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Personalized Reusable Face Masks with Smart Nano-Assisted Destruction of Pathogens for COVID-19: A Visionary Road

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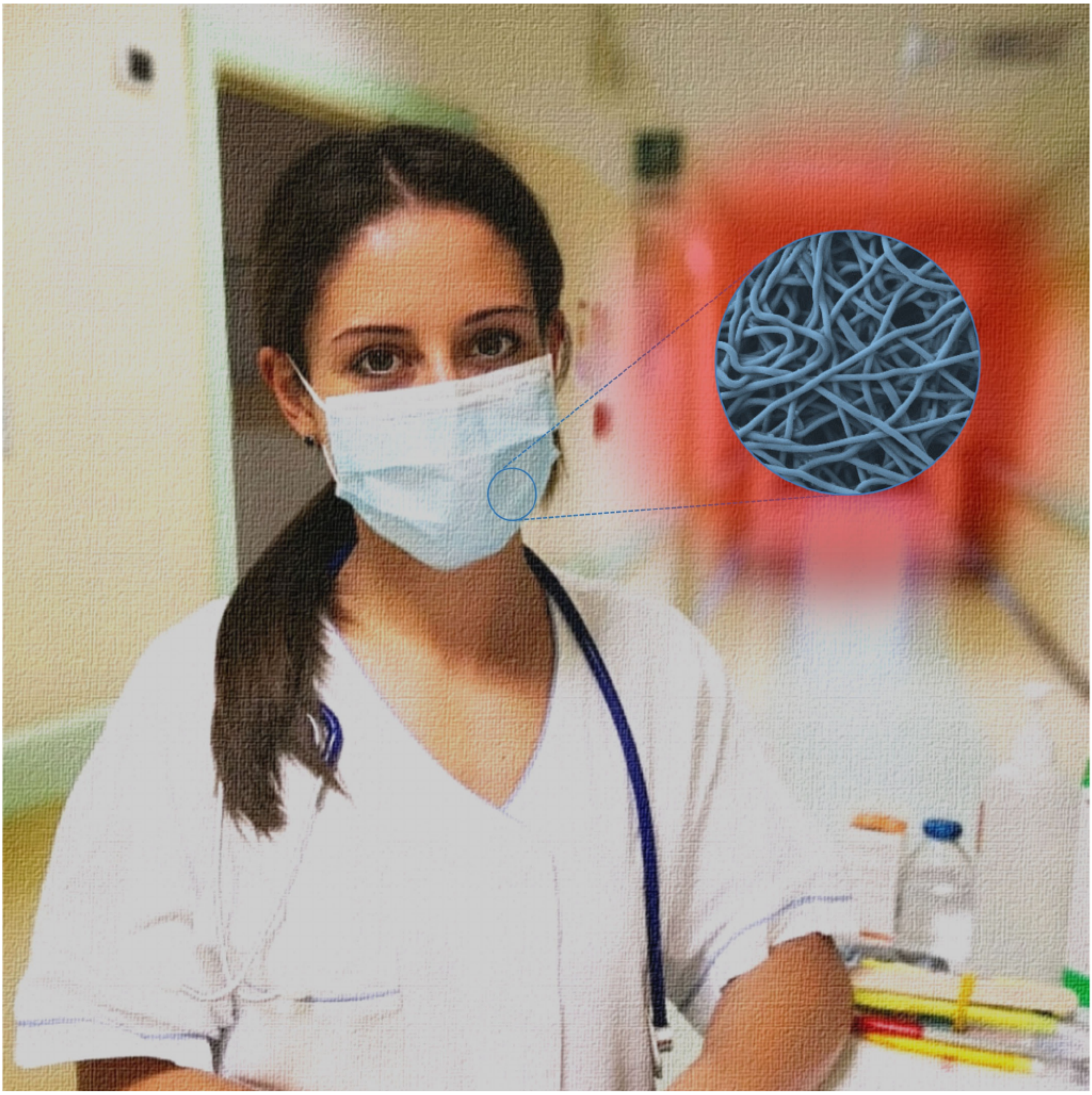

Abstract: The Coronavirus disease 2019 (COVID-19) emergency has demonstrated that the utilization of face masks plays a critical role in limiting the outbreak. Healthcare professionals utilize masks all day long without replacing them very frequently, thus representing a source of cross-infection for patients and themselves. Nanotechnology is a powerful tool with the capability to produce nanomaterials with unique physicochemical and antipathogen properties. Here, how to realize non-disposable and highly comfortable respirators with light-triggered self-disinfection ability by bridging bioactive nanofiber properties and stimuli-responsive nanomaterials is outlined. The visionary road highlighted in this Concept is based on the possibility of developing a new generation of masks based on multifunctional membranes where the presence of nanoclusters and plasmonic nanoparticles arranged in a hierarchical structure enables the realization of a chemically driven and on-demand antipathogen activities. Multilayer electrospun membranes have the ability to dissipate humidity present within the mask, enhancing the wearability and usability. The photothermal disinfected membrane is the core of these 3D printed and reusable masks with moisture pump capability. Personalized face masks with smart nano-assisted destruction of pathogens will bring enormous advantages to the entire global community, especially for front-line personnel, and will open up great opportunities for innovative medical applications.

Introduction

The Coronavirus disease (COVID-19) outbreak has dramatically highlighted the major shortcomings of personnel protective equipment (PPE) such as face masks, primarily utilized in healthcare facilities to protect both patients and workers.[1] In a time of pandemic, we are all aware that the rational use of face masks can drastically reduce infections and deaths and postpone the peak time of the epidemic evolution (Figure 1 a).[2] The necessity to realize a new generation of personalized and reusable face masks with high filtration levels, moisture pump technology, and self-sterilization properties is a mandatory need, especially for medical workers.

Pioneering breakthrough technologies aiming at realizing innovative, 3D printed, and reusable face masks with hierarchically arranged functionalities such as an elevated filtration

Figure 1. Application of personal protective equipment during the COVID-19 outbreak. (a) Photograph of a nurse using a surgical face mask during the treatment of patients not infected by coronavirus and (b) a frontline healthcare worker wears the typical set of personal protection equipment (including a FFP3 mask, goggles, a protective face shield, a protective suit, gloves, and boot covers) for the treatment of COVID-19 patients during the pandemic crisis in Italy (images courtesy of Tommaso Rondina). (c) Photograph showing three different types of face masks: surgical mask (left), FFP2 mask (center), and FFP3 face mask (right).

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levels, moisture pump capability, integrated and synergistically combined chemically driven and light-assisted self-disinfection properties have become a key task for scientists working in different research fields.

Nanofibers produced by the electrospinning technique, and molded/personalized in a face-like skeleton through 3D printing, can guarantee excellent comfort, a high filtration (efficiency $\geq 99\%$), and low-pressure drop.[3] The optimized facial comfort can be obtained by using 3D printing (Direct Digital Manufacturing; DDM) combined with personalized designs obtained from a library of 3D heads carried out from 3D scans of the head and neck of representative medical personnel.[4] Thanks to their large surface area-to-volume ratio, nanofibers have the extraordinary capability to filter nanoscale particles and absorb biological and chemical contaminants while ensuring thermal comfort through their radiative cooling properties.[5] The high filtration level and the moisture pump technology are enabled by utilizing a bilayer of electrospun membranes.

Inorganic nanoclusters (NCs) with tailored features, decorating the surface of fibrous materials, can be utilized for their chemically driven intrinsic bactericidal and antiviral activity, thus enabling an active methodology for minimizing the accumulation of harmful and living pathogens in the nanofiber pores.[6] To fully sterilize the potentially remaining pathogens, these nanofibers should be modified with highly photothermal efficient nanoparticles (NPs), possessing a broadband absorption spectrum, which are used for triggering a light-assisted (on-demand) photothermal disinfection.[7] Indeed, the ability of plasmonic NPs to convert a monochromatic (resonant) light into thermal energy (photothermal effect) has marked their utilization in cancer and other pathogenic disease treatments through the so-called photothermal therapy (PPT).[8]

This Concept presents a visionary approach in the field of PPT-based applications thanks to the possibility of exploiting light-assisted photothermal disinfection by using the extraordinary photothermal sensitivity of tailored plasmonic NPs.[9] The end goal is to provide guidance on the development of on-demand thermal disinfection of face masks by raising up the temperature (60 °C) by means of a suitable light source in a short-time interval with a moderate light intensity. Because of nanotechnology-assisted disinfection and the mechanical robustness provided by nanofibers, masks can be continuously chemically and on-demand thermally sterilized and can be utilized several times (non-disposable). Moreover, the developed multifunctional masks will act as a moisture pump thanks to the combination of a nanostructured electrospun desiccant layer with the photothermal responsive nanofibrous membrane, which will help to dissipate the humidity typically generated into the mask, strongly improving the comfort of mask users.[10] This elegant cascade-like mechanism represents a new vision in the field of reusable and personalized PPE because it enables the realization of new face masks based on a breakthrough technology able to guarantee excellent comfort, high filtration capability, low humidity levels, chemically assisted intrinsic bactericidal and antiviral activity and on-demand light-triggered disinfection, along with a comfortable microclimate under the mask.

Fighting the COVID-19 Outbreak

In the time of pandemic, disposable face masks are widely used by the public, and because they are not always disposed of correctly, there are tremendous ecological consequences such as wildlife damage and plastic pollution. It is worth mentioning that the estimated monthly production of masks necessary to protect citizens worldwide is at 129 billion pieces, the resulting waste is on the order of several tons every day.[11] New manufacturing technologies are racing all over the world, gathering a very reputable team of experts and professionals, to help provide a working solution to protect people from the pandemic. Unfortunately, all the proposed solutions, although challenging, do not combine all the most important requirements such as high filtration level ($\geq 95\%$) for nanometer scale particles, self-sterilization, moisture dissipation, eco-friendliness, and finally comfortableness. To address the global shortage owing to the coronavirus outbreak, factories are scrambling to produce many more face masks a day to keep up with the demand. However, healthcare workers are still subject to very high risks by the lack of sufficient face masks.[12] Moreover, because frontline medical professionals wear face masks over an extended period (8 to 10 h daily), they may be suffering from skin damage through sweating (absence of moisture dissipation system) and the rubbing (low comfortable fit) of the masks against the nose. In addition, medical workers cannot replace their face masks very frequently and for this reason, they are potentially forced to work with infected masks, thus representing a risk for patients, themselves, and their families. When face masks are donned, the relative humidity (RH) inside the facepiece strongly increases to a high level ($\mathrm{RH} \geq 75\%$) because of the exhaled breath, thus producing an additional lung inflammation.[10] In this context, moisture dissipation plays a vital role and the most diffused technique of dehumidification, which includes the mutual use of cooling and adsorbent devices, is bulky and very energy consuming.[13]

Today, healthcare professionals make up 10 % of Europe's workforce, but owing to the population growth, aging, and the rise of challenging diseases, the global economy is projected to create around 40 million new health sector jobs by 2030.[14] Disposable respirators and surgical masks are extensively used in healthcare settings (Figure 1 b). Hence, supply–demand gaps and increased amounts of medical waste from hospitals during pandemic situations are the most common problems to deal with. The recent COVID-19 pandemic has proven that there is an urgent need to develop new smart and effective PPE such as medical masks (Figure 1 c). By today's global count, 662 095 people have died across the world and among these are front-line healthcare personnel, who could not be saved because of the lack of PPE. According to WHO, health workers are at the front line of the COVID-19 outbreak response and as such are exposed to hazards that put them at higher risk of infection.[15] Italy has seen at least 176 doctors with coronavirus die and over several thousand healthcare workers have become infected.[16] Face masks have a rapidly increasing market value in response to consumer demand.[17]

The rising use of counterfeit products affects the price of the face masks and, consequently, the market growth.

