Stem Cell Reports
Report
ISSCR
OPEN ACCESS

Creating an HLA-homozygous iPS cell bank for the Brazilian population: Challenges and opportunities

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https://doi.org/10.1016/j.stemcr.2023.09.001

SUMMARY

Identifying human leukocyte antigen (HLA) haplotype-homozygous donors for the generation of induced pluripotent stem (iPS) cell lines permits the construction of biobanks immunologically compatible with significant numbers of individuals for use in therapy. However, two questions must be addressed to create such a bank: how many cell lines are necessary to match most of the recipient population and how many people should be tested to find these donors? In Japan and the UK, 50 and 100 distinct HLA-A, -B, and -DRB1 triple-homozygous haplotypes would cover 90% of those populations, respectively. Using data from the Brazilian National Registry of Bone Marrow Donors (REDOME), encompassing 4,017,239 individuals, we identified 1,906 distinct triple-homozygous HLA haplotypes. In Brazil, 559 triple-homozygous cell lines cover 95% of the population, and 3.8 million people would have to be screened. Finally, we show the contribution of the 30 most frequent triple-homozygous HLA haplotypes in Brazil to populations of different countries.

INTRODUCTION

The production and utilization of induced pluripotent stem (iPS) cells from human somatic cells is a highly promising source of cells for transplantation, aiming to replace diseased or damaged tissues in a wide range of conditions such as diabetes, heart failure, and neurodegenerative disorders (Borow et al., 2019; Song et al., 2015). Human iPS (hIPS) cells can be propagated indefinitely in an undifferentiated state while retaining pluripotency (Takahashi et al., 2007; Robinton and Daley 2012). However, their differentiated progeny express human leukocyte antigens (HLAs), which, in unmatched conditions, may cause graft rejection. To overcome rejection, one strategy is the creation of autologous stem cells. However, the cost and time necessary for producing patient-specific hiPS cells for cell therapy limit the broad adoption of this technique in clinical practice.

Therefore, creating a bank of HLA-typed iPS cells so that the best match could be selected would help reduce the likelihood of graft rejection. The importance of HLA-typed cell banks has long been recognized for treating severe blood diseases with allogenic hematopoietic stem cell transplantation (Turner et al., 2013). In these cases, a compatible donor is required, and a recipient family member is sought on a priority basis. Unfortunately, it is reported that a compatible family donor exists in approximately 12% of cases for extended families with common genotypes (Schipper et al., 1996), leaving most patients unattended. Registries of voluntary donors offer another possibility to find a compatible HLA-matched donor. The ideal number of donors in these registries can be predicted based on mathematical models that estimate matching, including the target population's frequency distribution of HLA alleles and haplotypes. Similarly, the number of cells necessary to enable HLA matching in the general population can be estimated (Taylor et al., 2005). It is then possible to select, for all potential recipients, a compatible donor with the best HLA match (Williams et al., 2016). Thus, an alternative approach for reducing the cost, time, and immunological rejection of cell therapies is to set up banks of HLA-haplotype iPS cell lines from homozygous HLA individuals.

In Japan, a cell bank size of only 30 iPS cell lines would provide a match for 82.2% of the population, and, if the bank size increased to 50 lines, 90.7% of people would be contemplated (Nakatsuji et al., 2008). Considering the UK population, after considering the full range of combinations of the known different HLA types that might be present in the population, a total of 405 theoretical homozygous HLA-A-B-DRB1 combinations would be needed to provide a match for all potential recipients represented by the 10,000 organ donors (Taylor et al., 2012). In Korea, 10 HLA-homozygous iPS cell lines would match 41.07% of the Korean population and could be used in other Asian populations, such as Japan (Lee et al., 2018).

In contrast, the Brazilian population is one of the world's populations with the highest admixture rate. Most individuals are mosaics of different subcontinental genomes, namely European, African, and Native American (Kehdy et al., 2015; Bharti and Investigator 2022). The main goal of this study is to address two major questions about creating an hiPS cell haplobank for the highly diverse and admixed Brazilian population. Initially, we must know how many homozygous cell lines would be necessary for HLA matching to the majority of recipients in our population (that is, the size of the homozygous HLA-haplotype bank). Second, it is essential to know how many donors should be tested to find homozygous donors, or, in other words, estimate the size of the HLA-type database necessary to find HLA-homozygous donors. The probabilities used for estimation in our model were retrieved from the relative frequency of haplotypes in the Brazilian National Registry of Bone Marrow Donors (REDOME).

