Reversal of Tumor-Mediated Immunosuppression

Johannes Vieweg, Zhen Su, Philipp Dahm, and Sergei Kusmartsev

Abstract

Therapeutic cancer vaccines, one form of active immunotherapy, have long been under investigation; consequently, several vaccine-based strategies have now moved from the bench to the clinical arena. Despite their tremendous promise, current vaccine strategies have shown only limited success in clinical settings, even in renal cell carcinoma (RCC), a prototypical malignancy for the application of immunotherapy. There is ample evidence that, especially in RCC, multiple immunosuppressive mechanisms exist that considerably dampen antitumor responses and weaken the activity of current immunotherapeutic regimens. Therefore, it will be necessary to reverse tumor-mediated immunosuppression before immunotherapies can successfully be applied. Recent insights into the nature and characteristics of the regulatory elements of the immune system have provided new opportunities to enhance vaccine-mediated antitumor immunity and, thereby, increase the chance for improving patient outcome. These new insights represent important considerations for the future design and application of more effective cancer vaccines against RCC and other cancers.

Antitumor vaccines are designed to activate and mobilize the host adaptive immune response against the tumor in an antigen-specific, targeted fashion. Despite considerable progress in the identification of tumor-associated antigens and the development of more effective vaccination platforms (1), the clinical results of therapeutic cancer vaccine have, thus far, been rather disappointing. Therefore, only a handful of cancer vaccines have advanced to phase 3 testing that could potentially lead to regulatory drug approval. A recent review evaluated the clinical outcomes after cancer vaccination and cited therapeutic responses rates ranging from 1.9% to 9.5%, depending on the design of the vaccine strategy (2). For a variety of reasons largely related to regulatory and protocol design considerations, virtually all investigational antitumor vaccines have been studied in patients with bulky or metastatic disease. Although even advanced-stage renal cell carcinoma (RCC) can be highly immunogenic, multiple immunosuppressive networks exist that propagate conditions that interfere with the development and activation of an effective antitumor response (3, 4). Studies have shown that the tumor microenvironment, composed of immune, tumor, stromal, and vascular cells, exerts profound immunosuppressive activity on antigen-presenting cells (APC) and T-effector cells by secretion of bioactive growth factors and cytokines, such as vascular endothelial growth factor, transforming growth factor-β, or interleukin (IL)-10 (5). Moreover, tumors are infiltrated by regulatory T cells (Tregs) and myeloid suppressor cells (MSC) that actively inhibit T-cell responses at the tumor site through direct cell-cell contact (6), secretion of nitric oxide (NO), or reactive oxygen species (7). Cumulatively, these factors favor conditions that allow tumors to escape immune recognition and foster the proliferation, survival, and metastatic potential of tumor cells. Thus, an urgent need exists to further define the mechanisms of tumor-mediated immunosuppression and to introduce novel therapeutic concepts able to correct this problem. This article discusses emerging strategies to reverse tumor-mediated immunosuppression by abrogating Treg- and MSC-induced suppression in the cancer patient. These approaches have been recently the focus of our studies to boost tumor-associated antigen-specific immunity in a vaccination setting and to improve patient outcome.

Regulatory T Cells

Tregs are functionally defined as T cells that inhibit or weaken immune responses by diminishing the activity of other cell types through direct or indirect modes of action (8–10). Their physiologic role is to protect the host from self-antigen–reactive T cells, thereby subverting autoimmunity with pathologic consequences. Because most tumor-associated antigens are predominantly self-antigens (11), Tregs also play a major role in suppressing the function and proliferation of tumor-specific CD4+ and CD8+ effector T cells. In rodent models, Tregs have also shown to suppress natural killer cell function in a transforming growth factor-β–dependent manner; therefore, it seems that Tregs can inhibit adaptive and innate immune responses in vivo (12). Tregs with immunosuppressive activity can be characterized by cell surface coexpression of CD4 and CD25 (IL-2 receptor α-chain) and constitute 5% to 10% of the peripheral CD4+ T-cell pool in healthy mice and human...
CD25+ Tregs are produced by the thymus and travel through the peripheral blood to tumors, bone marrow, and lymphatics. Treg homing to tumors is facilitated by distinct chemokine receptor interactions, such as CCR4/CCL22, and integrin expression, all of which may contribute to the selective retention and trafficking of Tregs at sites where immunoregulation is required (15, 16). In lymphatic tissues and tumors, Tregs suppress priming and activation of naive or tumor-specific T lymphocytes, respectively.

