UC Riverside

UC Riverside Previously Published Works

Title

Impact of protein coronas on nanoparticle interactions with tissues and targeted delivery.

Permalink

https://escholarship.org/uc/item/3qg8w508

Authors

Chou, Wei-Chun

Lin, Zhoumeng

Publication Date

2024-02-01

DOI

10.1016/j.copbio.2023.103046

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Curr Opin Biotechnol. Author manuscript; available in PMC 2025 February 01.

Published in final edited form as:

Curr Opin Biotechnol. 2024 February ; 85: 103046. doi:10.1016/j.copbio.2023.103046.

Impact of protein coronas on nanoparticle interactions with tissues and targeted delivery

Wei-Chun Chou[1,2], **Zhoumeng Lin**[1,2,*]

[1]Department of Environmental and Global Health, College of Public Health and Health Professions, University of Florida, Gainesville, FL 32610, USA

[2]Center for Environmental and Human Toxicology, University of Florida, Gainesville, FL 32608, USA

Abstract

A major challenge in advancing nanoparticle (NP)-based delivery systems stems from the intricate interactions between NPs and biological systems. These interactions are largely determined by the formation of the NP-protein corona (PC), in which proteins spontaneously adsorb to the surface of NPs. The PC endows the NPs a new biological identity, capable of altering the interactions of NPs with targeting organs and subsequent biological fate. This review discusses mechanisms behind PC-mediated effects on tissue distribution of NPs, aiming to provide insights into the role of PC and its potential applications in NP-based drug delivery.

Keywords

nanoparticle-protein corona; nanomedicine; drug delivery; pharmacokinetics; tissue distribution

Introduction

Significant advancement in nanomedicine, driven by the extensive usage of nanotechnology, has received substantial attention due to its potential in precise diagnosis, tumor targeting and effective treatments for a range of diseases [1–3]. Recently, there has been a substantial increase in the development of nano-sized delivery systems. This upsurge is attributed to their capacity to selectively deliver the payloads to the targeted tissues, which is capable of enhancing the effectiveness of nanomedicine and minimizing the side-effects [4,5]. Despite these substantial and promising advantages offered by their applications, nanomedicine often fails in later stages of development or clinical trials [6,7]. These issues arise from either excessive off-target or inadequate on-target accumulation of nanomedicine [8,9]. A critical factor has been attributed to the generation of protein corona (PC) and its impacts on the interactions between nanoparticles (NPs) and targeted organs. It has been well documented that when NPs are introduced into biological fluids, biomolecules (e.g., nucleic

*To whom correspondence should be addressed: linzhoumeng@ufl.edu; Address: Department of Environmental and Global Health, College of Public Health and Health Professions, University of Florida, 1225 Center Drive, Gainesville, FL 32610, USA.

Conflict of interest statement

The authors declare no conflict of interest.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

acids, proteins, lipids, and sugar moieties) spontaneously adsorb, interact, and evolve on the surface of NPs [10–12]. This process gives rise to a structure reassembling a crown called the biomolecular corona. The biomolecular corona's composition may determine the ultimate fate of NPs [13–15]. Among all biomolecules, the predominant biomolecules that form the biomolecular corona are proteins, known as NP-protein corona (PC) and most studies that investigate the impact of biomolecular corona formation have focused on PC [16]. The emergence of PC endows NPs with "biological identity" distinguishing it from its original physiochemical properties, leading to the modification in the pharmacokinetics and biodistribution characteristics, and subsequently cellular uptake of NPs [17,18]. In this review, we first discuss the impacts of PCs on the tissue-targeting ability and subsequently summarize targeting strategies based on various tissues. Recent advances and challenges in tissue-specific targeting strategies of NPs will then be discussed in depth followed by future perspectives. This review only focuses on targeting strategies for intravascularly administrated nanomedicines.

Impact of protein coronas on the tissue-specific targeting distribution

The targeting abilities of NPs are determined by functionalizing their surface with the targeting moieties (e.g., antibodies, small molecules, and nucleic acids), which can guide NPs to specific organs/tissues for drug delivery. However, the proteins absorbed on the surface of NPs can conceal the inherent or engineered reactivity of NPs, by blocking cell membrane receptors to inhibit internalization and lose the protection of NPs from opsonization (i.e., the immunological response that targets NPs for removal), causing rapid clearance and off-target accumulation [15,16]. Here, we discuss the mechanism of interactions of NPs with different target tissues with a particular focus on the brain, lungs, liver, and spleen.

The impact of protein coronas on brain-targeting capability

The blood-brain barrier (BBB), which serves as the endothelial barrier between the circulating bloodstream and the brain, is notably restrictive due to a relatively higher density of endothelial cells and tight junctions [19]. Thus, the BBB is able to prevent the delivery of NPs from extravasating into brain. Targeted strategy for the intravenously administered NPs across the BBB could potentially harness endocytosis process (Figure 1a). The process involves the recognition of specific receptors on the luminal endothelial cell membrane, followed by endocytosis into the endosome, intracellular transport, and ultimately exocytosis from the endothelium (Figure 1a) [20,21]. The use of transferrin (Tf)-conjugated NPs is the most commonly used targeting strategy to deliver drugs into the brain via receptor-mediated endocytosis pathway [22]. However, PC can act as a shield, preventing Tf from binding to Tf receptors and other receptors on the cell surface [23,24]. Dawson et al. [23] reported that Tf-conjugated NPs is unable to interact with Tf receptor on the cell membrane after incubation in serum, resulting from the shield effects of PC on the Tf protein. Xiao et al. [24] reported that the PCs impact the transcytosis of Tf-functionalized NPs through BBB and attenuate their ability to target brain tumor cells. Similarly, polymeric NPs coated with the HIV-1 trans-activating trans-activator peptide (known for being able to cross the BBB) and/or alpha neural/glial antigen 2 (known to be able to target oligodendrocyte precursor

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

cells) are unable to cross the BBB, neither specifically target oligodendrocyte precursor cells, likely because of the formation of PCs [25]. In addition to Tf-based delivery systems, the apolipoprotein (e.g., ApoE)-based strategies have also been reported as promising tools for brain-targeted delivery [26]. Certain surfactant-modified NPs, such as poly(ethylene glycol)-/polysorbate-modified NPs, have the capability to absorb apolipoproteins such as ApoE or ApoB, and thus forming the apolipoprotein-rich PCs after systemic administration. By interaction with lipoprotein receptors on the BBB, these proteins absorbed on the surface of NPs can facilitate the entry of NPs into the brain [27,28].

