. However, because of their nanometric dimension and high surface-to-volume ratio, NP fate associated with lung immune response can be completely different from lung delivery of free drugs [150]. In general, reports on the interaction of NPs with the lungs have focused predominately on the adverse effects of inhaled NPs for eco-environmental toxicological investigations [151,152] or their promising use as potential nanotherapeutics in lung cancer treatment [153,154]. Engineering inhaled or instilled NPs for advanced convectional and diffusional mechanisms may help to optimize their depositing in all lung regions [155]. NPs can demonstrate sustained drug release in lung tissue, as well as high bioavailability and translocation from lung epithelium to extrapulmonary organs, by modulating their surface using various methodologies [156,157]. As a result, this promising route of administration can be introduced as an alternative to systemic drug delivery systems with significantly reduced dosage [158]. Although several NP-based formulations have been studied for PDD against a wide range of pulmonary diseases, from cystic fibrosis to lung cancer [159,160], others are being developed to treat a variety of non-lung-associated disorders [161]. These studies focused primarily on the effects of the physicochemical properties of NPs in PDD and their clearance [27,162]. Several studies have also revealed some details about the molecular interaction of NPs with alveolar components and their biodistribution [119,141]. The clearance profile of NPs, as well as

their cytotoxicity and nanomedical applications, can be heavily influenced by PSf corona [10,163].

PSf function is crucial for the regular physiology of the lung. In several pulmonary-related disorders, biophysical changes of the PSf can be detected by different techniques. Although it has been widely reported in vitro that NPs stimulated alterations in the biophysical performances of PSf [29,164–166], further investigations are required when information is verified and conferred on clinical trials. In general, it has been shown that NP concentration and non-specific interactions with PSf can be considered as serious side effects against the reduction of biophysical function of PSf in vitro, however engineering the formation of SLB mediated by functionalization of NPs can result in improved PDD with low required NP concentration and high biocompatibility in vivo [122,130]. Furthermore, NPs accumulated in isolated lungs were associated with the lowest NP concentration used in the various studies [167–169]. Also, NP clearance by AMs, newly synthesized surfactant, and NP biodegradation could all influence the surfactant/NP ratio [141, 170]. Considering these approaches, it is surprising that NPs cause severe side effects on PSf performance in healthy individuals. However, for patients with lung-related disorders involving PSf dysfunction [77,171, 172], the detailed effects of NPs on PSf function must be investigated further. Importantly, NPs have been shown to cause pulmonary toxicity [173,174], which could magnify significant changes in PSf function in vivo, particularly in the context of predisposed airway diseases [14, 175]. Therefore, further biophysical investigations about the influence of therapeutic doses of NPs on the performance of PSf are required to verify this hypothesis.

Overall, it has been demonstrated that the introduction of NPs with various functional groups and surface charges alters the dynamic surface properties of the PSf in different ways. However, some strategies, such as PEGylating of NPs [176], steric shielding of NPs with bioinspired polymers [177], pre-coating [130], mechanical agitation [130], and functionalization with proteolipid [178] or ligand-based surfactant [179] can be used as potential strategies for the promising advancement of biocompatible nanomedicines (Table 3). The relevant information was well-reviewed in a paper published by Hidalgo et al. [81].

The ability of various NPs to interact with individual PSf constituents such as SPs or lipids is also thought to be an important factor in PSf function inhibition. As a result, the surface properties of NPs have been widely demonstrated to affect the adsorption patterns of SPs and could be related to the contribution in surface tension, phase behavior, and foaming capability of PSf. Detailed information about the interactions of NPs with PSf components can be used to rationally design and optimize colloidal nanocarriers for PDD. In general, overcoming physiological barriers, as well as the dissolution and adsorption performance of inhaled NPs, have a significant impact on the potential biomedical application of inhaled NPs in vivo.

10. Challenges and future perspective

To prevent excessive NP consumption and the side effects associated with the NP transfer to other tissues, targeted NPs can be delivered into the lung using a variety of non-invasive approaches. One remaining issue with NP delivery to the lungs is the fate of the NPs and their rapid clearance from the respiratory tract, which can be mitigated by tuning the physicochemical properties of the NPs, as summarized in Table 2. Based on personalized SP corona, it is possible to conclude that the composition of intracellular proteins from BALF in healthy lungs differs from that of lungs suffering from various diseases [98]. For example, mechanical stress-induced lung vascular injury can result in some serum protein leakage into the lung from the underlying vasculature, which can play a role in the variation of SP corona composition on the NPs. Furthermore, the presence of blood proteins on the surface of NPs can be attributed to nonvisible ruptures and relevant fluid contamination during BAL. The availability of human BALF is limited due to ethical and invasive concerns, and experiments on small animals are not recommended as a standard assay of the NP corona in PSf for animal welfare reasons. Therefore, this review may highlight the relevance of accurately choosing the media composition when exploring the fate, solubility, and dissolution rate of NPs in the lung system, particularly in the early stage of NP design and development in the treatment of lung diseases. In fact, the presence of proteins along with lipids can play a key role in the fate of NPs in the respiratory tract. Further investigations recruiting a wide variety of the NPs and media composition can help to extrapolate the behavior of NPs in the lung system.

