



COVID-19: Nanomedicine Uncovers Blood-Clot Mystery

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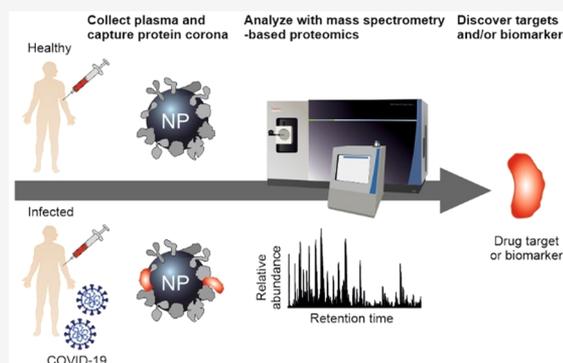
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ABSTRACT: Further complications associated with infection by severe acute respiratory syndrome coronavirus 2 (a.k.a. SARS-CoV-2) continue to be reported. Very recent findings reveal that 20–30% of patients at high risk of mortality from COVID-19 infection experience blood clotting that leads to stroke and sudden death. Timely assessment of the severity of blood clotting will be of enormous help to clinicians in determining the right blood-thinning medications to prevent stroke or other life-threatening consequences. Therefore, rapid identification of blood-clotting-related proteins in the plasma of COVID-19 patients would save many lives. Several nanotechnology-based approaches are being developed to diagnose patients at high risk of death due to complications from COVID-19 infections, including blood clots. This Perspective outlines (i) the significant potential of nanomedicine in assessing the risk of blood clotting and its severity in SARS-CoV-2 infected patients and (ii) its synergistic roles with advanced mass-spectrometry-based proteomics approaches in identifying the important protein patterns that are involved in the occurrence and progression of this disease. The combination of such powerful tools might help us understand the clotting phenomenon and pave the way for development of new diagnostics and therapeutics in the fight against COVID-19.

KEYWORDS: COVID-19, SARS-CoV-2, blood clotting, nanomedicine



INTRODUCTION

As of August 6, 2020, over 717 680 COVID-19-related deaths had been reported worldwide.¹ The intense and unprecedented effort to develop vaccines and new diagnostic technologies (including nanotechnologies^{2–4}) for the rapid identification of infected individuals offers the hope of eventually controlling this pandemic. Nevertheless, emerging effects of COVID-19 in addition to the well-known pulmonary symptoms (e.g., cardiovascular disorders^{5,6}) are also of immediate concern.

A major syndrome related to COVID-19 is blood clotting, which thus far is responsible for the deaths of ~20–30%^{7,8} of critically ill SARS-CoV-2-infected patients.⁹ This phenomenon is not yet fully understood. However, a very recent report suggests that one factor may be the presence of the ACE2 receptor—the same receptor that the coronavirus binds in order to enter lung cells. This receptor is located on the surface of the endothelial cells that line the blood and lymph vessels.¹⁰

Although blood-thinning medications are the obvious clinical choice to control blood clotting, determining appropriate dosing and the need for other aggressive strategies (e.g., blood transfusion) are critical in preventing/controlling complications, including stroke.⁹ Therefore, the development of new methods for rapid assessment of the severity of clotting could be of enormous help to clinicians. In addition, identifying the important protein patterns that are involved in the clotting process can help the scientific community to (i) better design

sensors for rapid assessment of clotting severity and (ii) design therapeutic biomolecules/drugs to prevent/delay the clotting process.