WHO have produced a document entitle "Advice on the use of masks in the context of COVID-19", published June 2020, which highlighted the potential harm and risks that should be taken into account when using face masks, such as: "self-contamination due to the manipulation of the mask by contaminated hands; potential self-contamination that can occur if medical masks are not changed when wet, soiled, or damaged; possible development of facial skin lesions, irritant dermatitis, or worsening acne, when used frequently for long hours; face masks may be uncomfortable to wear; false sense of security, leading to potentially less adherence to well-recognized preventive measures such as physical distancing and hand hygiene; risk of droplet transmission and of splashes to the eyes, if mask-wearing is not combined with eye protection; disadvantages for or difficulty wearing them by specific vulnerable populations such as those with mental health disorders, developmental disabilities, the deaf and hard of hearing community, and children; difficulty wearing them in hot and humid environments".[18]

In this context, the development of new personalized, non-disposable, high-quality medical masks made with functional fibrous antipathogen materials for healthcare workers has become a priority. Reaching this goal, it will be possible to provide environmentally friendly non-disposable reusable face masks and expect improved protection for healthcare workers, less plastic pollution, and better sales of high-quality face masks.

In addition, the accomplishment of this challenging objective will have several direct and indirect impacts. The most important social impact is that healthcare workers can protect themselves by having their own personal reusable face mask, thus reducing the possibility of infection transfer from one patient to another or to healthy people. The developed face mask has improved filtration efficacy enabling the fight with dangerous and small viruses. The mask will have an integrated humidity dissipation system keeping the inner environment dry. When the set aims are reached, it is possible to get rid of the pathogens as soon as they are in contact with the mask's surface. The developed technology will enable the user to reactivate the mask after specified time-periods using a suitable light source. In contrast to available respirators, our technology allows the realization of better contact with the face as each is specifically designed for every individual. We also see a clear economic impact by identifying that the mask must be reusable. It is possible to avoid the need to misuse disposable masks (no guarantee of effectivity and sterility) and reduce the amount of waste. According to the International Union for Conservation of Nature, at least 8 million tons of plastic (masks, gloves) end up in the oceans every year.[19] The new approach supports the green environment and therefore, this new technology will have an important environmental impact. Moreover, the new fabrication path we have identified will support the growth of novel industries having the expertise to use electrospinning and 3D printing technology and/or introduce these technologies to the preparation of antipathogen materials and face masks. The latter strengthens competitiveness through the novel advantages obtained in this highly competitive market. The brand-new envisaged material/mask will certainly create new market opportunities for researchers and initiate small/medium-size companies with the capability to manufacture high-quality materials and masks.

This Concept is a nanoscience-focused article, which plots a new visionary road towards the realization of innovative, sustainable, personalized, and non-disposable face masks with self-disinfection properties. Multifunctional hierarchical nanostructured materials, in a layer-by-layer (LbL) geometry, such as electrospun nanofibers, inorganic NCs, and plasmonic NPs enable the possibility to realize a breakthrough technology capable of generating a highly effective face mask with an active, white-light-triggered, nanotechnological-assisted, filter. Innovative materials, personalized designs, and unique mechanical and chemical-physical properties are the main gateway for world-renowned scientists to realize an ingenious and green technology for fighting the spread of airborne pathogenic diseases. This a ground-breaking scientific report targeting the realization of next-generation face masks with the capability to stockpile innovative materials and sophisticated technological processes with the highest impact in terms of filtration efficiency, functionality, self-sanitizing recyclability, and an effective fit/comfort to the range of head sizes/shapes based on a library of 3D heads. The ambitious goal is to go beyond any current technology paradigm in the field of highly innovative face masks by pioneering a set of interrelated and pervasive radical innovations devoted to introducing a breakthrough technology based on a 3D printed and personalized face masks possessing a self-disinfected filter made of nanostructured and stimuli-responsive materials. Uniqueness, novel technologies and materials, eco-friendliness, and innovation are the decisive differences that will allow us to set the bar high for a world-wide recognized breakthrough technological revolution.

The main objectives of this Concept are as follows:

1) To establish a new paradigm in the field of on-demand photothermal disinfection of pathogens by exploiting a novel route based on plasmonic nanomaterials activated by light;

2) To demonstrate the possibility to realize innovative and highly efficient face masks possessing a new humidity control mechanism thanks to the utilization of multilayer electrospun membranes;

3) To show the latest advances in the development of personalized 3D printed face masks based on a library of 3D heads acquired from representative medical personnel (digital twins);

4) To provide guidelines for the fabrication and the study of self-disinfected face masks by exploiting the light-activated bactericidal and antiviral properties of nanostructured materials.

These objectives can be reached only by exploring the latest outstanding results obtained in different scientific fields through a multidisciplinary methodological investigation of: photothermal responsive materials, plasmonic nanomaterials, electrospinning, digital twin technologies, and 3D printing.

Key Strategies for the Next Generation of Face Mask Development

Thermal destruction of pathogenic microorganisms for face mask applications

Disinfection is a process that refers to the thermal or chemical destruction of pathogenic microorganisms. Disinfection is less lethal than sterilization because it destroys harmful microorganisms without killing all the microbial forms (e.g., bacterial spores). Thermal disinfection is the oldest and simplest method of disinfection, which relies on the utilization of heat to kill bacteria and/or viruses (both enveloped and non-enveloped) by exposure to a specific temperature ($\approx$60–70 °C) for a short-time interval (1–2 min).[20] Thermal disinfection is widely used to sanitize medical equipment and laboratory waste in autoclaves. Typically, the inactivation mechanisms are based on damaging the protein structures. Indeed, when the temperature of microbial proteins is raised, they break down or become denatured.[21] Thermal surface disinfection typically enables moist heat to be delivered directly to contaminated surfaces by steam generators. The heat delivered to surfaces by the steam (uniform heating), besides being chemical-free, is strongly germicidal and, for this reason, it is routinely used to disinfect critical medical equipment. The COVID-19 outbreak has pointed out the weakness we are facing in terms of global shortage of face masks. Dry heat ovens have been shown to be effective for disinfecting, in particular, FFP2 and FFP3 respirators.[22] However, the main drawbacks related to the uniform thermal disinfection are: i) impossibility to confine the heating in the desired region; ii) time-consuming method because of the slow heat penetration rate; iii) the effect of time and temperature may lead to the degradation of some materials. Nanotechnology with the help of nanomaterials has presented a compelling solution for realizing a new generation of NPs with intrinsic antimicrobial and/or antiviral properties. In particular, antibacterial NPs have been synthesized from metals such as zinc oxide,[23] titanium dioxide,[24] silver,[25] and gold.[26] The ability of gold nanoparticles (Au NPs) to convert a monochromatic (resonant) light into thermal energy (photothermal effect)[27] has marked their utilization in cancer and other pathogenic disease treatments through the so-called photothermal therapy (PTT).[28] Taking advantage of this opportunity, the photothermal properties of NPs have been exploited for localizing and improving heat generation and penetration, thus opening a new road for realizing a synergistically combined photothermal treatment against bacteria and/or viruses.[29] Very recently, Zhong et al. have realized a new generation of reusable and photothermal assisted face mask with self-cleaning capability by exploiting the photothermal properties of a graphene layer.[30] Although the achieved results are very promising, one of the limitations is the low light absorption of graphene, thus reducing the photothermal conversion properties. We aim to pioneer a breakthrough approach in the field of PTT-disinfected face masks thanks to the possibility of exploiting a highly efficient photothermal disinfection process by utilizing the extraordinary photothermal properties of tailored gold nanorods (Au NRs).

As a proof of concept, the photothermal properties of the pristine and Au NR treated FFP2 respirator were experimentally studied by utilizing a thermo-optical setup described in detail elsewhere.[31] Briefly, we recall that under suitable light illumination, Au NRs absorb light (Figure 2a, left). Consequently, the absorbed energy produces an electronic transition of the external electrons from a fundamental (S_0) to an excited (S_1) state (Figure 2a, middle). The heating generated by the Au NRs is dissipated to the surrounding medium (Figure 2a, right).

A water dispersion of Au NRs was drop-cast on the respirator (Figure 2b). The sample was left to dry for about 20 min before being tested. The thermographic analysis (Figure 2c) acquired before turning on the laser beam ($t=0$ s) shows a uniform temperature distribution of about 20 °C. Conversely, upon near-infrared (NIR) light exposure, the absorbed light was efficiently converted into heat because of the plasmonic photothermal heating of Au NRs, thus reaching a maximum temperature of 75 °C in only 22 s (Figure 2d). This result is evidenced in the time-temperature profile (Figure 2e, red curve) obtained by selecting a circular region of interest, which includes the center of the illuminated region. The same experiments (same experimental conditions) were performed on the pristine area of the FFP2 (N95) respirator (outside the black circle, Figure 2b). The results did not show any significant increment of temperature (Figure 2e, blue curve), thus confirming, one more time, the outstanding properties of Au NRs to convert resonant light into heat.