Treg-mediated immunosuppression has been recognized as one major mechanism by which tumors can escape immune recognition and as a significant obstacle for the success of cancer immunotherapies. CD4+CD25+ Tregs have been detected at increased numbers in the peripheral blood of patients with metastatic RCC (14), melanoma (17), malignant glioma (18), and lung carcinoma patients (19) and have been shown to contribute to an immunosuppressive state. Moreover, accumulation of Tregs in metastatic ovarian carcinoma patients was associated with a significant reduction in overall patient survival (20).

**Targeting Regulatory T Cells**

Based on the fundamental role of Tregs in suppressing antitumor immunity, it has been hypothesized that depleting or functionally inactivating Tregs in cancer patients may represent a promising strategy to boost the efficacy of cancer immunotherapy protocols (21, 22). Fortunately, recent research has not only provided us with novel insights about the biology of Tregs and their suppressive activity but also provided us with solutions to overcome this obstacle in the cancer patient, thereby making cancer vaccines more effective.

For example, the CTLA-4 is constitutively expressed by Tregs. It seems that CTLA-4 regulates Treg function by two distinct mechanisms, one during functional development of Tregs and the other during the effector phase, when the CTLA-4 signaling pathway is required for T-cell suppression (23). This raised the specter that Tregs could be eliminated or inactivated in cancer patients, which in turn could promote the stimulation of an effective immune response (24, 25). Although recent clinical studies have shown that anti-CTLA-4 antibodies can induce significant tumor regressions and autoimmunity in a dose-dependent fashion, no effect on Treg levels or function was observed after anti-CTLA-4 therapy in patients with metastatic RCC and malignant melanoma (26). Therefore, it is likely that antibody-mediated CTLA-4 blockade enhances antitumor activity through abrogation of negative costimulatory signals rather than through Treg depletion or their functional inactivation.

Alternatively, treatment with cyclophosphamide, a chemotherapeutic agent with a dose-dependent, bimodal effect on the immune system, has shown to decrease Treg numbers in the tumor-bearing animals (27). Aside from transiently reducing Treg frequencies, additional mechanisms of cyclophosphamide action have been postulated that include direct inhibition of Treg function, enhancement of antigen presentation by tumors, or amplification of T11-biased CD4+ T-cell responses (12, 28). On the other side, it was shown recently that the cyclophosphamide-mediated effect on Tregs, even when applied at low doses, is rather unspecific because other CD4+ T-cell populations, such as naive CD4+ T cells (CD4+/CD25+) or memory/effector CD4+ T cells (CD4+/CD25hi), are profoundly depleted after cyclophosphamide treatment (29).

In 1995, Sakaguchi et al. (30) showed that CD4+ Tregs can be characterized by cell surface expression of the high-affinity IL-2 receptor α-chain, CD25. Subsequent studies have shown that Tregs can efficiently be depleted by antibodies targeting CD25 and that such treatment induced rejection of transplantable tumors by the host immune system (21, 22). These findings have formed the basis of efforts to augment vaccine-mediated antitumor immune responses by pretreatment with agents that lead to the preferential depletion of CD4+CD25+ Tregs using compounds targeting and killing cells expressing CD25. Human anti-CD25 monoclonal antibodies, such as basiliximab and daclizumab, have successfully been applied in transplantation settings to minimize the risk of organ rejection (31). However, their use in human Treg depletion protocols is limited because of their prolonged half-life, likely interfering with T-cell priming by killing vaccine-induced CD25-expressing T cells. Therefore, reagents that target CD25 should be strictly used in a prevaccination setting and must be omitted during the T-cell priming phase to avoid unspecific killing of activated, vaccine-induced T cells.