The impact of protein coronas on lung-targeting capability

When foreign NPs are within the bloodstream and tissues, they typically undergo clearance by the reticuloendothelial system (RES) [5,29]. RES, a part of the immune system, comprises a system of phagocytes such as macrophages and monocytes. These cells are primarily located on the vascular wall of the liver (i.e., Kupffer cells), spleen (i.e., splenic macrophages), kidneys (i.e., mesangial cells), and lung (i.e., lung macrophages). However, most NPs are typically taken up by liver Kupffer cells after systematic administration [30]. This sequestration presents a significant obstacle to achieving tissue-specific targeting of NPs. The PC consisting of apolipoprotein E (i.e., ApoE) absorbed to the surface of NPs might promote the phagocytosis of lung macrophages [31–34]. Scheffler et al. [33] reported that gold nanoparticles (AuNPs) bound with human serum albumin and ApoE can significantly accumulate in the lungs when compared to control NPs (i.e., citrate stabilized AuNPs). Kim et al. [32] synthesized a liposome consisting of 1,2-dioleoyl-3-trimethylammoniumpropane/ dioleoylphosphatidylethanolamine, which can specifically absorb apolipoprotein A-I to increase the accumulation in lung tumors and reduce the hepatic accumulation. Although there was an increased accumulation of NPs in the lungs, it did not have any benefit as the NPs were also rapidly eliminated by the RES. Recent studies have developed lipid NPs functionalized with specific protein antibodies (e.g., plasmalemma vesicle-associated protein) for lung-targeted mRNA delivery in vivo [31,35]. These lipid NPs can internalize into the lungs via the mechanism of caveolae-mediated endocytosis (Figure 1b) to achieve lung-selective targeting.

The impact of protein coronas on liver-targeting capability

Being the largest RES organ, the liver presents a heightened capability to eliminate NPs in comparison to other RES-rich organs (e.g., spleen, kidney, and lung). Based on the postulated mechanisms of hepatic sequestration of NPs in a previous study [36], the process of delivering NPs to liver is through the following steps: (1) interact with Kupffer cells and liver sinusoid endothelial cells, (2) if they escape from these cells, they would transport to the space of Disse, (3) interact with hepatocytes, and (4) if they escape from all of these cells, they will be eventually eliminated from the body (Figure 1c). While the exact molecular mechanisms governing interaction between Kupffer cells and PC is still not fully elucidated, several studies have identified several specific receptors that can bind to the PC on NPs and be recognized by Kupffer cells [37–40]. The phagocytosis of NPs by Kupffer cells is primarily mediated by opsonin proteins [e.g., immunoglobulins and complement (C3)] [41,42], leading to the NP accumulation in the liver and rapidly elimination from circulation [43–45]. Recent studies have identified the PC composition using analysis

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

of mass spectrometry, revealing that the highly-bound proteins involve opsonin proteins, especially complement C3 absorbed onto the surface of NPs [46,47]. On the other hand, to prevent the NPs interaction with Kupffer cells, one strategy is to coat NPs with neutral-charged polymers such as polyethylene glycol (PEG) to deter the opsonin proteins absorbed to the PC on the surface of NPs [48,49]. This method can prolong the circulation lifetime of NPs but it varies by the degree of PEGylation on the surface of the NPs [50].

The impact of protein coronas on spleen-targeting capability

In addition to the Kupffer cells in the liver, splenic macrophages also play an very important role in the uptake of NPs [51]. Tavares et al. [51] reported that spleen can sequester more NPs after removing liver Kupffer cells. In a mouse model where Kupffer cells were removed, the authors administered AuNPs and estimated the amounts of NPs in various tissues using both fluorescent-labeling optical imaging and element-based analysis through inductively coupled plasma–mass spectrometry (ICP-MS). They found significantly increased amounts of 50–200 nm NPs in spleen and concluded that the NPs might be removed by other RES organs when the major one (i.e., liver) is not functioning. Notably, the main mechanism for the removal of NPs from blood circulation in spleen is the internalization of opsonized NPs [52]. The formation of PCs on the NPs can promote the effects of opsonization of NPs by splenic macrophages. For example, if the composition of PCs consists of opsonized proteins such as complement, immunoglobulins and apolipoprotein [46,53,54] that can interact with the receptors on the surface of RES cells, NPs can be recognized by splenic macrophages and subsequently removed from circulation [55]. In addition to opsonized proteins, other proteins absorbed onto the surface of PCs have the capacity to be recognized by scavenger receptors [56]. The additional proteins introduce an additional mechanism to the clearance of NPs by RES [57]. The uptake of NPs by splenic macrophages usually takes place in the marginal zone (MZ) in spleen (Figure 1d). An earlier study [57] demonstrated that MZ macrophages can uptake polystyrene NPs. Notably, this uptake process does not rely on the lectin-like receptors but instead involves the scavenger receptors as well as the albumin-coating NPs. Additionally, it was observed that small liposomes (100–200 nm) exhibit a tendency for selectively internalized by MZ macrophages.

Role of protein coronas in the recent advances of organ-specific targeting strategies

In recent years, the growing understanding of PCs has paved the way for techniques to manipulate the adsorbed PCs on the surface of NPs [14,58]. This approach enables the utilization of these PCs for active targeting receptors on certain cells and thus harnessing the endogenous system for the purpose of organ-specific drug delivery [59]. There are two proposed strategies (Figure 2) to address the shielding role of the PC on targeted NPs (Tables 1–2).

Pre-coating strategy: Artificial engineering of protein coronas

This first strategy is the use of artificial PC on tissue-specific targeting delivery. The concept of the artificial PC involves pre-coating NPs before introducing them into biological

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

fluids to enhance the absorption of specific proteins that is capable of targeting to specific cells [27,28,60–73]. When these NPs interact with the blood proteins, they acquire the artificial PC that is able to actively target to the selective tissues [60]. For example, it was demonstrated that modifying the PC through polysorbate pre-coating can enhance apolipoprotein absorption on NPs and thus increasing the transport across the BBB [27,61,62,74]. In addition, Dal Magro et al. [27,61] reported that lipid NPs are able to increase the transport to the brain parenchyma and higher accumulation in the brain when incubated with apolipoprotein E4 or E-derived peptides *in vitro*, compared to unmodified particles. For liver targeting delivery, the absorption of apolipoprotein and complement on NPs was used to further promote the accumulations of NPs in liver [63]. The retinol binding protein [75] and lipoproteins [76] can target hepatocytes and serve as targeted ligands on the NPs to promote the long-term accumulation in liver. In another study, liposomes with positive charge functionalization were pre-coated with artificial PC and explored as possible nano-carrier for targeted delivery to tumor-related macrophages in cancer therapy [77]. One of the main challenges of the artificial PC approach, however, is that the active site of PC should be positioned in the outer corona layer to facilitate interaction with specific cell receptors. For example, although pre-coating silica NPs with the serum proteins γ-blobulins could enrich the PC with immunoglobulins and opsonin which have high targeting efficacy and recognized by macrophages, there was no substantial enhancement of macrophage uptake of NPs compared to NPs without pre-coating [78]. The authors concluded that other protein binding onto artificial PCs by non-specific protein-protein interactions results in the shielded effects and inhibits the interactions between opsonin and relevant receptors on the immune cells [78]. Hence, these findings underscore the importance of exposing the functional binding sites to cell receptors, which is difficult to manipulate from the spontaneous absorption of such proteins onto the surface of NPs.

