

# Black African and Latino/a identity correlates with increased plasmablasts in MS

Kiel M. Telesford, PhD, Ulrike W. Kaunzner, MD, PhD, Jai Perumal, MD, Susan A. Gauthier, DO, MPH, Xian Wu, MPH, Ivan Diaz, PhD, Mason Kruse-Hoyer, MD, Casey Engel, BA, Melanie Marcille, BA, and Timothy Vartanian, MD, PhD

## Correspondence

Dr. Telesford  
kit2003@med.cornell.edu  
or Dr. Vartanian  
tiv2002@med.cornell.edu

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## Abstract

### Objective

To determine the influence of self-reported Black African and Latin American identity on peripheral blood antibody-secreting cell (ASC) frequency in the context of relapsing-remitting MS.

### Methods

In this cross-sectional study, we recruited 74 subjects with relapsing-remitting MS and 24 age- and self-reported ethno-ancestral identity-matched healthy donors (HDs) to provide peripheral blood study samples. Subjects with MS were either off therapy at the time of study draw or on monthly natalizumab therapy infusions. Using flow cytometry, we assessed peripheral blood mononuclear cells for antibody-secreting B-cell subsets.

### Results

When stratified by self-reported ethno-ancestry, we identified significantly elevated frequencies of circulating plasmablasts among individuals with MS identifying as Black African or Latin American relative to those of Caucasian ancestry. Ethno-ancestry-specific differences in ASC frequency were observed only among individuals with MS. By contrast, this differential was not observed among HDs. ASCs linked with poorer MS prognosis and active disease, including IgM<sup>+</sup>- and class-switched CD138<sup>+</sup> subsets, were among those significantly increased.

### Conclusion

The enhanced peripheral blood plasmablast signature revealed among Black African or Latin American subjects with MS points to distinct underlying mechanisms associated with MS immunopathogenesis. This dysregulation may contribute to the disease disparity experienced by patient populations of Black African or Latin American ethno-ancestry.

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From the Brain and Mind Research Institute (K.M.T., T.V.), Weill Cornell Medicine; Department of Neurology (K.M.T., U.W.K., J.P., S.A.G., M.K.-H., C.E., M.M., T.V.), Weill Cornell Medicine; and Department of Healthcare Policy and Research (X.W., I.D.), Weill Cornell Medicine, New York.

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## Glossary

**ASC** = antibody-secreting cell; **BALAwMS** = Subjects with MS of Black African or Latin American self-identity; **CAwMS** = Subjects with MS of Caucasian self-identity; **DMT** = disease-modifying therapy; **HD** = healthy donors without MS; **Ig** = immunoglobulin; **MSSS** = MS Severity Scale Score; **NAT** = natalizumab therapy; **PBMC** = peripheral blood mononuclear cell; **SLE** = systemic lupus erythematosus; **T25-FW** = timed 25-foot walk.

Individuals with MS of Black African or Latin American self-identity (BALAwMS) are more likely to experience a severe disease course compared with individuals with MS of Caucasian self-identity (CAwMS).<sup>1,2</sup> Paraclinical measures of CNS inflammation (T2 lesion accumulation and lesion volume) may be pronounced,<sup>3,4</sup> whereas atrophy metrics, including brain and retinal degeneration, appear accelerated among BALAwMS compared with CAwMS.<sup>5-7</sup> Ethno-ancestry is clearly an important consideration in MS. Unfortunately, the paradox of ethno-ancestry being simultaneously relevant in MS yet underrepresented in both clinical and translational investigation is apparent both in clinical trials and observational research. We calculated an average of 2.7% of African Americans among total subjects enrolled in 7 clinical trials conducted between 2006 and 2017<sup>e1-e10</sup> for which demographic data were available (table 1). Furthermore, there are essentially no reports providing direct biological evidence of potential mechanisms underlying ethno-ancestry-based clinical disparity. Retrospective chart review implicates the contribution of antibody-secreting cells (ASCs), highlighting a relationship between elevated intrathecal IgG among African American patients with MS relative to Caucasian patients<sup>8</sup> and linking this differential to gray matter atrophy.<sup>9</sup> Indeed, plasmablasts and plasma cells, as ASCs derived from antigen-experienced B cells, appear to be important drivers of both inflammatory<sup>10-12</sup> and neurodegenerative aspects of MS pathogenesis.<sup>9,13,14</sup> ASCs are enriched within the CSF during active gadolinium-enhancing disease,<sup>12</sup>

ASC-derived intrathecal IgG correlates with CNS atrophy,<sup>9</sup> and IgM-producing ASCs are associated with aggressive disease course.<sup>15,e11</sup> The present cross-sectional study therefore investigates whether the peripheral blood of subjects with MS identifying with ethno-ancestral categories more likely to exhibit poorer prognosis reflects an identity-based differential ASC signature.

## Methods

### Standard protocol approvals, registrations, and patient consents

All study subjects were recruited according to Weill Cornell Medicine Institutional Review Board–approved protocol #1508016490R003. Subjects provided informed written consent at the Weill Cornell Medicine Multiple Sclerosis Center before study inclusion.