Another challenge is the separation of NPs from native PSf using magnetic and nonmagnetic methods. Given that the BALF contains a network of interacting conformations, the NP corona after interaction with PSf may not be as easily detectable in hard and soft corona, depending on the type of separation.

The lack of access to intact isolated single SPs and lipids in a complex BALF hinders the precise determination of the binding affinity of NPs towards different PSf structures. Exploring the time-dependent behavior of the adsorption layer in future could provide more information about the kinetics of PSf corona formation and determine which molecules have the greatest affinity for the surface of different types of NPs. It is also necessary to investigate how the formation of this PSf corona affects the interaction of NPs with biological systems. Furthermore, because formed vesicles and aggregated NPs interfere with the DLS signal, this technique is not a viable method for analyzing the adsorption of different PSf layers on the surface of NPs.

The size of NPs determined by TEM may be underestimated due to variations in dimension and colloidal stability. For example, it was found that TiO_2 NPs (14 nm) adsorbed a comparable number of proteins per NP compared with larger-sized polystyrene NPs (100 nm) [98]. It was seen that although the determined size of TiO_2 NPs by TEM was 14 nm in PBS, the hydrodynamic diameter determined by DLS was about 186 nm, indicating possible agglomeration of NPs in the solution.

Several contradictory outcomes have been reported about the PSf corona architecture, such as the spontaneous formation of SLB [92], monolayer [25] or multilayers of PLs [25,186,187], or hybrid NP–vesicle agglomerates after interaction of NPs with PSf [113]. Based on

Table 3
Strategies to regulate pulmonary surfactant (PSf) corona formation/inhibition to operate in the lung system.

Strategies	Approaches	Method	Application	Ref.
PSf corona inhibition	Development of a hydrophilic surface	Surface modification with PEG	Development of non-toxic NPs	[176]
		Surface modification with poloxamer	Development of non-toxic NPs	[65]
	Regulation of thickness and grafting density	Formation of large thickness (>3 nm) and brush conformation	Development of non-toxic NPs	[180]
	Physiochemical properties of coated layer	Poloxamer with high critical micelle concentration and low MW induced slight impact on the PS	Development of non-toxic NPs	[181]
PSf corona formation	Pre-coating	Pre-coating with Curosurf®)	siRNA delivery	[182]
	Lipid modification	DPPC modification	Modification of acute responses in cancer cells	[183]
			Development of stable DPPC-coated NPs	[184]
			Higher deposition therapeutic and long retention time efficacy	[185]

these reports, the spatial arrangement of PL membranes in relation to NPs, PL composition, and the presence of SPs can all have a significant impact on the formation of mono- or multi-coating layers, which can be further investigated in future studies.

Different NP uptake behavior by cells in the presence of PSf has been reported. It was discovered that surfactant reduces the uptake of SiO_2 NPs by murine macrophages and lung carcinoma cells [188] and by the delivery of siRNA-loaded dextran nanogels. This while the presence of surfactants containing SPs increased the cellular uptake of silver NPs [189] and proteolipid-coated nanogels [178]. Therefore, the physicochemical properties of NPs, as well as the presence of SPs at optimized concentrations, can influence the cellular uptake of NPs. Furthermore, different cells exhibit multiple uptake mechanisms, signifying that further research is needed to understand the fate of NPs in pulmonary alveoli.

According to theoretical simulations, inhaled NPs typically have irregular morphologies with heterogeneous surface characteristics. These are expected to affect the NP's bio-behavior in alveoli, as opposed to NPs with defined morphology and uniform surface chemistry used in computational studies. NPs have a high adsorption affinity for various contaminants, resulting in the formation of nanocomposites and associated combined cytotoxicity. Thus, by modulating the activation or inhibition of nano-bio interactions, the adsorption of other particulate compounds on the surface of inhaled NPs can further enhance their heterogeneity and relevant bioactivity. Further, NP transformations, such as PSf interaction and NP dissolution, may influence the fate of NPs after exposure to epithelial cells and AMs. As a result, the NP bio-behavior assessed by MD simulations in alveoli may differ from those observed in vivo, necessitating additional research.

In general, future studies should be developed to aid in the realization of this critical part of the bio-nano interface, as well as to reveal the cytotoxicity of incidentally inhaled NPs and to advance the targeted delivery of NPs to the deep lung.

