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Perspective

Diagnostic, Prognostic, and Therapeutic Use of Radiopharmaceuticals in the Context of SARS-CoV-2

Roger M. Pallares and Rebecca J. Abergel*

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ABSTRACT: The coronavirus disease 2019 (COVID-19) outbreak has devastated the healthcare systems and economies of over 200 countries in just a few months. The etiological agent of COVID-19, SARS-CoV-2, is a highly contagious virus that can be transmitted by asymptomatic and symptomatic carriers alike. While *in vitro* testing techniques have allowed for population-wide screening, prognostic tools are required to assess the disease severity and therapeutic response, contributing to improve the patient clinical outcomes. Moreover, no specific antiviral against COVID-19 exists at the time of publication, severely limiting treatment against the infection. Hence, there is an urgent clinical need for innovative therapeutic strategies that may contribute to manage the COVID-19 outbreak and prevent future pandemics. Herein, we critically examine recent diagnostic, prognostic, and therapeutic advancements for COVID-19 in the field of radiopharmaceuticals. First, we summarize the gold standard techniques used to diagnose COVID-19, including *in vitro* assays and imaging techniques, and then discuss how radionuclide-based nuclear imaging provides complementary information for prognosis and treatment management of infected patients. Second, we introduce new emerging types of radiotherapies that employ radioimmunoconjugates, which have shown selective cytotoxic response in oncological studies, and critically analyze how these compounds could be used as therapeutic agents against SARS-CoV-2. Finally, this Perspective further discusses the emerging applications of radionuclides to study the behavior of pulmonary SARS-CoV-2 aerosol particles.

KEYWORDS: *coronavirus, COVID-19, SARS-CoV-2, radionuclide, radiochemistry, positron emission tomography, radiotherapy*

1. MOTIVATIONS AND BACKGROUND

In December of 2019, a pulmonary disease called coronavirus disease 2019 (COVID-19) first emerged in the city of Wuhan, China and rapidly spread to the rest of the world.[1,2] The etiological agent of COVID-19 is SARS-CoV-2, a new type of coronavirus that showed highly efficient transmission between humans.[1,3] Symptomatic patients diagnosed with COVID-19 often displayed fever, respiratory complications, pneumonia, and dyspnea.[4] However, at early stages of the disease, asymptomatic carriers were also highly contagious,[5,6] causing a rapid and widespread virus transmission that resulted in several millions of people getting infected with COVID-19 in a few short months. Thus, on March 11, 2020, the World Health Organization officially declared COVID-19 a global pandemic.[7]

Current pandemic management strategies include early diagnosis, treatment, and long-term immunization. Because SARS-CoV-2 could be readily transmitted via asymptomatic carriers, several cost-effective and efficient testing techniques were implemented to recognize and isolate infected patients. The sequencing of the virus genome helped to identify a set of target genes for large-scale and high-fidelity screening via real-time polymerase chain reaction (RT-PCR) protocols.[8] Although most common COVID-19 clinical manifestations include fever, cough, fatigue, and dyspnea, advanced cases may cause respiratory failure through acute respiratory distress syndrome that can be fatal.[9,10] Hence, there is a need for sensitive prognostic tools that can assess disease severity and track patient evolution after treatment, particularly in severe cases. Regarding strategies to treat COVID-19 infection, available medicines have only served to alleviate patient symptoms, and no specific antiviral is commercially available for COVID-19 treatment at the time of writing this Perspective. Several drug candidates, however, have shown promising therapeutic capabilities *in vitro* and *in vivo*.[11−13] For long-term immunity, major international efforts have been made to develop a vaccine against COVID-19,[14] despite the irregularity of novel vaccine developments in recent years. For example, while a vaccine for H1N1 influenza was completed

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relatively rapidly because influenza-vaccine technology has been well-established for years, other recent epidemics, such as the SARS and Zika virus outbreaks, were contained before a vaccine was ever fully developed.[14]

SARS-CoV-2, along with SARS-CoV and MERS-CoV, belong to the β-coronavirus genus. Coronaviruses are a group of positive-sense, single-stranded ribonucleic acid (ssRNA) viruses with a characteristic spike glycoprotein envelope which mediates viral entry into the host cell.[15] Spike proteins can be divided in two parts: the S1 subunit, which binds to the host cell receptor (angiotensin-converting enzyme 2 or ACE2, in the case of SARS-CoV-2), and the S2 subunit, which mediates fusion of the viral and host cell membranes (Figure 1).[16] Because spike proteins are a key

