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Are CD45RO$^+$ and CD45RA$^-$ genuine markers for bovine memory T cells?

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Abstract

Effective vaccination induces memory T cells, which protect the host against pathogen re-infections. Therefore, detection of memory T cells is essential for evaluating vaccine efficacy, which was originally dependent on cytokine induction assays. Currently, two isoforms of CD45 tyrosine phosphatase, CD45RO expression and CD45RA exclusion (CD45RO$^+$/ CD45RA$^-$) are used extensively for detecting memory T cells in cattle. The CD45RO$^+$/CD45RA$^-$ markers were first established in humans around three decades ago, and were adopted in cattle soon after. However, in the last two decades, some published data in humans have challenged the initial paradigm, and required multiple markers for identifying memory T cells. On the contrary, memory T cell detection in cattle still mostly relies on CD45RO$^+$/ CD45RA$^-$ despite some controversial evidence. In this review, we summarized the current literature to examine if CD45RO$^+$/CD45RA$^-$ are valid markers for detecting memory T cells in cattle. It seems CD45RA and CD45RO (CD45RA/RO) as markers for identifying bovine memory T cells are questionable.

Keywords: Cattle, Memory, Markers, T cells, CD45RO, CD45RA, Vaccines, Cytokines

Introduction

Memory T cells induced by effective vaccines respond rapidly during pathogen re-challenge, ensuring immune protection to the host (Robinson and Amara 2005, Rosato et al. 2017, Iwasaki and Omer 2020). Therefore, detection of memory T cells is the gold standard for analyzing the efficacy of vaccines in humans and domestic animals like cattle (Flaxman and Ewer 2018). Currently, bovine memory T cells are detected as CD45RO$^+$/CD45RA$^-$ (Howard et al. 1991, Bembridge et al. 1995, Sopp and Howard 2001, Silflow et al. 2005, Maggioli et al. 2015, Frie et al. 2017, Mitoma et al. 2021), which were adopted a few years after their initial establishment in humans (Akbar et al. 1988a; Merkenschlager et al. 1988; Terry et al. 1988; Birkeland et al. 1989; Deans et al. 1989; Richards et al. 1990). However, in the last two decades, reports contrasting initial observations have been published in both humans and cattle. Several experiments have suggested that human memory T cells may express CD45RO or CD45RA or both (Arlettaz et al. 1999; Wills et al. 1999; Gattinoni et al. 2011; Ahmed et al. 2016; Hong et al. 2016; Jung et al. 2021). Similarly, some reports in cattle have contradicted CD45RO$^+$/CD45RA$^-$ as markers in the identification of memory T cells (Hagberg et al. 2008; Guerra-Maupome et al. 2019).

There are three subtypes of T cells: CD4$^+$, CD8$^+$ and γδ. While the immune memory by both CD4$^+$ and CD8$^+$ subtypes are the essential targets of most bovine vaccines, establishment of memory by γδ T cells is still under debate, despite some evidence supporting their recall responses (Blumerman et al. 2007, Lalor and McLoughlin 2016, Lau and Sun 2018, Comeau et al. 2020); for instance, recently, a *M bovis* specific γδ T cell subtype has been reported in cattle (Guerra-Maupome et al. 2019). Vaccine-induced effective memory can initiate protective immune responses upon pathogen re-challenge, as evidenced by decreased pathogen load, increased antigen-specific antibody titers, and appropriate induction of effector cytokines (Graham et al. 2006; Buddle et al. 2011;