Biomimetic approach to leverage protein coronas

The second method is so called the biomimetic approach [79–81]. The biomimetic method seeks to emulate natural biological environment and mechanisms by incorporating specific biological functionalities into synthetic NPs. This approach is aimed at achieving therapeutic effects or mitigating the adverse side effects associated with synthetic NPs. Following this concept, a wide array of biomimetic materials has been applied on the NPs, including coatings with endogenous proteins, cell membrane decoration, and biomolecule alterations [26,31,33,64,82–89]. Among these methods, the cell membrane decoration is one of the most useful and commonly used biomimetic approaches. For instance, the NPs decorated with cell membrane derived from a variety of cell types such as erythrocytes (i.e., red blood cells), which is capable of exhibiting the capability to diminish undesired immune reactions, circumvent elimination by macrophages and systemic clearance [90]. The red blood cells decorated NP delivery system had the lowest immunoglobulin absorption on the surface of PCs and prolonged circulation time. The red blood cell coatings reduce opsonization, leading to decreased interaction with macrophages [90]. Apart from the cell membrane decoration, the coating with endogenous proteins is another potent method. By pre-coated endogenous protein, the composition or abundant component of PCs can be manipulated to achieve stealth effect that extends circulation time and tissue-specific targetability. Dillard et al. [84] introduced a tissue-specific NP delivery system with endogenous protein coating

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

strategy. Their approach endows NPs with stealth effect, preserving their targeting ability in non-liver tissues such as lung and spleen by reducing the binding of ApoE to NPs and escaping RES clearance [84]. Similar approach was also used in other non-liver targeting NPs [31,33,86]. To minimize the impact from PCs while ensuring stability, recent studies have explored the modifications in the generation or composition of PCs through biomolecule modifications while preserving the natural functionalities of PC components. For example, Zhang et al. [82] developed an innovative NP brain-targeted system with biomolecular modification. This system utilizes a short, non-toxic peptide derived from beta-amyloid peptide (Aβ1–42) to control the protein corona component, which is capable of interacting with the lipid-binding domain of the brain-targeting apolipoproteins (e.g., ApoA1, ApoE, and ApoJ) and thus facilitating the brain transport via lipoprotein-mediated endocytosis. This approach has been applied to other brain- and liver-targeted NPs [26,83,85,89].

Perspectives, challenges and conclusions

In this review article, we try to discuss mechanisms about targeting strategies of NPs to specific tissues and the dual impacts of PCs on those strategies. The targeting mechanisms of NPs were categorized based on specific tissues, ranging from ligand- or non-ligand-induced endocytosis, phosphatiosomes, and opsonization of RES. However, most NPs will inevitably adsorb serum proteins, altering the targeting ability of NPs. Recent studies have developed artificial and biomimetic PCs to address these limitations. Both the use of artificial and biomimetic PCs confers a pre-determined biological identity onto the NPs, empowering them with desired properties including prolonged circulation, tissue-specific targeting, and the ability to engage in cell-to-cell interactions, by precisely manipulating the interactions between functional plasma proteins and the surface of NPs or NP-PC interface. However, these approaches are still constrained by certain critical challenges that are yet to be thoroughly evaluated. For example, the use of biomimetic materials onto NPs can raise concerns regarding the potential to trigger the immune responses and overall safety, especially when non-autologous proteins or viral components are involved. Also, the intricate structure and composition are still significant challenges on the reproducibility and reliability of artificial PCs. There is an urgent need to establish an innovative and comprehensive paradigm for designing smart nanomedicine. This might be achieved by combining precisely tailored chemical synthesis with the versatility and biocompatibility of biologics. In conclusion, we anticipate that as nanomedicine and nanotechnology continue to advance, the role of the PC in the delivery strategy of NPs will become more clearly elucidated. The ability to manipulate the generation of the PC on the surface of NPs has the potential to overcome organ-specific targeting challenges, enabling precise, efficient, and safe delivery of nanomedicine.

Acknowledgement

The work was supported by the National Institute of Biomedical Imaging and Bioengineering (NIBIB) National Institutes of Health (NIH) Research Grant Program (Grant #: R01EB031022).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

(•) of special interest

(••) of outstanding interest

1. Veiseh O, Tang BC, Whitehead KA, Anderson DG, Langer R: Managing diabetes with nanomedicine: challenges and opportunities. Nature Reviews Drug Discovery 2015, 14:45–57. [PubMed: 25430866]
2. Shi JJ, Kantoff PW, Wooster R, Farokhzad OC: Cancer nanomedicine: progress, challenges and opportunities. Nature Reviews Cancer 2017, 17:20–37. [PubMed: 27834398]
3. Jain RK, Stylianopoulos T: Delivering nanomedicine to solid tumors. Nature Reviews Clinical Oncology 2010, 7:653–664.
4. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R: Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov 2021, 20:101–124. [PubMed: 33277608]
5. Blanco E, Shen H, Ferrari M: Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nature Biotechnology 2015, 33:941–951.
6. Dordevic S, Gonzalez MM, Conejos-Sanchez I, Carreira B, Pozzi S, Acurcio RC, Satchi-Fainaro R, Florindo HF, Vicent MJ: Current hurdles to the translation of nanomedicines from bench to the clinic. Drug Deliv Transl Res 2022, 12:500–525. [PubMed: 34302274]
7. He H, Liu L, Morin EE, Liu M, Schwendeman A: Survey of Clinical Translation of Cancer Nanomedicines-Lessons Learned from Successes and Failures. Acc Chem Res 2019, 52:2445–2461. [PubMed: 31424909]
8. Wilhelm S, Tavares AJ, Dai Q, Ohta S, Audet J, Dvorak HF, Chan WCW: Analysis of nanoparticle delivery to tumours. Nature Reviews Materials 2016, 1.
9. Cheng YH, He CL, Riviere JE, Monteiro-Riviere NA, Lin ZM: Meta-Analysis of Nanoparticle Delivery to Tumors Using a Physiologically Based Pharmacokinetic Modeling and Simulation Approach. Acs Nano 2020, 14:3075–3095. [PubMed: 32078303]
10. Ke PC, Lin S, Parak WJ, Davis TP, Caruso F: A Decade of the Protein Corona. Acs Nano 2017, 11:11773–11776. [PubMed: 29206030]
11. Wan S, Kelly PM, Mahon E, Stockmann H, Rudd PM, Caruso F, Dawson KA, Yan Y, Monopoli MP: The “Sweet” Side of the Protein Corona: Effects of Glycosylation on Nanoparticle-Cell Interactions. Acs Nano 2015, 9:2157–2166. [PubMed: 25599105]
12. Zhang W, Chetwynd AJ, Thorn JA, Lynch I, Ramautar R: Understanding the Significance of Sample Preparation in Studies of the Nanoparticle Metabolite Corona. Acs Measurement Science Au 2022, 2:251–260. [PubMed: 35726252]
(•)13. Oh JY, Kim HS, Palanikumar L, Go EM, Jana B, Park SA, Kim HY, Kim K, Seo JK, Kwak SK, et al. : Cloaking nanoparticles with protein corona shield for targeted drug delivery. Nature Communications 2018, 9.The article presents an important insight into the use of the artificial protein corona shield as a targeting agent through regulating interactions between nanoparticles and biological systems.
14. Wang YF, Zhou YX, Sun JB, Wang XT, Jia YR, Ge K, Yan Y, Dawson KA, Guo ST, Zhang JC, et al. : The Yin and Yang of the protein corona on the delivery journey of nanoparticles. Nano Research 2023, 16:715–734. [PubMed: 36156906]
15. Farshbaf M, Valizadeh H, Panahi Y, Fatahi Y, Chen MW, Zarebkohan A, Gao HL: The impact of protein corona on the biological behavior of targeting nanomedicines. International Journal of Pharmaceutics 2022, 614.
(••)16. Mahmoudi M, Landry MP, Moore A, Coreas R: The protein corona from nanomedicine to environmental science. Nature Reviews Materials 2023, 8:422–438.State of the art review about the importance of the protein corona in applications of nanomedicine.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

