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Anticipating Resistance

REVIEW

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Deciphering Antigen Processing Machinery (APM) as One of the Determinants for Responsiveness of Affected Patients towards Anticancer Immunotherapy

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Abstract

Immunotherapy is one of the rising stars in the field of anticancer regiments. Aimed at reinvigorating immune cytotoxicity, this platform is capable of bulking up memory subsets by which protection against tumors is served. The most commonly applied immunotherapy is immune checkpoint inhibitor (ICIs) which received FDA approval for non-small lung cancer (NSLC) in 2014. The response toward ICI is closely related to the antigen processing machinery (APM) within which antigens are processed prior to loading onto the human leukocyte antigen (HLA) to induce cascade mechanisms for immune clearance. APM allows immune cell infiltration thus strengthens immunogenicity. Impaired components of the APM are frequently found in tumors because tumor progression requires tumor cells to acquire immune recognition evasion. Alterations in tumors' APM result in downregulation of HLA molecules and transformation of antigenic peptide repertoire presented to the T lymphocytes. Interactions of processed antigens (peptide)-HLA complex are critical for successful T cell priming and differentiation into cytotoxic effector cells. The interaction underlies not only ICI-related mechanism but also anticancer immunity in general where T cell subset can induce antitumor recognition only if a proper peptide-HLA complex is present. This feature, unfortunately, is missing in tumors. This Review highlights presentation of tumor-specific antigens to T cells in HLA-restricted manner which leads to their eradication. This is a pivotal point but in most cases is overlooked which might add some volume to the off-target and less functional of anticancer immunotherapy.

Keywords: antigen processing machinery (APM)- immune checkpoint inhibitors (ICIs)- immunogenicity

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Introduction

Immunotherapy has been one of the rising stars in the field of anticancer regiments for the last four decades [1]. This strategy is designed to reinvigorate immune cytotoxicity [2] and bulk up memory cells which are expected to provide long-term protection against tumors [3]. There are diverse platforms in immunotherapy ranging from dendritic cell (DC) therapy, either that applied as adoptive DCs or DC-based vaccine [4, 5], to immune checkpoint inhibitor (ICI) with the later mentioned received FDA approval for non-small lung cancer (NSLC) patients treatment in 2014 [6-8] and become the most commonly implemented among all anticancer immunotherapy platforms hitherto. ICI exhibits efficacy in tumor rejection and improves patients' survival rate by blocking the receptor-ligand interactions of immune checkpoint molecules. The response toward ICI is closely related to the antigen processing machinery (APM) within which antigens are processed prior to loading onto the human leukocyte antigen (HLA) to induce cascade mechanisms for immune clearance [9]. The APM comprises a network of cellular components essential for processing and presenting antigens to T cells by antigen-presenting cells (APCs). When there are impairments in the APM, the immune system's capacity to detect and react to cancer cells can be hindered, facilitating the emergence of tumors that can evade immune surveillance [10]. Key elements of the APM include proteasomes, which break down proteins into peptides; transporter associated with antigen processing (TAP), which carries peptides from the cytoplasm to the endoplasmic reticulum (ER); and human leukocyte antigen (HLA) molecules that display these peptides on APC surfaces for T cells to recognize [10]. Increasing evidence indicates that APM defects can play a significant role in tumorigenesis. Mutations in genes responsible for proteasomes or TAP can impair peptide generation for presentation on HLA molecules, limiting the immune system's ability to identify and combat cancer cells [10]. Furthermore, abnormalities in HLA molecules can diminish the immune response to tumors [11, 12].

In addition, APM facilitates immune infiltration thus enhance tumor immunogenicity [10-13]. Interactions of processed antigens (peptide)-HLA complex are critical for

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successful T cell priming and differentiation into cytotoxic effector cells [14]. The interaction underlies not only ICI-related mechanisms but also anticancer immunity in general [15, 16]. Tumors are particularly immunogenic [17]. The presentation of their specific antigens to T cells is carried out in an HLA-restricted manner, which leads to their eradication. Impaired components of the APM are frequently found in tumors because tumor progression requires tumor cells to acquire immune recognition and evasion [18]. Alterations in tumors' APM result in downregulation of HLA molecules and transformation of antigenic peptide repertoire presented to the T lymphocytes [19, 20]. In addition, APM facilitates immune infiltration thus enhance tumor immunogenicity [10-13]. As immunotherapy relies on the re-activation of T cells, this alteration impairs antitumor responses and leads to resistance [19, 20]. This review elucidates how APM performs its function and the biological and clinical consequences whenever each unit is impaired.

