# A Critical Look at Heavy Ion Beam Irradiation for Vaccine Development

Payman Rafiepour (PhD)[1], Seyed Mohammad Javad Mortazavi (PhD)[2,3]*, Lembit Sihver (PhD)[4,5,6]*

[1]Department of Nuclear Engineering, School of Mechanical Engineering, Shiraz University, Shiraz, Iran
[2]Ionizing and Non-ionizing Radiation Protection Research Center (INIRPRC), Shiraz University of Medical Sciences, Shiraz, Iran
[3]Department of Medical Physics and Engineering, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[4]Department of Radiation Physics, Technische Universität Wien, Atominstitut, 1040 Vienna, Austria
[5]Department of Chemistry and Chemical Engineering, Royal Military College of Canada, Kingston, ON, Canada
[6]Department of Physics, East Carolina University, Greenville, NC 27858, USA

## ABSTRACT

Recent studies offer valuable insights into viral inactivation for vaccine development. Schulze et al. have demonstrated the potential of heavy ion beam irradiation to create effective vaccines, which is particularly relevant in the context of airborne pandemics. Notably, the success in immunizing mice via intranasal administration with the inactivated influenza virus is encouraging, especially given the genetic similarities between influenza and SARS-CoV-2. However, the study raises important considerations. While heavy ion treatment shows advantages, there are concerns about viral inactivation completeness and the potential for surviving viruses, albeit at extremely low levels. Prolonged irradiation times and the risk of selective pressure leading to the evolution of resistant variants are highlighted. Biosafety concerns regarding accidental lab escape of resistant strains are crucial, emphasizing the need for caution during experiments. Moreover, limitations in Monte Carlo simulations of virus irradiation are discussed, pointing out the need for more comprehensive studies to assess the impact of secondary particles on virus inactivation under realistic irradiation conditions. Given these considerations, while the study presents a promising approach for vaccine development, further research is essential to address potential drawbacks and optimize the method for safe and effective application.

**Citation:** Rafiepour P, Mortazavi SMJ, Sihver L. A Critical Look at Heavy Ion Beam Irradiation for Vaccine Development. *J Biomed Phys Eng*. 2024;14(3):315-318. doi: 10.31661/jbpe.v0i0.2405-1765.

## Keywords

Heavy Ion Beam Irradiation; Vaccines; Viruses; Viral Inactivation

## Introduction

A recent study by Schulze et al. titled “Influenza Virus Inactivated by Heavy Ion Beam Irradiation Stimulates Antigen-Specific Immune Responses” [1] offers a valuable contribution to the field of viral inactivation for vaccine development. The authors convincingly demonstrate the potential of heavy ion beam irradiation as a method to create vaccines, particularly timely given the ongoing threat of airborne pandemics. We applaud the authors for reigniting interest in this approach. Professor Durante’s success in immunizing mice via intranasal administration with the inactivated influenza virus is particularly encouraging, especially considering the similarities between influenza and SARS-CoV-2 in their genetic makeup and replication [1].

However, to gain a more comprehensive picture, it’s important to consider additional aspects:

**Potential for Selective Pressure**

While heavy ion treatment offers clear advantages, there might be

*Corresponding authors:
Seyed Mohammad Javad Mortazavi
Department of Medical Physics, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
E-mail: mortazavismj@gmail.com

Lembit Sihver
Department of Radiation Physics, Technische Universität Wien, Atominstitut, 1040 Vienna, Austria
E-mail: lembit.sihver@tuwien.ac.at

Received: 14 May 2024
Accepted: 26 May 2024

limitations concerning viral inactivation completeness. The authors themselves acknowledge that a small percentage of viruses might remain active even after irradiation. While their calculations suggest this percentage would be extremely low (below 0.000000001% at a 50 kGy dose), the potential for even a small number of surviving viruses is concerning. Furthermore, the extended irradiation times needed (approximately 5 hours at 50 kGy with the employed settings) raise questions about viral heterogeneity. Viruses with inherent radiation resistance could be more likely to survive, potentially leading to the evolution of new, resistant variants with altered pathogenic properties. This risk of selective pressure is a crucial consideration, especially compared to methods like low-dose radiation therapy (LDRT), which don't exert such pressure [2].

**Biosafety Concerns**

Given the potential for generating resistant strains, it's imperative to exercise extreme caution during these experiments. Accidental lab escape of such a variant could have devastating consequences [3,4].