### Subject recruitment and study cohorts

Study subjects represent a convenience sample comprising individuals with clinically definite MS according to the 2010 McDonald criteria and healthy donors without MS (HD). We recruited subjects on natalizumab therapy (NAT) as a primary study subject population. This enabled study recruitment from among a relatively accessible patient population. Furthermore, this facilitated our investigation of intact ASC biology (despite disease-modifying therapy)<sup>e12</sup>

**Table 1** Underrepresentation of individuals of Black African self-identity in Phase III clinical trials for relapsing MS in the last decade

Clinical trial (year reported)	Total no. of subjects	No. (%) of CA	No. (%) of BAA
AFFIRM <sup>e1</sup> (2006)	627	603 (96)	10 (1.6)
SENTINAL <sup>e2</sup> (2006)	1,171	1092 (93)	39 (3.3)
FREEDOMS <sup>e3</sup> (2010)	1,272	Not reported	77 (6.1)
TRANSFORMS <sup>e4</sup> (2010)	1,292	1216 (94.1)	Not reported
TEMSO <sup>e5</sup> (2011)	1,088	1058 (97.3)	Not reported
DEFINE <sup>e6</sup> (2012)	1,234	969 (78.5)	26 (2.1)
CONFIRM <sup>e7</sup> (2012)	1,414	1191 (84.1)	27 (1.9)
CARE MS I <sup>e8</sup> (2012)	563 (IIT population)	532 (94.5)	Not reported
CARE MS II <sup>e9</sup> (2012)	798 (IIT population)	714 (89.5)	Not reported
OPERA I/OPERA II <sup>e10</sup> (2017)	1,656 (IIT population)	Not reported	72 (4.3%)

Abbreviations: BAA = Black or African American self-identity; CA = Caucasian self-identity.

inclusive of prospective pathogenic lymphocytes within the peripheral blood. MS NAT subjects required at least 3 prior doses for study inclusion. No subject had received lymphocyte-depleting therapies at any point before study draw. Study subjects were asked to self-identify according to ethno-ancestral categories for subsequent stratification. Individuals identifying with “Black African” or “Latin American/Hispanic” ancestry were combined into a single cohort as groups (BALA) based on risk for greater disease severity<sup>2,16</sup> relative to those identifying with “Caucasian/European ancestry” (CA). In addition to self-reported identity, we collected other demographic and clinical data for each cohort, including age (at study involvement), sex, disease duration, timed 25-foot walk (T25-FW), date since last clinical flare, and MS Severity Scale scores (MSSS).

### Sample collection, ASC frequency, and count determination

We isolated peripheral blood mononuclear cells (PBMCs) through density-gradient Ficoll centrifugation. Ficoll-spun buffy coats were harvested within hours of peripheral blood draws and resuspended in volumes of standard staining buffer equal to the original whole blood. We stained cells according to a standard protocol using the following BioLegend antibodies: CD19 PE/Cy7 (clone HIB19), CD20 PerCP (clone 2H7), CD27 brilliant violet 421 (clone M-T271), CD38 APC(clone HIT2), CD138 PE (clone MI15), IgD APC/Cy7(clone IA6-2), and IgM FITC (clone MHM-88). We performed flow cytometric analysis using a Becton Dickinson FACSVerse cytometer. We determined cell frequencies as the percent of a gated cell population among a parent cell population. Cell count was determined as the number of flow cytometry events within each defined analysis gate.

### Statistical analysis

The primary outcomes of this study are percent frequency of total CD19<sup>+</sup> ASCs, class-switched ASC subsets, and IgM<sup>+</sup> ASC subsets. In planning, the estimated sample size needed for a 2-sample means test was calculated based on preliminary data from natalizumab-treated subjects. Trends in the analysis for our additional study cohorts should be treated as exploratory in nature. Twenty-six subjects in each group were needed to detect a mean difference of 2 (SD: 2.5) in class-switched frequency between ethno-ancestral groups; 17 subjects in each group were needed to detect a mean difference of 1 (SD: 1) in IgM<sup>+</sup> ASC frequency, assuming alpha of 0.05 and power of 0.8. We calculated summary statistics using frequencies and proportions for categorical variables and mean, SDs, medians, and interquartile ranges for continuous variables. Demographic and clinical characteristics were compared between ethno-ancestry groups using the 2-sample *t* test, the Wilcoxon rank-sum test, or the Fisher exact test as appropriate. Bivariate analyses were used to determine the associations between age, sex, ethno-ancestry, MS disease status, MS disease duration, and outcome measures (i.e., percent frequency and absolute counts of total CD19<sup>+</sup> ASCs, class-switched ASC subsets, and IgM<sup>+</sup> ASC subsets) using simple linear regression or 2-sample *t* test. We further constructed multivariable linear regression models to assess

the associations between ethno-ancestry and outcome measures after adjusting for a priori hypothesized confounders age, sex, and MS disease duration. To assess the potential interaction (i.e., effect-measure modification) between ethno-ancestry and disease status in relation to outcome measures, we performed subgroup analyses for HD subjects and subjects with MS separately. All statistical tests were 2 sided, with a significance level of  $p < 0.05$ . All analyses were conducted with SAS version 9.4 (SAS Institute, Inc, Cary, NC).

### Data availability

Anonymized data not shown will be shared by request from a qualified investigator.

