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Letter to the Editor

Plasma Robot Engineering: The Next Generation of Precision Disease Management

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Abstract—Robotics, once combined with cold atmospheric plasma, represent key elements of the next generation of personalized medicine and contribute to the effective yet immediate response to pandemics. Plasma robots can serve as CAP delivery vehicle to assist in tumor therapeutics and viral disease prevention in addition to the already prevalent utilities of robots in precision surgery, diagnosis, and risk prevention. Plasma robots may develop at either the macro- or the micro- scale, successful navigations at which require joint effort from multiple research domains.

Keywords—Cold atmospheric plasma, Medical robot, Therapeutics, Diagnosis, Prevention, COVID-19.

INTRODUCTION

In response to the outbreak of COVID-19, the roles of robotics in managing public health and infectious diseases have been brought up-front including disease prevention, diagnosis and screening, patient care and disease management.[15] Apart from the prominent roles that robotics may play in social interactions and telecommunications, medical robotics, once armed with specific disease management tools, may have already been able to significantly enhance the living quality and prolong the longevity of diseased persons in clinics and will take on novel functionalities if combined with emerging therapeutic modalities such as cold atmospheric plasma (CAP). We bring into focus the novel role of CAP in preventing SARS-CoV-2 infection *via* destroying virus capsids and docking the primary receptor away from cell surface (unpublished), and the promising avenue of joining it together with robotics towards robotics-aided plasma medicine for the prevention and therapeutics of diseases, at both micro- and macro- scales, not limited to viral infection.

THE USE OF COLD ATMOSPHERIC PLASMA IN DISEASE MANAGEMENT

CAP belongs to the fourth state of matter and is a cocktail of reactive oxygen and nitrogen species.[3] Its roles in disinfection and wound healing have made it an effective tool in treating diabetic foot and reducing blood loss during surgery.[7] Its selectivity against cancer cells have been discovered in 2007 and proved in many types of tumors such as melanoma, pancreatic cancers, and breast carcinomas.[3] The first attempt of using CAP as an onco-therapeutic approach was conducted in 2016 where the life of a 75-year late-stage pancreatic patient was rescued. The efficacy of CAP is dose-dependent that could trigger, e.g., cell cycle arrest, autophagy, apoptosis and necrosis, by varying parameters of CAP and need to be precisely controlled to achieve desirable therapeutic outcome.[4] Such a precision could be only achieved by carefully programmed robotics. In cases where the loci of the malignancy are difficult to reach and/or accurate targeting is fundamentally important to disease cure and life quality such as when treating glioma, the aid of

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robotics to CAP in disease therapeutics is indispensable (Fig. 1a).

Importantly, the roles of CAP in preventing SARS-CoV-2 infection against human cells have been recently unveiled, opening the opportunity of establishing plasma robot for the purpose of COVID-19 prevention. By imposing cells with oxidative stress,[13] CAP resembles viruses and triggers cell natural immunogenic response to fight against viral invasion without hijacking cellular survival system and reproducing pathogens. This makes CAP a type of physical non-specific vaccine and the establishment of a robotic system to enhance our ability in tackling pandemic emergencies caused by other pathogens possible. US Medical Innovations have lately established Canady Helios™ Cold Plasma Hero™* System for COVID-19 therapy that could deliver reactive oxygen species (ROS) to the lung of the patients where virus capsids were destroyed (Fig. 1b). This makes CAP a possible tool for killing coronaviruses distributed in the environment or attached in the human/animal skin if developed into cleaning equipment/detergent or therapeutic ejection source, where robotics-assisted techniques are required for accurate distribution of CAP to infected tissues through throat without causing nausea and discomfort in the latter case (Fig. 1b). In addition, our study using live SARS-CoV-2 unveiled the role of CAP in docking ACE2, the primary receptor mediating SARS-CoV-2 entry to host cells, away from cell surface (unpublished), making CAP a novel type of vaccination approach immunizing cells to SARS-CoV-2 infection that is possibly developed into products such as nose spray.

CAP-activated medium (PAM) have offered additional flexibility to plasma therapeutic modalities, which can convey equivalent efficacy and activity as CAP within a few hours. Robotics made in nanoscale could function as nano-vehicles to intelligently carry PAM specifically to the targeted sites and return back once elicited the cargoes with the help of the monitoring system, and function as the preserving agent before use if made with specialized nanomaterials (Fig. 1c).

THE USE OF ROBOTS IN DISEASE MANAGEMENT

Robotics have been deployed for a diversity of disease management, including therapeutics, diagnosis, and infection prevention.