Synthesis of photothermal agents

Commonly, the main candidates of choice in terms of photothermal activity are synthetic organic dye molecules known as photosensitizers (PS; e.g., indocyanine green, porphyrins, naphthalocyanines, etc.).[32,33] The PS absorb light when exposed to NIR or visible irradiation sources and emit photons to return to the ground state in two ways: i) radiatively, a phenomenon known as fluorescence, and ii) non-radiatively by converting the energy into heat. Nonetheless, PS present one major limitation, specifically, low absorption capacities thus, implicitly, decreasing their photothermal conversion efficiencies. Moreover, their manipulation and implementation are difficult owing to their chemical instability; specifically, the irradiation process leads to the PS's degradation, thus losing their properties. To overcome these limitations, organic, metal-based, or combined nanomaterials and novel 2D materials have been developed in the literature and have proven their potential as photothermal generators.[34] Plasmonic NPs, in particular, owing to their unique optical properties, especially the Localized Surface Plasmon Resonance (LSPR), represent an appealing class of metal nanosystems worth exploiting. The LSPR appears because of the electromagnetic excitation of the conduction electrons located at the metal/dielectric interface, thus promoting an enhanced photo-absorption. Moreover, LSPR is highly dependent on the composition, medium, size, and shape of the plasmonic NPs.[35] Therefore, the high variety of

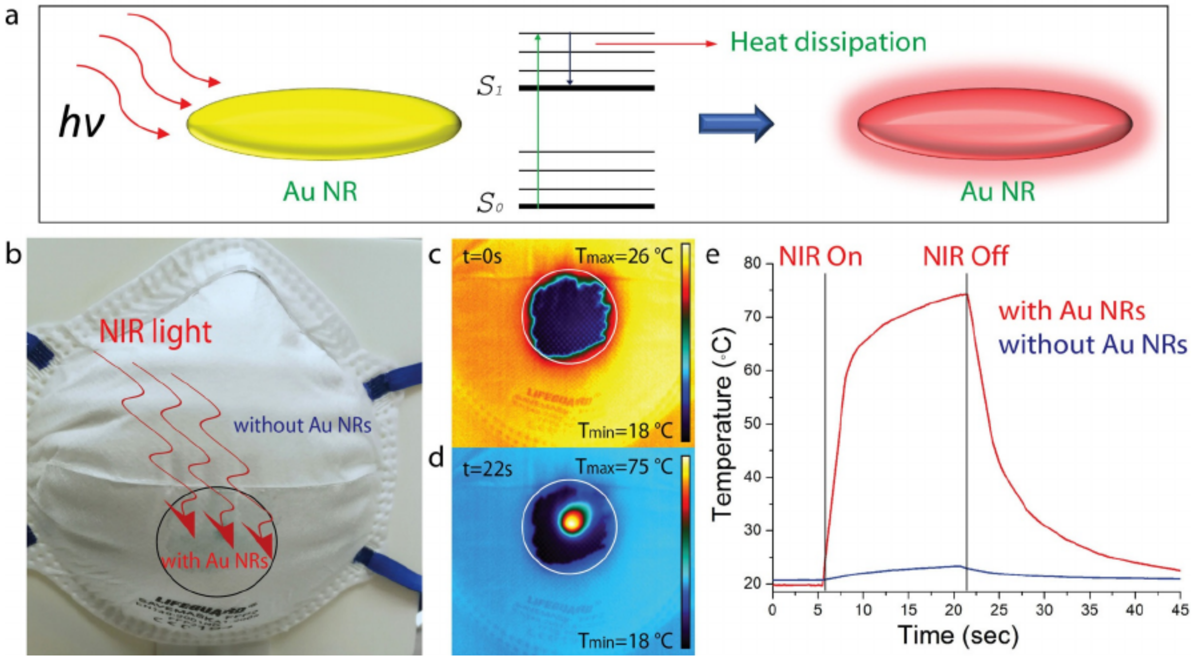

Figure 2. (a) Schematic of the photothermal conversion process of Au NRs upon light irradiation. (b) Photothermal responsive FFP2 (N95) respirator containing a drop-cast Au NRs dispersion (black circle) along with a thermographic view of the same region exposed to NIR laser ($\lambda = 810$ nm; $I = 200$ mW cm^{-2}) acquired at $t = 0$ s (c) and $t = 22$ s (d). (e) Temperature profiles of the pristine (blue curve) and Au NR-treated respirator by turning on and off the NIR laser beam. Water dispersed Au NRs ($C = 3.2\times10–9$ м) have longitudinal and transversal LSPR bands centered at 775 nm and 524 nm, respectively. The dynamic IR thermographic analysis was carried out by using a FLIR (A655sc) thermal camera, which produces thermal images of 640×480 pixels with an accuracy of ±2 °C. The thermal camera was suitably equipped with a close-up IR lens characterized by a magnifying factor of 2.9×, a spatial resolution (IFOV) of 50 μm, and a reduced working distance.

designs, ranging from nanospheres to nanocubes, triangular prisms, stars, rods, or bipyramid-shaped and dimensions leads to tunable and specific optical features, which, subsequently, allow their efficient implementation in biomedical applications, such as PPT-based applications. As such, by taking advantage of the fact that plasmonic NPs can be synthesized with well-defined morphologies and implicitly with optimized optical characteristics with regard to the irradiation source used, the photo-induced heat generation capability of NPs can be controlled and improved, ensuring the highest photothermal conversion efficiency for each specific application.

There has been a growing interest in the literature in utilizing, in particular, Au NPs as highly efficient photothermal converters as they can be easily synthesized by a two-step process (Figure 3 a), which allows various kinds of nanoparticles to be produced, showing different light–matter interactions. In fact, depending on the nanostructures' morphology, it is known that the absorption spectrum can present one or more LSPR bands (Figure 3): more precisely one single absorption band in the visible range generated by regular spherical or nanocubes-shaped NPs (Figure 3 b–d), or two major LSPR bands in the case of anisotropic shaped NPs (Figure 3 e–i); one at visible wavelengths owing to the transversal oscillations of the surface electron cloud and another longitudinal LSPR band, spanning from 600 to 1200 nm.[36] Experimentally, this longitudinal LSPR band located in the NIR biological window can be finely modulated by changing the aspect ratio (i.e., length/width) of the anisotropic NPs (e.g., nanorods, nanopyramids). Furthermore, Au NPs have been successfully transferred in different medical applications for centuries,[36] owing to their biocompatibility and the possibility to simply functionalize their surface with various functional groups (e.g., drug molecules, targeted antibodies of interest, etc.) owing to the presence of amine and thiol groups and to distribute them in the body. Additionally, they have been proven to be highly stable after several irradiation cycles proving thus their re-usability as photothermal agents.

Although Au nanospheres represent one of the earliest shape configurations investigated for PTT by El-Sayed and coworkers,[37] and their thermal properties have been recently compared by theoretical calculations based on Mie theory by the Djaker group,[38] a serious issue is the limited depth of light penetration in the visible spectrum, where the nanospheres absorb. For this purpose, gold nanobipyramidally shaped nanostructures (Au BPs) exhibit promising optical properties. Firstly, by using the seed-mediated growth approach, the LSPR response can be controlled with high precision throughout the electromagnetic spectrum from visible to the near NIR region by the simple variation of the seed concentration during the NPs growth process.[39] Apart from the fact that the NIR radiation does not harm the tissues owing to its optical transparency in this part of the electromagnetic spectrum, it has been proven that the absorption capability of elongated NPs increases with higher wavelengths of the LSPR,[40] enabling thus—implicitly—high photothermal conversion efficiencies. Furthermore, the intrinsic photothermal capabilities of different

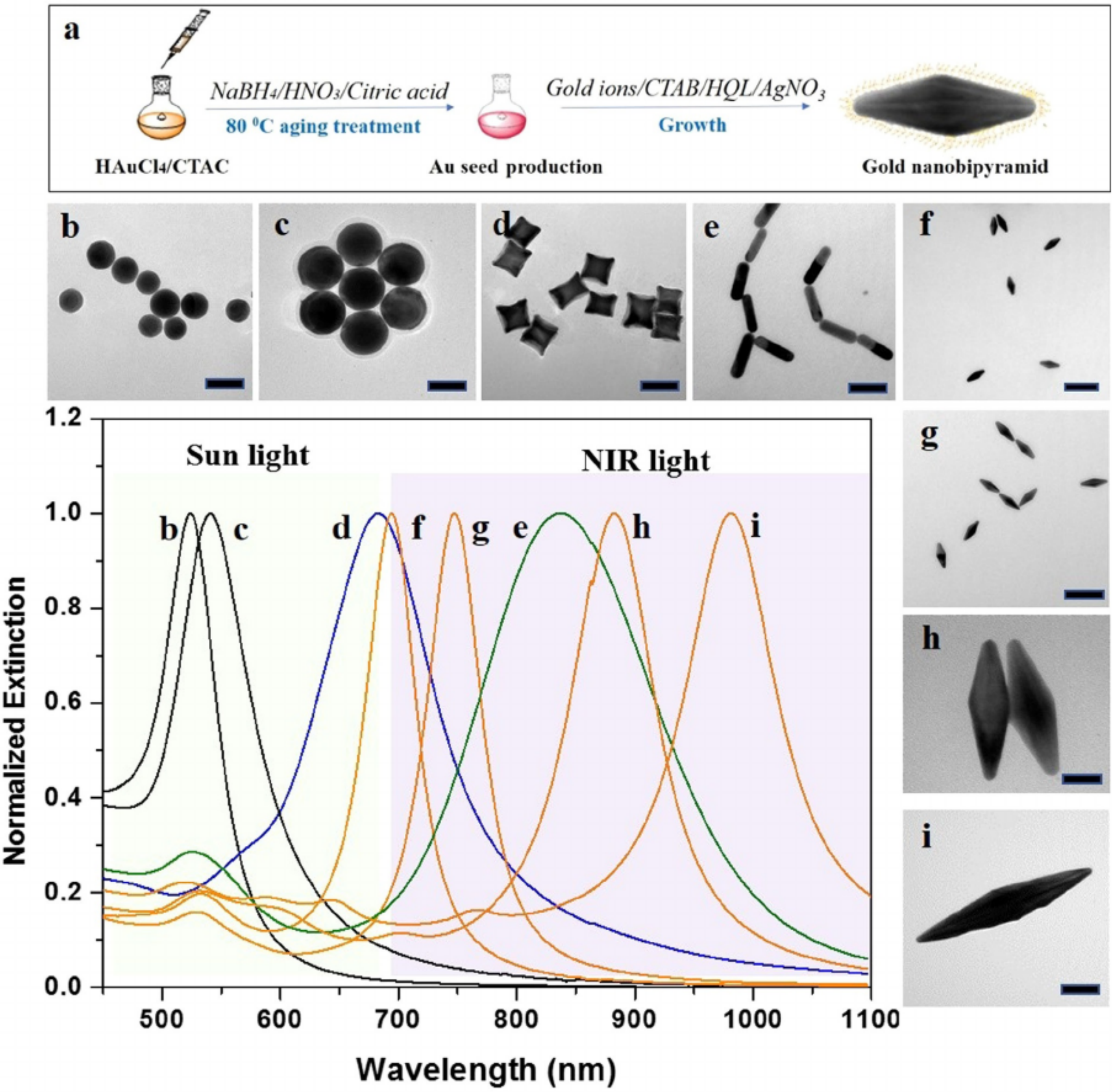

Figure 3. Synthesis and properties of plasmonic gold nanoparticles. (a) Schematic representation of the seed-mediated growth approach used for the preparation of Au BPs. Representative TEM images of the diversity of Au NPs and their corresponding normalized extinction spectra: (b, c) nanospheres with different diameters, (d) nanocubes, (e) nanorods, and (f–i) nanopyramids with different aspect ratios starting from 3.1 to 5.9. Scale bars: 50 nm.

aspect ratio Au NPs have been thoroughly analyzed by employing two NIR laser lines (i.e., 785 and 808 nm) by Campu et al., reporting photothermal conversion efficiencies up to 97% when the LSPR band is close to the resonance condition with utilized irradiation source,[41] thus conveying their suitability for further implementation for practical photothermal applications.