## Results

### Demographic and clinical characteristics

We enrolled a total of 54 subjects on natalizumab (“NAT”; 27 BALAwMS, 27 CAwMS), 20 subjects who were off drug at the time of study draw (“no disease-modifying drug [DMT]”; 12 BALAwMS, 8 CAwMS), and 24 HD subjects who lacked an MS diagnosis (“HD”; 11 BALA HD, 13 CA HD). Subjects were comparable in age, both within and between cohorts, whereas sex ratio varied. BALAwMS subjects exhibited a longer on average disease duration compared with CAwMS subjects, with this difference more pronounced in the no-DMT cohort (table 2). Clinically, there was some (albeit, nonsignificant) indication of greater acute disease activity and disability within BALAwMS compared with CAwMS subjects at the time of the draw. Thus, MSSS scores were greater, and T25-FW measures longer, among BALAwMS compared with CAwMS subjects in both NAT and no-DMT groups. Of these measures, only T25-FW in the NAT cohort reached statistical significance. Among our no-DMT cohort, BALAwMS subjects exhibited on average a shorter period since their last acute relapse than CAwMS. This was paralleled by a commensurate measure of months since previous high-dose steroid administration. The majority of subjects with MS in our study did not possess comorbidities. However, there were several reported autoimmune, rheumatoid, or oncologic indications: CAwMS NAT—eczema, mononucleosis, asthma, fibromyalgia, celiac disease, Graves disease, and malignant thyroid neoplasm; BALAwMS NAT—thyroid (diffuse goiter), asthma, irritable bowel syndrome, pituitary microadenoma, and positive antinuclear antibodies; CAwMS no DMT—ulcerative colitis, irritable bowel syndrome, hypothyroidism, and psoriasis; and BALAwMS no DMT—positive antinuclear antibodies.

### Subjects with MS of Black African or Latin American ethno-ancestral identity exhibit enhanced ASC frequencies over those of Caucasian identity

To test our hypothesis that stratifying our study sample according to ethno-ancestral cohorts at risk of severe disease (BALAwMS relative to CAwMS) would reveal a differential ASC frequency within the peripheral blood compartment, we first interrogated the PBMCs of subjects with MS on

**Table 2** Demographic and clinical characteristics for patients with MS and HD study participants

	MS NAT			MS no DMT			HD		
	CA	BALA	p Value	CA	BALA	p Value	CA	BALA	p Value
	N = 27	N = 27		N = 8	N = 12		N = 13	N = 11	
Age, y	35.37 (11.86)	32.63 (9.12)	0.35	34.88 (6.10)	37.17 (6.66)	0.45	29.33 (6.97)	32.82 (8.85)	0.30
Sex, no. (%)			0.1			0.17			0.36
Female	21 (77.8)	26 (96.3)		3 (37.5)	9 (75.0)		2 (15.4)	4 (36.4)	
Male	6 (22.2)	1 (3.7)		5 (62.5)	3 (25.0)		11 (84.6)	7 (63.6)	
Disease duration, median (IQR), mo	62 (26–106)	99 (45–148)	0.23	3 (0–70)	56 (13–132)	0.12	—	—	—
MSSS, median (IQR)	0.49 (0.23–2.60)	1.92 (0.23–4.79)	0.28	1.16 (0.89–2.64)	1.86 (0.59–5.90)	0.85	—	—	—
Undetermined values	5	9					—	—	—
T25-FW, s	3.70 (0.49)	4.29 (0.55)	0.009	3.85 (1.06)	5.30 (1.92)	0.35	—	—	—
Undetermined values	11	17		6	5		—	—	—
Days since last clinical flare, median (IQR)	—	—	—	146 (52.5–364.5)	56 (23–659)	0.90	—	—	—
Months since high-dose steroids, median (IQR)	—	—	—	8.80 (4.20–73.85)	3.30 (1.60–11.00)	0.35	—	—	—
None	—	—	—	4	3		—	—	—

Abbreviations: BALA = Black African or Latin American self-identity; CA = Caucasian self-identity; HD = healthy donors without MS; IQR = interquartile range; MSSS = MS Severity Scale Score; MS NAT = subjects with MS on natalizumab; MS no DMT = subjects with MS not on any disease-modifying therapy at the time of study participation; T25-FW = timed 25-foot walk.

Both demographic and clinical data were derived from chart review. Mean duration of MS is calculated from years since diagnosis to study draw. Data are given as mean (SD) except where indicated. The *p* values displayed were derived from 2-sample *t* test, Wilcoxon rank-sum test, or Fisher exact test. These were employed when comparing demographic and clinical characteristics between ethno-ancestry groups.

natalizumab. One of our most effective therapies, natalizumab, functions in MS by binding to the alpha-4 integrin subunit, essentially inhibiting the binding and trafficking of lymphocytes across the blood-brain barrier. In theory, this restricts otherwise pathogenic CNS-destined cells to the periphery.

