Plasma medicine: Opportunities for nanotechnology in a digital age

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Abstract
Advances in digital technologies have opened new opportunities for creating more reliable, time- and cost-effective, safer and mobile methods of diagnosing, managing and treating diseases. A few examples of advanced nano- and digital technologies are already FDA-approved for diagnosing and treating diseases. Plasma treatment is still emerging as a new healthcare technology, but it is showing a strong potential for treatment of many diseases including cancers and antimicrobial-resistant infections, with little or no adverse side effects. Here, we argue that with the ever-increasing complex healthcare challenges facing communities, including the ongoing COVID-19 pandemic, it is critical to consider combining unique properties of emerging healthcare technologies into a single multimodal treatment modality that could lead to unprecedented healthcare benefits. In this article, we focus on the healthcare opportunities created by establishing a nexus between plasma, nano- and digital technologies. We argue that the combination of plasma, nano- and digital technologies into a single multimodal healthcare package may significantly improve patient outcomes and comfort, and reduce the economic burden on community healthcare, as well as alleviate many problems related to overcrowded healthcare systems.

KEYWORDS
COVID-19, digital technology, nanotechnology, personalised medicine, plasma medicine

1 INTRODUCTION

Globalisation and technology cross-penetration are the common trends defining the future development of human society. This article examines the potential synergies between the plasma, nano- and digital technologies, to deliver benefits to health care. Here, we focus on the current state and recent advances in plasma
Plasma technologies and arising opportunities

Plasma technologies are being intensively investigated across many medical-related areas. Numerous experimental results with preclinical models reveal the potential benefit of plasma in the decontamination of wounds,[1] stimulation of wound healing[2] and in the destruction of cancer tumours.[3] Many of the encouraging results seen in preclinical models are also being clinically translated, with plasma treatments benefiting patients by decreasing the bacterial load on wounds[4] and accelerating wound healing,[5] as well as alleviating symptoms of cancers.[6] More important, the plasma treatments are generally painless and well-tolerated by patients, and without any major clinical side effects reported to date, indicating that plasma technologies can be implemented for relatively safe and effective clinical use.[7]

We emphasise that the above clinical developments of plasma medicine have been accomplished using relatively traditional (for the plasma field) medicine delivery technologies and great enthusiasm and efforts of the associated research community. However, there is now a growing trend in the use of sophisticated nanoscale and digital technologies to effectively diagnose, manage and cure diseases. This opens an opportunity to establish a nexus between plasma, nano- and digital technologies to offer more time- and cost-effective treatments that are personalised for each patient, providing potentially superior clinical and therapeutic outcomes. This is the point we aim to elaborate in this Expert Opinion article.

Purpose and motivation

In this study, we aim to provide a new perspective on how plasma technologies may work in conjunction with nano- and digital technologies to deliver health-related benefits, potentially deployable in common health care and clinical settings. The potential synergies are highlighted in Figure 1, where each arrow denotes interconnections between the three pairs of technologies, namely plasma–nano, plasma–digital and nano–digital. We note that establishing the nexus between plasma, nano- and digital technologies is not as far-fetched as one may think. The potential synergistic benefits from plasma–nano have already been demonstrated through experiments, for example, in the use of plasma to efficiently deliver nanocapsules through the skin barrier,[8] in plasma polymer nanocomposite antibacterial coatings[9] and in the combined use of plasma–nanomaterials for oncotherapies.[10] Moreover, a recent experimental study has demonstrated the beneficial plasma–digital link, where machine learning-based approaches were developed for the real-time diagnosis and control of a plasma source during treatments.[11] It is particularly intriguing to combine plasma, nano- and digital technologies into one healthcare package, which can potentially provide superior patient benefits.

