Proposal responding to: COVID-19 Basic, Translational and Clinical Research Funding

Opportunity

Targeted Electron Radiation Theranostics of COVID-19 by Laser Wakefield Accelerators (LFWA)

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SUMMARY

We propose to investigate targeted sterilization as well as diagnosis and therapy (theranostics) of the coronavirus disease 2019 (abbreviated COVID-19) by adopting a compact, flexible and tunable electron accelerator technology called laser wakefield acceleration (LWFA). LWFA is several orders of magnitude more compact than a conventional electron accelerator[1] and can target specific areas that may not be otherwise accessible. The targeting is performed by an electron beam emitted from the tip of thin fiber optic cable. Owing to the small size of LWFA devices, a portable unit could sweep specific portions of the human body or equipment for sterilization. Moreover, the output beams from LWFA are on the order of micrometers, enabling localized and precise direction and application of electrons.

The proposed treatment of COVID-19 will be performed in two steps: (1) In a bronchoscopy-liked procedure, an electron beam from a fiber optic cable can target specific parts of the lung. (2) The electron beam will interact with high-Z materials deposited into the lungs via two proposed methods: a) Physical, wherein a high-Z material (agent) is inhaled or injected and allowed to disperse in the lungs and b) Chemical, wherein a nanoparticle or an ACE2 protein both loaded with a high-Z material (agent) and specifically designed to target the virus, is introduced in the lungs via direct inhalation or injection. It is expected that the chemical agent will accumulate in the alveoli region where it seeks the viral infection.

The electron beam interacting with high-Z matter can undergo electron slowdown, production of secondary electrons, and production of Bremsstrahlung photons[2]. Therefore, the rationale for the agent irradiation is to drastically reduce electron penetration in the body while targeting only infected cells. This targeting method was motivated by a study that demonstrated that Auger electrons, generated by monoenergetic irradiation of high-Z loaded nanoparticles concentrated in cancer cells, destroyed a tumor mass[3]. Electron and photon bombardment can also inflict lethal damage to virus DNA and other infected regions.

The combination of a high-Z physical agent and an internally generated electron beam could lead to a localized dose deposition within the lungs. In a more advance prototype, loading of the chemical agent to targets cells could be up taken by the coronavirus, resulting in localized dose deposition in the infected lung region while sparing healthy tissue. This process could be similar to a high-dose rate lung brachytherapy treatment[4], but with a targeted agent highlighting the affected region and without a radioactive source.

SPECIFIC AIMS:

We propose an innovative electron beam delivery system by placing the compact LWFA electron device on a tip of a fiber laser, shown in Fig. 1a and inserting the fiber laser and the LWFA assembly directly into lungs as shown in Fig. 1b. In this internal delivery, low-energy electron energy is required. Accordingly, this proposal has two specific aims:

1. To diagnose and treat the coronavirus disease 2019 (COVID-19) using a compact and flexible electron accelerator technology called LWFA[1] (laser wakefield acceleration).
2. Localized delivery of this electron beam to high-Z materials deposited in the lungs using two-level sophistication:
    a. Physical targeting: To investigate the use of a specifically designed nanoparticle loaded with a high-Z material (agent) that can be inhaled and dispersed throughout lung's volume. Due to the systemic nature of viral infection, this treatment provides advantage by localizing dosage in the lung volume.
    b. Chemical targeting: To investigate the use of a specifically designed nanoparticle or ACE2 protein loaded with a high-Z material (agent) that can bind to the COVID-19 virus. This treatment provides advantage of providing treatment directly to infected sites.