For therapeutics, robotics could be used to enhance the precision, flexibility and controllability of surgical operations. Robot-assisted surgery (RAS), a milestone

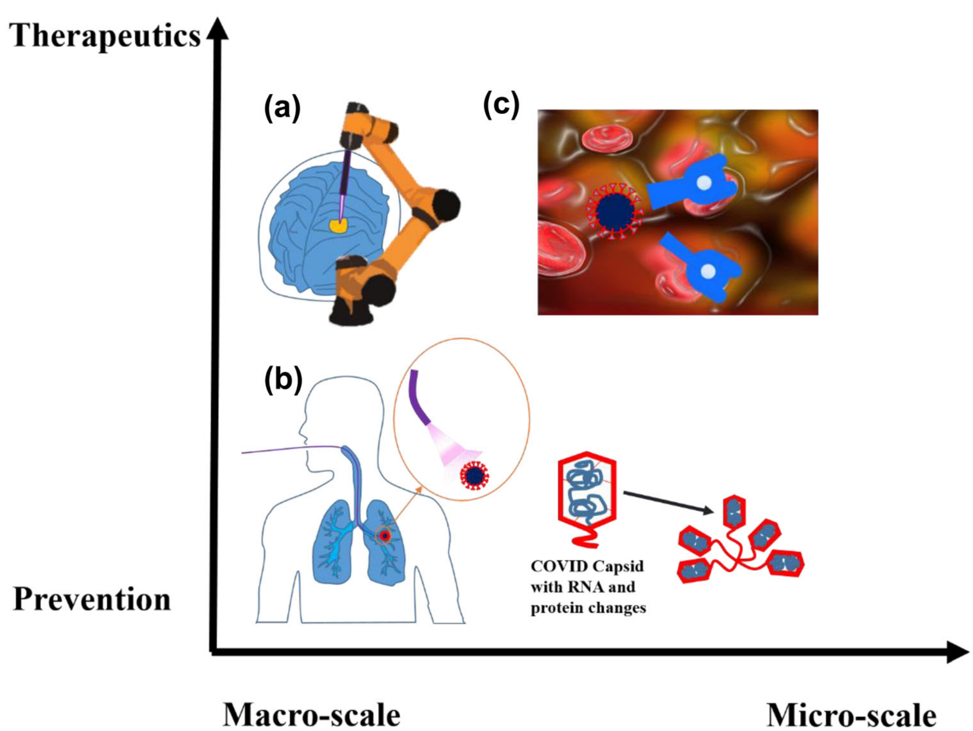

FIGURE 1. Example application schemes on plasma robots towards the next generation of precision medicine. Robots, at both the macro- and micro- scales, can help aid in disease therapeutics and prevention, with example application schemes including (a) robot-assisted CAP delivery for tumor therapeutics, (b) robot-assisted CAP delivery for COVID-19 prevention, and (c) nanorobot-assisted PAM delivery for tumor therapeutics.

in minimally invasive surgery (MIS), has been adopted by an increasing number of medical centers for surgeries in fields such as head and neck, thoracic, urology, gynecology, cardiac, colorectal, and spine.[14] Robot-assisted surgical system can insert instruments *via* multiple or single incisions. Flexible robot surgical systems have been established to enable natural orifice transluminal endoscopic surgery (NOTES) that could minimize or even eliminate skin incisions,[1] with the transoral surgery such as robot-assisted endoscopic submucosal dissection as a typical clinical example. Telerobotic surgical systems permit surgeons to perform operations on a patient from a remote site, taking advantages of one or multiple surgical instruments and a video telescope. Compared to surgical excision of cancers, other non-surgical procedures are emerging, such as ablation therapy (i.e., radiofrequency/microwave/laser ablation and cryoablation), radioactive particle implantation and minimally invasive CAP, where robots can serve to increase the therapeutic accuracy with the help of monitoring systems. Image-guided robot techniques have been used to guide the needle or nozzle to the targeted area for tumor ablation and implantation. Images from techniques such as magnetic resonance and ultrasound could help surgeons to precisely locate the ablation therapeutics to the targeted issues, and carefully programmed instruments could control highly flexible nozzles along the curved paths through tissue without vice-damage.

For disease diagnosis, combining robot and artificial intelligence in medical imaging can largely enhance the diagnostic precision.[5] Biopsy has been used to diagnose many types of cancers such as prostate, thyroid, liver tumors, where robots may play key roles. Robot-assisted needle positioning could largely enhance the target precision during biopsy. Image-guided robots can be used to guide accurate needle insertion during blood drawing. Flexible robot access can be used for biopsy in constrained intraluminal approach such as robotic minimally invasive biopsy in the lung.