Nanotechnology: A brief introduction

Nanotechnology involves the manipulation of virtually any system (which can include inorganic, organic, biological and chemical matter) at the molecular level to give a new functionality to the system by taking advantage of the unique properties at the nanoscale. Advances in nanotechnology have led to new innovations across many sectors including food[12] and agriculture,[13] renewable energy[14] and medicine,[15] just to name a few. Major advances in nanotechnology have already led to significant improvements in medical diagnosis and in the management and treatment of disease. This includes the development of “capsule endoscopy”[16] and the first U.S. Food and Drug Administration (FDA)-approved “smart pill” Pill Cam, which, as the name implies, is an easily swallowable pill encapsulating a camera. Pill Cam is an example of the clinical translation of nanotechnology research, where nanotechnology is used to develop a biocompatible coating (surrounding the capsule) resistant to strong stomach acids and digestive enzymes, and electronics to take multiple digital photos usually within the small intestine that cannot be reached by traditional
endoscopy and colonoscopy. Moreover, Pill Cam provides an example of the beneficial link between nanomedicines and digital technologies where nanotechnology is used to manufacture the endoscopic capsule at the molecular level and digital technology enables the images to be transmitted to a computer via sensors attached to the abdomen, enabling more accurate and early diagnosis of numerous diseases including cancers.

In addition to diagnosis, nanotechnologies are being translated into clinical use for treating diseases. Perhaps, one of the best examples of the clinical translation of nanotechnologies is seen in the development of nanoparticulate nanomedicines (NNMs). Some NNMs are commercially available for clinical use, and many more are currently undergoing clinical trials.17 Of these, liposomal formulations are the the most widespread form of NNMs and enable formulations consisting of highly toxic and/or poorly soluble drugs to be delivered safely and effectively to patients for clinical treatment.17 For example, a pegylated liposomal formulation containing the chemotherapeutic drug doxorubicin (sold under trade names Caelyx and Doxil) is clinically proven to be effective against metastatic breast cancer, ovarian cancer, multiple myeloma and AIDS-related Kaposi’s sarcoma.18

1.4 | Digital technologies for clinical medicine

In tune with developments of nanotechnologies, the digital revolution is expected to advance predictive healthcare practices and precision medicine, and reduce healthcare costs.19 Digital technologies have led to new approaches for disease treatment including systems medicine, utilising systems biology, which combines interdisciplinary experimental and computational holistic approaches to provide detailed understanding of complex biological mechanisms.20 At the heart of systems medicine are advanced computing and data storage technologies, and highly interdisciplinary teams involving clinicians, epidemiologists, biologists, computer scientists, statisticians and mathematicians.20 The ability to process large data sets has also paved the way for artificial intelligence (AI) in digital medicine.21 AI in medicine involves the emulation of human cognition through machine learning, in which computer algorithms learn from data to make decisions with minimal human intervention. Although the FDA is still developing a streamlined review pathway for AI-based medical technologies, a few systems have already been approved for marketing. This includes a semiautonomous software called ContaCT, marketed by Viz.ai, which operates in parallel with computed tomography (CT) image review by practitioners, to help medical professionals spot early signs of stroke. Another FDA-approved product is the medical device IDx-DR (www.eyediagnosis.co), which uses an autonomous AI system to diagnose signs of diabetic retinopathy in retinal images (without human intervention).

There is also a strong trend towards using AI for continuous digital patient monitoring, without the patient having to attend a clinic for diagnosis.22 Digital continuous care enables the real-time flow of data to medical professionals using digital technologies that record on-patient data (e.g., through implantable, wearable and external devices), transmit the information to smartphones and other external devices, store the data for example in a Secured Cloud and process the data to adapt the healthcare plan as required, with the information ultimately sent to the medical clinic for review and actioning.22,23

Another rapidly developing area of digital technologies is digital manufacturing; for example, digital printing and 3D printing are widely used for prototyping a range of products. These products include various healthcare products such as the surgical masks—the critical personal protective equipment during the ongoing COVID-19 pandemic. However, digital manufacturing of various nanomedicines and nanotechnology-enhanced drug delivery systems are in their very early stage and will be discussed as an opportunity in conjunction with the emerging digital plasma printing technologies.