Nanomedicine has so far furnished a unique opportunity for the development of robust and sensitive sensors.^{11–13} In addition, nanomedicine has shown great potential to be combined with proteomics approaches for disease detection and biomarker discovery applications.^{14–16} In fact, analysis of plasma proteins using advanced proteomics approaches is a well-documented strategy for biomarker discovery studies.¹⁷ Identifying such biomarkers has a significant clinical capacity not only for disease identification but also for finding the underlying mechanisms involved in disease occurrence and progression. One of the central challenges of the proteomics approaches is the complexity of the plasma proteome together with the vast dynamic range between the least and most abundant plasma proteins.¹⁷ Therefore, the development of strategies with the capacity to reduce the complexity and

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Table 1. Possible Mechanisms by Which Some Viruses Interfere with the Coagulation Cascade, Causing Bleeding Disorders or Thrombosis

mechanism	description	usual pathological outcome	example(s)	ref(s)
reduced platelet numbers or changes in their function	increased adherence or activation of platelets or change in platelet number due to secretion of autoimmune antibodies against platelets	hemorrhage	<ul style="list-style-type: none"> avian influenza (H5N1) SARS 	39, 40
damage to endothelial cells	<ul style="list-style-type: none"> inhibits the anticoagulation properties of endothelial cells by reducing heparan sulfate anticoagulant synthesis affects the production of coagulation regulatory substances such as protein C, a coagulation inhibitor enhances the procoagulant properties of endothelial cells by production of tissue factor or Von Willebrand factor (vWF) through attachment of inflammatory cells such as platelets or granulocytes, may reverse the antithrombotic properties of endothelial cells toward procoagulation 	thrombus formation	herpes viruses	41, 42
alteration of coagulation proteins	decrease or increase the level of coagulation factor: e.g., increased fibrinogen or factor VII may favor thrombosis, whereas decreased factors IX and X may lead to hemorrhage	either thrombus formation or hemorrhage	ebola virus	43
disruption of the function of natural anticoagulant	viral infection can decrease anticoagulant substances such as protein C, protein S, or antithrombin through either decreased synthesis or degradation by the host immune system	thrombus formation	hantavirus	44
alteration in fibrinolysis	decreased fibrinolysis due to increased serpin E1, an inhibitor of tissue plasminogen activator (tPA), or decreased tPA, leading to hyperfibrinolysis	either thrombus formation or hemorrhage	SARS	45

dynamic range of the plasma proteome may be useful for biomarker discovery applications

This Perspective describes the potential role of nanomedicine in point-of-care diagnosis of COVID-19 infection in patients at high risk of blood clotting as well as in determining appropriate treatment options by employing the synergistic role of nanomedicine and proteomics approaches.

■ HOW DO VIRUSES INDUCE BLOOD CLOTS?

The mechanism behind the recently observed blood-clotting phenomenon associated with COVID-19 remains unclear. However, we have much more data on other respiratory viruses such as SARS, MERS-CoV, H7N9, and H1N1. In fact, in patients suffering from these respiratory tract infections, typical signs of alteration in the coagulation system have been reported, such as thrombosis in small vessels or pulmonary capillaries and fibrin deposition or pulmonary hemorrhage.^{18–22} Similarly, in the 2003 SARS outbreak, signs of aberrant coagulation system function included vascular fibrin thrombi associated with pulmonary infarcts.²³

Despite the current lack of information, it is plausible that the interplay between the complement system, inflammation, and the coagulation system plays a central role in thrombosis formation in patients infected by SARS-CoV-2. Following any acute injury or attack by pathogens, the complement and coagulation systems are coordinately activated, regulating the response by limiting hemorrhage and counterattacking the invading pathogen.^{24–27} As its name implies, the complement system complements the humoral immune system by enhancing antibody-mediated immunity and increasing the ability of phagocytic cells such as macrophages and neutrophils to eliminate bacteria or viruses, attack and destroy pathogens in membranes, and clear damaged cells.²⁸ The complement system is composed of around 30 proteins circulating in the blood.²⁹ Upon any defense requirement, the complement proteins are extravasated from blood vessels and execute their immune function through different pathways.³⁰

