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REVIEW

Soluble triggering receptor expressed on myeloid cell-1 (sTREM-1): a potential biomarker for the diagnosis of infectious diseases

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Abstract **Sensitive and useful biomarkers for the diagnosis and prognosis of infectious diseases have been widely developed. An example of these biomarkers is triggering receptor expressed on myeloid cell-1 (TREM-1), which is a cell surface receptor expressed on monocytes/macrophages and neutrophils. TREM-1 amplifies inflammation by activating the TREM-1/DAP12 pathway. This pathway is triggered by the interaction of TREM-1 with ligands or stimulation by bacterial lipopolysaccharide. Consequently, pro-inflammatory cytokines and chemokines are secreted. Soluble TREM-1 (sTREM-1) is a special form of TREM-1 that can be directly tested in human body fluids and well-known biomarker for infectious diseases. sTREM-1 level can be potentially used for the early diagnosis and prognosis prediction of some infectious diseases, including infectious pleural effusion, lung infections, sepsis, bacterial meningitis, viral infections (e.g., Crimean Congo hemorrhagic fever and dengue fever), fungal infections (e.g., *Aspergillus* infection), and burn-related infections. sTREM-1 is a more sensitive and specific biomarker than traditional indices, such as C-reactive protein and procalcitonin levels, for these infectious diseases. Therefore, sTREM-1 is a feasible biomarker for the targeted therapy and rapid and early diagnosis of infectious diseases.**

Keywords soluble triggering receptor expressed on myeloid cells-1; infectious diseases; diagnosis and prognosis; biomarker

Introduction

Triggering receptor expressed on myeloid cell-1 (TREM-1), discovered by Bouchon *et al*. [1] in 2000, is a new immunoglobulin superfamily member that can be selectively expressed on the surface of a few subsets of myeloid lineage cells, including neutrophils and monocytes. TREM-1 is a transmembrane glycoprotein encoded by *TREM* genes located on human chromosome 6 and mouse chromosome 17 [2,3]. Five *TREM* genes have been discovered; *TREM-1–TREM-4* encode functional type I transmembrane globulin [4]. Unlike other members of the immunoglobulin superfamily, TREM-1 contains one extracellular Ig-like domain from residues Glu17 to Thr133; TREM-1 also contains a 70-amino-acid neck region linked to a 29-amino-acid transmembrane region and a 5-amino-acid intracellular region [2,3].

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Soluble triggering receptor expressed on myeloid cell-1 (sTREM-1) is a soluble TREM-1 that can be directly measured and tested in human body fluids, including serum, pleural effusion, sputum, and urine, during infections [1,2,5]. sTREM-1 lacks the transmembrane region but possesses the same extracellular region as TREM-1; therefore, the former can combine with the same ligands as the latter [2,5]. The origin of sTREM-1 has been explained with two hypotheses. In one of these hypotheses, sTREM-1 is encoded by a splice variant of the mRNA of TREM-1 [6]. Gingras *et al.* [5] found that the third exon is deleted in this variant. In the other hypothesis, sTREM-1 is generated through the proteolytic cleavage of mature cell-surface-anchored TREM-1 [7]. Regardless of the sTREM-1 source, the function of sTREM-1 in various diseases is important.

TREM-1 expression is upregulated in bacterial and fungal infection cases but is poorly expressed in non-infectious inflammatory diseases [8,9]. TREM-1 expression can be stimulated by bacterial lipopolysaccharide in infections and innate immune responses [8]. TREM-1