RESULTS

All the simulations were carried out using data from the REDOME database, created in 1993 in Brazil, for bone marrow transplantation purposes. REDOME gathers complete information from all Brazilian bone marrow donors. Since 1998, it has been coordinated by one single center, the National Cancer Institute (INCA), in Rio de Janeiro, Brazil.

We used only one sample space for simulation purposes, from where all data concerning donors' and recipients' profiles were retrieved. All bone marrow donors, in this case, were typed using standard serological or molecular methods. The decision between levels of typing is an economic issue, so we used two digits coding for this simulation.

Our model was based on two samplings with replacements. In the first sampling, a specific individual is selected as a "probable receptor" from the REDOME databank, with a probability pR_i of being sampled. This probability results from the relative frequency of that specific phenotype in our population: the more prevalent the phenotype, the higher this probability is. The second sampling determines our "possible donor" and involves the probability pD_i, built from the sum of the relative frequencies of all the genotypes that could match our donor. In fact, one recipient may receive cells from up to eight different triple-homozygous donors.

The Brazilian REDOME database had 4,017,239 individuals registered as bone marrow donors in 2019, encompassing 9,155 different haplotypes. We identified 20,460 (0.51%) triple-homozygous individuals, representing 1,906 different triple-homozygous haplotypes (donors). The HLA allelic profile contains 21 alleles in locus A, 36 alleles in locus B, and 13 in locus DRB1 (Table 1).

We used the population in the REDOME as a proxy of the Brazilian population to calculate how many homozygous cell lines would be necessary for HLA matching to most recipients. We estimate the cell bank size to cover 50%, 75%, 85%, and 95% of the Brazilian population should have 51, 157, 267, and 559 cells, respectively (Figure 1A). Considering the 30 most frequent haplotypes in low resolution, the cumulative coverage is almost 40% of the population (Table 2).

The second question is how many donors should be tested to find enough homozygous donors to cover a certain percentage of our population, determining the relation between registry size and the probability of finding a triple-homozygous donor. This analysis gives us the appropriate size of donor registries based on the population genetic profile of HLA genes. Since each recipient may receive cells from more than one donor, or, in other words, more than one phenotype may provide a match for a given recipient, if we want to cover 50% of the Brazilian population, we would have to test 2,008,610 persons; to cover 75% of people, we should test 3,012,932 individuals, and for a 95% coverage, 3,816,377 tests should be done. If we test a total of 4,017,239 individuals (the number of tested individuals in the REDOME database), we would have 99% of the Brazilian population covered (Figure 1B).

We also investigated the contribution of the 30 most frequent triple-homozygous HLA haplotypes in Brazil to populations of different countries. Using data from the Allele Frequency Net Database (AFND), including 369 studies comprising 10,534,828 individuals, we concluded that those haplotypes would cover 3,369,981 individuals (32% of the sample). The coverage in specific populations ranged from 41.8% of Caucasians in the United States to 3.7% in populations from East Asia.

In the United States, our 30 most frequent HLA-homozygous lines cover 1,881,349 (28.9%) people in a total population of 6,490,171 available in AFND. Considering only the African American population, 97,396 (10.8%) of a sample of 898,627 is covered. However, if we consider the population of Caucasians, 1,507,500 (41.8%) of a total of 3,604,098 individuals are covered. Concerning the Hispanic population, 219,039 (22.4%) out of 975,998 are covered, and the Alaska Natives added to American Indians have 5,561 (25.3%) of 21,943 covered. In contrast with the data above, for those of Asian origin, including Chinese, Japanese, and Korean, only 3.7% of 563,033 individuals are covered (Table 3).

