

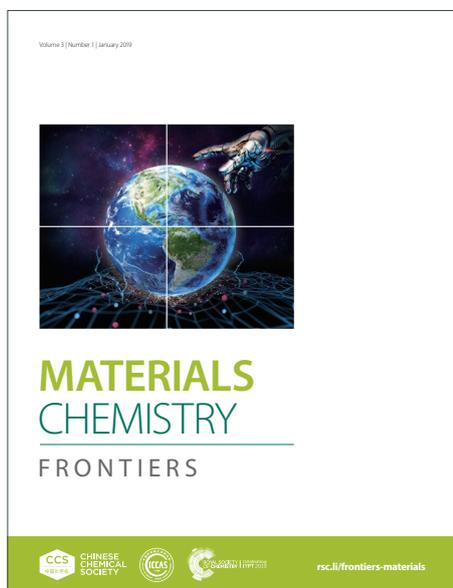
# MATERIALS CHEMISTRY

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# Biosafety Materials: An Emerging New Research Direction of Materials Science from COVID-19 Outbreak

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## Abstract

The Corona Virus Disease 2019 (COVID-19) pandemic is a serious biosafety event that poses a severe impact on the global society and economy. The importance of biosafety is once again being valued in the whole world. After the outbreak of COVID-19, governments of most countries are encouraged to speed up the development of biosafety, which places higher requirements on researchers in biosafety and relevant fields. Many problems were exposed in the outbreak of COVID-19 including no effective drugs and vaccines available, difficulty in fast or real-time virus detection, insufficient protective equipment and shortage of transportation equipment for infectious patients. To a large extent, these biosafety problems are greatly due to the limited biosafety related research on materials science. Currently, tremendous efforts on the research in materials science around the world have provided a wide variety of materials with peculiar properties to solve biosafety problems. This review tried to give a perspective on how the development of novel materials could help scientists tackling the challenges in biosafety. Considering the importance of materials science in biosafety field, it is urgent for us to officially propose the brand-new concept of “biosafety materials”, which could be a future scientific discipline that utilizes materials



science and theory together to produce materials as well as related products, equipment to solve biosafety problems. This paper here aims to call for the world-wide attention on the new discipline of biosafety materials as well as the active cooperation between materials scientists and the biosafety-related scientists to push forward its development

## 1. Biosafety - back into the spotlight once again

### 1.1 The outbreak of COVID-19 – reconsideration the importance of biosafety

The rapid development of modern biotechnology and the process of economic globalization have brought with a series of biosafety issues, such as the escape of genetically modified organisms, invasion of alien species, as well as the global outbreak of infectious diseases, *etc.*, which poses a huge threat to the species diversity, ecological environment and human society.<sup>1</sup> Until now, the continued deterioration of the COVID-19 pandemic has severely affected the society and economic development around the world.<sup>2-4</sup> In response to the unprecedented challenges from COVID-19 pandemic, the Chinese government decided immediately to include biosafety into its national security system, which brings the concept of “biosafety” into the spotlight again.<sup>5</sup>

The anthrax envelope bioterrorism attack resulted in several infected people after the event of September 11, 2001.<sup>6,7</sup> In 2014, the occurrence of laboratory safety accidents such as the infection of *Bacillus anthracis* and H5N1 influenza virus were mainly due to the low biosafety awareness.<sup>8-10</sup> Multiple consecutive reports of biosafety events attracted the international attention to biosafety issues. Currently, the outbreak of COVID-19 brings biosafety to the forefront of people’s consciousness, which fully strengthens the necessity of related scientific research in the field of biosafety.<sup>11,12</sup> After the outbreak of COVID-19, most national governments are encouraged to speed up the development of biosafety, which puts forward higher requirements for researchers in biosafety and relevant fields.<sup>13</sup> Therefore, it is necessary to enhance our awareness toward biosafety and implement dynamic real-time detection, identification and



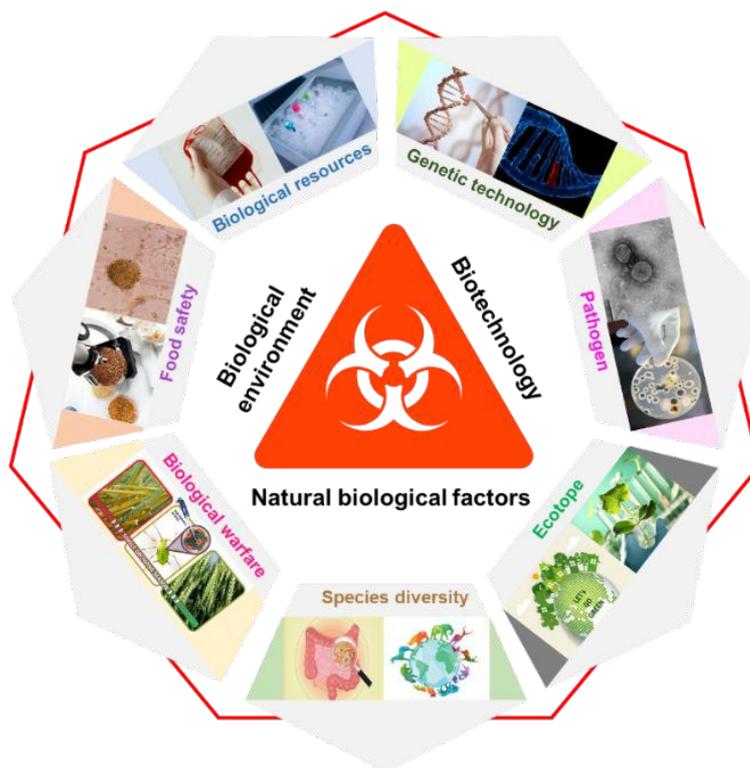
tracking of biosafety issues such as environmental disasters and biological threats, and to carry out surveillance and control measures immediately.

## 1.2 The research areas of biosafety

The concept of biosafety has already been defined by the scientific community.<sup>14-16</sup> It refers to the prevention and control of hazards caused by biological risk factors such as biotechnology and pathogen. However, there are two easily confusing concepts: biosafety and biosecurity.<sup>17</sup> Biosafety is the prevention of large-scale loss of biological integrity, focusing both on ecology and human health. It emphasizes passive prevention and control of unintentionally induced biotechnology and microbial biological hazards.<sup>18</sup> While biosecurity refers to proactive measures to prevent intentional biological hazards, and often refers to areas such as national security, biological weapon control, epidemic prevention management, food security, and species invasion.<sup>19</sup> Although the two words biosafety and biosecurity have some subtle differences in meaning, without special emphasis, biosafety is generally used. Therefore, in this paper, the term “biosafety” is used in all subsequent sections.

The research purpose of biosafety is taking effective measures against these biological threats. As summarized in Figure 1, research areas of biosafety cover a wide range of topics, including controlling infectious diseases, monitoring biotechnology risks, ensuring laboratory biological safety, protecting biological resources, preventing invasion of alien species, defending against biological warfare and biological terrorist attacks, *etc.*.





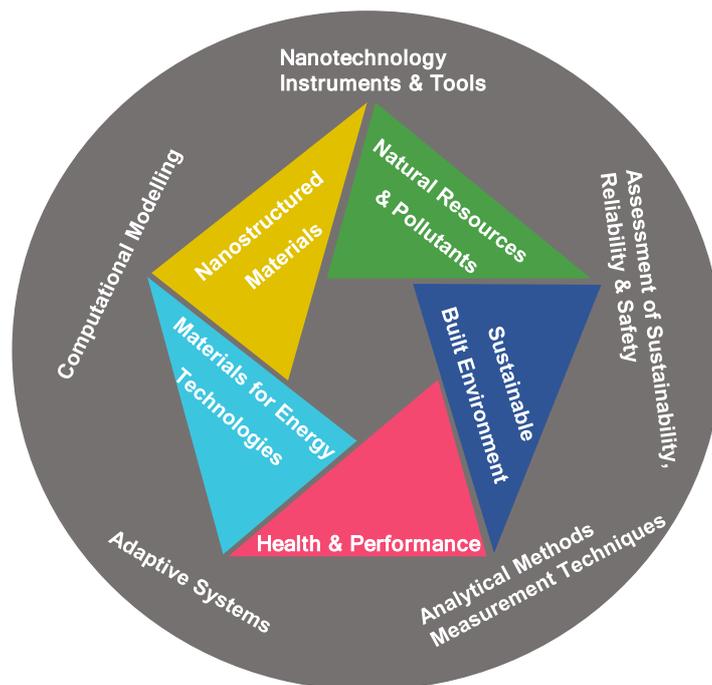
**Figure 1.** Research areas of biosafety

## 2. The proposal of biosafety materials science

### 2.1 Definition of biosafety materials science

Materials science has shaped the world around us ever since the dawn of civilization. A variety of game changing materials with peculiar properties have been developed to achieve unmet needs.<sup>20-24</sup> The Swiss Federal Laboratories for Materials Testing and Research (EMPA) briefly categorizes materials as: nanostructured materials, materials for energy technology, materials for natural resources and pollutants, materials for health and performance, and materials for sustainable built environment (Figure 2).<sup>25</sup> Over the past few decades, we have witnessed a revolution in materials science, and how it push forward the development of technology.



