REPORT

July 2022 to June 2023

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ABSTRACT

Since July 2022 our group has published 73 articles in peer-review journals. Most of the articles involved the collaboration of students and PIs from HUG-CELL. However, due to COVID-19 pandemic , a lot of effort was directed to Coronavirus studies that were undertaken in our center or in international collaborative Consortiums. On the other hand, other projects had to be slowed down and will be expanded in the next 2-3 years. Online activities included about 42 conferences, lectures and symposia which were presented by our team as well as Interviews to the Media and Science Dissemination Articles.

We published some of our research in high-impact journals such as Nature communication (IF=14.919) and Molecular Psychiatry (IF=15.992).

The applications of technology transfer included genetic counseling for about 1,171 families. Despite the difficulties imposed by the coronavirus pandemic, in the last year, a total of 14.000 genetic tests and about 400 NGS sequencing run services were performed at HUG-CELL EMU, as detailed in the report. We also deposited two international patents and established a new International patternship (Sophia Genetics).

The Center assisted 47 schools in the Laboratory in Schools project and trained 103 trained teachers to work on it; 33.000 students were benefited. Forty-two teachers were trained in the use of didactic materials. The Giant Cell was visited by 2,5 thousand people. The Center offered a 7-hour mini-course on Gene Therapy to journalists specializing in science communication from different states in Brazil, sponsored by Pfizer. On YouTube the scientific dissemination team idealized and produced 57 videos that addressed different subjects. On Instagram, 55 feed posts, 63 videos and 505 Stories were produced. The YouTube channel had 142,000 views, 6,500 hours assisted and 2.6 thousand new subscribers.

CONTENTS

PART 1- RESEARCH

Our main research results from **July 2022 to June 2023**, classified by our main objectives are:

A. Gene Identification and Mechanisms in Genetic Disorders

A1. Identification of new human genes in Mendelian and complex disorders.

A1.1. Mendelian Disorders

Genetic etiology of Mendelian syndromic obesity: Syndromic obesity (SO) refers to obesity with additional phenotypes, including intellectual disability (ID)/developmental delay (DD), dysmorphic features, or organ-specific abnormalities. SO is rare, has high phenotypic variability, and frequently follows a monogenic pattern of inheritance. However, the genetic etiology of most cases of SO has not been elucidated. In this study, we investigated 20 SO patients by whole-exome sequencing (WES) trios to identify causal genetic variants. Results: 4/20 patients had negative results for array comparative genomic hybridization (aCGH) analyses. In the remaining 15 patients, in addition to SNVs and indels, CNVs were also evaluated. Pathogenic/likely pathogenic (P/LP) SNVs/indels were detected in 6/20 patients (involving *MED13L, AHDC1, EHMT1, MYT1L, GRIA3, and SETD1A*), while two patients carried an inherited VUS. In addition, P/LP CNVs were observed in 3/15 patients (involving *SATG2*, *KIAA0442*, and *MEIS2*). All nine detected P/LP variants involved genes already known to lead to syndromic ID/DD; however, for only two genes (*EHMT1* and *MYT1L*) is the link with obesity well established. This is the first study applying a comprehensive genomic investigation of an SO cohort, showing a high diagnostic yield (~47%). Additionally, our findings suggested that several known ID/DD genes may also predispose individuals to SO.

One of the genes identified in this study is under functional analysis: Xia-Gibbs syndrome (XGS) is a syndromic form of intellectual disability caused by heterozygous *AHDC1* variants, but the pathophysiological mechanisms underlying this syndrome are still unclear. We developed two different functional models: three induced pluripotent stem cell (iPSC) lines with different loss-of-function (LoF) AHDC1 variants, derived by reprogramming peripheral blood mononuclear cells from XGS patients, and a zebrafish strain with a LoF variant in the ortholog gene (ahdc1) obtained through CRISPR/Cas9-mediated editing.

PIs: **Ana Krepischi**, Carla Rosenberg, Célia Koiffmann and Maria Rita Passos-Bueno
Phd student: Laura Machado Lara Carvalho
Publications: 1.*Genetic investigation of syndromic forms of obesity*
Carvalho LML, D'Angelo CS, Villela D, da Costa SS, de Lima Jorge AA, da Silva IT, de Oliveira Scliar M, Chaves LD, **Krepischi ACV**, Koiffmann CP, Rosenberg C. Int J Obes (Lond). 2022 Sep;46(9):1582-1586. doi: 10.1038/s41366-022-01149-5
doi : 10.1038/s41366-022-01149-5

2.*Establishment of iPSC lines and zebrafish with loss-of-function AHDC1 variants: Models for Xia-Gibbs syndrome.* Carvalho LML, Branco EV, Sarafian RD, Kobayashi GS, de Araújo FT, Santos Souza L, Moreira DP, Hsia GSP, Bertollo EMG, Buck CB, da Costa SS, Fialho DM, de Vasconcelos FTGR, Brito LA, de Souza Fraga Machado LE, Ramos IC, Pereira LDV, Koiffmann CP, Passos-Bueno MR, Oliveira Mendes TA, **Krepischi ACV**, Rosenberg C**.** Gene. 2023 Jun 30;871:147424. doi: 10.1016/j.gene.2023.147424

Novel breast cancer predisposing candidate genes identified in Brazilian families with hereditary breast cancer. It is estimated that 5 to 10% of breast cancer (BC) cases present strong hereditary components. Currently, patients with BC in hereditary breast cancer (HBC) syndrome families are frequently tested for germline mutations in the *BRCA1* and *BRCA2.* However, the pathogenic variants in these genes are identified in only 20% of all HBC cases, 8% of germline mutations are identified in a few other cancer predisposing genes, while most remain without a determined genetic etiology.
We identified 24 variants in 24 novel candidate genes that completely segregate with the BC in one of the 8 families studied.
Our findings contribute to characterizing the genetic background of HBC by presenting novel candidate genes for BC predisposition. The results of this study have great potential for informed clinical management by including novel predisposing genes in genetic tests offered to patients and their families.

PI: **Oswaldo Keith Okamoto** and **Ana Krepischi**
Publication: G Bandeira, K Rocha, M Lazar, S Ezquina, G Yamamoto, T Gollop, M Zatz, M Passos-Bueno, **A Krepischi**, **O Keith Okamoto**. Novel breast cancer predisposing candidate genes identified in Brazilian families with hereditary breast cancer. European Journal of Cancer, November, 2022https://doi.org/10.1016/S0959-8049(22)01455-1

Skewed X-chromosome Inactivation in Women with Idiopathic Intellectual Disability is Indicative of Pathogenic Variants: Intellectual disability (ID) is an early onset impairment in cognitive functioning and adaptive behavior, affecting approximately 1% of the population worldwide. Extreme skewing of X-chromosome inactivation (XCI) can be associated with ID phenotypes caused by pathogenic variants in the X chromosome. We analyzed the XCI pattern in blood samples of 194 women with idiopathic ID, using the androgen receptor gene (AR) methylation assay. Among the 136 patients who were informative, 11 (8%) presented with extreme or total XCI skewing (≥ 90%), which was significantly higher than expected by chance. Whole-exome data obtained from these 11 patients revealed the presence of dominant pathogenic variants in eight of them, all sporadic cases, resulting in a molecular diagnostic rate of 73% (8/11 patients). All variants were mapped to ID-related genes with dominant phenotypes: four variants in the X-linked genes DDX3X (an XCI escape gene; two cases), WDR45, and PDHA1, and four variants in the autosomal genes *KCNB1, CTNNB1, YY1,* and *ANKRD11*. Three of the autosomal genes had no obvious correlation with the observed XCI skewing. However, *YY1* is a known transcriptional repressor that acts in the binding of the XIST long noncoding RNA on the inactive X chromosome, providing a mechanistic link between the pathogenic variant and the detected skewed XCI in the carrier. These data confirm that extreme XCI skewing in females with ID is highly indicative of causative X-linked pathogenic variants, and point to the possibility of identifying causative variants in autosomal genes with a XCI role.

PIs: **Ana Krepischi,** Carla Rosenberg
PhD student: Laura Machado Lara Carvalho, Giovanna Tolezano
Master student: Luiza Chaves
Publications: Chaves LD, Carvalho LML, Tolezano GC, Pires SF, Costa SS, de Scliar MO, Giuliani LR, Bertola DR, Santos-Rebouças CB, Seo GH, Otto PA, Rosenberg C, Vianna-Morgante AM, Krepischi ACV. Mol Neurobiol. 2023 Jul;60(7):3758-3769
doi: 10.1007/s12035-023-03311-0

Biallelic variants in *DNA2* cause poikiloderma with congenital cataracts and severe growth failure reminiscent of Rothmund-Thomson syndrome: Monogenic disorders constitute a large group of diseases caused by one heterozygous variant or biallelic variants, depending of the pattern of inheritance, of great impact. Although in the last two decades, new sequencing technologies have contributed to uncover variants in several genes responsible for these phenotypes, limitations of these techniques could hamper the identification of the genetic defect in some of these disorders.

A group of individuals presenting a phenotype resembling Rothmund-Thomson syndrome, but not harboring variants in genes already known to be associated with this disorder (*RECQL4* and

ANAPC1), has been evaluated in our Center. Different genetic approaches have been applied to identified a novel gene (*DNA2*) associated with this phenotype.

PI: **Debora Bertola**
PhD Student: Ricardo Di Iazzaro Filho
Publication: *Biallelic variants in DNA2 cause poikiloderma with congenital cataracts and severe growth failure reminiscent of Rothmund-Thomson syndrome*. Di Lazzaro Filho R, Yamamoto GL, Silva TJ, Rocha LA, Linnenkamp BDW, Castro MAA, Bartholdi D, Schaller A, Leeb T, Kelmann S, Utagawa CY, Steiner CE, Steinmetz L, Honjo RS, Kim CA, Wang L, Abourjaili-Bilodeau R, Campeau PM, Warman M, Passos-Bueno MR, Hoch NC, **Bertola DR.** J Med Genet. 2023 Apr 13:jmg-2022-109119. doi: 10.1136/jmg-2022-109119

POLR1A variants underlie phenotypic heterogeneity in craniofacial, neural, and cardiac anomalies: The small number of individuals described with novel phenotypes hampers the complete phenotypic spectrum of these disorders. In order to contribute in these fields in rare skeletal disorders, collaborative studies have been done including individuals previously evaluated in our Center.

PI: **Debora Bertola**
Publications: 1-*POLR1A variants underlie phenotypic heterogeneity in craniofacial, neural, and cardiac anomalies*. Smallwood K, Watt KEN, Ide S, Baltrunaite K, Brunswick C, Inskeep K, Capannari C, Adam MP, Begtrup A, **Bertola DR**, Demmer L, Demo E, Devinsky O, Gallagher ER, Guillen Sacoto MJ, Jech R, Keren B, Kussmann J, Ladda R, Lansdon LA, Lunke S, Mardy A, McWalters K, Person R, Raiti L, Saitoh N, Saunders CJ, Schnur R, Skorvanek M, Sell SL, Slavotinek A, Sullivan BR, Stark Z, Symonds JD, Wenger T, Weber S, Whalen S, White SM, Winkelmann J, Zech M, Zeidler S, Maeshima K, Stottmann RW, Trainor PA, Weaver KN. Am J Hum Genet. 2023 May 4;110(5):809-825. doi: 10.1016/j.ajhg.2023.03.014.

2-Developmental genomics of limb malformations: Allelic series in association with gene dosage effects contribute to the clinical variability. Duan R, Hijazi H, Gulec EY, Eker HK, Costa SR, Sahin Y, Ocak Z, Isikay S, Ozalp O, Bozdogan S, Aslan H, Elcioglu N, **Bertola DR**, Gezdirici A, Du H, Fatih JM, Grochowski CM, Akay G; Baylor-Hopkins Center for Mendelian Genomics; Jhangiani SN, Karaca E, Gu S, Coban-Akdemir Z, Posey JE, Bayram Y, Sutton VR, Carvalho CMB, Pehlivan D, Gibbs RA, Lupski JR. HGG Adv. 2022 Aug 4;3(4):100132. doi: 10.1016/j.xhgg.2022.100132. eCollection 2022 Oct 13.

3-*Phenotypic and mutational spectrum of ROR2-related Robinow syndrome.* Lima AR,

Ferreira BM, Zhang C, Jolly A, Du H, White JJ, Dawood M, Lins TC, Chiabai MA, van Beusekom E, Cordoba MS, Caldas Rosa ECC, Kayserili H, Kimonis V, Wu E, Mellado C, Aggarwal V, Richieri-Costa A, Brunoni D, Canó TM, Jorge AAL, Kim CA, Honjo R, **Bertola DR**, Dandalo-Girardi RM, Bayram Y, Gezdirici A, Yilmaz-Gulec E, Gumus E, Yilmaz GC, Okamoto N, Ohashi H, Coban-Akdemir Z, Mitani T, Jhangiani SN, Muzny DM, Regattieri NAP, Pogue R, Pereira RW, Otto PA, Gibbs RA, Ali BR, van Bokhoven H, Brunner HG, Sutton VR, Lupski JR, Vianna-Morgante AM, Carvalho CMB, Mazzeu JF. Hum Mutat. 2022 Jul;43(7):900-918. doi: 10.1002/humu.24375. Epub 2022 May 10.

A1.2. Complex disorders

Challenges in molecular diagnosis of admixed individuals: The inference of genetic ancestry plays an increasingly prominent role in clinical, population, and forensic genetics studies. Several genotyping strategies and analytical methodologies have been developed over the last few decades to assign individuals to specific biogeographic regions. However, despite these efforts, ancestry inference in populations with a recent history of admixture, such as those in Brazil, remains a challenge. In admixed populations, proportion and components of genetic ancestry vary on different levels: (i) between populations; (ii) between individuals of the same population, and (iii) throughout the individual's genome. The present study evaluated 1171 admixed Brazilian samples to compare the genetic ancestry inferred by tri-/tetra-hybrid admixture models and evaluated different marker sets from those with small numbers of ancestry informative markers panels (AIMs), to high-density SNPs (HDSNP) and whole-genome-sequence (WGS) data. Analyses revealed greater variation in the correlation coefficient of ancestry components within and between admixed populations, especially for minority ancestral components. We also observed positive correlation between the number of markers in the AIMs panel and HDSNP/WGS. Furthermore, the greater the number of markers, the more accurate the tri-/tetra-hybrid admixture models. This study involved several members from HUGH-CEL

PIs: **Michel S. Naslavsky** and **Mayana Zatz**
Publications: *Challenges in selecting admixture models and marker sets to infer genetic ancestry in a Brazilian admixed population*. Escher LM, **Naslavsky MS**, Scliar MO, Duarte YAO, **Zatz M**, Nunes K, Oliveira SF. Sci Rep. 2022 Dec 8;12(1):21240. doi: 10.1038/s41598-022-25521-7.

Three generation families: analysis of de novo variants in autism: De novo variants (DNVs) analysis has proven to be a powerful approach to gene discovery in Autism Spectrum Disorder (ASD), which has not yet been shown in a Brazilian ASD cohort. The relevance of inherited rare variants has also been suggested, particularly in oligogenic models. We hypothesized that three-generation analyses of DNVs could provide new insights into the relevance of de novo and inherited variants across generations. To accomplish this goal, we performed whole-exome sequencing of 33 septet families composed of probands, parents, and grandparents (n= 231 individuals) and compared DNV rates (DNVr) between generations and those from two control cohorts. The DNVr in the probands (DNVr = 1.16) was marginally higher than in parents (DNVr = 0.60; p = 0.054), and in controls (DNVr = 0.68; p= 0.035, congenital heart disorder and DNVr = 0.70; p = 0.047, unaffected ASD siblings from Simons Simplex Collection). Moreover, most of the DNVs were found to have paternal origin in both generations (84.6%). Finally, we observed that 40% (6/15) of the DNVs in parents transmitted for probands are in ASD or ASD candidate genes, representing recently emerged risk variants to ASD in their families and suggest *ZNF536*, *MSL2* and *HDAC9* as ASD candidate genes. We did not observe an enrichment of risk variants nor sex bias of transmitted variants in the three generations, that can be due to sample size. These results further reinforce the relevance of de novo variants in ASD.

PI: **Maria Rita Passos-Bueno**
Students: Claudia I Samogy Costa and Gabriele da Silva Campos
Publications: *Three generation families: analysis of de novo variants in autism***.** Costa CIS , Campos GS , Montenegro EMS, Wang JIT , Marília Scliar, Frederico Monfardini , Elaine Cristina Zachi, Naila C. V. Lourenço, Ada J S Chan , Sergio L Pereira , Worrawat Engchuan , Bhooma Thiruvahindrapuram , Mehdi Zarrei , Stephen W Scherer, **Passos-Bueno MR**. European Journal of Human Genetics. 2023. https://doi.org/10.1038/s41431-023-01398-6

Rare coding variation provides insight into the genetic architecture and phenotypic context of autism: Some individuals with autism spectrum disorder (ASD) carry functional mutations rarely observed in the general population. We explored the genes disrupted by these variants from joint analysis of protein-truncating variants (PTVs), missense variants and copy number variants (CNVs) in a cohort of 63,237 individuals. We discovered 72 genes associated with ASD at false discovery rate (FDR) ≤ 0.001 (185 at FDR ≤ 0.05). De novo PTVs, damaging missense variants and CNVs represented 57.5%, 21.1% and 8.44% of association evidence, while CNVs conferred greatest relative risk. Meta-analysis with cohorts ascertained for developmental delay (DD) (n = 91,605) yielded 373 genes associated with ASD/DD at FDR ≤ 0.001 (664 at FDR ≤ 0.05), some of which differed in relative frequency of mutation between ASD and DD cohorts. The DD-associated genes were enriched in transcriptomes of progenitor

and immature neuronal cells, whereas genes showing stronger evidence in ASD were more enriched in maturing neurons and overlapped with schizophrenia-associated genes, emphasizing that these neuropsychiatric disorders may share common pathways to risk.

PI: **Maria Rita Passos-Bueno**
PhD Students: Claudia I Samogy Costa, Gabriele da Silva Campos and Ana Cristina Girardi
Autism Sequencing Consortium (ASC); Broad Institute Center for Common Disease Genomics (Broad-CCDG); iPSYCH-BROAD Consortium;
Publication: *Rare coding variation provides insight into the genetic architecture and phenotypic context of autism*. Fu JM, Satterstrom FK, Peng M, Brand H, Collins RL, Dong S, Wamsley B, Klei L, Wang L, Hao SP, Stevens CR, Cusick C, Babadi M, Banks E, Collins B, Dodge S, Gabriel SB, Gauthier L, Lee SK, Liang L, Ljungdahl A, Mahjani B, Sloofman L, Smirnov AN, Barbosa M, Betancur C, Brusco A, Chung BHY, Cook EH, Cuccaro ML, Domenici E, Ferrero GB, Gargus JJ, Herman GE, Hertz-Picciotto I, Maciel P, Manoach DS, **Passos-Bueno MR**, Persico AM, Renieri A, Sutcliffe JS, Tassone F, Trabetti E, Campos G, Cardaropoli S, Carli D, Chan MCY, Fallerini C, Giorgio E, Girardi AC, Hansen-Kiss E, Lee SL, Lintas C, Ludena Y, Nguyen R, Pavinato L, Pericak-Vance M, Pessah IN, Schmidt RJ, Smith M, Costa CIS, Trajkova S, Wang JYT, Yu MHC; Autism Sequencing Consortium (ASC); Broad Institute Center for Common Disease Genomics (Broad-CCDG); iPSYCH-BROAD Consortium; Cutler DJ, De Rubeis S, Buxbaum JD, Daly MJ, Devlin B, Roeder K, Sanders SJ, Talkowski ME. Nat Genet. 2022 Sep;54(9):1320-1331. doi: 10.1038/s41588-022-01104-0. Epub 2022 Aug 18. PMID: 35982160.