In Europe, we do not have information for all countries. However, the major contribution came from Germany, Poland, Portugal, Spain, Norway, and Croatia. The sample has 3,633,178 individuals, mainly from Germany (96%),

Table 1. Allele frequencies of the HLA-A, -B, and -DRB1 genes based on typing results for each HLA gene—considering all patients—and the relative frequency

A locus

HLA-A	N	Genomic frequency	n	Allelic frequency
01	991,473	0.0908	942,988	0.1727
02	2,815,403	0.2578	2,436,090	0.4462
03	1,001,180	0.0917	930,436	0.1704
11	577,712	0.0529	541,262	0.0991
23	567,497	0.0520	534,304	0.0979
24	1,077,242	0.0986	978,044	0.1791
25	135,290	0.0124	128,626	0.0236
26	358,916	0.0329	339,366	0.0622
29	493,343	0.0452	454,497	0.0832
30	589,799	0.0540	552,084	0.1011
31	512,675	0.0469	471,772	0.0864
32	346,690	0.0317	322,012	0.0590
33	337,881	0.0309	316,934	0.0580
34	87,894	0.0080	81,921	0.0150
36	58,873	0.0054	55,898	0.0102
43	770	0.0001	719	0.0001
66	110,563	0.0101	105,005	0.0192
68	677,529	0.0620	615,176	0.1127
69	19,665	0.0018	18,262	0.0033
74	138,028	0.0126	126,996	0.0233
80	21,765	0.0020	20,538	0.0038

B locus

HLA-B	n	Genomic frequency	n	Allelic frequency
07	753,389	0.0690	753,389	0.1380
08	550,405	0.0504	550,405	0.1008
13	169,727	0.0155	169,727	0.0311
14	580,961	0.0532	580,961	0.1064
15	1,010,698	0.0926	1,010,698	0.1851
18	512,680	0.0469	512,680	0.0939
27	240,486	0.0220	240,486	0.0440
35	1,277,037	0.1169	1,277,037	0.2339
37	116,431	0.0107	116,431	0.0213

Table 1. *Continued*

B locus

HLA-B	n	Genomic frequency	n	Allelic frequency
38	226,718	0.0208	226,718	0.0415
39	370,998	0.0340	370,998	0.0679
40	519,540	0.0476	519,540	0.0952
41	141,988	0.0130	141,988	0.0260
42	161,657	0.0148	161,657	0.0296
44	1,180,839	0.1081	1,180,839	0.2163
45	198,966	0.0182	198,966	0.0364
46	4,285	0.0004	4,285	0.0008
47	23,434	0.0021	23,434	0.0043
48	77,375	0.0071	77,375	0.0142
49	307,257	0.0281	307,257	0.0563
50	265,082	0.0243	265,082	0.0485
51	901,465	0.0826	901,465	0.1651
52	210,625	0.0193	210,625	0.0386
53	271,720	0.0249	271,720	0.0498
54	6,443	0.0006	6,443	0.0012
55	117,657	0.0108	117,657	0.0215
56	38,633	0.0035	38,633	0.0071
57	307,568	0.0282	307,568	0.0563
58	297,219	0.0272	297,219	0.0544
59	1,796	0.0002	1,796	0.0003
67	2,974	0.0003	2,974	0.0005
73	10,559	0.0010	10,559	0.0019
78	9,468	0.0009	9,468	0.0017
81	48,879	0.0045	48,879	0.0090
82	5,213	0.0005	5,213	0.0010
83	16	0.0000	16	0.0000

DRB1 locus

HLA-DRB1	n	Genomic frequency	n	Allelic frequency
01	1,084,612	0.0993	1,028,582	0.1884
03	1,069,711	0.0980	1,015,483	0.1860
04	1,365,429	0.1250	1,276,609	0.2338
07	1,413,774	0.1295	1,319,026	0.2416

(*Continued on next page*)

Table 1. *Continued*

DRB1 locus				
HLA-DRB1	n	Genomic frequency	n	Allelic frequency
08	679,544	0.0622	656,088	0.1202
09	190,245	0.0174	187,774	0.0344
10	219,230	0.0201	216,694	0.0397
11	1,307,580	0.1197	1,223,533	0.2241
12	181,414	0.0166	179,483	0.0329
13	1,472,574	0.1348	1,370,464	0.2510
14	452,605	0.0414	441,819	0.0809
15	1,071,871	0.0982	1,016,277	0.1861
16	411,599	0.0377	402,610	0.0737

30 most frequent HLA-A, -B, and -DRB1 alleles.

of which 39% are compatible with our 30 most frequent HLA phenotypes.

Israel (194,805 individuals) would have 19.8% coverage, and the region of western Asia, including Gaza, Iran, Iraq, Israel, Jordan, Saudi Arabia, Turkey, and the United Arab Emirates (241,770 individuals) would have 19.5% of its population covered. On the other hand, countries in South-East Asia (China, Hong Kong, Malaysia, Myanmar, and Taiwan) have only 3.7% coverage of 77,196 individuals. On the African continent, considering sub-Saharan and North Africa together, our bank would cover 14.2% of 1,020 individuals.