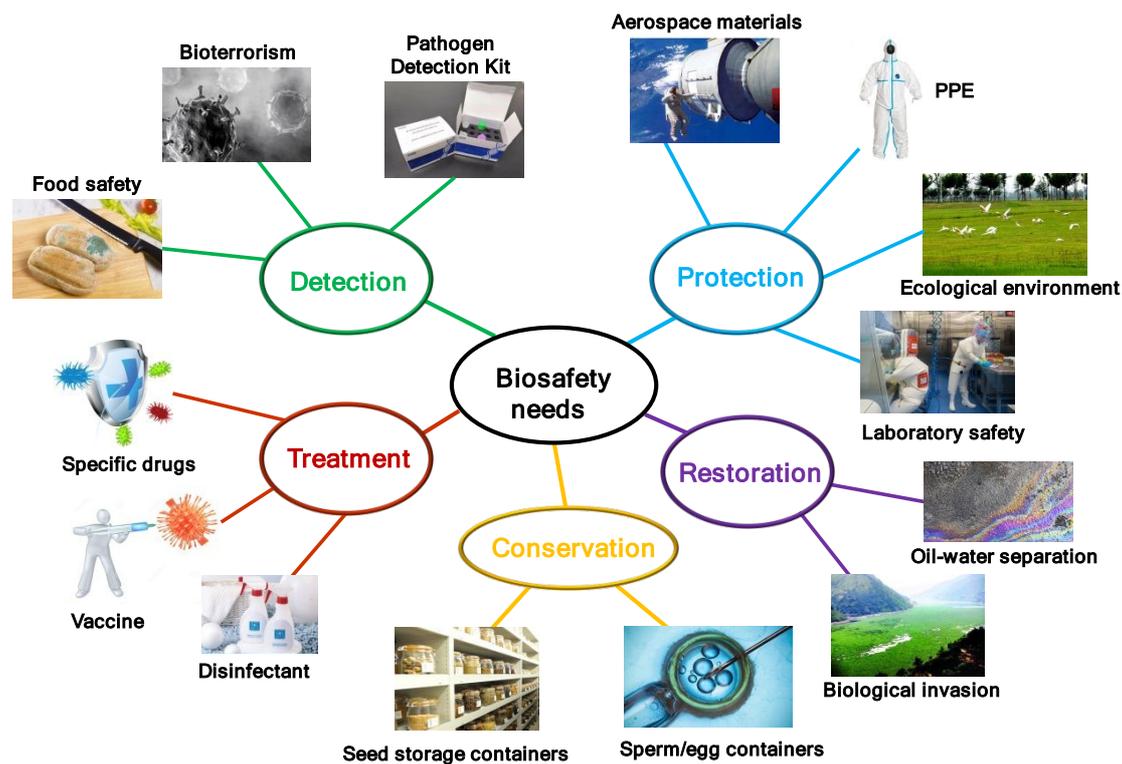


**Figure 2.** Classification of materials

At this stage, the entire world is still in shortage of effective materials in response to biosafety threats. In the COVID-19 pandemic, the lack of biological safety personal protection equipment (PPE) such as masks, protective clothing, goggles, and negative pressure ambulance, *etc.*, resulted in a failure for the protection of a number of medical professionals.<sup>26-30</sup> Moreover, insufficient sensitive and fast virus detection kits greatly impeded patients from being diagnosed, and resulted in rapid spread of this pandemic.<sup>31, 32</sup> Hence, the marriage of biosafety with materials science will greatly help resolving the existing challenges in biosafety fields, including detection and disinfection of pathogen, viral vaccines, PPE and biological species preservation (Figure 3).<sup>33-38</sup> Considering the development of materials science, the rational application of new materials can greatly help us solving the biosafety problems. Here, we therefore tried to give a perspective on how the development of novel materials could help scientists tackling the challenges in biosafety. It is urgent and timely for us to officially propose the brand-new concept of “biosafety materials”, which could be a future scientific discipline that utilizes material science and theory together to produce materials as well



as related products, equipment to solve biosafety problems. To the best of our knowledge, the concept of “biosafety materials” as well as “biosafety material science” has never been officially proposed yet, therefore, the development of the biosafety materials may still lack basic guiding ideology. As a result, researchers in materials science may not realize the problems and understand the challenges in biosafety, while researchers in biosafety may have no idea how materials can be applied to solve the biosafety problems they faced. Overall, it is of great significance and timely to put forward the brand-new concept of biosafety materials. By clarifying the concepts and the role as well as the importance of biosafety materials, relevant researchers can work together to design advanced biosafety prevention and control materials, which will eventually improve our ability to tackle biosafety-related problems.



**Figure 3.** Biosafety needs and their corresponding biosafety materials



## 2.2 Current challenges in the field of biosafety

To address biosafety-related issues with materials, the current challenges in the field need to be specified.<sup>39-41</sup> For example, the current mainstream pathogen detection method still largely relies on polymerase chain reaction (PCR), which is time-consuming and laborious. Point-of-Care Testing (POCT) devices are highly desired due to their convenience.<sup>42-45</sup> Luminescent materials provided a powerful tool to achieve sensitive and timely detection.<sup>46-48</sup> In Table 1, we briefly summarized the major challenges in biosafety from the perspective of materials science.

**Table 1.** Current challenges in biosafety

Biosafety Field	Category	Challenges
Pathogen Detection	Cultivation and identification	Detection process is time consuming
	Pathology instrumentation	
	Immunological detection	Low sensitivity, specificity
	Molecular biological detection	False negative results
Pathogen Disinfection	Physical disinfection (ultraviolet rays, high temperature, ionizing radiation, etc.)	Low efficiency
	Chemical disinfection (Alcohols, chlorine-containing disinfectants, phenols, quaternary ammonium salts, iodine-containing disinfectants)	Scented
		Hazardous chemical residues
		Drug-resistant
		Corrosive
		Personnel must leave the field during disinfection
Treatment drugs	Anti-bacteria drugs	Drug resistance
	Anti-viral drugs	The virus has no cell structure, few targets, and drug development is difficult
Vaccines	Inactivated vaccine	Slow R & D
	Live attenuated vaccine	Invalid after virus mutation
	Subunit vaccine	Safety issues
	Genetic engineering vaccine	Lack of good adjuvant
Protective equipment	Protective Suit	Poor anti-toxicity, breathability and heat dissipation
	Mask	
	Gloves	Low protection against aerosols
		Unable to be reused



Protection of biological resources	Protect plant resources	Extraction is easily contaminated
	Protect blood resources	Plant seeds are vulnerable to environmental restrictions
	Protection of human genetic resources	
Detection of biological invasion	Natural intrusion protection	Difficult to detect at the initial introduction stage
	Unintentional introduction of protection	Gene drift is prone to occur after invasion
	Intentional introduction of protection	
Protection of Ecosystem	Control of environmental pollution	Low oil-water classification efficiency
	Improving climate warming	Difficulty in detecting radiation species
	Protecting biodiversity	Low harmful gas adsorption rate
		Low removal rate of heavy metal pollution
Biochemical weapon	Biological weapon protection	Investigation difficulties
	Biological warfare agent protection	Large-scale Popular
	Chemical weapon protection	Easily misdiagnosed
	Bioterrorism protection	Ineffective vaccine
Genetic technology	Optimizing gmos	Gene drift
	Suppression of gene mutations	Negative changes in resistance
	Reduce or increase resistance	Genetic mutation
	Pharmaceutical biotechnology	Genes affecting non-target organisms
Food biosafety	Detection of carcinogens	Food shelf-life is too short
	Screening for contaminants	Easy to be contaminated by microorganisms
	Food preservation	
	Pesticide drug testing	Hard to detect carcinogens
Aerospace biosafety	Control of body environment	Cosmic Radiation
	Personal protection	Physical and Chemical Corrosion
	Aerospace lifesaving	Mechanical wear

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### 2.3 “Biomaterials” and “biomedical materials”

The term “biosafety materials” is also different from “**biomaterials**” and “**biomedical materials**”. A biomaterial is any substance that has been engineered to interact with biological systems for a medical purpose - either a therapeutic (treat, augment, repair or replace a tissue function of the body) or a diagnostic one.<sup>49-52</sup> As a science, biomaterials is about fifty years old. The study of biomaterials is called



biomaterials science or biomaterials engineering. It has experienced steady and strong growth over its history, with many companies investing large amounts of money into the development of new products. Biomaterials science encompasses elements of medicine, biology, chemistry, tissue engineering and materials science.<sup>53-55</sup> Biomedical materials are biomaterials that are manufactured or processed to be suitable for use as medical devices (or components thereof) and that are usually intended to be in long-term contact with biological materials.<sup>54, 56</sup> However, biosafety materials emphasize the use of materials for the prevention and control of biological safety issues. Taken together, Biosafety materials is different from both “biomaterials” and “biomedical materials”.

#### 2.4 “Biosafety materials” and “biosafety of materials”

The biological safety of materials is mentioned frequently when people study the biomaterials.<sup>57-59</sup> Herein, considering that the concepts of “biosafety materials” and “biosafety of materials” are confusing, a comprehensive comparison between them was provided here. “Biosafety materials” in essence can be “materials for biosafety”, which denotes the application of materials and related theory to tackle with biological safety issues. However, the later “biosafety of materials” denotes whether the materials are safe to biological systems, how the toxicity comes and to which extent there is the toxicity. In general, the “biosafety” in the term “biosafety materials” refers to biological safety, that is to say, the biological parameters such as virus and bacterial may cause safety issues to the environment and human body; however, the “biosafety” in the term “biosafety of materials” refers to the safety of certain materials to bio-organisms. The two biosafety are the same in written word, but they are the terms used in different research fields from different background, and the meanings and connotations vary greatly.

Taking nanomaterials as an example, when the concept of nanomaterials was just proposed, most scientists were attracted by the fascinating properties the nanomaterials



brought with, few people realized and considered their safety issues. In 2001, Prof. Yuliang Zhao from The National Center for Nanoscience and Technology in China firstly proposed the concept “biosafety of nanomaterials”, it is also termed as nanotoxicity (nano-safety).<sup>60</sup> Since then, the importance of negative side (such as toxicity) for nanomaterials has been realized by scientists around the world. They further established CAS (Chinese Academy of Sciences) Key Laboratory for Biological Effects of Nanomaterials and Nanosafety in China. However, biosafety nanomaterials refer to the use of nanotechnology and nanomaterials to address biosafety issues, which is significantly different from the concept of nanotoxicity as well as biosafety of nanomaterials. To better understand this, those two terms of “biosafety of materials” and “biosafety materials” are detailed compared in Table 2.

**Table 2.** Biosafety materials & biosafety of materials

Items	Biosafety materials	Biosafety of materials
Definition	Develop materials for prevention and control biological safety issues	Evaluate the side effect and toxicity of materials
Research content	Design and develop new materials for biosafety issues; evaluate their abilities for prevention and control of the biological threat.	Study the toxicity and toxicology of materials to biological species.
Research aim	Protect the health of human body and other species Conserve the biodiversity Protect the ecological environment Prevention and control other biological issues	Determine whether there is any toxicity of materials Understand to what extent the toxicity of materials is and how the toxicity comes Determine the possible acceptable dosage of materials
Research direction	Find the most efficient, the cheapest and the best materials to solve the biosafety issues	Reduce the toxicity of materials to human body.

