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Review

Infectious Considerations for Patients on Immune Checkpoint Inhibitors

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Abstract

Chronic inflammatory states lead to T cell exhaustion, characterized by reduced T cell proliferation and activity. Immune checkpoint inhibitors (ICPI) reactivate T cells to restore the immune system's natural defenses against foreign antigens. The widespread use of these agents in the treatment of malignancy has led to markedly reduced tumor burden and improved patient survival, sparking curiosity about their potential role in the treatment of other chronic inflammatory states, including infectious diseases. While ICPI have been associated with the development of several reactivated and opportunistic infections in patients with malignancy, recent studies also highlight the efficacy of these agents in managing infections alongside first-line antimicrobial therapy. Future research of ICPI should continue to build on our understanding of their infectious complications as well as their utility in preventing and treating infectious diseases.

Keywords

Immune checkpoint inhibitors; programmed cell death protein 1; cytotoxic lymphocyte-associated protein 4; cancer; immunotherapy

1. Introduction

The emergence of immune checkpoint inhibitors (ICPI) has revolutionized the field of cancer immunotherapy and provided new hope to patients with malignancy refractory to standard chemotherapy, radiotherapy, and surgical interventions. Yet despite the widespread use of these agents, our understanding of the relationship between ICPI and infectious diseases is still in its infancy. Reactivated and opportunistic infections have been reported in patients with cancer exposed to ICPI and several articles detail strategies to reduce these risks, such as screening and vaccinations prior to treatment initiation as well as antimicrobial prophylaxis throughout use. A growing body of literature concomitantly suggests ICPI may actually inform future treatment options for infectious diseases—especially those heavily dependent on T cell activity for suppression or cure, such as viral and mycobacterial infections.

This article provides a brief overview of the mechanisms of action, clinical applications, and immune-related adverse events associated with ICPI before focusing on the relevance of this therapy to both potential infectious risks as well as the future treatment of infectious diseases.

2. Overview of Immune Checkpoint Inhibitors

2.1 Mechanism of Action and Indications of Immune Checkpoint Inhibitors

Deranged elements of the patient's own immune system can facilitate the development and progression of malignancy [1]. Chronic inflammatory states can lead to genomic instability and carcinogenesis. Malignant cells which are poorly immunogenic or those with mechanisms designed to evade detection by the immune system perpetuate to ultimately create clinically-significant tumor burden. Immune checkpoint signals, normally responsible for downregulating T cell activity to allow for self-tolerance and prevent autoimmune disease, are manipulated to accept malignant cells as "self" and encourage tumor proliferation. In addition to suppressing cytokine and T cell production, established tumors enhance these inhibitory cell signals to curtail the antitumor response.

Cytotoxic lymphocyte-associated protein 4 (CTLA-4) and programmed cell death-1 (PD-1) receptors, as well as programmed cell death ligand-1 (PDL-1), proliferate on cell surfaces in response to antigen and cytokine exposure, interacting to collectively quiet T cell activity [2]. The interaction between the CD80/86 ligand of an antigen-presenting cell and the CTLA-4 receptor of a T cell, for example, promotes downstream cell signalling to inhibit its priming and activation. The interaction between the PDL-1 of an antigen-presenting cell and the PD-1 receptor of a T cell leads to T cell apoptosis and anergy. Immune checkpoint inhibitors consist of antibodies designed to interrupt these interactions, reducing downstream cell signals and reengaging the patient's natural antitumor defenses.

First studied in metastatic melanoma, ICPI were quickly and successfully applied to the treatment of advanced renal cell carcinoma, metastatic colon cancer, and advanced squamous non-small cell lung cancer (NSCLC) among others, significantly reducing tumor burden and improving patient survival. Currently-available ICPI target CTLA-4 (ipilimumab), PD-1 (nivolumab, pembrolizumab, and cemiplimab), and PDL-1 (atezolizumab, durvalumab, and avelumab) receptors. Anti-PD-1 agents have demonstrated superior efficacy in reducing tumor burden as compared to anti-CTLA-4 agents [2]. Combination therapy including both CTLA-4 and PD-1

inhibitors has been found to be superior to monotherapy for treatment of certain cancers, albeit with increased associated toxicities.

