Abstract: Despite accumulating preclinical data demonstrating a crucial role of cytotoxic T cell immunity during viral infections, ongoing efforts on developing COVID-19 vaccines are mostly focused on antibodies. In this commentary article, we discuss potential benefits of cytotoxic T cells in providing long-term protection against COVID-19. Further, we propose that gamma-ray irradiation, which is a previously tested inactivation method, may be utilized to prepare an experimental COVID-19 vaccine that can provide balanced immunity involving both B and T cells.

Keywords: SARS-CoV-2; COVID-19; Gamma-ray irradiated vaccine
reinfection [8,9]. Furthermore, a recent serological study reported that 40% and 12.9% of asymptomatic and symptomatic individuals, respectively, became seronegative within 2–3 months after infection [10]. Therefore, unless the vaccine induces immunity more efficiently than the live virus, one would expect that vaccine-induced antibodies will likewise be short lasting. Achieving sterilizing immunity by antibody-based vaccines may prove difficult.

Given the above, Tc cell immunity against coronaviruses may present an important aspect of any successful vaccine as it is thought to be long-lived. Recent studies have detected SARS-CoV-2 reactive T cells that are capable of expressing IFNγ and/or granzyme B in 40~60% of uninfected individuals [11,12]. Notably, this percentage increased to 80–100% for convalescent COVID-19 patients, suggesting that (1) unlike antibodies, Tc cells against coronaviruses persist in humans and can be detected months and/or years after an infection; (2) memory Tc cells are directed against conserved regions of coronaviruses and therefore are broadly cross-reactive; and (3) specific T cell responses are associated with recovery from SARS-CoV-2 infection. An implication based on these observations is that coronaviruses will be less likely to evade Tc cell immunity due to MHC class I polymorphism. Indeed, a potential benefit of T cell responses was recently demonstrated in two clinical studies that found an inverse correlation between severe COVID-19 and lower CD4+ and CD8+ T cell blood counts on admission [13,14]. Thus, there are realistic benefits for considering T cell-based vaccination approaches against COVID-19. Future studies are needed to determine whether Tc cell immunity influences the clinical course of SARS-CoV-2 infection and whether the presence of SARS-CoV-2 reactive Tc cells prior to an infection correlates with the development of less severe COVID-19. It is important to note, however, that T-cell-based vaccines will unlikely provide sterilizing immunity against SARS-CoV-2 since cytotoxic T cells will engage after an infection of host cells. Therefore, an ideal COVID-19 vaccine should stimulate both B and T cell immunity to complement each other to provide optimal protection against severe COVID-19.

Several forms (inactivated, recombinant protein, DNA, RNA, and viral-vector-based) of COVID-19 vaccine candidates are currently being evaluated in clinical trials. Whether these experimental vaccines are capable of providing protective T cell immunity in humans is currently unknown and should be investigated. In particular, DNA- and RNA-based vaccines, in theory, should generate MHC-I antigens in situ in a manner similar to natural viral infection. However, it should be noted that DNA vaccines have been tested against other infectious diseases in humans and have failed in the past to demonstrate the induction of strong immune responses [15–17]. As for inactivated and purified viral vaccines, a substantial amount of data exists in the literature that inactivated antigens are mainly dependent on the MHC-II pathway and therefore they are not anticipated to mount strong MHC-I-restricted immune responses [18–20]. Lastly, although several viral vectors are currently approved for human use, several challenges exist for their application. These include (1) immunodominance of the vector genes over transgenes; and (2) pre-existing anti-vector immunity due to natural exposure to the virus or induction of anti-vector immunity upon first use, which would not permit effective use of the same viral vector in the same patient.

Generally, the generation of Tc cell immunity requires live viral infection, and therefore most viral inactivation methods eliminate T cell immunogenicity. However, early studies in the 1970s and 80s have identified gamma-irradiation as a superior inactivation method that can better preserve T cell immunogenicity relative to other inactivation procedures. This favorable characteristic of gamma-irradiation can be attributed to the high penetrative strength of gamma-rays that cause direct damage to genetic material without altering structural proteins [21]. Therefore, gamma-irradiated viruses should be able to infect host cells without producing infectious progeny. Indeed, we have previously demonstrated that alphaviruses [22] and bunaviruses [23] can be rendered non-infectious by gamma-irradiation and yet still possess the capacity to generate cytotoxic T cell responses. We later applied gamma-irradiation to prepare an experimental influenza vaccine and reported that gamma-ray irradiated sterile influenza virus preparations promote Tc cell immunity [24–27]. Most importantly, gamma-ray irradiated influenza virus preparations were highly protective against heterologous
influenza infections, including H5N1 avian flu, in mice, and this T cell memory was found to be long-lived [24–26,28]. This experimental protocol of using low dose-rate sterilizing gamma irradiation of whole viruses for induction of long-lasting Tc cell immunity has been shown to be generally applicable if the immunodominant Tc cell determinants are located in structural virus proteins [24]. This approach may enable the SARS-CoV-2 spike protein to enter the class I MHC antigen presentation pathway [11].

The obvious strength of a gamma-ray irradiation approach is that virus replication can be eliminated while preserving its infectivity and immunogenicity, thus presenting the viral proteins to the immune system in a natural way, facilitating the induction of both T cell and humoral immunity. In addition, vaccine manufacturing has been greatly simplified, solely requiring cell culture virus growth, purification, and low-dose inactivation using a gamma ray source generally readily available for sterilization procedures of commercial products. Lastly, our previous work has also demonstrated an antigen dose sparing effect of gamma-irradiated virus in mice [27] (discussed in Furuya [29]). This, of course, is important during a pandemic when enough vaccine doses are needed to be manufactured with limited production capacity in a short time frame. Therefore, a gamma-ray irradiated virus vaccine could fulfill the unmet need for a safe, cost-effective, widely distributable COVID-19 vaccine.

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