Approaching Two Decades: Biomolecular Coronas and Bio–Nano Interactions

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ABSTRACT

It has been nearly two decades since the term "protein corona" was coined. This term has since evolved to "biomolecular corona" or "biocorona" to capture the diverse biomolecules that spontaneously form on the surface of nanoparticles upon exposure to biological fluids and drive nanoparticle interactions with biological systems. In this Perspective, we highlight the significant progress in this field, including studies on nonprotein components, lipid nanoparticles, and the role of the corona in endogenous targeting and organ specificity. We also discuss research opportunities in this field, particularly the need for improved characterization and standardization of analysis, and how recent advances in artificial intelligence can improve our understanding of the biomolecular corona in nanomedicine and environmental science.

ADVANCES IN BIOMOLECULAR CORONA STUDIES

The global impact of nanoparticles (NPs) has been witnessed through the deployment of lipid NP (LNP)-based mRNA vaccines during the COVID-19 pandemic. Despite this, there is still a limited understanding of the diverse interactions of NPs with biological systems—*i.e.*, bio–nano interactions—and how these interactions drive their transport, clearance, deposition, and function. However, it is well established that a dominant feature that influences bio–nano interactions is the spontaneous adsorption of biomolecules onto the surface of NPs upon their exposure to a biological environment, typically a fluid (*e.g.*, blood, interstitial fluid, mucus). This biomolecule coating is known as the biomolecular corona and has been the subject of research to understand bio–nano interactions and their influence on biological outcomes.[1,2]

Studies on protein interactions with surfaces, including colloids, have been reported for more than a century.[3] However, it was only in 2007 that the concept of a biomolecular corona on NPs was introduced. Although it was termed "protein corona" because studies began with the kinetics of protein association/dissociation on NPs, this term still dominates as most studies are based on protein adsorption from different biological fluids (biofluids).[1] Protein corona research has revealed that corona formation is governed by a range of parameters, including NP physicochemical properties (*e.g.*, size, charge, shape, and roughness)[4] and environmental parameters (*e.g.*, exposure time, temperature, and flow conditions).[5] Although most studies are carried out using plasma, there is greater interest in the effect of other biofluids on corona formation (*e.g.*, lymphatic fluid, mucus, cerebrospinal fluid)[4] and even biofluids within plants[6-8] to understand bio–nano interactions that govern NP fate and biological function. In addition, studies on the adsorption of nonprotein biomolecules (*e.g.*, lipids,[9-15] DNA,[16,17] and glycans[13,18,19])

have emerged, although further studies are needed to understand their role in bio–nano interactions (as we discuss later).

The biomolecular corona has been shown to influence bio–nano interactions at different levels, from the cellular internalization of NPs[20] to their phagocytosis by blood immune cells,[21] and *in vivo* NP biodistribution.[22] In 2017, we provided a perspective on the protein corona and its impact on bio–nano studies, emphasizing the importance of understanding and harnessing the biomolecular corona to drive biological outcomes in the coming decade.[23] Descriptions of the biomolecular corona have evolved from a "nuisance",[24] to the "fingerprint" of NPs,[25,26] to an "ally" for the exploitation of NPs.[27] In a recent study, the protein corona was implicated in the endogenous targeting of LNPs to specific organs.[28,29] Siegwart and co-workers showed that engineering the composition of an LNP led to specific binding by vitronectin, which promoted its targeting to the lung and uptake by specific cells that bind vitronectin.[28] These studies highlight the interplay between NP engineering and corona formation that can be exploited to drive biological fate. These also mark the growth of biomolecular corona studies on LNPs,[14,30-32] the current gold standard in nanomedicine owing to their global usage and impact, adding to our understanding of how LNPs behave *in vivo*.[33]

As we approach nearly two decades of biomolecular corona research, we provide a perspective on navigating the complexity in understanding the biomolecular corona and opportunities in harnessing the biomolecular corona to regulate bio–nano interactions (Figure 1). We highlight the latest advancements in experimental techniques and computational models that support this research, as well as emerging research directions that aim to bridge current knowledge gaps and that have potential for future advancements in nanomedicine (Figure 2).

Critical consideration of the differences between the "characterized biomolecular corona" and the "real biomolecular corona" is essential, as the characterization technique and processing of the biofluid can potentially alter the composition of the originally formed biomolecular corona.