The coagulation system consists of platelets, endothelial cells, and soluble blood proteins whose main responsibility is to initiate coagulation at the site of an injury.³¹ The process of coagulation takes place via an intrinsic or extrinsic pathway;

these pathways converge on factor X activation.³² The intrinsic pathway is activated by the exposure of endothelial collagen following injury inside the vascular system and involves plasma factors XII, XI, IX, and VIII. In contrast, the much quicker extrinsic pathway involves tissue factor (TF) and plasma factors I, II, and VII and is activated by external trauma or injury.³³ Key cells such as platelets play a central role in hemostasis by providing a surface upon which coagulation can take place and by releasing various mediators contributing to hemostasis.²⁶

Under normal conditions, the body can maintain a balance between procoagulant and anticoagulant mechanisms. However, studies have shown that viruses and inflammatory cells can induce activation of the immune system, which leads to massive secretion of complement proteins and immunoglobulins and alterations in all of the elements of the coagulation cascade. This in turn creates an imbalance in the coagulation system,³⁴ which can lead to both thrombotic and hemorrhagic complications.³⁵ Table 1 outlines the possible mechanisms by which viruses can interfere with blood coagulation mechanisms.

In addition, viral infections are known to alter coagulation proteins. For example, dengue viruses, which cause acute febrile disease after transmission through the bite of an infected mosquito, can decrease the activity of factors II, V, VII, VIII, IX, X, and XII, resulting in massive bleeding in the most severe form of the disease, dengue hemorrhagic fever.³⁶ Recent data from patients with SARS-CoV-2 indicate the presence of greatly elevated levels of several system coagulation markers such as D-dimer and fibrin/fibrinogen degradation products compared with healthy controls.^{37,38}

■ CURRENT NANOMEDICINE STRATEGIES FOR DIAGNOSIS AND TREATMENT OF THROMBOSIS

One of the major outcomes of COVID-19-related blood clotting is thrombosis. Theragnostic nanotechnologies have been developed to (i) diagnose thrombosis early and (ii) deliver thrombolytics/thrombosis inhibitors to the affected area. To efficiently target and deliver therapeutics, nanoparticles should be designed to target some thrombosis biomarkers. P-selectin, a cell adhesion molecule on the surfaces of activated endothelial cells and activated platelets; D-dimer, a fibrin degradation