17. Ren J, Andrikopoulos N, Velonia K, Tang H, Cai R, Ding F, Ke PC, Chen C: Chemical and Biophysical Signatures of the Protein Corona in Nanomedicine. J Am Chem Soc 2022, 144:9184–9205. [PubMed: 35536591]

18. Cedervall T, Lynch I, Lindman S, Berggard T, Thulin E, Nilsson H, Dawson KA, Linse S: Understanding the nanoparticle-protein corona using methods to quantify exchange rates and affinities of proteins for nanoparticles. Proceedings of the National Academy of Sciences of the United States of America 2007, 104:2050–2055. [PubMed: 17267609]

19. Gonzalez-Carter D, Liu X, Tockary TA, Dirisala A, Toh K, Anraku Y, Kataoka K: Targeting nanoparticles to the brain by exploiting the blood-brain barrier impermeability to selectively label the brain endothelium. Proc Natl Acad Sci U S A 2020, 117:19141–19150. [PubMed: 32703811]

20. Bramini M, Ye D, Hallerbach A, Nic Raghnaill M, Salvati A, Aberg C, Dawson KA: Imaging approach to mechanistic study of nanoparticle interactions with the blood-brain barrier. ACS Nano 2014, 8:4304–4312. [PubMed: 24773217]

21. Seo SJ, Chen MW, Wang HX, Kang MS, Leong KW, Kim HW: Extra- and intra-cellular fate of nanocarriers under dynamic interactions with biology. Nano Today 2017, 14:84–99.

(••)22. Terstappen GC, Meyer AH, Bell RD, Zhang W: Strategies for delivering therapeutics across the blood-brain barrier. Nat Rev Drug Discov 2021, 20:362–383. [PubMed: 33649582] An important review about the transport mechanisms of nanoparticles across the blood-brain barrier.

23. Salvati A, Pitek AS, Monopoli MP, Prapainop K, Bombelli FB, Hristov DR, Kelly PM, Aberg C, Mahon E, Dawson KA: Transferrin-functionalized nanoparticles lose their targeting capabilities when a biomolecule corona adsorbs on the surface. Nat Nanotechnol 2013, 8:137–143. [PubMed: 23334168]

24. Xiao W, Wang Y, Zhang H, Liu Y, Xie R, He X, Zhou Y, Liang L, Gao H: The protein corona hampers the transcytosis of transferrin-modified nanoparticles through blood-brain barrier and attenuates their targeting ability to brain tumor. Biomaterials 2021, 274:120888. [PubMed: 34029915]

25. Naidu PSR, Gavriel N, Gray CGG, Bartlett CA, Toomey LM, Kretzmann JA, Patalwala D, McGonigle T, Denham E, Hee C, et al. : Elucidating the Inability of Functionalized Nanoparticles to Cross the Blood-Brain Barrier and Target Specific Cells in Vivo. Acs Applied Materials & Interfaces 2019, 11:22085–22095. [PubMed: 31150197]

26. Zhang ZA, Xin X, Liu C, Liu YH, Duan HX, Qi LL, Zhang YY, Zhao HM, Chen LQ, Jin MJ, et al. : Novel brain-targeted nanomicelles for anti-glioma therapy mediated by the ApoE-enriched protein corona in vivo. Journal of Nanobiotechnology 2021, 19.

27. Dal Magro R, Ornaghi F, Cambianica I, Beretta S, Re F, Musicanti C, Rigolio R, Donzelli E, Canta A, Ballarini E, et al. : ApoE-modified solid lipid nanoparticles: A feasible strategy to cross the blood-brain barrier. J Control Release 2017, 249:103–110. [PubMed: 28153761]

28. Zensi A, Begley D, Pontikis C, Legros C, Mihoreanu L, Buchel C, Kreuter J: Human serum albumin nanoparticles modified with apolipoprotein A-I cross the blood-brain barrier and enter the rodent brain. Journal of Drug Targeting 2010, 18:842–848. [PubMed: 20849354]

29. Tang Y, Wang X, Li J, Nie Y, Liao G, Yu Y, Li C: Overcoming the Reticuloendothelial System Barrier to Drug Delivery with a “Don’t-Eat-Us” Strategy. ACS Nano 2019, 13:13015–13026. [PubMed: 31689086]

30. Ngo W, Ahmed S, Blackadar C, Bussin B, Ji Q, Mladjenovic SM, Sepahi Z, Chan WCW: Why nanoparticles prefer liver macrophage cell uptake in vivo. Advanced Drug Delivery Reviews 2022, 185.

(•)31. Qiu M, Tang Y, Chen JJ, Muriph R, Ye ZF, Huang CF, Evans J, Henske EP, Xu QB: Lung-selective mRNA delivery of synthetic lipid nanoparticles for the treatment of pulmonary lymphangioleiomyomatosis. Proceedings of the National Academy of Sciences of the United States of America 2022, 119.Novel techniques for lung-selective delivery of nanoparticles by specifically regulating the composition of protein coronas.

32. Kim SK, Foote MB, Huang L: The targeted intracellular delivery of cytochrome C protein to tumors using lipid-apolipoprotein nanoparticles. Biomaterials 2012, 33:3959–3966. [PubMed: 22365810]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

33. Schaffler M, Sousa F, Wenk A, Sitia L, Hirn S, Schleh C, Haberl N, Violatto M, Canovi M, Andreozzi P, et al. : Blood protein coating of gold nanoparticles as potential tool for organ targeting. Biomaterials 2014, 35:3455–3466. [PubMed: 24461938]

34. Fang CL, Wen CJ, Aljuffali IA, Sung CT, Huang CL, Fang JY: Passive targeting of phosphatiosomes increases rolipram delivery to the lungs for treatment of acute lung injury: An animal study. J Control Release 2015, 213:69–78. [PubMed: 26164036]

(••)35. Li Q, Chan CS, Peterson N, Hanna RN, Alfaro A, Allen KL, Wu H, Dall'Acqua WF, Borrok MJ, Santos JL: Engineering Caveolae-Targeted Lipid Nanoparticles To Deliver mRNA to the Lungs. Acs Chemical Biology 2020, 15:830–836. [PubMed: 32155049] A promising approach for developing the targeted delivery of nanoparticles to lung by pre-coating cell membrane-based protein corona on the surface of nanoparticles.

