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Tumor-Associated Macrophages in Personalized Cancer Vaccine Resistance

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Abstract

Personalized cancer vaccines (PCVs) use patient-specific tumor mutations to generate immune responses against neoantigens. Clinical studies in melanoma, pancreatic cancer, lung cancer, and other settings show that individualized vaccines can induce broad and durable neoantigen-specific T-cell responses, while recent randomized data support their use in combination with immune checkpoint blockade. Nevertheless, immunogenicity does not necessarily translate into durable tumor control. A major determinant is the tumor microenvironment (TME), where myeloid, stromal, vascular, metabolic, and extracellular-matrix programs can prevent vaccine-induced lymphocytes from reaching or functioning within tumor tissue. Tumor-associated macrophages (TAMs) are particularly important because they are abundant, plastic, spatially organized, and responsive to tumor-derived cytokines, hypoxia, lipids, metabolites, and signals from cancer-associated fibroblasts and lymphocytes. This review summarizes evidence linking TAM biology to the major steps required for successful personalized vaccination, including antigen presentation, T-cell recruitment, persistence, cytotoxicity, and resistance to inhibitory signaling. Rather than treating TAMs as a uniform M2 population, we emphasize transcriptionally and spatially distinct states, including TREM2+, SPP1+, CD163+/MRC1+, PD-L1+, and CD73+ macrophages. Mechanistically, TAMs can suppress immunity through PD-L1/PD-1 signaling, IL-10, TGF-β, arginine depletion, adenosine, lipid handling, lactate-associated metabolic adaptation, extracellular-matrix remodeling, and altered chemokine gradients. We then examine therapeutic approaches involving CSF1/CSF1R, PI3Kγ, TREM2, CD73/adenosine, innate immune agonism, and macrophage reprogramming. Importantly, direct clinical evidence proving that a defined TAM subset causes failure of personalized neoantigen vaccination remains limited. Therefore, TAM-mediated vaccine resistance should currently be regarded as a biologically plausible and testable mechanism supported by convergent evidence, rather than as an established clinical biomarker. Integrating tumor genomics with single-cell, spatial, and functional immune profiling may enable biomarker-guided combinations of personalized vaccination, TAM modulation, and checkpoint blockade.

Keywords: personalized cancer vaccine; neoantigen; tumor-associated macrophage; TREM2; SPP1; immunometabolism; tumor microenvironment; T-cell exhaustion; immune checkpoint blockade; precision oncology.

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Introduction

Personalized cancer vaccination has moved from a largely experimental concept toward a clinically testable precision-immunotherapy strategy. Tumor sequencing, HLA typing, improved neoantigen prediction, and advances in peptide, RNA, and viral-vector platforms now allow the selection and manufacture of patient-specific vaccine targets. Early melanoma studies established that individualized neoantigen vaccines can induce polyclonal T-cell responses, while more recent trials have extended the approach to pancreatic cancer, non-small-cell lung cancer, and other malignancies [1–8]. In the phase 2b KEYNOTE-942 trial, individualized mRNA-4157/V940 combined with pembrolizumab improved recurrence-free outcomes compared with pembrolizumab alone in resected high-risk melanoma, illustrating the potential value of combining antigen-specific vaccination with checkpoint blockade [1].

The central biological challenge is that a vaccine does not kill tumor cells directly. It creates or expands tumor-reactive lymphocytes that must subsequently enter the tumor, recognize antigen, survive repeated stimulation, and retain cytotoxic function. Clinical benefit therefore depends on both the quality of the vaccine-induced immune response and the accessibility and permissiveness of the tumor microenvironment [9–12]. Neoantigen clonality, antigen expression, HLA presentation, T-cell receptor repertoire, and immune-cell localization can all influence the final outcome [3,7,8,13].

TAMs are a major component of this microenvironment. They originate from tissue-resident macrophages and recruited monocyte-derived populations and are continuously remodeled by local signals. Contemporary single-cell and spatial analyses demonstrate that TAMs cannot be adequately described by the binary M1/M2 model. Instead, tumors contain multiple macrophage states with distinct lipid, interferon, complement, scavenger-receptor, antigen-presentation, tissue-repair, and extracellular-matrix programs [14–21]. Some states can support antitumor immunity, whereas others promote immune suppression, angiogenesis, invasion, and resistance to therapy. This heterogeneity is directly relevant to vaccination because the same tumor may contain macrophages that assist antigen presentation alongside macrophages that restrict the function of vaccine-induced T cells.