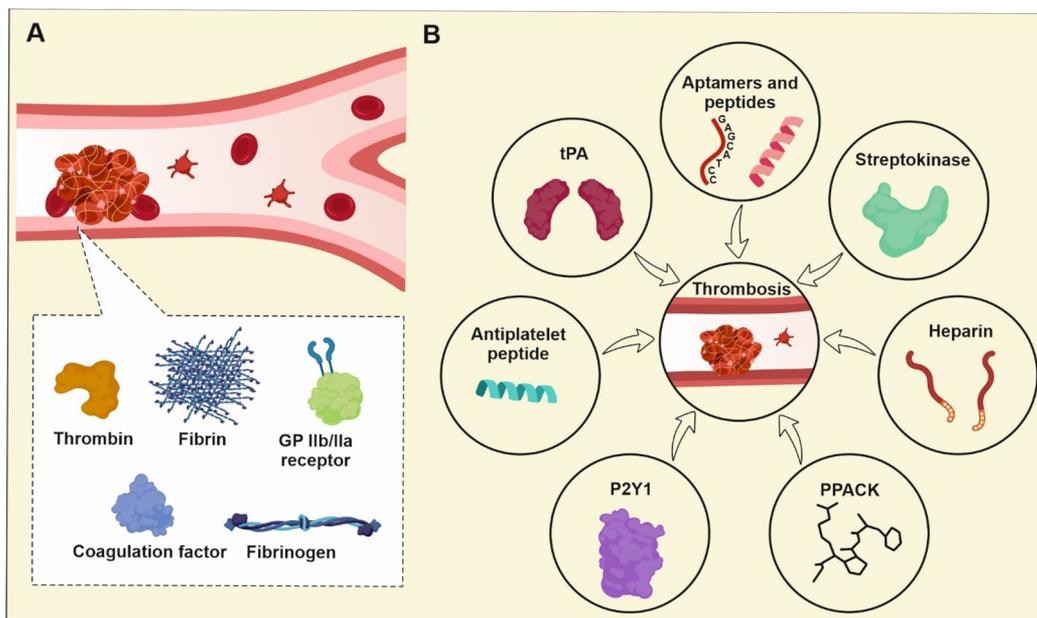


Figure 1. Examples of (A) thrombosis-specific biomarkers and (B) different types of biomolecules that are used in targeted nanoparticles for diagnosis and treatment of thrombosis. Abbreviations: tPA, tissue plasminogen activator; PPACK, D-phenylalanyl-L-prolyl-L-arginyl chloromethylketone. Adapted with permission from ref 75. Copyright 2020 Elsevier. Some features were created with BioRender (www.BioRender.com).

Table 2. Representative Examples of Targeted Nanocarriers for Treatment of Thrombosis with Efficacy Validations in Rat or Mouse Models

mechanism of action	payloads	nanocarriers	refs
delivery of clot-busting drugs	tissue plasminogen activator (tPA), hirulog, heparin, and streptokinase	iron oxide; micelle; carbon capsule; liposome; and copper	66–74
thrombin inhibitors	D-phenylalanyl-L-prolyl-L-arginyl chloromethylketone (PPACK) and aspirin		
platelet aggregation inhibitors	antiplatelet peptides, heparin, and P2Y1 agonist		

product; and E-selectin, a cell adhesion molecule that is expressed by cytokine-activated endothelial cells, have been reported to act as thrombosis biomarkers.⁴⁶ (Figure 1).

The current endeavor for addressing thrombosis using nanomedicine involves delivering nanoparticles loaded with antithrombotic agents to the thrombus sites through targeting of one or several proteins involved in coagulation (e.g., fibrin, thrombin, or hydrogen peroxide (H_2O_2)). Alternatively, targeting cells involved in the coagulation process, such as activated platelets, via cell-binding ligands has also been reported. Using H_2O_2 -responsive boronate antioxidant polymer (BAP) linked to fibrin-targeting lipopeptides, Kang et al. showed that the nanoparticles could deliver tirofiban to the thrombus site in rat models inhibiting the generation of H_2O_2 , therefore suppressing TNF- α and soluble CD40.⁴⁷ Similarly, by the use of iron oxide nanoparticle micelles functionalized with a fibrin-specific binding peptide as well as bare nanoparticles, thrombus sites have been detected using magnetic particle imaging.⁴⁸ Ultrasmall superparamagnetic iron oxide nanoparticles coated with fucoidan, a polysaccharide with high affinity for activated platelets, have been shown to attach to P-selectin and assist with in vivo diagnosis of thrombus formation.⁴⁹ Similarly, liposome nanoparticles surface-modified with cyclic Arg-Gly-Asp (RGD) can also be targeted to the activated platelet receptor integrin GPIIb-IIIa.⁵⁰ Several other examples have also demonstrated the feasibility of this approach (see examples in Table 2).

Although a wide range of targeted nanotechnologies have been developed for theragnostic applications for thrombosis, this approach has some shortcomings that may limit its future applications. Upon contact of nanoparticles with complex physiological fluids such as blood, a coating of biomolecules (mostly proteins) covers their surface. This layer, called the biomolecular/protein corona, gives a new identity to the nanoparticles.^{51–53} The formation of a biomolecular corona has several adverse effects⁵⁴ on therapeutic nanoparticles; important examples include shielding targeting species on the surface of nanoparticles,^{55–57} creating an additional barrier at the surface of drug-loaded nanocarriers,⁵⁸ and creating different biological identities across patients.^{59–64} Other issues such as the inherent thrombogenicity of nanoparticles also need to be considered. For example, TiO_2 nanoparticles cause platelet aggregation and therefore exacerbate thrombosis risk.⁶⁵

■ POTENTIAL APPLICATION OF NANOMEDICINE STRATEGIES FOR DIAGNOSIS AND TREATMENT OF THROMBOSIS: THE ROLE OF MASS-SPECTROMETRY-BASED PROTEOMICS