ASCs represent a continuum of antigen-activated B cells that, through differentiation into plasmablasts and mature plasma cells, dedicate metabolic and protein processing mechanisms to antibody production. For this study, we use the term ASCs as inclusive of plasmablasts and maturing plasma cells found in the blood. Despite heterogeneity across the ASC spectrum, these cells may be collectively identified as brightly positive for CD27 and CD38.<sup>17</sup> We have thus used this general definition to clarify the distinct total ASC population among blood-borne CD19<sup>+</sup> cells. We found the majority of circulating ASCs to express high levels of HLA-DR (and CD86), (figure e-1, links.lww.com/NXI/A158), consistent with recently generated plasmablast identity as shown by others.<sup>18</sup> Also in agreement with others, the majority of circulating CD27<sup>hi</sup>CD38<sup>+</sup> cells lack CD20 expression, whereas a substantial portion express CD138, possibly distinguishing these as apoptosis resistant,

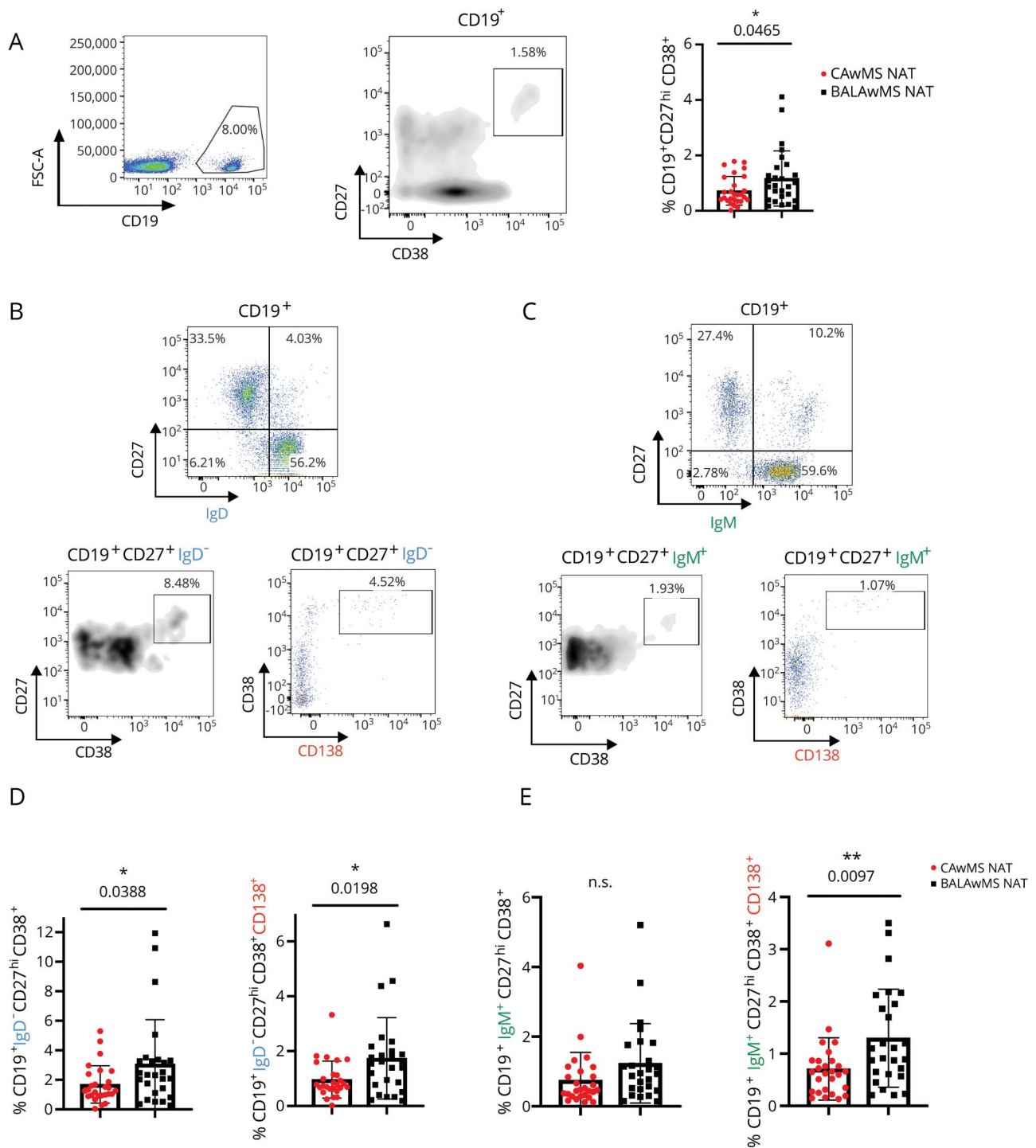
and perhaps bound for long-term residence in the bone marrow.