modulates inflammatory responses primarily through the DNA-activating protein 12 (DAP12) signaling pathway [1,10]. TREM-1/DAP12 pathway can be activated by recognizing soluble cell lysates induced by exogenous pathogens [11]. In addition to invading pathogens, endogenous ligands on cellular surfaces can be recognized by TREM-1; however, this phenomenon remains unexplored [11]. Concurrently, sTREM-1 exhibits anti-inflammatory properties and exerts a decay activity to activate TREM-1 in binding ligands for TREM-1 receptors [6]. As an immunoreceptor tyrosine-based activation motif (ITAM)-bearing transmembrane adapter protein expressed on the surface of natural killer cells and myeloid cells, DAP12 contains a short extracellular domain of only 13–16 amino acids; by comparison, DAP12-associating receptors possess long extracellular domains [12,13]. These receptors, including myeloid DAP12-associating lectin-1 (MDL-1), TREM receptor family, and signal regulatory protein β1 (SIRPβ1), consist of small cytoplasmic regions without signal transduction functions [12]. When DAP12 and its receptor form a complex, the cytoplasmic ITAM of DAP is phosphorylated, and the signaling pathway is consequently stimulated [5]. Receptor complexes then lead to the degranulation of neutrophils and release of interleukin (IL)-8, monocyte chemotactic protein-1, and tumor necrosis factor (TNF)-α, which can initiate and amplify inflammatory responses [1] (Fig. 1). The activation of neutrophils and monocytes then causes a series of intracellular changes, including calcium mobilization and tyrosine phosphorylation, which help amplify inflammation [1]. sTREM-1 levels can be measured through ELISA, and TREM-1 receptor expression on the surface of myeloid cells in blood or other body fluids can be determined through flow cytometry [11]. sTREM-1 levels, which can precisely correspond to the changes in TREM-1, can also be detected. TREM-1/sTREM-1 probably plays an important role in infectious diseases. Moreover, the single-nucleotide polymorphisms of TREM-1 are associated with the susceptibility and prognosis of different diseases, such as coronary artery disease (CAD), sepsis, septic shock, infective endocarditis, and intestinal Behcet's disease [14–19] (Table 1). However, sTREM-1 may participate in non-infectious diseases, which are discussed in a separate section. The underlying mechanism has yet to be fully clarified. Although the source of sTREM-1 remains elusive, the potential role of sTREM-1 in regulating infectious diseases has been extensively investigated. In this paper, different views on this component are summarized to discuss the close connection between sTREM-1 and infectious diseases.

sTREM-1 and infectious pleural effusion

Pleural effusion is a common complication of various diseases. The gold standard for diagnosing pleural effusions is Light's Criteria, which can differentiate a transudate from an exudate but is unable to identify fluid etiology [20]. Although numerous medical tests can help determine the pleural effusion etiology, it remains challenging. A new specific biomarker for diagnosing pleural effusion is urgently needed in clinical practice. Sim and Huang *et al.* [21,22] found that sTREM-1 levels in pleural fluid greatly exceed those in serum because they reflect the local inflammatory process, which is higher than the systemic one. Liu *et al.* [23] found that the sTREM-1 levels are significantly higher in para-pneumonic effusions than in tuberculous effusions. Similarly, Chan *et al.* [24] found that pleural sTREM-1 at a cut-off value of 374 pg/ml yields a sensitivity of 93.8% and a specificity of 90.9% in