1.5 | Analysis: Framework and scope

This discussion is focussed on the plasma–nano–digital nexus for applications in health care (Figure 1). By plasma, we refer to atmospheric-pressure, low-temperature sources. Plasma sources with a relatively high temperature, for example, those used for cauterisation, are outside the scope of this article. Establishing a credible link between the three technologies should provide new solutions that are cheaper and more effective in diagnosing, managing and ultimately curing diseases. Among these, links between nano and digital, nano and health, as well as digital and health technologies are relatively more advanced. Some of these cross-penetrating technologies already have demonstrated FDA-approved clinical applications. However, the clinical applications of plasma–nano, plasma–digital, and plasma–health synergies are still at relatively early stages of development. This is particularly true for the combined use of plasma, nano- and digital technologies in the healthcare and clinical settings, which creates major opportunities for research and development in the near future.
1.6 Plasma technologies: Features and achievements

Although the full clinical potential of plasma technologies is yet to be realised, the potential significant benefits of plasma in health has attracted considerable and rapidly growing interest worldwide. A significant body of research has already been established, which provides a solid scientific foundation for the future adoption of plasma technologies in medicine, and encouraging in vivo results have led to a number of plasma devices receiving the European Union (most commonly known as Conformité Européenne) accreditation for medical use in Europe. It is widely recognised that the unique properties of plasmas enable the technology to be potentially suitable for the treatment of many diseases and health conditions. The unique properties of plasma include the ability to readily generate a rich mixture of reactive oxygen and nitrogen species (RONS) when operated in air. The generated RONS are subsequently delivered by plasmas to biological environments. The same RONS generated by plasmas are also generated in our own bodies and are known to be important in disease intervention and maintenance of healthy body functions. Plasma also generates UV radiation and electric currents and electric fields that can also play a role in the biological phenomena described to date.

1.7 Structure of discussion

Herein, we critically examine how the unique features of plasmas can potentially be combined with the nano- and digital technologies, and the potential healthcare benefits that can be achieved by combining plasma, nano- and digital technologies into a single treatment modality. Sections 2 and 3 address the combinations of plasma–nano and plasma–digital technologies, respectively. Section 4 highlights some of the outstanding research needs and challenges of achieving the plasma–nano–digital nexus, and identifies the arising opportunities created by establishing this niche healthcare approach, particularly with respect to personalised medicine. This is exemplified by the (dream big!) approach to diagnose and treat the COVID-19 viral infection at home using home-based antiviral medicine production through a combination of plasma, nano- and digital technologies.

2 SYNERGY OF PLASMA AND NANOTECHNOLOGIES

We now use the selected advances in nanotechnologies for drug delivery (nanomedicine) as a framework to discuss areas where combination with plasma-specific effects may potentially complement and improve the effects offered by nanotechnology alone. The five areas of acknowledged success of nanomedicine are highlighted in Figure 2. In each area, nanotechnology is combined with traditional medical treatments such as ultrasound, heat treatment and others. We use these combinations as a basis to discuss how plasma effects may further enhance the combination-based treatments.

2.1 Plasma–nanotechnology in disease diagnostics and drug delivery

The application of nanomaterials as diagnostic and drug delivery tools in the field of medicine and health care is known as nanomedicine. In the diagnostics area, nanotechnology can significantly improve the diagnosis of early changes in molecular and cellular events (indicative of disease onset) by enhancing the performance of established techniques such as CT, magnetic resonance imaging (MRI), positron emission tomography and single-photon emission computed tomography (SPECT). For example, imaging contrast agents based on inorganic nanomaterials can increase the specificity, sensitivity and image resolution of collaborative imaging between MRI and CT, and thus improve the early diagnosis of tumours.

In the drug delivery area, custom-designed encapsulated nanomedicines can be highly specific for targeted drug delivery, which ultimately improves the onset of drug effects and intake. Although several nanomedicine anticancer drugs, such as Vyxeos (liposomal daunorubicin plus cytarabine) and Onivyde (liposomal irinotecan), have been approved by FDA, the success rate in the clinical translation of nanomedicines is still relatively low. Multiple biological, pharmaceutical and translational barriers contribute to this imbalance.

From this perspective, we observe that plasma technology presents opportunities in the fabrication of more effective nanoparticles for medical diagnostics (e.g., MRI) and drug delivery vehicles; also, it is used in conjunction with nanomedicine and conventional treatment modalities. Promisingly, nanomedicine and plasma treatments have the potential to be combined with tumour-targeted drug delivery, ultrasound and hyperthermia, as discussed below.