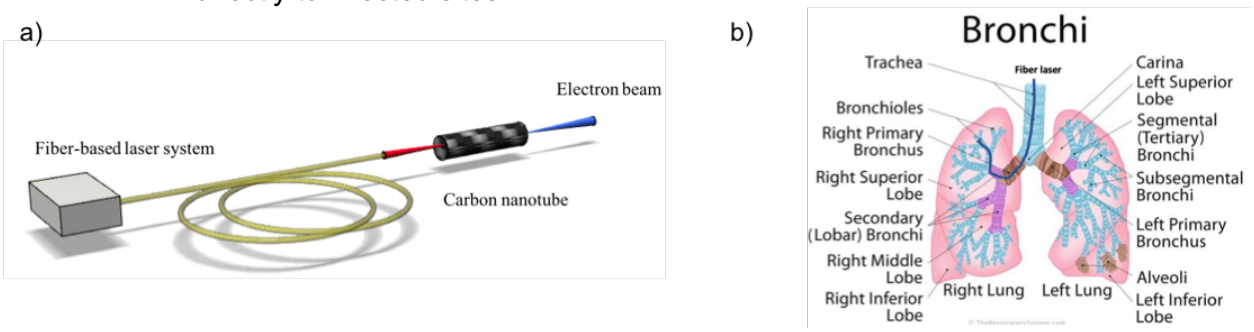

FIGURE 1: a) Schematic of a micrometer sized fiber-based laser system irradiating a carbon nanotube (CNT) to generate an electron beam. Not to Scale. Figure depicts the fiber flexibility and compact size. b) Schematic of fiber-based laser insertion into the lung through patient's trachea and bronchi. The electron beam is generated from the tip of the fiber, as shown in a.

The LWFA mechanism, invented by PI Dr. T. Tajima, can accelerate electrons over a distance of several microns by converting material (e.g. gas or carbon nanotubes) into plasma. Plasma is capable of sustaining 1000x times greater accelerating electric field[8] compared with a conventional linear accelerator (LINAC), which is limited by an electrical breakdown. Fiber lasers are laser systems in which the active gain medium is an optical fiber doped with rare earth elements; erbium or ytterbium are the most commonly used. Fiber optic cables are highly flexible with a small bending radius. LWFA could also be achieved using coherently added fibers known as Coherent Amplification Network[7] [CAN],

This proposal brings together collaborators from various departments at UCI, UCLA and École Polytechnique (France), as well as industry partners, to perform the highly interdisciplinary work of adopting the LWFA mechanism to novel clinical treatments for COVID-19. Dr. D. Roa is a Clinical Professor of Medical Physics at UCI, specializing in novel technologies for radiation theory. Dr. H. Moyses is an Assistant Clinical Professor at UCI and clinical radiation oncologist with an active practice. Dr. R. Jin is a Professor of Physiology & Biophysics at UCI, specializing in the molecular basis of human diseases. In addition to the inventor of LWFA, Norman Rostoker Professor of Physics at UCI Dr. T. Tajima, our team consists of Physics Nobel Laureate and expert in novel laser technologies, Prof. G. Mourou, and

experts in the LWFA mechanism, Dr. A. Necas (simulation) and Dr. A.E. Hussein (experiment). Dr. F. Tamanoi is a leader in the application of nanotechnology to cancer radiation therapy.

The proposed viral treatment approach was motivated by the work of Dr. F. Tamanoi that focused on selective cancer cell destruction[3]. This study demonstrated that gadolinium loaded mesoporous silica nanoparticles (Gd-MSN) up taken outside the cancer cell nucleus and exposed to a monochromatic X-rays resulted in almost complete destruction of the tumor, while sparing healthy cells. Selective cell damage was accomplished by tuning the X-ray energy to the Gd K-shell energy (50.25 keV) resulting in a release of low energy Auger electrons localized to the cancer cell, resulting in DNA damage and disruption of vital cellular functions.

From this study, it can be inferred that a coronavirus treatment with an external electron beam coupled with high-Z loaded agents is feasible. High-Z materials are chosen to increase local density and thus electron stopping, furthermore the photons interaction cross section scales as ~Z^3 (Z=79 for gold), which could release subsequent Auger electrons[3] or photoelectrons. However, high electron energy is required to externally penetrate the liquid-filled lungs with ~10 cm width[6]. Such beams may be generated using LWFA or a LINAC, but an external electron beam may result in electrons stopping in a healthy tissues and bones prior to reaching the infected lungs, limiting dose at the infected site and shortening the treatment time to avoid other complications. For internal delivery, low electron energy is required, and dose can be targeted to the infected sites.

IMPACT:

Currently, there is no treatment for COVID-19 and the general treatment of viruses in general concentrates on shortening the duration and decreasing the severity. **The proposed work addresses a crucial need in targeted radiotherapy treatments of viruses in the lungs.**

During the first half of the 20th century, radiotherapy was used to treat pneumonia with a remarkable cure rate[4]. However, radiotherapy treatments stopped in the 1930-40s due to the lack of a rigorous scientific justification. Almost 100 years later, we have witnessed the SARS outbreak (2002), the H1N1 pandemic (2009), MERS (2012) and now, the COVID-19 (2019-20) pandemic, each highly infectious and associated with acute respiratory distress. While this proposal concentrates on the treatment of COVID-19, we believe that the proposed techniques can be applicable to treat other respiratory infections.

