REPORT

July 2023 to June 2024

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HUMAN GENOME AND STEM CELL RESEARCH CENTER (HUG-CELL)

Universidade de São Paulo

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ABSTRACT

Since July 2023 our group has published 81 articles in peer-review journals, 18 abstracts in international meetings and 13 in National meetings. Most of the articles involved the collaboration of students and PIs from HUG-CELL as well as researchers from other Brazilian or international groups. Furthermore, our group has been involved in several international consortia. A total of 10 thesis were presented (7 PhDs and 4 Masters). Our group delivered 40 conferences. Online activities included 66 interviews , lectures and symposia which were presented by our team as well as Interviews to the Media and Science Dissemination Articles.

The applications of technology transfer included genetic counseling for about 1,330 families. In the last year, a total of 17,200 genetic tests and about 435 NGS sequencing services were performed at HUG-CELL EMU, as detailed in the report. We also expanded the types of tests in NGS analysis using bioinformatic analysis including the repeat-expansion mutations . We also implemented whole transcriptome analysis as a new service. Additionally, we collaborated with the diffusion group coordinated by Dr. Eliana Dessen Dessen aiming to expand the dissemination of our services to our scientific and medical communities, which resulted in ~ 30% increase in demand on genetic tests and genomic services.

The Center assisted 66 schools in the Laboratory Schools project and trained 71 teachers to work on it; 46,200 students were benefited. Furthermore, 21 High School students were trained to act as monitors during while the laboratories were in their schools. The Giant Cell was visited by 2,5 thousand people. In YouTube the scientific dissemination team idealized and produced 28 videos that addressed different subjects related to genetic and science. On Instagram (with 21,600 subscribers), 46 feed posts, 32 videos and 230 Stories were produced., The YouTube channel had 6,600 views, 6,500 hours assisted and 2,01 thousand new subscribers.

CONTENTS

PART 1- RESEARCH

Our main research results from **July 2023 to June 2024**, classified by our main objectives are:

A. Gene Identification and Mechanisms in Genetic Disorders

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

A1.1. Mendelian Disorders

Genetic etiology of Mendelian syndromic obesity: Syndromic obesity refers to obesity occurring with additional clinical findings, such as intellectual disability/developmental delay, dysmorphic features, and congenital malformations. We presented a narrative review regarding the genetic etiology, clinical description, and molecular diagnosis of syndromic obesity, which is a rare condition with high phenotypic variability and genetic heterogeneity. The following syndromes are presented in this review: Prader-Willi, Bardet-Biedl, Pseudohypoparathyroidism, Alström, Smith-Magenis, Cohen, Temple, 1p36 deletion, 16p11.2 microdeletion, Kleefstra, SIM1-related, Börjeson-Forssman-Lehmann, WAGRO, Carpenter, MORM, and MYT1L-related syndromes. RECENT FINDINGS: There are three main groups of mechanisms for syndromic obesity: imprinting, transcriptional activity regulation, and cellular cilia function. For molecular diagnostic, methods of genome-wide investigation should be prioritized over sequencing of panels of syndromic obesity genes. In addition, we present novel syndromic conditions that need further delineation, but evidence suggests they have a higher frequency of obesity. The etiology of syndromic obesity tends to be linked to disrupted neurodevelopment (central) and is associated with a diversity of genes and biological pathways. In the genetic investigation of individuals with syndromic obesity, the possibility that the etiology of the syndromic condition is independent of obesity should be considered. The accurate genetic diagnosis impacts medical management, treatment, and prognosis, and allows proper genetic counseling

PIs: **Ana Krepischi, Carla Rosenberg** and **Debora Bertola**
Pos-doc: Laura Machado Lara Carvalho

Publications: **Carvalho LML**, Jorge AAL, **Bertola DR, Krepischi ACV, Rosenberg C.** *A Comprehensive Review of Syndromic Forms of Obesity: Genetic Etiology, Clinical Features and Molecular Diagnosis*. Curr Obes Rep. 2024 Jan 26. doi: 10.1007/s13679-023-00543-y. Epub ahead of print. PMID: 38277088.

Germline mutations in cancer predisposition genes among pediatric patients with cancer and congenital anomalies: Childhood cancer has a poorly known etiology, and investigating the underlying genetic background may provide novel insights. A recognized association exists between non-chromosomal birth defects and childhood cancer susceptibility. We performed whole-exome sequencing and chromosomal microarray analysis in a cohort of childhood cancer with congenital anomalies. Relevant findings were detected in 55% of the syndromic individuals, mostly variants potentially underlying both phenotypes. We uncovered a remarkable prevalence of germline deleterious CPG variants, highlighting the significance of a comprehensive genetic analysis in pediatric cancer, especially when coupled with additional clinical signs. Moreover, our findings emphasized the potential for oligogenic inheritance, wherein multiple genes synergistically increase cancer risk. Lastly, our investigation unveiled potentially novel genotype-phenotype associations, such as *SETD5* in neuroblastoma, *KAT6A* in gliomas, *JAG1* in hepatoblastomas, and *TNFRSF13B* in Langerhans cell histiocytosis.