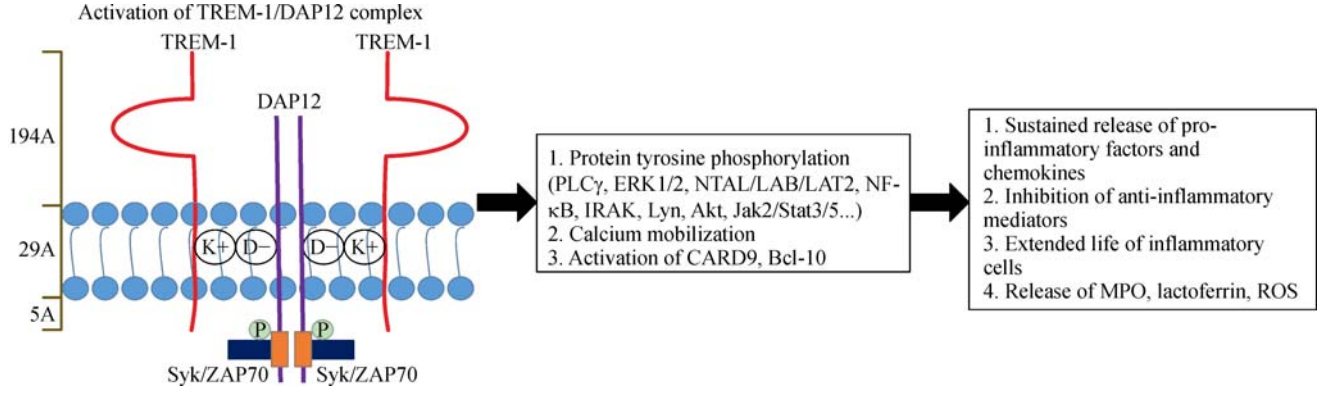

Fig. 1 Schematic of the signaling transduction of the TREM-1/DAP12 pathway. Unknown ligands, such as LPS, link to the Ig-V domain of TREM-1 under stimuli. Next, two glutamic acid residues (D−) within the membrane of DAP12 interact with two lysine residues (K+) of the TREM-1 transmembrane domain, thereby causing immunoreceptor tyrosine-based activation motifs (ITAM) on DAP12 to bind to protein tyrosine kinases, such as Syk and ZAP70. These protein tyrosine kinases cause the phosphorylation of ITAM, which activates inflammatory reactions downstream. (Schematic was drawn based on references [9, 11−13].)

Table 1 Single-nucleotide polymorphisms (SNPs) of TREM-1 associated with different diseases

Disease	Nationality	SNP	Reference
TREM-1 and coronary artery disease	Russian	rs4711668	Kutikhin *et al.* [13]
	Russian	rs2234237, rs6910730, rs9471535, rs4711668, rs1817537, rs2234246, rs3804277	Golovkin *et al*. [14]
TREM-1 and susceptibility to septic shock	Chinese	rs2234246	Peng *et al*. [15]
	Chinese	rs7768162, rs9471535, rs2234237	Chen *et al*. [16]
TREM-1 and sepsis prognosis	Chinese	rs2234237	Su *et al*. [17]
TREM-1 and the development of intestinal Behcet's disease	Korean population	rs9471535, rs3789205, rs2234237	Jung *et al*. [18]
TREM-1 and skin involvement of intestinal Behcet's disease	Korean population	rs9471535, rs3789205, rs2234237	Jung *et al*. [18]
TREM-1 and the risk of azathioprine use of intestinal Behcet's disease	Korean population	rs9471535, rs3789205, rs2234237	Jung *et al*. [18]

differentiating bacterial pleural effusion from tuberculous pleurisy. Huang *et al*. [22] included 109 patients and demonstrated the similarity between sensitivity and specificity in distinguishing bacterial effusions from effusions with other etiologies when a cut-off value is settled at 768.1 pg/ml. In bacterial pleural effusion, sTREM-1 levels are higher in empyema than in para-pneumonic effusions [24]. As a result, sTREM-1 has been proven a useful biomarker in the differential diagnosis of the etiology of pleural effusions. Moreover, Determann *et al.* [25] proved that sTREM-1 has advantages in detecting infections compared with C-reactive protein (CRP), a recognized indicator in the past. However, Porcel *et al.* [26] assert that sTREM-1 is not superior to CRP in separating infectious from non-infectious states. Notable differences in cut-off values can be attributed to the different specimen collection methods and the lack of standardization of the ELISA technique. However, most of these studies still supported the notion that pleural sTREM-1, at an appropriate cut-off value, can help differentiate between bacterial effusions and effusions from other etiologies. In conclusion, sTREM-1 may help clinicians to make an early diagnosis of empyema and guide the application of antibiotics.

sTREM-1 and lung infections

The early diagnosis of lung infections remains challenging, particularly in clearly identifying the cause of disease, because microbiological studies are often negative; this may delay the definitive diagnosis for 24–48 h. Novel methods are required to help clinicians make rapid and accurate diagnoses. Phua *et al.* [27] demonstrated that serum sTREM-1 levels are elevated in community-acquired pneumonia (CAP). Porfyridis *et al.* [28] found that early serum levels of sTREM-1 greater than 180 pg/ml in CAP are associated with unfavorable prognosis, supporting the results by Phua. Among CAP patients receiving treatment, Chao *et al.* [29] found that the level of sTREM-1 remained elevated in the non-response group, but rapidly decreased in the response group. A recent study demonstrated that high levels of serum sTREM-1 indicated poor outcomes in TB patients [30]. sTREM-1 level is a good predictor of the prognosis of lung infection patients. Moreover, sTREM-1 has great value in diagnosing numerous lung infections, such as lower respiratory tract infections [31,32]. Additionally, sTREM-1 assay in alveolar and peritoneal fluids is useful for assessing pulmonary and peritoneal infections in critical-state patients and discriminating between pulmonary and extra-pulmonary infections during acute respiratory failure [33]. sTREM-1 can be detectable and exists at different levels in sera and other body fluids, as well as pathological fluid at local inflammatory sites; moreover, it is associated with numerous diseases at a staggering rate and could generate new clinical applications and provide more scientific ideas in studying this biomarker. sTREM-1 might be a potent biomarker closely related to the entire lung infection process.