2.2 Immune-Related Adverse Events

Immune checkpoint inhibitors are not without risk. The restoration of previously-suppressed T cell activity endangers not only malignant cells, but also the patient's own cells, giving rise to a potential plethora of autoimmune manifestations. Immune-related adverse effects (IRAEs), including enterocolitis, dermatitis, pneumonitis, encephalopathy, and endocrinopathy, have been well-described in the literature and are listed as boxed warnings on the package inserts of these agents. Up to 90% of patients exposed to CTLA-4 blockade and 70% of those exposed to PD-1 blockade suffer IRAEs of varying severity, with life-threatening reactions observed most frequently in patients receiving combination therapy [3]. The risk of developing IRAEs appears to be dose-dependent for anti-CTLA-4 agents but not for anti-PD-1 or anti-PD-L1 agents. IRAEs often occur within the first 3-6 months of therapy and the majority of these cases either self-resolve or rapidly improve with steroids. However, immunosuppression such as high-dose steroids, tumor necrosis factor (TNF)-alpha inhibitors, azathioprine, and mycophenolate mofetil may be required to mitigate severe IRAEs [3].

As several IRAEs closely resemble infectious syndromes, it is imperative for the clinician to rule out infection prior to initiation of immunosuppressive therapy. Diarrhea, for example, should prompt stool testing to rule out enteric pathogens including *Clostridioides difficile* before immunosuppression is administered. Confirmation of colitis and evaluation for infectious etiologies with colonoscopy or sigmoidoscopy is indicated for patients with persistent diarrhea and a negative noninvasive workup [3]. Viral hepatitis should be considered and evaluated in a patient with new elevation in liver function tests before a diagnosis of hepatotoxicity as an IRAE is made. Pulmonary toxicity typically manifests with a dry cough, progressive dyspnea, and fine inspiratory crackles; once congestive heart failure is ruled out and a computerized tomography (CT) scan of the chest is obtained to confirm suspected pneumonitis, immunosuppression can be started. Should the patient worsen on therapy, however, infectious etiologies such as *Pneumocystis jirovecii* pneumonia (PJP) must be considered and bronchoscopy performed [3].

3. Infectious Complications in Patients Receiving Immune Checkpoint Inhibitor Therapy

3.1 Infectious Complications Associated with Immunosuppression Used to Treat Immune-Related Adverse Events

Immunosuppression used to treat IRAE may precipitate the development of infectious complications in up to 20% of patients treated with ICPI [4]. Higher incidence of infection has been observed in association with anti-CTLA-4 agents compared to anti-PD-1 agents and with a combination of ICPI as compared to anti-CTLA-4 or anti-PD-1 monotherapy; both observations are likely related to increased incidence of IRAEs with anti-CTLA-4 agents and ICPI combination therapy [5, 6]. The largest retrospective cohort study to date, conducted by Del Castillo *et al*., included 740 patients with melanoma treated with ICPI at Memorial Sloan Kettering Cancer Center [6]. The majority of patients (73.2%) received CTLA-4 blockade with ipilimumab. Serious infections, defined as those requiring hospitalization or parenteral antimicrobials, were observed in 54

patients (7.3%) and predominantly included bacterial pneumonias and bloodstream infections. Ten cases of *Clostridioides difficile*-associated diarrhea, three cases of PJP, three cases of herpes zoster, and one case of *Strongyloides* hyperinfection were reported [6]. Nine patients (17%) were thought to have died as a consequence of their infection. The mean duration from initiation of ICPI therapy to development of infection was 135 days (range 6-491 days), with 80% of infections occurring during the first six months of ICPI therapy. The use of steroids and the use of infliximab to treat IRAE were associated with significantly increased risk of serious infections (odds ratio 7.71 and 4.74, respectively) [6].

Case reports and case series have described examples of severe bacterial and viral infections, invasive fungal infections, and disseminated mycobacterial infections in patients who developed IRAEs treated with immunosuppression [4]. The first cases of PJP were reported in two patients with advanced melanoma successfully treated with ipilimumab in 2015 [7]. Both patients suffered immune-related colitis which resolved with steroids and infliximab therapy, but presented to medical attention within months with new respiratory symptoms [7]. Kyi *et al*. described a 68-year-old man with metastatic melanoma who underwent treatment with ipilimumab complicated by immune-related colitis [8]. Although his gastrointestinal symptoms improved with steroids and infliximab, a surveillance chest CT scan demonstrated cavitating pulmonary infiltrates and subsequent bronchoscopy revealed invasive pulmonary aspergillosis. Voriconazole and amphotericin B were initiated but the patient ultimately expired. Fournier's gangrene and cytomegalovirus (CMV) viremia following IRAEs treated with immunosuppression have also been noted by this group [8].