To sum up, the development of highly active photothermal plasmonic systems by simply optimizing their morphological characteristics with regard to the irradiation source employed, such as solar light, different NIR lasers, or LEDs will ensure that we achieve the highest photothermal conversion efficiency for the implementation of an efficient light-triggered effect in specific applications.

Metal nanoclusters: combining pathogen detection and elimination

The spread of viruses and the development of antibiotic resistance in microorganisms is an increasing public health concern, which is mainly caused by inappropriate use and disposal of antibiotic and antimicrobial agents,[42] amplified by the frequency of travel and also related to misuse of PPE[43] especially in healthcare facilities where multidrug-resistant bacteria[44] and nosocomial infections develop and spread.[43]

In this regard, suitably designed nanomaterials can represent a promising weapon to fight the development of multidrug-resistant bacteria and to hamper the increase of nosocomial infections. Indeed, a huge number of studies are devoted to the design and synthesis of nanomaterials with antimicrobial and antiviral properties, to the investigation of the mechanism behind these properties, and to the incorporation of nanomaterials in suitable matrices to convey antipathogenic properties to textiles,[24] surfaces,[45] medical devices,[46] and PPE.[42,47] Unlike antibiotics, nanomaterials, and in particular metallic NPs can perform multiple bactericidal actions as they can simultaneously disrupt the bacterial membrane and target intracellular components to hinder the proper functioning of the cellular machinery, ultimately resulting in disturbances in respiration and inhibition of cellular growth.[44] The ensemble of these effects decreases the probability of developing antibiotic resistance in bacteria because the same pathogen should produce multiple concurrent gene mutations.[44,48] Remarkably, metal NPs have been demonstrated to show also antiviral activity both itself and as an adjuvant in antiviral therapy.[49] It is well established that the antimicrobial capability of noble metal NPs (Ag,[50] Au,[51] Cu[52]) are essentially related to their morphology and to their surface chemistry.[53] A plethora of synthetic procedures has been reported to prepare noble metal NPs with extremely high control of their morphology, surface chemistry, and, consequently, their chemical-physical features.[54] Among noble metal-based nanomaterials, metal nanoclusters (NCs) have received increasing attention owing to their unique properties, which offer a plethora of opportunities in several application fields.[55,56] NCs are tiny NPs formed by a small number of atoms (from a few to a few hundred) in a size that does not exceed 5 nm, a dimensional regime that bridges the gap between NPs and molecular compounds. Their peculiar dimensions determine their original physicochemical and optoelectronic properties, not detected in traditional metallic NPs, which make NCs significantly different from their larger counterparts. Beyond enhanced catalytic properties, NCs, unlike NPs, exhibit photoluminescence properties. This striking difference in terms of optical properties, although it is still under investigation, is essentially associated with the interplay of several parameters such as the quantum confinement effect, discrete energy levels, ligand-to-metal and metal-to-metal charge transfer, and the synergistic effect between the protection ligand and the core.[57] Furthermore, their extremely reduced dimensions allow NCs to easily penetrate the cell membrane.[58] It turns out that these unique properties of NCs have been exploited as a powerful tool for photoluminescence-based detection and discrimination of pathogens, providing a straightforward signal readout. Indeed, bacterial cells can be quantified by exploiting both the NCs fluorescence quenching, induced by pH alteration or aggregation, and NCs fluorescence enhancement, which can occur when NCs are suitably designed to achieve selective enzymatic reactions once they have been internalized in the bacterial cells. Although there is still room for improvement with respect to cell selectivity, NCs can be purposely functionalized with specific molecules such as enzymes, immunoglobulins, or peptides[58] on the bacterial cell surface to achieve selectivity for bacterial cell recognition.

Further NCs of Au,[59] Ag,[60] and Cu[61] were also exploited to construct colorimetric and fluorimetric detection methods for virus recognition. An emerging application of metal NCs and, in particular of Cu NCs, is their use as broad-spectrum antibacterial agents. Metal NCs indeed overcome some detrimental features of conventional antibacterial metal NPs such as release of metal ions, lack of an appropriate capping ligand, aggregation in high ionic strength conditions, and passivation by biomacromolecules. Although Ag NCs[62] and Au NCs[63] were successfully exploited as antibacterial agents, Cu NCs combine the benefits of broad-spectrum antimicrobial properties, high yield in mild synthetic conditions, and affordability.[55,64] Moreover, Cu NCs display further advantages for theranostic applications because Cu is an essential trace element in the human body and its excess can be effectively removed.[55]

Excellent bactericidal properties were observed for Cu NCs synthesized by the ligand-assisted method (Figure 4a) in the presence of antibiotic molecules such as the tannic acid[65] or the bacitracin[66] used directly in situ as NC stabilizing agents. The synergistic effect between Cu NCs and the antibacterial organic molecule essentially consists of the damaging of the cell membrane of a Gram-positive bacteria (Bacillus *subtilis*)[65] and in the increased reactive oxygen species (ROS) production.[66] Further, wound-healing in vivo studies showed the ability of Cu NCs to catalyze the generation of hydroxyl radicals ($^{\bullet}OH$) in the presence of H_2O_2.[67] Recent investigations, focused on the intrinsic antibacterial properties of Cu NCs, demonstrated bactericidal and bacteriostatic properties[68] and, remarkably, a great bactericidal activity against different types of bacteria including both non-multidrug-resistant bacteria (*Escherichia coli, Salmonella enteritidis, Pseudomonas aeruginosa, and Staphylococcus aureus*) and multidrug-resistant bacteria (methicillin-resistant *S. aureus*).[64]

Therefore, Cu NCs combine into one nanomaterial both antipathogen and detection properties. This unique behavior makes Cu NCs promising building blocks for the development of visionary nanotechnology based devices able to perform synergically the detection and the elimination of pathogens as sketched in Figure 4b. However, further fundamental investigations are necessary to better understand their optical properties, develop robust synthesis and surface engineering protocols, immobilize and organize Cu NCs on suitable surfaces, and, remarkably, to integrate Cu NCs in polymeric matrices selected for target applications.

Electrospinning of functional membranes

One of the main challenges in the field of polymer material science is the development of methods able to produce miniaturized structures with high surface area, maximized mechanical and optical properties, as well as new unique features (Figure 5a).[69] Among a few techniques devoted to building polymer micro- and nanostructures, electrospinning is considered the most promising and outstanding method owing to its versatility and wide range of potential applications.[70] One-dimensional (1D) nanostructured materials developed by electrospinning have been recently considered as fascinating candidates for the production of nanomaterial-based devices with tunable features and exceptional functionalities.[71] Electrospinning is an ultrathin fiber fabrication technique aiming at transforming