PIs: **Ana Krepischi**
PhD: Gustavo Dib Dangoni, pos-doc

Publications: **Dangoni GD**, Teixeira ACB, da Costa SS, Scliar MO, Carvalho LML, Silva LN, Novak EM, Vince CSC, Maschietto MC, Sugayama SMM, Odone-Filho V, **Krepischi ACV**. *Germline mutations in cancer predisposition genes among pediatric patients with cancer and congenital anomalies*. Pediatr Res. 2024 Apr;95(5):1346-1355. doi: 10.1038/s41390-023-03000-7. Epub 2024 Jan 5. PMID: 38182823.

Clinical Characterization and Underlying Genetic Findings in Syndromic Microcephaly Associated with Neurodevelopmental Disorders: Neurodevelopmental disorders (NDD) are commonly associated with microcephaly, due to perturbations in brain development and functioning. We investigated the genetic basis of syndromic microcephaly accompanied by NDD. Pathogenic/likely pathogenic variants were identified in 19 families (18 genes) with a diagnostic yield of approximately 45%. Nearly 86% of the individuals had global developmental delay/intellectual disability and 51% presented with behavioral disturbances. Additional frequent clinical features included facial dysmorphisms (80%), brain malformations (67%), musculoskeletal (71%) or cardiovascular (47%) defects, and short stature (54%). Our findings unraveled the underlying genetic basis of microcephaly in half of the patients, demonstrating a high diagnostic yield of WES for microcephaly and reinforcing its genetic heterogeneity. We expanded the phenotypic spectrum associated with the condition and identified a potentially novel gene (CCDC17) for congenital microcephaly. We identified biallelic KNL1 variants in two siblings from a non-consanguineous family with microcephaly and intellectual disability. KNL1 is the central component of the KNL1-MIS12-NSL1 (KMN) network, which acts as the signaling hub of the kinetochore and is required for correct chromosomal segregation during mitosis. The two siblings carry a frameshift variant predicted to prematurely truncate the transcript and undergo nonsense mediated decay, and an intronic single nucleotide variant (SNV) predicted

to disrupt splicing. An in vitro splicing assay and qPCR from blood-derived RNA confirmed that the intronic variant skips exon 23, significantly reducing levels of the canonical transcript. Protein modeling confirmed that absence of exon 23, an inframe exon, would disrupt a key interaction within the KMN network and likely destabilize the kinetochore signaling hub, disrupting mitosis.

PIs: **Ana Krepischi, Debora Bertola** and **Carla Rosenberg**
PhD: Giovanna Tolezano

Publications: **1) Tolezano GC**, Bastos GC, da Costa SS, Scliar MO, de Souza CFM, Van Der Linden H Jr, Fernandes WLM, Otto PA, Vianna-Morgante AM, Haddad LA, Honjo RS, Yamamoto GL, Kim CA, **Rosenberg** C, Jorge AAL, **Bertola DR, Krepischi ACV**. *Clinical Characterization and Underlying Genetic Findings in Brazilian Patients with Syndromic Microcephaly Associated with Neurodevelopmental Disorders*. Mol Neurobiol. 2024 Jan 5. doi: 10.1007/s12035-023-03894-8. Epub ahead of print. PMID: 38180615.

2) Fellows BJ, **Tolezano GC**, Pires SF, Ruegg MSG, Knapp KM, **Krepischi** ACV, Bicknell LS. *A novel KNL1 intronic splicing variant likely destabilizes the KMN complex, causing primary microcephaly*. Am J Med Genet A. 2024 Mar;194(3):e63468. doi: 10.1002/ajmg.a.63468. Epub 2023 Nov 8. PMID: 37937525.