### 3. State-of-the-Art of biosafety materials

Although the concept of “biosafety material science” has not been officially proposed yet till far, we still could find a number of studies related to biosafety



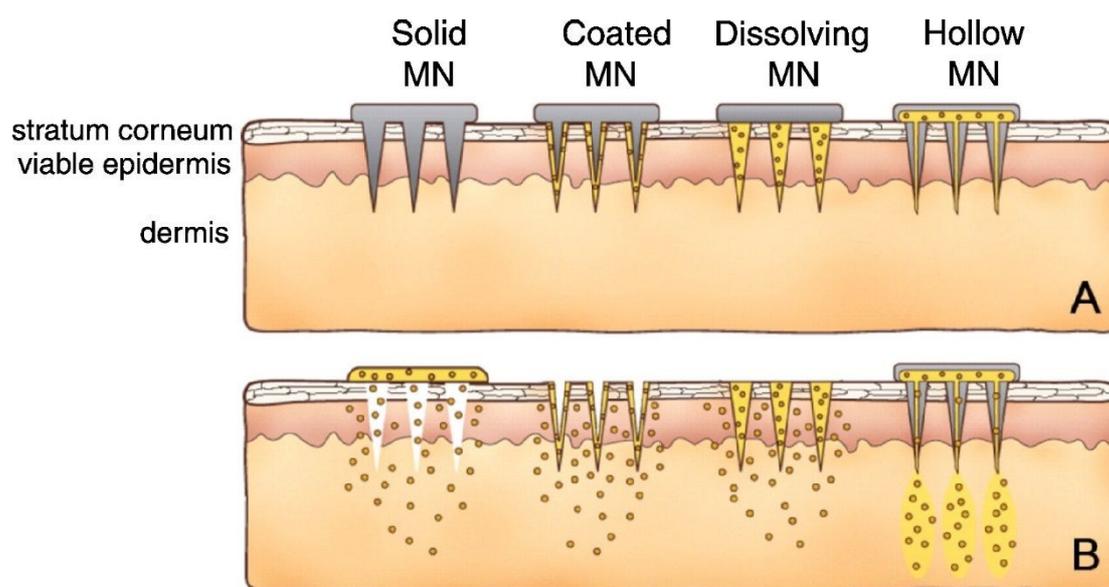
materials have been carried out, including pathogen detection,<sup>61-63</sup> virus detection,<sup>64-68</sup> prevention and control of infectious diseases,<sup>69-71</sup> PPE,<sup>72-75</sup> preservation of biological and human resources,<sup>76-79</sup> biological invasion monitoring,<sup>80-82</sup> biological weapons and biological terrorist defense,<sup>83-87</sup> *etc.*. Herein, the state-of-the-art biosafety materials are discussed in depth, which provides a comprehensive understanding for researchers in the related field and could help one to push forward this concept in the newly emerging field.

### 3.1 Biosafety materials for viral vaccines

The long battle history between virus and human has proven that vaccination is the best solution to completely contain the spread of virus.<sup>88-90</sup> It effectively prevents disease through boosting the immune system against a pathogen. Since there are safety concerns on viral delivery system, several biosafety materials have been extensively investigated for *in vivo* delivery and controlled release of viral vaccines including liposomes, polymers, cationic proteins and biological membranes.<sup>91, 92</sup> Viral vaccines can be delivered in the form of DNA, mRNA or protein,<sup>93</sup> all of which can be easily enzymatically degraded when enter the blood circulation.<sup>94, 95</sup> Take SARS-CoV-2 for example, it contains 1273 amino acids, with a molecular weight of about 140 kDa. The DNA encoding SARS-CoV-2 would be more than 3800 bp.<sup>96</sup> To protect the vaccine in circulation and help them be endocytosed into the cells, delivery vehicles are required. Moderna utilizes ionizable liposomes to carry negatively charged mRNA for the SARS-CoV-2 spike protein.<sup>97, 98</sup> The phase I clinical trial is underway in Seattle, (NCT04283461, USA.). Moreover, research shows that polymers such as low-molecular-weight polyethyleneimine (PEI) modified with fatty chains and poly ( $\beta$ -amino) esters (PABEs) can be designed to deliver DNA and mRNA.<sup>92, 99</sup> In addition, protamine, as a natural cationic protein, can form complexes with negatively charged nucleic acids, thereby being utilized to deliver mRNA-based therapeutics and stimulate immune response.<sup>92</sup> Furthermore, biological membranes such as red blood cell membranes and extracellular vesicles including exosomes, apoptotic bodies and



microvesicles can be isolated and utilized for delivery of biomolecule-based vaccines.<sup>100, 101</sup> Recently, microneedle patch, as a novel drug delivery system, has attracted extensive scientific interests due to its excellent property such as painless penetration, excellent therapeutic efficacy. It provides a highly efficient transdermal delivery system to create sophisticated devices with superior nature for biomedical applications. Gambotto's group in University of Pittsburgh developed SARS-CoV-2 vaccine based on microneedle arrays (Figure 4).<sup>102</sup> Compared to the traditional subcutaneous needle injection, MNA SARS-CoV-2 subunit vaccines elicited strong and long-lasting antigen-specific antibody responses. In summary, biosafety materials are of great importance in the development of biomolecule-based therapeutics and are already used to combat viral infection.



**Figure 4.** Biosafety materials based on microneedle patch for SARS-CoV-2 vaccine delivery (reproduced with permission from Kim *et al.*<sup>102</sup>) (A) Solid MNs pierce through the outer layers of the skin, leaving open space. (B) Vaccine is diffuse into the skin through opened pores.



## 3.2 Biosafety materials for pathogen detection

### 3.2.1 Biosafety materials for viral detection

Since the development of vaccines and drug usually takes as long as several years, which means there is possibly no effective way to protect against infectious pathogenic microorganisms at the early stage of infectious disease outbreaks.<sup>103</sup> Hence, early detection of the virus turns out to be the key to combating the spread of infectious disease. This is because the information from tests helps governments make public health decisions about measures to control and prevention of the outbreak. Reverse transcriptase polymerase chain reaction (RT-PCR) has been widely used as a gold standard for virus detection. Although it can provide a reliable result, the process for detection is laborious and time-consuming. Normally, it can take several days or up to even one week for people to obtain results on an exceptional circumstance, which could make one lose the best timing to control the disease outbreak. Rapid virus detection system such as POCT, with high sensitivity and selectivity are highly desired in the clinic. Emerging materials with peculiar properties provide new options to meet this unmet demand.

Microfluidic is a revolutionary technology that manipulate small amounts of fluidics ( $10^{-9}$ - $10^{-18}$ L), thereby becoming powerful in viral detection. Yeh *et al.* reported a portable and high-throughput microfluidic VIRRION platform containing carbon nanotube arrays.<sup>104</sup> VIRRION not only effectively captured different viruses by size, but also performed real-time nondestructive identification of virus using surface-enhanced Raman spectroscopy (SERS) coupled to a machine learning and database. The research team validated this device using different subtypes of avian influenza A viruses and human samples with respiratory infections, reporting the successful enrichment of rhinovirus, influenza virus and parainfluenza viruses. This device is also reported to maintain stoichiometric viral proportions when samples contain more than one type of virus, suggesting it could also be functional in cases where coinfection has occurred. The processing time (including viral enrichment as well as detection) took only a few minutes with a 70-fold enrichment enhancement. The sensitivity of this

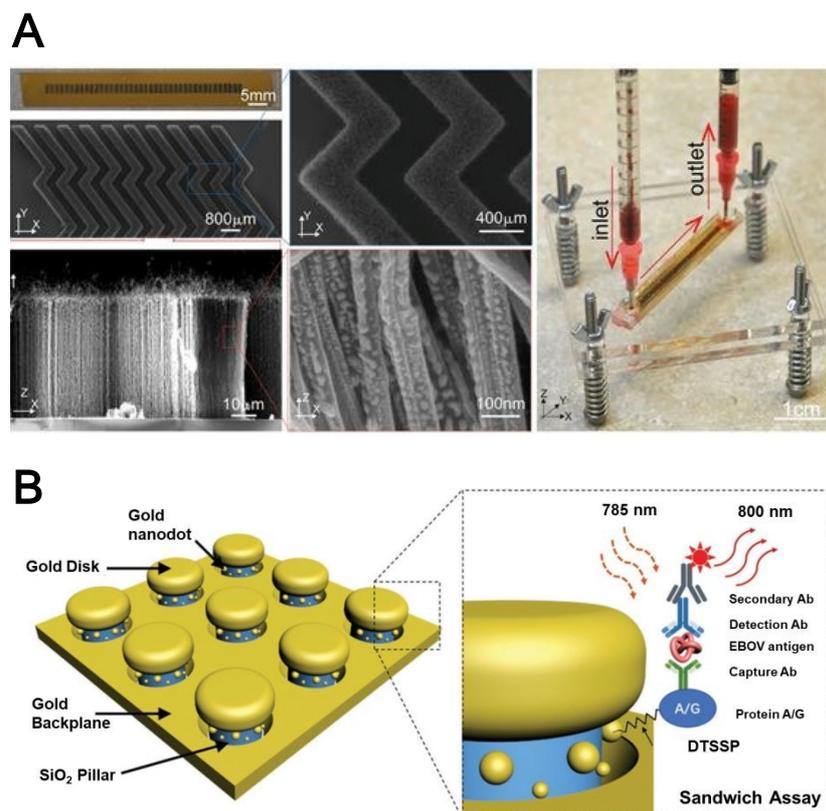


system can reach as little as  $10^2$  EID<sub>50</sub>/mL, with a virus specificity of 90%, indicating the potential to realize POCT. Furthermore, Sun *et al.* designed a point-of-care microfluid system integrated with a smartphone for live virus detection. The detection limit is comparable to the traditional RT-PCR, with the result achieved in 30 minutes.<sup>105</sup> Hence, microfluid technology endows the detection system with appealing versatility and reliability, exhibiting distinct advantage over traditional RT-PCR.

The outbreak of the Ebola virus (EBOV) in West Africa underscored the need to develop highly sensitive tests to diagnose as early as possible. Chou *et al.* developed a 3D plasma nanoantenna measurement sensor as an on-chip immunoassay platform for ultra-sensitive detection of EBOV antigen (Figure 5B).<sup>106</sup> Compared with the flat gold substrate, the EBOV sensor exhibited a significant increase in fluorescence intensity. Nano-antenna-based biosensor could detect EBOV soluble glycoprotein at a concentration as low as 220 fg.mL<sup>-1</sup>. The sensitivity of this biosensor is 240,000 times higher than existing FDA (Food and Drug Administration)-recommended immunoassay-based tests. This sensor can be further adapted to a universal biosensing platform for other viruses. Zheng *et al.* utilized carbon nanotubes to develop a portable device that can selectively capture virus through their size.<sup>107</sup> This carbon nanotube assay can selectively capture and aggregate viruses in diluted samples based on the size of the virus, thus increasing the detection threshold of the virus by a factor of 100. During the whole isolation process, no antibody is required for detection, which simplifies the operation for viral detection.