Studies have been conducted of sTREM-1 and ventilator-associated pneumonia (VAP), a pneumonia that occurs more than 48 h after the initiation of endotracheal intubation and mechanical ventilation; moreover, it is the most common complication in intubated patients and substantially increases ICU patient mortality rate [34]. An overestimation of VAP occurs when the diagnosis is based on clinical suspicion and results in unnecessary antibiotic therapy [35]. Dupuy *et al*. [36] reported that sTREM-1 might be a potent biomarker in antibiotic therapy in the future. Tests using sTREM-1 may help in diagnosing and eliminating unnecessary antibiotic exposure in the patient. Gibot *et al.* [37,38] found that rapid detection of sTREM-1 in bronchial alveolar lavage (BAL) fluid is useful for differentiating patients receiving mechanical ventilation for bacterial or fungal pneumonia from those without pneumonia, particularly for patients with untypical manifestations. Furthermore, sTREM-1 levels in non-directed bronchial lavage fluid (NBLF) increased significantly during a 6-day period until the day of VAP diagnosis,

suggesting that a cut-off value of 200 pg/ml preceded by an increase of 100 pg/ml is diagnostic for pneumonia in ventilated patients [39]. Moreover, sTREM-1 can be detected in the exhaled ventilator condensate (EVC) collected from the expiratory line of patients receiving mechanical ventilation. The study demonstrated that sTREM-1 detection in EVC may improve the ability of clinicians to distinguish patients with VAP from those without pneumonia; however, further research is needed on account of the small study sample [40]. Similar results were proven in the diagnosis of VAP in patients after cardiac surgery [41]. These results showed the wide clinical prospect of sTREM-1 in VAP. Moreover, a prospective observational study by Grover *et al.* [42] demonstrated that a biomarker panel, including cellular and soluble TREM-1, could differentiate VAP from non-VAP more precisely than by detecting a single biomarker, although the level of sTREM-1 is significantly more elevated in VAP than in non-VAP. Similar to other diseases, sTREM-1 concentrations in BAL fluid can prompt prognosis in VAP patients. A study that included 35 VAP patients showed that dynamic sTREM-1 levels in BAL fluids during the first 7–9 days of VAP treatment had better prognostic ability than APACHE II scores in predicting outcomes, and this may help the physician in regulating antibiotic use [43].

However, not all studies support the use of detecting sTREM-1 in VAP patients. Two articles published in 2009 showed that the differences between the mean sTREM-1 concentrations in patients with definite VAP and those with definite absence of VAP or patients without confirmed VAP were not statistically significant, implying that measuring sTREM-1 in bronchial alveolar lavage fluid (BALF) samples as a diagnostic test for VAP may not be discriminative [44,45]. Several reasons may explain these inconsistent findings, including the different methods for sTREM-1 detection, different diagnostic criteria for VAP, and antibiotics use before sample collection. Therefore, studies with large populations using similar study designs, similar standardized study methods, sample collection, and analysis are necessary.