3.2 Reactivated Infections Observed with Immune Checkpoint Inhibitor Therapy

In contrast to the above experience, Uchida *et al*. observed the rapid progression of known, chronic pulmonary aspergillosis in a 65-year-old man with NSCLC who was treated with nivolumab but never experienced an IRAE [9]. Although the patient had been exposed to multiple cycles of cytotoxic chemotherapeutic agents (carboplatin, paclitaxel, and docetaxel) before PD-1 blockade, acute exacerbation of respiratory symptoms and the development of a fungal ball in his previously-stable right upper lobe cavitating infiltrate only manifested after 20 cycles of nivolumab [9]. In reengaging the patient's natural defences against NSCLC, the authors suggest ICPI may produce a hyperactive response to dormant pathogens akin to the immune reconstitution inflammatory syndrome (IRIS) seen after the initiation of antiretroviral therapy in patients with human immunodeficiency virus (HIV) infection [9]. A retrospective cohort study of 167 patients with NSCLC who received nivolumab suggested that infections can occur independent of additional immunosuppression for IRAE in this population [10]. The prevalence of diabetes mellitus was higher amongst the 32 patients who suffered infectious complications as compared to those who did not, but exposure to cytotoxic chemotherapy prior to nivolumab and immunosuppression post-nivolumab did not differ between groups [10]. In fact, the median number of nivolumab cycles was not associated with infectious diseases in this study.

Reactivated infections such as latent *Mycobacterium tuberculosis* (MTB) are well-documented in patients administered ICPI, further suggesting the development of an IRIS-like response to dormant pathogens. The first case of pulmonary tuberculosis identified after the initiation of ICPI therapy occurred in an 87-year-old man with stage IA nodular sclerosis Hodgkin's lymphoma who

was treated with pembrolizumab [11]. Fujita *et al*. later described a 72-year-old man with progressive stage IV NSCLC who responded to nivolumab therapy but subsequently suffered pulmonary tuberculosis [12]. Biopsy specimens of associated lung nodules showed diffuse lymphocytic infiltrations suggestive of an excessive immune response. The patient's MTB interferon gamma release assay (IGRA) was newly-positive, indicative of recent conversion [12]. Chu *et al*. reported the case of a 59-year-old man with stage IV adenocarcinoma of the lung treated with nivolumab who developed a pericardial effusion and signs of pericardial tamponade [13]. A pericardial biopsy sample demonstrated granulomatous inflammation and acid-fast bacilli with MTB growing on culture of the pericardial effusion specimen [13]. None of the patients above developed IRAE or received additional immunosuppression.

3.3 Other Reported Infections Complications of Immune Checkpoint Inhibitor Use

Few randomized controlled trials have used the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) to report infectious complications with ICPI use, though the mechanisms behind these reported observations have not been fully defined [14]. KEYNOTE010, a randomized controlled trial evaluating the efficacy of pembrolizumab versus docetaxel in the treatment of 1034 patients with advanced NSCLC, noted that 0.6-1.2% of those administered pembrolizumab (n = 691) developed grade 1-2 (mild to moderate) lymphopenia. This finding may partially explain the mechanism behind opportunistic infections associated with administration of anti-PD-1 agents [15]. The study reported a total of grade 1-2 pulmonary infections in four patients, grade 1-2 oral candidiasis in one patient, and grade 1-2 urinary tract infection in one patient. Three patients suffered grade 3-4 pulmonary infection, defined as a severe or life-threatening adverse event requiring hospitalization or urgent intervention. Grade 3-4 leukopenia was also described in 1% of patients administered nivolumab (n = 135) in CheckMate 017, a randomized controlled trial evaluating the efficacy of this anti-PD-1 agent as compared to docetaxel in 272 patients with melanoma [16]. A phase 2, multicenter, single-arm study evaluating the safety of nivolumab in 117 patients with refractory NSCLC reported a grade 3-4 herpes zoster infection in one patient and a grade 3 pulmonary infection suspected to be responsible for the death of another patient [17]. The infectious complications reported in each study were not specifically correlated with presence of IRAEs or administration of immunosuppression.