Denileukin diftitox (OntakR) is a recombinant fusion protein that contains the catalytic and membrane translocation domain of diphtheria toxin. The binding domain for the diphtheria toxin receptor, however, is deleted and replaced by the human IL-2 gene, which allows for targeting of CD25-expressing cells. Denileukin diftitox is characterized by a short plasma half-life of 58 min and dissociation constant of 10 pmol/L (32). Accordingly, the plasma concentration of denileukin diftitox will reach ineffective serum levels to eliminate CD25+ Tregs after ~6 h. The cytotoxic action of denileukin diftitox occurs as a result of binding to the high-affinity IL-2 receptor, subsequent internalization, and enzymatic inhibition of protein synthesis, ultimately leading to cell death. This drug has been approved by the Food and Drug Administration for treatment of cutaneous T-cell leukemia/lymphoma (33) and has also been used for the treatment of other lymphomas and acute steroid-refractory graft-versus-host disease (34). In two recent reports, denileukin diftitox was used as an off-label reagent to deplete Tregs in the peripheral blood of six patients with metastatic ovarian carcinoma (35), whereas, in the second study, 12 patients with malignant melanoma and 1 with metastatic RCC were treated (36). In the former study, a statistically significant reduction of circulating CD4+/CD25+/FOXP3+ Tregs were observed after a single i.v. infusion of denileukin diftitox. Moreover, T-cell interferon-γ production increased significantly as Treg numbers declined. Interestingly, in one subject, reduction of CA-125, a serum marker for ovarian cancer burden, and transient resolution of metastatic metastases were observed 2 months after the initiation of therapy. These positive results differed to some extent from...
those reported by Attia et al. (36), who failed to show significant Treg depletion in melanoma patients treated with multiple cycles of denileukin diftitox administered at a relatively low dose (9 μg/kg), whereas subjects treated at a higher dose level 1(18 μg/kg) experienced a small, albeit statistically significant, reduction of overall FOXP3 mRNA expression in their peripheral blood mononuclear cells.

We have reported recently the results of a clinical study, in which a combinatorial regimen consisting of denileukin diftitox and a dendritic cell–based vaccine was used in patients with metastatic RCC. Based on preclinical data (21, 22), we hypothesized that denileukin diftitox–mediated Treg depletion is capable of enhancing the efficacy of dendritic cell–based cancer vaccination. We showed that denileukin diftitox is able to selectively eliminate CD25 high-expressing Tregs from the peripheral blood mononuclear cells of metastatic RCC patients without inducing toxicity on other cellular subsets with intermediate or low expression of CD25 (14). Denileukin diftitox–mediated Treg depletion resulted in enhanced stimulation of proliferative and cytotoxic T-cell responses in vitro, but only when denileukin diftitox was omitted during the T-cell priming phase. In patients with metastatic RCC, denileukin diftitox profoundly reduced the numbers of CD4 + /CD25 high Tregs, significantly reduced FOXP3 mRNA expression in CD4 + T cells isolated from the peripheral blood of the treated RCC patients, and abrogated Treg-mediated immunosuppressive activity in vivo. Strikingly, denileukin diftitox–mediated elimination of Tregs followed by vaccination with RNA-transfected dendritic cells significantly improved the stimulation of tumor-specific T-cell responses in RCC patients when compared with vaccination alone.

Cumulatively, these data provided the first evidence to date that depletion of Tregs can actually enhance vaccine-induced T-cell responses against tumor antigens in a clinical setting. Therefore, depletion of Tregs or abrogation of Treg-mediated immunosuppression represents a novel means to enhance the efficacy of cancer vaccines. Further investigation with a larger patient population will be necessary to define the full potential of this strategy in ultimately achieving antitumor immunity with clinical effect. For such studies, it will be critical to collect precise information on Treg depletion and vaccine-induced T-cell response and, ultimately, address the clinical efficacy of such strategy in cancer patients.