While the benefits of the conventional use of nanoparticles for therapeutic applications in thrombotic patients may be affected because of biomolecular/protein corona formation, this in turn may create unique opportunities for diagnostic applications (Figure 2).^{62,64} In fact, the composition of the biomolecular coronas formed on the surface of identical nanoparticles strongly

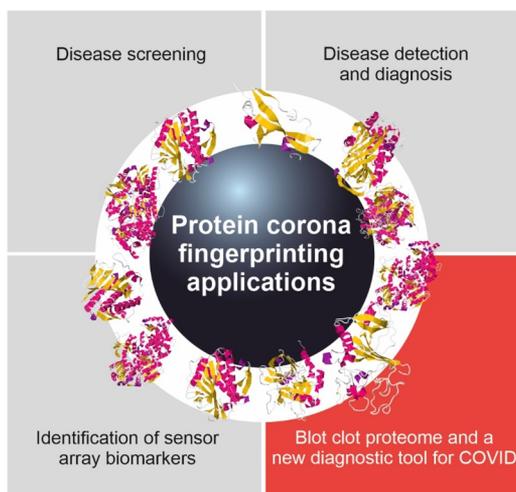


Figure 2. Current applications of protein coronas in disease detection as well as their potential future utility in diagnosis of COVID-19.^{16,125} Protein structures were taken from the RCSB Protein Data Bank.

depends on the disease(s) the plasma donor has. This results in the concepts of “personalized” and “disease-specific” protein coronas, where a unique role is assigned to the biomolecular corona in catching disease-specific biomarkers and disease diagnosis.^{61,62,76–80}

Currently, mass spectrometry (MS) is the gold standard for analysis of plasma composition as well as protein corona composition. Advances in the past decade have turned proteomics into an unprecedented tool for routine investigation of the proteome⁸¹ with regard to variations in protein abundances and post-translational modifications (PTMs) as well as biochemical and thermal stability. With the recent advent of single-cell proteomics,⁸² the imaginable application space of proteomics has expanded exponentially.

According to the human plasma proteome draft of 2017, 3509 proteins have been quantified reliably in plasma in a compilation of 178 individual experiments.⁸³ Thousands of proteins can now be measured with state-of-the-art MS-based plasma proteomics.^{84–86} Despite huge investments, apart from classic blood biomarkers approved by the U.S. Food and Drug Administration, few new biomarkers have entered the clinical setting. Most of these biomarkers are abundant proteins that can be readily measured in plasma. A major challenge with plasma proteomics is to retain proteome coverage when analyzing larger sample cohorts. The main analytical difficulty to tackle is the presence of highly abundant proteins such as albumin (55% of the total protein mass in plasma). Seven proteins constitute 85% of the total protein mass in plasma.⁸⁷ Peptides from abundant proteins crowd the spectra, hindering comprehensive profiling of the plasma proteome and making in-depth analysis of plasma cohorts challenging. Plasma depletion strategies are available,⁸⁸ but the high cost and time-consuming nature of these methods makes them unlikely to be applicable in large cohorts. In this line, indirect analysis of nanoparticle biomolecular/protein coronas can provide an advantage in biomarker discovery by enriching plasma and lowering the plasma proteome complexity and providing a new type of information.

The benefits of MS methods for the identification of blood-clotting disorders induced by viruses such as SARS-CoV-2 can be followed in two distinct and interrelated approaches. In general, plasma and serum are suitable accessible biofluids for biomarker discovery or differential diagnostic analyses.⁸⁹ These

biofluids harbor rich sources of information on the health status of individuals and have been exploited for years to inform the medical decision-making process.⁹⁰ In this line, comparative proteomics of healthy and patient samples plays a major role in either pattern discovery or biomarker discovery. The first approach mainly relies on comparative biomolecular pattern detection and does not aim for individual biomacromolecules. To characterize the distinctive patterns in diseases such as COVID-19 infection, individual biomarker discovery can be facilitated using advanced MS techniques. Therefore, we can develop nanoparticle-based assays that have the ability to adsorb proteins of interest on the surface of nanoparticles and make identifiable detection signals through color changes, electric signals, and so forth. These two approaches are elaborated in the following sections.