We uncovered a significant differential, with BALAwMS exhibiting on average a greater frequency of total ASCs compared with CAwMS (figure 1A). The majority of these ASCs were class-switched IgD<sup>-</sup> (figure 1, B and D left panel), with a smaller proportion of IgM<sup>+</sup> ASCs (figure 1, C and E left panel). We further assessed CD38<sup>+</sup>CD138<sup>+</sup> subpopulations based on recent work, which implicates these ASCs as significant intrathecal contributors to inflammatory gadolinium-enhancing MS.<sup>12</sup> Both class-switched and IgM<sup>+</sup>-CD38<sup>+</sup>CD138<sup>+</sup> ASCs were significantly enhanced among BALAwMS compared with CAwMS (figure 1, D and E, respectively, right panels). Our findings were similar after adjusting for age, sex, and disease duration (table e-1, links.lww.com/NXI/A159)

### Ethno-ancestry-based differential ASC frequency is present among those with MS and not HDs

Although natalizumab possesses a targeted mechanism of action, we wished to examine our findings without its influence. To investigate the generalizability of our findings

**Figure 1** Subjects with MS self-identifying with Black African or Latin American ethno-ancestry exhibit heightened peripheral blood ASC frequencies



Peripheral blood samples from subjects with MS on natalizumab were stratified according to self-identified ethno-ancestry at risk of more severe MS, CawMS (n = 27), and BALAwMS (n = 27). Percent frequency of different ASC populations was compared between these cohorts. (A) Representative gating strategy for ASCs; CD27<sup>hi</sup> CD38<sup>+</sup> total ASCs were selected from CD19<sup>+</sup> cells for downstream phenotypic subset analysis. (B) Representative gates for class-switched IgD<sup>-</sup> CD27<sup>+</sup> total ASCs and CD38<sup>+</sup> CD138<sup>+</sup> subpopulation. (C) Representative gates for IgM<sup>+</sup> ASCs. (D and E), Average frequencies of previously described class-switched (D) and IgM<sup>+</sup> (E) ASC populations; error bars represent SD, *p* values determined by the 2-sided *t* test. ASC = antibody-secreting cell; BALAwMS = subjects with MS of Black African or Latin American self-identity; CAwMS = subjects with MS of Caucasian self-identity; NAT = natalizumab therapy.

beyond the influence of natalizumab, and to examine whether our observations were present in individuals without MS, we extended MS subject enrollment to

include those not on any established DMT. Among these subjects, approximately 60% were treatment-naive, having never been exposed to any DMT. Those with any previous

exposure to therapy had been off of DMT for at least 2 months before study participation.

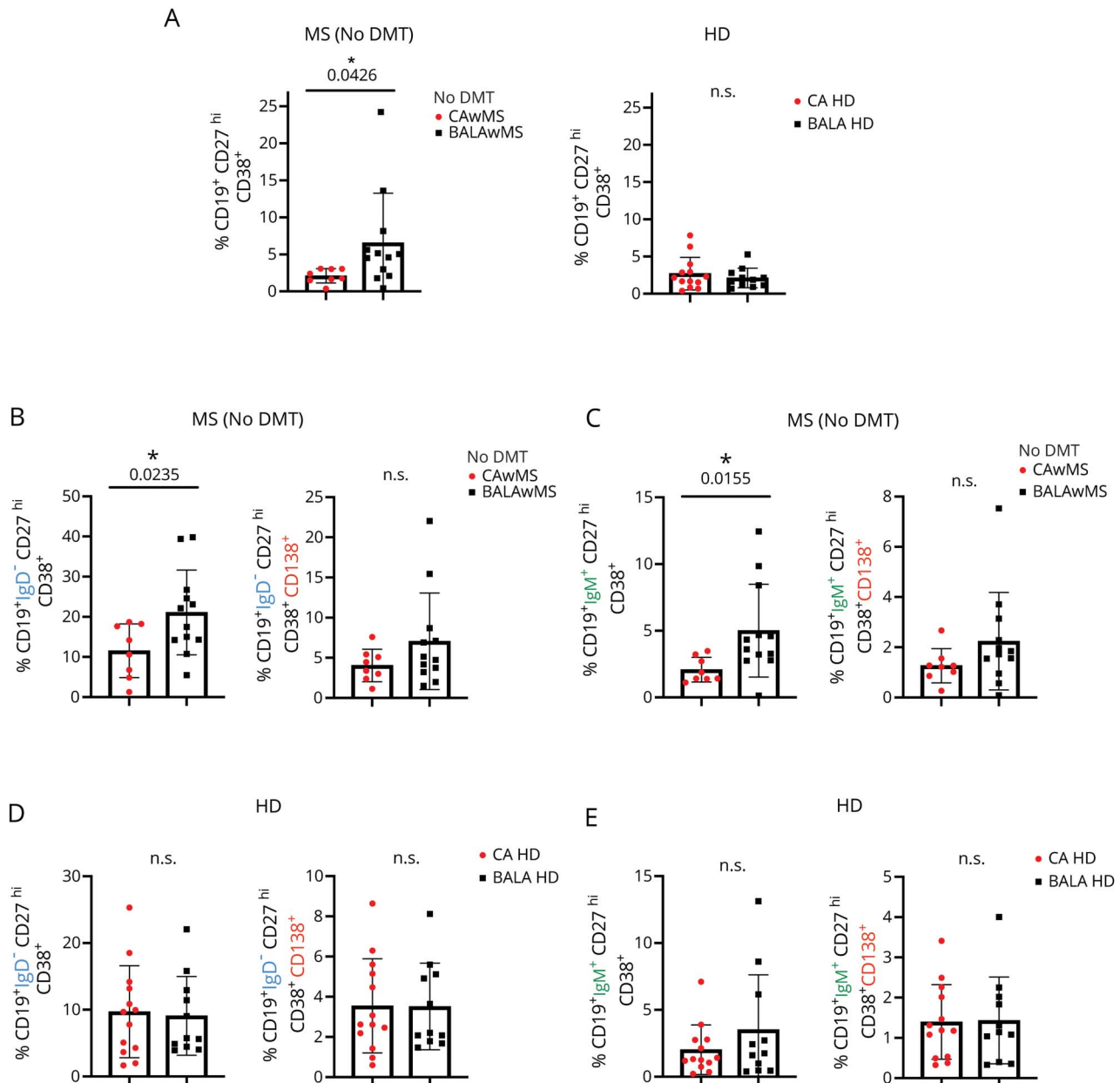
Our analysis of these cohorts demonstrated an ethno-ancestry-dependent discrepancy in ASC frequency, with this difference present across essentially all ASC subsets found among natalizumab and off-treatment MS subjects (figure 2, A–C). To determine whether this ethnicity-dependent difference was associated with MS, we performed the same phenotypic analysis among HDs. In stark contrast