sTREM-1 and sepsis

Sepsis is a systemic response to infection. No gold standard exists for diagnosing sepsis because the traditional biological markers, like CRP and PCT, often overlap with other non-infectious causes of systemic inflammation, and no biological markers have been satisfactory [46–49]. The potential value of sTREM-1 in dealing with sepsis has attracted investigators' attention. Gibot *et al*. and other researchers [38,50,51] found that plasma sTREM-1 levels at a cut-off value of 60 ng/ml yield a positive success ratio of 8.6 and a negative likelihood ratio of 0.04 for differentiating patients with sepsis from those with non-infectious cases with systemic inflammatory response syndrome. Moreover, sTREM-1 is of great value for early diagnosis and assessment of severity and prognosis of neonatal sepsis [52–54]. Furthermore, sTREM-1 level is a good predictor of septic patients [55,56]. Moreover, sTREM-1 might have value in exclusively diagnosing infections in postoperative patients with secondary peritonitis [57]. Giamarellos-Bourboulis *et al.* [58] argued that sTREM-1 kinetics are similar to IL-10, which play an anti-inflammatory role in the septic process. Thus, sTREM-1 protects the body during inflammation. They hypothesized that changes in sTREM-1/TNF-α ratios could determine the progression from sepsis, to severe sepsis, and to septic shock [58]. A prospective cohort study showed that sTREM-1 levels in survivors are lower than those in non-survivors and yielded a sensitivity of 85.7% and a specificity of 75.7% at a cut-off value of 252.05 pg/ml, demonstrating that sTREM-1 is a good prognostic indicator [59]. Zhang *et al.* [60] found that sTREM-1 levels are the more sensitive and specific index in the diagnoses and assessment of septic severity compared with CRP and PCT. Unfortunately, sTREM-1, along with PCT and CRP, could not determine whether new fevers are due to bacteria or not; however, the sTREM-1 level is able to assess the prognosis of bacteremia [61]. In contrast, sTREM-1 is a poor prognostic factor in patients with infection [62]. The ability of sTREM-1 in distinguishing sepsis from non-infectious SIRS was suspected in several studies [63–68]. However, when combined with other sepsis markers, the assay may significantly improve clinicians' ability to differentiate patients with sepsis from those with systemic inflammations of non-infectious origin [66,69]. In addition to serum sTREM-1, Su *et al.* [70] explored the diagnostic potential of urine sTREM-1 for early sepsis identification, severity prognosis assessment, and secondary acute kidney injury (AKI). TREM-1 testing is more sensitive than testing for WBC, serum CRP, and serum PCT during early sepsis diagnosis and is a good predictor for secondary AKI [70,71]. Moreover, Dai *et al.* [72,73] reported that sTREM-1 level is significantly increased in critically ill patients with sepsis-associated AKI compared with non-AKI septic patients whose predictive and diagnostic values were just as good as neutrophil gelatinase-associated lipocalin (NGAL) and cystatin-C (Cys-C), which are two traditional biomarkers. In addition to sepsis-related AKI, serum sTREM-1 is reported to be an independent risk factor for N-terminal pro-B-type natriuretic peptide (NT-proBNP) in sepsis-associated myocardial dysfunction [74,75]. sTREM-1 is closely related to the severity and prognosis of *Streptococcus pyogenes*-induced sepsis [76]. Therefore, sTREM-1 can be used in sepsis-associated organ dysfunction and other clinical conditions. In conclusion, sTREM-1 is a promising biomarker in clinical practice for sepsis.

sTREM-1 and bacterial meningitis

Bacterial meningitis has high morbidity and mortality [77]. Unfortunately, its diagnosis and treatment remain a conundrum for doctors because making a timely etiological diagnosis is difficult due to the cerebral spinal fluid cultures not being sensitive and, therefore, take long to process. The sTREM-1 level in cerebrospinal fluid (CSF) may be helpful as a biomarker for the presence of bacterial meningitis, leading to successful patient care. A retrospective cohort analysis showed that CSF sTREM-1 levels at a cut-off value of 20 pg/ml yield a sensitivity of 73%, a specificity of 77%, and an area under curve (AUC) of 0.82 when discriminating between patients with and without bacterial meningitis; moreover, CSF sTREM-1 levels are associated with prognosis [78]. sTREM-1 has been suggested to be upregulated in the CSF of patients with bacterial meningitis with high specificity [79]. The CSF sTREM-1 level may be helpful in diagnosing and prognosticating meningitis. Furthermore, Liu *et al.* [80] found sTREM-1 to be more rapid and accurate when they detected decoy receptor 3 (DcR3) and sTREM-1 in combination rather than sTREM-1 or DcR3 alone. However, current research on adults has small sample sizes, therefore, large-scale prospective studies are needed, particularly studies with children, to confirm the value of sTREM-1 measurement in diagnosing bacterial meningitis to assess its prognostic significance accurately.