The hypothesis addressed in this review is therefore not that all TAMs cause vaccine failure. Rather, specific TAM states and spatial niches may create barriers between vaccine-induced T cells and malignant cells. This distinction is important because broad macrophage depletion could remove beneficial immune functions. The translational objective should be selective depletion, inhibition, or reprogramming of immunosuppressive TAM states while preserving macrophages that support tissue homeostasis and antitumor immunity [16–25].

Personalized Vaccination Meets a TAM-Dominated Tumor Microenvironment

PCV development is a multistep process: tumor sampling and sequencing are followed by somatic-variant identification, HLA typing, neoantigen prediction, prioritization, vaccine design, manufacturing, administration, and immune monitoring. Peptide, RNA, DNA, and viral-vector platforms can encode multiple patient-specific targets, potentially broadening the immune repertoire and reducing the likelihood that immune escape through loss of one antigen will dominate [3,7,8,13,26–30]. The clinical literature now supports several important principles. First, vaccines can generate robust neoantigen-specific T-cell responses. Second, CD4+ and CD8+ responses can both contribute to efficacy. Third, clinical benefit is influenced by tumor burden, antigen clonality, immune contexture, and combination therapy. Fourth, a strong peripheral immune response does not ensure productive intratumoral activity.

This last point creates a logical interface with TAM biology. Vaccine-induced T cells must cross vascular and stromal barriers, navigate chemokine gradients, penetrate tumor nests, and remain metabolically competent. TAMs can influence each of these steps indirectly or directly. They can alter endothelial activation and angiogenesis, remodel extracellular matrix, interact with fibroblasts, produce immunoregulatory cytokines, express inhibitory ligands, and consume or redistribute nutrients [14–25,31–36].

The evidence should nevertheless be interpreted carefully. Direct prospective clinical studies showing that a defined TREM2+, SPP1+, CD163+, or CD73+ TAM population predicts failure of an individualized neoantigen vaccine are not yet established. Most mechanistic evidence comes from broader cancer-immunotherapy studies, preclinical models, tumor profiling, and studies of checkpoint resistance. The strongest conclusion at present is therefore that TAMs constitute a plausible and therapeutically relevant component of the resistance network surrounding personalized vaccination, while the magnitude and clinical specificity of this effect remain to be determined.

TAM Heterogeneity and Mechanisms of Vaccine Resistance

TAM phenotype is shaped by tumor-cell signals, CSF1/CSF1R activity, chemokines, hypoxia, extracellular metabolites, lipids, apoptotic material, cytokines, extracellular matrix, and reciprocal interactions with fibroblasts and lymphocytes. Markers such as CD68, CD163, MRC1/CD206, MARCO, MSR1/CD204, TREM2, SPP1, FOLR2, PD-

L1, and CD73 are useful for identifying macrophage states, but none should be interpreted as a universal surrogate for a single functional phenotype [14–21,37–40].

TREM2 has received particular attention because it marks macrophage states associated with lipid handling and immunoregulatory programs in several tumor contexts. In mouse models, TREM2 modulation can remodel the myeloid compartment and improve response to PD-1 blockade [17]. These findings provide a mechanistic rationale for asking whether TREM2-rich niches also restrict vaccine-induced T cells. However, translating this concept into PCV cohorts requires direct measurement of TREM2 state, vaccine-specific T-cell activity, and clinical response.

SPP1+ macrophages represent another state of interest. SPP1/osteopontin is associated with matrix remodeling, angiogenesis, migration, and tumor-supportive programs in multiple cancers. Spatial localization may be as important as abundance: an SPP1+ population positioned at tumor–stroma interfaces could have different consequences from an SPP1+ population within an inflamed immune niche. Thus, future vaccine studies should move beyond bulk TAM counts and characterize macrophage identity together with anatomical position [18,20,41].