to our findings in subjects with MS, there was virtually no difference in ASC frequency found among HDs (figure 2, A, D, and E).

### Class-switched ASCs are differentially enriched among subjects with MS of Black African or Latin American ethno-ancestral identity

Frequencies of both class-switched and IgM<sup>+</sup> ASCs were significantly enhanced among subjects with MS of Black African or Latin American compared with Caucasian ethno-

**Figure 2** Ethno-ancestry-based differences in ASC frequency are present among subjects with MS but not HDs



Average frequencies of previously described total CD19<sup>+</sup>(A), class-switched CD19<sup>+</sup>IgD<sup>-</sup> (B and D) and unswitched CD19<sup>+</sup>IgM<sup>+</sup> (C and E) ASC populations. CAwMS (n = 8) and BALAwMS (n = 12); CAHD (n = 13) and BALAHD (n = 11). Error bars represent SD, *p* values determined by the 2-sided *t* test. ASC = antibody-secreting cell; BALA HD = healthy donors without MS of Black African or Latin American self-identity; BALAwMS = Subjects with MS of Black African or Latin American self-identity; CAwMS = Subjects with MS of Caucasian self-identity; CA HD = healthy donors without MS of Caucasian self-identity.

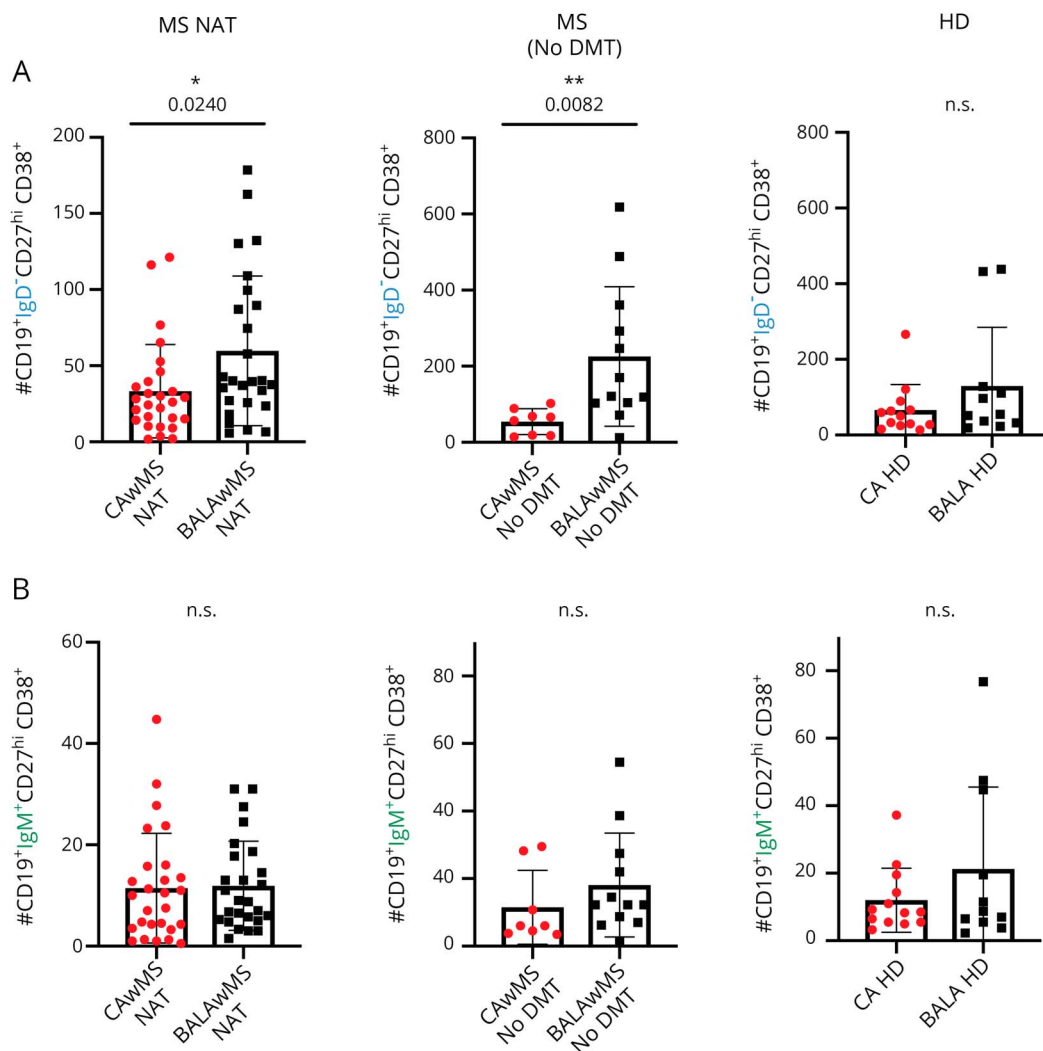
ancestry. To ascertain whether these frequencies (representative of ASCs derived from precursor B cells) affected overall circulating numbers of these cells, we compared flow cytometry event counts of class-switched and IgM ASCs among our cohorts. In contrast to heightened frequency differences across both switched and unswitched classes in the context of MS, only class-switched (figure 3A) but not IgM<sup>+</sup> ASCs were differentially enriched in subjects of Black African or Latin American identity compared with those of Caucasian ethno-ancestry (figure 3B).