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**Figure 5.** Biosafety materials for virus capture and detection. (A) High-throughput microfluidic VIRRION platform containing carbon nanotube arrays for influenza virus capture and identification. (B) Schematic illustration of 3D plasmonic nanoantenna array for EBOV sensor. Adapted from ref. Chou *et al.*

Nanoenzymes, as functional nanomaterials with enzyme-like characteristics, have gained tremendous attention in the biosensing system.<sup>108, 109</sup> For example, nanoenzymes demonstrated remarkable sensitivity and specificity in detecting avian influenza A (H5N1) virus. Ahmed *et. al.* utilized Au NP as peroxidase to amplify the signal for avian influenza A virus detection (Figure 6A).<sup>110</sup> This dual enhanced colorimetric immunosensor enabled the detection of H5N1 with a limit of detection (LOD) as low as 1.11 pg/mL, suggesting that it was more sensitive than the ELISA or bioassays based on plasmonic. It has been further applied to detect other avian influenza A viruses such as H4N6 and H9N2. In addition, Yan's group developed a Fe<sub>3</sub>O<sub>4</sub> magnetic nanoparticles (MNP) based nanoenzyme-strip for EBOV detection which is 100-fold more sensitive than the standard strip method, thereby providing a valuable simple screening tool for diagnosis of various pathogens (Figure 6B).<sup>111</sup>



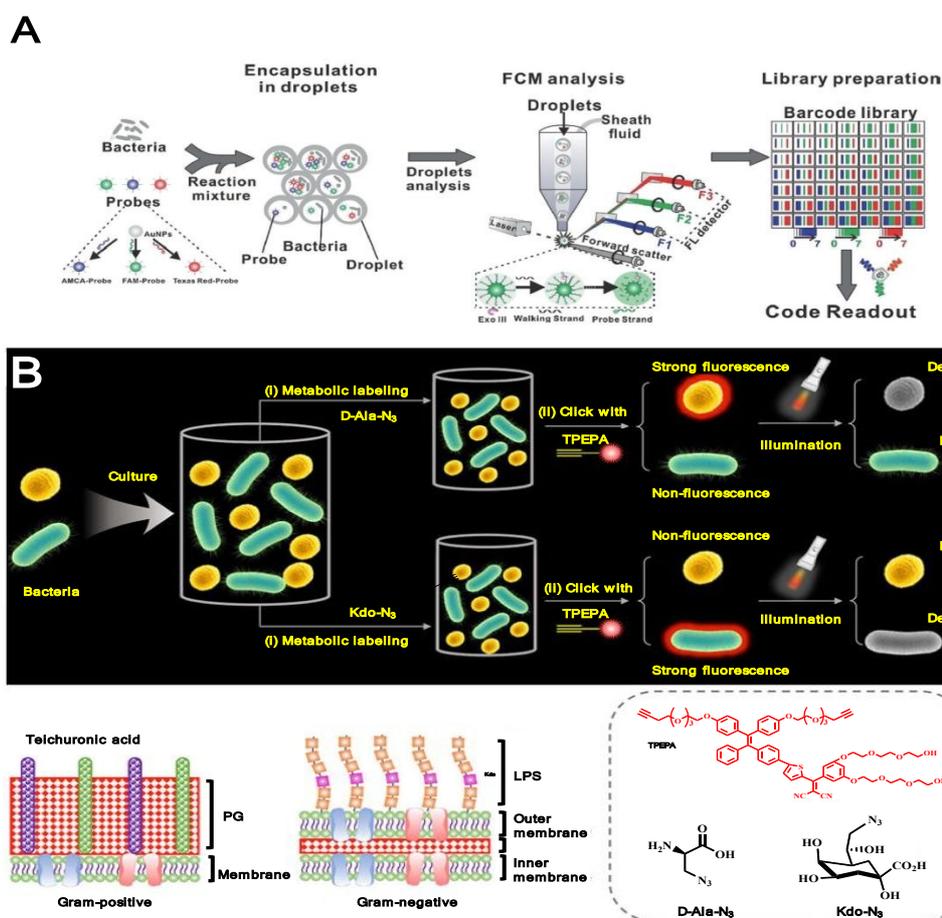


highly sensitive detection of bacteria (1 CFU/ml), exhibiting a promising manner for bacteria detection.

Traditional fluorescent probes have the effect of aggregation-induced quenching (ACQ), and complex physiological environments can reduce the selectivity and sensitivity of fluorescent probes.<sup>115, 116</sup> In contrast, molecules with aggregation-induced emission (AIE) effect can overcome the shortcomings of traditional fluorescent molecules, and no complicated washing steps are required due to their property of low fluorescent background.<sup>117, 118</sup> These advantages of AIE molecules endow the sensitivity and reliability to the detection system.<sup>119-121</sup> Liu *et al.* designed a bioorthogonal fluorescence turn-on probe TPEPA for discrimination and precise ablation of bacterial pathogens.<sup>122</sup> TPEPA (tetraphenylene polyethylene glycol AIEgen) is a kind of AIE photosensitizer with good water solubility, and the alkynyl group can be linked to the azide group *via* the click reaction (Figure 7B). Taking advantage of the difference in bacterial structures, TPEPA can discriminate pathogens *via* selective imaging of metabolically decorated Gram-negative bacteria with Kdo-N<sub>3</sub> and Gram-positive bacteria with D-Ala-N<sub>3</sub>, respectively, thus achieving the selective detection and killing of bacteria *in situ*. The use of fluorescent properties of organic materials solves the problems of difficulty in accurately identifying pathogens in a short time.<sup>123-</sup>

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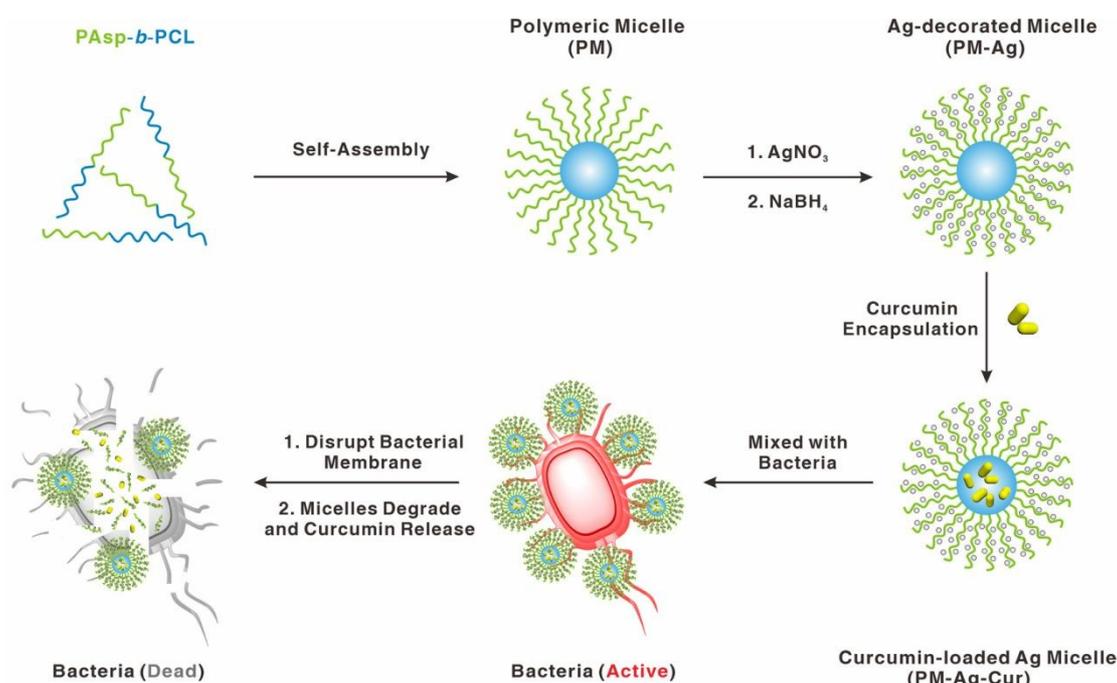
**Figure 7.** Biosafety materials for bacteria detection. (A) Schematic of SDwalker-Drop platform for the super-multiplex bacterial phenotype analysis. (B) Schematic illustration of AIE material for discrimination and precise ablation of bacterial pathogens. Adapted from ref. Liu *et al.*

### 3.3 Biosafety materials for disinfection

The wide use of disinfection is beneficial in preventing infectious disease and thus results in a public health benefit. It relies on physical or chemical methods to eliminate pathogens that stay on different transmission vehicles, thereby cutting off the transmission route to prevent and control the spreading of infection. The various chemical compounds such as alcohol, iodine-containing disinfectants, chlorine-containing disinfectants, peroxides, phenols, and quaternary ammonium salts have been widely used as disinfectant. However, these compounds suffered from multiple drawbacks such as harmfulness and corrosive nature



Nanomaterials exhibit antimicrobial effect owing to their high surface-area-to-volume ratio and unique physical and chemical properties. Particularly, tremendous attention have been paid to Ag NPs due to the practical applications in our daily life, They have been widely used in different sectors such as silver-based air/water filters, textile, animal husbandry, biomedical and food packaging *etc.*<sup>127</sup> Huang *et al.* designed a novel polymeric micelle for simultaneously decorating of Ag NPs and encapsulating of curcumin as a combination strategy to improve the antibacterial efficiency (Figure 8).<sup>128</sup> Through rational design, the aggregation of Ag NPs could be avoided, and the solubility of curcumin was improved at the same time. Excellent antibacterial activity toward Gram negative *P.aeruginosa* and Gram positive *S.aureus* has been well demonstrated, thereby proving its potential in disinfection.



**Figure 8.** Biosafety materials based on Ag NPs for disinfection. Schematic illustration for the formation of silver-decorated polymeric micelles encapsulating curcumin simultaneously for enhanced antibacterial activity