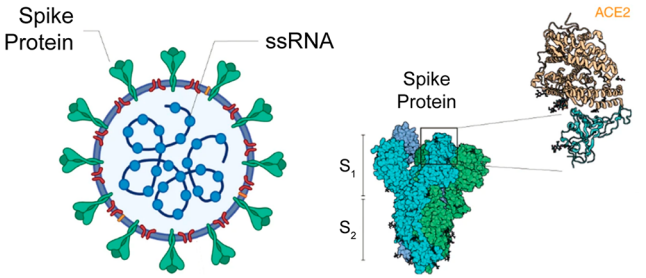

Figure 1. Etiological agent SARS-CoV-2 and spike protein. Schematic illustration of SARS-CoV-2 and spike protein with S_1 and S_2 subunits highlighted. Adapted with permission from ref 16. Copyright 2020 Springer Nature.

component of infection and are exposed on the surface of the virus, novel vaccines have focused on developing neutralizing antibodies for spike proteins. Lastly, based on the identification of viral nucleotides, both SARS-CoV-2 and SARS-CoV were likely zoonotically transmitted to humans by bats.[17] The several recorded spillovers of coronaviruses from animals to humans as well as the detection of multiple coronaviruses in bats may forecast new epidemics in the future.[18] Hence, current efforts to develop novel diagnostic and therapeutic strategies against SARS-CoV-2 will likely yield improved capabilities for the current and future outbreaks.

In this Perspective, we summarize the recent advances in the field of radiopharmaceuticals for COVID-19 diagnosis, prognosis, and therapy and offer prospects for emerging opportunities. We initially describe the state of the art in the diagnosis of COVID-19 and analyze how imaging techniques based on radiotracers can provide clinically relevant information for patient prognosis and treatment management. Moreover, using as a starting point a recent debate on whether external beam radiotherapy could be used to treat COVID-19 pneumonia, we explore new emerging types of radiotherapies that use immunoconjugates to obtain selective cytotoxic effects and how those constructs could be used against SARS-CoV-2. Finally, a new use for radionuclides to model the behavior of COVID-19 aerosol particles is discussed.

2. DIAGNOSIS AND IMAGING OF COVID-19 PATIENTS

Serological assays and RT-PCR are the most common *in vitro* tests to diagnose viral infections such as COVID-19 in patients.[19−21] RT-PCR is particularly useful at the early stages of the infection, given that it can detect viral genomes independent of a patient's immunological response.[8,22] Thus, RT-PCR has become the gold standard technique for COVID-19 diagnosis with newly developed assays providing results in just 45 min.[23] However, a high incidence (between 2 and 29%) of false negative results has raised concerns regarding its diagnostic reliability, particularly in asymptomatic patients.[24−27]

In addition to *in vitro* assays, high-resolution computed tomography (CT) imaging of the chest is a preferred technique for screening, diagnosing, and monitoring patient recovery from COVID-19 induced pneumonia.[28,29] This imaging technique employs multiple X-ray measurements from different angles to generate specific cross-sectional images of body parts,[30,31] providing anatomic information on the patient (Figure 2). CT can identify COVID-19 related lesions and

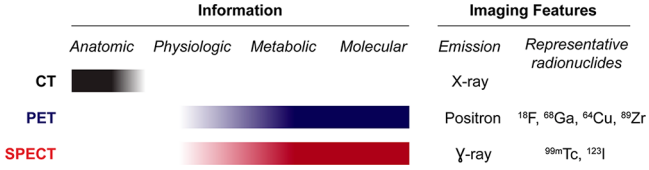

Figure 2. Comparison between different nuclear imaging techniques.

track disease progression: at early stages, plaques, nodules, and ground-glass density lesions can be observed in a patient's lungs, and as the pneumonia worsens, the amount of damaged tissue increases.[32] CT sensitivity for COVID-19 diagnosis is at 97.2%, which improves the sensitivity values initially reported for RT-PCR (83.3%).[33] Thus, it has been recommended to isolate patients with positive CT findings even if they have negative RT-PCR results.