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Blodörn et al. 2014; Taylor et al. 2015). Memory T cells, including $CD4^+$ and $CD8^+$ subtypes, play critical roles in inducing these responses and protecting the host from re-infection with pathogens (Laidlaw 2015; Kandel et al. 2021). Unlike their short-lived counterparts in humans (Doherty et al. 1996; Sierra et al. 2002; Hammarlund et al. 2003), long-lived memory $CD4^+$ T cells could be induced in cattle (Rhodes et al. 1999; Brown et al. 2002; Norimine et al. 2002; Mitoma et al. 2021), which can enhance the cytotoxic function of parasite-specific $CD8^+$ T cells under in vitro conditions (Taracha et al. 1997), and assist in the activation of B cells (Brown et al. 1994; Norimine et al. 2002). Specifically, vaccines against the intracellular pathogens such as Foot and mouth disease virus (FMDV), Bovine viral diarrhea virus (BVDV), and *Mycobacterium tuberculosis* induce antigen-specific memory $CD8^+$ T cells, which mount effective cytotoxic responses in synergy with the memory $CD4^+$ T cells (Childerstone et al. 1999; Rhodes et al. 1999; Gaddum et al. 2003; Hogg et al. 2009; Maggioli et al. 2015; Elnaggar et al. 2021). Additionally, memory $CD4^+$ T cells might reinforce memory B cell responses (Brown et al. 1994, Norimine et al. 2002), and increase the production of pathogen-specific antibodies against bovine extracellular pathogens such as *Cooperia oncophora* and *Fasciola hepatica* (Skirrow and BonDurant 1990, Kooyman et al. 2002, Kanobana et al. 2003, Kandel et al. 2021). Despite the debate in γδ T cells, memory $CD4^+$ and memory $CD8^+$ subtypes are the hallmarks of effective vaccination in cattle.

Even though several assays are available, none can detect all antigen-specific memory T cells. So far, the most common method for identifying memory T cells has been cytokine induction assays, where peripheral blood mononuclear cells (PBMCs) from healthy individuals were stimulated with PMA and ionomycin, followed by either monensin or brefeldin A (BFA) (Picker et al. 1995, Bining and Miller 1997, Hamann et al. 1997, Waldrop et al. 1997, Bercovici et al. 2000, Kemp and Bruunsgaard 2001, Sattler et al. 2009). Alternatively, PBMCs or lymphoid cells from the immune animals were stimulated with specific antigens in vitro to induce the production of cytokines such as interferon-gamma (IFNγ) and/or interleukin-4 (IL4) by the antigen-specific memory T cells, which could be detected through ELISpot or flow cytometry (Calarota and Baldanti 2013, Flaxman and Ewer 2018). In addition to the cytokine induction assay, currently, memory T cells can be easily identified using markers in flow cytometry. In this regard, human research has utilized multiple markers besides CD45RA/RO (Wills et al. 1999; Gattinoni et al. 2011; Mahnke et al. 2013; Jung et al. 2021); for example, several proteins including CD127, CD27, CD95, CD11a, CD18 and CD28 have been included in the evaluation of human memory $CD8^+$ T cells (Hamann et al. 1997, Samji and Khanna 2017, Martin and Badovinac 2018). Nonetheless, bovine memory T cells are commonly detected using $CD45RO^+/CD45RA^-$, despite conflicting evidence (Hagberg et al. 2008; Guerra-Maupome et al. 2019; Kandel et al. 2022). Recently, we sought to validate $CD45RO^+/CD45RA^-$ as markers for memory T cells in cattle using the conventional cytokine induction assay (Kandel et al. 2022). A weak correlation between CD45RA/RO expression and memory T cells in cattle was revealed (Kandel et al. 2022). In this review, we examined the current literature, and discussed some of our findings to assess the reliability of $CD45RO^+/CD45RA^-$ as authentic markers for memory T cells in cattle.

Alternative splicing generates CD45RA/RO in humans

CD45, a tyrosine phosphatase membrane protein, is expressed commonly on the surface of multiple immune cells, including T lymphocytes (Tonks et al. 1988; Hermiston et al. 2003). In humans, the CD45 precursor mRNA (i.e., CD45 pre-mRNA) contains at least 33 coding regions, also known as exons. Differential splicing at exons A/4, B/5 and C/6 leads to the generation of multiple protein products called CD45 isoforms (Gerdy et al. 2000; Hermiston et al. 2003; Lynch 2004; Tong et al. 2005; Holmes 2006). Among the isoforms, high molecular weight, CD45RA, includes A/4 but excludes exons B/5 and C/6, whereas the low molecular weight counterpart, CD45RO, excludes all (4/A, 5/B and 6/C), as shown in Fig. 1. Unfortunately, the information on CD45 splicing has not been explored in cattle, but genetic analysis suggests that at least six CD45 isoforms may exist, of which, some have already been detected at the protein level using antibodies (Bembridge et al. 1995; Guerra-Maupome et al. 2019; Jonsson et al. 2021; Kandel et al. 2022).