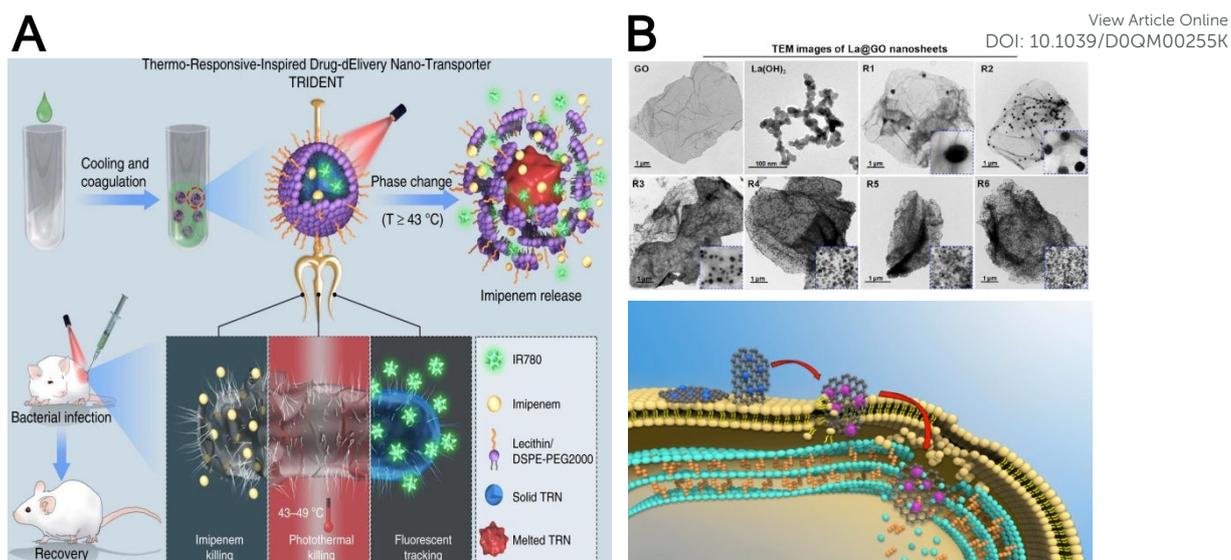


### 3.4 Biosafety materials for treatment drugs

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The discovery of anti-microbial agents revolutionized our strategy to treat bacteria disease in the twentieth century.<sup>129, 130</sup> However, misuse and outright abuse of antibiotics result in multidrug-resistant (MDR) pathogenic bacteria. Nanotechnology-based antibacterial strategies significantly enriched tools to fight against MDR bacteria. As shown in Figure 9A, Liang's group designed a near infrared (NIR) - activated TRIDENT (Thermo-Responsive-Inspired Drug-Delivery Nano-Transporter) for effectively eradicating clinical methicillin-resistant *Staphylococcus aureus*.<sup>131</sup> Imipenem (IMP, a broad-spectrum antibiotics) and IR 780 (a photosensitizer molecule) were encapsulated to fabricate a smart triple-functional thermo responsive nanoparticles. The temperature rises generated by NIR not only melted the nanotransporter *via* a phase change mechanism, but also damaged bacterial membranes to facilitate imipenem permeation, thereby achieving robust bactericidal capabilities *via* chemo-photothermal therapy. The unique properties of carbon-based materials significantly aid people in dealing with antimicrobial resistance. As shown in Figure 9B, Zheng *et al.* designed a La@GO nanocomposite library for the killing of antibiotic-resistant bacteria.<sup>132</sup> Unlike conventional antibiotics or Ag, long-term exposure of La@GO at sub-MIC for 30 days did not induce detectable secondary resistance in *E. coli*. A novel extracellular multitarget invasion (EMTI) mechanism was also proposed to explain the result, which helps scientists to develop a more specific system based on this system. The first antibiotic penicillin was discovered at 1928. After that, numerous lives have been saved, and a variety of antibiotics contributed to the control of the infectious disease. However, there are very few antibiotics under development now, and we are running out of effective antibiotics. Novel materials with versatile properties provided new strategies to treat MDR bacteria and virus, providing a different route to overcome drug resistance.





**Figure 9.** Biosafety materials for combatting MDR bacteria. (A) Schematic illustration of Near infrared (NIR)-activated TRIDENT for antibiotic-resistant bacteria killing. (B) Graphene oxide nanocomposite for preventing the evolution of antimicrobial resistance.

### 3.5 Biosafety materials for PPE

Served as the first defense line in the fight against the virus, the high-performance PPE is crucial for protecting frontline medical professionals as well as the general public.<sup>133, 134</sup> Current PPE suffers from poor light resistance, and no antimicrobial effect is provided. Furthermore, it is difficult for PPE materials to be effectively disinfected under the premise of good preservation.<sup>135, 136</sup> Hence, stable and protective materials with broad antimicrobial spectrum are in high demand.

For stopping the spread of highly infectious diseases, air filtration turns out to be an efficient passive pollution control strategy. Nevertheless, most of the commercial air purifiers solely rely on dense fibrous filter, which can effectively remove particulate matter but lack antibacterial activity. Li *et al.* designed a series of metal-organic frameworks (MOFs) with photocatalytic bactericidal properties to fabricate a nano-fiber membrane.<sup>137</sup> It can effectively produce biocidal reactive oxygen species (ROS) that are driven by sunlight (Figure 10A). Specifically, a zinc-imidazolate MOF (ZIF-8) exhibits almost complete inactivation of *Escherichia coli* (*E. Coli*) (>99.9999%



inactivation efficiency) in saline within 2 h of simulated solar irradiation.<sup>138</sup> This MOFilters provides new insights into the sustainable, self-charging, and adaptive development of protective materials, which represents the next generation PPE. Moreover, polymer material was developed to make face mask protection equipment (Figure 10B). Liu *et al.* designed a novel self-powered electrostatic adsorption face mask (SEA-FM) based on the poly(vinylidene fluoride) electrospun nanofiber film (PVDF-ESNF) and a triboelectric nanogenerator (TENG).<sup>138</sup> Up to 99.2% particulates removal efficiency can be achieved, which is much higher than that of the commercial mask. After the outbreak of COVID-19, the demand for masks has exploded all over the world. However, the disposal of massive number of single-use masks poses a significant environmental threat for society. To ease this problem, reusable and recyclable graphene masks with outstanding superhydrophobic and photothermal performances have been developed by Li *et al.* The high surface temperature of the masks under solar illumination can effectively sterilize the surface viruses. It is believed that more advance materials can be properly applied by scientists to produce multi-functional masks.<sup>135</sup>

Surgical suits are special clothing required by doctors to perform surgical operations. The materials used need to possess protective properties to block viruses and bacteria from invading medical personnel. It should be of sterilization, dust-free and disinfection resistance, but also can be of bacteria isolation, antibacterial and comfort. In this context, a three-layer antiviral surgical suit with non-woven spunbond polypropylene, polyester and microporous PTFE film has been developed.<sup>139</sup> Plasma technology is used to treat the outer layer of spunbond polypropylene. The results showed that the plasma-treated surgical gown had a 99.04% reduction in microbes compared to the non-plasma-treated surgical gown, providing a microbial barrier for medical staff.<sup>140-143</sup>

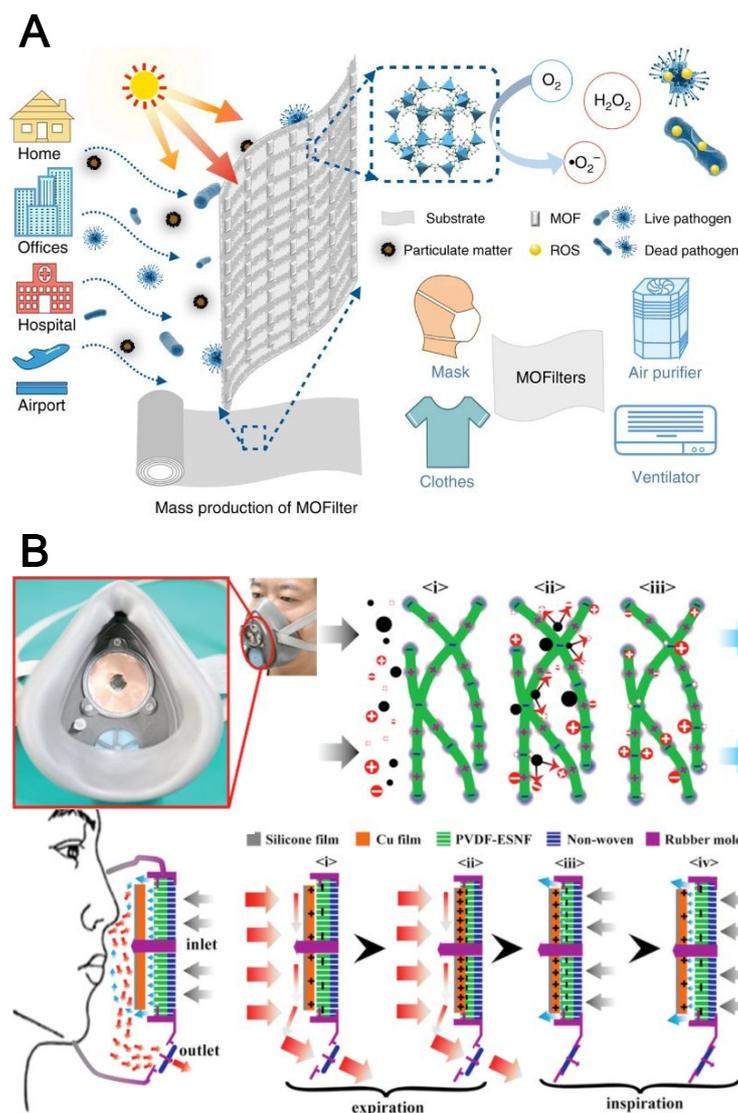
The respirator is a kind of sanitary products, generally refers to worn in the nose and mouth to filter the air entering the nose and mouth, in order to achieve the role of blocking harmful gases, odors, droplets, viruses and other substances. Masks have a

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certain filtering effect on the air entering the lungs. When respiratory infectious diseases are prevalent and when working in a polluted environment such as dust, wearing a mask is necessary to keep people safe.<sup>144, 145</sup> The novel material fabrication technology like 3D printing has been applied to manufacture masks.<sup>146</sup> N95 Filtering Facepiece Respirator was customized designed for medical staff. Comfort and fit are essential while wearing a FER, especially for those medical professionals who need to work a long time to treat patients. The face seal prototypes of masks were prepared with Acrylonitrile Butadiene Styrene (ABS) plastic using 3D printing, which provided improved contact pressure for users.





**Figure 10.** Biosafety materials for PPE with antimicrobial capacity. (A) Schematic illustration of metal-organic framework (MOF)-based filter. (B) Schematic illustration of the filtration mechanism of the polymeric material mask.

### 3.6 Biosafety materials for protection and preservation of biological resources

With economic globalization, environmental pollution and global warming, biodiversity has undergone unprecedented challenges. The preservation of biological resources provides a guarantee for the biodiversity of ecological system. Generally, biological genetic resources mainly include the extraction and protection of animal and plant genetic materials such as biological gene, sperms and eggs.<sup>147-150</sup> The major



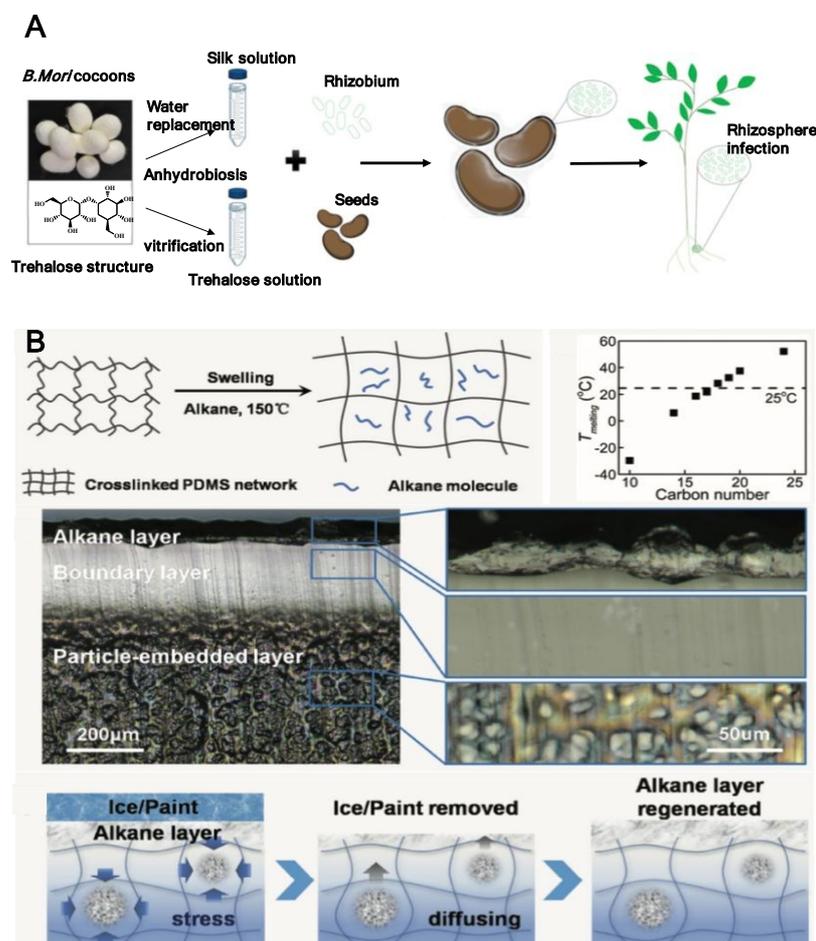
shortcomings for the current protection method are low survival rate of seeds and uncontrollable mutation could happen. Cheng *et al.* discovered that PVP (polyvinylpyrrolidone) and PVPP (polyvinylpolypyrrolidone) could effectively remove multiple phenolic compounds and terpenoids during the process of extracting DNA.<sup>151</sup> Therefore, an appropriate amount of PVP or PVPP to the DNA extraction solution can improve DNA purity, remove polysaccharides, and reduce polyphenol contamination. This is a good example that biosafety materials displayed protective significance on genetic resources. The PVP method now has been accepted as one of the most used DNA extraction techniques, thereby indicating the development of materials does change the technic in protecting biological resources.<sup>152-155</sup>