HLA- worldwide Genetic diversity: *HLA-B* is among the most variable gene in the human genome. This gene encodes a key molecule for antigen presentation to CD8+ T lymphocytes and NK cell modulation. Despite the myriad of studies evaluating its coding region (with an emphasis on exons 2 and 3), few studies evaluated introns and regulatory sequences in real population samples. Thus, *HLA-B* variability is probably underestimated. We applied a bioinformatics pipeline tailored for HLA genes on 5347 samples from 80 different populations, which includes more than 1000 admixed Brazilians, to evaluate the *HLA-B* variability (SNPs, indels, MNPs, alleles, and haplotypes) in exons, introns, and regulatory regions. We observed 610 variable sites throughout *HLA-B;* the most frequent variants are shared worldwide. However, the haplotype distribution is geographically structured. We detected 920 full-length haplotypes (exons, introns, and untranslated regions) encoding 239 different protein sequences. *HLA-B* gene diversity is higher in admixed populations and Europeans while lower in African ancestry individuals. Each *HLA-B* allele group is associated with specific promoter sequences. This *HLA-B* variation resource may improve HLA imputation

accuracy and disease-association studies and provide evolutionary insights regarding *HLA-B* genetic diversity in human populations.

PIs: **Michel Naslavsky** and **Mayana Zatz**
This study is a collaboration between the group of Prof. Erick Castelli and our group.
Publications: 1- *HLA-G genetic diversity and evolutive aspects in worldwide populations*. Erick C Castelli, et.al.. Scientific Reports volume 11, Article number: 23070 (2021).

2- *Immunogenetics of HLA-B: SNP, allele, and haplotype diversity in populations from different continents and ancestry backgrounds*. Nayane dos Santos Brito Silva, Andreia da Silva Souza, Heloisa de Souza Andrade, Raphaela Neto Pereira, Camila Ferreira Bannwart Castro, Nicolas Vince, Sophie Limou, **Michel Satya Naslavsky, Mayana Zatz**, Yeda Aparecida de Oliveira Duarte, Celso Teixeira Mendes-Junior, Erick da Cruz Castelli. HLA 2023 02 April 2023 https://doi.org/10.1111/tan.15043

DNA methylation patterns suggest the involvement of *DNMT3B* and *TET1* in osteosarcoma development: DNA methylation may be involved in the development of osteosarcomas. Osteosarcomas commonly arise during the bone growth and remodeling in puberty, making it plausible to infer the involvement of epigenetic alterations in their development. As a highly studied epigenetic mechanism, we investigated DNA methylation and related genetic variants in 28 primary osteosarcomas aiming to identify deregulated driver alterations. Aberrant DNA methylation was spread throughout the osteosarcomas genomes. We identified 3146 differentially methylated CpGs comparing osteosarcomas and bone tissue samples, with high methylation heterogeneity, global hypomethylation and focal hypermethylation at CpG islands. Differentially methylated regions (DMR) were detected in 585 loci (319 hypomethylated and 266 hypermethylated), mapped to the promoter regions of 350 genes. These DMR genes were enriched for biological processes related to skeletal system morphogenesis, proliferation, inflammatory response, and signal transduction. Both methylation and expression data were validated in independent groups of cases. Six tumor suppressor genes harbored deletions or promoter hypermethylation (DLEC1, GJB2, HIC1, MIR149, PAX6, and WNT5A), and four oncogenes presented gains or hypomethylation (ASPSCR1, NOTCH4, PRDM16, and RUNX3). Our analysis also revealed hypomethylation at 6p22, a region that contains several histone genes. Copy-number changes in DNMT3B (gain) and TET1 (loss), as well as overexpression of DNMT3B in osteosarcomas provide a possible explanation for the observed phenotype of CpG island hypermethylation. While the detected open-sea hypomethylation likely contributes to the well-known osteosarcoma genomic instability, enriched CpG island hypermethylation suggests an underlying mechanism possibly driven by overexpression of DNMT3B likely resulting in silencing of tumor suppressors and DNA repair genes.

PI: **Ana Krepischi**
PhD student: Sara Pires
Publication: *DNA methylation patterns suggest the involvement of DNMT3B and TET1 in osteosarcoma development*. Pires SF, de Barros JS, da Costa SS, de Oliveira Scliar M, Van Helvoort Lengert A, Boldrini É, da Silva SRM, Tasic L, Vidal DO, **Krepischi ACV**, Maschietto M. Mol Genet Genomics. 2023 May;298(3):721-733. doi: 10.1007/s00438-023-02010-*8*

High-Resolution Magic-Angle-Spinning NMR in Revealing Hepatoblastoma Hallmarks: Cancer is one of the leading causes of death in children and adolescents worldwide; among the types of liver cancer, hepatoblastoma (HBL) is the most common in childhood. Although it affects only two to three individuals in a million, it is mostly asymptomatic at diagnosis, so by the time it is detected it has already advanced. There are specific recommendations regarding HBL treatment, and ongoing studies to stratify the risks of HBL, understand the pathology, and predict prognostics and survival rates. Although magnetic resonance imaging spectroscopy is frequently used in diagnostics of HBL, high-resolution magic-angle-spinning (HR-MAS) NMR spectroscopy of HBL tissues is scarce. Using this technique, we studied the alterations among tissue metabolites of ex vivo samples from (a) HBL and non-cancer liver tissues (NCL), (b) HBL and adjacent non-tumor samples, and (c) two regions of the same HBL samples, one more centralized and the other at the edge of the tumor. It was possible to identify metabolites in HBL, then metabolites from the HBL center and the border samples, and link them to altered metabolisms in tumor tissues, highlighting their potential as biochemical markers. Metabolites closely related to liver metabolisms such as some phospholipids, triacylglycerides, fatty acids, glucose, and amino acids showed differences between the tissues.

PI: **Ana Krepischi**
PhD student: Maria Prates Rivas; Pos-doc: Talita Aguiar
Publication: *High-Resolution Magic-Angle-Spinning NMR in Revealing Hepatoblastoma Hallmarks*.Tasic L, Avramović N, Jadranin M, Quintero M, Stanisic D, Martins LG, Costa TBBC, Novak E, Odone V, Rivas M, Aguiar T, Carraro DM, Werneck da Cunha I, Lima da Costa CM, Maschietto M, **Krepischi AC.** Biomedicines. 2022 Dec 1;10(12):3091. doi: 10.3390/biomedicines10123091

The largest Latin America Genomic databank of Brazilian elderly admixed individuals: Since 2010, a joint effort between HUG-CELL and USP Public Health School SABE follow-up cohort (Health, Well-being and Aging) led to the largest Brazilian census-based DNA collection with whole-genome sequencing data. The whole-genome sequencing of three SABE cohorts

(n=1,171) identified over 65 million variants (2 million absent elsewhere), novel HLA haplotypes and mobile element insertions, 65Mb genomic regions absent in genome reference, improved imputation of admixed individuals. SABE genomic data contributed for testing breast cancer polygenic risk scores, HLA haplotypes and selection of methods for admixture analyses. In addition, variant occurrence and frequency were associated with familial hypercholesterolemia, and variant consequences in protein folding were explored. SABE genomic dataset allowed for a comprehensive description of pharmacogenomic variants in a Brazilian population, leading to insights into population-specific effect sizes in potentially clinical variants. Technical procedures in epigenetic calls were discussed using two time-points collected across SABE subjects. Access to the post-mortem neuropathological cohort of the BioBank for Aging Studies allowed analyses of ancestry effects on neuropathology, including a differential effect of *APOE* variants on Alzheimer's disease.

PIs: **Michel Naslavsky** and **Mayana Zatz**
Publication: *Whole-genome sequencing of 1,171 elderly admixed individuals from Brazil*. **Naslavsky MS**, Scliar MO, Yamamoto GL, Wang JYT, Zverinova S, Karp T, Nunes K, Ceroni JRM, de Carvalho DL, da Silva Simões CE, Bozoklian D, Nonaka R, Dos Santos Brito Silva N, da Silva Souza A, de Souza Andrade H, Passos MRS, Castro CFB, Mendes-Junior CT, Mercuri RLV, Miller TLA, Buzzo JL, Rego FO, Araújo NM, Magalhães WCS, Mingroni-Netto RC, Borda V, Guio H, Rojas CP, Sanchez C, Caceres O, Dean M, Barreto ML, Lima-Costa MF, Horta BL, Tarazona-Santos E, Meyer D, Galante PAF, Guryev V, Castelli EC, Duarte YAO, Passos-Bueno MR, **Zatz M.**. Nat Commun. 2022 Mar 4;13(1):1004. doi: 10.1038/s41467-022-28648-3

A2. Elucidation of mechanisms to explain phenotype, clinical variability, and non-penetrance in genetic disorders

A2.1. Neuromuscular disorders

Nemaline Myopathy in Brazilian Patients: Molecular and Clinical Characterization: Nemaline myopathy (NM), a structural congenital myopathy, presents a significant clinical and genetic heterogeneity. Here, we compiled molecular and clinical data of 30 Brazilian patients from 25 unrelated families. Next-generation sequencing was able to genetically classify all patients: sixteen families (64%) with mutation in *NEB*, five (20%) in *ACTA1*, two (8%) in *KLHL40*, and one in *TPM2* (4%) and *TPM3* (4%). In the *NEB*-related families, 25 different variants, 11 of them novel, were identified; splice site (10/25) and frameshift (9/25) mutations were the most common. Mutation c.24579 G>C was recurrent in three unrelated patients from

the same region, suggesting a common ancestor. Clinically, the “typical” form was the most frequent and caused by mutations in the different NM genes. Phenotypic heterogeneity was observed among patients with mutations in the same gene. Respiratory involvement was very common and often out of proportion with limb weakness. Muscle MRI patterns showed variability within the forms and genes, which was related to the severity of the weakness. Considering the high frequency of *NEB* mutations and the complexity of this gene, NGS tools should be combined with CNV identification, especially in patients with a likely non-identified second mutation.

PI: **Mariz Vainzof**
Publication: *Nemaline Myopathy in Brazilian Patients: Molecular and Clinical Characterization*. Gurgel-Giannetti J, Souza LS, Yamamoto GL, Belisario M, Lazar M, Campos W, Pavanello RCM, Zatz M, Reed U, Zanoteli E, Oliveira AB, Lehtokari VL, Casella EB, Machado-Costa MC, Wallgren-Pettersson C, Laing NG, Nigro V, **Vainzof M.** Int J Mol Sci. 2022 Oct 9;23(19):11995. doi: 10.3390/ijms231911995.PMID: 36233295

Malignant hyperthermia phenotype-genotype correlations: In a long term collaboration with Dr. Helga C. Almeida Silva, from the Federal University of SP, we have been studying several aspects in families with malignant hyperthermia susceptibility. A new international collaborative study, " Functional consequences of *RYR1* mutations on the human immune system".was established with Prof. Susan Treves of the Department of Biomedicine, Basel University Hospital.

PI: **Mariz Vainzof** and geneticist responsible for the MH group.
Collaboration with Dr. Helga Cristina Almeida da Silva, Malignant Hyperthermia Unit - Discipline of Anesthesiology, Pain and Intensive Care - Federal University of Sao Paulo

Predictive factors of the contracture test for diagnosing malignant hyperthermia in a Brazilian population sample: a retrospective observational study: Malignant Hyperthermia (MH) is a pharmacogenetic, hereditary and autosomal dominant syndrome triggered by halogenates/succinylcholine. The In Vitro Contracture Test (IVCT) is the gold standard diagnostic test for MH, and it evaluates abnormal skeletal muscle reactions of susceptible individuals (earlier/greater contracture) when exposed to caffeine/halothane. To assess variables that correlate with IVCT in Brazilian patients referred for MH investigation due to a history of personal/family MH, we examined IVCTs of 80 patients investigated for MH between 2004–2019. The mean age of the sample was 35±13.3 years, and most of the

subjects were female (43% or 54%) and MH susceptible (60%). Of the 20 subjects undergoing genetic investigation, 65% showed variants in *RYR1/CACNA1S* genes. We found no difference between the positive and negative IVCT groups regarding age, sex, number of probands, presence of muscle weakness or myopathy with muscle biopsy showing cores. Regression analysis revealed that the best predictors of positive IVCT were male sex (+12%), absence of muscle weakness (+20%), and personal MH background (+17%). Positive IVCT results have been correlated to male probands in early publications. Furthermore, normal muscle strength has been confirmed as a significant predictor of positive IVCT while investigating suspected MH cases.

PI: **Mariz Vainzof**
Publication: *Predictive factors of the contracture test for diagnosing malignant hyperthermia in a Brazilian population sample: a retrospective observational study*. de Mello JM, Andrade PV, Santos JM, Oliveira ASB, **Vainzof M**, do Amaral JLG, Almeida da Silva HC. Braz. J Anesthesiol. 2023 Mar-Apr;73(2):145-152. doi: 10.1016/j.bjane.2022.06.010. Epub 2022 Jul 11.PMID: 35835312

Rhabdomyosarcoma associated with core myopathy/malignant hyperthermia: combined effect of germline variants in *RYR1* and *ASPSCR1* may play a role?: Rhabdomyosarcomas have been described in association with thyroid disease, dermatomyositis, Duchenne muscular dystrophy, and in muscular dystrophy models but not in patients with ryanodine receptor-1 gene (*RYR1*) pathogenic variants. We described here an 18-year-old male who reported a cervical nodule. Magnetic resonance images revealed a mass in the ethmoidal sinus corresponding to rhabdomyosarcoma. As his father died from malignant hyperthermia (MH), *an in vitro* contracture test was done and it was positive for MH susceptibility. Muscle histopathological analysis in the biopsy showed the presence of cores. Molecular analysis using NGS sequencing identified germline variants in the *RYR1* and *ASPSCR1* genes. This report expands the spectrum of diseases associated with rhabdomyosarcomas and a possible differential diagnosis of soft tissue tumors in patients with *RYR1* variants.

PI: **Mariz Vainzof** and **Ana Krepischi**
Posdoc: Anne C.B.Teixeira
Publication: *Rhabdomyosarcoma associated with core myopathy/malignant hyperthermia: combined effect of germline variants in RYR1 and ASPSCR1 may play a role?* Pamela V. Andrade, Joilson M. Santos, Anne C.B. Teixeira, Vanessa F. Sogari, Michelle S. Almeida, Fabiano M. Callegari, **Ana C.V. Krepischi**, Acary S.B. Oliveira, **Mariz Vainzof**, Helga C.A. Silva. Manuscript in revision, Genes, 2023

A2.2.Structural Variation in Genetic Disorders

Burden of rare copy number variants in head size: study of Brazilian patients and mining databases: Abnormal head size presents heterogeneous genetic etiology linked to several neurodevelopmental disorders (NDD). Copy number variants (CNVs) are a causal mechanism of disease whose investigation is a crucial step for unraveling the molecular basis of any genetic condition. Our first purpose was to investigate the burden of rare CNVs in microcephalic individuals and to review genes and CNV syndromes associated with microcephaly (doi: 10.1007/s10803-022-05853-z.). We performed chromosomal microarray analysis (CMA) in 185 Brazilian patients with microcephaly and evaluated microcephalic patients carrying < 200 kb CNVs documented in the DECIPHER database. Additionally, we reviewed known genes and CNV syndromes causally linked to microcephaly through the PubMed, OMIM, DECIPHER, and ClinGen databases. Rare clinically relevant CNVs were detected in 39 out of the 185 Brazilian patients investigated by CMA (21%). In 31 among the 60 DECIPHER patients carrying < 200 kb CNVs, at least one known microcephaly gene was observed. Overall, four gene sets implicated in microcephaly were disclosed: known microcephaly genes; genes with supporting evidence of association with microcephaly; known macrocephaly genes; and novel candidates, including *OTUD7A*, *BBC3*, *CNTN6*, and *NAA15*. In the review, we compiled 957 known microcephaly genes and 58 genomic CNV loci, comprising 13 duplications and 50 deletions, which have already been associated with clinical findings including microcephaly. We reviewed genes and CNV syndromes previously associated with microcephaly, reinforced the high CMA diagnostic yield for this condition, pinpointed novel candidate loci linked to microcephaly deserving further evaluation, and provided a useful resource for future research on the field of neurodevelopment. On the other hand, macrocephaly frequently occurs in single-gene disorders affecting the PI3K-AKT-MTOR pathway; however, epigenetic mutations, mosaicism, and CNVs are emerging relevant causative factors, revealing a higher genetic heterogeneity than previously expected. The aim of this second study was to investigate the role of rare CNVs in patients with macrocephaly and review genomic loci and known genes (10.3390/genes13122285). We retrieved from the DECIPHER database de novo <500 kb CNVs reported on patients with macrocephaly; in four cases, a candidate gene for macrocephaly could be pinpointed: a known microcephaly gene-*TRAPPC9*, and three genes based on their functional roles-*RALGAPB*, *RBMS3*, and *ZDHHC14*. From the literature review, 28 pathogenic CNV genomic loci and over 300 known genes linked to macrocephaly were gathered. Among the genomic regions, 17 CNV loci (~61%) exhibited mirror phenotypes, that is, deletions and duplications having opposite effects on head size. Identifying structural variants affecting head size can be a preeminent source of information about pathways underlying brain development. In this study, we reviewed these genes and recurrent CNV loci associated with macrocephaly, as well as suggested novel potential candidate genes deserving further studies to endorse their involvement with this phenotype.

PIs: **Ana Krepischi**, **Carla Rosenberg**, **Debora Bertola**, **Maria Rita Passos-Bueno**
PhD student: Giovanna Tolezano; IC student: Giovanna Civitate
Publications: 1- *Burden of Rare Copy Number Variants in Microcephaly: A Brazilian Cohort of 185 Microcephalic Patients and Review of the Literature*. Tolezano GC, Bastos GC, da Costa SS, Freire BL, Homma TK, Honjo RS, Yamamoto GL, **Passos-Bueno MR,** Koiffmann CP, Kim CA, Vianna-Morgante AM, de Lima Jorge AA, **Bertola DR**, **Rosenberg C**, **Krepischi ACV.** J Autism Dev Disord. 2022 Dec 11. doi: 10.1007/s10803-022-05853-z.