Taken together, our observations show an identity-dependent differential of ASC frequency in the context of MS, and support the existence of alternative underlying immunopathogenesis across different ethno-ancestries.

## Discussion

The major finding of our investigation was the significant ethno-ancestry-based differential of peripheral blood ASC subsets examined among subjects with MS but not HD subjects. Both interventional and observational clinical studies reveal a clear pathogenic role for blood-borne, CNS-infiltrating B cells in MS.<sup>19–21</sup> There appears to be crosstalk between the peripheral blood and CNS as demonstrated by clonal sequencing approaches.<sup>22,23</sup> For instance, recent observations by Eggers et al.<sup>12</sup> suggest that it is predominantly peripheral blood memory B cells and derived CD138<sup>+</sup> plasma cells that are associated with CNS pathology during active inflammatory MS. Continued crosstalk between the blood and CNS may lead to an accumulation CNS-resident ASCs. Several lines of

**Figure 3** Numbers of class-switched but not IgM<sup>+</sup> ASCs are elevated according to ethno-ancestry among subjects with MS



Average number of circulating ASCs for each subject cohort as obtained through event counts derived from flow cytometry gates described prior. Class-switched CD19<sup>+</sup>IgD<sup>-</sup> ASCs (A); unswitched CD19<sup>+</sup>IgM<sup>+</sup> ASCs (B). Error bars represent SD, *p* values determined by the 2-sided *t* test. ASC = antibody-secreting cell; BALA HD = healthy donors without MS of Black African or Latin American self-identity; BALAwMS = Subjects with MS of Black African or Latin American self-identity; CAwMS = Subjects with MS of Caucasian self-identity; CA HD = healthy donors without MS of Caucasian self-identity; NAT = natalizumab therapy.

evidence point to a pernicious ectopic humoral response within CNS tissue, likely maintained by CD138<sup>+</sup> apoptotic-resistant plasma cells.<sup>12,24,e13</sup> These include the existence of pathogenic autoantibodies,<sup>13,14,25,e14</sup> persistence of intrathecal antibodies despite peripheral CD20<sup>+</sup> memory B-cell depletion,<sup>26</sup> and observations of follicle-like aggregates in progressive MS.<sup>27</sup> Our study reveals remarkable trends consistent with, and additive to, previous observations that implicate differential intrathecal humoral responses in patients consistently shown to be at risk of aggressive manifestation of MS.<sup>8,9</sup> We note that although our BALAwMS cohort exhibited an increased disease manifestation, this current study is not powered to assess the clinical differences. Nonetheless, having been conducted using peripheral blood, our work highlights the potential value of this accessible compartment for subsequent research into questions of ethno-ancestry and MS.

Taking into account data supporting a B cell-centric view of MS immunopathogenesis, and previous work showing enhanced intrathecal humoral responses among African Americans with MS, we suggest that among BALAwMS, CNS-infiltrating B cells may be more likely driven toward ASC differentiation. Our findings provide plausibility for this scenario, as ASC frequency used as the primary outcome in our study, alludes to the tendency of B cells to adopt a plasmablast or plasma cell fate. Given the importance of migration between peripheral blood and CNS in MS, it is possible that the tendencies observed in the periphery may be recapitulated in the CNS. In their retrospective study, Rinker et al.<sup>8</sup> do not distinguish leukocyte categories among the overall increase in intrathecal white blood cells among African American patients with MS over Caucasian counterparts. Thus, in addition to examining the question of intrathecal plasma cell burden, future work with BALAwMS should examine transcriptional mechanisms associated with plasma cell fate. In addition, although intrathecal IgM is associated with a poor MS course,<sup>15</sup> there is no study to our knowledge that examines whether IgM oligoclonal bands are enriched among BALAwMS relative to other subpopulations. Our finding that frequencies of IgM<sup>+</sup> ASCs are significantly enhanced in this population warrants such an investigation. However, only class-switched and not IgM<sup>+</sup> ASC numbers were differentially elevated among subjects with MS, pointing to the likely involvement of class-switch recombination mechanisms alongside ASC differentiation biology. Our work thus facilitates numerous avenues for future study in an effort to better understand and treat aggressive MS.