3.4 Screening and Prevention of Infectious Complications of Immune Checkpoint Inhibitors

As multiple factors have been implicated in the development of severe infections after exposure to ICPI, from subsequent administration of immunosuppression to hyperactive T cell responses to the intrinsic properties of these agents, several groups have recommended preventive measures to reduce infectious risk. Patients with mycobacterial, fungal, or chronic viral infections have been almost universally excluded from existing clinical trials demonstrating the safety and efficacy of ICPI, so strategies for ICPI use in these populations are largely based on expert opinion and closely resemble those used in patients receiving tumor necrosis factor-alpha inhibitors [18].

Non-invasive screening, such as tuberculin skin testing or IGRA for latent tuberculosis infection (LTBI) and serologies for endemic fungal mycoses, hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV infection, may be prudent prior to starting therapy [4, 5]. Identification of select infections

can allow for prompt initiation of antimicrobial treatment in conjunction with ICPI, though as of this publication, there are no clear recommendations to initiate itraconazole or fluconazole prophylaxis for positive histoplasma or coccidioides serologies, respectively. Although there are similarly no guidelines for ICPI use in patients with LTBI, ICPI should be held in the context of active disease [19]. The safest time to restart ICPI therapy after initiation of antituberculous therapy remains unclear [19]. Chronic HBV merits antiviral prophylaxis with lamivudine for the duration of ICPI [20]. Hepatitis C virus and HIV infections are not contraindications to ICPI therapy, but patients should be closely monitored for signs and symptoms of IRIS especially if receiving concomitant antiviral therapy [21]. There is no evidence to suggest that antiviral therapy should be withheld in patients who are candidates for or who are actively receiving ICPI. Prophylaxis for PJP should be prescribed to patients who experience IRAEs requiring treatment with at least 20 milligrams of prednisone per day (or the equivalent) for at least four weeks [4]. Herpes virus prophylaxis for the duration of immunosuppression should be considered [22].

Administering age-appropriate vaccinations to patients who require ICPI therapy remains controversial; while enhanced T cell activity may improve serologic responses in these particularly vulnerable patients, additional antigen presentation may theoretically raise the risk for the development of infectious diseases or IRAE [22]. The first retrospective, multicenter study designed to explore the efficacy of influenza vaccination in oncologic patients treated with ICPI reviewed 300 patients and reported a significantly higher incidence of influenza lung infection among the 79 patients who were vaccinated (24.1% versus 11.8% unvaccinated; odds ratio = 2.4, p = 0.009) [23]. Despite suffering a higher incidence of influenza lung infection, however, vaccinated patients experienced greater one-year overall survival than their unvaccinated counterparts (86.7% versus 66.7%, p = 0.02) [23]. Two retrospectives studies of influenza vaccination in patients treated with ICPI did not find significantly elevated incidences of IRAE among vaccinated patients [24, 25]. On the other hand, a prospective study noted that over half of 23 vaccinated patients treated with anti-PD-1 or anti-PD-L1 agents suffered IRAEs, with 26% of these graded as severe [26]. Further prospective trials evaluating the safety and efficacy of vaccinations in this population are merited.

4. Future Uses of Checkpoint Inhibitors in Treating Infectious Diseases

4.1 Immune Checkpoint Receptor Expression in Infectious Diseases and the Effect of ICPI

Both malignancy and certain infectious diseases are states of chronic antigen presentation, resulting in the upregulation of CTLA-4, PD-1, and PD-L1 receptors. The inhibitory responses set into motion by these receptors are collectively described as T cell exhaustion, which reduces severe tissue damage due to a hyperactive immune system triggered by foreign antigens [2]. Just as CTLA-4 and PD-1 receptor enhancement have been demonstrated in the context of various cancers, liver biopsies have confirmed the presence of high levels of PD-1+ CD4 and CD8 T cells in patients with chronic HBV or HCV infection and cerebrospinal fluid of patients with HIV infection showed HIV-specific PD-1+ CD8 T cells [2]. Upregulated CTLA-4 and PD-1 expression in peripheral CD4 and CD8 T cells has been observed in HIV, CMV, and *Plasmodium* spp. Infections [2, 27]. *Mycobacterium tuberculosis* exposure is associated with increased PD-1 receptor expression in

multiple cell types found in granulomatous infections including CD4 and CD8 T cells, regulatory T cells, B cells, neutrophils, and NK T cells [2].