Although chest CT shows high sensitivity for COVID-19 pneumonia diagnosis, imaging modalities that employ radiotracers can also yield accurate diagnostic results while providing additional information.[34] For instance, in January of 2020, before the COVID-19 outbreak was formally recognized, positron-emitting fluorodeoxyglucose (^{18}F) was administered to four patients with respiratory symptoms and fever in Wuhan, China.[35] Fluorodeoxyglucose (^{18}F) is a glucose analogue, where a hydroxyl group has been replaced by a positron-emitting fluorine-18 radionuclide. Hence, the radiotracer is preferentially taken by certain cells and tissues, such as tumor cells in cancer patients,[36] and by macrophages and neutrophils in patients suffering from inflammation associated with infection,[37] and its location can be determined by positron emission tomography (PET). All four Wuhan patients showed pulmonary lesions, including ground-glass opacities and/or lung consolidations in at least two pulmonary lobes in their scans. Moreover, the lesions had a high fluorodeoxyglucose (^{18}F) uptake and indicated evidence of lymph node involvement. In retrospect, a comprehensive review of the clinical data presented and patients' medical histories strongly suggested infection with COVID-19. A characteristic increase in radiotracer uptake by infected pulmonary tissue was later confirmed among patients with COVID-19 positive RT-PCR results (Figure 3).[38,39] The characteristic radiological features and metabolic activities associated with COVID-19 induced pneumonia were also observed in asymptomatic patients undergoing fluorodeoxyglucose (^{18}F) PET-CT procedures.[40] These results are consistent with previous MERS-CoV cases, in which significant fluorodeoxyglucose (^{18}F) uptake was observed among MERS-

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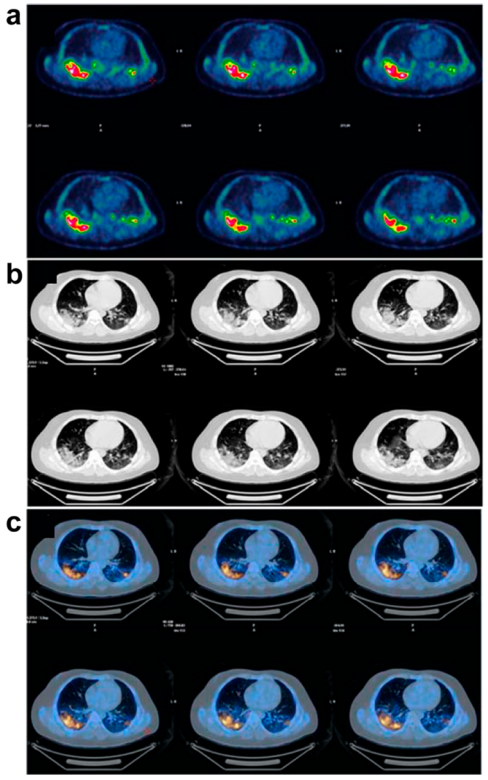

Figure 3. Transaxial images of COVID-19 patient thorax by PET-CT. (a) PET with fluorodeoxyglucose (^{18}F) radiotracer, (b) low-dose CT, and (c) fused images of COVID-19 patient thorax. The images show high fluorodeoxyglucose (^{18}F) uptake at the basal lower lobe bilaterally with consolidation and ground glass opacity. Adapted with permission from ref 38. Copyright 2020 Science Publishing Group.

CoV patients with pneumonia.[41] Although PET-CT using fluorodeoxyglucose (^{18}F) radiotracers is not feasible for population-wide screening, this imaging technique offers a means of identifying the prevalence of COVID-19 among high-risk, asymptomatic patients with underlying conditions.[42] Because the radiotracer uptake is dependent on nonspecific inflammatory response and can provide vital information on overall immune activation, PET-CT scans have therefore been suggested for COVID-19 prognosis and treatment management.[43] To date, all radiotracers used to image SARS-CoV-2 induced pneumonia by PET have been based on fluorine-18. We expect, however, that other commonly used positron-emitting radionuclides such as carbon-11, nitrogen-13, oxygen-15, gallium-68, copper-64, or zirconium-89[44] will also be explored for imaging COVID-19 patients in the near future.