Plasma treatments can be used to not only enhance the delivery of nanomedicines, but also to concomitantly increase the RONS concentrations in the biological tissue fluid and tissue, which can potentially act in synergy with nanomedicines for treatment of disease (Figure 2b) and improve the pharmacokinetics...
and pharmacodynamics of drugs. In particular, transdermal drug delivery is an area where the plasma–nano link may have an early impact on health care. For example, nonthermal dielectric barrier discharge (DBD) plasma systems applied directly to skin can generate an electric field of up to 100 kV/cm across the skin’s surface. This inherent property of certain DBD plasmas makes them particularly useful tools for efficiently delivering biologically relevant materials including dextrans, nanoparticles, liposomes and proteins into the epidermal and dermal skin layers.

In addition to skin, plasma can also readily enhance the permeability of cell membranes through synergistic action of electric fields and RONS during the plasma treatment. An increased cell membrane permeability through plasma treatments can significantly enhance the cellular uptake of nanoparticles. For example, DBD plasma treatments can increase cell uptake of Au

FIGURE 2 Plasma and nanomedicine-based combination therapies. (a) Integrating nanomedicine and plasma in multimodal chemotherapy. (b) Exploiting nanomedicine and plasma for ratiometric drug co-delivery. (c) Cotreating to improve penetration, perfusion and extravasation of nanomedicine and plasma species in tumour microenvironment (TME). (d) Ultrasound and microbubbles can increase penetration in the delivery of nanomedicine and plasma-generated reactive oxygen species (ROS) into tissue. (e) Hyperthermia can be used to locally trigger drug release from temperature-sensitive liposomes and ROS generated by plasma. Parts of figure adapted from van der Meel et al. with major modifications from original, with permission.
nanoparticles (AuNPs) by up to 25-fold. The increased cell uptake of the AuNPs enhanced AuNP-dependent cytotoxicity in U373MG cells by increasing AuNP endocytosis and trafficking to lysosomes.

2.2 | Multimodal treatments

Integrating nanomedicines and plasma in multimodal chemotherapy can potentially be used to reduce side effects and improve patient outcomes (Figure 2a). The opportunity for plasma technologies stems from recent plasma applications to synthesise nanoparticles and modify redox environments in cell and tissue treatments. Indeed, recent studies of plasma applications in cell treatment have indicated that reactive oxygen species (ROS) generated by the plasma can destroy cancer cells by altering intracellular regulatory factors, whereas the potentially toxic effects of ROS are mitigated by normal cells through adaptation of their normal metabolic activity.

The combined use of plasmas with nanoparticles has been investigated. For example, AuNPs used in conjunction with atmospheric-pressure plasma treatments were shown to enhance the killing of glioblastoma cells, indicating a potential beneficial synergistic effect of plasma and nanoparticles on glioblastoma cancer therapy. Furthermore, the synergistic effects of liquid media treated with plasma (commonly referred to as plasma-activated media) and nanomaterials have been shown to enhance cytotoxicity in cancer cells.

2.3 | Plasma–nanophotodynamic therapy

The typical structure and function of cancer tumours usually limit oxygen generation and diffusion, which results in hypoxic conditions. The increase in oxygen tension and oxidative stress within solid tumours, therefore, offers potential strategies to help overcome tumour resistance to conventional treatments (e.g., chemotherapy and radiotherapy). Plasma treatments can potentially increase oxygen tension and oxidative stress within tumours through the delivery of ROS. Similarly, the use of nanotechnology in photodynamic therapy can increase oxidative stress tumours with photosensitiser (PS) nanoparticles. The PS nanoparticles can generate ROS from O₂ upon activation at a specific wavelength of light. It is possible that plasma technologies in combination with PS nanoparticles could be used for the future development of new strategies for overcoming cancer resistance to chemotherapy and radiotherapy.