Malignancy and certain infectious diseases are also similar in their dependence on cell-mediated immunity for eradication and cure, and T cell exhaustion can potentiate both disease processes. Antiretroviral and antituberculous therapy partially work by downregulating expression of CTLA-4, PD-1, and PD-L1 receptors to boost T cell activity against their respective target organisms [27]. Given its success in cancer immunotherapy, ICPI use in the treatment of infectious diseases has been extensively explored in pre-clinical studies. Several in vitro studies noted increased immune system responsiveness with PD-1 blockade in samples obtained from patients with MTB and chronic HBV infections, characterized by enhanced cytokine, T cell, and NK cell activity [2]. PD-1 and PD-L1 blockade improved HIV-specific CD4 and CD8 T cell activity, increased NK cell-mediated cytokine secretion and degranulation and killing of target cells, and ultimately reduced HIV-infected cell counts [28]. In fact, PD-1 expression on CD8 T cells has been associated with impaired CD4 T cell reconstitution [27]. In vitro PD-L1 blockade on peripheral bone marrow cells of hematopoietic stem cell transplant recipients with chronic CMV disease led to increased CMV-specific CD8 T cell counts and activity as well [2]. These studies collectively suggest that ICPI can reactivate foreign antigen-specific defenses not only in the context of malignancy, for which they were originally designed, but also in the context of chronic infectious states.

4.2 Immune Checkpoint Inhibitor Use in the Management of Chronic Infections

Parasitic, mycobacterial, and viral infections are heavily reliant on cellular immunity and particularly difficult to eradicate, making these global challenges worthy targets for ICPI research. Animal models in chronic infectious diseases have been used to explore clinical outcomes of parasitemia and viral clearance as well as overall survival as they relate to ICPI use. For example, Xiao *et al*. used a mouse model of chronic *Toxoplasma gondii* infection to show two weeks of PD-1 blockade encouraged T cell migration into the leptomeninges, choroid plexus, subependymal tissue, and proximal brain parenchyma to ultimately reduce the number of brain cysts by 77% [29]. While PD-1 expression on T cell has been associated with impaired clearance of malaria infections, ICPI has been demonstrated to reverse this process and improve antiparasitic T cell responses in mice models of several *Plasmodium* spp. [30]. Yet mice infected with *Plasmodium berghei* suffered increased incidence of cerebral malaria with ICPI enhancement of T cell activation and interferon-gamma production, alluding to the fine balance that immune checkpoint blockade must strike between curing disease and inflicting tissue damage [27]. Similarly, the role of ICPI in treating mycobacterial infections such as MTB is still controversial; while T cell activation may aid pathogen clearance, precipitation of collateral damage in such cases as pulmonary tuberculosis and TB meningitis remains a concern [30].

Immune checkpoint blockade in the management of chronic viral infections looks promising. Anti-PD-1 agent use in simian immunodeficiency virus-infected rhesus macaques has resulted in improved HIV-specific CD8 T cell proliferation [27]. Interestingly, this was especially pronounced in macaques not receiving antiretroviral therapy (ART), suggesting that immune checkpoint blockade is very much dependent on foreign antigen presentation reduced by concomitant ART. Clinical outcomes including lower levels of viremia, delayed time to death, and delayed viral rebound after combined antiretroviral therapy was ceased were noted in macaques exposed to ICPI as compared

to controls [27, 31]. Future research aims to determine if enhanced HIV-specific CD8 T cell function can successfully eliminate HIV-infected CD4 cells and reverse HIV latency to achieve cure.