For disease prevention including pandemic such as COVID-19, robots could help reduce disease prevalence through keeping a safe distance between patients and health individuals. High-risk infection imposes a great challenge to all aspects of health management, such as surgeons' exposure to infected patients and cross-infection risk among patients during surgical procedures.[12] With the help of the 5G network that is featured by ultra-low latency, robotic system for telemedicine has emerged.[2] During remote surgery, the surgeons could operate in low protection room with reduced requirements on medical resources including the medical staff and shortened patient hospital stay as a result of minimal invasion.[8]

DISCUSSION

To this end, we could foresee two directions for plasma robot development. At the macroscopic scale, CAP can be combined with highly flexible catheter-based manipulator to deliver CAP *via* an intervention approach. Apart from robot-assisted nasopharyngeal and oropharyngeal swabbing, flexible robotic manipulator can precisely position CAP in the upper respiratory tract to take on actions. In addition, robotic-assisted bronchoscopy can deliver CAP to remote and hidden parts of the lung that are difficult to reach otherwise. Ion Intuitive Surgical (FDA approval, by Intuitive Surgical Inc.), an endoluminal robot that uses ultra-thin robotic catheter with advanced maneuverability to navigate deep into the peripheral lung, is an ideal example. Although CAP could be introduced into the respiratory track of a patient through a ventilator or continuous positive airway pressure (CPAP), using robots could avoid complications such as ventilator-associated pneumonia that are typically associated with prolonged duration of mechanical ventilation and ICU stay [9] due to largely shortened treatment time as a result of enhanced precision. At the microscopic scale, exploring nanomaterials with particular functionalities (such as drug packaging and activity preservation) and modifying their surfaces to enable self-directed targeted delivery vehicles represents another direction that is particularly useful for being combined with PAM. Self-direction could be achieved by monitoring the robots through luminescence detection as driven by chemical or physical properties enabled through e.g., surface etching, modification or labeling. This requires not only expertise from the field of robots and medical care, but also nanomaterials and chemistry.

Robots, either at the macroscopic or micro-scale, could be intelligently combined with CAP or PAM for disease therapeutics and prevention. The multi-modality nature of CAP and its diverse medical applications including both therapeutics and prevention make it an ideal tool for disease management. The strong requirement of CAP on dose control[4] and the ability to reach diverse organs to act on its multi-faceted functionalities make the chaperone role of robots, featured by accuracy and flexibility in size and design, irreplaceable.

Plasma robots, by combining both robots and CAP, represent key elements of the next generation of personalized medicine as featured by cancer therapeutics and contribute to the establishment of effective medical prevention system in response to urgent pandemic caused by emerging pathogens. Successful establishment of such robotic systems requires the wide application of CAP in achieving the aforementioned therapeutic functionalities in clinics and delicate design of the robot operational system for accurate CAP delivery and dose control. While the former needs proof from multiple clinical trials, the latter replies on delicate design on the mechanical configuration, electronic circuitry and control system. Robots for transluminal operation with CAP need to have a long reachability and be extra small in diameter. Hyper redundant, continuum or concentric-tube structure are potential solutions, where decoupling transmission, variable stiffness structure, and flexible material represent challenging goals in this area. The electronic circuitry can be developed for powering CAP at the end instruments, actuating the robot and processing the signals from the sensors. The power processing unit for CAP may have a wide frequency range, the optimization of which is essential for plasma quality and stability. The need of a high frequency for CAP source requires a careful circuit design on electromagnetic compatibility to avoid any potential negative influence on the performance of the robot located in the proximity to the power. A standard electronic interface at the robot terminal may also be designed to make it adjustable to various CAP devices. At the macro scope, the electronic parts of robots with long reachability may be placed at the base end to reduce the payload except for distal sensors such as endoscopes. At the micro scope, highly integrated micro-electromechanical systems and *ex vivo* magnetic field producing electronic circuity system are good approaches for robot miniaturization. Besides, the control system is complex due to the high degree of freedoms, nonlinearity, high requirement of operational precision. Robotic operation can completely depend upon human control using the 'master–slave' mode or be autonomous. In some cases, CAP needs to be precisely positioned to the targeted tissue for, e.g., accurate scanning, and thus requires the design of a highly stable tracking control to increase the level of autonomy without sacrifice the safety.[10] To autonomously position CAP to the targeted issue through a certain passage using a continuum robot, visual and haptic sensors could be combined as the input so that robots with high degree of freedoms could be controlled along the navigated path *via* force sensing.[6] The positioning algorithm needs to take into account of error compensation as such robots are typically tendon driven and with high flexibility. Regarding both the task to be accomplished and the robot device design, the control system needs to be capable of coping well with various environments uncertainties and varied system parameters.[11] Taken together, success in navigating at the two directions of plasma robot development, i.e., macro- and micro-, requires domain knowledge from mechanics, physics, medicine, nanomaterials, chemistry, computational scientists, as well as close cross-disciplinary collaborations.

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AUTHOR CONTRIBUTIONS

XD conceptualized the study and prepared the initial draft. HL participated in manuscript conceptualization and writing. MN contributed to manuscript finalization. All authors contributed to manuscript revision, and read and approved the submitted version.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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