2.4 | Control of acidity in microenvironments

An altered pH in disease microenvironments (e.g., cancer tumours) is a critical factor affecting the effectiveness of drug delivery, especially nanomedicines. Plasma treatments can decrease the pH of the tissue fluid or tissue by formation of peroxynitrous acid. This provides opportunity to combine plasma treatments with nanoparticles conjugated to drugs where the drugs are released on demand under acidic pH microenvironments. The variation of pH with plasma treatments has the added advantages of being a relatively quick (almost immediate) and reversible process, which leaves no toxic chemical residues as compared with many established chemical methods.

2.5 | Localised thermal effects in combined treatments

Localised temperature variation is yet another mechanism that affects the efficiency in the delivery of nanomedicine. Hyperthermia can be used to locally trigger drug release from temperature-sensitive liposomes with a typical size of a few 10s of nanometres. This treatment results in higher drug concentrations at the pathological site and less systemic drug exposure (Figure 2c). More importantly, such delicate localised treatment can be used in cases that require a precise balance between drug efficacy and toxicity. Atmospheric-pressure plasmas can also increase temperature and may be combined with nanotechnologies in the future to induce hyperthermia (e.g., above 40°C) in tissues, which could be advantageous to enhance cell death, for example, in cancer therapy. Hyperthermia may increase the membrane fluidity, thus facilitating the incorporation of plasma-generated ROS into cells, which can induce cell death through excessive oxidative stress.

2.6 | Magnetic field effects

Magnetic fields can transform the functional states and performance of nanocarriers used to deliver medicines. For example, alternating magnetic fields improved the performance of the anticancer drug DOX@FMT-MC encapsulated within a magnetic field-responsive hydrogel for the treatment of colon carcinoma both in vitro and in vivo in a mouse subcutaneous xenografted tumour model. It is possible that magnetic fields generated by the charged particles in plasmas may also enhance certain effects of magnetic nanoparticles, such as by increasing the superparamagnetic transition temperature for treatment of cancer tumours.
3 | SYNERGY OF PLASMA AND DIGITAL TECHNOLOGIES

The potential synergy between plasma and digital technologies is particularly evident through plasma-assisted digital manufacturing, digital control and automation of plasma-based processes. This includes nanoparticle production, which, in turn, could be utilised in plasma-assisted nanomedicine applications discussed in Section 2.

3.1 | Plasma–digital printing in advanced manufacturing

Plasma printing, a form of additive manufacturing (AM), involves the use of digital 3D design data to build up a component in layers through plasma-assisted deposition of materials. Compared with, for example, solid-material milling, AM is more time- and cost-effective and offers increased versatility with respect to design limits, manufacturing and raw materials. AM, therefore, can accelerate growth and innovation in the traditionally linear and time-consuming manufacturing processes,[47,48] thus changing the future technological landscape.[44]

3.2 | Plasma-enhanced advanced manufacturing

Overcoming current limitations of AM (also referred to as 3D printing) in nanoscale manufacturing and creating nanoarchitected matter at industry-relevant conditions require more effective control over the manufacturing processes.[49] Plasma technologies have recently been utilised to overcome challenges recognised in the AM industry. This includes improvements in the mechanical properties of polymeric materials by the combination of plasmas and polymer-based 3D printing, and the use of thermal plasmas in the synthesis of metal alloys and ceramics in a nanoparticulate form.[48] Moreover, we also note here that the plasma process offers more sustainable approaches for 3D printing and nanoparticle synthesis, because it is an environment-friendly and cost-effective technology, eliminating requirements for chemical treatments or harmful solvents.

3.3 | Plasma printing as a standalone technology

The application of plasma technology in printing processes commenced in the early 2010s (distinctive features are captured in Figure 3). For example, micrometre-scale plasma discharges (microplasma) based on a sandwiched electrode–dielectric barrier–electrode design were used for printing chemical features with a resolution of 50–70 μm,[50] with the desired pattern inscribed in the conductive electrode surface or the dielectric barrier layer. An advantage of the microplasma printing process is that it can support roll-to-roll continuous plasma processing on a flexible polymer film for manufacturing at an industry-relevant scale.[48] As mentioned in Section 3.2, it is possible to combine the capability of plasma coating with 3D printing into a single system, which could be useful for virtually an endless number of possible applications. One such application includes the manufacture of bone tissue implant materials. In this example, a plasma jet system was used to chemically functionalise the interior and exterior surfaces of implants with a cell growth-promoting coating.[48,51] We envisage that similar implantable materials could be obtained in the future using 3D plasma printing technologies in a single process (as opposed to chemical functionalisation of prefabricated materials).