DISCUSSION

Using human skin fibroblasts or peripheral blood mononuclear cells to create autologous pluripotent stem cells potentially minimizes rejection problems associated with cell therapies. However, despite recent advances in autologous pluripotent stem cell therapies, such personalized therapies may not be feasible to implement on a large scale (Bharti and Investigator 2022). Furthermore, since pluripotent cells, and especially their derivatives, are immunogenic (Williams et al., 2016), iPS cells should be derived from homozygous individuals for at least the HLA-A, HLA-B, and HLA-DRB1 loci in order to decrease T cell-mediated rejection. In this way, the possibility of having a preselected phenotype of iPS cell lines elicits greater opportunities for matching in cell therapy. To address these issues, we estimated the frequencies of HLA homozygotes in the Brazilian population from the observed frequencies of three HLA locus haplotypes (A-B-DR) at a broad two-digit resolution based on data retrieved from REDOME. These data comprise 4,017,239 non-related individuals registered in REDOME.

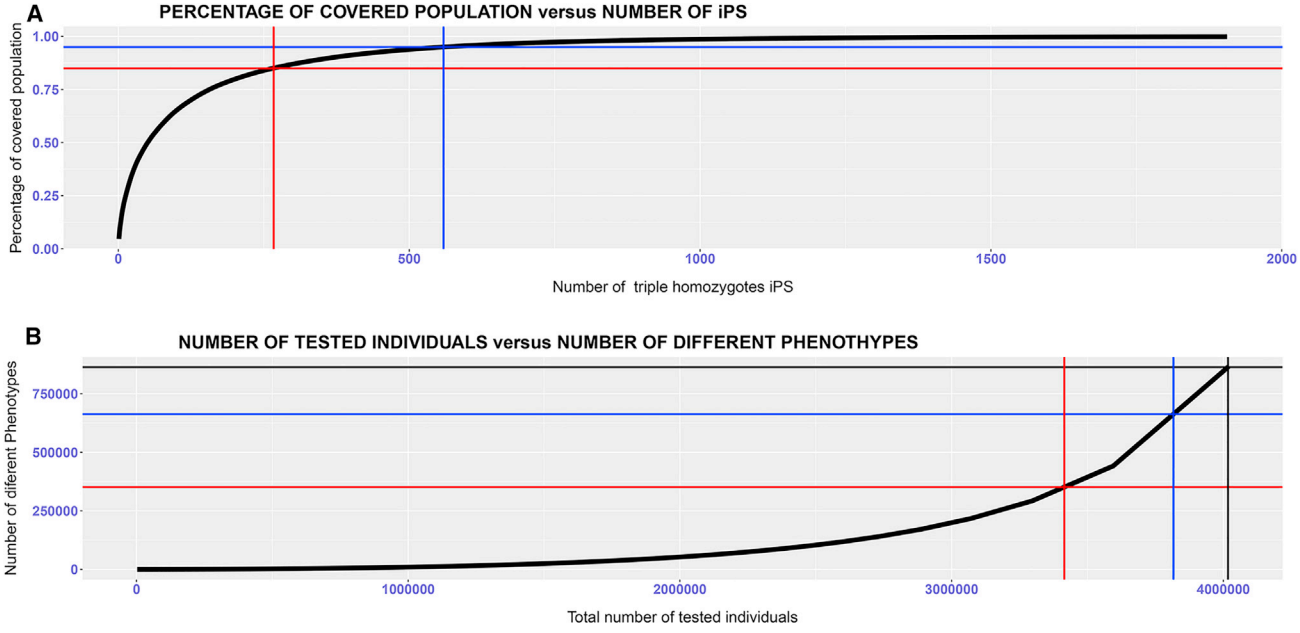

Figure 1. Number os iPS lines needed (A) and individuals tested (B) to cover the Brazilian population

(A) Estimated numbers of iPS cell lines homozygous for HLA-A, HLA-B, and HLA-DRB1 to cover the Brazilian population, ordered according to their frequencies. The red and blue lines represent 85% (267 iPS cells) and 95% (559 iPS cells) of the population covered, respectively.

(B) Relation between the number of people to be tested and the number of different triple homozygous; the red and blue lines represent 85% and 95% coverage. HLA-A, -B, and -DRB1 alleles.