The protection of plant seeds is also a crucial biosafety issue.<sup>156, 157</sup> Seed enhancement technologies play a pivotal role in supporting food security by enabling the germination of seeds in degraded environments. Marelli *et al.* combined silkworm cocoon S molecules and trehalose to design a new seed coating method.<sup>158</sup> As shown in Figure 11 (A), this formulation is capable of precisely coating seeds with biofertilizers and releasing them in the soil to boost seed germination and mitigate soil salinity. This coated seed yielded plants that grew faster and stronger in the presence of saline soil. Hence, this study opens the door to the application of advanced biosafety materials to precision agriculture, introducing the drug delivery concept to seed protection. Furthermore, polymeric materials have been proven to reduce environmental side effects and improve seed survival, suggesting the importance of composite materials in the protection of biological resources.<sup>159-162</sup>



Cryopreservation is the most classical way to preserve human genetic resources.<sup>163</sup>

The mechanical damage effect of ice crystals is the major problem in cryopreservation. Inspired by the regenerable solid epicuticular wax on land plant leaf surface, Wang *et al.* developed a solid organogel materials with regenerable sacrificial alkane surface (Figure 11B).<sup>164</sup> This type of surface material is demonstrated to be of great practical importance for tackling solid deposition, such as anti-icing, antigraffiti, and antifouling. Compared with the ice adhesion strength of aluminum ( $372.2 + 47.4$  kPa) and PDMS ( $146.3 + 9.5$  kPa), the ice adhesion strength of solid organic gel was reduced to  $68.8 + 10.4$  kPa. The adhesion value remains almost unchanged when the temperature decreased from  $-20$  to  $-70$  °C, indicating its potential for cryopreservation of natural biological resources.



**Figure 11.** Biosafety materials for protection and preservation of biological resources.

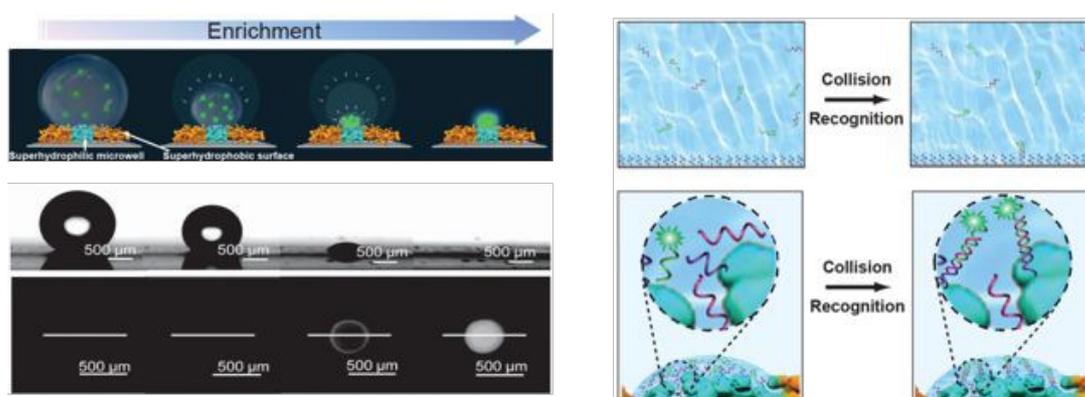
(A) Biosafety materials based on silk fibroin and trehalose for seed coating that can



boost germination and mitigate abiotic stressors. (B) Principle of the solid organogel material to cryopreserve biological resources.

### 3.7 Biosafety materials for prevention of biological invasion

Biological species invasion has been considered as one of the most critical ecological disturbance that threatens native biodiversity.<sup>165-167</sup> In 1996, the global invasive species project was launched. Since then, the biological invasion has been focused on and heavily studied.<sup>168, 169</sup> Biological invasions can be divided into several stages: introduction, escape, population establishment and harm. Except for purposeful introduction, the early detection of other invasion ways is challenging. If the invasion reaches a detectable range, it is hard to be removed. Hence, early detection is crucial to prevent biological invasion. The development of genetic detection technology has facilitated the detection of biological invasions. Wang *et al.*<sup>170</sup> developed a sensitive nucleic-acid sensing platform based on superhydrophilic microwells spotted on a superhydrophobic substrate (Figure 12). The difference of wettability facilitated the conversion of trace analyte between microporous and surrounding substrate into superhydrophilic microporous materials. Due to the condensation enrichment effect, the ultratrace DNA detection was realized, and the detection limit reached  $2.3 \times 10^{-16}$  M. The genome of certain species can be rapidly determined using a gene library, enabling the fast identification of invading species.



**Figure 12.** Biosafety materials for early detection of biological invasion. Ultratrace DNA detection based on superhydrophilic microwells spotted on a superhydrophobic substrate.



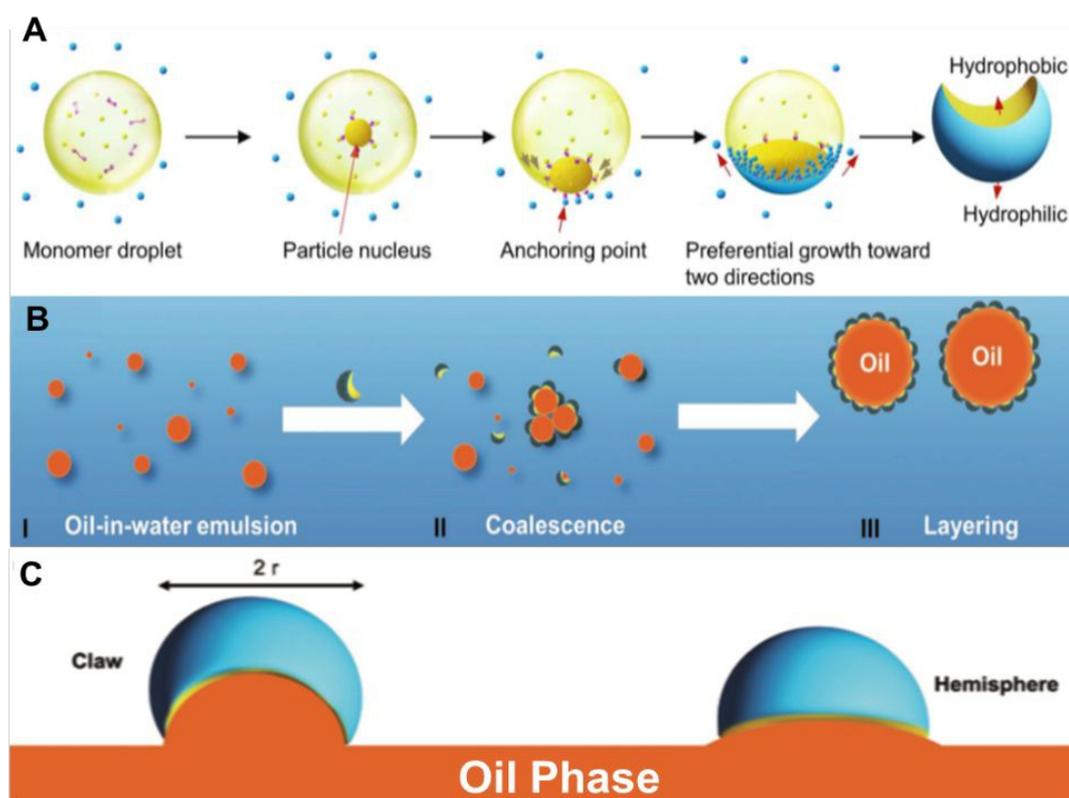
Since invasive alien species have no natural enemy, they can rapidly settle in the new environment and quickly grow into an overlord community, eventually destroying the local ecosystem and inhibiting the growth of other local species. The loss of biodiversity in ecosystems further leads to irreversible consequences, such as the disappearance of forests, pastures degradation, water pollution, *etc.*. Hence, in addition to early detection of biological invasion, it is of great significance to effectively eliminate invaded alien species. Fortunately, biosynthesis of metal nanoparticles provided a more environment friendly approach to fight against invaded alien species. Oscillatoria, as one of the most common cyanobacterial genera known to produce neurotoxins, has negative impacts on the aquatic organisms. To stop the growth of oscillatoria, the Ag-NPs biosynthesized by specific alga exerted outstanding negative impacts on oscillatoria, which significantly alleviated environment burden through green synthesis.<sup>171</sup> Similar biosynthesis strategy has also been found on treating controlling of vector mosquitoes. The plant synthesized AgNPs developed by Rajakumar *et al.* can effectively eliminate mosquitoes, providing an effective way to control mosquito-borne disease.<sup>172</sup> Hence, the development of materials science provided bio-friendly alternatives for prevention of biological invasion, enriching our methods to deal with difficulty environmental related issue.

### 3.8 Biosafety materials for protection of ecological environment

The ecological environment is a prerequisite for ensuring species diversity. The 2010 Deepwater Horizon oil spill in the Gulf of Mexico has been regarded as the worst environmental disaster in the United States, which release about 4.9 million barrels of crude oil, and brought a huge impact on ecological system. The efficient and cost-effective separation manner for spilled oil is in great need. Janus particles are colloidal particles with more than a single type of surface chemistry or composition, which provided a proper system for oil separation. Song *et al.* developed magnetic Janus particles with a convex hydrophilic surface/concave oleophilic surface, realizing the rapid and efficient separation of microscaled tiny oil droplets from water (Figure 13).<sup>173</sup>



Ren *et al.*<sup>174</sup> developed a phase selective organic gelling agent, which not only shows the ability to selectively condense oil from oily water, but also can easily separate colloidal oil and water from the human body. This powder gelator was empowered with remarkable ability to attain rapid gelation of crude oils of widely ranging viscosities within minutes at room temperature.