The success of radiotracers for imaging COVID-19 lesions has sparked interest in novel imaging agents that combine radionuclides with targeting vectors. These radiological agents have the potential for enhancing the sensitivity and specificity of the imaging techniques. For instance, macrophages play a key role in the immunological response to SARS-CoV-2 and, when activated, express folate receptor-beta proteins, which can be targeted with folic acid.[45,46] Hence, ^{18}F-AzaFol, a folic acid-based PET imaging agent that is under clinical trials for metastatic cancer of the ovaries and lungs[47] has been proposed as radiotracer for macrophage activity imaging in COVID-19 patients to support clinical decision-making.[48] This strategy is supported by a previous preclinical study that used ^{18}F-AzaFol to image and monitor macrophage-driven lung diseases.[49] Other potential candidates to image COVID-19 associated pneumonia could include ^{18}F-labeled FEDAC[50] and mannose-presenting ^{64}Cu radiotracers,[51] which target receptors overexpressed on activated macrophages, or blood cells such as macrophage activated killer cells labeled with ^{111}In-oxime.[52]

The radiolabeling of white blood cells has also been applied to other imaging modalities such as single-photon emission computed tomography (SPECT), where gamma-emitting radionuclides are used as imaging tracers. ^{99m}Tc-exametazime-labeled leukocytes, which have been used to detect acute infection sites,[53] also revealed pulmonary infections in COVID-19 patients.[54] Lastly, another strategy to image COVID-19 infections with gamma-emitting radionuclides could be targeting the SARS-CoV-2 entry receptor (i.e., ACE2) by repurposing already established autoradiography protocols, which radiolabel angiotensin II (an ACE2 substrate) with ^{125}I.[55] In summary, there is a renewed academic and clinical interest in developing new radiopharmaceuticals and repurposing existing ones for COVID-19 imaging to obtain new pathomechanistic insights and enhanced prognosis capabilities.[56]

Lastly, the radioisotope ^{11}C has been used to improve the understanding of SARS-CoV-2 particle retention and deposition in the respiratory tract after ambient air intake. To that end, Evangelista et al. used a modified version of the lung deposition model developed by the International Committee of Radiological Protection (IRCP),[57] which calculates region-specific deposition of aerosol particles in the lungs as well as particle clearance through various pulmonary regions. This model was modified to represent a semiempirical approach that is based on algebraic equations derived from relevant theoretical and experimental results. The IRCP lung model was refined to examine SARS-CoV-2 with the conception that the virus has an "environmental half-life" based on its environmental degradation prior to lung deposition. Subsequently, viral degradation was experimentally determined and replicated in a model with ^{11}C-loaded aerosol particles as this isotope has a radioactive decay rate similar to the virus environmental degradation rate.[58] Applying the IRCP model, the authors of this work observed a high retention of SARS-CoV-2 in the extrathoracic region with lower viral fraction deposition in the alveolar section. This finding was consistent with previous clinical reports, confirming the validity of the model.

3. THERAPEUTIC STRATEGIES AGAINST COVID-19

In the absence of an antiviral that can effectively treat SARS-CoV-2 infection, Kirkby et al. proposed to use low doses (<100 cGy) of radiation to treat COVID-19 induced pneumonia in patients.[59] A strong reaction followed this article, with several publications supporting the consideration of radiotherapy for applications in COVID-19 treatment based on the anti-inflammatory activity of low dose radiation.[60−64] In contrast, other groups argued that current scientific evidence does not justify any clinical trial of low dose radiotherapy for COVID-19 pneumonia,[65−67] since the reported clinical studies investigating the potency of radiotherapy against viral pneumonia (published between the 1930s and 1970s) were conducted following protocols that did not abide by today's clinical standards.[68]

The discussion surrounding utilization of external beam radiation for treatment of COVID-19 pneumonia has increased attention toward other emerging forms of radiotherapy, with

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more selective cytotoxic effects. For instance, targeted radiotherapy (Figure 4) is a clinical strategy in which

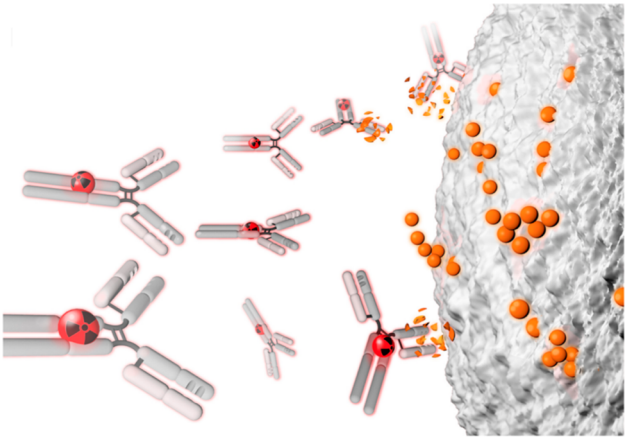

Figure 4. Targeted radiotherapy working principle. The radionuclide-carrying antibody binds to the epitope, while the isotope decay events damage the target. In the case of COVID-19, the radiation is expected to compromise SARS-CoV-2 extracellular virions. Adapted with permission from ref 86. Copyright 2020 Society of Nuclear Medicine and Molecular Imaging.