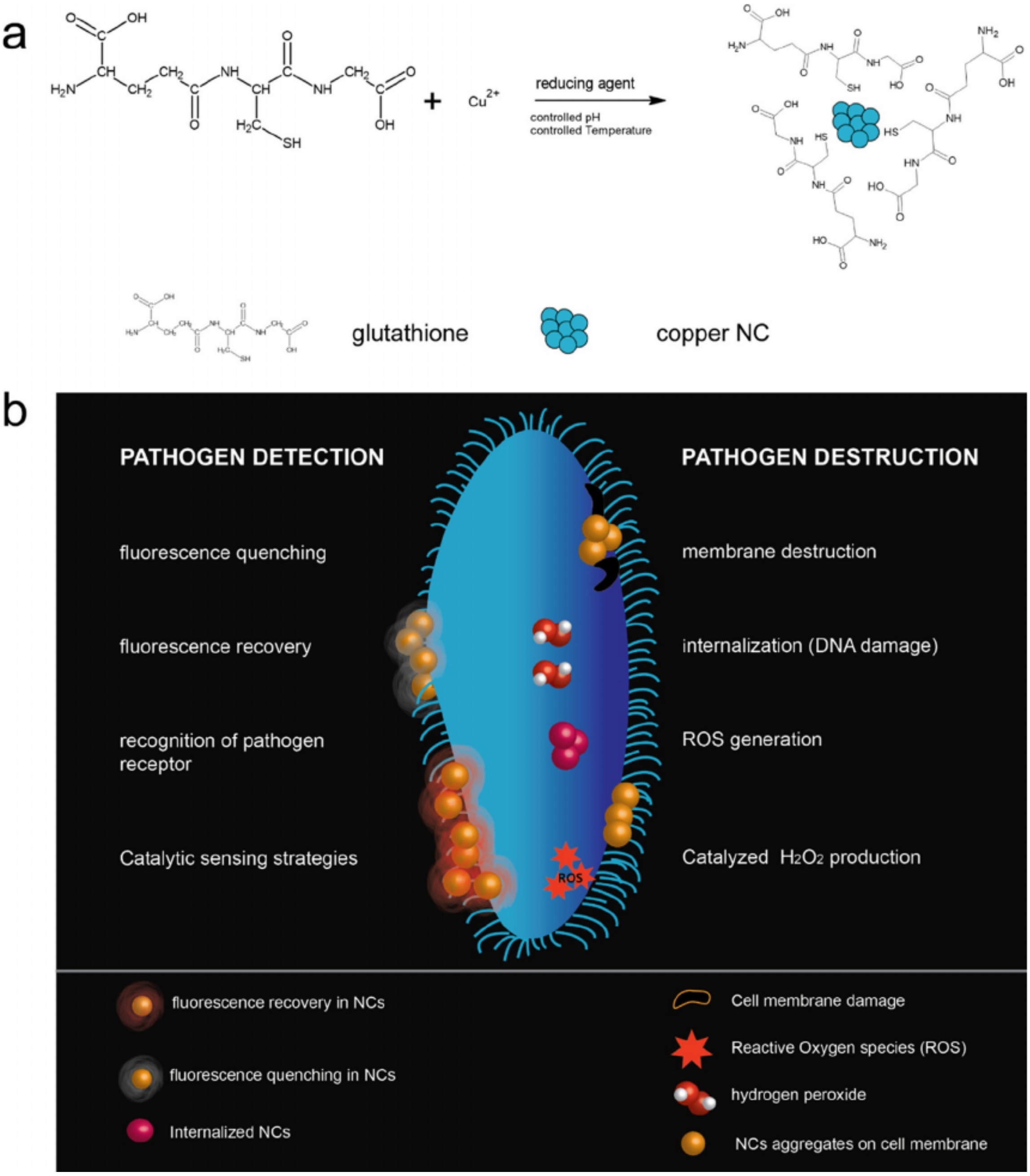

Figure 4. Inorganic nanocluster synthesis and applications. (a) General reaction scheme for the synthesis of Cu NCs by the "ligand-assisted method". The general protocol consists of reducing a copper salt by a strong reducing agent in the presence of an organic ligand (glutathione in this case) as a stabilizing agent. The reaction temperature and the pH are among the main control parameters for Cu NC preparation. (b) Schematic showing the mechanisms of pathogen detection (left side) and pathogen destruction (right side) enabled by metallic nanoclusters. NCs can be employed as biosensors by exploiting a range of strategies, promoting their photoluminescence quenching, or recovery according to their chemical composition and their surface chemistry. NCs also display bactericidal properties as they can be easily internalized in the cells, cause cell membrane rupture, increase ROS production, and H_2O_2 with consequent damage to DNA.

polymer masses into nanofibers. It offers various advantages, including producing high surface area materials, system miniaturization, tunable porosity, and the ability to manipulate the nanofiber composition to obtain novel properties and functions.[72] The high surface area makes these fibers interesting and promising platforms for all the applications that require an elevated number of active sites per unit volume. For this reason, during the last decade, electrospun nanofibers have found applications in several fields: filtration, optics, insulation, biomedical devices, protective clothing, conducting devices, sensors, catalysis, photovoltaics, fuel cells, and energy storage.[73] Moreover, electrospinning has been demonstrated to be a very flexible and adaptable technique. Indeed, additional tools and features can be added to the basic setup to obtain fibrous materials with specific properties.

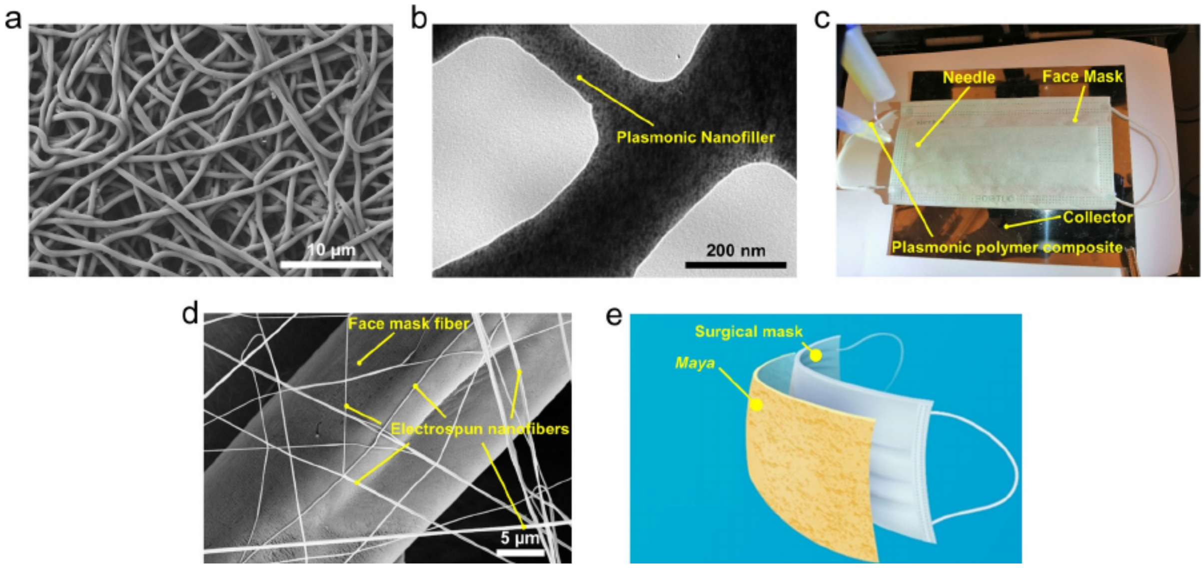

Figure 5. Electrospinning as a powerful tool to increase the efficiency and safety of face masks. (a) SEM image of a typical example of electrospun polycaprolactone (PCL) nanofibers highlighting the formation of a nonwoven mat. (b) TEM image of composite nanofibers comprising polyaniline (PANI) and inorganic plasmonic nanofillers (Au NPs) fabricated by electrospinning. (c) Photograph showing the typical setup for electrospinning used during the deposition of nanofibers onto the external surface of a surgical face mask. (d) SEM image of electrospun polyacrylonitrile (PAN) nanofibers on the filter fabric of a surgical mask. (e) Schematic showing the application of a "*Maya*" sticker as an additional electrospun membrane for masks to increase respirator effectiveness and microbial protection.

Electrospinning, which is the most efficient technique for elongating and aligning polymer chains to form nanofibers with a well-defined structure, is particularly interesting to fabricate continuous polymer 1D nanostructures with controllable structures as well as optical and electrical properties. Pierini et al. investigated the application of electrospinning for developing nanofibers with enhanced light–matter interaction.[72] Electrospun CoP(3DDT)(C_{60}HT) nanofibers were fabricated and fully characterized, showing a high degree of polymer chain order, which helps to improve interchain π–π stacking and the development of well-structured copolymer crystallites. These features contribute to a more efficient radiation absorption, confirming the huge potential of electrospinning. The enhanced optical features are attributed to well-packed and properly oriented polymer chains as well as the well-defined hierarchical architecture obtained from polymer chain stretching. These results suggest that the structure optimization obtained by electrospun nanofibers' application plays a pivotal role in the development of effective nanomaterial with light-harvesting properties.

Additionally, the physical properties of electrospun nanofibers could be easily tuned by the addition of nanofillers.[74] The possibility of fabricating electrospun polymer-based nanocomposites offers the possibility to increase the mechanical properties and electrical and optical features. In addition, creating a homogeneous system is challenging, and a few factors play a vital role in property improvements, such as nanofiller concentration, distribution, and orientation. Additionally, the presence of inorganic NPs in the starting polymer solution could trigger changes in the polymer crystallinity during the electrospinning process, which in turn leads to mechanical property modifications.[75] The use of plasmonic NPs as fillers was explored by the Pierini research group to enhance the nanostructure properties.[75,76] The application of Au NPs in this field is convenient owing to the possibility to disperse them in the starting polymer solution fully and finally obtain homogeneous composite nanofibers (Figure 5 b); moreover, the final material allows NP release to be avoided and the photothermal responsivity to be precisely modulated, which is a vital factor for PTT applications.

Electrospinning offers another important advantage in the development of functional face masks (Figure 5 c), indeed the technical features of the method allow the nanofibers to be deposited directly onto the surface of commercially available respirators, forming an additional nanometric layer capable of furnishing brand-new properties (e.g., hydrophobicity, self-cleaning, filtration, photoresponsivity).[77] The main challenge of this procedure is the development of an anchoring point between the face mask's external layer and the electrospun layer. This problem can be overcome thanks to the adaptability of this technique; indeed, process parameters can be optimized to guarantee an adequate attachment between the mask surface and the electrospun membrane (e.g., reducing the needle–mask distance, wet fibers will be deposited, which favors the physical mask–mat adhesion). Moreover, the intrinsic porosity of masks promotes the electrospun nanofiber anchorage onto their surface (Figure 5 d).

Electrospun nanofibrous mats have been recently applied as additional tools to enhance the properties of commercial respirators used during the COVID-19 pandemic period. The research group of Eyal Zussman explored this possibility and developed a sticker to upgrade surgical masks called "*Maya*" (Figure 5 e).[78] The "*Maya*" sticker, which can be easily fixed to the outer surface of medical masks, has been designed to protect the respirators, trapping nanometric particles and efficiently neutralizing viruses from droplets that might reach the mask surface thanks to the new functionalities given by its electrospun nanofibers. Another interesting material has been designed by the Il-Doo Kim group following this concept.[79] They have recently designed an electrospun nanostructured membrane that can be used as an additional filter for tissue-based face masks. The materials formed by aligned nanofibers with a diameter of 100–500 nm can maintain excellent filtering efficiency even after being hand washed more than 20 times.

Despite the great steps forward in the fabrication of more effective respirators offered by the direct in situ functionalization of face masks with electrospun fibers as well as the production of supplementary materials that can be added to masks, the development of brand-new filters as the core of novel functional face mask is the most promising breakthrough strategy. From this view, electrospun plasmonic nanofibers are envisaged for the development of multifunctional membranes that can offer outstanding filtration performance, photothermal pathogen destruction, as well as moisture pump capability.

Wang et al. proposed a novel humidity pumping concept based on a multilayer moisture-permeable structure, which allows moisture transport with little heat loss.[80] They designed a proof-of-concept microscale prototype based on a desiccant film and a photothermal coating layer, which was successfully applied as a dehumidifying indoor system without any auxiliary unit, thus consuming no electricity. Starting from this concept, the research team of Bin Ding, strongly enhanced the efficiency of this kind of device, translating the technology from the micro- to the nanoscale by using electrospinning.[81] They developed an effective polyacrylonitrile (PAN)-based composite membrane for sunlight-driven dehumidification. This wood-inspired moisture pump is based on an electrospun bilayer nanofibrous membrane with continuous indoor dehumidification features. The structure is based on the combination of a PAN/metal–organic framework (MOF)/LiCl desiccant layer for the conversion of gaseous water to liquid water and it traps into the membrane and a PAN/carbon black photothermal layer, which converts sunlight to heat to dissipate the collected water (Figure 6a). Additionally, the formed wood-like cellular networks and interconnected open channels could perform moisture pumping and vapor exhaling. Finally, this novel nanostructured membrane was tested as a smart window, and this innovative concept could be applied to solve the problem of moisture accumulation under face masks during their extensive use by medical workers on the condition that more suitable and safer materials would be found to substitute MIL-101(Cr) and carbon black as desiccant and photothermal agents, respectively.