2- *Rare CNVs and Known Genes Linked to Macrocephaly: Review of Genomic Loci and Promising Candidate Genes*. Bastos GC, Tolezano GC, **Krepischi ACV**. Genes (Basel). 2022 Dec 4;13(12):2285. doi: 10.3390/genes13122285.

Chromosomal microarray analyses from 5778 patients with neurodevelopmental disorders and congenital anomalies in Brazil: Chromosomal microarray analysis (CMA) has been recommended and practiced routinely since 2010 both in the USA and Europe as the first-tier cytogenetic test for patients with unexplained neurodevelopmental delay/intellectual disability, autism spectrum disorders, and/or multiple congenital anomalies. However, in Brazil, the use of CMA is still limited, due to its high cost and complexity in integrating the results from both the private and public health systems. Although Brazil has one of the world's largest single-payer public healthcare systems, nearly all patients referred for CMA come from the private sector, resulting in only a small number of CMA studies in Brazilian cohorts. To date, this study is by far the largest Brazilian cohort (n = 5788) studied by CMA and is derived from a joint collaboration formed by the University of São Paulo and three private genetic diagnostic centers to investigate the genetic bases of neurodevelopmental disorders and congenital abnormalities. We identified 2,279 clinically relevant CNVs in 1886 patients, not including the 26 cases of UPD found. Among detected CNVs, the corresponding frequency of each category was 55.6% Pathogenic, 4.4% Likely Pathogenic and 40% VUS. The diagnostic yield, by taking into account Pathogenic, Likely Pathogenic and UPDs, was 19.7%. Since the rational for the classification is mostly based on Mendelian or highly penetrant variants, it was not surprising that a second event was detected in 26% of those cases of predisposition syndromes. Although it is common practice to investigate the inheritance of VUS in most laboratories around the world to determine the inheritance of the variant, our results indicate an extremely low cost-benefit of this approach, and strongly suggest that in cases of a limited budget, investigation of the parents of VUS carriers using CMA should not be prioritized.

PI: **Ana Krepischi; Carla Rosenberg; Debora Bertola** (former PI **Angela Morgante**)

Publications: *Chromosomal microarray analyses from 5778 patients with neurodevelopmental disorders and congenital anomalies in Brazil*. **Krepischi ACV**, Villela D, da Costa SS, Mazzonetto PC, Schauren J, Migliavacca MP, Milanezi F, Santos JG, Guida G, Guarischi-Sousa R, Campana G, Kok F, Schlesinger D, Kitajima JP, Campagnari F, **Bertola DR**, **Vianna-Morgante A**, Pearson PL, **Rosenberg C**. Sci Rep. 2022 Sep 7;12(1):15184. doi: 10.1038/s41598-022-19274-6.

A2.3. Neurodegeneration

Intracellular dynamics and protein aggregation in neurodegeneration: During the last year we evaluated the effects of *RHOT-1* gene deletion in a cellular model (the yeast *Saccharomyces cerevisiae*) of Parkinson's Disease. Alpha-synuclein aggregation is a hallmark of Parkinson's disease (PD). Mutants A30P and A53T alpha-synuclein exacerbate the toxicity of alpha-synuclein, which includes oxidative stress, mitochondrial and endoplasmic reticulum (ER) dysfunctions. In yeast, Gem1 (Miro/Rhot mammalian orthologue) coordinates mitochondrial dynamics and ER homeostasis, which is impaired in the presence of mutant alpha-synuclein and can lead to cell death. In this study, we demonstrated that deletion of Gem1 gene protects cells from A53T alpha-synuclein toxicity, reduced ER stress and increased ability to deal with oxidative stress. These results suggest that deletion of Gem1 activates pathways that strengthen cells against other stressful agents such as the presence of mutant alpha-synuclein. In other study we evaluated the therapeutic effects of vitamin D3 on the morphology and neurodegeneration of the olfactory bulb in the trisomic mice model of Alzheimer Disease (AD) and Down syndrome (DS) since olfactory dysfunction may be an early clinical symptom of AD. Recent studies have demonstrated that vitamin D3 exerts neuroprotective effects in mouse models of AD. Results demonstrated that trisomy 21 causes morphofunctional abnormalities in the olfactory bulb of control trisomic mice. Moreover, vitamin D3 could represent a therapeutic target to attenuate morphological and molecular alterations in olfactory bulb.

PI: **Merari de Fátima Ramires Ferrari**

Publications 1- *Absence of Gem1 (mammalian Miro/Rhot) mitigates alpha-synuclein toxicity in a yeast model of Parkinson's disease*. Melo TQ, Palma FR, Gomes F, Netto, LES. **Ferrari MFR.** Molecular And Cellular Neuroscience, doi: 10.1016/j.mcn.2022.103757

2-*Vitamin D3 supplementation may attenuate morphological and molecular abnormalities of the olfactory bulb in a mouse model of Down syndrome*. Gomes FC, Santos IBF, Stephani C M, **Ferrari MFR,** Galvis-Alonso O, Goloni-Bertollo EM, Melo-Neto JS, Pavarino EC.. Tissue & Cell, https://doi.org/10.1016/j.tice.2022.101898

Trying to understand clinical variability in amyotrophic lateral sclerosis: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that mainly affects the motor system. It is a very heterogeneous disorder, so far more than 40 genes have been described as responsible for ALS. The cause of motor neuron degeneration is not yet fully understood, but there is consensus in the literature that it is the result of a complex interplay of several pathogenic processes, which include alterations in nucleocytoplasmic transport, defects in transcription and splicing, altered formation and/or disassembly of stress granules and impaired proteostasis. These defects result in protein aggregation, impaired DNA repair, mitochondrial dysfunction and oxidative stress, neuroinflammation, impaired axonal transport, impaired vesicular transport, excitotoxicity, as well as impaired calcium influx. We argue here that all the above functions ultimately lead to defects in protein synthesis. Fused in Sarcoma (*FUS*) is one of the genes associated with ALS. It causes ALS type 6 when mutated and is found mislocalized to the cytoplasm in the motor neurons of sporadic ALS patients (without *FUS* mutations). In addition, FUS plays a role in all cellular functions that are impaired in degenerating motor neurons. Moreover, ALS patients with *FUS* mutations present the first symptoms significantly earlier than in other forms of the disease. Therefore, the aim of this review is to further discuss ALS6, detail the cellular functions of FUS, and suggest that the localization of FUS, as well as protein synthesis rates, could be hallmarks of the ALS phenotype and thus good therapeutic targets.

PI: **Mayana Zatz**
Posdoc Student: Amanda Assoni
Collaboration: Floris Foijer
Publication: Amyotrophic Lateral Sclerosis, FUS and Protein Synthesis Defects. Assoni AF, Foijer F, **Zatz M**. Stem Cell Rev Rep. 2023 Apr;19(3):625-638. doi: 10.1007/s12015-022-10489-8. Epub 2022 Dec 14

A2.4. The search for modifier variants

Protective variants in Duchenne muscular dystrophy: A form of dystrophinopathy with mild or subclinical neuromuscular signs has been previously reported in a family of Labrador retrievers. Markedly and persistently elevated creatine kinase activity was first noted at 6 months of age. Skeletal muscle biopsies revealed a dystrophic phenotype, with dystrophin non-detectable on western blotting and immunohistochemical staining, and with increased utrophin expression. In this report we demonstrate with Western blotting that α-dystroglycan is present at essentially normal levels. Whole genome sequencing has also now revealed an approximately 400kb tandem genomic DNA duplication including exons 2-7 of the *DMD* gene that was inserted into intron 7 of the wild type gene. Skeletal muscle cDNA from 2 cases contained *DMD* transcripts as expected from an in-frame properly-spliced exon 2-7 tandem

insertion. A similar 5' duplication involving *DMD* exons 2-7 has been reported in a human family with dilated cardiomyopathy but without skeletal myopathy. This is the 3rd confirmed mutation in the *DMD* gene in Labrador retrievers.

PI: **Mayana Zatz** and Diane Shelton
Collaboration: Louis Kunkel group and James R Mickelson group
Publication: *Tandem duplication within the DMD gene in Labrador retrievers with a mild clinical phenotype.* Shelton GD, Minor KM, Vieira NM, **Kunkel LM**, Friedenberg SG, Cullen JN, Guo LT, **Zatz M**, Mickelson JR.. Neuromuscul Disord. 2022 Oct;32(10):836-841. doi: 10.1016/j.nmd.2022.08.001. Epub 2022 Aug 6

A3. Epigenetics and diseases

How DNA damage and Genome Instability can be implicated in human disease?: Several DNA syndromes are related with deficiencies with DNA damage repair. This is the case of patients with xeroderma pigmentosum (XP), who have increased frequency of skin tumors. During this period, our work focused mainly on XP variant cells and patients, deficient in the translesion synthesis (TLS) DNA polymerase eta (Pol eta). This interesting protein has special features that allow it to bypass sunlight-induced DNA lesions, suppressing tumors. A review containing a detailed analyses of the Pol eta structure and the effects of mutations that lead to the XP-V syndrome helps to understand its function *(Feltes and Menck, 2022).* A further study involves the first description of the participation of Pol eta in cell defense against temozolomide, a tumor chemotherapeutic agent for glioblastoma *(Latancia et al, 2023*). Working with tumors from XP-V patients, we were able to identify specific mutation signatures that occur in the absence of Pol ela, related to sunlight, but also from oxidation stress and potentially tabac-induced damage. Moreover, retrotransposon insertions were found to be highly increased in tumors from XP patients, indicating that Pol eta also protect cells from transposition *(Corradi et al, 2023).* Further work, searching for mutations in tumors from other XP patients confirm the specificity of certain mutation signatures in XP-V patients *(Yurchenko et al., 2023).* Also, the analyses of proteomics from human cells infected with the intracellular parasite *Trypanosome cruzi* confirmed previous observations that the genome of host cells are damaged, and DNA damage responses are induced, possibly as part of the infection process *(Florentino et al, 2023).* Finally, a book chapter describes technologies involved in the detection of DNA damage in human cells *(Leandro et al, 2022).*

PI: **Carlos Frederico Martins Menck**
Publications: 1-*Current state of knowledge of human DNA polymerase eta protein structure and disease-causing mutations*. Feltes BC, **Menck CFM**.. Mutat Res Rev 790:108436. 2022.

2-*DNA polymerase eta protects human cells against DNA damage induced by the tumor chemotherapeutic temozolomide*. Latancia MT, Moreno NC, Leandro GS, Ribeiro VC, de Souza I, Vieira WKM, Bastos AU, Hoch NC, Rocha CRR, **Menck CFM**.. Mutat Res Genet Toxicol Environ Mutagen 878:503498. 2022.

3- *Mutational signatures and increased retrotransposon insertions in xeroderma pigmentosum variant skin tumors.* Corradi C, Vilar JB, Buzatto VC, de Souza TA, Castro LP, Munford V, De Vecchi R, Galante PAF, Orpinelli F, Miller TLA, Buzzo JL, Sotto MN, Saldiva P, de Oliveira JW, Chaibub SCW, Sarasin A, **Menck CFM**.) Carcinogenesis. 17: bgad030. Epub online. 2023

4- *Genomic mutation landscape of skin cancers from DNA repair-deficient xeroderma pigmentosum patients.* Yurchenko AA, Rajabi F, Braz-Petta T, Fassihi H, Lehmann A, Nishigori C, Wang J, Padioleau I, Gunbin K, Panunzi L, Morice-Picard F, Laplante P, Robert C, Kannouche PL, **Menck CFM**, Sarasin A, Nikolaev SI. Nat Commun. 14(1):2561. 2023

5- *Trypanosoma cruzi infection changes the chromatin proteome profile of infected human cells.* Florentino PTV, Vitorino FNL, Mendes D, da Cunha JPC, **Menck CFM**. J. Proteomics. Vol. 272 vol. 272, 10 February 2023, 104773. doi.org/10.1016/j.jprot.2022.104773

6- *Useful protocols to study DNA damage*. Leandro GS, Latancia MT, Quintero-Ruiz N and **Menck CFM**.. In Epigenetics and DNA damage/Translational Epigenetics Series. Ed. MG Jasiulionis, Academic Press, Oxford, UK, vol 33, Chapter 14, pp 255. 2022

mir152 hypomethylation as a mechanism for non-syndromic cleft lip and palate: Non-syndromic cleft lip with or without cleft palate (NSCLP), the most common human craniofacial malformation, is a complex disorder given its genetic heterogeneity and multifactorial component revealed by genetic, epidemiological, and epigenetic findings. Epigenetic variations associated with NSCLP have been identified; however, functional investigation has been limited. Here, we combined a reanalysis of NSCLP methylome data with genetic analysis and used both in vitro and in vivo approaches to dissect the functional effects of epigenetic changes. We found a region in mir152 that is frequently hypomethylated in NSCLP cohorts (21-26%), leading to mir152 overexpression. mir152 overexpression in human neural crest cells led to downregulation of spliceosomal, ribosomal, and adherens junction genes. In vivo

analysis using zebrafish embryos revealed that mir152 upregulation leads to craniofacial cartilage impairment. Also, we suggest that zebrafish embryonic hypoxia leads to mir152 upregulation combined with mir152 hypomethylation and also analogous palatal alterations. We therefore propose that mir152 hypomethylation, potentially induced by hypoxia in early development, is a novel and frequent predisposing factor to NSCLP.

PI: **Maria Rita Passos-Bueno**
Researcher: Lucas Alvizi University College London (UCL)
Publication: *mir152 hypomethylation as a mechanism for non-syndromic cleft lip and palate*. Alvizi L, Brito LA, Kobayashi GS, Bischain B, da Silva CBF, Ramos SLG, Wang J, **Passos-Bueno MR**. Epigenetics. 2022 Dec;17(13):2278-2295. doi: 10.1080/15592294.2022.2115606. Epub 2022 Sep 1. PMID: 36047706

Neural crest E-cadherin loss drives cleft lip/palate by epigenetic modulation via pro-inflammatory gene-environment interaction: Gene-environment interactions are believed to play a role in multifactorial phenotypes, although poorly described mechanistically. Cleft lip/palate (CLP), the most common craniofacial malformation, has been associated with both genetic and environmental factors, with little gene-environment interaction experimentally demonstrated. Here, we study CLP families harbouring *CDH1*/E-Cadherin variants with incomplete penetrance and we explore the association of pro-inflammatory conditions to CLP. By studying neural crest (NC) from mouse, *Xenopus* and humans, we show that CLP can be explained by a 2-hit model, where NC migration is impaired by a combination of genetic (*CDH1* loss-of-function) and environmental (pro-inflammatory activation) factors, leading to CLP. Finally, using in vivo targeted methylation assays, we demonstrate that *CDH1* hypermethylation is the major target of the pro-inflammatory response, and a direct regulator of E-cadherin levels and NC migration. These results unveil a gene-environment interaction during craniofacial development and provide a 2-hit mechanism to explain cleft lip/palate aetiology.

PIs: **Maria Rita Passos-Bueno** and Roberto Mayor University College London (UCL)
Researcher: Lucas Alvizi University College London (UCL)
Student: Diogo Nani (MS), PosDoc: Luciano A. Brito and Gerson Kobayashi
Publication: Neural crest E-cadherin loss drives cleft lip/palate by epigenetic modulation via pro-inflammatory gene–environment interaction. Alvizi L, Nani D, Brito LA, Kobayashi GS, **Passos-Bueno MR**, Mayo R.. Nat Commun 14, 2868 (2023). https://doi.org/10.1038/s41467-023-38526-1.

B.The 80plus Project

Regional differences regarding the occurrence of falls and associated factors in two populations of Brazilian longevous people: Few studies have explored regional asymmetries and their implications for health policies regarding episodes of falls among the population of ≥80 years old in continental and developing countries like Brazil with deep inequalities and sociocultural differences. The aim of this study was to evaluate the occurrence of falls and their association with functional capacity and nutritional status in the oldest individuals living in two municipalities in the Northeast and Southeast of Brazil.The sample was composed of 415 adults. From the total, 32.3% reported having fallen in the last year, 24.7% in Brejo dos Santos and 37.8% in São Paulo. The results pointed out a lower prevalence of falls in longevous people from Brejo dos Santos than in those from São Paulo and differences regarding the associated factors, showing heterogeneity between the two populations; indicating the need for public policies and effective programmes aimed at preventing falls based on the maintenance or increase of functional capacity.

PI: **Mayana Zatz**
Collaboration from our group and Prof. Silvana Santos
Publication*: Regional differences regarding the occurrence of falls and associated factors in two populations of Brazilian longevous people*. Silva JMM, Freitas JLGS, Nóbrega JCL, Medeiros JB, Simões RFM, Olinda R, Santos JLF, Duarte YAO, **Zatz M**, Matheson D, **Santos S**, Menezes TN.. BMC Geriatr. 2022 Dec 2;22(1):931. doi: 10.1186/s12877-022-03630-2.

C.Therapies in Genetic Disorders

C1. Pre-Clinical studies with murine stem cells

Effect of low-intensity training on the brain and muscle in the congenital muscular dystrophy 1D model: Congenital Muscular Dystrophy type 1D (MDC1D) is characterized by a hypoglycosylation of α-dystroglycan protein (α-DG), and this may be strongly implicated in increased skeletal muscle tissue degeneration and abnormal brain development, leading to cognitive impairment. However, the pathophysiology of brain involvement is still unclear. Low Intensity exercise training (LIET) is known to contribute to decreased muscle degeneration in animal models of other forms of progressive muscular dystrophies. The objective of this study

was to analyze the effects of LIET on cognitive involvement and oxidative stress in brain tissue and gastrocnemius muscle. Male homozygous (Largemyd−/−), heterozygous (Largemyd+/−), and wild-type mice were used. To complete 28 days of life, they were subjected to a low-intensity exercise training (LIET) for 8 weeks. After the last day of training, 24 h were expected when the animals were submitted to inhibitory avoidance and open-field test. The striatum, prefrontal cortex, hippocampus, cortex, and gastrocnemius were collected for evaluation of protein carbonylation, lipid peroxidation, and catalase and superoxide dismutase activity. LIET was observed to reverse the alteration in aversive and habituation memory. Increased protein carbonylation in the striatum, prefrontal cortex, and hippocampus and lipid peroxidation in the prefrontal cortex and hippocampus were also reversed by LIET. In the evaluation of the antioxidant activity, LIET increased catalase activity in the hippocampus and cortex. In the gastrocnemius, LIET decreased the protein carbonylation and lipid peroxidation and increased catalase and superoxide dismutase activity. In conclusion, it can be inferred that LIET for 8 weeks was able to reverse the cognitive damage and oxidative stress in brain tissue and gastrocnemius muscle in MDC1D animals.