3.4 | Plasma–nano printing technologies

Plasma modifications of printed nanomaterials at atmospheric pressure offer interesting opportunities to synergise plasma, nano- and digital technologies aimed at healthcare-related applications. A plasma-based process was used to modify the nanoscale roughness and chemical composition of a 3D-printed bone-scaffold surface, which promoted attachment and proliferation of osteoblast and mesenchymal stem cells.[52] Similar to the plasma processing of textiles and other fibre-based textured materials, plasma treatments may also be adapted to improve the surface features of electrospun nanofibres, for tuning pore size and surface wettability properties.[53]

3.5 | Plasma printing of nanoparticles

Plasma printing using metal nanoparticles generated in atmospheric-pressure plasmas is one of the most recent developments at the interface of plasma, nano- and digital technologies.[54] The process typically involves the use of a plasma jet where inorganic precursors (e.g., metal salts) are nebulised into a gas stream. The precursor is subsequently transported by the gas flow into the region of plasma ignition for the generation of the metal nanoparticles. The plasma jet delivers and deposits the nanoparticles on the target surface with the aid of digital micropositioning control. The described approach has been used to print AuNPs (typically in the 5–10 nm
size range) with nanoscale and microscale features such as vertically oriented graphenes, which have nanoscale edges and micrometre-sized walls. The plasma-printed AuNPs were applied for surface-enhanced Raman scattering to detect biological molecules including proteins, nucleic acids, carbohydrates, lipids, primary metabolites and natural products. This example demonstrates the exciting possibility of developing similar approaches for the plasma printing of nanoparticles in other biomedical applications related to plasma medicine, which opens opportunity for future cross-disciplinary research. Further examples of plasma applications in digital printing can be found in a recent review.\[55\]

### 3.6 Plasma and AI

As highlighted in Section 1.2, AI can potentially be exploited to improve the plasma treatment processes through machine-based learning. For example, real-time diagnostics and data processing and feedback to the plasma control unit can potentially be used to maintain optimal and/or consistent plasma operational parameters (which ideally need to be continually varied to adapt to continuous changes in the surrounding environment and in the biological target during treatments). In addition, reinforcement learning (RL) can also be implemented for learning-based control of plasma jet health-related treatments. RL was shown to be effective at controlling temperature over substrates with different thermal and electrical properties during treatment with a kiloHertz AC-driven plasma jet.\[55\]

The abovementioned AI- and RL-based plasma treatment approaches highlight the opportunity for the future development of safer, more effective plasma-based therapies utilising digital technologies.

### 4 OUTLOOK, OPPORTUNITIES AND RESEARCH NEEDS

#### 4.1 General outlook

The discussions and arguments presented in this article suggest that the synergy of the plasma, nano- and digital technologies is certainly achievable and can be applied in the healthcare and clinical settings. This overall positive and enthusiastic outlook is based on the proven achievements of plasma-based approaches in health care (plasma medicine), biotechnology (plasma biology and plasma biotechnology), nanotechnology (plasma nanoscience and nanotechnology) and digital diagnostics and control of plasma processes. These achievements should be regarded as the solid backbone of many existing cross-penetrating technologies such as bio-nanotechnology, nanomedicine, digital materials' processing (e.g., printing including 3D printing), digital process control and automation, digital medicine and some others.

Although these technologies seem promising, all areas of plasma applications in conjunction with nano- and digital technologies require substantial improvements, both in terms of breadth and depth. This is particularly apparent when a synergistic approach is aimed to contribute to health care and medicine. However, the early stage of such complementary cross-disciplinary approaches should be regarded as an opportunity to engage even more with researchers developing medical, nano- and digital technologies that are poised to shape the future of humankind in the coming decades.