■ DEVELOPMENT OF SENSORY NANOMEDICINE TO ASSESS THE RISK OF BLOOD CLOTTING

The unique feature of the biomolecular/protein corona is that its proteins have almost no correlation with their plasma concentrations.^{52,91,92} In other words, the biomolecular corona offers a novel type of proteomics data (in terms of the number and type/category of proteins and their concentrations) that is totally different from similar data on plasma proteins. In a recent study, we demonstrated a proof of concept that disease-specific biomolecular coronas, in combination with unsupervised and supervised classification approaches, offer the unique capacity to detect and discriminate various types of cancer⁹³ and neurodegenerative disorders.⁹⁴ In our system, rather than detecting a specific biomarker, the sensor array provides pattern recognition of the corona protein composition adsorbed on the surface of distinct nanoparticles (e.g., liposomes with various surface chemistries). Our results show that the pattern of corona composition derived from the nanoparticle sensor array provides a unique “fingerprint” for each type of cancer.

The current knowledge applicable to the development of *ex vivo* sensory nanobased technologies to monitor the risk of thrombosis specially from viral disease is very limited. In addition, using the same concept, the proteomics information retrieved from the biomolecular/protein corona may be used for the development of sensory nanomedicine for fast diagnosis of blood clotting and its severity. This is very useful for the synergistic role of nanomedicine and proteomics approaches, as the profiles of biomolecular/protein coronas can significantly reduce the complexity and dynamic range of the human proteome.

■ PROTEOMICS TECHNOLOGIES ENABLE BIOMARKER DISCOVERY: IMPLICATIONS FOR COVID-19

By combining biomolecular/protein corona and MS-based approaches, we may identify the important single proteins that are involved in the COVID-19 blood-clotting process. In the case of COVID-19, for disease mechanism studies or biomarker discovery, proteomics can be used for comparative analysis of plasma among healthy and infected individuals as well as severely ill patients. Another important layer of information can be obtained if such studies are coupled with biomolecular/protein corona analysis. Since proteins recovered from nanoparticle coronas have been shown to have significant differences with plasma proteins in terms of concentration and representation, protein corona patterns can be exploited for

biomarker (pattern) discovery under different disease conditions. For this purpose, plasma from both patients and healthy individuals can be incubated with nanoparticles, creating a corona array that can be subsequently analyzed by proteomics techniques. Many studies have identified this concept for several life-threatening diseases such as cancers and neurodegenerative diseases.^{16,60,95–101}

Once the biomolecular/protein corona is captured, the proteome can be processed and subjected to LC–MS/MS analysis. If the focus is on the most abundant corona proteins, label-free techniques can be used. For example, using this approach, Hadjidemetriou et al. showed that the protein corona formed on PEGylated liposomes (HSPC:Chol:DSPE-PEG2000) following intravenous administration in melanoma (B16-F10)- and lung carcinoma (A549)-bearing mice was enriched by tumor-specific protein compared with control plasma samples that revealed none of those proteins.⁹⁷

As mentioned above, label-free analysis of plasma suffers from shallow proteome coverage and over-representation of missing values, especially in analysis of large cohorts. One solution is to perform data-independent acquisition, where only a set number of precursor ions are selected and analyzed by MS/MS. Through this method, Bruderer et al. analyzed 1508 plasma samples in a fast and robust way, identifying 408 proteins on average per acquisition (319 proteins in 90% of all acquisitions).¹⁰² These can be further combined with targeted MS strategies to selectively quantify a defined subset of analytes, in this case complement proteins, immunoglobulins, and clotting factors most relevant to COVID infection.¹⁰³ Alternatively, samples can be multiplexed by isobaric neutron-coded TMT reagents or similar labeling technologies and fractionated to provide a deeper snapshot of the corona state, at the cost of expense and analytical time. Human Plasma Proteome Project (HPPP) considerations and recommendations regarding plasma proteomics study design, sample collection, quality measures, processing workflows, MS data acquisition, data processing, and bioinformatic analysis have been reviewed elsewhere.¹⁰⁴