36. Poon W, Zhang YN, Ouyang B, Kingston BR, Wu JLY, Wilhelm S, Chan WCW: Elimination Pathways of Nanoparticles. Acs Nano 2019, 13:5785–5798. [PubMed: 30990673]

37. Lu K, Dong S, Xia T, Mao L: Kupffer Cells Degrade (14)C-Labeled Few-Layer Graphene to (14)CO(2) in Liver through Erythrophagocytosis. ACS Nano 2021, 15:396–409. [PubMed: 33150787]

38. Campbell F, Bos FL, Sieber S, Arias-Alpizar G, Koch BE, Huwyler J, Kros A, Bussmann J: Directing Nanoparticle Biodistribution through Evasion and Exploitation of Stab2-Dependent Nanoparticle Uptake. Acs Nano 2018, 12:2138–2150. [PubMed: 29320626]

39. Chao Y, Karmali PP, Mukthavaram R, Kesari S, Kouznetsova VL, Tsigelny IF, Simberg D: Direct recognition of superparamagnetic nanocrystals by macrophage scavenger receptor SR-AI. ACS Nano 2013, 7:4289–4298. [PubMed: 23614696]

40. Yan Y, Gause KT, Kamphuis MM, Ang CS, O'Brien-Simpson NM, Lenzo JC, Reynolds EC, Nice EC, Caruso F: Differential roles of the protein corona in the cellular uptake of nanoporous polymer particles by monocyte and macrophage cell lines. ACS Nano 2013, 7:10960–10970. [PubMed: 24256422]

41. Saha K, Rahimi M, Yazdani M, Kim ST, Moyano DF, Hou S, Das R, Mout R, Rezaee F, Mahmoudi M, et al. : Regulation of Macrophage Recognition through the Interplay of Nanoparticle Surface Functionality and Protein Corona. ACS Nano 2016, 10:4421–4430. [PubMed: 27040442]

42. Andersen AJ, Hashemi SH, Andresen TL, Hunter AC, Moghimi SM: Complement: alive and kicking nanomedicines. J Biomed Nanotechnol 2009, 5:364–372. [PubMed: 20055082]

43. Liu T, Choi H, Zhou R, Chen IW: RES blockade: A strategy for boosting efficiency of nanoparticle drug. Nano Today 2015, 10:11–21.

44. Jokerst JV, Lobovkina T, Zare RN, Gambhir SS: Nanoparticle PEGylation for imaging and therapy. Nanomedicine 2011, 6:715–728. [PubMed: 21718180]

45. Caracciolo G, Cardarelli F, Pozzi D, Salomone F, Maccari G, Bardi G, Capriotti AL, Cavaliere C, Papi M, Lagana A: Selective targeting capability acquired with a protein corona adsorbed on the surface of 1,2-dioleoyl-3-trimethylammonium propane/DNA nanoparticles. ACS Appl Mater Interfaces 2013, 5:13171–13179. [PubMed: 24245615]

(•)46. Vu VP, Gifford GB, Chen F, Benasutti H, Wang G, Groman EV, Scheinman R, Saba L, Moghimi SM, Simberg D: Immunoglobulin deposition on biomolecule corona determines complement opsonization efficiency of preclinical and clinical nanoparticles. Nat Nanotechnol 2019, 14:260–268. [PubMed: 30643271] This article highlights the presence of protein coronas can enhance the deposition of the third complement protein and thus reducing the targeting ability of nanoparticles.

47. Pinals RL, Yang D, Rosenberg DJ, Chaudhary T, Crothers AR, Iavarone AT, Hammel M, Landry MP: Quantitative Protein Corona Composition and Dynamics on Carbon Nanotubes in Biological Environments. Angew Chem Int Ed Engl 2020, 59:23668–23677. [PubMed: 32931615]

48. Cahn D, Duncan GA: High-Density Branched PEGylation for Nanoparticle Drug Delivery. Cellular and Molecular Bioengineering 2022, 15:355–366. [PubMed: 36444352]

49. Allen RJ, Mathew B, Rice KG: PEG-Peptide Inhibition of Scavenger Receptor Uptake of Nanoparticles by the Liver. Molecular Pharmaceutics 2018, 15:3881–3891. [PubMed: 30052459]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

50. Perrault SD, Walkey C, Jennings T, Fischer HC, Chan WCW: Mediating Tumor Targeting Efficiency of Nanoparticles Through Design. Nano Letters 2009, 9:1909–1915. [PubMed: 19344179]

51. Tavares AJ, Poon W, Zhang YN, Dai Q, Besla R, Ding D, Ouyang B, Li A, Chen J, Zheng G, et al. : Effect of removing Kupffer cells on nanoparticle tumor delivery. Proceedings of the National Academy of Sciences of the United States of America 2017, 114:E10871–E10880. [PubMed: 29208719]

52. Cataldi M, Vigliotti C, Mosca T, Cammarota M, Capone D: Emerging Role of the Spleen in the Pharmacokinetics of Monoclonal Antibodies, Nanoparticles and Exosomes. International Journal of Molecular Sciences 2017, 18.

53. Chen F, Wang G, Griffin JI, Brenneman B, Banda NK, Holers VM, Backos DS, Wu L, Moghimi SM, Simberg D: Complement proteins bind to nanoparticle protein corona and undergo dynamic exchange in vivo. Nat Nanotechnol 2017, 12:387–393. [PubMed: 27992410]

54. Yeo ELL, Cheah JUJ, Thong PSP, Soo KC, Kah JCY: Gold Nanorods Coated with Apolipoprotein E Protein Corona for Drug Delivery. Acs Applied Nano Materials 2019, 2:6220–6229.

55. He XY, Wang J, Tang YQ, Chiang ST, Han TZ, Chen Q, Qian CX, Shen XS, Li RX, Ai XZ: Recent Advances of Emerging Spleen-Targeting Nanovaccines for Immunotherapy. Advanced Healthcare Materials 2023.

56. Walkey CD, Olsen JB, Guo HB, Emili A, Chan WCW: Nanoparticle Size and Surface Chemistry Determine Serum Protein Adsorption and Macrophage Uptake. Journal of the American Chemical Society 2012, 134:2139–2147. [PubMed: 22191645]

57. Demoy M, Andreux JP, Weingarten C, Gouritin B, Guilloux V, Couvreur P: In vitro evaluation of nanoparticles spleen capture. Life Sciences 1999, 64:1329–1337. [PubMed: 10227589]

(•)58. Li ZB, Wang YQ, Zhu JJ, Zhang YC, Zhang WJ, Zhou M, Luo C, Li ZG, Cai B, Gui SY, et al. : Emerging well-tailored nanoparticulate delivery system based on in situ regulation of the protein corona. Journal of Controlled Release 2020, 320:1–18. [PubMed: 31931050] A comprehensive review about the formation of protein coronas and nanoparticles' physicochemical properties that can influences its formation. This article also highlights the latest technology to regulate the formation and composition of protein coronas.

(••)59. Wang S, Zhang J, Zhou H, Lu YC, Jin X, Luo L, You J: The role of protein corona on nanodrugs for organ-targeting and its prospects of application. J Control Release 2023, 360:15–43. [PubMed: 37328008] This article presents a comprehensive review and summarizes the latest articles about the tissue-specific delivery of nanoparticles by regulating composition of protein coronas.