Mouse models of chronic HBV, a viral infection similarly prone to latency, note that the combination of antivirals (entecavir), therapeutic vaccination, and anti-PD-L1 agents lead to seroconversion and complete viral clearance in some animals [27]. Clinical trials for nivolumab use in patients with chronic HBV are ongoing. The first randomized, placebo-controlled study of anti-PD-1 blockade in HCV-infected patients reported 10 of 35 patients exposed to the agent and one of the seven patients exposed to placebo achieved a significantly reduced viremia [32]. Six of the patients administered ICPI suffered IRAEs; one was categorized as grade 4 hepatotoxicity [32].

4.3 Immune Checkpoint Inhibitor Use in the Management of Sepsis and Acute Infections

ICPI use may additionally aid in the management of acute infectious disease states. Though often known for its hyperinflammatory consequences, sepsis also precipitates immunoparalysis characterized by predominantly anti-inflammatory responses. T cell exhaustion, first identified in chronic infectious states, can occur during the immunoparalysis phase of sepsis, resulting in increased T cell apoptosis and lymphopenia [33]. While effective at reducing collateral tissue damage, such responses may be counterproductive in eradication of the culprit pathogen and potentially allow for the development of secondary nosocomial or opportunistic infections. Chang *et al*. evaluated blood samples of 43 septic patients and 15 critically-ill non-septic patients and noted enhanced PD-1 expression on CD8 T cells of septic patients compared to non-septic patients, even more so with increased length of stay in the intensive care unit [33]. When these CD8 T cells were incubated overnight in isotype (inactive) control antibody, those of septic patients manifested a 70% increase in apoptosis as compared to those of non-septic patients; CD8 T cells incubated in anti-PD-1 antibody had a highly significant decrease in apoptosis [33]. Several other pre-clinical studies have lent further support to the potential role for ICPI in addressing the immunosuppressive manifestations of sepsis to improve survival, as reviewed elsewhere [34].

Burns, a major injury often leading to secondary and opportunistic infections, are similarly characterized by both hyperinflammatory states and dysregulated immune function, leading to enhanced immune checkpoint receptor expression on T cells. Patil *et al*. used a mouse model of burn injury followed by superinfection with *Pseudomonas aeruginosa* or *Staphylococcus aureus* on day 4 postburn to demonstrate that PD-L1 blockade improved CD4 and CD8 T cell counts and interferon-gamma secretion, while reducing plasma cytokine levels [35]. This resulted in bacterial clearance and improved survival for both pathogens. In pseudomonal wound infection, anti-PD-L1 agents also reduced organ failure as defined by wound-associated elevations in blood urea nitrogen and transaminases [35]. A case report of a previously-healthy 30-year-old woman who suffered traumatic burns, femoral osteomyelitis, and deep wound infections was diagnosed with sepsis secondary to invasive mucormycosis [36]. She was started on liposomal amphotericin B and posaconazole and underwent extensive surgical debridement, with nivolumab dosed ten days after initiation of combination antifungal coverage. Her lymphocyte counts, CD8 T cells, and CT scans gradually improved and the patient was successfully discharged 80 days after admission [36].

5. Conclusions

The relationship between ICPI and infectious diseases will become clearer in the coming years due to the increasing number of indications and global availability of these agents. Varying degrees of severity of IRAEs including dermatitis, pneumonitis, and enterocolitis occur in up to 90% of patients exposed to ICPI therapy and often resemble infectious syndromes; thus, it is of utmost importance to rule out infections appropriate to the patient's clinical presentation prior to initiation of immunosuppressive therapy. Infections associated with ICPI have been predominantly attributed to the immunosuppressive agents used to treat IRAEs, but other mechanisms behind the development of reactivated and opportunistic infections have been reported. Hyperresponsive cellular immunity precipitating an IRIS-like reaction and intrinsic effects of ICPI themselves such as lymphopenia/leukopenia can both heighten the risk of infectious complications in patients with progressive or refractory malignancy. Non-invasive screening methods to evaluate for latent infections such as tuberculosis, hepatitis, and HIV are merited before initiation of ICPI to guide treatment of LTBI, HCV, and HIV as well as prophylaxis of HBV. However, there are no clear recommendations regarding prophylaxis for fungal infections, LTBI, or HSV. On the other hand, by reengaging the immune system's natural defenses, ICPI may have a significant role to play in the prevention and treatment of both acute and chronic infectious diseases. Continued collaboration amongst oncologists and infectious disease clinicians can further our understanding of these agents' risks and potentials.

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