On the other hand, the same corona analysis can be applied to the SARS-CoV-2 virus itself as a natural nanoparticle. Since the biomolecular/protein corona is associated with nanoparticle bioactivity, different coronas from plasmas of different individuals might react differently with biological entities. For example, in an interesting study, Ezzat et al.¹⁰⁵ demonstrated that respiratory syncytial virus (RSV) and herpes simplex virus type 1 (HSV-1) are covered by rich and unique biomolecular/protein coronas in different biofluids. They further showed that the corona affects viral infectivity and induction of immunity. Viruses were shown to bind amyloidogenic peptides and to catalyze amyloid formation by surface-assisted nucleation. HSV-1 could even catalyze aggregation of amyloid- β peptide (A β 42) in animal models. The authors indicated that the viral corona is a critical factor dictating virus–host interactions. A similar strategy can be employed to study COVID–host interactions in different patients.

Biomarker discovery, target deconvolution, and mechanism elucidation are among the most important applications of proteomics. In comparison with other omics technologies, proteomics is of utmost importance in such studies, as proteins are the main functioning units in any given biosystem and proteomics is the only system-wide tool that provides information on both protein production and degradation as well as PTM states and protein stability. In a cellular context, proteomics can be used to analyze pathways that are modulated

by a perturbation.¹⁰⁶ Usually, such pathways mirror the underlying biological phenomenon and provide hints on mechanisms and druggable proteins, targets, or biomarkers that can be pursued.

■ COVID-19 BLOOD-CLOT MYSTERY

The effects of viral infection on coagulation are noted above. Since COVID-19 infection is associated with aberrant coagulation cascade, resulting in serious alteration of coagulating factors and other mediators, timely detection of rising levels of complement proteins, immunoglobulins, and clotting factors in blood plasma could provide the information necessary for clinicians to choose the right strategy (e.g., appropriate dosing of blood-thinning medications) and aggressiveness of treatment to prevent the lethal consequences of massive blood clotting such as heart and/or brain strokes.

Analysis of the biomolecular/protein corona profiles of many nanoparticles (e.g., silica,¹⁰⁷ polystyrene,¹⁰⁷ and gold⁵⁸) has revealed the capacity of the corona in absorption of complement proteins, immunoglobulins, and/or coagulants, which can be extremely helpful for detection of sudden increases in the abundance of these proteins in blood plasma. We have shown that precoating of nanoparticles with specific proteins (e.g., immunoglobulins) can significantly improve the recruitment of similar proteins from blood plasma.¹⁰⁸ Therefore, precoating nanoparticles with clot-related proteins such as fibrinogen, fibrin, factor VIII, factor XIII, tissue plasminogen activator, or protein Z could significantly intensify the recruitment of similar proteins into the corona, creating a unique opportunity for the development of a sensitive and robust approach for rapid identification of even subtle signs of clotting in plasma. These protein-enriched coronas can be detected through well-developed colorimetric sensing platforms, including smartphone-readable systems for detection and discrimination of multiple proteins.¹⁰⁹ In addition, well-designed (opto)-plasmonic nanoparticles¹¹⁰/nanosensors¹¹¹ (e.g., gold^{110,112}) may identify changes in the secretion of blood-clotting proteins by generating colored solutions amenable to detection with the naked eye or point-of-care devices. For example, by the use of the protein corona in combination with the enzyme-mimetic activity of gold nanoparticles (i.e., polyhedral oligomeric silsesquioxane polymer-caged), a sensitive colorimetric analysis was developed for the identification of metallothioneins, which are important biomarkers for heavy-metal poisoning.¹¹³ As another example, a colorimetric assay based on gold nanosensors functionalized with antisense oligonucleotides was developed to target the nucleocapsid phosphoprotein of COVID-19 for diagnosis of SARS-CoV-2-infected people using the naked eye.¹¹⁴