APM gene signature

APM plays a crucial role in the immune response against tumors and pathogens by generating and presenting peptides on HLA class I molecules [15]. This complex system involves multiple components, including proteasomes, TAP transporters, and various chaperones [16, 17, 21] as outlined below in Table 1.

Defects in HLA class I APM are frequently observed in various types of cancer, with prevalence ranging from 35.8% in renal cancer to 87.9% in thyroid cancer [50]. APM defects are associated with poor prognosis and reduced patient survival in many malignancies [51]. Moreover, they can negatively impact the efficacy of T cell-based immunotherapies, including checkpoint inhibition [52, 51]. The majority of APM defects (>75%) are caused by epigenetic mechanisms or dysregulated signaling, suggesting potential for correction through targeted strategies [52]. Understanding and addressing these APM abnormalities may improve clinical outcomes and enhance the effectiveness of immunotherapies in cancer treatment [51].

Defects in HLA class I APM allow immune evasion by tumor cells

Anticancer immunity, which is naturally aimed at effectively terminating cancer cells, is preceded by a series of stepwise events termed the Cancer Immunity Cycle. This starts when neoantigens resulting from oncogenesis are released and captured by dendritic cells (DCs) to be processed. Immunogenic signals that include proinflammatory cytokines and factors released by dying tumor cells are crucial to specify the immune effector mechanisms [15]. Post-processing, DCs will present the antigens that have been uploaded onto HLA class I to CD8T cells through cross-presentation [16]. "Cross-dressing" a term coined by Yewdell and Haerfar was proposed to delineate antigen presentation within which DCs acquire the performed peptide-HLA class I complexes from neighboring DCs or tumor cells and activate CD8+ T cells without further peptide processing [17, 21, 22]. HLA class I-driven killing by CD8+ T cells necessitate licensing by DCs via MHC class II-dependent activation of CD4+ helper T cells. HLA class II on DCs serves to mount humoral immune responses and to instruct regulatory T cells (Treg) and memory T cells. DCs constitutively synthesize HLA class II. Limited exposure to self-peptide-loaded HLA class II provides cues that favor immune tolerance when the costimulatory signals are not present [23].

HLA class I antigen and APM component expression are aberrant in malignancies. Due to their association with a poor prognosis and potential importance in immune checkpoint inhibitor (ICI)-based immunotherapy, HLA class I and APM anomalies are considered to have clinical value. In head and neck squamous cell carcinoma (HNSCC), normalization of APM component expression may be promoted by IFN-γ treatment, suggesting that APM anomalies are caused by deregulation rather than structural gene abnormalities. Tumors that express defective APM components can grow more aggressively [53].

Aberrant expression pattern of proteasome subunit

The DC-captured neoantigens are processed in the ubiquitin-proteasome system. Initially, the proteasomes will chop off endogenous proteins tagged by ubiquitin into oligopeptides with 8–13 amino-acid long to enable effective presentation by HLA class I. Tumor cells that are exposed to inflammatory stimuli or oxidative stress up-regulate immunoproteasomes. The catalytic activity of the immunoproteasomes produces diverse non-self-peptides which will be cleaved prior to trafficking to the endoplasmic reticulum (ER) by TAP protein to be loaded onto newly synthesized HLA class I to form a peptide-HLA class I complex. Subsequently, the complex is released from ER then exocytosed into the plasma membrane for presentation to CD8+ T cells [25]. However, this is aberrantly regulated in the case of cancers causing troublesome for an instant tumor cells eradication.