**Myeloid Suppressor Cells**

The concept that antigen-specific immune responses can control tumor growth is well established. However, it has also become evident that tumors have developed rather sophisticated mechanisms to evade the antitumor immune response, allowing them to proliferate and metastasize into normal tissues. Growing tumors exert profound inhibitory effects on the immune system by directly interfering with the differentiation, function, and activation of APCs, such as dendritic cells. Dendritic cells exposed to tumor-derived factors can trigger T-cell dysfunction or unfavorable responses, such as T cell–producing cytokines – producing T cells or may even induce Tregs. Moreover, up-regulation of signal transducer and activator of transcription (STAT) 3 (37) or secretion of tumor-derived growth factors and cytokines, such as vascular endothelial growth factor, transforming growth factor-β, granulocyte-macrophage colony-stimulating factor, IL-10, or prostaglandin E2, have all been shown to arrest differentiation of APCs from their myeloid progenitors and trigger accumulation of MSCs (38–40). Several studies have now shown that the numbers of MSCs are dramatically increased in the peripheral blood of tumor-bearing animals and cancer patients, but not in healthy counterparts, whereas the numbers of APC, such as dendritic cell, are decreased (38). In addition, there seems to be a positive correlation between MSC frequencies in the peripheral blood compartment and the stage of the tumor. Murine or human MSCs arise from the bone marrow and other hematopoietic organs and exert profound immunosuppressive activity in the tumor-bearing host by inhibiting antigen-specific T- and natural killer cell responses and even inducing T-cell tolerance (41). MSC populations are enriched in the peripheral blood and tumor compartment and carry the phenotype of partially differentiated granulocyte-macrophage and monocytic lineage myeloid precursors. Under certain experimental conditions, these progenitors can differentiate into APCs, such as macrophages and dendritic cells. Specifically, it was shown that murine and human MSCs can differentiate under the influence of certain cytokines and differentiation factors into more mature cell types both in vitro and in vivo (42, 43). These manipulations were associated with a reversal of MSC-mediated immunosuppression and with enhancement of vaccine efficacy, suggesting the potential for a novel therapeutic anticancer strategy.

MSCs induce immunosuppression by using two enzymes involved in arginine metabolism [i.e., inducible NO synthase (iNOS) 2, which generates NO, and arginase I (ARG1), which acts by L-arginine depletion; ref. 44]. In addition to amino acid starvation, MSCs can block T-cell function through the production of reactive oxygen species and NO. Studies have shown that MSCs and macrophages residing in the tumor microenvironment secrete high levels of ARG1 and iNOS, thereby creating a hostile milieu for T cells and cells of the

### Table 1. Human myeloid immunosuppressive cell populations reported in current literature

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Mechanism</th>
<th>Tumor system/model</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD15 + (48)</td>
<td>H2O2</td>
<td>Metastatic adenocarcinomas of the pancreas, colon, and breast</td>
</tr>
<tr>
<td>CD15 +, CD11b +, CD14 – (50)</td>
<td>ARG1</td>
<td>RCC</td>
</tr>
<tr>
<td>Lin -, DR – (46)</td>
<td>N/A</td>
<td>HNSCC, non–small cell lung carcinoma, and breast cancer</td>
</tr>
<tr>
<td>DR -, Lin CD33 +/1 *</td>
<td>ROS/NO</td>
<td>RCC</td>
</tr>
</tbody>
</table>

Abbreviations: H2O2, hydrogen peroxide; HNSCC, squamous cell carcinoma of the head and neck; N/A, not applicable; ROS, reactive oxygen species.

innate immune system (44). Arginase and iNOS secretion is regulated by signal transducer and activator of transcription 1 and signal transducer and activator of transcription 6, genes involved in interferon-α/γ signaling and in the negative regulation of antitumor responses (41, 45). Although early studies have focused on identifying the phenotype and function of MSCs in rodent tumor models (Table 1), more recent reports have also identified immune suppressive myeloid cell populations in cancer patients (46, 47). In these studies, several cell surface markers that include CD14, CD33, CD11b, and CD15 were used to define and track MSC subsets in cancer patients (Table 2). Schmielau and Finn (48) were the first to report that oxidative stress is responsible for reduced T-cell function. Although the precise mechanism of its action in vivo has yet to be clearly defined, recent studies have suggested that oxidative stress is responsible for reduced expression of CD3ζ chain and impaired T-cell activity (49).

Recently, peripheral blood cells from patients with metastatic RCC were found to possess increased arginase activity (50). The cellular subset with the highest arginase activity was consistent with a MSC population carrying a CD11b+CD15−/CD41− phenotype (Table 2). T cells isolated from the RCC subjects showed markedly decreased cytokine production and CD3ζ expression. Conversely, depletion of the CD11b+CD41− MSCs was able to restore these defects. In summary, accumulation of MSCs in cancer patients favors conditions that allow tumors to escape immune recognition and promote progressive growth of malignant cells. Therefore, there is considerable interest in developing strategies that allow targeting and eliminating MSCs in immunotherapy protocols.