More importantly, the nature of plasma-based approaches should be regarded as assistive, enabling technologies, which can work in synergy with other technologies, to deliver tangible outcomes in the
envisaged (e.g., clinical) applications. The associated practical benefits should be appreciated by the practitioners representing the relevant industries to the extent that they are willing to invest in plasma devices and processes and to hire appropriately trained personnel.

### 4.2 Dream big: personalised plasma–nano–digital medicine

We do realise that some of the opportunities that we present below may sound like a dream at this stage. Yet, a dream often leads to the vision, strategy and the plan, followed by specific projects leading to new knowledge and practical outcomes. This is why we will put forward one overarching dream as an example and then highlight the research needs to make this dream come true.

Our dream is the *personalised plasma–nano–digital medicine*. Imagine a sick person who wants to get diagnosed and be treated successfully even without leaving his/her home. Such a need is particularly critical during the lockdown induced by the COVID-19 global pandemic, which has wrecked all imaginable aspects of human life in just a few months since the epidemic outbreak in late December 2019 in China. The successful outcomes in virus spread control are contingent upon deep social isolation, which necessitates the widely adopted quarantine measures. Under such personal isolation conditions, in addition to the overwhelming overload of the healthcare system, visits to a doctor may not even be possible.

Under such conditions, the first step is to collect body fluid(s) and subject them to the approved disease test kit, for example, a device which can detect antibodies in blood of a person infected with SARS-CoV-2 coronavirus that causes the COVID-19 infection. After the suitable digital device reads the information presented by the test kit, the integrated AI system should be able to determine if the test returns positive (infected) or negative (not infected) results, and then guide the patient to take further actions. If the infection is mild, recovery at home may be possible, whereas if the infection leads to severe pneumonia-like symptoms, there is no alternative to the specialised treatment in infectious disease hospitals, with severe cases requiring intensive care units.

How could nano-, digital and plasma technologies possibly be combined to facilitate personalised diagnosis and treatment of the coronavirus infection? We suggest this could be through the preparation of a treatment drug after the digital prescription by the “AI doctor” in the event of the mild infection and the prescribed recovery from home. However, caution should be taken due to the commonly accepted limited reliability of the “AI doctors” (which is presently at the research and development stage), necessitating the personal general practitioner to check the symptoms, test results, and so forth, and validate (with or without modifications) the prescription made by the AI doctor, in the foreseeable future. Once the drug is prescribed, the integrated personalised plasma–nano–digital pharmaceutic device would produce the drug, in either liquid or solid forms. In this case, the drug might be developed through a combination of plasma and nanotechnologies alongside conventional chemical and molecular biology processes.

### 4.3 Big dream—New research needs

How to make the above dream come true? Certainly, one needs to identify what needs to be studied, identify the knowledge gaps and develop the research study, that is, the things we learn during graduate studies and continue learning throughout our lives. Without trying to be exhaustive, we will only present a few ideas for some of the obvious research and development needs arising from the interesting *personalised plasma–nano–digital medicine* opportunity introduced above.

#### 4.3.1 Disease-specific and nonspecific drugs

This opportunity is eternal, and with the emergence of more diseases, more drugs will be needed. Given the long lead time from drug (e.g., antiviral vaccine) discovery to the approved clinical applications, the demands for both disease-specific (e.g., vaccine targeting COVID-19 infection) and nonspecific (generic immunity-boosting) drugs are escalating. As currently there are only a handful of reliable, disease-specific antiviral drugs, the needs and opportunities in the discovery and development of target-specific drugs are becoming more critical.

#### 4.3.2 Home-made antiviral nanovaccines

Vaccines are commonly made using inactive viruses or nanoparticles engineered with the specific viral features, such as the whole spike or a special host receptor recognition protein of a SARS-CoV-2 coronavirus. This opens the (yet) elusive opportunity to devise small plasma-based devices where nanoparticles could be engineered and mixed with the vaccine media, which could also be activated by plasmas.
4.3.3 | Home-printed, nanotechnology-enhanced antiviral masks

Future efforts should aim to develop plasma devices which can sterilise antiviral (e.g., common N95 surgical) masks and print the whole mask layers of customised sizes and even porosity to capture virus-containing aerosols of certain sizes. Furthermore, plasma printing is already capable to print antipathogenic Ag nanoparticles on many substrates including soft fibrous tissues.