NAVIGATING BIOMOLECULAR CORONA COMPLEXITY: FACTORS THAT INFLUENCE CORONA COMPOSITION

Robust characterization of the biomolecular corona is important to accurately identify the biomolecules or subset of biomolecules that drive the biological fate of NPs. While it is well known that the biomolecular corona composition is governed by a range of factors,[4] the complexity of understanding and applying biomolecular corona knowledge come from the use of biofluids from different sources and the characterization technique or workflow employed in independent biomolecular corona studies. These methodological differences introduce variability that can potentially influence the characterization results. As a result, comparing findings across different studies becomes inherently flawed and may lead to inconsistent interpretations.[34] Moreover, this lack of standardization undermines the ability to reliably predict the efficacy of nanomedicines based on previous data, raising concerns about the reproducibility and translational potential of these findings.

The type of biofluid (*e.g.*, blood, mucus, and cerebrospinal fluid) influences the formation and composition of the biomolecular corona. Accordingly, the administration site, hence different tissue and biofluid exposure, can also influence corona composition,[35] which can have downstream effects on bio–nano interactions. Within the same type of biofluid (*e.g.*, blood), differences in the composition of the biofluid, and thus biomolecular corona, can arise from different species[36] and individuals of the same species but of different genders,[37] ages,[38] nutritional status,[39] and

pathological states.[40,41] For example, in person-specific biomolecular coronas, the levels of immunoglobulin and complement proteins in the biomolecular corona were correlated with the extent of NP–blood immune cell association.[21]

Critical consideration of the differences between the "characterized biomolecular corona" and the "real biomolecular corona" is essential, as the characterization technique and processing of the biofluid (such as plasma samples prepared from different anti-coagulants[42]) can potentially alter the composition of the originally formed biomolecular corona. Typical *in situ* characterization techniques, *e.g.*, fluorescence correlation spectroscopy,[43] isothermal titration calorimetry,[44] and *in situ* synchrotron-radiation circular dichroism,[45] enable characterization of the thickness and changes in the dynamics of the biomolecular corona with minimal interference to the biomolecular corona formation. However, compositional analysis of the biomolecular corona using *ex situ* techniques requires isolating biomolecular corona-coated NPs from biofluids (*ex situ*) and subsequent extensive sample purification and digestion before compositional analysis using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). Therefore, *ex situ* techniques involve a high level of interference (*e.g.*, centrifugation) to the original NP–biofluid system, and only biomolecules that have a high affinity to the NPs (often referred to as the hard corona[46]) are preserved and characterized. In addition, different digestion methods, *e.g.*, in-gel, in-solution, and on-particle, have been shown to influence the recovered corona components.[47,48] Furthermore, a recent study revealed variations in the protein corona across different proteomic core facilities:[34] identical corona samples analyzed at different LC-MS/MS facilities yielded different protein datasets, with only 1.8% of 4022 proteins commonly identified. This highlights the challenge in comparing protein corona datasets across different studies with independent LC-MS/MS workflows and the need to be vigilant in the interpretation of protein corona research.[34]

OPPORTUNITIES

Developing Standardized and Advanced Characterization Techniques. Owing to the wide range of factors that can potentially influence the characterization of the biomolecular corona, developing and optimizing a "workflow standard" for biomolecular corona sample preparation and analysis is essential.[49] Similar to the Minimum Information Reporting in Bio–Nano Experimental Literature (MIRIBEL) standard, which covers materials characterization, biological characterization, and details of experimental protocols in bio–nano research,[50] the Minimum Information about Nanomaterial Biocorona Experiments (MINBE) standard[51] has been proposed by Chetwynd *et al*. for biocorona research. The wide variability in protein datasets obtained from LC-MS/MS across different facilities could be reduced if, for instance, the research community were to adopt standard protocols on methodologies, analysis, reporting, and data interpretation.[34] LC-MS/MS remains a valuable tool in the compositional analysis of the biomolecular corona. The use of internal standards in LC-MS/MS could facilitate comparison across independent studies. For example, the incorporation of quality control samples (*e.g.*, mixtures of synthetic peptides),[52] positive controls (biofluid sample without NPs), and negative controls (NPs in pure water) is necessary to assess instrument sensitivity and consistency, evaluate data quality, and avoid contamination from NPs.[51]