The initial research in humans suggested that expression of CD45RA marks the naïve, and that of CD45RO indicates memory T cells (Akbar et al. 1988a, Merkenschlager et al. 1988, Richards et al. 1990, Wallace and Beverley 1990, Litjens et al. 2008, Machura et al. 2008), which was similarly established in cattle soon after (Howard et al. 1991; Bembridge et al. 1995). Although how CD45RO is spliced in cattle is unknown, a protein of a molecular weight similar to that in humans (i.e., 180 kDa) was precipitated (Bembridge et al. 1995), using the most popular monoclonal antibody clone IL-A116 (Bembridge et al. 1995; Ballingall et al. 2001; Endsley et al. 2006; Denis et al. 2011; Hogg et al. 2011; Blunt et al. 2015; Maggioli et al. 2015; Frie et al. 2017; Elnaggar et al. 2021; Jonsson et al. 2021; Mitoma et al. 2021). Similarly, there are ten monoclonal antibodies that recognize the high molecular weight isoform in cattle (Dutia et al. 1993, Howard and

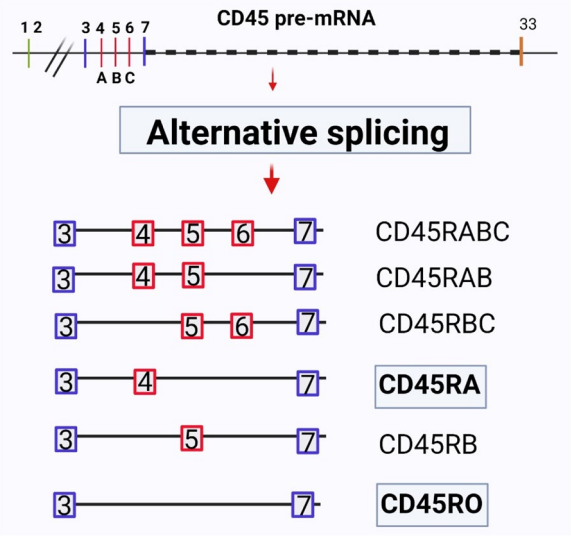

Fig. 1 Splicing of CD45 pre-mRNA results in generation of distinct isoforms. The figure demonstrates alternative splicing of CD45 isoforms in humans as information on cattle has not been published yet. CD45 pre-mRNA has 33 exons in humans, numbered from 1 to 33 in this figure. Differential splicing of exons 4/A, 5/B and 6/C generates at least six CD45 isoforms. The shortest CD45RO is generated by skipping all three differentially spliced exons. This figure was adapted from mini review published by Bio-Rad Laboratory (Bio-Rad Laboratories, Inc 2016), and modified/animated with https://biorender.com/

Naessens 1993); among them, clones CC76 and GC6A have already been applied to detect the bovine homologue of CD45RA (Endsley et al. 2007; Denis et al. 2011; Kandel et al. 2022).

Memory T cells are not restricted to CD45RO$^+$/CD45RA$^-$ in humans

Human memory T cells have been extensively detected using CD45RA/RO as markers. Initially, research suggested CD45RO+/CD45RA- T cells as memory (Akbar et al. 1988b; Birkeland et al. 1989; Deans et al. 1989), as they demonstrated antigen-specific proliferation, and enhanced B cell activation in vitro (Morimoto et al. 1985, Akbar et al. 1988b, Sanders et al. 1988, Lecomte and Fischer 1992); these results led to the establishment of initial paradigm, which supported that after antigen stimulation the naïve T cells downregulate CD45RA and highly upregulate CD45RO to become memory (Table 1). However, an increasing number of evidence in the past two decades have contrasted the initial paradigm. A number of studies have reported that memory T cells could be found within both CD45RO$^+$ and CD45RA$^+$ fractions (Michie et al. 1992; Callan et al. 1998; Wills et al. 1999; Lee et al. 2001; Khan et al. 2002; Gattinoni et al. 2011; Ahmed et al. 2016; Jung et al. 2021). Specifically, a subset of CD45RA$^+$ T cells express features similar to those shown by antigen-primed memory population, which is contrary to the established paradigm that defines them as the naïve T cells (De Jong et al. 1992; Hintzen et al. 1993; Okumura et al. 1993; Roederer et al. 1995; Richards et al. 1997; Caccamo et al. 2018). Importantly, the expression of CD45 isoform on the surface of human memory T cells has been found interchangeable (Hamann et al. 1997; Arlettaz et al. 1999; Wills et al. 1999; Gattinoni et al. 2011). For example, TEMRA, a newly defined subset of memory T cells re-expressed CD45RA (Willinger et al. 2005; Tian et al. 2017; Verma et al. 2017; Vandamme et al. 2020), and demonstrated effective immunity against pathogens such as dengue virus (DENV) in humans (Tian et al. 2017; Tian et al. 2019). Moreover, identification of human memory T cells only based on CD45 isoform expression has been suggested unreliable in both CD4$^+$ and CD8$^+$ subtypes (De Jong et al. 1992; Hintzen et al. 1993; Hamann et al. 1997). As a result, a combination of markers, including CD45RA/RO, are being used for characterization of different subsets of memory T cells (De Jong et al. 1992, Callan et al. 1998, Samji and Khanna 2017, Martin and Badovinac 2018, Jung et al. 2021). To illustrate, a subset of memory CD4$^+$ T cells called stem cell like memory (T_{scm}) has been characterized based on their expression of CD45RA/RO, CD95, CD122 and CD11a (Gattinoni et al. 2011; Ahmed et al. 2016). In summary, human memory T cells are heterogenous, and not