One known pathway to kill the virus is ultraviolet-C (UV-C) radiation[5]. UV-C light is suitable for inflicting fatal damage to the viral RNA/DNA makeup. In theory, UV-like radiation could be delivered to the COVID-19 infected sites by means of aims 2 a) and b), in which a physical or chemical targeting agent could be administered to the patient via direct inhalation or injection. In the case of chemical targeting, the agent would bind to the infected cells specifically, highlighting the affected region that would subsequently be irradiated by the LWFA electron beam.

APPROACH AND INNOVATION:

In phase one, we propose to perform theoretical and computational study based on the low energy electron generation by laser irradiation of near-critical density of carbon nanotube (or carbon foam)[9]. The laser pulse length, along with the focal spot and intensity are free parameters to be varied in simulations performed with the particle-in-cell (PIC) code EPOCH[10]. A 2D simulation is sufficient to capture the most salient physics and yet be computationally feasible to perform a large parameter scan. The goal of simulations is to demonstrate a realistic parameter regime that can generate electrons with sufficient energy to penetrate the lungs assuming a fiber laser tip located at the end of bronchus, bronchi and bronchioles, shown in Fig. 1b. Such positioning is a tradeoff between a high-energy and single stagnation point (bronchus) vs. a low-electron energy with constant repositioning (bronchioles) to irradiate a single lung.

In phase two, we propose to sample the electron source energy distribution generated in phase one and transport electrons inside the infected lung impregnated with the agent. These simulations will be performed with the Monte Carlo code MCNP[11]. We propose to adapt the ORNL MIRD lung phantom (as shown in Fig. 2) for the MCNP, which already provides the nuclide weight ratio in a healthy lung and will be modified to include the agent. The goal of this study is to generate secondary electrons and photons in an energy range to effectively disrupt the virus.

In parallel to phases one and two, we propose the development of a specific high-Z carrying agent – ACE2. This will be performed in silico study using the spike glycoprotein (S protein) of coronaviruses protrudes from the viral envelope, which mediates viral entry by binding human receptor, angiotensin-converting enzyme 2 (ACE2), and fusing viral and cellular membranes. We will express and purify the recombinant virus-binding domain of human ACE2, which is reported to bind to the virus S protein with a high affinity around 20 nM. We can then load a high-Z element, such as Gd, to our recombinant ACE2, so that ACE2 will bring Gd specifically to the virus, without targeting healthy human cells. At the same time, we are developing anti-SARS-CoV-2 antibodies. When available, we could use these antibodies to deliver the high-Z element to the viruses.

POTENTIAL FOR EXTRAMURAL FUNDING:

This is an innovative and novel treatment technology that could provide a huge advancement in contact radiation treatment in terms of precise guidance and targeting. Furthermore, this could open new treatment possibilities while improving existing ones, particularly in the field of high-dose rate brachytherapy. The elimination of radioactive sources to deliver a brachytherapy treatment, which has been the hallmark for decades, provides benefits in terms of radiation safety, elimination of source replacement due to decay, and reduction of shielding costs.

The next stage of this theoretical and simulation work will be experimental demonstration of suitable electron beams via LWFA driven by fiber laser systems and fiber laser delivery. We expect that these could be attractive features that would catch the attention of industries, from pharmaceutical to laser and optical companies, as well as government funding agencies (e.g. NIH, NSF and DOE).

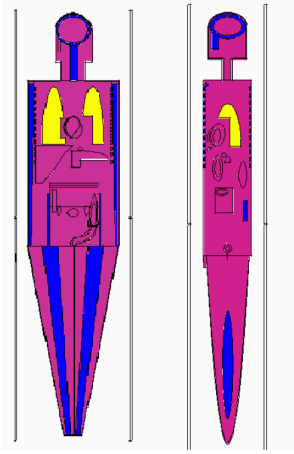

FIGURE 2: MCNP representation of lungs based on the Oak Ridge National Lab MIRD phantom.

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