In addition to a workflow standard, technical advances in the comprehensive characterization of the original biomolecular corona formed on NPs in biofluids will help reduce differences between the characterized and real biomolecular coronas and minimize the likelihood of misinterpreting correlations between the NP corona composition and downstream biological responses. Some emerging techniques have shown promise in realizing the isolation and in-depth analysis of biomolecular coronas with reduced interference to the original bio–nano systems. For example, *in*

situ click-chemistry reactions have enabled the cross-linking of weakly bound corona, *i.e.*, soft corona, onto the hard corona and preservation of the soft corona after purification.[53] Affinity chromatography techniques have enabled the mild separation of NPs from biofluids without affecting the biomolecular corona composition using a His-tagged anti-poly(ethylene glycol) (PEG) single-chain variable fragment, which has affinity to the PEGylated liposomes and column.[54] The "fishing" method developed by Chen and co-workers has enabled spatiotemporal monitoring of biomolecular corona formation and controllable elution of the soft corona through NP immobilization on biosensors and multistep washing.[55] These studies provide strategies for isolating the original biomolecular corona formed on NPs from biofluids by exerting minimal disturbances to the bio–nano systems or "fixing" the original corona before purification. Moreover, significant efforts have been made toward advancing *in situ* characterization techniques for comprehensively unraveling the complexities of the biomolecular corona.[56] For example, photocatalytic proximity labeling[57] offers opportunities in improving the spatiotemporal resolution of biomolecular corona labeling to clarify the dynamic formation of biomolecular corona. Differential dynamic microscopy enables the quantification of *in situ* protein adsorption and monitoring of NP aggregation *in vitro* and *in vivo*.[58]

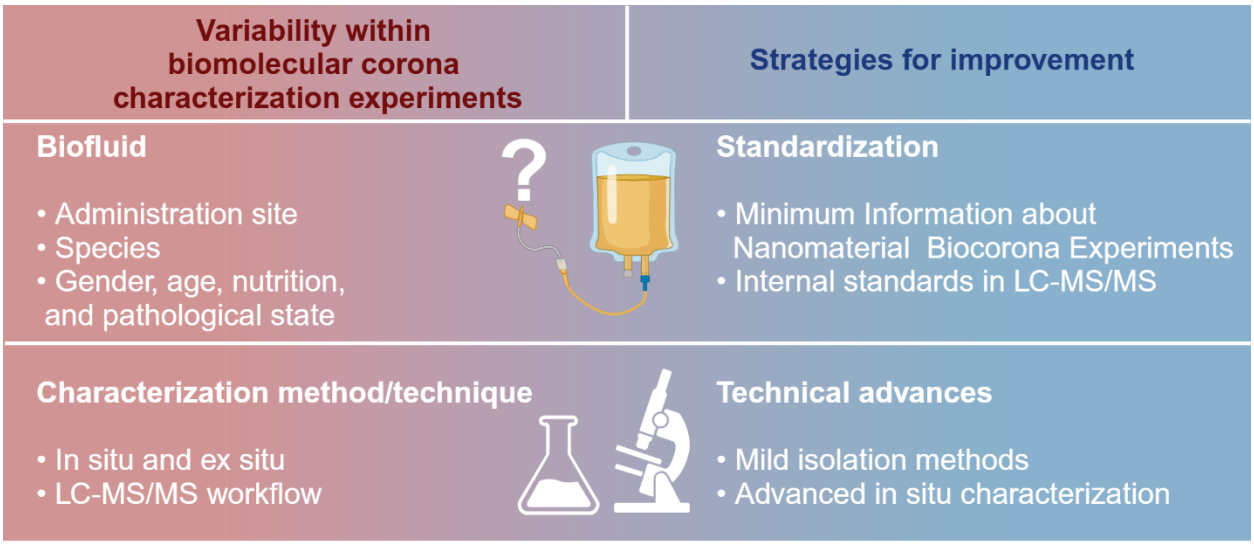

Figure 1. Variability within biomolecular corona characterization experiments from the biofluid source to the characterization method and technique. Strategies for minimizing variability by standardizing and applying technical advances in the characterization of the biomolecular corona. Created with BioRender.com.