PI: **Mariz Vainzof**
Publication: *Effects of low-intensity training on the brain and muscle in the congenital muscular dystrophy 1D model.* Comim CM, Soares JA, Alberti A, Freiberger V, Ventura L, Dias P, Schactae AL, Grigollo LR, Steckert AV, Martins DF, Junior RJN, **Vainzof M**, Quevedo J..Neurol Sci. 2022 Jul;43(7):4493-4502. doi: 10.1007/s10072-022-05928-w. Epub 2022.PMID: 35182274

C2. Safety-related concerns in cell therapy

Safety-related concerns in cell therapy: Mesenchymal stem cells (MSCs) are multipotent cells found in various tissues and are easily cultivated. For use in clinical protocols, MSCs must be expanded to obtain an adequate number of cells, but a senescence state may be instituted after some passages, reducing their replicative potential. In this study, we report a case where MSC derived from an elderly donor acquired a senescence state after three passages. The bone marrow was aspirated from a female patient submitted to a cell therapy for the urinary incontinence protocol. Controls were established using BM-MSC from healthy donors and used for senescence and gene expression assays. The patient's MSC expansion using AS displayed an early senescence state. In order to understand the role of AS in senescence, MSCs were then submitted to two different culture conditions: 1) with AS or 2) with FBS supplementation. Senescence state was assessed after 24 h, and no statistical differences were observed between the two conditions. However, patients' cells cultured with AS displayed a higher number of senescence cells than FBS medium after 48 h ($p = 0.0018$). Gene expression was performed in both conditions; increased expression of *KLF4* was observed in

the patient's cells in comparison to healthy controls (p = 0.0016); reduced gene expression was observed for *NANOG* (p = 0.0016) and SOX2 (p = 0.0014) genes. Telomere length of the patient's cells was shorter than that of a healthy donor and that of a patient of similar age. Osteocyte differentiation seemed to be more diffuse than that of the healthy donor and that of the patient of similar age. MSCs could enter a senescence state during expansion in early passages and can impact MSC quality for clinical applications, reducing their efficacy when administered.

PI: **Oswaldo Keith Okamoto**
Colaboration with the groups of Dr. M.A. T. Bortolini & Dr. R. Castro (Federal University of São Paulo) and Dr. J.M. Kutner (Albert Einstein Hospital).
Publication: *Senescence State in Mesenchymal Stem Cells at Low Passages: Implications in Clinical Use*. Alves-Paiva RM, do Nascimento S, de Oliveira D, Coa L, Alvarez K, Hamerschlak N, **Okamoto OK**, Marti LC, Kondo AT, Kutner JM, Bortolini MAT, Castro R, Preto de Godoy JA.. Frontiers in Cell and Developmental Biology, v. 10, p. 1-10, 2022.

D.The Covid 19 Pandemic

Our group undertook different studies related to COVID-19 as well as a collaboration in an international consortium: COVID HUMAN GENETIC EFFORT

D1. Increased susceptibility or resistance to COVID-19

The search for life-threatening COVID-19 did not identify any gene reaching genome-wide significance. Under a recessive model, the most significant gene with at-risk variants was *TLR7*, with an OR of 27.68 (95%CI 1.5–528.7, $P = 1.1 \times 10^{-4}$) for biochemically loss-of-function (bLOF) variants. We replicated the enrichment in rare predicted LOF (pLOF) variants at 13 influenza susceptibility loci involved in TLR3-dependent type I IFN immunity (OR = 3.70[95%CI 1.3–8.2], $P = 2.1 \times 10^{-4}$). This enrichment was further strengthened by (1) adding the recently reported *TYK2* and *TLR7* COVID-19 loci, particularly under a recessive model (OR = 19.65[95%CI 2.1–2635.4], $P = 3.4 \times 10^{-3}$), and (2) considering as pLOF branchpoint variants with potentially strong impacts on splicing among the 15 loci

(OR = 4.40[9%CI 2.3–8.4], $P = 7.7 \times 10^{-8}$). Finally, the patients with pLOF/bLOF variants at these 15 loci were significantly younger (mean age [SD] = 43.3 [20.3] years) than the other patients (56.0 [17.3] years; $P = 1.68 \times 10^{-5}$).

Rare variants of TLR3- and TLR7-dependent type I IFN immunity genes can underlie life-threatening COVID-19, particularly with recessive inheritance, in patients under 60 years old.

PI: **Mayana Zatz**
Posdoc: Mateus Vidigal, Monize Silva- Former IC and currently PhD student
Publication: *Rare predicted loss-of-function variants of type I IFN immunity genes are associated with life-threatening COVID-19*. Daniela Matuozzo, et al. INTERNATIONAL COVID CONSORTIUM.. Genome Medicine 15:22, 2023

D2. Immunogenetics of susceptibility or resistance to SARS-CoV-2

Inherited and acquired errors of type I interferon: Since the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)/coronavirus disease 2019 (COVID-19) pandemic, global sequencing efforts have led in the field of inborn errors of immunity, and inspired particularly by previous research on life-threatening influenza, they have revealed that known and novel inborn errors affecting *type I interferon* immunity underlie critical COVID-19 in up to 5% of cases. In addition, neutralizing autoantibodies against type I interferons have been identified in up to 20% of patients with critical COVID-19 who are older than 80 years and 20% of fatal cases, with a higher prevalence in men and individuals older than 70 years. Also, inborn errors impairing regulation of type I interferon responses and *RNA degradation* have been found as causes of multisystem inflammatory syndrome in children, a life-threatening hyperinflammatory condition complicating otherwise mild initial SARS-CoV-2 infection in children and young adults. Better understanding of these immunologic mechanisms can aid in designing treatments for severe COVID-19, multisystem inflammatory syndrome in children, *long COVID*, and neuro-COVID.

PI: **Mayana Zatz**
Posdoc: Mateus Vidigal, Monize Silva- Former IC and currently PhD student
Publication: Publication: *Inherited and acquired errors of type I interferon immunity govern susceptibility to COVID-19 and multisystem inflammatory syndrome in children*. Bucciol G, COVID Human Genetic Effort, Meyts I. J Allergy Clin Immunol. 2023 Apr;151(4):832-840. doi: 10.1016/j.jaci.2023.02.003. Epub 2023 Feb 24

Impact of SARS-CoV-2 infection and COVID-19 on patients with inborn errors of immunity: Since the arrival of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019, its characterization as a novel human pathogen, and the resulting coronavirus disease 2019 (COVID-19) pandemic, over 6.5 million people have died worldwide—a stark and sobering reminder of the fundamental and nonredundant roles of the innate and adaptive immune systems in host defense against emerging pathogens. Inborn errors of immunity (IEI) are caused by germline variants, typically in single genes. IEI are characterized by defects in development and/or function of cells involved in immunity and host defense, rendering individuals highly susceptible to severe, recurrent, and sometimes fatal infections, as well as immune dysregulatory conditions such as autoinflammation, autoimmunity, and allergy. The study of IEI has revealed key insights into the molecular and cellular requirements for immune-mediated protection against infectious diseases. Indeed, this has been exemplified by assessing the impact of SARS-CoV-2 infection in individuals with previously diagnosed IEI, as well as analyzing rare cases of severe COVID-19 in otherwise healthy individuals. This approach has defined fundamental aspects of mechanisms of disease pathogenesis, immunopathology in the context of infection with a novel pathogen, and therapeutic options to mitigate severe disease. This review summarizes these findings and illustrates how the study of these rare experiments of nature can inform key features of human immunology, which can then be leveraged to improve therapies for treating emerging and established infectious diseases.

PI: **Mayana Zatz**
Posdoc: Mateus Vidigal, postdoc,Monize Silva- Former IC and currently PhD student
Publications: Impact of SARS-CoV-2 infection and COVID-19 on patients with inborn errors of immunity.Tangye SG, COVID Human Genetic Effort consortium. J Allergy Clin Immunol. 2023 Apr;151(4):818-831. doi: 10.1016/j.jaci.2022.11.010. Epub 2022 Dec 13.

Impact of SARS-Cov-2 infection in Turner syndrome: Here we investigated the impact of coronavirus infection in volunteers with Turner syndrome . They showed a delayed or insufficient humoral immune response to SARS-CoV-2 (particularly immunoglobulin G) and a decrease in interferon-γ production by cluster of differentiation (CD)4+ and CD8+ T lymphocytes after stimulation with toll-like receptors 7/8 agonists. In contrast, we observed a higher cytotoxic activity in the volunteers with TS than the volunteers without TS after phorbol myristate acetate/ionomycin stimulation, particularly granzyme B and perforin by CD8+ and natural killer cells. Interestingly, two volunteers with TS carry rare genetic variants in genes that regulate type I and III interferon immunity. Following previous reports in the literature for other conditions, our data showed that patients with TS may have an impaired immune

response against SARS-CoV-2. Furthermore, other medical conditions associated with TS could make them more vulnerable to COVID-19.

PI: **Mayana Zatz**
Postdoc: Mateus Vidigal
Collaboration: Edecio Cunha-Neto team and Maria N. Sato team
Publication: *Immunological evaluation of young unvaccinated patients with Turner syndrome after COVID-19.* de Castro MV, Silva MVR, Oliveira LM, Gozzi-Silva SC, Naslavsky MS, Scliar MO, Magalhães ML, da Rocha KM, Nunes K, Castelli EC, Magawa JY, Santos KS, Cunha-Neto E, Sato MN, **Zatz M**.. Int J Infect Dis. 2023 Apr;129:207-215. doi: 10.1016/j.ijid.2023.01.042. Epub 2023 Feb 8.

Immunogenetics of resistance to SARS-CoV-2 infection in super olders: Although older adults are at a high risk of severe or critical Covid-19, there are many cases of unvaccinated centenarians who had a silent infection or recovered from mild or moderate Covid-19. We studied three Brazilian supercentenarians, older than 110 years, who survived Covid-19 in 2020 before being vaccinated. Despite their advanced age, humoral immune response analysis showed that these individuals displayed robust levels of IgG and neutralizing antibodies (NAbs) against SARS-CoV-2. Enrichment of plasma proteins and metabolites related to innate immune response and host defense was also observed. None presented autoantibodies (auto-Abs) to type I interferon (IFN). Furthermore, these supercentenarians do not carry rare variants in genes underlying the known inborn errors of immunity, including particular inborn errors of type I IFN. These observations suggest that their Covid-19 resilience might be a combination of their genetic background and their innate and adaptive response.

PIs: **Mayana Zatz, Maria Rita Passos-Bueno, Michel Naslavsky**
Postdoc: Mateus Vidigal
Collaboration with the groups of Erick Castelli, Gilberto Domont, Jean-Laurent Casanova
Publication: *The oldest unvaccinated Covid-19 survivors in South America.* de Castro MV, Silva MVR, **Naslavsky MS**, Scliar MO, Nunes K, **Passos-Bueno MR**, Castelli EC, Magawa JY, Adami FL, Moretti AIS, de Oliveira VL, Boscardin SB, Cunha-Neto E, Kalil J, Jouanguy E, Bastard P, Casanova JL, Quiñones-Vega M, Sosa-Acosta P, Guedes JS, de Almeida NP, Nogueira FCS, Domont GB, Santos KS, **Zatz M**. Immun Ageing. 2022 Dec 7;19(1):61. doi: 10.1186/s12979-022-00319-3.

Recessive inborn errors of Type I IFN immunity: Recessive or dominant inborn errors of type I interferon (IFN) immunity can underlie critical COVID-19 pneumonia in unvaccinated adults. The risk of COVID-19 pneumonia in unvaccinated children, which is much lower than in unvaccinated adults, remains unexplained. In an international cohort of 112 children (<16 yr old) hospitalized for COVID-19 pneumonia, we report 12 children (10.7%) aged 1.5–13 yr with critical (7 children), severe (3), and moderate (2) pneumonia and 4 of the 15 known clinically recessive and biochemically complete inborn errors of type I IFN immunity: X-linked recessive TLR7 deficiency (7 children) and autosomal recessive IFNAR1 (1), STAT2 (1), or TYK2 (3) deficiencies. Fibroblasts deficient for IFNAR1, STAT2, or TYK2 are highly vulnerable to SARS-CoV-2. These 15 deficiencies were not found in 1,224 children and adults with benign SARS-CoV-2 infection without pneumonia ($P = 1.2 \times 10$) and with overlapping age, sex, consanguinity, and ethnicity characteristics. Recessive complete deficiencies of type I IFN immunity may underlie ∼10% of hospitalizations for COVID-19 pneumonia in children.

PI: **Mayana Zatz**
Postdoc: Mateus Vidigal
Publication: *Recessive inborn erros of type I IFN immunity in children with COVID-19 pneumonia.* Zhang Q, Matuosso D, Le Pen J, Lee D, Moens L, Asano T, Bohlen J, Liu Z, Monca-Velez M, Kendir-Demirkol Y, Jing H,, Bizienl L, Marchal A, Abolhassani H, Delafontaine S, Buccioli G, Covid Human Genetic Effort, Bayhan GI, Keles S, Kiykim A, Hancerli S, Haerynck F, Florkin B, Hatipoglu N, Ozcelik T, Morelle G, **Zatz M**, Ng LFP, Chien Lye D, Young BE, Yee-Sin Leo, Dalgard CL, Lifton RF, Renia L, Meyts I, Jouanguy E, Hammarström L, Pan- Hammarström Q, Boisson B, Bastard P, Su HC, Boisson-Dupuis S, Abel L, Rice CM, Shen-Ying Zhang, Cobat A, Casanova JL.. J Exp Med (2022) 219(8):20220131 https://doi.org/10.1084/jem. 20220131

PART 2 - TRANSFER OF TECHNOLOGY/ TECHNOLOGY APPLICATIONS

As transfer of technology, our proposal is to translate scientific and technological advances into services, as follows:

Sequencing Facility (EMU - Equipamento Multiusuário / Multiuser Equipment - FAPESP): In these last 5 years, we have implemented the HUG-CELL EMU <https://genoma.ib.usp.br/central-multiusuariosfapesp-e-usp-multi/79>. Currently it contains three sequencing apparatus: ABI 3730 DNA Analyzer sequencer (Applied Biosystems), MiSeq and NovaSeq6000 (Illumina). We also increased our infrastructure for storage (about 150% of our previous storage capacity) and data processing to approximately 1.5 petabytes by acquiring a new storage server [Storage Infortrend Gen2 with redundant controllers, 8 10GbE SFP+ ports, 256GB Cache, and 72 x 16 TB disks (net capacity after RAID6: 900 TB)]. Therefore, currently we have adequate infrastructure for holding whole-exome and whole-genome sequences for both research and diagnosis purposes. This sequencing facility is registered at the multi-user facility at USP (https://uspmulti.prp.usp.br/public/centrais/11).

a) **Genetic tests and sequencing services:** We have updated the web page of the non-profit laboratory for genetic tests <https://genoma.ib.usp.br/labteg/> with the inclusion of Genetic Counseling. We have implemented novel tests in the last year, with the inclusion of the detection of pathogenic expansion at *C9orf72*, which is associated with neurodegenerative phenotypes, and analysis of *EIF4A3* expansion, associated with the autosomal recessive craniofacial disorder Richieri-Costa-Pereira syndrome. We are constantly checking the quality of our pipelines and improving them as necessary. In 2022-2023, we have incorporated two pipelines for CNV detection in exome analysis and we are currently testing a pipeline for CNV detection in whole-genome sequencing with low and high coverage. Also in this regard, through a collaboration between HUG-CELL and DASA, we are investigating CNVs using a low-pass WGS strategy (lpWGS 1x) in research samples of 1,600 individuals with intellectual deficiency, autism spectrum disorders or oral cleft. It is of note that these pipelines are used not only for routine genetic tests and genetic counseling for families with affected patients, but also in HUG-CELL research.

During the last year and a half (2022 to June 2023), we have performed about 14.106 genetic tests (MLPA/disease specific CNVs, fluorescent PCR, Triple-PCR for expansion, NGS panels, exome sequencing, whole genome sequencing, RNA sequencing, Sanger sequencing and aCGH). NGS services have been done for different research Institutes, such as FIOCRUZ, FMUSP, IAL, UFAL, UNICAMP and UNIFESP: library construction + sequencing runs for 365

samples (exome sequencing, whole genome sequencing, RNA sequencing) and also 44 sequencing runs from libraries prepared by the researcher/client. Except for aCGH test, which is done in the cytogenetic facility coordinated by two of our CEPID members (C Rosenberg, AC Krepischi), all the others were performed at the HUG-CELL facilities.
The quality and reliability of our genetic tests have been certified yearly by the European Molecular Genetics Quality Network (EMQN).

b) **Genetic counseling service:** Genetic counseling of families with affected patients includes diagnosis, testing the patients and when appropriate "at-risk carriers", orientation about prognosis, management and genetic counseling. About 1723 consultations were performed by our team. A written report, including results of genetic tests, were provided for the attended individuals.

c) **DATABASES:** We have developed, and hosted in our servers, a public access website <http://abraom.ib.usp.br>- ABraOM - Arquivo Brasileiro Online de Mutações) to provide information on the frequency of SNV/indel variants detected in 1171 Brazilian healthy individuals that are part of the São Paulo city elderly cohort studied at our center (SABE cohort; dataset1 = 609 whole exome sequence; dataset 2 = 1171 whole genome sequencing). These datasets have provided valuable information for precision medicine through the interpretation of pathogenicity of variants identified in genetic tests in Brazil and around the world. The corresponding paper has recently been published in Nature Communications (Naslavsky et al., 2022). In addition to the aggregate datasets provided by open access ABraOM, the individual-level data (BAM and gVCF files) from the 1171 WGS are available for researchers who can access under request both datasets at the European Genome-phenome Archive <https://ega-archive.org/studies/EGAS00001005052>. We have opted to discontinue the development of the software DesBraVar in view on currently available options. We are discussing the use of Franklin genoox (https://franklin.genoox.com/clinical-db/home) platform as it offers a friendly pipeline for human genome analysis and the creation of a database of the variants of our sequenced samples.

d) **Startups:** Our center is partly incubating two startups: 1) Vyro biotherapeutics (http://vyrobio.com), with the main aim to develop oncolytic therapies based on Zika virus to brain cancer. 2) Xenobrasil - Desenvolvimento e Pesquisas sobre Xenotransplante no Brasil Ltda., with the main aim to develop technical approaches based on gene editing to generate pig organs as alternative source for human transplantation.

e) **Patents:** Two patents were internationally deposited:

• PHARMACEUTICAL KIT AND USES THEREOF | [PHARMAZEUTISCHES KIT UND VERWENDUNGEN DAVON]; Authors: Oswaldo Okamoto; Mayana Zatz; Carolini Kaid Dávila, (...) (Universidade de São Paulo). European Patent Application Patent numberEP3785722 (document published 2021)Patent Cooperation Treaty Application Patent number WO2019204888 (document published 2019)

• COMPOSITIONS AND METHODS OF TREATING MUSCULAR DYSTROPHY | [ZUSAMMENSETZUNGEN UND VERFAHREN ZUR BEHANDLUNG VON MUSKELDYSTROPHIE]; Authors: LINDBLAD-TOH, Kerstin; KUNKEL, Louis M.; VIEIRA, Natassia M.(...) (The Broad Institute, Inc. (...))European Patent Application Patent numberEP3207048 (doc published 2017)United States Patent and Trademark Office Pre-Granted Publication Patent number US20170224758 (doc published 2017) European Patent ApplicationPatent numberEP3785722 (doc published 2021)

f) **Patternships:** The genome multi-user facility has established a partnership with Sophia Genetics, an international company that developed a platform, SOPHiA DDM™ platform, that enables analysis of human exomes for molecular diagnosis. They are now expanding their services by including genetic tests by exome and whole genome sequence, which will be in part sequenced in our facility.

g) **Income resources administration:** The income of the paid services is used to pay for activities not supported by our current grants or the University, such as technicians' salaries, equipment maintenance, reagents for the genetic tests, and building maintenance. The income of the paid services has been carried out by Fundação Faculdade de Medicina USP (FFM) and Fundação Universidade de São Paulo (FUSP).