### Targeting MSCs

Among the strategies that interfere with MSC-dependent immunosuppression, depleting antigranulocyte antibodies have been used to eliminate MSCs in rodent tumor models (51). However, these antibodies were not sufficiently selective and chronically treated mice developed opportunistic infections. In addition, several combinations of growth factors that promoted MSC differentiation into APCs have been shown to provide only minor effects in reducing MSCs in tumor-bearing animals (43).

Alternatively, the use of differentiation agents, such as all-trans-retinoic acid, to induce forced MSC maturation in vivo was raised recently as a practical option to overcome MSC-mediated immunosuppression. This proposition was based on the demonstration that systemic treatment with all-trans-retinoic acid was capable of reducing the frequencies of immature MSCs, thereby abrogating their inhibitory activity in vivo (43). Although all-trans-retinoic acid did not show any direct effect on tumor growth, it was capable of mediating antitumor immunity by mediating differentiation of MSCs into dendritic cells, macrophages, and granulocytes. All-trans-retinoic acid–mediated reduction of MSCs improved both CD4+ and CD8+ T-cell responses and significantly enhanced the efficacy of cancer vaccination (43).

As an alternative strategy to reduce MSC inhibitory function, it was shown recently that nitro-aspirin given orally reversed immunosuppression and enhanced the therapeutic effectiveness of cancer vaccination in tumor-bearing animals (52). Proposed mechanisms of action include nitro-aspirin–mediated inhibition of cyclooxygenase and prostaglandin, potentially interfering with the inhibitory enzymatic activities of MSCs. Finally, gemcitabine, a chemotherapeutic drug used to treat various forms of cancer, has shown efficacy in reducing Gr-1+/CD11b+ MSCs in animals bearing large tumors of different origin (53). Reduction of MSCs was accompanied by an increase in the antitumor activity of CD8+ T cells and markedly enhanced antitumor efficacy, suggesting that gemcitabine may be a practical strategy for the reduction of MSCs in humans that could be evaluated in conjunction with active or passive immunotherapy approaches.

### Summary

Recent research has not only provided novel insights about the mechanisms that hinder the generation of antitumor immune responses in the tumor-bearing host but also delivered clinically applicable solutions to overcome these obstacles by directly targeting the responsible defect. Many studies have shown that the growth of tumors, including RCC, is often associated with a decline in immune function, and therapeutic vaccines alone are often ineffective to overcome tumor-mediated immunosuppression (54). In

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### Table 2. Murine myeloid immunosuppressive cell populations reported in current literature

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Mechanism</th>
<th>Tumor system/model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr-1+, CD11b+ (40)</td>
<td>ROS/NO</td>
<td>Metastatic colon carcinoma</td>
</tr>
<tr>
<td>Gr+, CD11b+ (56)</td>
<td>ARG1 + iNOS</td>
<td>Colon carcinoma, lymphoma</td>
</tr>
<tr>
<td>Gr-1+, CD11b+ (57)</td>
<td>ARG1</td>
<td>T-cell lymphoma</td>
</tr>
<tr>
<td>Gr-1+, CD11b+ (58)</td>
<td>TGF-α</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>Gr+, CD11b+ (45)</td>
<td>ARG1, STAT6</td>
<td>Metastatic mammary carcinoma</td>
</tr>
<tr>
<td>Tumor-infiltrated CD11b+ (44)</td>
<td>ARG1</td>
<td>Lewis lung carcinoma (3LL)</td>
</tr>
<tr>
<td>Tumor-associated F4/80+ (59)</td>
<td>TNF-α, iNOS</td>
<td>3-Methylcholanthrene-38 (MCA-38) induced sarcoma</td>
</tr>
<tr>
<td>Tumor-associated F4/80+ (41)</td>
<td>ARG1 + iNOS, STAT1</td>
<td>Colon carcinoma, T-cell lymphoma, fibrosarcoma, and sarcoma</td>
</tr>
<tr>
<td>Gr-1+, CD115+ (60)</td>
<td>N/A (induction of Treg)</td>
<td>Colon carcinoma</td>
</tr>
</tbody>
</table>