Table 2. Estimated and cumulative percentage of HLA-matched individuals in the Brazilian population with a low-resolution panel of 30 homozygous cells

HLA-A	HLA-B	HLA-DRB1	Number of patients covered	Percentage of patients covered	Accumulated percentage of patients covered
01	08	03	184,035	4.581131469	4.581131469
02	44	07	138,497	3.447566849	8.028698317
29	44	07	91,173	2.269543833	10.29824215
02	07	15	84,021	2.09151111	12.38975326
02	35	11	80,443	2.002444963	14.39219822
02	44	13	74,365	1.851147019	16.24334524
02	51	08	66,178	1.647350332	17.89069557
33	14	01	58,208	1.448955365	19.33965094
02	51	13	56,936	1.417291827	20.75694277
02	40	04	50,550	1.258326926	22.01526969
02	35	04	45,524	1.133216122	23.14848581
02	15	13	44,308	1.102946576	24.25143239
24	35	11	44,229	1.100980051	25.35241244
03	35	01	41,722	1.038574006	26.39098645
02	07	01	40,204	1.000786859	27.3917733
02	15	16	39,616	0.98614994	28.37792325
03	07	15	38,968	0.970019459	29.3479427
02	35	03	37,886	0.943085537	30.29102824
03	35	15	37,604	0.93606579	31.22709403
02	40	11	36,328	0.904302682	32.13139671
02	44	11	35,768	0.890362759	33.02175947
02	50	07	35,295	0.878588503	33.90034798
24	15	13	30,819	0.767168695	34.66751667
02	51	14	30,332	0.755045941	35.42256261
24	07	15	29,994	0.746632202	36.16919481
30	42	03	29,956	0.745686279	36.91488109
02	14	01	29,673	0.738641639	37.65352273
02	51	04	27,417	0.682483666	38.3360064
30	18	03	27,095	0.674468211	39.01047461
02	44	04	25,980	0.646712829	39.65718744

Coverage of world populations by 30 most frequent Brazilian haplotypes.

REDOME frequency distributions confirm that certain combinations of HLA genes may be found in the general population at a higher prevalence than expected due to disequilibrium linkage among class I and class II, migration, and regional color/race background of Brazilians (Boquett et al., 2020; Torres et al., 2017). For this reason, any

Table 3. Sample size used for calculations and the percentage of coverage of the 30 most frequent triple-homozygous HLA haplotypes in Brazil to populations of different countries

AFND region	Groups	Sample size	Percentage covered
USA	all Americans	6,490,171	28.99
	African American	898,627	28.987
	Caucasian	3,604,098	41.83
	Hispanic	975,998	22.44
	Alaska Natives and Native Americans	21,943	25.34
	Asian origin	563,033	3.66
Europe	all countries	3,633,178	39.04
	Germany	1,375,028	39.29
	Poland	44,448	38.93
	Portugal	60,739	25.48
	Spain	7,507	38.69
	Norway	4,510	56.40
	Croatia	4,000	20.42
	Italy	1,649	55.00
Western Asia	total	241,770	19.52
	Israel	194,805	19.86
South-East Asia	total	77,196	3.7
Africa	total	1,020	14.21

estimation of HLA-haplotype banking of iPS cells must also consider other differences in the profile of haplotypes, such as ethnicity, sex, ABO blood types, and Lewis antigen types. Nonetheless, population-specific matching probability is the main key parameter to provide the benefit of unrelated stem cell donor registries and recruitment efforts.

Currently, haplobanks are available or being organized in some countries (Yoshida et al., 2023; Stacey, 2023). Moreover, efforts to build an international network to register and supply iPS cell lines from national biobanks are being discussed to enable full access to cell therapies for individuals with different ancestral backgrounds (Sullivan et al., 2020). Considering the possibility of creating a global network of iPS cell banks, we hypothesize that, given the admixture of African, Indigenous, and European ancestries in Brazil, our genetic diversity might provide iPS cells that may cover other countries. In fact, we can cover 32% of 10,534,828 people extracted from AFND using our 30 most frequent homozygous donors. Comparing all data available by race, the average coverage would be 39%–41% for Caucasians, 10%–14% of African descendants (data manly retrieved from the USA and African regions), 25.3% from Alaska Natives together with Native Americans, and less than 4% of the Asian population. In Brazil, those 30 most frequent HLA cells would cover 39.6% of our population. This discrepancy between different populations shows the importance of an initiative to constitute a world iPS bank, to which Brazil could contribute considerably.