Table 1. Selected TAM states relevant to personalized cancer vaccination

Marker/state	Biological features	Potential effect on vaccine-induced immunity	Interpretive caution
CD68	Broad macrophage marker; lysosomal/phagocytic activity	Useful for estimating total macrophage burden	Does not define an immunosuppressive state
CD163 / MRC1(CD206)	Immunoregulatory and tissue-remodeling programs	May associate with reduced T-cell activity in some tumors	Context- and tumor-dependent
TREM2+	Lipid-associated, immunoregulatory state	Potential checkpoint resistance and suppressive niche	Direct PCV-specific clinical validation is lacking
SPP1+	Matrix remodeling, migration, angiogenesis	May contribute to T-cell exclusion and stromal barriers	Function depends on spatial context
PD-L1+	Inhibitory ligand expression	Can inhibit PD-1+ vaccine-induced T cells	May be induced by inflammation and therapy
CD73+	Extracellular AMP→adenosine metabolism	Adenosine can suppress T/NK-cell effector function	Often part of a broader CD39/CD73 axis
ARG1+	Arginine metabolism	Nutrient depletion can impair T-cell proliferation	Expression and functional importance vary by model
FOLR2+ / tissue-resident	Tissue-resident/homeostatic features	May coexist with immune-supportive niches	Not intrinsically synonymous with protumor activity

Immune suppression and T-cell dysfunction

One mechanism is direct inhibition of T-cell effector activity. PD-L1 expressed by macrophages can engage PD-1 on activated T cells and contribute to reduced signaling, cytokine production, proliferation, and cytotoxicity. The importance of myeloid PD-L1 varies by tumor type and treatment context, but it provides a mechanistic link between macrophage-rich niches and checkpoint-sensitive T-cell dysfunction [22,42]. TAMs can also produce IL-10 and TGF-β, both of which influence inflammatory circuits, T-cell differentiation, cytotoxic function, and stromal organization. TGF-β is particularly relevant to tumors with dense extracellular matrix and fibroblast activity, where it can reinforce lymphocyte exclusion [43–45].

TAMs may therefore amplify the consequences of chronic antigen exposure. Vaccine-generated T cells that reach a tumor may encounter persistent antigen, inhibitory receptors, suppressive cytokines, and poor metabolic conditions. Exhaustion is not simply an on/off state; it comprises differentiated cellular states with distinct progenitor and terminal characteristics. Consequently, TAM-mediated signals may influence the trajectory and reversibility of T-cell dysfunction rather than acting as a single binary suppressive switch [46,47].

Metabolic reprogramming and nutrient competition

The metabolic environment of solid tumors is characterized by variable oxygenation, acidity, nutrient depletion, high lactate, altered lipid availability, and intense competition for glucose and amino acids. TAMs adapt to these conditions through changes in glycolysis, oxidative phosphorylation, fatty-acid metabolism, amino-acid utilization, and intracellular lipid storage [31–36,48]. These changes can affect macrophage function while simultaneously modifying the environment experienced by T cells.

Arginine metabolism is one example. ARG1-expressing macrophages can reduce extracellular L-arginine, a nutrient required for lymphocyte proliferation and protein synthesis. Tryptophan metabolism, glutamine handling, glucose consumption, and lactate signaling can similarly influence immune-cell fitness. Importantly, these pathways are interconnected: tumor-derived metabolites can reprogram macrophages, and macrophage metabolic activity can further modify the local metabolite pool [31–36,48].

Adenosine provides another metabolic checkpoint. Extracellular ATP generated during tissue stress can be converted through ectonucleotidase pathways, including CD39 and CD73, to adenosine. Adenosine receptor signaling can suppress T-cell and NK-cell function and contribute to an immune-resistant niche. CD73 expression on macrophages and other stromal cells therefore represents a potentially actionable component of the vaccine-resistance network, although clinical efficacy of adenosine-axis combinations remains context dependent [49,50].

Lipid metabolism is increasingly recognized as a defining component of TAM biology. Lipid-rich tumor environments can induce macrophage programs involving scavenger receptors, lipid uptake, and oxidative metabolism. TREM2 is one marker associated with such states. These metabolic programs may support macrophage survival and immunoregulatory activity in nutrient-stressed tumors, creating a connection between macrophage metabolism and immune resistance [17,31–36].