PART 3 - EDUCATION OUTREACH

A. High School Support Program

A1 - Project: Laboratory classes at school - https://genoma.ib.usp.br/laboratorio-nas-escolas/42. The Center assisted 47 schools in the Laboratory in Schools project (**Annex 4, Table 1**), lending itinerant laboratories to teachers. The laboratories remained in each of the schools for a period of 3 weeks. 103 teachers received 16 hours of technical and pedagogical support and were trained to use 6 kits that enable the development of laboratory classes related to the cellular basis of Genetics (**Annex 4, Table 2**). On average, 700 students per school participate in laboratory classes, totaling 33.000 students benefited.

A.2. Instructional support project

https://genoma.ib.usp.br/materiais-didaticos/43 -

Forty-two teachers from public High Schools, managed by the Teaching Directorates of the Midwest and Osasco regions, were trained in the use of didactic materials, belonging to the Center for Studies on the Human Genome and Stem Cells. Such materials are available for loan at three centers located in the Department of Genetics at IBUSP, and in the aforementioned Regional Directorates. The aim of the project is to help teachers overcome some of the teaching and learning difficulties presented by the abstract nature of some Genetic concepts. On average, annually about 100 teachers make use of such borrowed materials. In addition, the user manuals and protocols for these materials are available on the Genome website. (**Annex 4 - Table 3**).

A.3. Scientific Exhibitions The “Giant Cell”

https://genoma.ib.usp.br/celula-gigante/60, a scenic cell amplified 130,000 times and a set of complementary activities designed to facilitate the understanding of cell concepts were visited by 2.500 people in September, during USP Professions Fair.

B. Mini course for journalists

The Center offered a 7-hour mini-course on Gene Therapy to journalists specializing in science communication from different states in Brazil, sponsored by Pfizer. The theoretical part consisted of 5 lectures given by researchers from the center. This was followed by a visit to the facilities of the Center for the Study of Human Genome and Stem Cells and practical

demonstrations of methodologies for obtaining cells for experimental therapy procedures, cell reprogramming and differentiation and generation of CRISPR cell lines (November 10, 2022).

C. Projects having the public as target

The main objective of the scientific dissemination actions is to approach the public that seeks knowledge and quality information, also creating proximity between the public, science and scientists. On social networks, HUG-CELL is known as GenomaUsp and is present on YouTube, Facebook and Instagram. The outreach team produced scientific dissemination content for the public, remaining attentive too to High School teachers as a target audience of the posts. Because of this we collected them on the Genoma website where they are available to be used as didactic material (https://genoma.ib.usp.br/posts-educativos-em-pdf/82).

On YouTube https://www.youtube.com/genomausp between July/2022 and June 2023, the scientific dissemination team idealized and produced 57 videos that addressed different subjects. Details are in **Annex 4, Table 4A**. The total views in the last year, including old videos, was 181,702.

On Instagram https://www.instagram.com/genoma.usp/ the same YouTube videos were posted, as well as others related to HUG-CELL research or educational subjects. These posts bring enlightening illustrations, in carousel format, language appropriate to the public and references to popular culture, without sacrificing scientific rigor. In the period covered by the report, 55 feed posts, 63 videos and 505 Stories were produced (**Annex 4, Table 4B**).

The number of followers on GenomaUSP media continues to grow and, by May 2022, corresponds to 12,000 on Facebook, 19,300 on Instagram and 9,210 on YouTube. Between July 2022 and May 2023, the YouTube channel had 181,702 views, 5 thousand hours watched and 2,400 new subscribers.

Annex 1 - Publications in peer reviewed journals, books and patents

From July 2022 until June 2023, our group has published 73 journal articles (all listed below), 14 abstracts in National meetings, and 18 abstracts in International meetings. During this period, our graduate students submitted 6 Master Theses and 9 Doctoral Dissertations. About 42 conferences, lectures and symposia were presented done by our team

1.1. Book and book Chapters

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2. Kim CA, **Bertola DR,** Albano LMJ, Kawahira RSH. Série Manual do Médico-Residente do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo-Genética Médica. E-Book. São Paulo: Atheneu, 2022, v.1. p.696.

3. Leandro GS, Latancia MT, Quintero-Ruiz N and **Menck CFM**. Useful protocols to study DNA damage. In Epigenetics and DNA damage/Translational Epigenetics Series. Ed. MG Jasiulionis, Academic Press, Oxford, UK, vol 33, Chapter 14, pp 255. 2022

1.2 Articles

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2. Alvizi L, Nani D, Brito LA, Kobayashi GS, **Passos-Bueno MR**, Mayo R. Neural crest E-cadherin loss drives cleft lip/palate by epigenetic modulation via pro-inflammatory gene–environment interaction. Nat Commun 14, 2868 (2023). https://doi.org/10.1038/s41467-023-38526-1

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10.1007/s12015-022-10489-8. Epub 2022 Dec 14.

5. Bandeira G, Rocha K, Lazar M, Ezquina S, **Yamamoto G**, Gollop T, **Zatz M**, **Passos-Bueno MR**, **Krepischi A**, **Okamoto OK**. Novel breast cancer predisposing candidate genes identified in Brazilian families with hereditary breast cancer. EJC, GENETICS| Volume 175, supplement 1, S39, 17 november 2022, DOI: https://doi.org/10.1016/S0959-8049(22)01455-1

6. Barreiro RAS, Almeida TF, Gomes CS, Monfardini F, Farias AA, Tunes GC, GM Souza, Duim E, Correia JS, Coelho AVC, Caraciolo MP, **Duarte YAO**, **Zatz M**, **Amaro E**, Oliveira JB, Bitarello BD, Brentani H, **Naslavsky MS**. Assessing the risk stratification of breast cancer polygenic risk scores in two Brazilian samples. medRxiv. doi: https://doi.org/10.1101/2022.09.09.22279721

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9. Bertholim-Nasciben L, Scliar MO, Debortoli G, Thiruvahindrapuram B, Scherer SW, **Duarte YAO**, **Zatz M**, Suarez-Kurtz G, Parra EJ, **Naslavsky MS**. Characterization of pharmacogenomic variants in a Brazilian admixed cohort of elderly individuals based on whole-genome sequencing data. Front Pharmacol. 2023 May 10;14:1178715. doi: 10.3389/fphar.2023.1178715. eCollection 2023.

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Annex 2 - Meetings, Conferences, Lectures

2.1. Abstract: National Meetings

1. Carvalho LML et. al. “Development of Cellular and animal models for The XIA-GIBBS Sindrome”. In: Genética 2022 - Sociedade Brasileira de Genética (SBG) - Natal, RN, 12-15 September 2022.

2. Chaves EF, Almeida A, Pasa ID, Honjo RS, Yamamoto G, Kim CA, **Krepischi A**, Silvia Costa, **Vianna Morgante AM**, **Bertola DR.** SIX2-related frontonasal dysplasia in a familial case with additional clinical findings: broadening the phenotypic spectrum. **XXXIII Congresso Brasileiro de Genética Médica**, Curitiba, Paraná, From 28 th to September - 1 october 2022.

3. Corradi C, Vilar JB, de Souza TA, Castro LP, Munford V, De Vecchi R, Galante PAF, Buzatto VC, Chaibub SCW, Sarasin A, **Menck CFM**. Mutational signatures of Xeroderma Pigmentosum variant patients’skin tumors. Presented as a poster at the X-Meeting X Perience 2021, from 27 to 29/10/2021.

4. Corradi C, Vilar JB, de Souza TA, Castro LP, Munford V, De Vecchi R, Galante PAF, Buzatto VC, Chaibub SCW, Sarasin A, **Menck CFM**. Whole-exome sequence and mutational signature analysis of Xeroderma Pigmentosum variant patients’ skin

tumors. Presented as a poster and oral presentation at the **XV Congresso da Mutagen-Brasil**, virtual meeting, from 12 to 15/11/2021.

5. Kobayashi GS, Hsia GS, **Passos-Bueno MR**. Modelling early human craniofacial development with iPSCs: uncovering novel disease mechanisms. In: Symposium - Migration and differentiation: from cell to embryo (online). **XXI Congress of the Brazilian Society for Cell Biology**. 07/15/2022.

6. Latancia MT, Leandro GS, Bastos AU, Moreno NC, Jardim D, Rocha CRR, **Menck CFM**. Unraveling the role of Translesion Synthesis Polymerases in Temozolomide Resistance Mechanism. Presented as poster at the GENETICA 2021 – **Brazilian Congress of Genetics**, virtual meeting from 13 to 16/09/2021.

7. Leoncio JC, Batissoco AC, Haddad LA, **Mingroni-Netto RC.** In silico analyses of the protein-protein interaction network of Connexin 26 In**: 67th Braziilan Congress of Genetic**s, 2022, Natal. **Livro de Resumos**. , 2022. v.67. p.562 – 562.

8. **Menck CFM**. How I learned DNA damage and repair and mentored with these scientific questions, in Brazil. Presented as an oral Lecture, at the Genetica 2022, **67th Brazilian Congress of Genetic**s, from September 12th to 15, 2022, Natal, RN, Brazil.

9. **Menck CFM.** A necessária avaliação da Pós graduação pela CAPES, para o bem da qualidade do país. Apresentado oral na **74ª Reunião da SBPC**, de 23 a 28 de julho de 2022, Brasília, DF, Brazil.

10. Naufal MG, Pasa ID, Ali TM, Marcarini BG, Murillo, EML, Jacob, RE, Lopes MAB, Francisco RPV, Menezes Filho HC, Carvalho, DR, Yamamoto GL, Honjo RS, Kim CA, **Bertola DR. "**Osteopenia and bent bones: radiological signs not only found in Osteogenesis Imperfecta." **XXXIII Congresso Brasileiro de Genética Médica**, Curitiba, Paraná, From 28 th to September - 1 october 2022.

11. Pasa ID, Ali TM, Marcarini BG, Lopes MAB, Francisco RPV, Menezes Filho HC, Migliavacca M, Yamamoto G, Honjo RS, Kim CA, **Passos-Bueno MR**, **Bertola DR. "**Molecular analysis of severe cases of osteogenesis imperfecta". **XXXIII Congresso Brasileiro de Genética Médica**, Curitiba, Paraná, From 28 th to September - 1 october 2022.

12. Ramos IC, Branco EV, **Passos-Bueno MR**. Altered Neuronal Morphology in "Heterozygous Cells for Loss-of-Function Variant in TBCK". In: GENÉTICA 2022 - **Sociedade Brasileira de Genética** (SBG) - Natal, RN, 12-15 September 2022.

13. Val VP, Almeida DCAL, Castro MAA, Pires LVL, Linnenkamp BWD, Yamamoto G, Honjo RS, Kim CA, **Bertola DR** . "Noonan-like syndrome disorder with loose anagen hair: a clinical-genetic study of nine Brazilian individuals." **XXXIII Congresso Brasileiro de Genética Médica**, Curitiba, Paraná, From 28 th to September - 1 october 2022.

14. Wang JYT, Sampaio RO, Kobayashi GS, Polanczyk GV, Fujita A, Yamamoto GL, **Naslavsky, MS**, Santoro ML, **Passos-Bueno MR**. Calculation of polygenic risks associated with Executive Functions of 500 children using Low-Pass Whole-Genome Sequencing data. X-Meeting 2023. In: **19th International Congress of the Brazilian Association of Bioinformatics and Computational Biology** (AB3C), 13-16 June 2023, Curitiba, Paraná, Brazil.

2.1. Abstract: International Meetings

1. Bandeira G, Rocha K, Lazar M, Ezquina S, Yamamoto G, Gollop T, **Zatz M**, **M Passos-Bueno MR**, **Krepischi A**, **Okamoto OK**. Novel breast cancer predisposing candidate genes identified in Brazilian families with hereditary breast cancer. volume 175, supplement 1, s39, november 2022. DOI: https://doi.org/10.1016/S0959-8049(22)01455-1 (**13th European Breast Cancer Conference -EBCC**-13; 16 - 18 November 2022).

2. Borges VM, Horimoto ARVR, **Mingroni-Netto RC,** Nato A.Essential hypertension genomic regions from linkage analysis studies In: **Annual Meeting of the American Society of Human Genetic**s, 2022, Los Angeles. 2022. p.P. A3814.

3. Borges VM, Horimoto ARVR, Wijsman EM, Kimura L, Meyer D, **Mingroni Netto RC,** Nato A. Pathway analysis of genome-wide linkage analysis regions on essential hypertension in African-derived Brazilian Quilombo populations In: **30th Conference of Intelligent Systems for Molecular Biology**, 2022, Madison.30th Conference of Intelligent Systems for Molecular Biology. , 2022. p.L-018

4. Branco EV, Costa CIS, Fiuza MA, Girardi ACS, Ramos I, Kobayashi G, Carvalho LML, Krepischi ACV, **Passos-Bueno MR**. SHANK3-Catenin Interaction and the Clinical Features of Phelan-Mcdermid Syndrome. In: "**International Society for Autism Research** (INSAR) 2023", May, 3-6, 2023, Stockholm, Sweden.

5. Do Carmo GG et.al. "Novel Breast Cancer Predisposing Candidate Genes Identified In Brazilian Families With Hereditary Breast Cancer. In: **13th European Breast Cancer Conferenc**e, 16-18 November 2022, Barcelona, Spain.

6. Ferreira RS, Araujo BHS, **Okamoto OK**. Assessment of Oncolytic Virus Specificity and Cytotoxicity in a Hybrid Glioblastoma-cerebral Organoid Model, , Neuro-Oncology, Volume 24, Issue Supplement_7, November 2022, Page vii292, https://doi.org/10.1093/neuonc/noac209.1134 (**Society for Neuro-Oncology's 27th Annual Scientific Meeting**).

7. Herwood M, Ewing R, Kaid C, Mitsugi TG, **Okamoto OK**. Employing the Zika Virus to kill paediatric nervous system tumour cells. Neuro-Oncology, Volume 24, Issue Supplement_7, November 2022, Page vii45, https://doi.org/10.1093/neuonc/noac209.178 (**Society for Neuro-Oncology's 27th**

Annual Scientific Meeting).

8. Kerbauy L, Coa LL, Sielski MS, Godoy JAP, Kondo AT, Azevedo JTC, Barbosa A, **Okamoto OK**, Kutner JM, Hamerschlak N, Paiva RMA. Clinical Validation of Automated Manufacture of Autologous CD19 CAR-T Cells for Treatment of B Neoplasia. Blood 140 (Supplement 1), 4930-4930. (**American Society of Hematology annual meeting**, 2022/11/15).

9. Kerbauy LN, Coa L, Kondo AT, Godoy JAP, Bello I, **Okamoto OK**, Kutner JM, Hamerschlak N, Alves-Paiva RM. Umbilical Cord Blood NK Cells Stability After Cryopreservation: An off The Shelf Strategy For Adoptive Immunotherapy Against acute Myeloid Leukemia. In: **International Society for Cell & Gene Therapy - 28th Annual Meeting, 2022**, San Francisco. Cytotherapy, 2022. v. 24. p. s124-s124.

10. Kerbauy LN, Coa L, Sielski MS, Godoy JAP, Kondo AT, Azevedo JTC, Barbosa JR, **Okamoto OK**, Kutner JM, Hamerschlak N, Alves-Paiva RM. Clinical Validation of Automated Manufacture of Autologous CD19 CAR-T Cells for Treatment of B Neoplasia. In: **Annual meeting of the American Society of Hematology**, 2022, New Orleans. Blood, 2022. v. 140. p. 4930.

11. Latancia MT, Moreno NC, Leandro GS, Bastos AU, Martins DJ, Rocha CRR, **Menck CFM**. Unraveling DNA polymerases Iota, Kappa and Eta role on Temozolomide treatment. Presented as oral presentation at the **13 th International Conference on Environmental Mutagenesis**. Ottawa, Canada from 27/08 to 01/09/2022. Recipient of the Hollaender Travel Award from Environmental Mutagenesis and Genomics Society.
12. Marcarini B, Pasa I, Yamamoto G, Rocha L, Castro M, Pires L, Linnenkamp B, Honjo R, Olveira L, Kim C, **Passos-Bueno MR**, **Bertola DR.** Next-generation seuquencing applied to skeletal disorders: a tem-year experience ina Tertiary Center in Brazil. **International Society of Skeletal Dysplasias (ISDS) Meeting**, Santiago, Chile, 24 - 27 August, 2022.

13. **Menck CFM**. Does the Error Prone DNA polymerase eta replicate pyrimidine dimers correctly? Oral presentation at the Symposium How cells tolerate and replicate DNA damage? **13rd International Conference of Environmental Mutagenesis**. Ottawa, Canada, From August 27th to September 1st, 2022.

14. Nato A, Borges V M, **Mingroni Netto RC**, Horimoto ARVR.I ntegvar: A pipeline to integrate variant strenght from prioritizers and annotations In: **Annual Meeting of the American Society of Human Genetics**, 2022, Los Angeles.Annual Meeting of the American Society of Human Genetic**s**. , 2022. p.P A3864

15. Pasa I, Ali T, Marcarini B, Almeida A, Lopes MA, Francisco R, Carvalho D, Menezes H, Yamamoto G, Honjo R, Kim C, **Passos-Bueno MR**, **Bertola DR.** Molecular analysis of severe cases of osteogenesis imperfecta and other rare low-minerla density disorders. **International Society of Skeletal Dysplasias (ISDS) Meeting**, Santiago, Chile, 24 - 27 august, 2022.

16. Ribeiro DL, Latancia MT, Mendes D, Rocha CRR, **Menck CFM**. Translesion DNA polymerases in Temozolomide Resistance: Cytotoxic and Antiproliferative Analysis in Glioblastoma Spheroids in vitro. Hollaender Travel Award Winner - Environmental Mutagenesis and Genomics Society (EMGS) – **13rd International Conference on Environmental Mutagenesis**. Ottawa, Canada, From August 27 th to September 1 st , 2022.