We hope that the publication of the current data will entice the existing bone marrow donor registries to share data that would allow more precise calculations of the dimension of a global iPS cell bank to supply the world population with this important source of advanced therapy for regenerative medicine.

EXPERIMENTAL PROCEDURES

Corresponding author

Further information and requests concerning our database and calculations should be addressed to us and will be carried through by the corresponding authors, Antonio Carlos Campos de Carvalho (acarlos@biof.ufrj.br) and Marcio Lassance Martins de Oliveira (lassance.ncc1701@gmail.com).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- All data of Brazilian HLA profiles used in our model were retrieved from REDOME at a low level using two digits coding for HLA-A, HLA-B, and HLA-DRB1. Some of these data may be appreciated on the REDOME official website, https://redome.inca.gov.br/institucional/dados/. Data from other countries came from the AFND available at http://www.allelefrequencies.net/.
- This paper does not report any original code. Additional information regarding all the data reported may be provided by the corresponding authors upon request. All calculations were made using R version 4.3.1 (Beagle Scouts).

Processing Brazilian data

In order to answer the questions about the actual coverage of our bank in the Brazilian population and the number of people that would be necessary to build the bank given the HLA profile, we used two different approaches. The first contemplated the existence of our bone marrow databank (REDOME), wherein the donors are known, as well as the frequency of genotypes. Therefore, we can infer its coverage by counting possible donors in ascending order of frequency, not considering it as a random draw.

The second approach is solely based on the genotype profile of the population, with no information whatsoever regarding the donors. The second approach is solely based on the genotype profile of the population, with no information whatsoever regarding the donors. To determine how many people we would need to test and the number of different phenotypes covered by this tested population, we built a statistical model as if two draws were realized, one for the recipient and the other for the donor.

Thus, the probability that a recipient randomly sorted possesses a given genotype i is designated pR_i and is retrieved from the frequency of that specific genotype. On the other hand, the probability that a donor will match the genotype i is designated pD_i.

For any recipient, the non-match complementary event (all donors have a type different of the recipient i) has a probability $(1 - pD_i)$. We shall suppose now a sorting of N randomly chosen donors. The probability of a non-match event is the joint probability of each event: $(1 - pD_i)^N$. Therefore, the probability of finding at least one match is given by $1 - (1 - pD_i)^N$.

As the types of future recipients are not given when the registry is designed, we shall consider the expectation of these probabilities through M different genotypes, regarding the two draws, in a population with a total of N donors:

$$\pi = \sum_{i=1}^{M} pR_i \times \left[1 - (1 - pD_i)^N\right]$$

Since each recipient may receive cells from more than one donor, or, in other words, more than one genotype may provide a match for a given recipient, pD_i is a sum of probabilities, each of which represents the chance for appropriate match.

Let us designate the frequency of each donor genotype by pd_j. We will define that, for each recipient, there is a set of donor genotypes j in a way that the sum of the probabilities is represented as

$$pD_i = \sum_{j=1}^{S} pd_j$$

where S is the number of defined genotypes in the donor population.

Finally, connecting the two equations above, we have the expectation of finding at least one match:

$$\pi = \sum_{i=1}^{M} pR_i \times \left[1 - \left(1 - \sum_{j=1}^{S} pd_j\right)^N\right]$$

Now we may determine a value of N in a way that gives us the desired value of population coverage.

ACKNOWLEDGMENTS

We thank Professor Simon Richard Griffiths and Professor Carlos Tomei from the mathematics department at the Pontifical Catholic University of Rio de Janeiro. This work was funded by grants from the Department of Science and Technology of the Ministry of Health (DECIT-MS) and the National Research Council (CNPq) 443890/2018-8 and FAPERJ.

AUTHOR CONTRIBUTIONS

Writing – original draft, and formal analysis, M.L. Conceptualization, supervision, and writing – review & editing, A.C.C.C. Conceptualization, supervision, and writing – review & editing, L.V.P. Validation, B.R.T. Investigation, M.M.L. and E.J.M.S. Data curation, supervision, and writing – review & editing, L.C.P.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: May 20, 2022
Revised: August 31, 2023
Accepted: September 1, 2023
Published: September 28, 2023

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