Table 1 CD45RA/RO expression on the human memory T cells

T cell subtype	Memory related to CD45RA/RO	References
CD4$^+$ T cells	CD45RO$^+$	(Akbar et al. 1988a, Merkenschlager et al. 1988, Wallace and Beverley 1990, Litjens et al. 2008, Machura et al. 2008)
	CD45RA$^+$	(Warren and Skipsey 1991, Zola et al. 1992, Richards et al. 1997, Wilamasundera et al. 1998, Gattinoni et al. 2011, Ahmed et al. 2016)
	CD45RO$^+$ CD45RA$^+$	(Arlettaz et al. 1999)
CD8$^+$ T cells	CD45RO$^+$	(Richards et al. 1990, Machura et al. 2008)
	CD45RA$^+$	(Callan et al. 1998, Wills et al. 1999, Faint et al. 2001, Gattinoni et al. 2011, Ahmed et al. 2016)

strictly restricted to $CD45RO^+/CD45RA^-$, but could also exist as $CD45RA^+/CD45RO^-$ and $CD45RO^+/CD45RA^+$.

Establishment of $CD45RO^+/CD45RA^-$ as marker for memory T cells in cattle

In cattle, antigen-specific memory T cells are examined with cytokine induction assays, and $CD45RO^+/CD45RA^-$ markers in flow cytometry (Silflow et al. 2005; Endsley et al. 2006; Blunt et al. 2015; Maggioli et al. 2015; Guerra-Maupome et al. 2019; Elnaggar et al. 2021), which were established a few years after their initial discovery in humans.

Historically, Bembridge et al. demonstrated that the ovalbumin (OVA)-specific memory $CD4^+$ T cells were CD45RO+ in cattle (Bembridge et al. 1995). They isolated $CD45RO^+$ and $CD45RO^-$ $CD4^+$ T cells from OVA-immunized PBMCs and tested their antigen-specific proliferative responses. The CD45RO+ fraction demonstrated a significantly higher capacity to proliferate than $CD45RO^-$ (Bembridge et al. 1995). Further, when both fractions were stimulated with autologous PBMC or Con A for 27 h, only the $CD45RO^+$ samples showed signals for IFNγ and IL4 in polymerase chain reaction (PCR), indicating the association of CD45RO expression with memory T cells in cattle (Bembridge et al. 1995). However, there was some disagreement in the CD8+ T cell subtype, as *Theileria*-specific memory $CD8^+$ T cells were found in both $CD45RO^+$ and $CD45RO^-$ fractions (Howard et al. 1991; Bembridge et al. 1995).