17. Yamamoto G, di Lazzaro R, Silva T, Castro M, Bartholdi D, Schaller A, Zweier C, Utagwa C, Steiner C, Honjo R, Kim C, **Passos-Bueno MR**, Hoch N, **Débora Bertola.** Oral presentations: Rothmund-Thomson syndrome type I with growth hormone deficiency is associated with a not-previously described gene in na autosomal recessive inheritance pattern in seven families**. International Society of Skeletal Dysplasias (ISDS) Meeting**, Santiago, Chile, 24 - 27 august, 2022.

18. Yamamoto G, Di Lazaro R, da Silva T, Rocha L, Bartholdi D, Schaller A, Zweier C; Honjo RS, Utagawa C, Steiner C, Kim CA, **Passos-Bueno MR**, Hoch NC, **Bertola DR**. Pôsters: Rothmund Thomson syndrome with congenital cataracts and severe growth restriction is associated with a not previously described gene in an autosomal recessive inheritance pattern in seven families. **American Society of Human Genetics (ASHG) Meetin**g, Los Angeles, Ca, United States, October 2 -29th, 2022.

2.3. Conferences, Symposia, Round Tables, Lectures

1. Andrade PV, Santos JM, Teixeira ACB, Sogari VF, Almeida MS, Callegari FM, **Krepischi ACV**, Oliveira ASB, **Vainzof M**, Silva HCA Rhabdomyosarcoma, malignant hyperthermia, core myopathy, and RYR1/ASPSCR1 variants: A case study.

2. **Bertola DR**. Moderator: Session 8 (Clinical and Observational Studies). 15º International Skeletal Dysplasia Society (ISDS) Meeting, Santiago, Chile, August 27th, 2022.

3. **Bertola DR**. Sessão de Temas Livres - Sessão de Temas Livres: Apresentação oral. Sessions XXXIII Congresso Brasileiro de Genética Médica, Curitiba, PR, 28/09 a 01/10 de 2022.

4. Bertola DR. Caso Clínico – Casos sem diagnóstico. Sessions XXXIII Congresso Brasileiro de Genética Médica, Curitiba, PR, 28/09 a 01/10 de 2022.

5. de Mello JM, de Andrade PV, dos Santos JM, Oliveira ACB, **Vainzof M**, do Amaral JLG, da Silva HCA. Analysis of the factors that influenced the concordant/discordant diagnosis of the European and North American contracture tests. EMHG MEETING, Valencia, May 2023.

6. **Ferrari MFR**. Lecture: Successful Innovative Undergradutate Programs at USP. “J-WEL MIT Week - Architectures of Learning.” Cambridge, MA. March – 2023.

7. **Ferrari MFR**. Lecture: Extracellular Chaperones and Dispersion of Protein Aggregates. “1st Portugal & Brasil Joint Meeting.” Coimbra, Portugal. July – 2022.

8. **Ferrari MFR**. “Federation of European Neuroscience Societies (FENS) Forum”. July – 2022, Paris France.

9. **Ferrari MFR**, Queiroz EO, Sakugawa AYS, Wilson MR. Poster presentation:Extracellular Clusterin mitigates alpha-synuclein dispersion. In: Federation of European Neuroscience Societies (FENS) Forum. July – 2022, Paris France.

10. Monegaglia NV, **Ferrari MFR**, Barboza R. Poster presentation: Effect of parthenolide in LPS-Induced microglial Neuroinflammation In. Federation of European Neuroscience Societies (FENS) Forum. July – 2022, Paris France.

11. **Mingroni-Netto RC.** Aconselhamento Genético. Palestra Faculdade de Medicina da USP - Curso de Pós-Graduação em Endocrinologia. Inst.Promotora/financiadora: Faculdade de Medicina da USP. São Paulo, SP, 2022.

12. **Mingroni-Netto RC**. Aula Magna : Aconselhamento Genético: desafios contemporâneos. 3o CONFEBIO- Conferência Nacional de Biologia; Inst.promotora/financiadora: Conselho Federal de Biologia. Brasília, DF. 2022.

13. **Mingroni-Netto RC.** Dilemas Éticos da Informação Genética, 3o Curso de Férias em Genética e Evolução. Inst. Promotor/financiador: Instituto de Biociências da USP. São Paulo, SP, 2022.

14. **Naslavsky MS**. Poster presentation: Global and local ancestry modulate APOE association with Alzheimer's neuropathology and cognitive outcomes in an admixed sample. Alzheimer’s Association International Conference. July 2022, San Diego.

15. **Naslavsky MS**. Oral presentation: Local ancestry around APOE and global ancestry modulate Alzheimer's neuropathology and cognitive outcomes in an admixed sample of Brazilians. Alzheimer’s Association International Conference Advancements: APOE. March 2023, St. Louis.

16. **Naslavsky MS**. Oral presentation: Testes genéticos diretos ao consumidor. II Simpósio de Aconselhamento Genético Multidisciplinar: Atuação e Perspectivas. May 2023, Online.

17. **Naslavsky MS**. Oral presentation: Ancestralidade: fronteira entre genômica e bioética. IX Simpósio de Bioética Hospitalar. November 2023, Online.

18. **Naslavsky MS**. Oral presentation: Como uma base de dados genômicos de brasileiros contribui para a medicina de precisão? 67th Brazilian Congress of Genetics. September 2023, Natal.

19. **Naslavsky MS**. Oral presentations: Projeto SABE: Como uma base de dados genômicos de brasileiros contribui para a medicina de precisão? Simpósio "All the way from bench to bed - new perspectives on Precision Medicine” - Instituto para Pesquisa do Câncer de Guarapuava. March 2023, Guarapuava.

20. **Naslavsky MS**. Oral presentations: Ancestralidade global e local no gene *APOE* modulam o risco para neuropatologias e declínio cognitivo na doença de Alzheimer.

Simpósio "All the way from bench to bed - new perspectives on Precision Medicine" - Instituto para Pesquisa do Câncer de Guarapuava. March 2023, Guarapuava.

21. **Vainzof M**, Rocha de Vasconcelos FTG, Almeida CF, Bitoun M, Ishiba R, Souza LS, Ribeiro-Junior AF, Souza BW, Zogby IA, Saldys NG. Skeletal muscle injury by electroporation – a model to study degeneration/regeneration pathways murine models for NMD. 17th International congresso on Neuromuscular diseases, 5-9 july, 2022 Brussel, Belgium.

22. **Vainzof M**, Souza LS, Rocha de Vasconcelos FTG, de Andrade PV, dos Santos JM, Oliveira ASB, da Silva HCA. Correlation between phenotypical variability and RYR1 variants haplotypes in a family with Malignant Hypertermia suggesting additive effect of polymorphic variants.

23. **Vainzof M.** Round Table. Influence of NGS on the old diagnostic algorithms. IV Latin American Congress on Neuromuscular diseases, Bogota, 1-3 junho 2023.

24. **Zatz M.** Medicina do future. The Power of knowledge- Singularity Brazil - 27 June 2022.

25. **Zatz M.** Latest researches at the Hug-Cell, Tel-Aviv University-13 July.

26. **Zatz M.** Acesso a genômica- Organized lecture by Valor econômico, Illumina, Globo, Folha de S.Paulo. 28 July 2022.

27. **Zatz M.** Brazilian advances in xenotransplantation -Veterinary school- USP. 13 August 2022.

28. **Zatz M.** Keynote speaker- The genomics in an aging world. The Environmental Mutagenesis and Genomics Society (EMGS) 2023- Ottawa-Canada. 28 August 2022.

29. **Zatz M.** Illumina Genomic Forum. S. Diego- California. 29 September 2022.

30. **Zatz M.** Ilumina Forum- inequitable publishing. S. Diego, California. 20 September 2022.

31. **Zatz M.** Genética: Conhecimento possível mas adequado? IX Simpósio de BIOÉTICA Hospitalar, São Paulo, SP. 19 November 2022.

32. Gomes HCA, Raia S, **Zatz M**. Xenotransplante: Novo núcleo de tecnologia avançada. IPT. São Paulo, SP. 30 November 2022.

33. **Zatz M**. Como o maior banco genömico de idosos da América Latina contribui para a medicina de precisão, Illumina. 8 December 2022.

34. **Zatz M**. A medicina do futuro- IV Curso de férias em Genética- Instituto de Biociências. São Paulo, SP. 6 February 2023.

35. **Zatz M**. O futuro da medicina- Aula inaugural da disciplina de endocrinologia da UNIFESP. São Paulo, SP. 2 March 2023.

36. **Zatz M**. Genetics, stem cells and the future of Medicine- keynote speaker- International Congress of Human Genetics- Capetown, South Africa. 22 March 2023.

37. **Zatz M**. Health and Longevity- keynote speaker- TERMIS Annual International Conference, Boston, April 2023.

38. **Zatz M**. Futuro da Medicina- Curso de Pós- graduação FAAP. São Paulo, SP. 22 April.

39. **Zatz M**. Como ser um centenário saudavel- Congress on Brain Behavior and Emotions, 2023, Florianopolis, SC. 7 June 2023.

40. **Zatz M**. Doenças genéticas raras- Aspectos Legais e Éticos - Reunião da OAB. 13 June 2023.

41. Z**atz M**. The Medicine of the future has started- Seminar series- University of Ottawa + Carleton University. 14 June 2023.

42. **Zatz M**. Congenital zika syndrome and COVID-19: lessons from twins. Twins Congress , Budapest, 2023

Annex 3 - Theses and Dissertations, Awards

3.1. PhD Theses

1. Name: Lucila N. Kerbauy
Title: Expansão de células NK com atividade anti-tumoral: aplicações em imunoterapia adotiva e mecanismos imunológicos envolvidos.
Orientador: **Oswaldo Keith Okamoto.**
Program: Pós-graduação Biologia/Genética, Instituto de Biociências, USP.

2. Name: Amanda Faria Assoni
Title: The role of neurodegeneration-associated proteins in ALS and medulloblastoma.
Orientador: **Oswaldo Keith Okamoto.**
Program: Pós-graduação Biologia/Genética, Instituto de Biociências, USP; Co-Supervisor: Floris Foijer, Post-graduation course in Biochemistry, University of Groningen, The Netherlands. (Double degree program).

3. Name: Antonio Fernando Ribeiro Júnior
Title: Estudo de proteínas envolvidas na diferenciação tardia do músculo esquelético e seu papel no processo distrófico
Orientador: **Mariz Vainzof**
Doutorado- Programa Biologia e Genética - Instituto de Biociências da Universidade de São Paulo
Inst. Financiadora: Capes.
Defesa: 24/02/2023

4.Name: Giovanna Cantini Tolezano
Title: Estudo de Alterações Cromossômicas e Variantes Gênicas Associadas à Microcefalia
Orientador: **Ana Cristina Victorino Krepischi**
Co-Orientador: **Debora Bertola**
Doutorado em Genética - Instituto de Biociências da Universidade de São Paulo
Inst. Financiadora: CNPq.
Defesa: 04/19/2023

5.Name: Laura Machado Lara Carvalho
Title: Investigação das bases genéticas da obesidade sindrômica e de mecanismos moleculares relacionados à fisiopatologia
Co-Orientador: **Ana Cristina Victorino Krepischi**
Doutorado em Genética - Instituto de Biociências da Universidade de São Paulo.
Inst. Financiadora: Fapesp
Defesa: 01/17/2023

6.Name: Luciana Bertholim Nasciben
Title: Marcadores farmacogenéticos baseados em dados genômicos de uma coorte de idosos da cidade de São Paulo e o panorama da farmacogenômica no Brasil
Orientador: **Michel Satya Naslavsky**
Programa Epidemiologia da Faculdade de Saúde Pública - USP
Defesa: 06/22/2022

7.Name: Marcela Teatin Latância
Title: Papel da síntese translesão na resistência à cisplatina e TMZ em células de glioma.
Orientador: **Carlos Frederico Martins Menck**
Doutorado no Programa Interunidades em Biotecnologia, Universidade de São Paulo, SP
Defesa: 09/06/ 2022

8.Name: Livia Luz Souza Nascimento
Título: Neurodegeneração no Envelhecimento: Lições da Síndrome de Cockayne
Orientador: **Carlos Frederico Martins Menck**
Doutorado em Microbiologia, Instituto de Ciências Biomédicas da Universidade de São Paulo
Defesa: 28//2/2022.

9.Name: Davi Jardim Martins
Title: Participação de DNA polimerase iota na ausência de Pol eta na síntese translesão de células humanas irradiadas com luz UV
Orientador: **Carlos Frederico Martins Menck**
Doutorado em Microbiologia, Instituto de Ciências Biomédicas, Universidade de São Paulo
Defesa: 04/11/ 2022

3.2. Master Degree

1. Name: Adolfo Alexis Rojas Hidalgo
Orientador: **Michel Naslavsky**

Title: “Redes de interacción molecular como herramienta para mejorar el cálculo de puntajes de riesgo poligénico y su aplicación en cáncer de mama”
Program: Universidad de Chile
Date: 04/10/2022

2.Name: Jennifer da Costa Leôncio
Title: Análise In Silico da Rede de Interação Proteína-Proteína da Conexina 26
Orientador: **Regina Célia Mingroni Netto**
Programa de Pós-graduação Biologia/Genética, Instituto de Biociências, USP
Defesa: 2022
Inst. Financiadora: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior

4.Name: Camila Cristina Avila Martins
Title: Estudo da Metilação do DNA na hipertensão essencial em populações Afro-brasileiras
Orientador: **Regina Célia Mingroni Netto**
Programa de Pós-graduação Biologia/Genética, Instituto de Biociências, USP
Defesa: 2022
Inst. Financiadora: CNPq

3.Name: Luíza Dias Chaves
Title: Padrão de inativação do cromossomo X em mulheres portadoras de deficiência intelectual
Orientador: **Ana Cristina Victorino Krepischi**
Mestrado em Mestrado profissional em aconselhamento genético - Instituto de Biociências da Universidade de São Paulo
Defesa: 06/07/2022

5.Name: Camila Galvão Lopes
Title: “Caracterização de variantes De novo em exomas de indivíduos com Transtorno do Espectro Autista”
Orientador: **Maria Rita dos Santos e Passos-Bueno**
Mestrado Genética – Instituto de Biociências da Universidade de São Paulo
Date: 04/26/2023

6.Name: William Kleber Martins Vieira
Título: Correção do gene POLH mutado em células humanas com CRISPR/Cas
Orientador: **Carlos Frederico Martins Menck**
Pós-Graduação em Microbiologia, do Instituto de Ciências Biomédicas, USP.
Defesa: 10/05/2022

3.3 Awards

Second best presentation Award.
Latancia MT, Leandro GS, Moreno NC, Bastos AU, Ribeiro VC, de Souza I, Hoch NC, Rocha CRR, **Menck CFM**. DNA Polymerase Eta Protects Human Cells against DNA damage induced by Chemotherapeutic agent Temozolomide. Presented as poster discussion talk on II Fórum de Pesquisa Translacional, virtual meeting from 31/01 to 01/02/2022.

First place Award by the Associação Paulista de Medicina de Presidente Prudente, emparceria Laboratório Marlene Spir.
Latancia MT, Moreno NC, Leandro GS, Bastos AU, Rocha CRR, **Menck CFM**. Papel da Síntese da Traslesão na resistência à Temozolomida em Células de Glioma. Abstract presented at the 28º Prêmio Científico Doutor Odilo Antunes de Siqueira, Presidente Prudente/SP on 15/10/2021.

Awarded as the best Genetic and/or Genomics XPress presentation.
Feltrin RS, de Souza TA, Durham AM, **Menck CFM**. Microbial diversity profiles in extreme environments of Antarctica. Presented at X-Meeting XPerience 2021, virtual meeting from 27 to 29/10/2021.

Best poster presentation
XXXIII Congresso Brasileiro de Genética Médica – 28/09/2022 to 01/10/2022 in Curitiba, PR: Next-generation sequencing applied to skeletal disorders: a tem year experience in a Tertiary Center in Brazil. Bruno G Marcarini, Isabela D Pasa, Guilherme L Yamamoto, Leticia Rocha, Matheus Castro, Lucas Pires, Bianca Linnnekamp, Rachel Honjo, Luiz Oliveira, Chong Kim, Maria Rita Passos-Bueno, **Débora Bertola**

Best poster presentation
Reviewers´Choice pôster Annual Meeting American Society of Human Genetics – 25/10/2022 to 29/10/2022- in Los Angeles, CA: PB1964*. Rothmund Thomson syndrome with congenital cataracts and severe growth restriction is associated with a not previously described gene in an autosomal recessive inheritance pattern in seven families. G. Yamamoto; R. Di Lazaro; T. da Silva; L. Rocha; D. Bartholdi; A. Schaller; C. Zweier; R. S. Honjo; C. Utagawa; C. Steiner; C. A. Kim; M. Passos-Bueno; N. C. Hoch; **D. R. Bertola**.

Annex 4 - Education Out Reach

4.1. Interviews to the Media

1. **Ferrari MFR**. Participação em entrevista "Humanos modernos produzem mais neurônios do que Neandertais". **Rádio US**P e **Jornal da USP**. 16/09/2022 https://jornal.usp.br/atualidades/humanos-modernos-produzem-mais-neuronios-cerebrais-do-que-neandertais-mostra-estudo/

2. **Naslavski MS, Mingroni-Netto RC.** Medicina P4**.** (preditiva, preventiva, personalizada e participativa) : O papel da Genômica e dos Biólogos na Medicina do futuro. **Canal Youtube CFBio**, **15/03/2023 <** MEDICINA P4: O papel da Genômica e dos Biólogos na Medicina do futuro – YouTube

3. **Passos-Bueno MR**, **Rosenberg C**, **Zatz M**. Best Genetics Scientists in Brazil. **Research.com**, 21/12/2022 <https://research.com/scientists-rankings/genetics/br>

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4.3. Tables

Table 1 schools were assisted by the Laboratório nas Escolas project from July to November 2022 and from February to June 2023.