In this report, we used the term “ethno-ancestry” to both highlight and encapsulate the complexity around societal (ethnicity) and biologic (ancestry) heritage. As with other studies examining the influence of ethno-ancestral categories and MS, we find some value in the use of self-identification according to broad labels to establish study cohorts. However, we recognize that all such labels, whether ethno-ancestry, race, or other variants, ultimately represent combinations of socially constructed institutional and cultural designations.<sup>28,29</sup> Such categories are

ultimately poor reflections of the subtle differences between individuals,<sup>30</sup> whereas their use may be also confounded by sociohistoric narratives.<sup>e15</sup> Future studies, particularly those seeking to unravel the interplay between ethno-ancestry and disease, should emphasize molecular genetic and epigenetic delineations. In addition to demonstrably transcending broad ancestral categories, underlying molecular genetic factors may be affected by socioeconomic<sup>31</sup> and behavioral<sup>32,33</sup> influences important to shaping disease incidence and prognosis.

Ethno-ancestry-based immunologic differences are long-established observations.<sup>34</sup> However, these are largely described in immunity and vaccination studies among presumably healthy individuals.<sup>35,36</sup> For instance, total serum IgG concentrations are more likely elevated among “black” relative to “white” individuals<sup>34</sup>; African American recipients of HIV gp120 vaccination generated significantly greater neutralizing antibody responses compared with whites assessed in a separate study<sup>35</sup>; similarly, according to National Health and Nutritional Examination Survey data, seroprevalence of IgG antibody specific to mumps virus was highest among individuals identifying as “non-Hispanic black” and lowest among “non-Hispanic whites.”<sup>36</sup> Our work is the first to directly demonstrate ethno-ancestry-based immunologic difference in the context of MS. Nonetheless; there are several limitations to our study. These include a cross-sectional design, convenience sample, and the limited resolution provided by broad ethno-ancestral categories. Very few subjects had undergone lumbar puncture procedures as part of standard of care; as such, we were unable to directly relate peripheral differentials with intrathecal antibody burden as reported prior. Despite these limitations, we provide evidence of an ethno-ancestry-dependent peripheral blood ASC differential concordant with observations of intrathecal humoral responses.

Over the past 16 years,<sup>2,7,37</sup> observational studies revealed greater clinical severity and poorer prognosis among individuals of the Black African diaspora, including those identifying within the spectrum of Latin American identity.<sup>2,16</sup> Both overt and indirect evidence support ethno-ancestry as a critical factor in MS. A primary role for B cells in MS pathogenesis unequivocally shown in 2008<sup>11,38</sup> is not only accentuated in individuals of Black African heritage<sup>8</sup> but parallels similar ethno-ancestry-based B cell-driven dysregulation in other conditions.<sup>39,40</sup> For instance, memory B cells from African American patients with systemic lupus erythematosus (SLE) exhibit an activated phenotype relative to Caucasian patients.<sup>39</sup> Furthermore, plasmablasts are associated with disease activity in SLE. African Americans with SLE exhibit a pronounced plasmablast transcriptomic signature in conjunction with heightened clinical severity relative to Caucasian subjects.<sup>40</sup> Thus, our results have interdisciplinary implications, as they are consistent with a burgeoning trend of possibly differentially regulated B-cell biology as a nexus through which ethno-ancestry-based disease severity disparities may manifest.<sup>39,40</sup> Understanding what mediates these differences may be key to unlocking



major advancements in diagnostics and therapy, both for MS and other maladies.

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## Disclosure

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## Appendix Authors

Name	Location	Role	Contribution
<b>Kiel M. Telesford, PhD</b>	Weill Cornell Medicine	Author	Designed and conceptualized the study; analyzed the data; and drafted the manuscript for intellectual content
<b>Ulrike W. Kaunzner, MD, PhD</b>	Weill Cornell Medicine	Author	Contributed to project design, rationale, and patient/subject recruitment
<b>Jai Perumal, MD</b>	Weill Cornell Medicine	Author	Contributed to data acquisition, data analysis, manuscript writing, and patient/subject recruitment
<b>Susan A. Gauthier, DO, MPH</b>	Weill Cornell Medicine	Author	Contributed to data acquisition, study design, and patient/subject recruitment
<b>Xian Wu, MPH</b>	Weill Cornell Medicine	Author	Conducted biostatistical data analysis, manuscript writing, and manuscript revision for intellectual content

## Appendix (continued)

Name	Location	Role	Contribution
<b>Ivan Diaz, PhD</b>	Weill Cornell Medicine	Author	Conducted biostatistical data analysis and manuscript revision for intellectual content
<b>Mason Kruse-Hoyer, MD</b>	Weill Cornell Medicine	Author	Contributed to data acquisition, data analysis, patient/subject recruitment, and manuscript revision
<b>Casey Engel, BA</b>	Weill Cornell Medicine	Author	Contributed to data acquisition, data analysis, patient/subject recruitment, and manuscript revision
<b>Melanie Marcille, BA</b>	Weill Cornell Medicine	Author	Contributed to data acquisition, data analysis, and patient/subject recruitment
<b>Timothy Vartanian, MD, PhD</b>	Weill Cornell Medicine	Author	Contributed to study design and conceptualization, data interpretation, and manuscript revision for intellectual content

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