The same concepts as explained above can be used in optical sensory nanoparticles (e.g., gold) as a rapid and portable kit to monitor the sudden release of complement-based proteins in the plasma of patients who are critically ill with COVID-19. Such techniques for rapid detection of the release of clot-related proteins can help clinicians predict the severity of blood clotting and therefore administer the right dosage of drug-thinning medications to prevent stroke and other life-threatening conditions.

In addition to the point-of-care approaches for monitoring the risk and severity of blood clotting, the biomolecular corona may also be analyzed with omics techniques (e.g., proteomics, metabolomics, and/or lipidomics) to gather data regarding the patterns of biomolecules involved in blood-clotting phenomena,

which may yield a deeper understanding of the mechanisms underlying this aspect of COVID-19's effects. For example, we showed that depending on the type of disease, the composition/profile of biomolecules that form at the surface of nanoparticles upon their interactions with biological fluids is different.⁶¹ Using the biomolecular corona formed on sensory nanoparticles, we were then able to discern protein patterns that are useful in identifying various types of cancers and gather useful information regarding the association of protein patterns with each cancer type.¹⁶

Identification of proteins distinctively involved in COVID-19-related blood clotting may help illuminate the underlying mechanisms and pathways, guiding the scientific community to new therapeutic approaches. Identifying the important proteins can also help in the development of new targeted nanomedicine for rapid monitoring of the release of such proteins, which will provide a huge clinical advantage in assessing the risk of blood clotting and its severity in COVID-19-infected patients.

■ FUTURISTIC STRUCTURAL BIOMARKER DISCOVERY BY BIOMOLECULAR/PROTEIN CORONA ANALYSIS

Thermal proteome profiling (TPP)¹¹⁵ is a recent breakthrough that added a novel protein stability dimension in proteomics. This method is based on combining the cellular thermal shift assay (CETSA)¹¹⁶ with multiplexed quantitative proteomics. The underlying assumption in CETSA and TPP is that binding of a protein to a molecule can change its thermal stability. Therefore, TPP can be used for proteome-wide monitoring of protein stability.¹¹⁷ Apart from drug target engagement analysis, this method enables the analysis of protein stability in different cellular states,^{118,119} monitoring of protein stability in different tissues,¹²⁰ and studies of protein complexes.¹²¹ In addition, a TPP-based method called system-wide identification of enzyme substrates by thermal analysis (SIESTA) was recently devised for studying the effect of PTMs on protein stability.¹²² Very recently, a high throughput (16-fold) version of TPP called the proteome integral solubility alteration (PISA) assay¹²³ has been developed that reduces the amount of starting biomaterial and analysis time as well as the number of missing values.

Combination of these recent proteomics approaches with the unique aspect of protein coronas (i.e., in reducing the complexity and dynamic range of plasma proteins) might help envision a future where changes in protein stability (due to the presence of different proteoforms, conformations or PTMs as well as protein–protein interactions) might be exploited as structural disease biomarkers¹²⁴ in addition to the classic analysis of protein abundances.

■ OUTLOOK

This Perspective has offered insights about the possibility of using nanomedicine, and specifically nano–bio interfaces, to develop point-of-care devices for ex vivo monitoring of the risk and severity of blood clotting in COVID-19 infection, which would greatly help clinicians make appropriate medical decisions to prevent or minimize the damage associated with clotting. In addition, analysis of corona profiles by omics techniques could help the scientific community better understand the mechanisms underlying blood clotting, laying the groundwork for the development of new therapeutics. Obviously, these efforts require integrated functioning among many stakeholders,¹²⁶ including researchers with expertise in

biological sciences, physical sciences, virology, nanomedicine, and medical sciences¹²⁷ as well as funding agencies and device/drug developers.

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Notes

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