**Figure 13.** Biosafety materials for separating spilled oil from water. (A) Schematic illustration of the principle of hydrophilic/oleophilic magnetic Janus particles. (B) Schematic of the separation of tiny oil droplets by Janus particles. (C) Schematic of the two different types of Janus particle.

Heavy metals are harmful and toxic pollutants that are difficult to degrade. They will not only cause degradation of the soil quality, but also enter the human body through direct contact or the food chain. In recent years, scientists have gradually realized that heavy metals have a massive impact on the microbial in soil, which



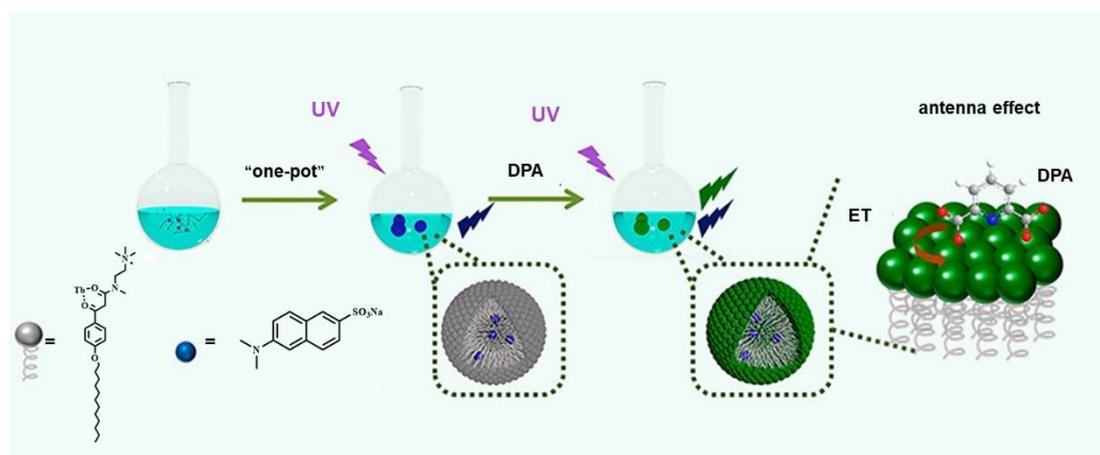
eventually influence soil microbial activity, microbial community, and soil enzyme activity. To ameliorate this condition, the scientists developed novel materials to remove heavy metal pollution on the soil ecosystem.<sup>175</sup> Lian *et al.* developed a simple and economical path to prepare mercapto-functionalized nanosilica.<sup>176</sup> Nanosilica, which has excellent compatibility with soils, is chosen as the matrix. This biosafety material was able to efficiently remediate Pb/Cd contaminated soils, exhibiting a high immobilization efficiency of 99.12% and 98.23% towards Pb and Cd, respectively.<sup>176</sup> In addition to silica, carbon based materials have also been selected to deal with this problem due to their excellent absorption capacity, providing versatile methods to protect the ecological environment.<sup>177, 178</sup>

### 3.9 Biosafety materials for protection against bioterrorism

Bioterrorist attack has been regarded as the most important biosecurity threats in modern society. Monitoring as well as medical and health response is the two most critical measures for preventing bioterrorism. The biological warfare agents for terrorists to use for attack includes *Bacillus anthracis*, *Brucella*, *Rickettsia prowazekii*, *Yersinia pestis*, *etc.* Those agents are mainly spread through aerosols, food or water sources. Bioterrorism possesses the characteristics of strong infectivity, strong concealment, simple production process, and a large range of the impact. Anthrax spores have been selected as an ideal biological weapons since they are highly lethal to human beings and animals.<sup>179-181</sup> Rapid detection method for anthrax spores is in great demand. As shown in Figure 14, Tang *et al.* designed a rare earth functionalized micelle nanoprobe for ratiometric fluorescence detection of anthrax spores biomarker, pyridinedioic acid (DPA).<sup>182</sup> The detection strategy was ascribed to Tb<sup>3+</sup> ions in lanthanide functionalized micelle, which can be sensitized to emit the intrinsic luminescence upon addition of DPA due to the presence of energy transfer when DPA chromophore coordinated with Tb<sup>3+</sup> ion. This nanoprobe can detect DPA within a linear range of 0-7  $\mu\text{M}$  in a few seconds, and the detection limit is up to 54 nM. It is believed



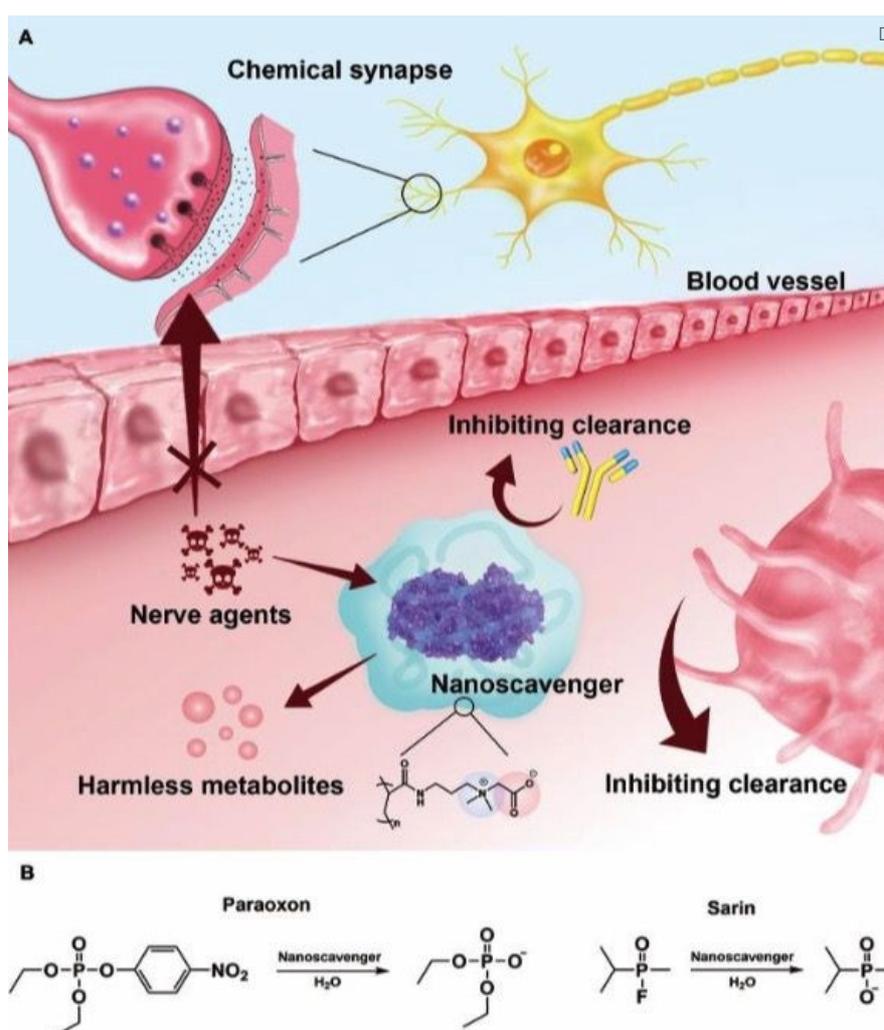
that the defense of biological weapons can be strengthened through incorporating novel materials with peculiar properties to the detection system.



**Figure 14.** Biosafety materials based on a ratiometric fluorescence lanthanide functionalized micelle for anthrax spores biomarker detection. Schematic illustration of “One-pot” self-assembly of terbium functionalized micelle in  $H_2O$  and the response property for DPA. Adapted from ref. *Tang et al.*

Because of the acute neurotoxicity caused by biological weapons, saving the victims after exposure remains challenging. Neuro-drugs are organophosphorus compounds (OPS) that block the communication between nerve and organ, which has been used as biological weapons.<sup>183-185</sup> Jiang *et al.* developed a nanoscavenger, which had a long-term protective effect on OPS poisoning in rodents (Figure 15).<sup>186</sup> It could catalyze the decomposition of toxic OPS, and exhibit excellent pharmacokinetic characteristics and negligible immune response in OP poisoned rats. In a guinea pig model, the single prophylactic administration of nanoscavengers effectively prevented the lethality after repeated exposure to sarin within one week, demonstrating the translational significance of nanoscavenger in clinical and military settings.





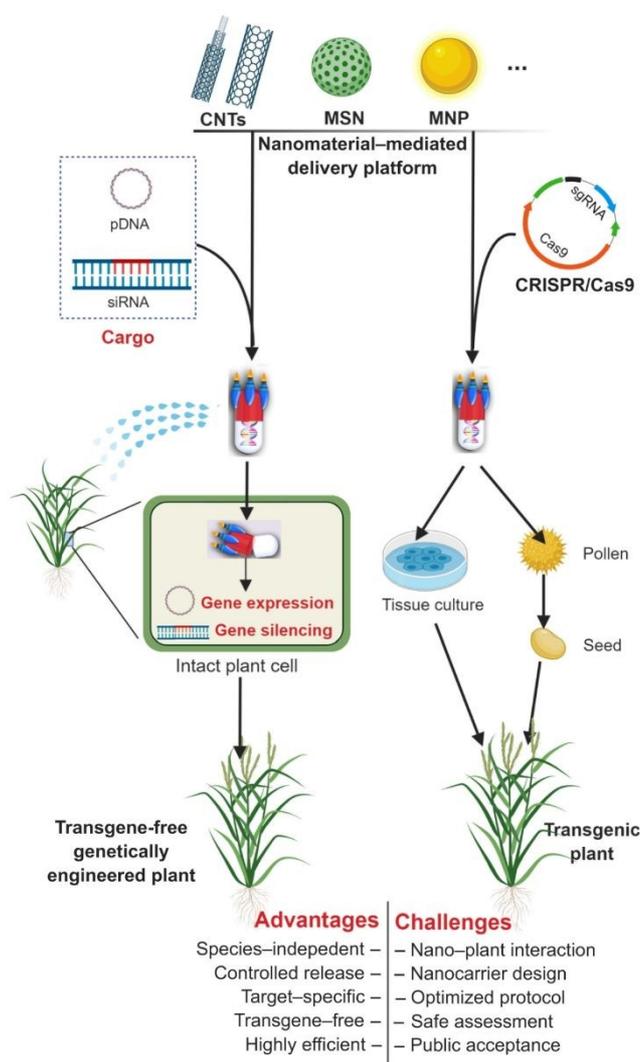
**Figure 15.** Biosafety materials as a nanoscavenger to remove neuro-drugs. (A) Schematic illustration of the protection mechanism of the nanoscavengers. (B) Hydrolysis of paraoxon and sarin mediated by the nanoscavengers.