Sopp and Howard further investigated the expression of CD45RO in the IFNγ- and IL4-inducing memory T cells in healthy cattle (Sopp and Howard 2001). They stimulated the PBMCs or lymphocytes isolated from different lymphoid tissues with PMA, ionomycin and BFA for 5 h at 37°C, and tested their expression of CD45RO (Sopp and Howard 2001). The majority of memory T cells that produced IFNγ and IL4 were $CD45RO^+$ (Sopp and Howard 2001). With contradictory evidence on the $CD8^+$ subtype, the evidence from Bembridge et al. and Sopp and Howard collectively suggested $CD45RO^+$ as a marker for detecting memory T cells in cattle (Bembridge et al. 1995, Sopp and Howard 2001). Further, these findings were supported by a number of observations, where in vitro stimulated antigen-specific memory T cells expressed CD45RO (Totté et al. 2010; Denis et al. 2011; Totte et al. 2013; Maggioli et al. 2015; Elnaggar et al. 2021), but downregulated the expression of CD45RA (Sopp and Howard 2001, Endsley et al. 2007, Denis et al. 2011). While $CD45RO^+/CD45RA^-$ markers were primarily used to detect memory T cells in cattle, additional molecules such as CD62L and/or CCR7 were also included for further characterization of memory T cells into effector memory (Tem: $CD62L^-/CCR7^-$) and central memory (Tcm: $CD62L^+/CCR7^+$) subsets (Endsley et al. 2007; Blunt et al. 2015; Maggioli et al. 2015), which is consistent with previously published human findings (Sallusto et al. 2004). While T_{cm} cells display stem cell like characteristics and differentiate into effector memory subsets, those of T_{em} exhibit rapid effector functions in vitro (Sallusto et al. 1999; Sallusto et al. 2004; Mahnke et al. 2013).

$CD45RO^+/CD45RA^-$ as markers for memory T cells is controversial in cattle

Although commonly used for detecting memory T cells, $CD45RO^+/CD45RA^-$ markers have also been challenged by some published reports in cattle (Table 2). Memory T cells in cattle may not always express CD45RO, and therefore can also be detected in the $CD45RO^-$ fraction. For instance, when PBMCs from the vaccinated cattle were stimulated with homogenate derived from *Dictyocaulus viviparous,* Hagberg et al. did not found antigen-specific proliferation in the CD45RO expressing $CD4^+$ and $CD8^+$ T cell subtypes (Hagberg 2008; Hagberg et al. 2008) (Table 2). In support, experiments on memory $CD8^+$ T cells have also generated inconsistent

Table 2 CD45RO expression on the bovine memory T cells

T cell subtype	Memory related to CD45RA/RO	References
$CD4^+$	$CD45RO^+$	(Howard et al. 1989, Sopp and Howard 2001, Totté et al. 2010, Blunt et al. 2015, Maggioli et al. 2015, Elnaggar et al. 2021, Mitoma et al. 2021)
	$CD45RO^+/CD45RA^-$	(Sopp and Howard 2001, Endsley et al. 2007, Denis et al. 2011)
	$CD45RO^-$	(Hagberg et al. 2008, Kandel et al. 2022)
$CD8^+$	$CD45RO^+$	(Sopp and Howard 2001, Denis et al. 2011, Elnaggar et al. 2021)
	$CD45RO^+/CD45RA^-$	(Denis et al. 2011)
	$CD45RO^-$	(Bembridge et al. 1995, Hagberg et al. 2008, Kandel et al. 2022)
γδ	$CD45RO^+$	(Howard et al. 1992, Collins et al. 1996, Blumerman et al. 2007)
	$CD45RO^-$	(Kandel et al. 2022)

results (Howard et al. 1991; Bembridge et al. 1995; Stabel et al. 2007; Hogg et al. 2009; Denis et al. 2011); while *S. uberis* specific memory $CD8^+$ T cells were detected within the $CD45RO^+$ (Denis et al. 2011), *Theileria parva* specific memory $CD8^+$ T cells were also observed in the $CD45RO^-$ fraction (Howard et al. 1991, Bembridge et al. 1995). Moreover, recent data suggest that the expression of CD45RO in the *M. bovis* specific γδ subtype is not associated with memory (Guerra-Maupome et al. 2019). Importantly, in support to these contradictory findings, we recently reported the presence of $CD45RO^-$ memory T cells in $CD4^+$, $CD8^+$, and γδ subtypes (Kandel et al. 2022). In fact, we demonstrated that 20% of examined cattle (7 out of 28) do not express CD45RO on their T cells (designated as RO null); and, the absence of CD45RO does not affect their CD45RA expression (Kandel et al. 2022). Furthermore, IFNγ and IL4 producing memory T cells were induced in the RO null cattle, in a frequency similar to those in RO+, suggesting that induction of memory T cells in cattle might not necessarily depend on CD45RO expression. In RO+ cattle, a fraction of IFNγ and IL4 inducing memory T cells were found $CD45RA^+$ with a relatively higher frequency in CD8+ (>50%) than in the $CD4^+$ subtype (<20%), which was similarly noticed in RO null (Kandel et al. 2022). Furthermore, in each subtype, the proportion of total $CD45RA^+$ T cells in RO^+cattle was not significantly different from those in RO null (Kandel et al. 2022). These findings indicate that, at least in the RO null cattle, the transition from CD45RA to CD45RO isoform was not detected, which contradicts the initial hypothesis. In γδ T cell subtype, almost 90% of the cells were $CD45RO^+$, but only 10% of them induced IFNγ (Kandel et al. 2022). Altogether, a weak association between CD45RA/RO expression and memory were detected in each subtype, suggesting that the relevance of $CD45RO^+/CD45RA^-$ as memory T cell marker in cattle is still controversial (Table 2).