Here, we envisage using the electrospinning technique to fabricate two functional nanofibrous membranes, which will be the key structural elements of an innovative mask with the light-assisted destruction of pathogens and moisture pumping features (Figure 6b, c). The two membranes will be merged to finally form a dual layer electrospun membrane. The inner electrospun membrane will guarantee structural stability, outstanding filtration properties, and hygroscopicity, resulting in an efficient collection of the moisture accumulated between the skin and the mask. The outer nanostructured layer is formed from polymer nanofibers filled with photo-responsive agents (i.e., Au NPs).[75] The structure will show an engineered surface characterized by the presence of Cu NCs with antimicrobial properties anchored onto the fiber surface. Moreover, a post-electrospinning thermal treatment can ensure the physical stability of the construct. This hierarchical structure will guarantee high filtration performance and an efficient and fast light-responsiveness, which is crucial to generate heat upon irradiation, thus killing pathogens on demand. Finally, the bilayer membrane will additionally act as an excellent moisture pump, which will dissipate the humidity generated between mouth/nose and the mask thanks to the hygroscopic features of the inner layer and the photothermal properties of the outer membrane.

3D printing and digital technologies

DDM is a family of emerging technologies, which enable the fabrication of a digital design without the use of complex tooling or molds.[4] This means that the design can be modified just prior to fabrication, which means that all products fabricated can be personalized.

The COVID-19 crisis arising from the pandemic has led many to seriously reappraise the nature of the supply chains for critical healthcare and other goods. The shortages of personal protective equipment and essential medical equipment such as ventilators and face shields led groups of engineers to turn to alternative solutions and many saw the solution lay with direct digital manufacturing.[82] At CDRSP-IPLEIRIA, a center of excellence in the field of Direct Digital Manufacturing, the research team was quickly involved in these activities and Figure 7a shows an example of a face shield component that can be quickly manufactured on a desktop 3D printer, providing a local supply chain.

Mass production was one of the successes of the 19th and 20th centuries, exploiting such technologies as injection molding of plastics and textile productions.[83] These technologies produce low-cost goods at the disadvantage of long lead times both with regards to the complexity of the specialist tooling or materials required. In contrast, direct digital manufacturing offers the capacity to produce objects directly from a digital design without the need for specialist tooling or molds.[84] As a consequence, the time span from concept to product is very short. Direct digital manufacturing is a family of technologies including 3D printing[85] and stereolithography,[86] which have developed out of ideas originally seen as a rapid route to prototypes to assist in the design process.[87] These technologies are now seen as an important manufacturing method as well as a critical component of Industry 4.0, the so-called 4th Industrial Revolution.[88] We use the term of Direct Digital Manufacturing as it provides an umbrella term for all of these new manufacturing technologies whether they involve additive or subtractive processes and technologies, which involve different scales of structure and design, for example, electrospinning of nanofibers.[89]

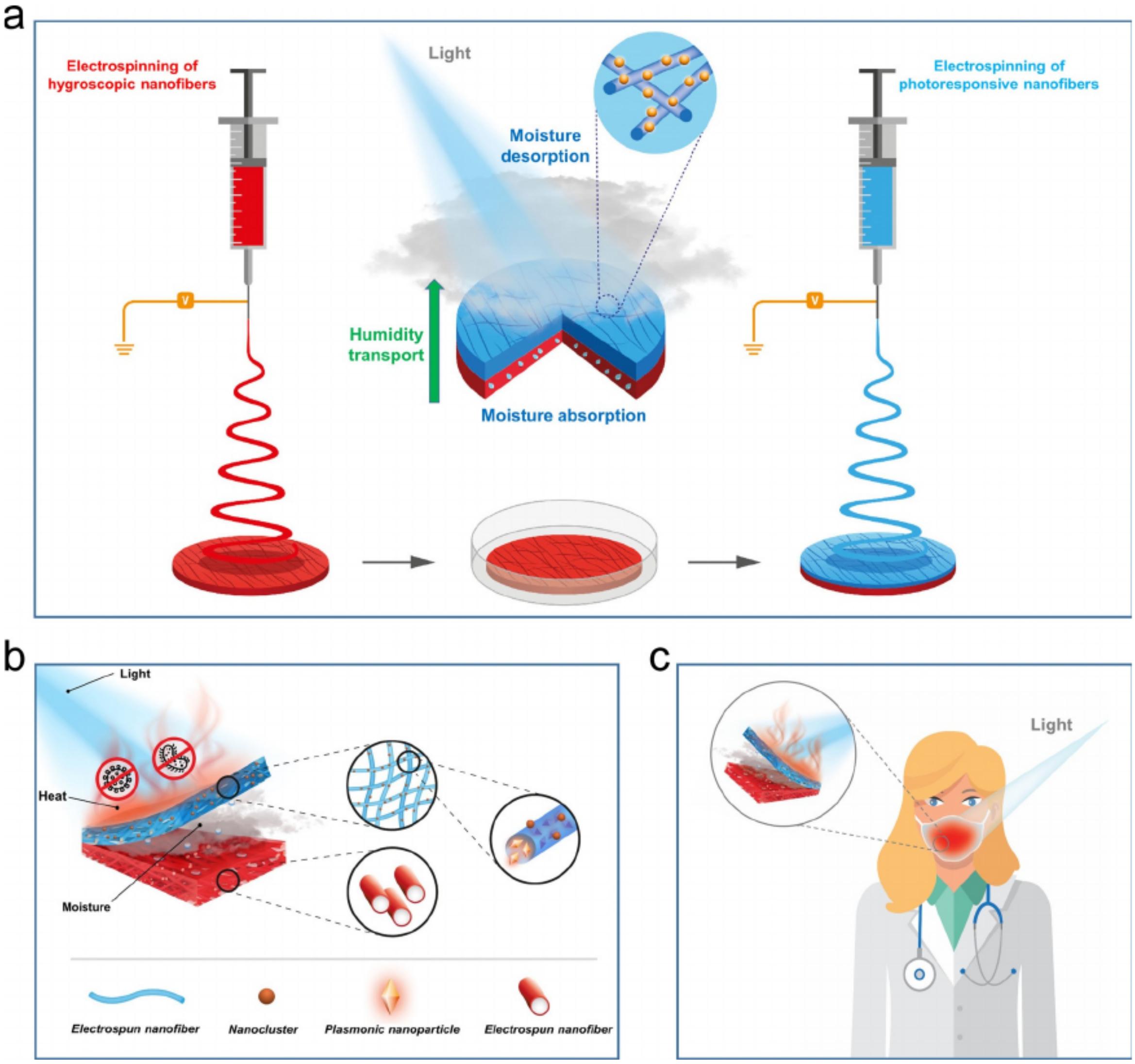

Figure 6. Multifunctional electrospun bilayer nanofibrous membranes. (a) Schematic illustration of the fabrication of biomimetic bilayer nanofibrous membranes with light-activated dehumidification features. The photoresponsive electrospun nanofibers were directly electrospun on the wood-like network substrate of the hygroscopic nanofibers. The middle image shows the moisture transport process of the bioinspired light-responsive bilayer membrane developed by Bin Ding and his co-workers. (b) Sketch showing the chemical, morphological, and structural properties of a multifunctional membrane for biomedical application. The inner (passive) electrospun layer is a nanostructured desiccant material able to effectively filtrate external agents (e.g., viruses) and absorb moisture accumulated between the mask and the face skin. This nanofiber-based material is highly hygroscopic with a fast moisture absorption thanks to the high surface area-to-volume ratio offered by electrospun nanomaterials. The outer (active) layer can be activated on demand by light to destroy pathogens through PTT and to allow the desorption of the water entrapped into the membrane structure. (c) Schematic displaying the application model of an electrospun bilayer nanofibrous structure in which the membrane is used as the multifunctional core structure of an on-demand sanitized face mask with the ability to dissipate moisture.

The COVID-19 crisis has helped to draw attention to the key concept of design imposed at the point of manufacturing; however, we see this as rather missing the major goal to be achieved by fully implementing the digital nature of manufacturing. Current manufacturing focuses on form and achieves the complexity of function by combining several parts usually prepared from different materials with differing properties. All consumer goods are produced in this way, in some cases leading to longer and more complex supply chains, as can easily be observed in the case of just-in-time supplies for the automobile assembly.[90] There are two examples of current manufacturing processes for polymers that warrant our attention in this context. The first is the use of polypropylene, an important industrial thermoplastic used to prepare objects such as vials and storage boxes in which the lid is a continuous part of the object through a natural or living hinge.[91] This is achieved by the design of the injection mold to produce a thin strip between the body and the lid in which the polymer melt flow conditions lead to a high level of molecular orientation in the hinge strip. This configuration imparts the properties required for the hinge to function as a hinge with a substantial lifetime. There are designs for other objects, including a face piece respirator, which uses natural hinges to allow the mask to respond dynamically to the jaw movements of the wearer.[92] The