### 3.10 Biosafety materials for genetic technology

The emergence of genetic technology directly broke the original pattern of science and promoted the development of medical, agricultural and other fields. However, it also brought with problems such as gene mutation and hybridization, indicating the double-sidedness of gene technology. Conventional genetic engineering technique target the nuclear genome, resulting in problems about the proliferation of foreign genes to weedy relatives. Target delivery to specific organelle is highly desired for plant genetic engineering, which can be achieved *via* nanoparticle mediated transformation.



Wong *et al.* designed a gene carrier based on chitosan-complexed single-walled carbon nanotubes (SWNTs) for chloroplast transformation.<sup>187</sup> The nanotube carrier could deliver plasmid DNA to chloroplast of different plant species without external biolistic or chemical aid, thereby rendering a chloroplast transgene delivery platform for mature plants across different species. In Figure 16, wang *et al.* summarized a series of functionalized nanomaterials which provided diverse platforms that are capable of traversing barriers (*e.g.*, multilayered cell walls) to deliver exogenous plasmid pDNA and siRNA in to intact plant cells.<sup>188</sup>



**Figure 16.** Biosafety materials for plant genetic engineering. Multiple nanotechnology-based materials and cargos for gene deliver have been developed, improving our ability to specifically deliver gene editing agents.



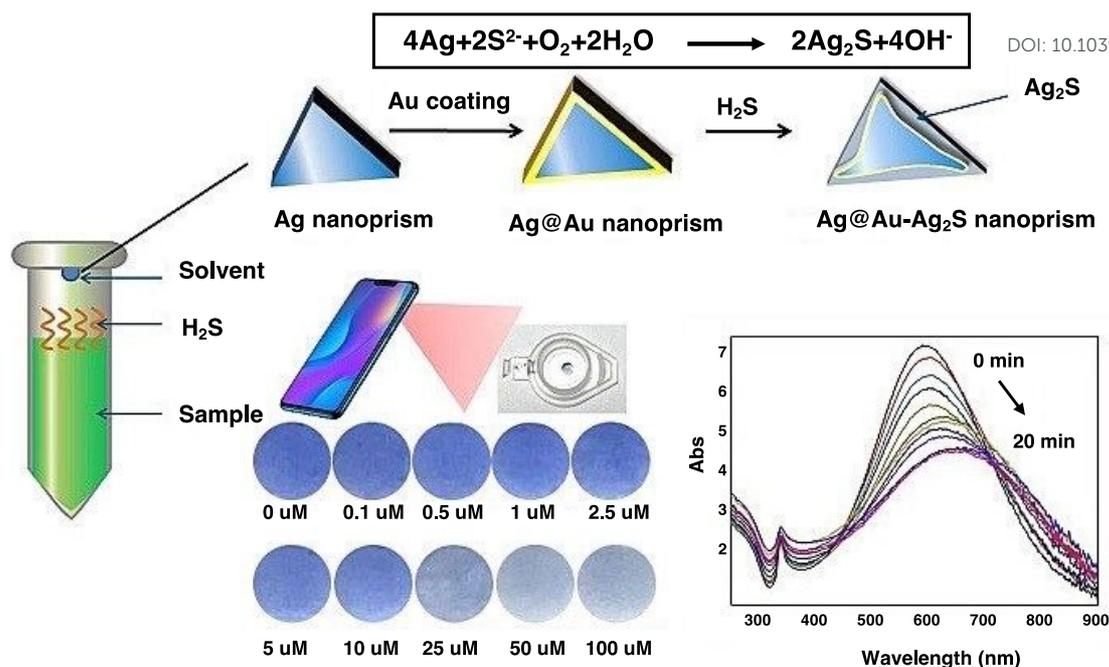
### 3.11 Biosafety materials for food safety

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The food safety as a global public health issue, has been regarded as a biosafety problem.<sup>189-191</sup> The major issues in food safety are summarized as following: (1) The presence of microorganisms directly causes the mold. It can easily spread during the process of production, distribution and packaging;<sup>192-195</sup> (2) The emergence of additives greatly helps manufacture produce food that meets certain requirements, but if the amount of food additives used exceeds the standard level, it will pose a serious threat to human health;<sup>196, 197</sup> (3) The overuse of chemical fertilizers and pesticides leads to severe pollution and food safety problems, which places a vast threat burden in human health.<sup>198,199</sup> To tackle these challenges, materials scientists proposed various solutions for food safety problems in testing, packaging, and storage.<sup>200-203</sup>

Hydrogen sulfide (H<sub>2</sub>S) with rotten egg odor is produced in rotten food. Rapid and sensitive detection of H<sub>2</sub>S is important to forewarn of food spoilage or pollution incidents with respect to this gas. Tang *et al.* prepared Ag@Au core-shell nanoprobe combined with headspace single-drop microextraction (HS-SDME).<sup>204</sup> Smartphone nanocolorimetry with the aid of smartphone camera and color picker software was applied to detect and quantify the H<sub>2</sub>S (Figure 17). The sensitivity of this nanocolorimetric approach reach to 65 nM limit of detection limit, which represents an idea *in situ* analytical approach to H<sub>2</sub>S determination. Hence, the development of biosafety materials provides technical support for food safety.



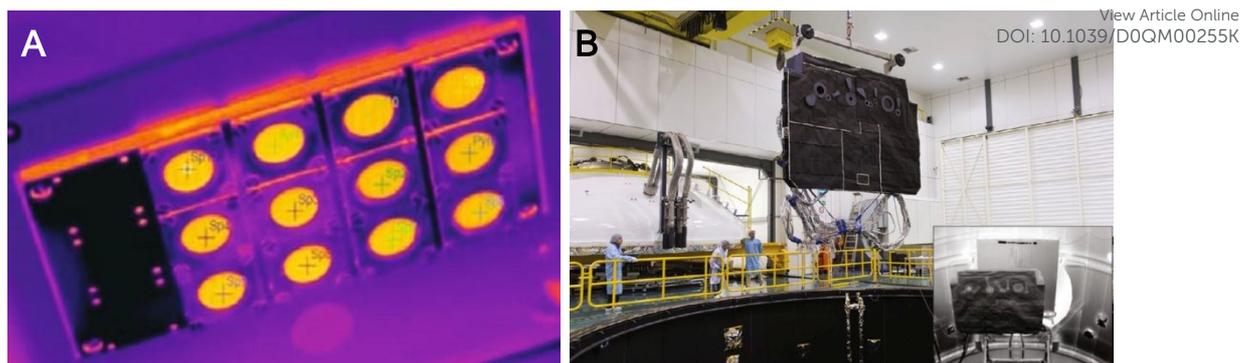


**Figure 17.** Biosafety materials for food safety. Schematic illustration of the H<sub>2</sub>S sensing mechanism based on Ag@Au core-shell nanoprobe.

### 3.12 Biosafety materials for aerospace safety

The space radiation environment is mainly composed of the Milky Way cosmic rays, solar high-energy particles, and particles in the radiation zone of the near-Earth anomaly zone. After a long-term analysis of space radiation environment, NASA has officially listed astronauts as radioactive workers in the 1980s, which indicated that aerospace safety is a biosafety problem. Doherty *et al.* reported a high-absorptivity/high-emissivity bone char-based thermal control surface known as SolarBlack for use on rigid and flexible metallic substrates, including titanium, aluminium, copper alloys (Figure 18).<sup>205</sup> This technology has been qualified for use on the Solar Orbiter heat shield's front surface, thereby providing astronauts with biological safety protection.<sup>206</sup>





**Figure 18.** Biosafety materials for aerospace safety. (A) SolarBlack material samples during testing in the Synergist Temperature Accelerated Testing (STAR) facility in the ESA/ ESTEC center. (B) Solar orbiter heatshield based on SolarBlack technology.

The harm caused by an impact accident in a space environment directly leads to a devastating consequence. A polymer material that can self-heal within one second after impact has been developed to solve this problem.<sup>207</sup> The rapid reaction rates was achieved by thiol-ene-alkylborane formulations, providing astronauts with biological safety protection at the physical level, which ensures the safety of human life and improving the efficiency of related work in the process of exploring space.

#### 4. Outlook and prospects

In summary, a variety of materials, such as polymers, MOFs, graphene, carbon nanotubes, *etc* have already been successfully applied in the field of biosafety, but no clear definition and detailed plan on the development of biosafety materials have been given yet. Numerous reports on the progress of materials science prove that it can help effectively solve the difficult biosafety problems. To the best of our knowledge, we are the first one that officially proposes the brand-new concept of “biosafety materials” to specify the role of materials science in biosafety, aiming at raising the awareness of the scientific community to actively integrate the two different subjects together and advocate the marriage of two concepts. This brand-new concept of “biosafety materials”



could help solving problems related to biosafety. Since the biosafety covers a wide range topic from pathogen detection, biological invasion prevention, protection and prevention of biological resources, genetic technology, *etc.*, solely relying on a single discipline to address those issues in biosafety is impossible. The integration of biosafety and materials science can significantly facilitate the development of effective biosafety materials, thus providing a powerful toolbox for professionals to solve biosafety-related problems.

Overall, despite the significant progress in recent years, the development of biosafety materials is still at an early stage, and great efforts should be made to improve the current technologies and facilitate the development of biosafety materials. The following measures are suggested as below:

First, biosafety materials science majors should be opened in universities and research institutes, to strengthen biosafety materials science disciplines, train professional teams, and perfect the biosafety materials professionals in basic research in the field of infectious diseases. The development of biosafety materials could support future work on the traceability and transmission of pathogens of high incidence, sudden infectious diseases, understanding infection and pathogenic mechanisms, and finding out the anti-infection means; Second, scientific research laboratories and research centers related to biosafety materials science as well as research platforms should be built to strengthen the integration of relevant scientific research, which finally can improve the biosafety research system; Third, professional associations related to biosafety materials science should be established and opening up professional journals and magazines to expand the influence of biosafety materials science is necessary; Finally, well-known enterprises should grow up which are specialized in biosafety materials to develop related products and equipment for biosafety issues. Biosafety materials research and development centers could be further built in these enterprises to support people's health, social stability, and national security.

Taken together, the globalization makes the current biosafety threat not just a problem for a single country. No country can protect itself from biological risks without



cooperation with other countries. Hence, we hope scientists from all over the world to share data and information to use biosafety materials collaboratively tackle biosafety risks. Finally, we sincerely hope that biosafety materials science will become an independent discipline in the near future, and can flourish worldwide. The government will soon pay more attention to the development of biosafety materials science. More and more researchers can realize its importance and join the research community to explore more and more biosafety materials as well as related products and equipment. Ultimately, the development of biosafety materials science will provide a solid guarantee for the health and well-being of peoples, economic prosperity, and national security worldwide.

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