radionuclides emitting α-particles, β^--particles, or Auger electrons are delivered to tumors.[69−71] The main advantages of α-particles are their high linear energy transfer and short penetration depth, which concentrate the cytotoxic effect.[72] α-Emitters, however, present much larger recoil energies during their decay, causing a higher release of daughters from the radiopharmaceutical compound compared to other radionuclides such as β and Auger electron emitters.[73] Because radionuclides are conjugated to targeting vectors, including antibodies and cell surface receptor-binding peptides,[74] only cancerous cells tend to be exposed to radiation, while surrounding healthy tissue is primarily unaffected. Examples of promising therapeutic immunoconjugates include ^{225}Ac-HuM195, a lintuzumab conjugate for myeloid leukemia treatment,[75] and ^{227}Th-DOTA-trastuzumab, for HER-2 positive breast and ovarian cancer treatment.[76] Moreover, several new formulations, wherein α-generators and targeting vectors are functionalized at a high density on nanoparticle surfaces, have shown high therapeutic performances,[77−79] and there is increasing interest in developing targeted alpha therapy strategies for the treatment of infectious diseases.[80] For instance, several radioimmunoconjugates that targeted infected cells (rather than the viruses itself) have been developed to eliminate the virus reservoirs and prevent their propagation.[81,82] Recently, the first antibodies targeting SARS-CoV-2 spike proteins were discovered, providing the missing part in the development of radioimmunoconjugates that directly bind to the virus.[83,84] Furthermore, several epitopes targeted by these antibodies are highly conserved in other coronaviruses,[85] making such antibodies ideal candidates for targeting SARS-CoV-2 as well as other related viruses. An early example of immunoconjugate approaches to COVID-19 radiotherapy was developed by Pillarsetty et al., wherein a CR3022 antibody was combined with a β^--emitting ^{131}I-complex for therapeutic purposes.[86] The authors, however, did not report *in vitro* or *in vivo* evaluation of the therapeutic performance of the radioimmunoconjugate. It is worth noting that viruses have relatively low radiosensitivity with most D_{10} values (i.e., doses necessary to cause a one-log reduction in titer) reported in the kGy range for ^{60}Co gamma photons.[87] Furthermore, the small size of the SARS-CoV-2 virus (ca. 75 nm)[88] may represent a challenge for targeted radiotherapy because the linear energy transfer of ionizing particles such as alpha particles is low at sub-μm and a few μm range from the radionuclide.[89,90] Therefore, it is unclear at the moment whether targeted radiotherapy is a feasible strategy against SARS-CoV-2 infections, and further studies are needed to determine its possible therapeutic value.

4. SUMMARY AND OUTLOOK

In the midst of the COVID-19 pandemic, an urgent need for diagnostic and prognostic strategies with improved sensitivity has emerged. Although we believe RT-PCR will remain the gold standard for population-wide screening, CT is currently the most sensitive technique for COVID-19 diagnosis and is also the most reliable technique for monitoring patient recovery from SARS-CoV-2 induced pneumonia. A combination of CT scans and radiotracer-based imaging tools such as PET and SPECT have provided complementary information for prognosis and treatment management, especially in high-risk patients with underlying conditions. Promising fluorodeoxyglucose (^{18}F) studies have sparked renewed interest in developing new radiotracers and repurposing already existing ones for COVID-19 imaging. With regards to therapeutics, the success of targeted radiotherapy in oncological settings suggests the potential for utilizing radioimmunoconjugates against SARS-CoV-2 infections. A few preclinical studies are currently being published, and more are expected to emerge in the near future.

AUTHOR INFORMATION

Corresponding Author

Rebecca J. Abergel − *Chemical Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, California 94720, United States; Department of Nuclear Engineering, University of California, Berkeley, California 94720, United States;* orcid.org/0000-0002-3906-8761; Email: abergel@berkeley.edu

Author

Roger M. Pallares − *Chemical Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, California 94720, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsptsci.0c00186

Notes

The authors declare no competing financial interest.

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