(••)60. Khan S, Sharifi M, Gleghorn JP, Babadaei MMN, Bloukh SH, Edis Z, Amin M, Bai Q, Ten Hagen TLM, Falahati M, et al. : Artificial engineering of the protein corona at bio-nano interfaces for improved cancer-targeted nanotherapy. J Control Release 2022, 348:127–147. [PubMed: 35660636] This review summarizes the approaches about the cancer-targeted delivery efficiency by artificial engineering of the protein corona on the bio-nano interface.

61. Dal Magro R, Albertini B, Beretta S, Rigolio R, Donzelli E, Chiorazzi A, Ricci M, Blasi P, Sancini G: Artificial apolipoprotein corona enables nanoparticle brain targeting. Nanomedicine-Nanotechnology Biology and Medicine 2018, 14:429–438. [PubMed: 29157979]

62. Suzuki K, Adiguzel D, Shinotsuka T, Ishibashi R, Eguchi I, Oshima H, Taniguchi R, Thalhammer S, Takeda K: Tunable plasma lipoprotein uptake/transport across the blood-brain barrier. Colloids and Surfaces a-Physicochemical and Engineering Aspects 2014, 442:157–163.

63. Chinen AB, Guan CXM, Ko CH, Mirkin CA: The Impact of Protein Corona Formation on the Macrophage Cellular Uptake and Biodistribution of Spherical Nucleic Acids. Small 2017, 13.

64. Huo TT, Yang YF, Qian M, Jiang HL, Du YL, Zhang XY, Xie YB, Huang RQ: Versatile hollow COF nanospheres via manipulating transferrin corona for precise glioma-targeted drug delivery. Biomaterials 2020, 260.

65. Zensi A, Begley D, Pontikis C, Legros C, Mihoreanu L, Wagner S, Buchel C, von Briesen H, Kreuter J: Albumin nanoparticles targeted with Apo E enter the CNS by transcytosis and are delivered to neurones. Journal of Controlled Release 2009, 137:78–86. [PubMed: 19285109]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

66. Nagayama S, Ogawara K, Minato K, Fukuoka Y, Takakura Y, Hashida M, Higaki K, Kimura T: Fetuin mediates hepatic uptake of negatively charged nanoparticles via scavenger receptor. International Journal of Pharmaceutics 2007, 329:192–198. [PubMed: 17005341]

67. Cai HT, Ma YH, Wu ZR, Ding YY, Zhang P, He X, Zhou JR, Chai ZF, Zhang ZY: Protein corona influences liver accumulation and hepatotoxicity of gold nanorods. Nanoimpact 2016, 3–4:40–46.

68. Akinc A, Maier MA, Manoharan M, Fitzgerald K, Jayaraman M, Barros S, Ansell S, Du XY, Hope MJ, Madden TD, et al. : The Onpattro story and the clinical translation of nanomedicines containing nucleic acid-based drugs. Nature Nanotechnology 2019, 14:1084–1087.

69. Witzigmann D, Kulkarni JA, Leung J, Chen S, Cullis PR, van der Meel R: Lipid nanoparticle technology for therapeutic gene regulation in the liver. Advanced Drug Delivery Reviews 2020, 159:344–363. [PubMed: 32622021]

70. Yallapu MM, Chauhan N, Othman SF, Khalilzad-Sharghi V, Ebeling MC, Khan S, Jaggi M, Chauhan SC: Implications of protein corona on physico-chemical and biological properties of magnetic nanoparticles. Biomaterials 2015, 46:1–12. [PubMed: 25678111]

71. Nkanga CI, Chung YH, Shukla S, Zhou JC, Jokerst JV, Steinmetz NF: The in vivo fate of tobacco mosaic virus nanoparticle theranostic agents modified by the addition of a polydopamine coat. Biomaterials Science 2021, 9:7134–7150. [PubMed: 34591046]

72. Prapainop K, Witter DP, Wentworth P: A Chemical Approach for Cell-Specific Targeting of Nanomaterials: Small-Molecule-Initiated Misfolding of Nanoparticle Corona Proteins. Journal of the American Chemical Society 2012, 134:4100–4103. [PubMed: 22339401]

73. Rodriguez PL, Harada T, Christian DA, Pantano DA, Tsai RK, Discher DE: Minimal “Self” Peptides That Inhibit Phagocytic Clearance and Enhance Delivery of Nanoparticles. Science 2013, 339:971–975. [PubMed: 23430657]

74. Cox A, Andreozzi P, Dal Magro R, Fiordaliso F, Corbelli A, Talamini L, Chinello C, Raimondo F, Magni F, Tringali M, et al. : Evolution of Nanoparticle Protein Corona across the Blood-Brain Barrier. ACS Nano 2018, 12:7292–7300. [PubMed: 29953205]

75. Hsu CY, Chen CH, Aljuffali IA, Dai YS, Fang JY: Nanovesicle delivery to the liver via retinol binding protein and platelet-derived growth factor receptors: how targeting ligands affect biodistribution. Nanomedicine (Lond) 2017, 12:317–331. [PubMed: 28078954]

76. Bottger R, Pauli G, Chao PH, Al Fayez N, Hohenwarter L, Li SD: Lipid-based nanoparticle technologies for liver targeting. Adv Drug Deliv Rev 2020, 154–155:79–101.

77. Giulimondi F, Digiacomo L, Pozzi D, Palchetti S, Vulpis E, Capriotti AL, Chiozzi RZ, Lagana A, Amenitsch H, Masuelli L, et al. : Interplay of protein corona and immune cells controls blood residency of liposomes (vol 10, 3686, 2019). Nature Communications 2020, 11.

(•)78. Mirshafiee V, Kim R, Park S, Mahmoudi M, Kraft ML: Impact of protein pre-coating on the protein corona composition and nanoparticle cellular uptake. Biomaterials 2016, 75:295–304. [PubMed: 26513421] This study investigated the feasibility of regulating protein corona composition to promote targeted nanoparticle uptake by specific types of cells. They demonstrated that the protein coronas of nanoparticles that were pre-coated with γ-globulins, were enriched with immunoglobulins and complement factors, and thus easier to induce the opsonin-induced phagocytosis by macrophages in comparison to uncoated nanoparticles.

79. Nguyen TDT, Aryal S, Pitchaimani A, Park S, Key J, Aryal S: Biomimetic surface modification of discoidal polymeric particles. Nanomedicine 2019, 16:79–87. [PubMed: 30529792]

80. Pitchaimani A, Nguyen TDT, Aryal S: Natural killer cell membrane infused biomimetic liposomes for targeted tumor therapy. Biomaterials 2018, 160:124–137. [PubMed: 29407341]

(••)81. Hu CM, Zhang L, Aryal S, Cheung C, Fang RH, Zhang L: Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform. Proc Natl Acad Sci U S A 2011, 108:10980–10985. [PubMed: 21690347] This study reports a cell-membrane based biomimetic approach in the tissue-specific delivery of nanoparticles.