Racanelli and colleagues, [54] found that decitabine, a DNA methyltransferase inhibitor, restored the expression of several proteasome subunits in myeloma which suggested the involvement of promoter methylation alterations and epigenetic regulation [26]. In renal cell carcinoma cell lines (caki-2), the loss of TAP1 and latent membrane protein 2 (LMP2) in the earliest steps of IFN-γ signaling pathway result in the inability of the caki-2 to upregulate the HLA class I APM [27]. Melanoma cell lines, in addition to the aforementioned components, showed that the lack of inducibility of HLA class I surface expression by IFN-γ treatment was associated by the deletion of JAK2 chromosome 9. Furthermore, the JAK2-deficient cells appeared to be resistant to the antiproliferative effects of IFN-γ [28]. With these significances being shown, proteasome has been validated as an anticancer drug target. However, researchers are yet to resolve severe toxicity, drug resistance and a no show effect when this applied in solid tumors [29].

ICI Resistance

Although in some cases, ICIs are successfully inducing expected immune responses from the affected patients, the number of resistance cases raises day by day which

Table 1. Genes that Play Significant Roles in APM

Genes	Function of the protein encoded by the gene
β2-microglobulin (β2m)	β2-microglobulin (B2M) serves as a crucial stabilizing element for the α chain of HLA, which is responsible for binding peptides that are then presented to T cells [22]. When mutations occur in B2M or when it is lost entirely, cancer cells can evade immune detection, a phenomenon noted in patients with melanoma who show resistance to checkpoint blockade therapies [23]. Tumors harboring B2M mutations tend to present elevated levels of neoantigens and greater infiltration by immune cells, indicating a potential compensatory response to immune pressure [24].
The transporter associated with antigen processing (TAP)	TAP, composed of TAP1 and TAP2 subunits, plays a crucial role in antigen presentation by transporting peptides into the endoplasmic reticulum for loading onto HLA class I molecules [26]. The peptide transport mechanism involves two channels, with shorter peptides (8-10 mers) moving more quickly than longer ones (15-mers) [27]. Cancer cells and viruses often target TAP to evade immune recognition, leading to the development of TAP-independent processing pathways [28]. Cancer-associated mutations and viral proteins can interfere with peptide transport by altering the conformation of the transport tunnel [27].
Calreticulin (CALR)	CALR is a multifunctional protein primarily located in the endoplasmic reticulum, playing crucial roles in antigen processing and presentation for adaptive immune responses [29]. CALR supports the assembly and expression of HLA class I molecules, ensuring normal antigen presentation [30]. CALR can act as an immunologic adjuvant, translocating itself and tumor-associated antigens to the cell surface, inducing specific antitumor immune responses [31].
HLA class I	HLA class I proteins are present on the surfaces of nucleated cells and play a vital role in the immune system by facilitating the activation of CD8+ T cells and modulating the function of natural killer (NK) cells. These HLA class I molecules consist of a trimeric structure, which includes a heavy chain, β2m, and a peptide. The T-cell receptors on CD8+ T cells interact with the peptide-binding domain located distally on the membrane, while the CD8 co-receptors bind to the membrane-proximal regions of the peptide-HLA class I complexes. This interaction is crucial as it provides the necessary signal for the activation of CD8+ T cells [33].
HLA class II	HLA class II antigen-processing machinery plays a crucial role in presenting antigenic peptides to CD4+ T cells, influencing immune responses and potentially affecting clinical outcomes in cancer [34]. B cells utilize this pathway to process and present antigens, shaping both B and T cell fates [35].
Endoplasmic Reticulum Aminopeptidase (ERAP)	ERAPs trim N-terminal residues from antigenic precursor peptides in the endoplasmic reticulum to generate optimal-length peptides for MHC class I molecules [34]. ERAP1 has multiple functions beyond antigen processing, including secretion into the extracellular milieu to activate immune cells and enhance pro-inflammatory cytokine expression [35]. ERAP2, while complementary to ERAP1, has distinct roles in shaping MHC-I-bound immunopeptidomes and influencing cellular cytotoxic immune responses [36].
Sec61	Sec61 mediates the process of transporting antigens into the cytosol for cross-presentation. As a component of the trimeric translocon and part of the endoplasmic reticulum-associated degradation (ERAD) system, Sec61 plays a crucial role in moving proteins into the endoplasmic reticulum (ER) during translation and in exporting misfolded proteins from the ER to the cytosol for degradation by the proteasome. Down-regulation of this protein's subunits being Sec61α1 and Sec61γ results diminished antigen export into the cytosol, which in turn lowered cross-presentation efficiency, suggesting that Sec61 is likely vital for the regulation of intracellular antigen transport [37].
Heat shock protein-90 (HSP90)	HSP90 plays a crucial role in antigen presentation and processing, contributing to both innate and adaptive immune responses. HSP90 is involved in the HLA class I antigen presentation pathway, enhancing the presentation of tumor antigens on HLA class I molecules [38]. Low-level inhibition of HSP90 can amplify and diversify the antigenic repertoire presented by tumor cells, potentially improving immune recognition of cancers [39]. As a molecular chaperone, HSP90 is central to cellular proteostasis, assisting in the maturation of various client proteins with the help of cochaperones [40].
Proteasome β subunit (PSMB)	PSMB represents a distinct proteasome isoform that functions in processing intracellular antigens for presentation by HLA class I thus facilitating recognition by the immune system [41] . It was reported that the mRNA levels of PSMB4 and PSMB7 were markedly elevated in cancerous tissues when compared to normal counterparts [42,43]. In addition, PSMB8 was found to be overexpressed in gastric cancer specimens [44], while PSMB2 showed a significant correlation with chronic myelogenous leukemia [45]. However, there remains a lack of thorough analysis regarding these PSMB subunit genes hitherto [46].
Derlin-3	Derlin-3, a member of the derlin family, plays a crucial role in endoplasmic reticulum-associated degradation (ERAD) and cellular stress responses. It is involved in the formation and regulation of ERAD complexes, particularly under ER stress conditions (Eura et al., 2020). Derlin-3 has been implicated in cancer progression, with its overexpression associated with malignant phenotypes in breast cancer cells and poor patient prognosis [47]. While not directly linked to antigen processing and presentation, Derlin-3's role in ERAD may indirectly influence these processes, which are critical for immune responses mediated by dendritic cells [48].
Calnexin (CANX)	Calnexin, a type I integral endoplasmic reticulum (ER) membrane protein, plays a crucial role in protein folding, quality control, and antigen presentation [49,50]. As part of the calnexin cycle, it functions as a lectin chaperone, binding to monoglucosylated glycans and recruiting function-specific chaperones to assist in protein folding [51].