11. Conclusion

This review attempted to shed light on the formation of PSf coronas on the surface of NPs as well as similar mechanisms involved in NP transport across the air-blood barrier. These details can aid in understanding how PSf modulates the nanotoxicology of inhaled NPs and provide some useful guidelines for developing an NP-based complex for promising PDD. To optimize such strategies, a more thorough examination of the PSf corona that appears around inhaled NPs, whether as a toxic particle or a drug carrier, is required. In future studies, it is essential to explore the PSf corona's composition and artificial modulation, which may have a significant impact on their fate and potency at the targeted site of action. It is, therefore, crucial to analyze the spatial distribution and kinetics of PSf corona formation onto the NPs to predict NP–cell interaction and increase their biocompatibility in the lung system.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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Dr. Vahid Serpooshan did his BSc and MSc in Materials Science and Engineering at Sharif University (Tehran, Iran, 1998-2003) and his PhD in biomaterials and tissue engineering at McGill University (Montreal, Canada, 2007-2011). His PhD thesis research focused on the design and optimization of scaffolding biomaterials for bone tissue engineering applications. Following his PhD, Dr. Serpooshan worked for 7 years at Stanford University School of Medicine as Postdoctoral Fellow (Pediatric Cardiology) and Instructor (Stanford Cardiovascular Institute). At Stanford, Dr. Serpooshan’s training and research were mainly centered on developing a new generation of engineered cardiac patch device to repair damaged heart tissue following myocardial infarction (heart attack). The engineered patch was successfully tested in mouse and pig models and is now in preparation for clinical trials. He also worked on enabling technologies for human-machine hybrid cardiac tissue, using 3D bioprinting to assemble complex arrays of interfaces between synthetic and biological materials. In 2018, Dr. Vahid Serpooshan joined Emory University and Georgia Institute of Tech as Assistant Professor of Biomedical Engineering and Pediatrics, where his multidisciplinary team is now working on a variety of 3D bioprinting-based tissue engineering and disease modeling projects.

Dr. J (Jan) H von der Thüsen received his training at the Universities of Cambridge, London, and Leiden. He is lead thoracic pathologist at the Department of Pathology and Clinical Bioinformatics of the Erasmus Medical Centre in Rotterdam, researching the integrated pathology of neoplastic and non-neoplastic thoracic diseases, including the pathology of lung and mediastinal cancer.

Timo ten Hagen is a professor at the department of Pathology and head of the Precision Medicine in Oncology (PrMiO) and the Nanomedicine Innovation Center Erasmus (NICE). After an MSc in medical microbiology from the University of Utrecht, and an MSc in applied immunology at the Centers for Disease Control and Emory University in Atlanta, he did a PhD at the Erasmus MC in Rotterdam. During his PhD he started to collaborate with the Department of Surgery resulting in the supervision of his first PhD candidate before his own PhD project was ended. In 1995 he joined the department of Surgery and established the Laboratory for Experimental Surgical Oncology. In 2019 he expanded his horizon and established his lab within the department of Pathology to further his work on interaction of nanosystems with tumor pathophysiology and understanding of factors driving cancer progression.

During the first years Dr. ten Hagen and his team studied the application of local chemotherapy in combination with tumor necrosis factor alpha (TNF). He discovered that TNF increases local drug accumulation and therefore response to therapy. He extended these observations to systemic treatment with nano-carrier-based chemotherapy in combination with hyperthermia. Initially this part of his research was aimed at improvement of local accumulation of a chemotherapeutic. Currently the focus is on how tumor pathophysiology and nanosystems interact. First by alteration of the nanocarriers and compounds, which is supported by his senior researcher Dr. Reza Amin. Second, by alteration of the tumor pathophysiology.

Secondly, Dr. ten Hagen and his team are interested in understanding what drives tumor progression at the microenvironmental and cellular level. In specific, he focusses on the individual capacities a tumor cell might have and how these relate to progression. For this purpose fresh isolates from patients are collected, tumor cells generated and tested in vitro and in vivo. The biological data is linked with clinical parameters, tumor progression and patient outcome and with genetic data.

Thirdly, and connected to the drug delivery program, Dr. ten Hagen together with his Senior Researcher Dr. Ann Seynhaeve study the architecture, behavior and response to therapy of the tumor associated vasculature. In particular interaction between endothelial cells, other vessel-associated cell types (pericytes, smooth muscle cells), and tumor cells is studied. Understanding principal and specific differences between tumor and healthy vasculature is used to develop and aid nanosystems and combination therapies for cancer.

To better study drug delivery and to be able to observe tumor cell behavior Dr. ten Hagen established an intravital microscopy platform, with high-end confocal and multi-photon microscopes. His intravital window systems allow in vivo examination of processes in the living mouse at the sub-cellular level. He demonstrated for instance processing of liposomal doxorubicin (DOXIL) by tumor cells and proofed the slow release of doxorubicin by these liposomes, which is most likely the reason why DOXIL is not as effective as expected.

Currently Dr. ten Hagen and his group are performing research on nano-carrrier based drug delivery using so-called smart drug delivery systems (SDDS), which is intended to establish a predictive model for optimal therapy. Real-time in vivo imaging is used to feed computer models in which predictions can be based. He studies liver cancer treatment with smart drug delivery devices in combination with mild hyperthermia. For this a mini RF hyperthermia unit is developed for local heating of liver tumors, which is MRI compatible and allows high resolution intravital imaging. He studies trafficking of drug steered and controlled through smart drug delivery devices by high and super resolution imaging. And, recently he uses immune-active SDDS (iSDDS) for immune therapy to combat cancer.