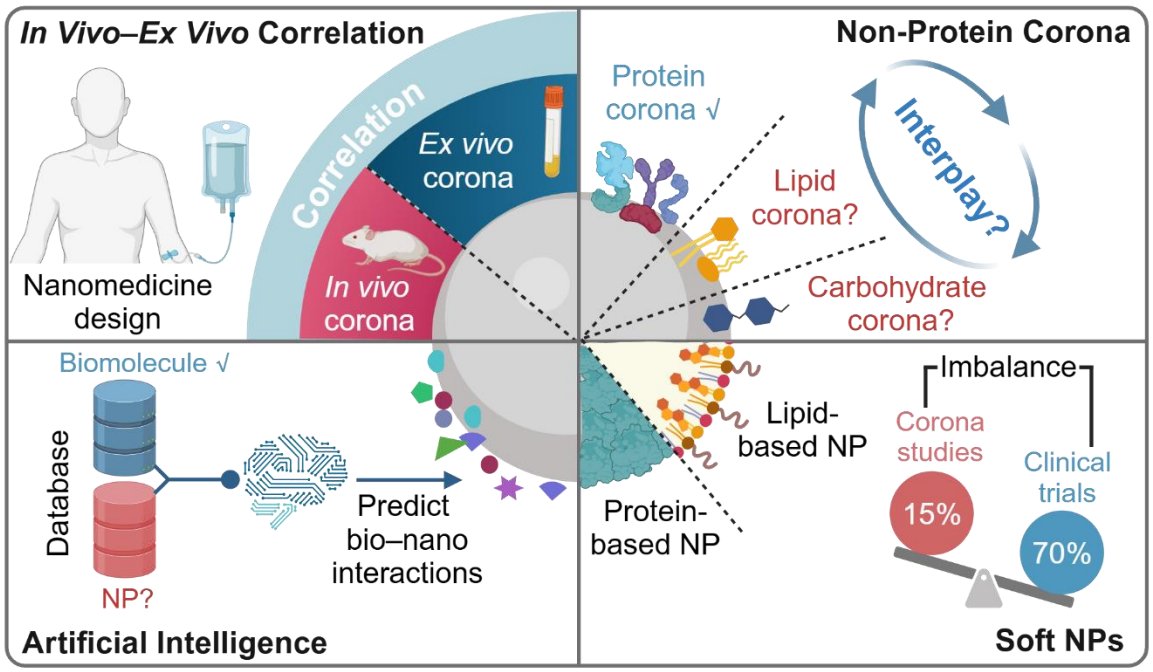

Figure 2. Future research directions proposed for a more comprehensive understanding of the biomolecular corona: exploring and establishing correlations between *in vivo* and *ex vivo* coronas; investigating nonprotein components of the biomolecular corona; applying AI for biomolecular corona studies; and advancing biomolecular corona studies on soft NPs. Created with BioRender.com.

Exploiting Correlations between *In Vivo* and *Ex Vivo* Coronas. Although the number of *in vivo* corona studies is increasing, owing to their more authentic representation of the biomolecular corona, *ex vivo* corona studies provide a fundamental platform for probing real-time bio–nano interactions at the nanoscale in a controllable manner, *e.g.*, monitoring changes in NPs upon

exposure to biofluids.[59] Moreover, *in vivo* corona studies are challenged, and thus limited by, for instance, ethical and regulatory hurdles, sample size, variability within the sample groups, and accessibility to specific tissue or organs for studies.[27] Additionally, the knowledge gained from animal models may not necessarily apply to humans, given the differences in biofluid composition in different biological systems.

Evaluating *in vitro–in vivo* correlation (IV–IVC) is essential toward the clinical translation of pharmaceuticals and the requirements for IV–IVC were issued by the U.S. Food and Drug Administration in 1997.[60] Many drug formulations that exhibit prolonged drug release properties, such as metoprolol, have been developed and optimized using IV–IVC models.[61] However, developing IV–IVC models for NPs faces challenges, mostly due to differences in composition between the *ex vivo* and *in vivo* biomolecular corona. Although *ex vivo* biomolecular corona studies are unlikely to completely replace *in vivo* corona studies, they can provide valuable insights and guide the design of NPs. For example, an *ex vivo* corona study showed that the anchor length of PEG-lipids influenced the shedding kinetics of PEG-lipids from LNPs in serum,[59] which provided insights in tuning the *in vivo* pharmacokinetics of LNPs by using PEG-lipids of different anchor lengths.[62]