High Schools	Schools Board
2022	
EE Prof. Manuel Ciridião Buarque	Midwest
EE Pereira Barreto	Midwest
EE Prof. Andronico Mello	Midwest
EE Virgília Rodrigues A. de Carvalho Pinto	Midwest
EE Solon Borges dos Reis	Midwest
EE Antônio de Almeida Junior	Osasco
EE Jardim Santa Maria III	Osasco
EE São Paulo da Cruz	Osasco
EE Prof Newton Espírito Santo Ayres	Osasco
EE Telmo Coelho Filho Major	Osasco
EE Prof Lucy Anna Carroso Latorre	Osasco
EE Julia Lopes de Almeida	Osasco
EE Prof Maria Augusta Siqueira	Osasco
EE Glória Azedia Bonetti	Osasco
EE José Ribeiro de Souza	Osasco
EE Prof Neuza de Oliveira Prévide	Osasco
EE Paulo Freire Educador	Osasco
EE Prof Ernesto Thenn de Barros	Osasco
2023	
EE Prof Almeida Júnior	Midwest
EE Prof Samuel Klabin	Midwest
EE Prof. Daniel Paulo Verano Pontes	Midwest
EE Emiliano Augusto Cavalcanti de A. Melo	Midwest
EE Romeu de Moraes	Midwest
EE Costa Manso	Midwest
EE José Monteiro Boanova	Midwest
EE Prof Emygdio de Barros	Midwest
EE Oswaldo Walder	Midwest
EE Odair Martiniano da Silva – Mandela	Midwest
EE Antônio Carlos da Trindade	Osasco
EE Claudinei Garcia	Osasco
EE Maria Augusta Siqueira	Osasco
EE Luiz Lustosa	Osasco
EE Neuza de Oliveira Prévide	Osasco
EE Francisco Matarazzo	Osasco
EE José Edson	Osasco
EE Casabona	Osasco
EE Julia Lopes Almeida	Osasco
EE Alcyr Oliveira Porciuncula	Osasco
EE Aureliano Leite	Osasco
EE Gamabarini	Osasco
EE Oguiomar Ruggieri	Osasco

EE Almeida Jr	Osasco
EE Ricardo Genésio	Osasco
EE Armando Gaban	Osasco
EE Santa Maria II	Osasco
EE Ernesto Thenn	Osasco
EE Orlando Geríbola	Osasco
EE Benedito Caldeira	Osasco
EE Ernesto Thenn	Osasco
EE Orlando Geríbola	Osasco
EE Benedito Caldeira	Osasco

Table 2 - 103 High School Teachers were trained to work in the Practical Classes at School Project, belonging to the Teaching Boards of the Osasco Region (02/28/2023) and Midwest (03/01/2023).

High Schools	Science and Biology Teachers	School Board
Ceneart	Marcos Viana da Silva	Osasco
EE Alcyr de Oliveira Porciúncula	Eduardo Barbosa	Osasco
EE Antônio Almeida Junior	Aline Morais Barroso	Osasco
EE Antônio Carlos Trindade	Marco Antonio Monteiro	Osasco
EE Antônio Raposo Tavares	Leines A Cirelli Oliveira	Osasco
EE Armando Gabam	Regiane Fernandes	Osasco
EE Armando Gaban	Lorrane M Simões	Osasco
EE Benedito Caldeira	Romulo de Carvalho*	Osasco
EE Cel. Antônio de Paiva	Thais Lima da Silva	Osasco
EE Claudinei Garcia	Daniele E O V Real	Osasco
EE Deputado Guilherme Almeida	Fabiana Carvalho	Osasco
EE Dr. Américo Marco Antônio	Rafael Fernandes de Oliveira	Osasco
EE Educador Paulo Freire	Vitor M C Cabeleiro	Osasco
EE Eloi Lacerda	Antônio Rocha	Osasco
EE Ernesto Then de Barros	Marcos Viana da Silva*	Osasco
EE Ernesto Then de Barros	Ester Alves Correa	Osasco
EE Fanny Monzoni Santos	Nicole R C de Rezende	Osasco
EE Gloria Azedia Bonetti	Katia A Batista	Osasco
EE Graciliano Ramos	Maria d Lourdes Oliva	Osasco
EE Irma Gabriela	Rômulo de Carvalho	Osasco
EE Jardim Santa Maria III	Ester Alves Correa*	Osasco
EE José Geraldo Vieira	Valquíria Fornarolli	Osasco
EE Jose Liberatt	Lucilene Costa Souza	Osasco
EE José Maria Rodrigues Leite	Danielle M. Reis Sena Alves	Osasco
EE Julia Lopes Almeida	Lorena Sales Fernandes	Osasco
EE Luiz Lustosa	Ingrid Catarino	Osasco
EE Major Telmo Coelho Filho	Vitor Henrique Corredor	Osasco
EE Maria Augusta de Siqueira	Ana Beatriz Alves	Osasco
EE Oguiomar Ruger	Gabriela Costa dos Santos	Osasco
EE Orlando Geribola	Marina S Barbosa	Osasco
EE Prof. Alice Velho Teixeira	Erica Aparecida Silva Garcia	Osasco
EE Prof. Francisco Casabona	Giovanna Ap.C Domiatti	Osasco
EE Prof. José Edson Martins	Leandro Dias dos Santos	Osasco

EE Prof. José Jorge	Juliana P Lima	Osasco
EE Prof. Newton do Espirito Santo Ayres	Gabriela Mileni E R da Silva	Osasco
EE Prof. Rosa Bonfiglioli	Camila Candelo	Osasco
EE Ricardo Genesio da Silva	Geovana B. de Oliveira	Osasco
EE Rosa Bonfiglioli	Gabriela F C Silva	Osasco
EE Rosa Bonfiglioli	Rafael de Barros Novaes	Osasco
EE São Paulo Da Cruz	Maria Francionante	Osasco
EE Tarsila do Amaral	Roberto Talarin	Osasco
EE Vicente Peixoto	Antonio Carlos Dias Junior	Osasco
EE Walter Negreli	Cristiane Soares da Silva	Osasco
EE.José Ribeiro de Souza	Guilherme Nogueira Martins	Osasco
EE Prof. Alberto Torres	Ligia Novac Souza	Midwest
EE Prof. Aristides de Castro	Camila Beatriz Moraes Contrucci de Souza	Midwest
EE Prof. Daniel Paulo Verano Pontes	Fellipe Steinmeyer	Midwest
EE Prof. Manuel Ciridião Buarque	Leandro Nhoncance	Midwest
EE Samuel Klabin	Barbara da Silva Ernandes	Midwest
EE Solon Borges dos Reis	Pâmela Tavares da Silva	Midwest
	João Luís de Abreu Vieira	Midwest
EE Thomázia Montoro	Neide Miwako Hossokawa	Midwest
EE Virgílio Rodrigues de A. Carvalho Pinto	Antônio José Morato Pinto Gonçalves	Midwest
EE Prof. Andronico de Mello	George Rissio Lourenço	Midwest
	Nádia Naiane do Nascimento de Macedo	Midwest
EE. Prof. Architiclino Santos	Vivian Alexandre de Oliveira	Midwest
EE Dr Kyrillos	Carolina Ferreira Torres	Midwest
EE Pereira Barreto	Lilian Colombine Etchebehere	Midwest
EE Prof. Almeida Junior	Diego Arruda Filgueira	Midwest
EE Dona Ana Rosa de Araujo	Rubens Pimenta Maciel	Midwest
	Ana Paula Rodrigues de Souza	Midwest
EE Anhanguera	Thais Resende Diniz	Midwest
	Renan Arruda Amorim Rezende	Midwest
EE Prof. Antônio Alves Cruz	Cleber Faustino dos Santos	Midwest
	Fabiana Cordeiro Pereira	Midwest
EE Deputado Augusto do Amaral	Juliana Miguel Torres	Midwest
EE Carlos Maximiliano Pereira dos Santos	Lucélia Batista Lima	Midwest
EE Ministro Costa Manso	Claudia Sonehara Cavalcanti de Arruda	Midwest
EE Emiliano Augusto Cavalcante de Albuquerque e Melo	Priscila Ortega	Midwest
EE Prof. Emydio de Barros	Camila Vitorino dos Santos	Midwest
	Juliana Cristina Parise Gobbo	Midwest
EE Prof.Flavia Vizibeli Pirro	Ana Caroline Bambirra Falvella	Midwest
EE Godofredo Furtado	Carolina de Castilho Peneque Garcia	Midwest
	Donata Mahmud Silva	Midwest

EE Prof. Guiomar Rocha Rinaldi	Eveline Souza da Cruz	Midwest
	Luiza Mel Falcão Pereira	Midwest
EE Prof. José Monteiro Boanova	Marceli Barros Brito	Midwest
	Emily Nascimento Faverin	Midwest
EE Prof. Lourenço Filho	Rosemary Nakano Cavalli Rodrigues	Midwest
EE Prof. Lourival Gomes Machado	Silvia Denise da Silva	Midwest
EE Prof. Lygia de Azevedo Souza e Sa	Jéssica Paranhos Estácio	Midwest
EE Prof. Maria Eugênia Martins	Luciano Inácio Pereira	Midwest
EE Prof. Maria Ribeiro Guimaraes Bueno	Adriana Rosendo da Silva	Midwest
	Francine dos Santos Aguiar	Midwest
EE Martim Francisco	Maria Fernanda da Costa Oliveira	Midwest
EE Prof. Napoleão de Carvalho Freire		Midwest
EE Odair Martiniano da Silva Mandela	Regiane Fernandes Alexandrino	Midwest
	Carlos Roberto Cardoso Ferreira	Midwest
EE Oswaldo Aranha	Edgard Emanuel de Morais Lopes	Midwest
	Erika Fernanda de Oliveira Ramos Ferreira	Midwest
EE Prof. Oswaldo Walder	Rafaela Pereira Maia LucieneChaves	Midwest
EE Prof. Paulo Rossi	Patrícia Amistá Bianchi	Midwest
EE Prof. Pedro Fonseca	Orlando Luiz Amado Giarletti	Midwest
	Thais Renata Rabanea	Midwest
EE Pereira Barreto	Lilian Colombini Etcheberehe	Midwest
EE Dr Reinaldo Ribeiro da Silva	Ewerton da Silva Souza	Midwest
EE Romeu de Moraes	Lisandre Camila de Oliveira	Midwest
EE Samuel Klabin	Barbara S Ernandes	Midwest
EE Solon Borges dos Reis	Pamela Tavares da Silva João Luis de Abreu Vieira	Midwest
EE Tomazia Montoro	Neide Miwako Hossokawa	Midwest
EE Virgílio Rodrigues Alves de Carvalho Pinto	Monique da Silva Losano	Midwest
	Antonio José Morato Pinto Gonçalves	Midwest

*****_Teacher who teaches in two schools_

Table 3 – 42 High School Teachers from the Midwest Board were trained to work on the Didactical Material Project (12/04/2023)

High Schools	**Science and Biology**	
EE Prof. Alberto Torres	Ligia Novac Souza	
EE Pro. Alberto Levy	Marcos Adão Ramirez Gonçalves	
EE Prof. Aristides de Castro	Camila Beatriz Moraes Contrucci de Souza	
EE Prof. Daniel Paulo Verano Pontes	Fellipe Steinmeyer	
EE Prof. Manuel Ciridião Buarque	Leandro Nhoncance	
EE Prof. Andronico de Mello	George Rissio Lourenço	
	Nádia Naiane do Nascimento de Macedo	

EE Dr Kyrillos	Carolina Ferreira Torres	
EE Prof. Almeida Junior	Diego Arruda Filgueira	
EE Dona Ana Rosa de Araujo	Rubens Pimenta Maciel	
	Ana Paula Rodrigues de Souza	
EE Anhanguera	Thais Resende Diniz	
EE Prof. Antonio Alves da Cruz	Fabiana Cordeiro Pereira	
EE Deputado Augusto do Amaral	Juliana Miguel Torres	
EE Carlos Maximiliano Pereira dos Santos	Lucélia Batista Lima	
EE Ministro Costa Manso	Claudia Sonehara Cavalcanti de Arruda	
EE Emiliano Augusto Cavalcante de Albuquerque e Melo	Priscila Ortega	
EE Prof.Flavia Vizibeli Pirro	Ana Caroline Bambirra Falvella	
EE Godofredo Furtado	Carolina de Castilho Peneque Garcia	
	Donata Mahmud Silva	
EE Prof. Guiomar Rocha Rinaldi	Eveline Souza da Cruz	
	Luiza Mel Falcão Pereira	
EE Prof. José Monteiro Boanova	Marceli Barros Brito	
	Emily Nascimento Faverin	
EE Prof. Lourenço Filho	Rosemary Nakano Cavalli Rodrigues	
EE Prof. Lourival Gomes Machado	Vera Lúcia Fernandes Pereira Gião	
EE Prof. Maria Ribeiro Guimaraes Bueno	Adriana Rosendo da Silva	
	Silvia Denise da Silva	
EE Odair Martiniano da Silva Mandela	Carlos Roberto Cardoso Ferreira	
EE Oswaldo Aranha	Edgard Emanuel de Morais Lopes	
	Erika Fernanda de Oliveira Ramos Ferreira	
EE Prof. Oswaldo Walder	Rafaela Pereira Maia Luciene Chaves	
EE Prof. Paulo Rossi	Patrícia Amistá Bianchi	
EE Prof. Pedro Fonseca	Orlando Luiz Amado Giarletti	
	Thais Renata Rabanea	
EE Dr Reinaldo Ribeiro da Silva	Ewerton da Silva Souza	
EE Romeu de Moraes	Lisandre Camila de Oliveira	
EE Samuel Klabin	Barbara S Ernandes	
EE Solon Borges dos Reis	João Luis de Abreu Vieira	
EE Tomazia Montoro	Neide Miwako Hossokawa	
EE Virgílio Rodrigues Alves de Carvalho Pinto	Antonio José Morato Pinto Gonçalves	

Table 4. On social networks, HUG-CELL is known as GenomaUsp and is present on YouTube, Facebook and Instagram. Production between July, 2022 and May2023.

4.A. Youtube (57 videos)

Subjects	Number of videos	Views
ABC Animal Models	6	1.769
Instructional Material	9	5.379
III Symposium on Genetics of Autism Spectrum Disorder	13	3.225
Decoding DNA - Mayana Zatz Program on Rádio USP	20	2.149
Straight from the Genome	1	331
Is it in the DNA?	5	4.925
Similar but Different	2	792
Fake news about genetic engineering	1	447

Total de visualizações neste período (incluindo vídeos antigos) = 181.702

4.B. Instagram (55 feed posts, 63 videos and 505 Stories)

Subject	Posts	Videos	Stories
Genetic counseling	11	3	96
Animal Models	4	7	35
Similar but Different		3	10
Announcement about fellowships, events, calls for volunteers and petitions, publicizing symposiums	1	1	17
Instructional Material	8	1	60
Is it in the DNA	5	5	50
Autism	3	13	22
Vaccines	1	2	5
Genetic deseases	11	2	58
Commemorative dates	1	1	21
Science heroes	4		45
How Science works	1	2	7

Aging	3		19
Decoding DNA - Program on Rádio USP		19	
Cultural tips	2		14
Curiosities of genetics		1	
Disclosure of services to researchers and physicians		1	12
USP Professions Fair		1	13
Reaction to Fake News		1	
GenomeUSP in the media			21

Annex 5 – Personnel

Scientific Initiation - IS	
Supervisor	**Student**
Ana Cristina V. Krepischi	Davi Mendes Campos Fialho
	Bianca Kurashima
	Larissa Moreira
	Maisa Ganz Sanchez Sennes
Luis Eduardo Soares Netto	Sophia Beltrame de Oliveira Lima
	Melissa Siolin Martins
	Júlia Maria de Almeida Silvino
Maria Rita Passos Bueno	Luara Beatriz Gheler de Novaes
	Eloah Camargo Pregnolato
Mariz Vainzof	Luiza Albuquerque Toledo
	Isabela de Aquino Zogbi
	Nathalia Gagliardi Saldys
Michel Naslavsky	Camila Takase Hosoe
Merari de Fátima Ramires Ferrari	Bruno José Teixeira de Melo
	Hilton Pires de Camargo Júnior
	Julia Bressan da Silva
	Larissa Correia Lopes
	Lucas Calado de Almeida.
	Maria Carolina Boer Copstein.

	Matheus da Silva Palazzi
	Pedro Martins de Freitas
	Rafael Levy da Silva Camões
	Sarah Stephanie Mauricio de Abreu
	Thais Alexandre Falkembach Andreis
Regina Célia Mingroni Netto	Ianca Rosa Dias
	Ruan Carlos Salvador
	Ana Julia Natucci Mergulhão
	Stella Diogo Cavassana
Oswaldo Keith Okamoto	Isabela Fonseca de Oliveira Granha

Master MSc

Supervisor	Student
Ana Cristina V. Krepischi	Ana Dantas
	Gustavo Dib Dangoni
Debora Romeo Bertola	Taccyanna Mikulski
Carlos Frederico Martins Menck	William Kleber Martins Vieira
Maria Dulcetti Vibranovsk	Henry Bonilla Bruno
Maria Rita Passos Bueno	Adriana Domigues de Souza (1)
	Diogo Andrade Nani
	Igor Cabreira Ramos
Merari de Fátima Ramires Ferrari	Luann Fostter
Michel Naslavsky	Airi Carvalho
	Gabriel do Nascimento Santos
	Gustavo Pukar Augusto (1)
	Leonardo Carvalheira (1)
	Mariana Bardella
	Thiago Pires (1)
Regina Célia Mingroni Netto	Beatriz Cetalle Schiavo
	Camila Cristina Avila Martins
	Jennifer Leôncio
	Alice Kei Endo
	Ianaê Ichikawa Ceschin.
	Lucas Carvalho Price
	Maria Susana J. Marodin

	Rodolfo Sanches Ferreira.
	Thais Regina dos Santos
	Thiago Giove Mitsugi

(1) Mestrado profissional

Doctorate - PhD	
Supervisor	**Student**
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	Davi Jardim Martins.
	Davi Mendes
	Lívia Luz Souza Nascimento
	Maira Rodrigues de Camargo Neves
	Marcela Teatin Latancia
	Matheus Molina Silva
Debora Romeo Bertola	Ricardo di Lazaro Filho
	Leticia Alves da Rocha
Edson Amaro Jr	Kelly Regina Cotosck
	Liana Guerra Sanches da Rocha
	Marcia Renata Hidalgo Marques
	Paulo Rodrigo Bazan
Luis Eduardo Soares Netto	Angélica Ramos
	Maria Tereza Oliveira Batista.
	Rogério Luis Aleixo Silva
Maria Dulcetti Vibranovsk	Ana Beatriz Stein M. Ferretti
	Camila Correia Avelino
Michel Naslavsky	Frederico Monfardini
	Samantha Paco
Mariz Vainzof	Felipe Tadeu Galante Rocha de Vasconcelos
	Lucas Santos e Souza
Maria Rita Passos Bueno	Claudia Ismania Samogy Costa
	Debora Cabral de Carvalho Corrêa
	Elisa Varella Branco

	Gabriella Shih Ping Hsia
Merari de Fátima Ramires Ferrari	Alan Moreira Henrique
	Luísa Machado Pinheiro
	Romina Horianski
Mayana Zatz	Joyce Esposito de Souza
	Kayque Alvez Telles Silva
	Lara Borges Pacheco
	Monize Silva
	Raiane Ferreira
	Sabrina Kaori Kadowaki
Regina Célia Mingroni Netto	Gabriel Bandeira do Carmo
	Giovanna Cantini Tolezano
	Laura Machado Lara Carvalho
	Sara Ferreira Pires