4.3.4 | Plasma polymer nanocomposite coatings on textiles

There are numerous strategies for developing antimicrobial surfaces utilising low-temperature, low-pressure plasma technologies. A very effective strategy has been to incorporate nanoparticulates in the form of inorganic metals and metal oxides into plasma polymer coatings that can be deposited in one step. These coatings have shown a high efficacy against target pathogens. It is possible that similar coatings can also be developed against viruses, and as such they may be used as antiviral coatings on masks and other protective garments.

4.3.5 | Home-made sanitising liquids

Whereas the abovementioned nanotechnology-enhanced antiviral drugs will require quite a long time to be developed and approved, some simpler healthcare products could be customised and fabricated at home. For example, plasma-activated water contains significant amounts of hydrogen peroxide at reduced pH, which can be customised depending on the cause (e.g., specific bacterial strains or viruses) of pathogenic contamination of surfaces, using simple and portable plasma discharges, in a digitally programmed way. In a more advanced setting, plasma discharges digitally monitored and controlled by AI and positioned using digital positioning tools could be used along with nanotechnology-based pathogen recognition systems, to eradicate harmful bacteria and viruses, specifically in the areas of detected contamination.

4.3.6 | Reliable and safe plasmas for home use

The plasma devices are envisaged for personalised, easy and safe use even at home. Portable battery-operated plasma devices are presently available and are being developed for commercial use in several countries. The key considerations for the utility in the future plasma–nano–digital devices are reliability, electric and chemical safety, easy adjustments, reproducibility and ability to operate over a long term. Such devices have not been used yet for either nanotechnology or digital printing applications. Although some community efforts are on the way, we are not aware of any currently published efforts.

4.3.7 | Small portable diagnostic kits

Reliable and cost-effective personal diagnostic test kits are on the agenda of personalised medicine. More important, plasmas have already been routinely used in inductively coupled plasma mass spectrometry (a large and expensive system) to ionise samples for species detection and chemical analysis. We envisage the possibility to scale down the plasma sources for integration into small portable diagnostics, for example, in a microfluidic chip format.

4.3.8 | Pathogen sterilisation

Although we note that plasma is not approved by FDA for sterilisation, numerous studies have demonstrated the broad-spectrum antimicrobial properties and surface cleaning capability of plasma devices. If plasma treatments also prove equally effective against viruses, it should be possible to develop low-cost plasma devices to replace the use of hand sanitisers and disinfection agents, which have been used worldwide during the ongoing COVID-19 pandemic.

These selected research needs are just the tip of the iceberg. It is clear that the number of possibilities and opportunities is almost infinite. This is particularly true at the triple junction between the nano-, plasma and digital technologies, where the synergy is expected to deliver benefits to health care and medicine.

5 | CONCLUSION

The purpose of this article was to provide new insight into the manner by which the field of plasma medicine might advance using both nanotechnology and digital platforms. We have highlighted a few of the many possibilities created by combining plasma with nano- and digital technologies such as the development of superior nanoparticulate medicines, drug delivery systems and AI
approaches for more effective plasma-based treatments. The review also explained how the creation of new personalised plasma–nano–digital medicine could be used to alleviate future global healthcare crises such as the recent COVID-19 pandemic by providing quicker patient treatments without the risk of disease transmission to the community and healthcare providers. This one (potentially many) example(s) demonstrates the potential significant socioeconomic benefits afforded through the establishment of combined plasma–nano–digital healthcare practices.

Living in this troublesome current pandemic time, we should be cautious of the future, not only because we can expect even deadlier and more global viral outbreaks in the future, but also because there is a large number of other health and medical-related issues where the synergy of the nano-, plasma and digital technologies can contribute. It is the perfect time to consider unmet research needs that will aid the development of new healthcare approaches to help us live happier and healthier. Strengthening collaborative cross-disciplinary efforts will help make this ultimate and most important for all of us dream come true, let us dream about what matters most...and act!

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