CD45RA/RO expression is strongly associated with distinct T cell subtypes in cattle

Our analysis further suggests that CD45RA/RO expression is associated with distinct bovine T cell subtypes. Within the total lymphocytes, most (~90%) of the cells expressed either CD45RA or CD45RO, and the frequency of $CD45RA^+$ cells was significantly higher than that of $CD45RO^+$ (Kandel et al. 2022). However, when T cells were analyzed, differential clustering of CD45RA/RO expression were noticed in each subtype. While CD45RA expression was high in $CD8^+$ (around 80%), CD45RO was dominantly expressed in $CD4^+$ (about 60%) and γδ (about 90%) subtypes (Kandel et al. 2022). Furthermore, when CD45RA/RO expressions in IFNγ- and IL4-inducing memory T cell subtypes were examined, similar pattern of clustering were consistently detected. While the cytokine-producing cells within $CD8^+$ T cells were mostly $CD45RA^+$, those within the $CD4^+$ and γδ subtypes were $CD45RO^+$ (Kandel et al. 2022). Interestingly, our data is supported, at least partially, by some evidence reported in cattle (Bembridge et al. 1995, Sopp and Howard 2001, Guerra-Maupome et al. 2019), and humans (Prince et al. 1992; Zola et al. 1992; Qin et al. 1993; Cossarizza et al. 1996; Sathaliyawala et al. 2013; Yang et al. 2014). Therefore, we believe that CD45RA/RO expression is strongly related to T cell subtypes in cattle.

Appropriate functions of CD45RA/RO isoforms are largely unknown

The specific functions of CD45RA and CD45RO isoforms are not well defined in mice and humans (Trowbridge and Thomas 1994, Penninger et al. 2001, Hermiston et al. 2005), and have not been studied in cattle. Apparently, results from the transgenic mouse models and transfected cell lines were hard to interpret due to suboptimal expression of these isoforms on their T cells. Although no conclusive results were obtained, experiments indicated that a certain level of isoform expression is required for T cells to function optimally (Dawes et al. 2006). With contradictory results, the appropriate function of CD45RA/RO in T cells is largely unknown (Mittler et al. 1991; Janeway Jr 1992; Leitenberg et al. 1996; Dornan et al. 2002).

Conclusions

Detection of memory T cells is essential for examining the efficacy of bovine vaccines. Memory T cells in cattle are often detected as $CD45RO^+/CD45RA^-$, but some reports have questioned these markers. Recently, we found that CD45RA/RO expression is not associated with cytokine-producing memory T cells in cattle, further questioning their reliability as markers for bovine memory T cells. In fact, CD45RA/RO expression is highly associated with distinct T cell subtypes. Future research should identify novel biomarkers for memory T cells in cattle and examine the functions of CD45RA and CD45RO proteins in bovine T cells.

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Authors' contributions

Zhengguo Xiao, Anmol Kandel, and Akanksha Hada wrote the manuscript. All authors have read and approved the manuscript.

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Availability of data and materials
Data will be shared upon request by the readers.

Declarations

Ethics approval and consent to participate
These studies have been reviewed and approved by the Institutional Animal Care and Use Committee at the University of Maryland (R-FEB-18-06 approved on 02-05-2018 and R-Jan-21-02 approved on 01-12-2021).

Consent for publication
Informed consent was obtained from all subjects involved in the study.

Competing interests
The author declares that he/she has no competing interests. Author Zhengguo Xiao was not involved in the journal's review or decisions related to this manuscript.

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