(••)82. Zhang Z, Guan J, Jiang ZX, Yang Y, Liu JC, Hua W, Mao Y, Li C, Lu WY, Qian J, et al. : Brain-targeted drug delivery by manipulating protein corona functions. Nature Communications 2019, 10.This study shows that the brain-specific delivery of nanoparticles can be enhanced by manipulating protein corona functions.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

83. Guan J, Jiang ZX, Wang MK, Liu Y, Liu JC, Yang Y, Ding TH, Lu WY, Gao CL, Qian J, et al. : Short Peptide-Mediated Brain-Targeted Drug Delivery with Enhanced Immunocompatibility. Molecular Pharmaceutics 2019, 16:907–913. [PubMed: 30666875]

(••)84. Dilliard SA, Cheng Q, Siegwart DJ: On the mechanism of tissue-specific mRNA delivery by selective organ targeting nanoparticles. Proceedings of the National Academy of Sciences of the United States of America 2021, 118.This is an important study because it describes the mechanisms of tissue-specific delivery of tarted nanoparticles.

85. Kim KR, Kim J, Back JH, Lee JE, Ahn DR: Cholesterol-Mediated Seeding of Protein Corona on DNA Nanostructures for Targeted Delivery of Oligonucleotide Therapeutics to Treat Liver Fibrosis. Acs Nano 2022, 16:7331–7343. [PubMed: 35500062]

86. Cheng Q, Wei T, Farbiak L, Johnson LT, Dilliard SA, Siegwart DJ: Selective organ targeting (SORT) nanoparticles for tissue-specific mRNA delivery and CRISPR-Cas gene editing. Nature Nanotechnology 2020, 15:313-+.

87. Cao MJ, Cai R, Zhao LN, Guo MY, Wang LM, Wang YC, Zhang LL, Wang XF, Yao HD, Xie CY, et al. : Molybdenum derived from nanomaterials incorporates into molybdenum enzymes and affects their activities in vivo. Nature Nanotechnology 2021, 16:708-+.

88. Shen LM, Tenzer S, Storck W, Hobernik D, Raker VK, Fischer K, Decker S, Dzionek A, Krauthauser S, Diken M, et al. : Protein corona-mediated targeting of nanocarriers to B cells allows redirection of allergic immune responses. Journal of Allergy and Clinical Immunology 2018, 142:1558–1570. [PubMed: 29382591]

89. Huang JS, Huang HL, Wang YY, Xu B, Lin MZ, Han SS, Yuan YY, Wang Y, Shuai XT: Retinol-binding protein-hijacking nanopolyplex delivering siRNA to cytoplasm of hepatic stellate cell for liver fibrosis alleviation. Biomaterials 2023, 299.

(••)90. Miao YQ, Yang YT, Guo LM, Chen MS, Zhou X, Zhao YG, Nie D, Gan Y, Zhang XX: Cell Membrane-Camouflaged Nanocarriers with Biomimetic Deformability of Erythrocytes for Ultralong Circulation and Enhanced Cancer Therapy. Acs Nano 2022, 16:6527–6540. [PubMed: 35426300] This study introduces the latest method to develop the cell membrane based biomimetic approach on cancer nanomedicine for extending the circulation time.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

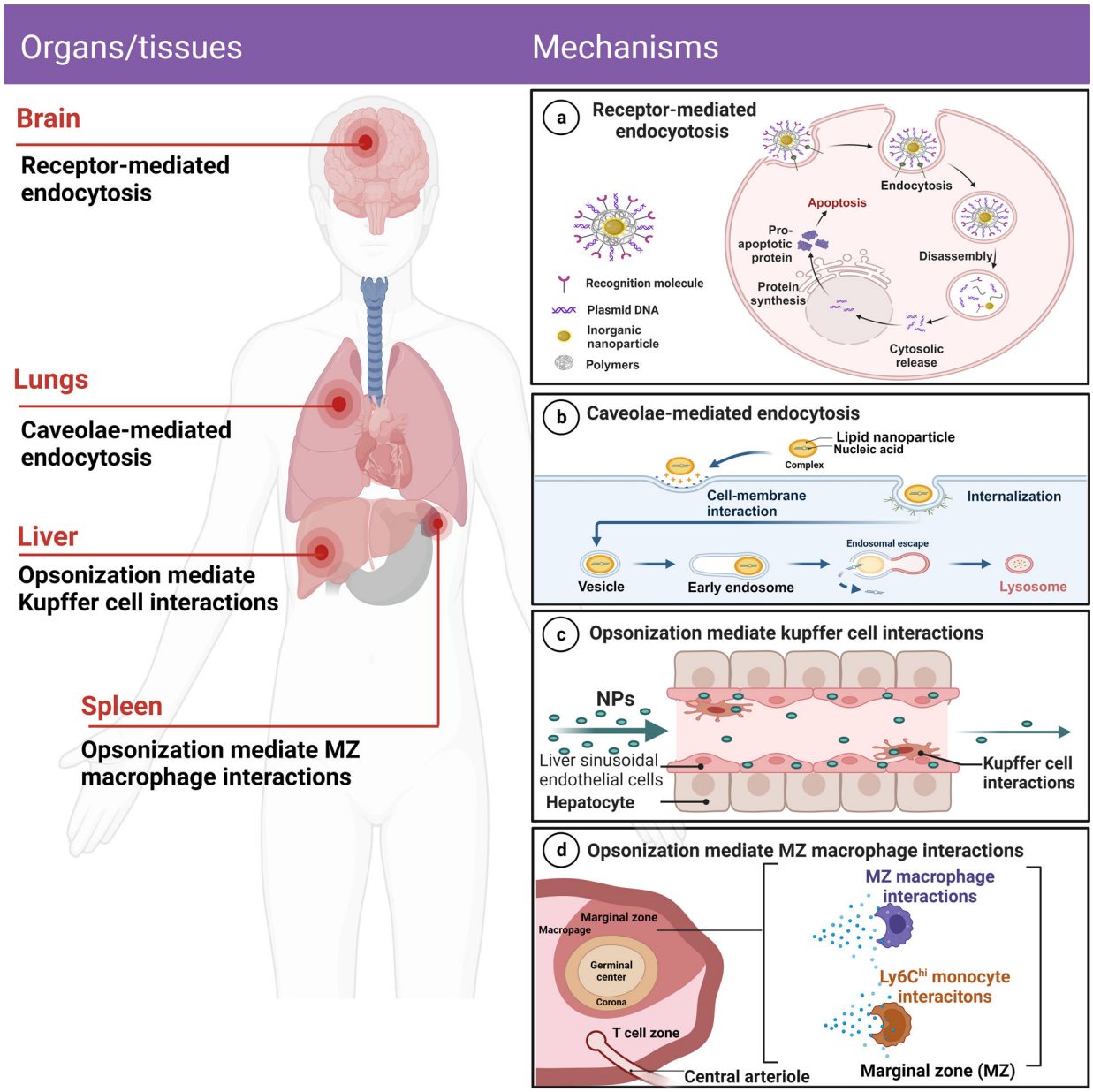

Figure 1.