elevates concerns. The mechanism of ICI resistance, which is best exemplified in the case of NSCLC is illustrated below (Figure 1). Steps 1 to 3 are closely linked to APM where the immunogenic cancer antigens are produced to be surveyed by the patrolling T cells. Improper execution of these procedures leads to resistance. For patients with advanced NSCLC, this represents a barrier to improving their clinical prognosis after therapy [30, 55]. According to data gathered from 65 Spanish institutions for the Lung Cancer Patients Covid-19 illness (GRAVID) study, stage III NSCLC with metastases or incurable illness accounted for approximately 79.2% of all cases [31]. When ICIs like nivolumab and ipilimumab are used as first-line therapy for advanced NSCLC, a significant progression-free survival (PFS) is observed. The target of this inhibitor is programmed cell death [31]. These inhibitors specifically targets cytotoxic T lymphocyte antigen-4 (CTLA-4), as well as programmed cell death ligand-1 (PD-L1) and programmed cell death (PD-1), expressed on tumor and immune cells [32].

Resistance can develop when these procedures are not followed accurately [30]. Unfortunately, this occurs in most patients. The response rates to PD-1 inhibitors are between 40% and 70% for conditions such as melanoma, Merkel cell carcinoma, Hodgkin's lymphoma, and tumors exhibiting high microsatellite instability (MSI), as described in [34]. It is crucial to recognize that resistance is associated with ineffective chemotherapy in approximately 90% of cancer cases, heightening the chances of cancer spread and complicating treatment strategies [35]. This poses a significant challenge that researchers worldwide are striving to address.

ICI resistance takes place either primarily or acquired. Each has different pathways where ultimately lead to irresponsiveness toward ICI treatments. The dichotomized pathways are shown in Table 2.