Abbreviations: STAT, signal transducer and activator of transcription; TGF-α, transforming growth factor-α; TNF-α, tumor necrosis factor-α.
addition, most vaccination strategies lack sufficient activity to counteract antigen-specific immune tolerance and to generate a potent and durable T-cell response in the cancer patient (55). Advances in molecular and cellular biology have shown the existence of cellular subsets that considerably dampen immune responses in the cancer patient. Because several pathways are involved that hinder T-cell function, it is likely that a combination of interventions that affect multiple immunosuppressive pathways or mechanisms may eventually yield more effective strategies and provide therapeutic benefit in humans. These strategies may represent important elements for the design of multimodal treatment strategies and provide a roadmap for the development of successful immunotherapies in the next decade.

**Open Discussion**

Dr. Rini: Can you clarify the nature of FOXP3 and where it is expressed?

Dr. Vieweg: Transcript factor FOXP3 is an intranuclear protein expressed by regulatory T cells.

Dr. Sosman: Some studies have shown that interleukin 2 (IL-2) increased regulatory T cells, but others have correlated responses with a drop in regulatory T cells. Is that phenomenon relevant?

Dr. Vieweg: I agree with the notion that systemic IL-2 increases the number of Tregs in renal cancer patients. A lot of the controversy regarding enhanced or decreased Treg numbers resulted from the lack of relevant markers. Tregs are now defined as triple-positive cells expressing CD4, C25, and FOXP3.

Dr. Kwon: A recent paper has indicated that one of the most commonly used depleting antibodies from murine studies, in fact, does not deplete T regs (Kohm AP, McMahon JS, Podolj JR, et al. Cutting edge: anti-CD25 monoclonal antibody injection results in the functional inactivation, not depletion, of CD4+ CD25+ T regulatory cells. J Immunol. 2006;176:3301-3305.). All it does is increase CD25 turnover. How do you know you are getting depletion of your target population? Is there a possibility that something like Ontak might be blocking the receptor and precluding measurement of that cell population?

Dr. Vieweg: In our study, we used Ontak, which is a fusion protein, but not an antibody, to deplete Tregs in metastatic renal cancer patients and found significant reduction of the number of triple-positive CD4+, CD25, and FOXP3 cells. Also, we looked at FOXP3 message amplified from sorted Tregs pre and post Ontak and found FOXP3 mRNA copy numbers to be reduced after treatment. Finally, functional assays demonstrated a qualitative improvement of T-cell immunity 4 days after Ontak treatment. Cumulatively, these findings suggest that Ontak reduced Treg numbers in cancer patients. Since Ontak is a fusion protein that, unlike antibodies, is quickly internalized, I believe that receptor blocking unlikely represents a major bias in our study.

Dr. Kwon: I cannot understand how an IL-2 fusion protein is going to demonstrate specificity toward this one cell population when CD25 is so ubiquitously expressed among all immunocytes.

Dr. Vieweg: You are right that CD25 is expressed on all activated T cells, but the selectivity of Ontak to deplete Tregs with very high CD25 expression is a dose-dependent phenomenon. As shown in our paper, a 5 nmol/L dose selectively depleted Tregs with high expression of CD25, but not other CD4 T cells with intermediate or low CD25 expression.

Dr. Atkins: Would it be reasonable to consider combining Ontak with IL-2.

Dr. Vieweg: I suggested this strategy many times, since it makes sense. I believe that Steven Rosenberg from the NCI has treated several patients with this strategy, but I am unaware about the results of this study work.

Dr. Atkins: What was the clinical efficacy in the patients you treated?

Dr. Vieweg: Although we see improved T-cell responses after combined Treg depletion and vaccination, the bottom line is we need to vaccinate more often. In our published study, we immunized only 3 times, which, admittedly, was suboptimal. We have now new data, suggesting clinical responses after applying a prime-boost strategy. For example, when we vaccinate against the self-antigen telomerase reverse transcriptase, we now apply six doses weekly for priming and then boost on a monthly basis. Although we have treated only a limited number of patients at this point, in a prostate cancer setting, we see frequently serum prostate-specific antigen reductions after this prime boost regimen. We are currently initiating a phase 2 study to more directly answer the question regarding clinical efficacy.

**References**


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