A schematic illustration of organ-specific targeting mechanisms of nanoparticles (NPs). (a) NPs cross the blood–brain barrier via receptor-mediated endocytosis. (b) Lung-selective targeting via caveolae-medicated endocytosis. (c) Opsonization mediate Kupffer cell interactions. (d) Opsonization mediate splenic macrophage interactions. Figure created with BioRender.com.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

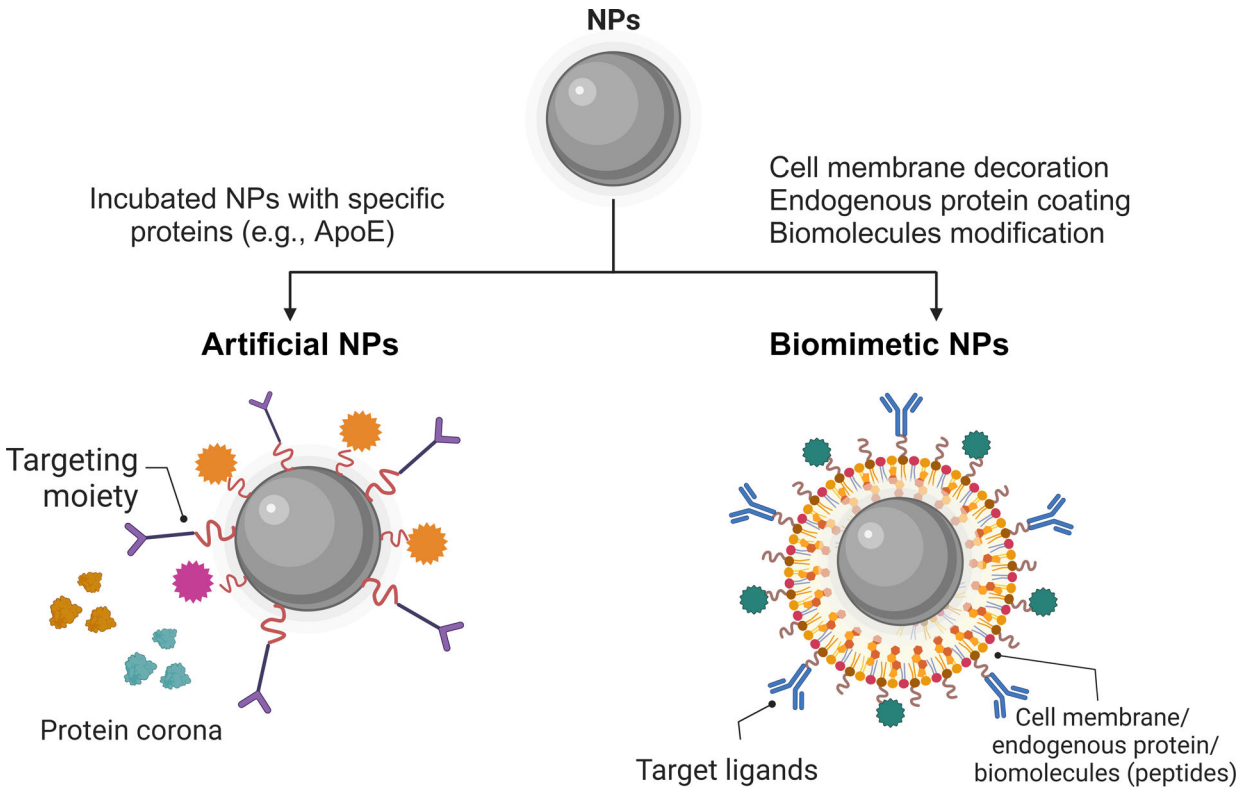

Figure 2.

Illustration of advanced nanoparticles (NPs) delivery systems for organ-specific targeting. Two advanced NPs delivery strategies have been developed for organ-specific targeting: artificial and biomimetic approaches. In the artificial approach, NPs are pre-incubated with specific proteins like apolipoprotein, lipoprotein, transferrin, and peptides before introduction into biological fluids. The biomimetic approach involves decorating NPs with cell membranes, endogenous proteins, or biomolecules to confer targeting capabilities to the NPs. Figure created with BioRender.com.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1.

Artificial protein corona-based organ-targeting strategies.

Target organs	Type of nanoparticles	Proteins	Mechanisms	Ref.
Brain				
	LNPs	Apo E; Apo E4	Lipoprotein-medicated endocytosis	[27,61]
	AuNPs	Apo B100	Lipoprotein-medicated endocytosis	[62]
	HSA-NPs	Apo I	Lipoprotein-medicated endocytosis	[28,65]
	PNP	Tf	TfR-medicated endocytosis	[64]
Lung				
	PEG-NPs	CD47	Unknown	[73]
Liver				
	SNAs	C1q A, C1q B, and C1qC	Opsonin-mediated phagocytosis	[63]
	PNP	Fetal globulin	SR-medicated phagocytosis	[66]
	AuNPs	Albumin	Opsonin-mediated phagocytosis	[67]
	LNPs; HAS-NPs	Apo E	Opsonin-mediated phagocytosis	[68–70]
Spleen				
	V-NPs	Opsonin	Opsonin-mediated phagocytosis	[71]
	QDs	Apo B-100	Opsonin-mediated phagocytosis	[72]

Note: Apo, apolipoprotein; Tf, transferrin; LNPs, lipid nanoparticles; AuNPs, gold nanoparticles; HSA-NPs, human serum albumin nanoparticles; PNPs, polymer nanoparticles; PEG-NPs, polyethylene glycol nanoparticles; SR, Scavenger receptors; SNA, Spherical nucleic acids; V-NPs, virus nanoparticles; QDs, Quantum dots; Vtn, vitronectin; RES, reticuloendothelial system.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2.

Biomimetic protein corona-based organ-targeting strategies.

Target organs	Biomimetic Approach	Type of nanoparticles	Proteins	Mechanisms	Ref.
Brain					
	Biomolecule modification	LipNPs	Apo A1, E, J	Lipoprotein-medicated endocytosis	[82]
	Biomolecule modification	LipNPs	Apo E	Lipoprotein-medicated endocytosis	[83]
	Biomolecule modification	PTX/Aβ-CN-PMs	Apo E	Lipoprotein-medicated endocytosis	[26]
Lung					
	Endogenous protein coating	LNPs	Albumin, fibrinogen	Caveolae-medicated endocytosis	[31]
	Endogenous protein coating	LNPs	ApoE, β2-GPI, or Vtn	Caveolae-medicated endocytosis	[84]
Liver					
	Biomolecule modification	RcP-NPs	RBP4	RBP receptor-medicated uptake	[89]
	Biomolecule modification	DNA tetrahedron	Lipoproteins	Lipoprotein-medicated endocytosis	[85]
Spleen					
	Endogenous protein coating	LNP	Apo H	Opsonization/spleen-targeted delivery via phagocytosis	[84,86]
	Endogenous protein coating	LNP	Apo E, Fg, C3	Opsonization/spleen-targeted delivery via phagocytosis	[33,87]
	Cell membrane decoration	DEX-NPs	C3b	Opsonization/spleen-targeted delivery via phagocytosis	[88]

Note: Apo, apolipoprotein; Tf, Transferrin; LNPs, lipid nanoparticles; LipNPs, Liposomal nanoparticles; AuNPs, gold nanoparticles; RcP, Retinol-conjugated polyetherimine; RBP, Retinol binding protein; Fg, fibrinogen; C3, complement 3; DEX-NPs, dextran-coated ferrous nanoparticles.