Focusing on the role of APM in resistance to ICI, the TRACERx 100 consortium conducted an analysis of 258 tumor regions derived from 88 acquired tumors, comprising 56% adenocarcinomas and 78% lung squamous cell carcinomas. This study revealed significant disruptions in antigen presentation, characterized by LOH in HLA or mutations in APM components. Notably, complete loss of β2m was observed exclusively in nonresponders to ICI treatment, while various alterations of the β2m gene including absence of tumor-specific expression, frameshift mutations, or LOH were identified in 30% of these nonresponding tumors [36]. Supporting these findings, Rasmussen et al. [16] utilized metadata to further elucidate how APM regulation contributes to ICI resistance. Their analysis highlighted a tumor with normal expression of HLA class I and β2M, which exhibited a longer partial response (PR) compared to those with mixed APM patterns and those with initial absence of β2M mutations but later developed a frameshift mutation. This later mentioned prompted a transition of the therapy platform from talimogene laherparepvec (TVEC) combined with pembrolizumab to temozolomide which ultimately leading to a more sustained PR [37]. This convergence of data underscores the intricate relationship between APM integrity and the efficacy of ICI therapies in diverse tumor environments.

APM expression signature shapes responsiveness toward ICIs

Antitumor immunity is determined by tumor antigenicity and the tumor-specific antigen presentation by antigen presenting cells (APCs). Therefore, the expression signature of the APM in the tumor-immune microenvironment (TIME) becomes a predictive biomarker for responsiveness to ICIs [38]. As described in the previous section (Aberrant Expression Pattern of Proteasome Subunit), effective antigen presentation requires a coordinated series of intracellular events

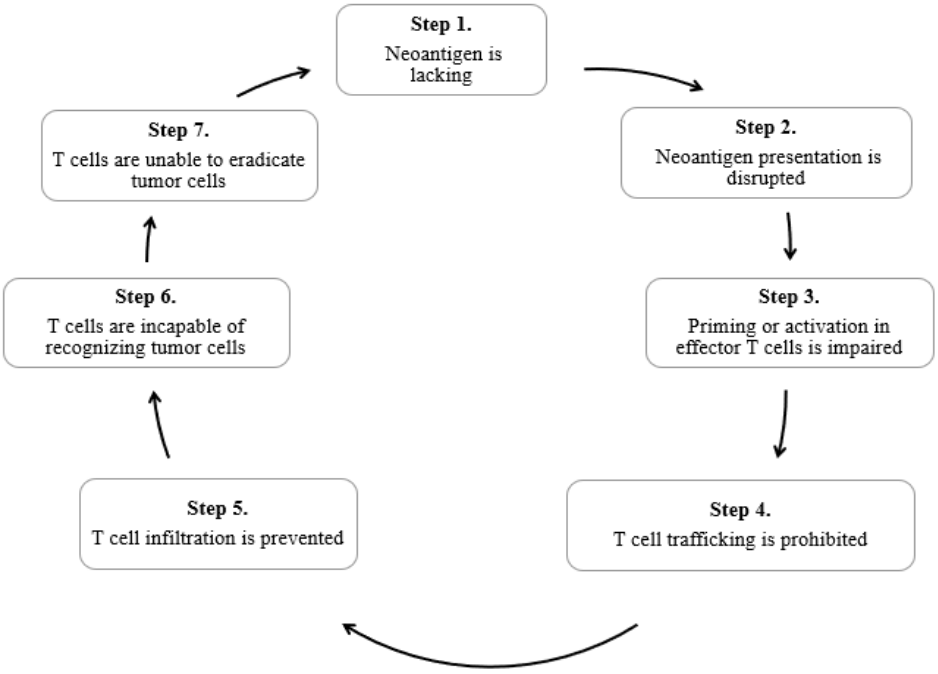

Figure 1. Cycle of ICI Resistance

Table 2. Molecular Features of Primary vs Acquired Resistance (Adapted from [35]).

Primary Resistance	Acquired Resistance
	Step 1
Low tumor mutational burden (TMB)	Lost mutations encoding for putative tumor-specific neoantigens
	Step 2
Lacking antigen-presenting machinery components	Low HLA class I expression due to acquired homozygous loss of β2m
Dysfunction of DCs	
	Step 3
Inhibition of DC recruitment by WnT/β-catenin or PGE2	
	Step 4
Downregulation of chemokines such as CXCL9 and CXCL 10	
	Step 5
Upregulation of VEGF and TGF-β	
	Step 6
Downregulation of expressed neoantigens	
	Step 7
Driver genes mutation	Upregulation of immune checkpoints and immune suppressive cytokines such as PD-1, LAG-3, Tim-3 and CD38
Inactivation of tumor suppressor genes	
Dysfunction in IFN-γ pathway	
Upregulation of immune suppressive cytokines and cells	
Upregulation of alternative co-inhibitory immune checkpoint molecules	
Regulation of immune checkpoint via epigenetic modifications	