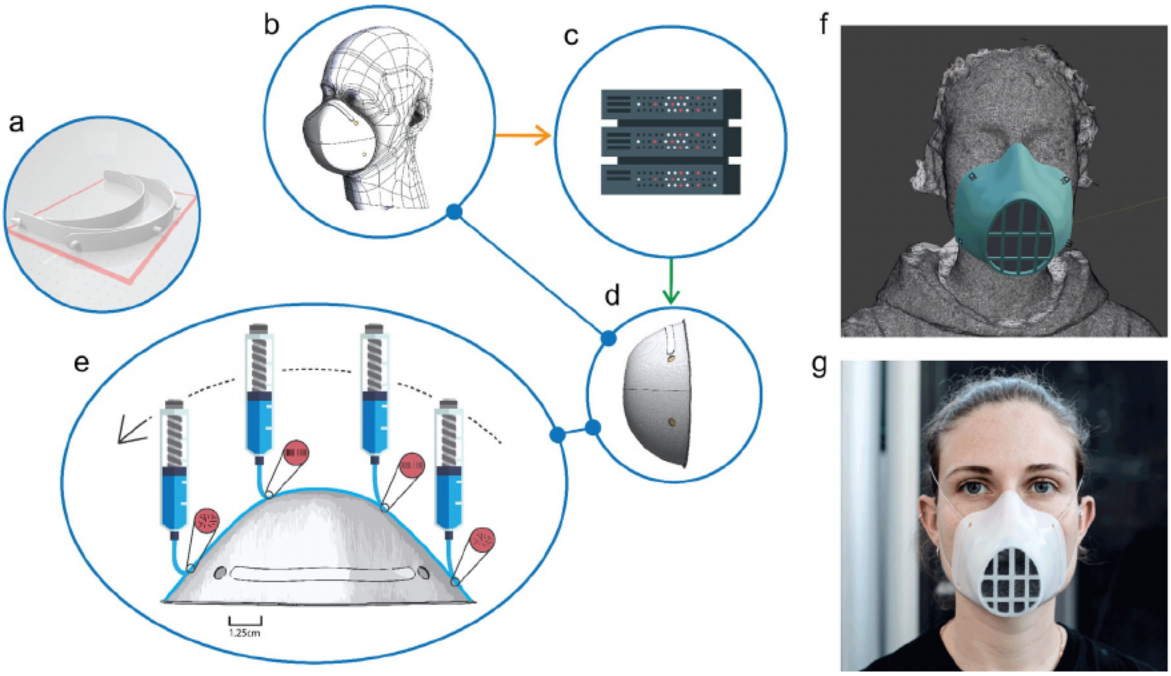

Figure 7. Sketch illustrating the 3D printing process steps. (a) 3D printed component of a low-cost face shield developed at CDRSP-IPLEIRIA during the COVID-19 crisis. (b) Digital twin model based on an anthropomorphic head complete with a breathing system and sensors to measure pressure drop flux, temperature, humidity. (c) Test station provides the data for the digital twin system, which in turn optimizes the fabrication process. (d) Mask fabrication. (e) Isotropic material deposited at the edge of the mask to allow it to conform to the facial profile whereas the center of the mask frame is deposited with a stiffer anisotropic morphology to maintain the overall shape of the mask. The different morphologies are evidenced in the red insets. (f) A mesh 3D model of a face mask user obtained from a 3D scan of the wearer. (g) Photograph of a personalized MY FACE MASK respirator with replaceable filter fabricated by 3D printing.

second is that the wearable feel of textiles is imparted during manufacturing.[93] These approaches have led CDRSP researchers to consider whether it is possible to extend the concept of design imposed at the point of manufacturing during direct digital manufacturing to impose properties during manufacturing. Using time-resolved small-angle X-ray scattering measurements performed during 3D printing, Pinheiro et al. were able to discover a new methodology to control the semi-crystalline morphology of the printed material. Figure 7 demonstrates how this can be achieved during 3D printing or more correctly during an extruder driven deposition system. Tojeira et al., in a study of 3D printed scaffolds for use in tissue engineering, discovered that by adjusting the process parameters of the 3D printer, they could print elements that exhibited different morphologies.[94] With one set of processing parameters, it was possible to deposit a semi-crystalline polymer with a more or less isotropic distribution of chain folded lamellar crystals. Moreover, other parts of the same object materials could be deposited with a high level of preferred alignment of the chain folded lamellar crystals, by adjusting other processing parameters. These two different configurations resulted in a variation in the measured modulus of the deposited material by a factor of two. Finally, these results were confirmed by using in situ measurements during 3D printing using a novel 3D printer mounted on the NCD-SWEET ALBA synchrotron beam-line. In other words, within the same object, we can deposit material with different mechanical properties to suit the object's design and function. These lead directly to a complete digital definition of the object, both with regard to form and properties and this digital definition can be imposed at the point of manufacturing. Now, as exciting as this is, we need to identify how we might design objects for such manufacturing processes and how the interplay between design and properties can be optimized.

A digital twin is a virtual version of a physical object or process, used to understand, mimic, and predict the physical object or process performance and characteristics.[95] The idea of digital twins grew out of the concept of mirroring developed at the start of the 21st Century, particularly by scientists at NASA.[95] Since that time, there have been many papers published about the concept but few specific practical examples or case studies. A project at CDRSP underlined the value of the digital twin concept to utilize all of the available "know-how" in industrial manufacturing.[96] In the last few years, manufacturers (for example Siemens, General Electric, and others) have publicly discussed their development work in this area and software companies have launched new products to provide support for such industrial activities. A recent paper shows some of the advantages in product or process development, where Ye et al. have used finite element analysis methodologies to support optimization of the product and the manufacturing process.[97] In this impactful work, we will test the mask by using an anthropomorphic head phantom (Figure 7 b) complete with a breathing system and sensors to measure the pressure drop across the mask, the flux, and the temperature on the face and other environmental parameters including humidity (Figure 7c). These outputs are fed directly to the digital twin framework built by using finite element analysis, which can tune the microscopic models involved in the operation of the mask (Figure 7d). The mask will be manufactured by using direct digital manufacturing to conform to the facial contours of a head, which in turn were obtained by using the 3D image of a head of, for example, a specific hospital worker. A number of different heads will be studied and fabricated, and this will allow the digital twin to adapt to the requirement of differing head shapes and facial features. In turn, the digital twin will be able to optimize the design of the mask, using the possibility to define form and function at the point of manufacturing for a specific person dependent on their age and medical condition (Figure 7e). This will transform the so-called personal protective equipment from mass production to tailored personalized equipment for each medical personnel in the hospital. The use of digital twin models in life sciences is essential to reduce or even eliminate the need for in vitro and in vivo studies, saving costs and the life of many animals.

An Italian private company (WASP-CSP s.r.l) translated the above-mentioned concepts to develop and commercialize 3D printed and perfectly ergonomic face masks, following the facial features as a second skin: MY FACE MASK.[98] To reach this goal, an open-source software that, starting from the 3D scan of the face, permits customization and fabrication of a tailored mask for every single user was developed. The software reprocesses user photographs taken with a standard smartphone camera from a distance of one meter to create 3D meshes (Figure 7f). The final personalized mask produced by using 3D printing technology has a perfect connection between face and respirator contours and features a replaceable filter (Figure 7g).

Challenges: From Material Characterization to In Vitro and In Vivo Efficacy Tests

As a parallel task to the materials development, structural information (e.g., morphology, crystallinity, homogeneity) about the polymers and used plasmonic NPs should be obtained by using scanning electron microscopy (SEM), transmission electron microscopy (TEM), X-ray diffractometry, and energy-dispersive X-ray (EDX)-elemental SEM analysis. Vibrational spectroscopy (FTIR, Raman) enables understanding and acquisition of additional information about chemical composition and possible solid-state transformations. The release of the NPs from electrospun matrices should be monitored by using atomic absorption spectrophotometry (AAS). The effect of material thickness and homogeneity of the NPs distribution should be separately revealed to understand differences for the NPs release behavior and bioactivity. Fibrous material mechanical properties and biodegradability should be tested by using standardized tensile strength measurements and for biodegradability weight loss as well as atomic force microscopy (AFM) can be used. All these characterization methods should be treated as a starting point for the next deep characterization of the material applicability. This research step is a standard procedure during the nanomaterial fabrication and does present some specific challenges, and the analysis of the material antipathogen features represents a barrier in the development of effective devices.

In vitro/in vivo efficiency characterization of nanostructured materials enables us to understand the properties of the developed materials and their potential to be used for the manufacturing of reusable face masks with smart nano-assisted destruction of pathogens (the term refers to the mask applied on the face, but according to the filtration efficacy level it can be classified as a respirator). In vitro/in vivo efficiency characterization should be performed in parallel with the electrospinning of nanomaterials to understand the obtained structures and their functionality. In vitro/in vivo characterization of face masks enables us to understand the efficacy, safety, and comfortability of the final face mask. Several tests can be derived from the European or US testing of material guidelines, although the in vitro and in vivo characterization owing to the totally new concept and technology of the mask also requires the development of new testing methods and/or modification of the conventional methods. Indeed, it is likely that even totally new approaches (e.g., digital twin models) can be used as explained in the *3D printing and digital technologies* section. The most important guidelines are the medical device ISO 10993-5:2009 guideline, Organization for Economic Co-operation and Development (OECD) standards and European Committee for Standardization (CEN) respiratory protective device standards (EN 149:2001 + A1) and international medical face mask and respirator filtration performance standards (ASTM2100:11; EN14683:2005; EN149:2001 + A1:2009). Owing to the presence of nanomaterial, also nanomaterial testing EU regulations (COM(2012)542; REACH, ECHA) should be followed.

After complete physicochemical and morphology characterization (using vibrational spectroscopy and microscopic analyses such as SEM, TEM, AFM, mechanical analysis), in vitro analysis of nanostructured materials and face masks should be performed to reveal the bioactivity, efficacy, and safety of the materials. Standard face masks rely on physical filtration, which collects and accumulates pathogens on the surface or within the mask materials. The pathogens can remain viable and infectious for extended periods of time within such face masks.[99,100] Recent randomized controlled trials with healthcare workers showed that respirators, if worn continually during a shift, were effective but not if worn intermittently.[101] For the recent COVID-19 virus outbreak, the evidence of aerosolization of the virus in the hospital ward highlights the risk of inadvertent exposure for healthcare workers and supports the use of airborne precautions at all times on the ward.[102–104] In the case where antipathogen properties are designed into the structure, the efficacy involves both physical filtration together with the inactivation of pathogens on the surface of the mask. For such nanomaterials and face masks, in addition to the particle filtration efficiency (PFE), which is required by the standard approved respirators and NIOSH NaCl test method, bacterial filtration efficiency (BFE) and virus filtration efficiency (VFE), and antipathogen activity of the material should be tested by using biological aerosols, such as viral and bacterial aerosols. As an additional advancement, conducted biological tests should enable us to determine whether the viruses/bacteria attached on the surface of the mask can be efficiently killed by the presence of metal NPs and/or under external irradiation (which enables the mask to be re-sterilized). Hence, it will be determined whether the pathogens captured efficiently by the material will be also efficiently killed. BFE will be determined by using suggested pathogens (*S. aureus ATCC 6538*) and different viruses (bacteriophages and BSL2/BSL3 level viruses) for VFE determination as there are no standardized methods available for VFE. A specially designed VFE setup is needed to study the effectiveness of nanostructured materials to inhibit pathogen penetration. These biological methods have not shown superior results compared with the PFE measurements,[105] however, owing to the different properties of viruses, bacteria, and fungi compared with non-biological particles, biological tests are needed for full understanding,[106] specifically, owing to the effect of aerosolization.