Other infectious diseases

A recent study demonstrated that sTREM-1 level is significantly higher in patients with Crimean Congo hemorrhagic fever, a viral infection, than in the control group at a cut-off value of 405.9 pg/ml, with a sensitivity of 94.9% and a specificity of 87.5% [81]. Similarly, sTREM-1 level is significantly higher in dengue patients than healthy individuals [82]. sTREM-1 may be valuable in diagnosing viral infections apart from bacterial and fungal infections. Moreover, Cui *et al.* [83] demonstrated that plasma and BALF sTREM-1 are markedly elevated in immune-compromised *Aspergillus*-infected rat model. sTREM-1 might be a useful marker in infected burn wounds [84]. Therefore, sTREM-1 is associated with various infectious diseases, and is believed to be far more than discussed above. This inspires us to explore the pathogenesis of infection and sTREM-1.

Non-infectious diseases

sTREM-1 is an attractive molecule in infectious diseases and non-infectious inflammatory diseases. sTREM-1 is a crucial part of innate immune responses, which leads to the release of pro-inflammatory cytokines and chemokines [85]. Essa *et al.* [86] found sTREM-1 levels, just like CRP and TNF-α, are significantly elevated in patients with chronic kidney disease on hemodialysis. sTREM-1 levels have been associated to bronchiectasis and disease-modifying anti-rheumatic drug (DMARD)-naive early rheumatoid arthritis (ERA), an autoimmune disease with chronic inflammation in the synovial joints [87–89]. In addition to pulmonary infection, sTREM-1 levels were reported to be increased significantly in patients with chronic obstructive pulmonary disease and differ in 3 clinical classifications [27]. Furthermore, TREM-1/sTREM-1 has a relationship with gout and febrile neutropenia [90,91]. Additionally, serum sTREM-1 is upregulated in inflammatory bowel disease patients, but its correlation to the disease activity remains uncertain [92,93]. In 2011, Hermus *et al.* [94] showed that sTREM-1 is increased in patients with CAD and peripheral artery disease (PAD). This study is the first to demonstrate the key role of sTREM-1 in atherosclerosis. Apart from benign diseases, TREM-1 expression is significantly high in several types of cancer. TREM-1 is expressed in hepatocellular carcinoma (HCC) cells and hepatic stellate cells, a type of tumor-associated cell; and TREM-1 is related to tumor progression and HCC prognosis [95,96]. Yuan *et al.* [97] found TREM-1 expression level is significantly high in patients with non-small cell lung cancer. TREM-1 is reported to be useful in differential diagnosis of craniopharyngioma [98]. In conclusion, sTREM-1 and TREM-1 are potential biomarkers for infectious and non-infectious diseases.

Conclusions

sTREM-1 is essential for myeloid cell-mediated inflammatory responses, as demonstrated by previous studies. Although the ability of sTREM-1 in diagnosing infectious diseases remains controversial, sTREM-1 detection is a promising technique for targeted therapy in sepsis diagnosis. The origin and release mechanisms of sTREM-1, particularly the molecular structure of its natural ligand and the accurate interaction between them, are unclear. However, we can predict these characteristics by using TREM-1, which is already known. TREM-1 forms a “head-to-tail” dimer with an extracellular V-type immunoglobulin-like domain (Ig-V) comprising approximately 120 amino acids [3,12]. The Ig-V, providing two possible binding sites for ligands, is followed by a region of approximately 70 amino acids that link to the transmembrane part of TREM-1 [99]. Additionally, TREM-1/DAP12 pathway affects both innate and adaptive immune responses, which provide insights into the clinical perspectives of sTREM-1 [12]. Further studies should focus on the molecular mechanisms of sTREM-1 and

infectious diseases to understand its interactions during redox reactions and with inflammatory factors. Additional evidence should also be obtained to support the predictive and prognostic role of sTREM-1 in infections from large-scale multi-center studies enrolling a substantial number of patients, particularly children and neonates. Fortunately, this molecule has been extensively investigated. These problems can be solved, and breakthroughs can be achieved in terms of the control and treatment of inflammatory diseases. sTREM-1 is a possible indispensable biomarker for clinical applications.

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Compliance with ethics guidelines

Changlin Cao, Jingxian Gu, and Jingyao Zhang declare that they have no competing interests. This manuscript is a review and does not involve a research protocol requiring approval from relevant institution review board or ethics committee.

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