that involve APM proteins, which play a crucial role in the modulation of immune responses [39]. In the ER, HLA class I heavy chain and β2m assembly takes place. During this event, calnexin, calreticulin, and the thiol oxidoreductase ERp57 are present to guard the correct folding of the HLA class I-β2m complex before the complex associates with tapasin and subsequently with TAP-peptide complexes [40]. The HLA class I- β2m then travels to plasma membrane via the Golgi apparatus [41].

Thompson and colleagues investigated gene signatures that might have certain impacts on the APM. They generated an APM score (APS) by employing APM-associated genes be that β2m, CALR, NLRC5, PSMB9, PSME3, RFX3 and HSP90AB and correlating them with the therapeutic response, progression free survival (PFS) and overall survival (OS) in NSCLC. Their results showed that the APM score was markedly higher in responder. The score alone was correlated with an inflammation score based on the established T cell inflamed resistance gene expression profile [42]. This pattern is validated by Shen and colleagues with BRCA+ breast cancers. The APM gene set being included in this study was more diverse: B2M, CALR, CANX, ERAP1, ERAP2, HLA-A, HLA-B, HLA-C, PDIA3, PSMB5, PSMB6, PSMB7, PSMB8, PSMB9, PSMB10, TAP1, TAP2 and TAPBP. It was observed that lower APS exhibited worse OS and PFS in BRCA cohort [43]. In addition, five most significant processes were annotated in the study included leukocyte cell-cell adhesion, mononuclear cell differentiation, leukocyte cell-cell adhesion, regulation of T cell activation and T cell activation [43]. Gong and Karchin, [13] recently used bulk and single-cell transcriptome datasets to describe four APM clusters linked to unique immunological features, cancer markers, and patient prognosis in melanoma. Their model matched other results that showed a higher response to ICI was associated with immunogenically hot tumors with high baseline APM expression prior to therapy, as opposed to cold tumors with low APM expression [44].

The APS, which combines tumor mutational burden and APM gene expression, outperforms other biomarkers in predicting ICI response across multiple cancer types [56]. Defects in APM components, particularly HLA class I, are common in tumors and negatively impact neoantigen presentation to cytotoxic T lymphocytes [15]. Certain anticancer therapies, including chemotherapy and targeted therapies, can upregulate APM component expression, potentially enhancing ICI efficacy [15]. Taking all these together, it is evident that understanding APM will lead to reliable prediction on whether the patients respond to anticancer immunotherapy to allow the cancer immunity to occur properly that ultimately elicits clinical favorable outcome [15, 57]. This is critical to ensure that the therapy induces favorable effects to the patients not to plant potentially latent adverse effects which might be more debilitating than the cancer itself. On the omics perspective, APM is receiving more attention to be tailored with other oncogenesis-related genes in order to provide a more comprehensive landscape of gene interplay through which both cancer progression and inhibition can be

precisely measured [56, 58, 59].

In conclusion, although anticancer immunotherapy is initially designed to reinvigorate immune system and strengthen recognition against tumor antigens, it is not necessarily the case with every patient. The case number of resistance is rising that propel researchers to investigate it using diverse approaches. A few published reports support the evidence of APM playing a significant role in determining the fate of immune system response against tumorigenesis. This was clearly shown in both in vivo settings as well as in the actual clinical samples from various cancer subtypes. Those types with low APM score tend to develop resistance and less responsive toward ICI, the most applied immunotherapy platform thus far. APM is highly associated with the regulation of HLA, a molecule that will carry the processed tumor- or neoantigens to be presented to the, mainly, CD8+ T cell subset to induce anticancer cytotoxicity. These significances render APM potential as targets for anticancer therapy.

Author Contribution Statement

IN solely developed the theoretical foundation, collected and screened the relevant literature, drafted and edited the manuscript.

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Conflict of interest

There is no conflict of interest to declare.

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