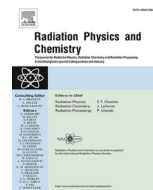




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## Proposal on the use of Xenon-133 against COVID-19

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### ABSTRACT

Since we are able to bring ionizing radiation in the form of a gas cloud to the respiratory system, we have wondered whether Xenon-133 inhalation could be exploited as a treatment option against Covid-19 respiratory virus infections, and urge colleagues in the scientific research community who have the capability to do so to explore the merits of using Xenon-133 in this way to determine whether its usefulness against the Covid-19 virus is indeed genuine.

Covid-19, a disease caused by the SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) virus is known to involve the passages of the nasopharynx and airways of the lung via the receptor for the enzyme angiotensin-converting enzyme 2 (ACE2) which is most abundant on the surface of type II alveolar cells of the lungs (Verdecchia et al., 2020). Although ACE2 receptors are also found in the digestive system, a recent study of tissue taken from infected rhesus macaque tissue found that the majority of viruses are found in the lungs (10E9–10E11 RNA copies/gram of tissue) (e.g., virions) with other parts of the respiratory system (nasal mucosa, pharynx, trachea, bronchus, tonsil and lymph nodes) accounting for an additional 10%, compared to numbers found in the digestive system (10E3–10E7 RNA copies/gram of tissue) (Sender et al., 2020).

Since nuclear medicine, utilizing a clinically routine procedure referred to as a Pulmonary Ventilation study (Mettler and Guiberteau, 2006) can bring ionizing radiation in the form of a gas cloud directly to the respiratory system through the continuous closed circuit breathing of radioactive Xenon-133 (<https://capintec.com/product/xenon-133-rebreathing-systems>), we propose exploring its usefulness as an additional tool to target and treat Covid-19. Our hypothesis is that electrons from this radionuclide would inflict direct and indirect molecular damage to the SARS-CoV-2 single-stranded RNA virus within the respiratory system locations.

Xenon-133, an inert gas, releases as part of its decay profile Ultra-low-energy electrons (ULEE), conversion, beta and Auger electrons (Kocher, 1988) generally termed Auger electrons. Some of these ULEEs are close to the energies of electrons cited in recent published Monte Carlo calculations on electron beam irradiation (Zhang et al., 2020; Feng et al., 2020) as having produced optimal energy deposition and

ionization in the target coronavirus.

Auger electron decay is characterized by a cascade of very short-range electrons. Because of this, Auger electrons, unlike externally applied radiation, deposits a large fraction of their energy in nanoscopic volumes (Rezaee et al., 2014). It is this intense local deposition of energy that might be expected to directly damage virus RNA of encountered virus particles within the respiratory space.

Similarly, it is known that when ionizing radiation deposits its energy in matter, it produces large amounts of ions, radicals, and excited secondary electrons with initial kinetic energies below 100 eV (Huels et al., 2003). These transients may also be expected to possibly lead to substantial physical and chemical modifications of the medium and induce further virus RNA damage.

Internal dosimetry schema of the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine (Bolch et al., 2009) is unsuitable to assess a damage potential to something the size of a virus particle. MIRD calculations only provide for assessment of the absorbed dose to whole organs, tissue subregions, voxelized tissue structures, and individual cellular compartments.

To evaluate the efficacy of Auger electrons at the molecular range, researchers were able to use a nanodosimetric model developed from the cellular dosimetric model developed from the MIRD committee approach (Rezaee et al., 2014). One of the conclusions from this model was that the absorbed dose from <18 eV ULEEs emitted from the Auger-electron radionuclide <sup>125</sup>I in a nanometric volume of DNA (i.e., 4.2 nm<sup>3</sup>) substantially contributed to single-strand break (SSB) and double-strand break (DSB) lesions within DNA, with SSBs produced in relatively higher amounts.

Their results indicated absorbed doses within the nanometric volume

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to be, depending on the specifics of the experimental condition, 272 and 205 kGy, resulting from absorption of only 12.1 and 9.1 eV. They found a threshold energy for rupturing the DNA phosphodiester bond at 3.2 eV, and concluded from this that the deposited energy by ULEEs from this nuclide should in principle be sufficient to induce more than one strand break.

There are as one might expect differences due to measurement uncertainties and variations in the percent intensities and energies between  $^{125}\text{I}$  as used in these experiments and the  $^{133}\text{Xe}$  being considered in this proposal. But if one were to allow that the energies of these two nuclides were comparable, one could calculate a rough estimate of approximately  $2\text{E}11$  decay events occurring at typical diagnostic administered activities of  $^{133}\text{Xe}$  (15 mCi with a 5-min continuous rebreathing period). From this, using 12 eV, the average energy per decay of  $^{125}\text{I}$  in their model, one could derive a potential  $>6\text{E}10$  bond breaks occurring.

Whether absorbed doses from these ULEE electrons would indeed cause radiation induced critical damage to the virus in-vivo is unknown, and in our opinion, would require actual in-vivo experimentation. A major factor would be the actual proximity of the virus RNA in relation to this internal energy source within the respiratory spaces. But the potential based upon this information and these approximations is promising.

MIRD calculations classify this radionuclide at the above referenced diagnostic administered activities, to be of minimal risk, with an effective dose of only 0.405 mSv (40.5 mrem) (<http://www.doseinfo-radar.com>). Further dose escalation either through increasing the administered activity, increasing the rebreathing period, or both, would be manageable if higher administered activities were found to be required to produce a therapeutic effect.

This form of treatment would be one of the few methods of directly targeting the virus to potentially control the viral load at these sites. And it would be best suited to treat carriers of the virus or individuals in the early stages of the disease since patient cooperation would be needed in handling the inhalation of the agent.

An additional benefit to such an approach if Xenon-133 were found to be effective against the Covid-19 virus as we hypothesize, would be that the therapeutic impact on the virus would be direct and not mediated through immunological mechanisms, and would therefore prove valuable against any mutations of the coronavirus that might arise over time.

It is our hope that colleagues in the scientific research community who have the capability to do so will explore the merits of using Xenon-133 in this way to determine whether its usefulness against the Covid-19 virus is indeed genuine.

## Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

## CRediT authorship contribution statement

**Frank P. Dawry:** Conceptualization, Writing - original draft, Writing - review & editing. **Aldo N. Serafini:** Writing - review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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