In addition, advanced *ex vivo* models, *e.g., ex vivo* whole blood model[21,63-65] and organ-on-a-chip systems,[66] serve as powerful tools for simulating *in vivo* environments and predicting *in vivo* behaviors of NPs, which can facilitate the screening and optimization of NP formulations. For example, we demonstrated the application of an *ex vivo* human blood leukemia model that compensated for the compromised immune system of in-bred mouse models, making it possible to mimic the tumor cell targeting and off-targeting behaviors of NPs in complex human blood environments.[65]

Investigating Nonprotein Components of the Biomolecular Corona. Numerous studies have focused on the protein components of the biomolecular corona, as proteins have key functions in cell signaling and immune responses and protein characterization techniques are well established. In contrast, the roles of nonprotein components in the biomolecular corona of NPs—*e.g.*, lipids, nucleic acids, and carbohydrates—are poorly understood, despite their presence in different types of biofluids.[67-69] Several studies have identified carbohydrates in biomolecular coronas and highlighted the roles of glycans on NPs in influencing the cell uptake of NPs and regulating immune responses.[13,18,19] Studies on lipid coronas have also revealed high lipid abundance and diversity on NP surfaces in lung fluids and plasma/serum,[15] as well as the role of the lipid corona in influencing the cellular uptake of NPs and *in vivo* efficacy of nanomedicines.[9-12,31] A multidimensional compositional analysis of proteins, lipids, cell-free DNA, and metabolites in the biomolecular corona also advances the multi-omics biomarker landscape for nanomedicine-based diagnosis.[16,17]

In addition to investigating how different classes of components in the biomolecular corona directly influence bio–nano interactions, an interesting research direction is to investigate the interplay among different classes of biomolecules and its subsequent influence on bio–nano interactions. For example, a recent study showed that a high level of cholesterol in mice led to the formation of an apolipoprotein-enriched biomolecular corona onto NPs, which increased NP targeting to liver, spleen, and brain.[14]

Applying Artificial Intelligence for Biomolecular Corona Studies. Artificial intelligence (AI)—including machine learning, natural language processing, and robotics—has emerged as a powerful tool for enhancing automation and improving decision-making processes. Research efforts on integrating AI into biomolecular corona studies dates back to 2014.[70] Machine learning

models, such as quantitative structure–activity relationships,[70,71] random forest classification,[72-74] and neural network deep learning,[75] have been used to predict the composition of biomolecular coronas[72,74] and biological behaviors of NPs.[70,71,73,75] Presently, AI-integrated biomolecular corona studies mainly focus on hard NPs (*e.g.*, gold NPs,[70,71,73,75] silver NPs,[72] and carbon nanotubes[74]) rather than soft NPs[73] (such as LNPs). This is likely because the robust synthesis and functionalization methodology of hard NPs, as well as the facile isolation of the biomolecular corona from hard NPs, enable the generation of large databases for AI analysis. In addition, AI tools are sufficiently powerful to modify a given model according to subtle variances in the input data. Therefore, the generation of accurate AI models requires the detailed and reliable characterization of the NP properties and biomolecular corona compositions, which emphasizes the importance of standardizing biomolecular corona studies.

AI has made groundbreaking and ever-changing advancements in the accurate prediction of protein structures and biomolecular interactions in recent years, as exemplified by DeepMind's Alphafold,[76,77] and these techniques could potentially contribute to the understanding of the biomolecular corona in terms of the structure and interaction of biomolecules. For example, AlphaFold 3 enables the prediction of the joint structure of biomolecular complexes formed from proteins, nucleic acids, ions, and small molecules using a diffusion-based architecture,[77] and the integration of NP properties into the model training database offers possibilities to predict the interactions between NPs and biomolecules. Additionally, machine learning models have been used to identify nuances in the raw LC-MS/MS data of tumor and nontumor tissues for clinical disease detection,[78] which could potentially be applied to detect functional composition in the biomolecular corona of NPs. Although applying AI to bio–nano interaction studies still faces challenges, *e.g.*, data size, diversity, and interpretability,[79] ongoing research and development in

AI-driven bio–nano interaction studies will facilitate the understanding and the design of nanomedicines.