Antipathogen activity and safety of the nanostructured materials and face masks can be tested in vitro (Figure 8a, b), ex vivo (Figure 8c), and in vivo (Figure 8d). Antiviral and antibacterial properties should be studied by using biorelevant pathogens and testing the killing efficiency under external light. The Kogermann research group has experiences in setting up new in vitro/ex vivo/in vivo test systems for the analysis of antipathogen electrospun nanomaterials.[107–109]

These methods can be used and modifications can be performed to improve the model system's biorelevance. Ex vivo models are one step closer to the in vivo testing, giving already more biorelevant information about the properties of the nanomaterials.[110] Safety can be tested on different relevant commercially available eukaryotic cell-lines and antipathogen activity can be tested on various relevant pathogens (e.g., influenza, Coronavirus 299E, *S. aureus ATCC 6538*; *EN14683:2019+AC:2019* strain, *Candida albicans*). Cytotoxicity

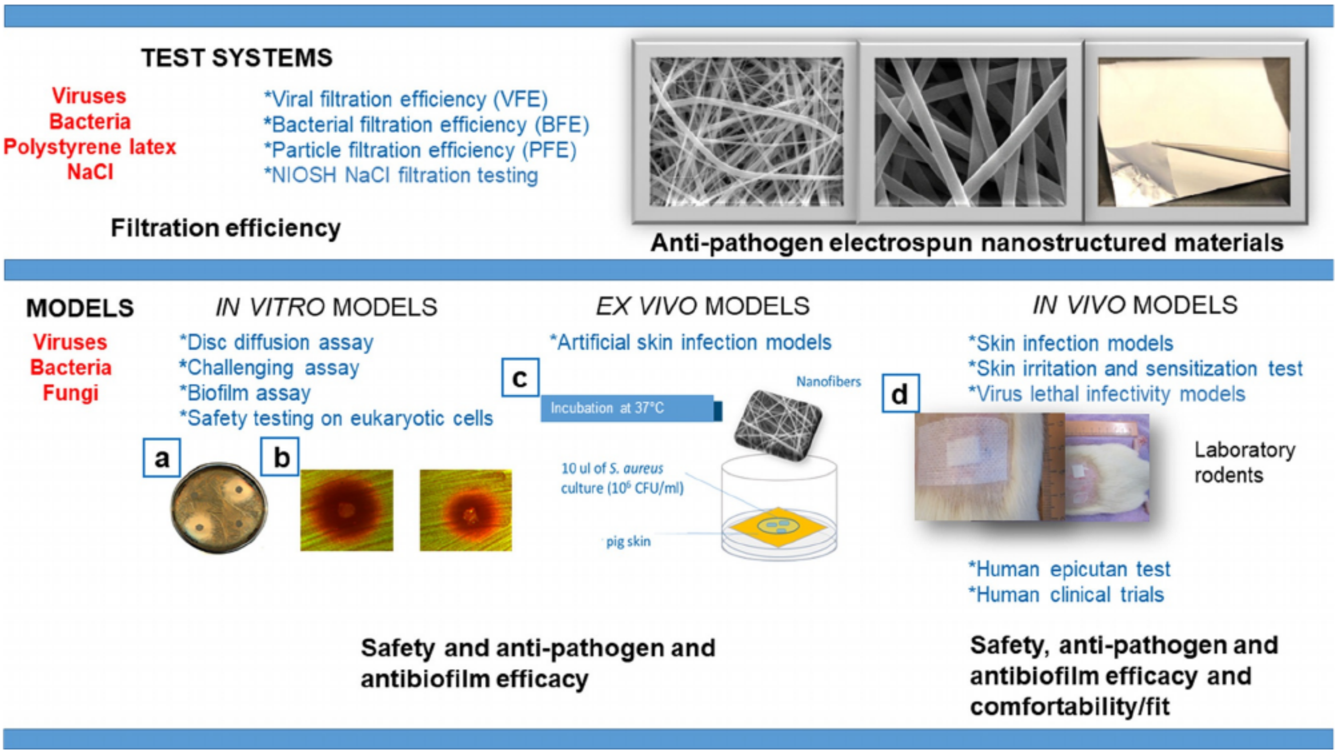

Figure 8. In vitro/ex vivo/in vivo test systems for the analysis of antipathogen electrospun nanostructured materials and face masks. The testing of nanostructured materials and face masks made from such materials for their antipathogen efficiency can be divided into different steps. The first step consists of different test systems providing information about the filtration efficiency: viral filtration efficiency (VFE), bacterial filtration efficiency (BFE), particle filtration efficiency (PFE), and NIOSG NaCl filtration testing. All these testing setups must consider the nanomaterial related properties as well as the test particle/organism related properties. More biorelevant is to mimic the actual conditions faced during the mask-wearing (aerosolized particles/organisms). The second step consists of different model systems that enable us to understand the antipathogen activity and safety of the nanostructured materials and face masks. These can be split into in vitro, ex vivo, and in vivo models. Viruses, bacteria, and fungi can be used for these assays as model pathogens. In vitro models. (a) Schematic shows disc diffusion assay (*E. coli* CFT073) for testing the antibacterial efficiency of electrospun antibacterial agent chloramphenicol-loaded polycaprolactone (PCL) and PCL with polyethylene oxide matrices with appropriate positive and negative controls. (b) Schematics show model bacteria (*E. coli* MG1655) made chloramphenicol responsive (GFP as a control protein for expression (green) and a red mScarlet-I as a reporter protein) and produce red fluorescent marker protein only in the presence of antimicrobial agent. The fluorescent proteins allow monitoring of the release and antibacterial activity of antibacterial agent from two different nanostructured matrices (images courtesy of Mariliis Hinnu). Ex vivo models. (c) Schematic of artificial skin infection model, which enables us to test nanostructured materials for the anti-biofilm and antimicrobial activity. In vivo models. (d) Nanostructured material on rat skin (together with secondary dressing) enabling us to investigate the skin irritation and sensitization of electrospun nanostructured materials. Both animals and humans can be used for the in vivo testing, although information about comfortability and fit of face masks can only be obtained from human trials. Compared with conventional materials and masks (not providing any antipathogen activity), nanostructured materials and reusable face masks with smart nano-assisted destruction of pathogens need to be analyzed for the reactivation capability and long-lasting antipathogen activity.

testing reveals the safety of the nanomaterial as well as the safety of the used functional NPs and tests the possible leaching of NPs from the nanofibrous matrix. It is known that safer NP systems can be obtained after encapsulation into polymeric carriers.[111] In vivo safety can be tested by using animal skin models (e.g., rabbit, rodents) and irritation epicutan tests on human volunteers. Antipathogen activity and filtration efficiency can be tested by using animal infection models, determining the concentrations of virus/bacteria in an animal after exposure to the virus and/or bacteria in aerosol form.[112] In parallel to valuable information about the protective properties of the nanomaterial and face mask, these animal models also enable us to shed light on viral or bacterial behavior.[113] However, the epicutan testing on human volunteers allows testing of the microbial cleanliness after specific time-periods of usage and allows additional information to be obtained about the comfortability during use (humidity, temperature, a fitness test as well as a fit check test) and during sterilization under the external light source illumination. The latter information cannot be obtained from animal studies.

All testing methods should be designed to have alternative options in case some tests do not provide the expected outcomes or difficulties appear during testing. For example, various model bacteria, fungi, and viruses should be tested to investigate the antipathogen activity. Different model system setups should be tested for filtration efficacy testing. In vitro eukaryotic cell tests prior to in vivo animal and human tests are crucial steps for understanding the safety of the NP-loaded antipathogen nanomaterials. Again, various cell-lines should be tested. Different animal models enable an understanding of the suitability of the nanomaterial and face mask material to protect from pathogens and, simultaneously, collect information that the material/face mask itself does not damage the skin. Human tests provide important information about the comfortability of the face mask and most likely larger clinical trials also enable a comparison of the effectivity of the face masks compared with control respirators.

In conclusion, testing the efficiency of the developed technology against viruses remains one of the bottlenecks in the development of effective materials designed to protect against flu-like viral infections.

Summary and Outlook

The COVID-19 pandemic is a global health emergency, and it represents the greatest challenge we have experienced since World War II. We have all learnt that the pandemic is more than a health crisis because it has the strength to produce significant economic and political effects. Before a specific vaccine is developed and utilized widely, we have to learn to live with this new coronavirus while minimizing the risk of transmission. Among the few basic rules we are all aware of, such as social distancing and handwashing with soap, face masks represent a formidable weapon for minimizing the risk of infection between people. However, face masks are currently in short supply and there is very limited evidence that non-medical face masks are effective and, in addition, they are not very well tolerated by certain population groups. For all the aforementioned reasons, there is a need to develop next-generation face masks with a set of fundamental requirements such as: high filtration capabilities, elevated comfort level, moisture pump technology, and self/assisted disinfection properties (Figure 9). Thanks to nanotechnology development, in recent years, it has been possible to design functional devices with unique chemical-physical characteristics. Taking advantage of that, in this Concept, we have tracked a new visionary road for realizing innovative and nanotechnology-driven face masks.

Nanofibers produced by the electrospinning technique and personalized from a library of 3D heads, through a DDM technique, ensure a high filtration level, the moisture pump technology and an elevated comfort level. Engineered and active nanomaterials, decorating the electrospun nanofibers, such as Cu NCs are utilized for their chemically driven intrinsic bactericidal and antiviral activity whereas Au NPs turn out to be excellent photoconverters for exploiting a synergistically assisted photothermal disinfection. The proposed innovation gives a clear vision for the realization of the environmentally friendly next generation of face masks.

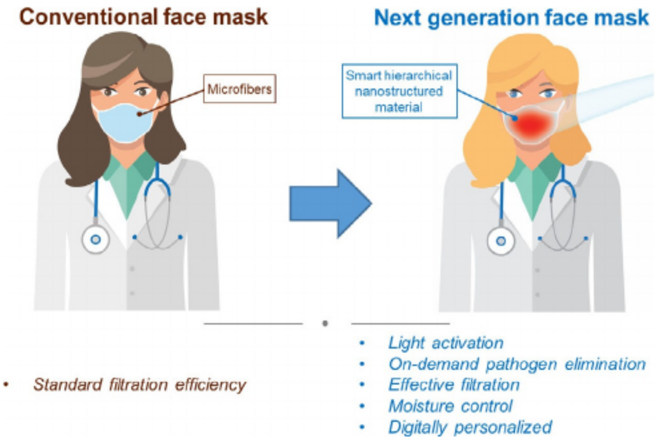

Figure 9. Scheme presenting the novel features given by the development of the next generation of face masks. Commercially available conventional respirators offer different ranges of filtration efficiency obtained by using polymer-based microfibrous structures. The next generation of face mask is designed by applying a brand-new concept, which combines the unique properties of electrospun nanofibers, plasmonic nanoparticles, inorganic nanoclusters, and 3D printed structures. The employment of a functional smart hierarchical nanostructured material furnishes novel fascinating properties to the face mask, including: light activation, on-demand pathogen elimination, effective filtration, moisture control, and the possibility to digitally personalize the final respirator.

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Conflict of interest

The authors declare no conflict of interest.

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