Antigen presentation, dendritic cells, stroma, and spatial organization

The first assumption in a vaccine-response model is that more antigen-specific T cells should produce more tumor killing. In reality, the quality and location of antigen presentation matter. Dendritic cells are specialized for priming naïve T cells, while macrophages can capture tumor material and shape local inflammatory signals. TAMs may alter dendritic-cell recruitment and maturation through cytokines and chemokines and can participate in the organization of suppressive myeloid niches [18,25,51].

TAMs also interact with cancer-associated fibroblasts (CAFs), endothelial cells, and extracellular matrix. CAF–TAM communication can reinforce chemokine production, matrix remodeling, angiogenesis, and T-cell exclusion. In this setting, macrophage targeting alone may be insufficient because the suppressive niche is maintained by multiple interacting compartments [9,52]. Spatial transcriptomics and multiplex imaging are therefore particularly relevant to PCV research. The question is not only how many TAMs are present, but whether vaccine-induced T cells are physically and functionally adjacent to tumor cells or instead confined to stromal regions enriched in suppressive macrophages and fibroblasts [53].

Therapeutic Opportunities

The therapeutic implication of TAM biology is not necessarily to remove macrophages. Macrophages perform essential tissue functions and can, under appropriate conditions, support antigen presentation, phagocytosis, and inflammatory immunity. A more precise strategy is to interfere with the recruitment, survival, signaling, or metabolic programs of suppressive TAM states, or to reprogram them toward immune-supportive phenotypes [23–25,37,54–58].

CSF1/CSF1R inhibition can reduce or alter selected macrophage populations. Preclinical studies demonstrate that the effect depends strongly on tumor type, treatment timing, and macrophage dependence. Broad depletion can be incomplete or even counterproductive if macrophage populations with antitumor functions are also removed [55,56]. For PCVs, the most rational application may therefore be biomarker-guided CSF1R modulation rather than empiric depletion.

PI3Kγ is another target of interest because myeloid PI3Kγ signaling can regulate immunosuppressive transcriptional programs. Preclinical studies have shown that PI3Kγ inhibition can relieve macrophage-mediated suppression and improve antitumor immune responses, including in combination with checkpoint blockade [57,58]. Whether this improves personalized vaccine efficacy specifically remains to be established.

TREM2 targeting is attractive because it may allow selective modulation of a macrophage state rather than global macrophage depletion. Experimental work has shown that TREM2 modulation can remodel the myeloid landscape and enhance anti-PD-1 activity [17,59]. A rational PCV trial could test TREM2-directed therapy in tumors enriched for TREM2+ macrophages while measuring vaccine-specific T-cell expansion and intratumoral function as pharmacodynamic endpoints.

The CD73/adenosine axis provides a complementary metabolic strategy. If vaccine-induced T cells are present but functionally suppressed in an adenosine-rich microenvironment, CD73 or adenosine-receptor blockade could increase the probability that these cells retain effector activity. Combination studies should account for the fact that CD73 is expressed by multiple stromal and malignant compartments, so response cannot automatically be attributed to macrophage targeting alone [49,50].

Reprogramming approaches may ultimately be more durable than depletion. Innate immune agonists, CD40 stimulation, TLR or STING activation, cytokine engineering, and metabolic rewiring can alter macrophage state. Recent work with engineered cytokine systems illustrates the possibility of shifting protumor macrophage programs toward antitumor phenotypes [60]. The challenge is achieving local activation without systemic inflammatory toxicity.

Table 2. Potential barriers and combination strategies

Barrier	Representative mediators	Potential consequence	Candidate strategy
Checkpoint inhibition	PD-L1/PD-1	Reduced T-cell signaling and cytotoxicity	PD-1/PD-L1 blockade
Suppressive cytokines	IL-10, TGF-β	T-cell dysfunction and exclusion	Cytokine/pathway modulation
Arginine depletion	ARG1	Reduced lymphocyte proliferation	ARG1/metabolic targeting
Adenosine	CD39/CD73, A2A/A2B	Suppressed T/NK-cell function	CD73 or adenosine-receptor blockade
Lipid-associated TAM state	TREM2, scavenger receptors	Immunoregulatory niche	TREM2/lipid-state modulation
ECM remodeling	SPP1, MMPs, TGF-β	Physical T-cell exclusion	Matrix/stromal targeting
Macrophage recruitment	CSF1/CSF1R, CCL2	Accumulation of suppressive TAMs	CSF1R/chemokine-axis inhibition
Myeloid signaling	PI3Kγ/SYK	Suppressive transcriptional program	PI3Kγ/SYK modulation
CAF–TAM crosstalk	Chemokines, TGF-β, CSF1	Persistent suppressive niche	Combined stromal/TAM approaches
Metabolic stress	Glucose, lactate, lipids, hypoxia	Reduced T-cell fitness	Context-specific metabolic intervention