Biomolecular corona studies, which are aimed at understanding bio–nano interactions and advancing the design of next-generation nanomedicines, largely focus on hard NPs, primarily because of the challenges in isolating soft NPs from biofluids.

Biomolecular Coronas on Soft NPs. Compared with hard NPs, soft NPs, such as LNPs, polymeric NPs, and protein-based NPs, are more widely used for drug delivery applications owing to their high biocompatibility and drug-encapsulation capabilities.[80,81] However, biomolecular corona studies, which are aimed at understanding bio–nano interactions and advancing the design of next-generation nanomedicines, largely focus on hard NPs, primarily because of the challenges in isolating soft NPs from biofluids. For example, biomolecular studies on the most clinically relevant NPs—*i.e.*, LNPs and protein NPs comprising 44% and 26% of all types of NPs in clinical trials, respectively[82]—are disproportionately underrepresented, accounting for only around 12% and 3% of the total studies, respectively.[49] Magnetic adsorption[31] and size exclusion chromatography combined with membrane ultrafiltration[83] have been used to isolate soft NPs from biofluids, compensating for the shortcomings of traditional ultra-centrifugation methods that are ineffective in separating high-density components in biofluids (*e.g.*, lipoproteins and endogenous vesicles) from NPs and cause potential damage to NP integrity.[84]

In addition, despite extensive studies on the functionalization of soft NPs with targeting moieties, it remains challenging to achieve efficient targeting and improved efficacy of soft NPs with minimal nonspecific targeting *in vivo*. For example, studies have revealed the key roles of specific corona proteins in regulating LNP distribution in organs and blood immune cell interactions—wherein apolipoprotein E facilitates targeted delivery to liver hepatocytes[85] and

across the blood–brain barrier,[86] β2-glycoprotein I may enhance spleen specificity,[28] and anti-PEG antibodies may promote phagocytosis of LNPs by monocytes and neutrophils in blood.[64,87] However, the roles of those specific biomolecules in bio–nano interactions need further validating using different models, *e.g.*, wild-type *versus* knock-out mice.[88] Moreover, the extent to which these biomolecules govern NP interactions with biological systems and whether the influence of those corona proteins is universal to NPs of different formulations remain unclear.

SUMMARY AND OUTLOOK

Since the concept of "protein corona" was first established in 2007, studies on the biomolecular corona have emphasized its key role in influencing NP properties and downstream biological responses, *e.g.*, *in vivo* fate, drug delivery efficacy, and immune responses. A range of *in situ* and *ex situ* characterization techniques have been developed to investigate the dynamic evolution, structure, and composition of the biomolecular corona. However, it is important to think critically about the differences between the "characterized biomolecular corona" and the "real biomolecular corona" because the method/technique employed for characterizing the biomolecular corona can potentially alter the composition of the originally formed biomolecular corona. Moreover, it remains unclear whether the "characterized biomolecular corona" can accurately represent the "real biomolecular corona" in bio–nano interactions. Advancements in high-throughput *in situ* analytical techniques are needed to understand the dynamic interplay between NPs and the biological environment. Additional studies are needed on comparisons between independent studies, given the possible large systematic discrepancy in the characterization of the biomolecular corona produced by different analysis workflows. Exploring coronas composed of biomolecules from different classes, including proteins, lipids, carbohydrates, and nucleic acids, will also be beneficial to gaining a comprehensive understanding of the biomolecular corona. Furthermore,

additional biomolecular corona studies on clinically relevant NPs, such as LNPs, are needed. This would help expedite the clinical translation of nanomedicines. Moreover, interdisciplinary collaborations between scientists with expertise in materials engineering, biology, immunology, and computer science, as well as the standardization and optimization of biocorona experimental design across the world, will help accelerate the design of safer and more effective NP-based nanomedicines.

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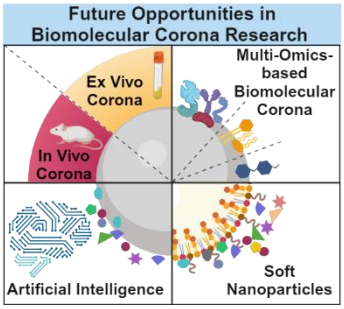
Future Opportunities in Biomolecular Corona Research
Ex Vivo Corona
In Vivo Corona
Multi-Omics-based Biomolecular Corona
Artificial Intelligence
Soft Nanoparticles