**Limitations in Monte Carlo Simulations of Virus Irradiation**

There are some limitations in Monte Carlo simulations of virus irradiation. First, the indirect effects of radiation (i.e., due to the interactions of free radicals following water radiolysis) are not taken into account, which makes sense due to the absence of liquid water around the virus [5]. Second, Monte Carlo simulation studies are usually performed only for a single virus placed in a vacuum or a water medium as an aerosol [5-8]. The dimensions of the radiation source are considered to be the same size as the virus, and all primary particles (here, iron ions) completely pass through the virus. Therefore, the interactions of heavy charged particles with equipment and holders (with materials such as plastic, ice, etc.) and the possible production of secondary photons and electrons are not considered. The cross-sectional data available in track structure Monte Carlo codes, suitable for nano- and micro-scale simulations, are usually valid for liquid water [9]. Simplifying the simulation of the environment surrounding the virus is justified and interesting to compare different linear-energy-transfers (LET). Nevertheless, more studies are needed for a dosimetric investigation of a specific beam at specific depths. In experimental conditions, on the one hand, due to the relatively high volume of the viral sample and on the other hand, due to the spot scanning irradiation system, there is a possibility that a virus is not exposed to a direct impact of a primary iron ion. Although a sufficient dose is delivered to the entire target volume, the dose in some areas may be caused by secondary particles resulting from the interactions of heavy charged particles. The generated secondary particles can be a factor that structurally damages the spike proteins and takes us away from the goal of a "clean" inactivation. However, directly irradiating a single virus with iron ions may be impossible in an experimental situation, but this is what has been implemented in previous simulations [5-8]. Therefore, a comprehensive simulation study is needed to examine the impact of the produced secondary particles at different depths of an iron ion beam (especially at the Bragg peak location) on virus inactivation, considering more realistic irradiation conditions. Figure 1 shows two possible cases for simulation: 1- A single virus in a water medium with the ice density placed behind two layers of plastic. 2- The same arrangement but with a large number of viruses that are exposed to radiation in a specific volume. In each case, the volume of the box containing the virus as well as the thickness of the layers may be changed, and the effect of secondary particles can be investigated. Primary and secondary particles are shown in red and black arrows, respectively, in Figure 1.

## Conclusion

In conclusion, Professor Durante and his

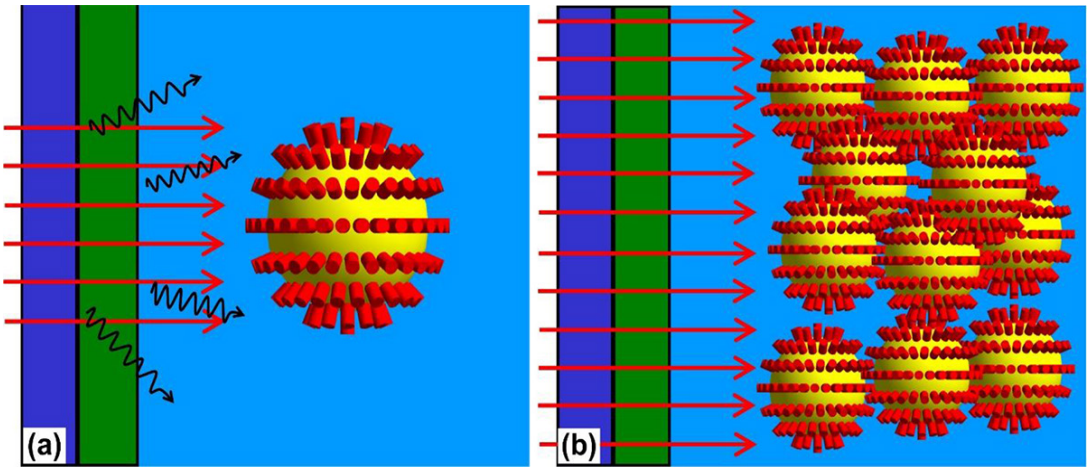


**Figure 1:** (**a**) A single virus irradiated in a water medium behind two layers of plastic. (**b**) A large number of viruses irradiated at the same time. Primary and secondary particles are shown in red and black arrows, respectively. The dimensions are not to scale.

colleagues present a promising avenue for vaccine development. However, a thorough evaluation of potential drawbacks, particularly regarding selective pressure and biosafety, is crucial before widespread adoption. Further research is necessary to optimize this method and ensure its safe and effective application.

## Authors' Contribution

SMJ. Mortazavi, P. Rafiepour and and L. Sihver conceived of the presented idea. All authors provided critical feedback and helped shape the research, and manuscript.

## Conflict of Interest

SMJ. Mortazavi and L. Sihver, as the Editorial Board Members, were not involved in the peer-review and decision-making processes for this manuscript.

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