An Integrated Precision-Immunology Model

The most clinically testable model is a three-layer combination: personalized vaccination generates tumor-specific T cells; checkpoint blockade releases inhibitory signaling; and TAM modulation improves the environment in which those T cells must operate. This framework is consistent with the growing clinical experience of combining neoantigen vaccines with PD-1 pathway inhibition and with extensive preclinical evidence that myeloid remodeling can improve checkpoint responses [1,17,54,59].

Importantly, treatment sequencing may matter. Vaccination before or after surgery may be used to reduce tumor burden and antigenic complexity; checkpoint blockade may be required during the expansion and effector phases; and TAM-directed treatment could be timed to the period when vaccine-induced T cells enter the tumor. These hypotheses require prospective testing because macrophage depletion, immune activation, and vaccination may have different optimal windows.

A useful biomarker strategy would combine tumor genomic variables with immune and spatial measurements. Candidate variables include neoantigen clonality, predicted HLA presentation, T-cell receptor clonality, interferon-γ signatures, CD8+ T-cell density, TAM abundance, TREM2/SPP1/CD163/CD73 states, and spatial proximity between TAMs and T cells. Single-cell RNA sequencing and spatial transcriptomics can resolve cellular states and neighborhoods, while multiplex immunohistochemistry or imaging can provide clinically deployable spatial biomarkers [20,53].

Such profiling could distinguish at least three biologically different scenarios. In an immune-excluded tumor, the priority may be stromal and macrophage remodeling to enable trafficking. In a T-cell-infiltrated but suppressive tumor, checkpoint and metabolic interventions may be more relevant. In a tumor with low antigenicity or poor antigen presentation, TAM targeting alone is unlikely to compensate for inadequate vaccine design. This framework emphasizes that TAM therapy should be matched to the dominant resistance mechanism rather than applied uniformly.

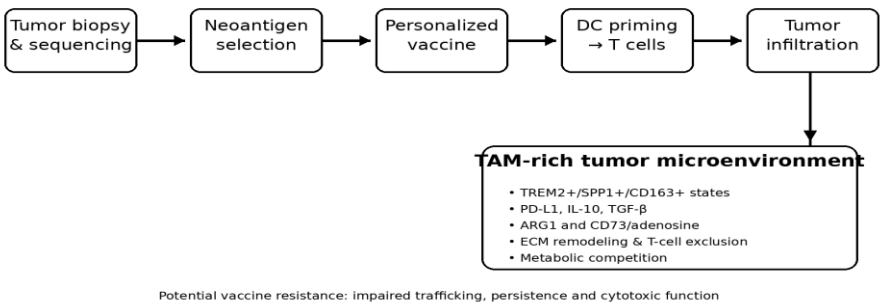

Figure 1. Conceptual pathway linking individualized vaccine development to a TAM-rich tumor microenvironment. The figure illustrates a mechanistic hypothesis rather than a validated clinical sequence.