Pos Doctorate/Visiting Researcher

Supervisor	Name
Ana Cristina V. Krepischi	Veniamin Fishman (*)
	Laura Cardoso
Carla Rosenberg	Darine Vilella
Luis Eduardo Soares Netto	Ana Luiza Dorigan de Matos Furlanetto
	Fernando Gomes
Maria Rita Passos Bueno	Ana Luiza Bossolani Martins
	Gerson Kobayashi
Mariz Vainzof	André Luis Fernandes dos Santos
Mayana Zatz	Danyllo Felipe Oliveira
	Felipe de Souza Leite. Início
	Luiz Carlos Caires Junior
	Lylyan Fragoso Pimentel
	Ma Hui Ling
	Mateus Vidigal de Castro
	Thalita Figueiredo Cunha

Oswaldo Keith Okamoto	Elisa Helena Farias Jandrey
Regina Célia Mingroni Netto	Anne Teixeira Barbosa
	Talita Aguiar

(*) **Visiting Researcher -** Genomic Mechanisms of Development group - ICG SB RAS - Novosibirsk Russia

Laboratory Technicians and Assistants

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	USP	Silvia Souza da Costa
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	CEPID/IB-USP	Marici Leite Salviano
	USP	Job Carvalho Bezerra
Luis Eduardo Soares Netto	USP	Simone Vidigal Alves
	USP	Thiago Geronimo Alegria
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	HUG-CELL/FFM	Carolina Régoli Dias
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	HUG-CELL/FUSP	Jaqueline Yu Ting Wang
	USP	Kátia Maria da Rocha
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	HUG-CELL/FFM	Marília de Oliveira Scliar
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	USP	Monize Lazar Magalhães
	USP	Naila Cristina V. Lourenço
	USP	Roberto Rivelino de Camargo
	USP	Simone Gomes Ferreira
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Mariz Vainzof	HUG-CELL/FUSP	Letícia Nogueira Feitosa
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Regina Célia Mingroni Netto	USP	Israel Rubio

Bioinformatics Support / Information Technology

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Administrative/ Finance

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Celia P. Koiffmann	USP	Luceleni da Silva
Eliana M.B. Dessen	USP	Luciana Cristina A.Oliveira
Maria Rita Passos-Bueno	HUG-CELL/FUSP	Caissa Santos C. da Silva
Mayana Zatz	HUG-CELL/FUSP	Márcia Góes Teixeira
	USP	Marta Rita Celestino de Macêdo
	USP	Wagner Falciano

Annex 6 – Plans for 2024-2025

Xenotransplantation: This project which was initiated 5 years ago aiming to use pigs 'organs for transplantation in humans. It has been supported by a private company (EMS) , FAPESP and S.Paulo government, through the CCD project. The project is coordinated by Prof. Silvano Raia from FMUSP, Mayana Zatz from HUG-CELL and a group of students, technicians and collaborators. To achieve this goal we are creating pigs genetically modified in order to prevent acute rejection. Our team at HUG-CELL was able to generated embryos where three pig genes responsible for acute rejection were knockdown . More than 200 embryos were generated and in May they were inserted in female pigs. Pregnancy was already confirmed in two animals and it is expected to have the first piglets born in September. We are currently starting to build two pig facilities (one in Cidade Universitária Campus and the other in IPT) where the next generations of pigs will be born in an environment free of pathogens. Our plan is to start the first transplants with kidneys aiming at patients who are currently in hemodialysis and have no compatible donor.

PIs : **Silvano Raia, Ernesto Goulart** and **Mayana Zatz**
Team: Luiz Carlos Caires (posdoc), Luciano Abreu Brito (posdoc), Michelle Araujo posdoc and a team of students and technicians

The search for protective variants: Our group has shown for the first time that it is possible to have a functional muscle despite the lack of dystrophin in exceptional (golden retriever muscular dystrophy) GRMD dogs and in two rare Duchenne muscular dystrophy (DMD) patients able to walk independently in their twenties. We identified a rare mutation (frequency of less than 1 in 1000) associated to the Notch pathway in these two mildly affected patients ,which was absent in all severe DMD cases and may represent a protective (P) variant against muscle degeneration. This project is underway by our group at Hug-Cell and with the collaboration of the group of Louis Kunkel, at Harvard Hospital in Boston. We have generated a mice model affected by muscular dystrophy with the P variant, and the animals are being evaluated by our former pos-doc student , Felipe Leite, who is now in Lou´s Kunkel lab. Furthermore , we have established a collaboration with the team of Prof. Eckhard Wolf from Munich who will generated a pig with the same P mutation. We hope that our research may be translated in a novel approach to treat muscular dystrophies, for which there is currently no effective therapy.
In addition to this strategy, identifying elderly carrying pathogenic variants associated with Mendelian disorders but without corresponding manifestation is leading to a comprehensive study with their families searching potential protective variants.

PIs: **Mayana Zatz and collaboration with Lou Kunkel. Michel Naslavsky**
Team: Felipe Leite (posdoc), Joyce Esposito (PhD student), Igor Neves (PhD student), Mariana Bardella (Master's student).

Aging and resistance against COVID-19: The world population is aging and there is a great interest in promoting health span. We have identified a cohort of individuals older than 90 who were cured from COVID or remained asymptomatic. Among them there is a group of centenarians and some super-centenarians (older than 110 years old). We plan to undertake a whole genome sequencing (WGS) in this cohort aiming to identify genetic variants associated to resilience. We will generate IPS-derived cell lines and brain organoids from healthy centenarians aiming to enhance our understanding on the underlying mechanisms/factors related to healthy aging. Furthermore, we will analyze through a multi-omic approach the *in vitro* impact of Sars-cov-2 infection virus before and after the infection. This project received a grant from the Health Minister and CNPq, Project coalizão.

PIs: **Mayana Zatz**, **Michel Naslavsky**, **Maria Rita Passos-Bueno**
Team: Mateus Vidigal (posdoc), Amanda Fassoni (posdoc), Danyllo Oliveira (posdoc), Vivian Romanholi Cória (MD), Joyce Esposito de Souza (PhD student), Kayque Alves Telles da Silva (PhD student), Lara Borges Pacheco (PhD student), Sabrina Kaoi Kadowaki (PhD student), Raiane O Ferreira (PhD student).

Zika virus and brain tumors: Our group has shown that zika virus can be an important ally in destroying brain tumors for which there is currently no effective treatment. We plan to expand this project investigating the outcome of intrathecal zika virus injections in dogs bearing spontaneous brain tumors. In a collaboration with the team from ICESP (Instituto de cancer do Estado de São Paulo) we will generate organoids from brain tumors removed during surgery. Aiming to enhance our understanding on Zika virus potential to destroy different tumors, we will infect these organoids with zika virus in vitro.

PIs: **Mayana Zatz** and **Oswaldo Keith Okamoto**
Student: Ma Hui Ling (posdoc), Raiane Ferreira (PhD student)

How DNA damage and Genome Instability can be implicated in human disease and aging? : For the following years we will continue our work on the identification of mutations in

patients related to DNA repair diseases, mostly xeroderma pigmentosum. We hope we will be able to cover an important portion of Brazilian patients, who agreed to have their exome sequenced, and have a distribution of the genes mutated, and novel mutations in Brazil. We also plan to explore mechanisms of carcinogenesis responsible for tumors in XP. Although most of the mutations are C>T at dipyrimidine sites, indicating they are targeted to pyrimidine dimers, many of the mutations are C>A, consistent with an effect of oxidative stress in their cells. Also, our findings showed a high frequency of retrotransposon insertions in tumors from XP-variant patients. The mechanisms responsible for these mutations will now be investigated in vitro, irradiating cells from XP-V patients with UVA. The role of DNA damage in the process of aging will be explored in pluripotent cells, either from nucleotide excision repair defective patients (CS and TTD), or in cells from centenarian patients. A search for oxidative stress responses in these cells, and for potential endogenous damage will be the main goals for the next period of this project.

PI: **Carlos Frederico Martins Menck**

Impaired myogenesis and the process of cell migration in immortalized myoblasts from patients with different forms of muscular dystrophies: Skeletal muscle impairment in genetic muscular dystrophies is markedly characterized by cycles of degeneration and regeneration. The regeneration is usually inefficient, leading to a progressive loss of muscle mass. Our recent studies with mice dystrophic models, however, have shown maintenance of an active regenerative process in the muscles along the time, with the maintenance of a significant pool of satellite cells with proliferative capacity, and formation of new muscle fibers. Nonetheless, these newly formed fibers remain smaller and with fewer myonuclei, compatible with a defective regenerative process. To better understand this compromised mechanism, we are studying the myogenesis in the dystrophic muscle using a cellular model of immortalized myoblasts from NMD patients and normal controls.
In this project we intend to study the migration pattern of transformed myoblasts, obtained from patients with different neuromuscular diseases, to evaluate the effect of primary mutations in this process. Furthermore, the role of the VMA21 gene in exacerbated myogenesis in XMEA will be assessed through its silencing in normal muscle cell lines, using the CRISPR-cas9 system.. The analyses are performed using the estimation of the fusion index and the diameter of the myotube. The ability of myoblats to migrate will be evaluated in a transwell migration assay.

PI: **Mariz Vainzof**
Student: Antonio Fernando Ribeiro Junior (PhD), Lucas Santos e Souza (PhD)), Brandow Willy (MS), Isabella de aquino Zogbi (IC), Luiza Albuquerque Coelho (IC)

Haplotypes in the RYR1 gene acting as modifier of the dystrophic phenotype.
We recently identified a family with eight malignant hyperthermia susceptibility (MHS) patients, in which a known pathogenic mutation in RYR1 was identified only in two of them. Clinical signals however, were present in six additional patients. The reason for their clinical phenotype was investigated looking for additional polymorphisms in the RYR1 gene. We identified four different haplotypes segregating within the family, suggesting a possible participation in muscle phenotype variability, worsening the clinical course, when present in one allele, or associated with the already known mutation in the second allele. The pattern of segregation of variants in the RYR1 could suggest the importance of studying the complete genotype in RYR1, including more frequent variants organized in specific haplotypes, acting as modifier of the phenotype. We are now investigating if this haplotype in the RYR1 gene could be acting as modifiers of the phenotypes in other NMD.

PI: **Mariz Vainzof**
Student: Lucas Santos e Souza (PhD), Brandow Willy (MS), Isabella de aquino Zogbi (IC), Luiza Albuquerque Coelho (IC)

The process of muscle degeneration and regeneration with aging, in mouse models for neuromuscular disorders: Skeletal muscle has a remarkable capacity to regenerate after injuries mainly due to a reservoir of precursor cells named satellite cells (SCs), which are responsible for after-birth growth and response to lesions. Upon injury, the regenerative response includes SCs exit of quiescence, activation, proliferation and fusion to repair or form new myofibers. This process is accompanied by inflammation, with infiltration of immune cells, primarily macrophages. Every phase of regeneration is highly regulated and orchestrated by many molecules and signaling pathways. The elucidation of players and mechanisms involved in muscle degeneration and regeneration is of extreme importance, especially for therapeutic strategies for muscle diseases. We recently developed a model of muscle injury induced by electroporation, which is an efficient method to induce muscle damage in order to follow the steps involved in degeneration and regeneration. This methodology can be employed to study alterations in gene expression and the process of satellite cell recruitment, both in healthy and dystrophic/myopathic animal models for muscular dystrophy (Almeida and Vainzof, 2020), and muscle regeneration with age. Recent studies have identified tubular aggregates (ATs) in muscle fibers of elderly male mice, in an event dependent on the age of the animal. Now, we are evaluating muscle regeneration in elderly mice normal and with different forms of dystrophies, trying to point out the role of myo-aggregates (ATs and myogranules). Understanding the mechanistic differences in muscle regeneration between young and old muscles elderly, with and without muscular dystrophies, may be important in aiming future therapies.

PI: **Mariz Vainzof**

Student: Antonio Fernando Ribeiro Junior (PhD), Lucas Santos e Souza (PhD), Felipe Tadeu Galante R. de Vasconcelos (PhD), Brandow Willy (MS), Isabella de aquino Zogbi (IC), Luiza Albuquerque Coelho (IC)

Neurodevelopmental disorders (NDDs): Neurodevelopmental disorders (NDDs) are complex and heterogeneous conditions involving a disruption of brain development, leading to intellectual disability among others. Genomic tests can partially elucidate the underlying molecular architecture disclosing different types of genetic alterations, which span from single nucleotide variants (SNVs) to large chromosomal rearrangements. However, there are challenges in establishing genotype-phenotype correlations and disentangling the pathophysiology of monogenic mutations. In addition, part of the studied cases of idiopathic intellectual disability remains without a definitive molecular diagnosis even after extensive genetic screening, including those with identified variants of uncertain significance. The pathogenic role of noncoding genetic alterations emerges only recently, including structural variations (SV), which carry the potential to exert a substantial influence on human diseases; yet SVs pose as a challenge to detect and interpret. As new technologies are developed, SVs can be characterized, leading to further advancements. In the following two years, we intend to deepen the understanding of the role of diverse *AHDC1* pathogenic variants in causing Xia-Gibbs syndrome and its variable expressivity, using two functional models already established in our group (*AHDC1*-mutatted IPSs cell lines and zebrafish), besides expand the cohort of Brazilian patients with Xia-Gibbs syndrome in the study. We also will investigate the impact of previously detected SVs in specific phenotypes by using a combined approach of genomic (optical genome mapping and whole-genome sequencing) and epigenomic (RNAseq and Hi-C) technologies, aiming to provide novel biological insights, besides molecular diagnosis underlying rare diseases.

PI: **Ana Krepischi**

Genetic architecture and mechanisms to understand clinical variability in genetic disorders: We aim to continue our work on the characterization of the genetic architecture of Autism (referred to as autism spectrum disorder or ASD) and severe Childhood Apraxia of Speech (CAS), which also is commonly associated with ASD. In order to achieve this goal, we have been using the following strategies: a) analyzing three-generation families (that is, ASD probands, their parents, and grandparents); b) characterizing the rare genetic variants in the coding region (whole exome analysis) of autistic individuals and respective controls and combining transcriptome and epigenetics to identify the functional effects of the candidate variants at neuronal cells; c) characterizing rare genetic variants (potentially de novo variants)

in a cohort of 93 CAS. We expect that our approaches will lead to a better understanding of the combination of type and number of damaging variants necessary to lead to Autism and identifying novel genes associated with CAS. We also aim to continue our projects to understand the molecular basis of clinical variability and incomplete penetrance associated with phenotypes. To achieve these goals, we have selected two disease models: Phelan McDermid Syndrome (PMS), a neurodevelopmental disorder associated with Autism, and Treacher Collins syndrome (TCS), a craniofacial condition. To address our questions, we are modeling PMS, TBCK syndrome, and TCS in a dish by using induced pluripotent cells (iPSCs) derived from somatic cells of affected individuals and controls. These cells have been differentiated in the tissue of interest for each disease: neuronal cells (PMS, TBCK) or neural crest cells (TCS). RNAseq analysis and other cellular measurements (p.ex, proliferation, differentiation efficiency) have been used to address our questions.

PI: **Maria Rita dos Santos e Passos-Bueno**

Functional studies related to genetic variants causative of hearing loss in Brazilian families: The previously CEPID funded projects allowed the collection of a large sample of patients with hearing loss, which allowed the identification of novel genes and novel variants, candidate to explain hearing loss in Brazilian families. Many of these genes and variants and their effects will be under study using different types of cell models and functional studies. Induced Pluripotent Stem Cells (IPS cells) will be obtained from individuals with hearing loss and will be used in different assays, such as immunoprecipitation, co-immunoprecipitation, PCR Real Time and RNASeq, in order to assess RNA and protein expression. Parameters related to oxidative stress will also be determined to find a connection between mitochondria and oxidative stress to the pathogenesis of hearing loss.

PI: **Regina Célia Mingroni Netto**
Collaborators: Dr. Luciana Haddad, Dr. Luis Netto and Dr. Karina Lezirovitz (FMUSP).

African-ancestry modulation of Alzheimer's risk: We aim to identify genomic variants of African (AFR) and admixed ancestries associated with Alzheimer's disease (AD) based on the hypothesis that AFR local ancestry (LA) of APOE, APOE-related, and other AD-related loci modulate AD risk. Blacks and Latinos are 1.5-2x more likely to develop dementia than non-Hispanic Whites. We showed that
AFR had a lower neuropathological burden but had worse cognitive outcomes in admixed Brazilians. This association was attenuated in those with AFR local ancestry on apolipoprotein E (APOE) ε4. We will perform whole-genome sequencing (WGS) and innovative genomic

approaches to leverage a population-based, well-characterized clinicopathological sample of 2,000+ admixed Brazilians (Biobank for Aging Studies, BAS). We will characterize the entire genome for AFR, European (EUR), and Native American (NAM) global and local ancestries (GA/LA) and functionally annotate AD-related genes to measure ancestry differentially effects on AD outcomes.

PI: **Michel S. Naslavsky,** in collaboration with Claudia Suemoto (FMUSP) and Lea Grinberg (FMUSP/UCSF). Partial funding for whole-genome sequencing from the Alzheimer's Association (Awardee: Michel Naslavsky)
Students: Gabriel Nascimento (Master's), Samantha Paco (PhD) and Frederico Monfardini (PhD).

Genomics of African-Brazilian populations related to cardiovascular risks: Cardiovascular risk factors (CVRFs) comprise complex biological traits and behavioral patterns that increase risk for cardiovascular disease. The leading CVRFs include hypertension, obesity, unhealthy diet, low physical activity, dyslipidemia, smoking, and diabetes. We will focus on three CVRFs: essential hypertension (EH), obesity (OB) and hypercholesterolemia (HC). Different genetic mapping strategies, combining linkage studies, family based association studies, GWAS and admixture mapping , will be used to reveal chromosomal Regions of Interest (ROI) and candidate variants associated to EH, OB and DL in samples collected from a Brazilian African-descent population from Remnants from Quilombos: a total of 1320 samples collected by the group over the last decades with, presently, 650 individuals genotyped in ~650,000 single nucleotide polymorphisms (SNPs) using the Affymetrix Axiom Human Origins1 Array, 56 with Whole Exome Data and 96 with WGS (Whole Genome Data). More samples with WES and WGS will be available during the development of the project. Data will be compared to genomic and phenotypic data available in All of Us dataset, a Research Program with various types of data (e.g., biological, health, social, and environmental) aside from whole-genome sequencing (WGS) data. AoU dataset version 6 has a total of 66,692 admixed Hispanic or Latino participants. Also, we will employ the "The 1200 Brazilian completely sequenced genomes from the SABE Project (*Saúde, Bem Estar e Envelhecimento*; Health, Well Being and Aging), available in our own research center. The final aim of the research is to provide association data (odds ratios) adjusted by admixture, that will allow the development of PRS (Polygenic Risk Scores) suitable to admixed populations, with emphasis on admixed Brazilian African-descendent populations, underrepresented in global genomic databases.

PIs : **Regina Célia Mingroni Netto and Michel Naslavski**
National Collaboration: Dr. Diogo Meyer
International Collaboration: University of Marshall, WV, EUA, with a team coordinated by Dr. Alejandro Nato Jr.