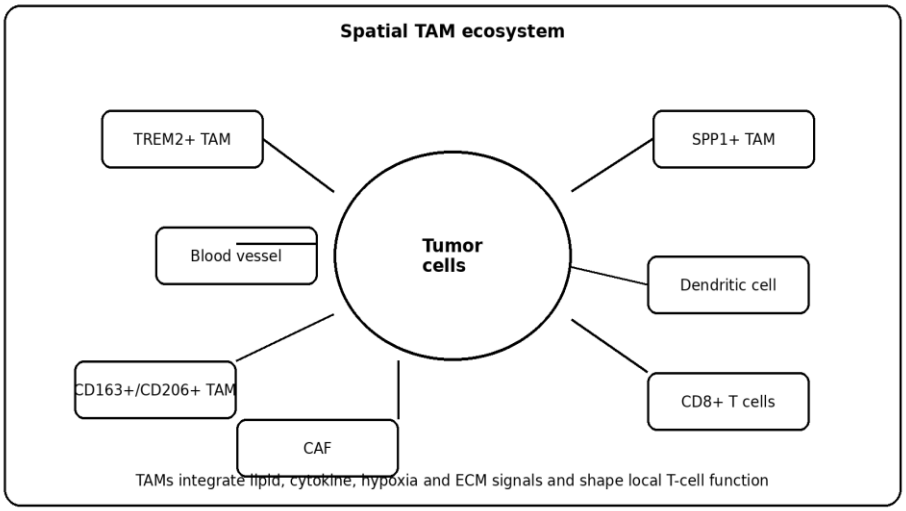

Figure 2. Representative spatial organization of macrophage states, tumor cells, fibroblasts, dendritic cells, vasculature, and CD8+ T cells. Functional consequences are expected to vary by tumor and anatomical niche.

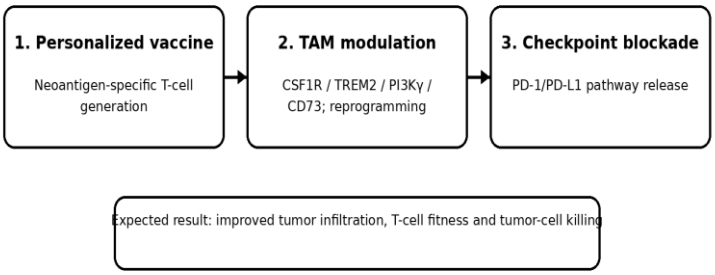

Figure 3. Proposed combination strategy integrating personalized vaccination, TAM modulation, and checkpoint blockade. Prospective clinical studies are required to define the optimal target, sequence, and biomarker.

Future directions and limitations

Several uncertainties should guide the next generation of studies. First, the field needs direct evidence linking specific TAM states to PCV outcomes rather than extrapolating exclusively from checkpoint or conventional immunotherapy studies. Second, TAM identity should be measured longitudinally because vaccination, surgery, radiotherapy, chemotherapy, and checkpoint blockade can all remodel myeloid states. Third, macrophage abundance should be separated from macrophage function and spatial position. Fourth, the possibility of beneficial TAM states should be preserved in trial design. Finally, the manufacturing and logistical constraints of individualized vaccines must be considered alongside biological resistance mechanisms [3,7,8,13,26].An ideal prospective trial would obtain pretreatment and on-treatment biopsies, perform genomic and HLA analysis, quantify vaccine-specific T-cell responses in blood, and use single-cell or spatial profiling to characterize TAM states. Patients could then be stratified according to TREM2/SPP1/CD73/PD-L1 signatures or broader myeloid programs. Such studies could determine whether TAM signatures are predictive biomarkers, pharmacodynamic markers, or merely correlates of an already established immune-resistant state.

Conclusion

Personalized cancer vaccines can generate potent and durable neoantigen-specific immunity, but successful vaccination requires more than immune priming. Vaccine-induced T cells must enter tumors and remain functional in a

metabolically and immunologically hostile environment. TAMs are well positioned to regulate this interface because they integrate inflammatory, metabolic, stromal, and vascular signals and can establish spatial niches that either support or suppress antitumor immunity.

Current evidence supports a mechanistic model in which selected TAM states—particularly TREM2+, SPP1+, CD163/MRC1+, PD-L1+, and CD73+ populations—may contribute to vaccine resistance through checkpoint signaling, suppressive cytokines, metabolic competition, adenosine, extracellular-matrix remodeling, and interactions with other stromal cells. However, the specific causal contribution of these states to failure of personalized neoantigen vaccination remains incompletely validated clinically. Future trials should therefore avoid treating TAM markers as established PCV-response biomarkers until prospective evidence is available. The most promising translational direction is a biomarker-guided combination strategy: personalize the antigen, characterize the immune microenvironment, and selectively modulate the dominant suppressive macrophage program while releasing T-cell checkpoints. This approach could transform TAMs from a generalized obstacle into a tractable component of precision immunotherapy.

Declarations

Competing Interests

The authors declare that they have no known financial conflicts of interest or personal relationships that could have influenced the work presented in this manuscript.

Ethical approval

This review article does not include any new studies involving human participants or animals conducted by the authors.

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Availability of data and materials

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