Update consensus guidelines on the management of Phelan McDermid syndrome: Phelan-McDermid syndrome (PMS) is a genetic condition caused by SHANK3 haploinsufficiency and characterized by a wide range of neurodevelopmental and systemic manifestations. The first practice parameters for assessment and monitoring in individuals with PMS were published in 2014; recently, knowledge about PMS has grown significantly based on data from longitudinal phenotyping studies and large-scale genotype-phenotype investigations. The objective of these updated clinical management guidelines was to: (1) reflect the latest in knowledge in PMS and (2) provide guidance for clinicians, researchers, and the general community. A taskforce was established with clinical experts in PMS and representatives from the parent community. Experts joined subgroups based on their areas of specialty, including genetics, neurology, neurodevelopment, gastroenterology, primary care, physiatry, nephrology, endocrinology, cardiology, gynecology, and dentistry. Taskforce members convened regularly between 2021 and 2022 and produced specialty-specific guidelines based on iterative feedback and discussion. Taskforce leaders then established consensus within their respective specialty group and harmonized the guidelines. The knowledge gained over the past decade allows for improved guidelines to assess and monitor individuals with PMS. Since there is limited evidence specific to PMS, intervention mostly follows general guidelines for treating individuals with developmental disorders. Significant evidence has been amassed to guide the management of comorbid neuropsychiatric conditions in PMS, albeit mainly from caregiver report and the experience of clinical experts. These updated consensus guidelines on the management of PMS represent an advance for the field and will improve care in the community. Several areas for future research are also

highlighted and will contribute to subsequent updates with more refined and specific recommendations as new knowledge accumulates.

PI: **Maria Rita Passos Bueno**

Publication: Srivastava S, Sahin M, Buxbaum JD, Berry-Kravis E, Soorya LV, Thurm A, Bernstein JA, Asante-Otoo A, Bennett WE Jr, Betancur C, Brickhouse TH, **Passos Bueno MR**, et al. *Update consensus guidelines on the management of Phelan McDermid syndrome*. Am J Med Genet A. 2023 Aug;191(8):2015-2044. doi: 10.1002/ajmg.a.63312. Epub 2023 Jul 1.PMID: 37392087 Review.

Heterozygous variants in TBCK cause a mild neurologic syndrome in humans and mice:TBCK-related encephalopathy is a rare pediatric neurodegenerative disorder caused by biallelic loss-of-function variants in the TBCK gene. After receiving anecdotal reports of neurologic phenotypes in both human and mouse TBCK heterozygotes, we quantified if TBCK haploinsufficiency causes a phenotype in mice and humans. Using the tbck+/- mouse model, we performed a battery of behavioral assays and mTOR pathway analysis to investigate potential alterations in neurophysiology. We conducted as well a phenome-wide association study (PheWAS) analysis in a large adult biobank to determine the presence of potential phenotypes associated with this variant. The tbck+/- mouse model demonstrates a reduction of exploratory behavior in animals with significant sex and genotype interactions. The concurrent PheWAS analysis of 10,900 unrelated individuals showed that patients with one copy of a TBCK loss-of-function allele had a significantly higher rate of acquired toe and foot deformities, likely indicative of a mild peripheral neuropathy phenotype. This study presents an example of what may be the underappreciated occurrence of mild neurogenic symptoms in heterozygote individuals of recessive neurogenetic syndromes..

PI: **Maria Rita Passos Bueno**
Students: Elisa Varella Branco (PhD student), Igor R. Cabreira (Master student)

Publication: Nair D, Diaz-Rosado A, **Varella-Branco E, Ramos I**, Black A, Angireddy R, Park J, Murali S, Yoon A, Ciesielski B, O'Brien WT, **Passos-Bueno MR**, Bhoj E. *Heterozygous variants in TBCK cause a mild neurologic syndrome in humans and mice*. Am J Med Genet A. 2023 Oct;191(10):2508-2517. doi: 10.1002/ajmg.a.63320.

The Contribution of Next-Generation Sequencing to the Identification of Novel Causative Variants: Waardenburg syndrome (WS) is characterized by hearing loss and pigmentary abnormalities of the eyes, hair, and skin. The condition is genetically heterogeneous, and is classified into four clinical types.. Six genes are already known to be associated with WS but molecularly undetected patients remain. This study aimed to pinpoint causative variants using different NGS approaches in a cohort of 26 Brazilian probands with

possible/probable diagnosis of WS1 (8) or WS2 (18). Causative variants were detected in 20 of the 26 probands analyzed, these being five in *PAX3*, eight in *MITF*, two in *SOX10*, four in *EDNRB*, and one in *ACTG1* (type 2 Baraitser-Winter syndrome, BWS2). The detection rate of the causative variant was 77%, confirming the superior detection power of NGS in genetically heterogeneous diseases.

PI: **Regina Celia Mingroni Neto**
Students: William Bertani Torres (MSc), Larissa Antunes do Nascimento (MSc)

Publication: **Bertani-Torres W**, Lezirovitz K, Alencar-Coutinho D, Pardono E, da Costa SS, **Antunes LDN**, de Oliveira J, Otto PA, Pingault V, **Mingroni-Netto RC**. *Waardenburg Syndrome: The Contribution of Next-Generation Sequencing to the Identification of Novel Causative Variants.* Audiol Res. 2023 Dec 21;14(1):9-25. doi: 10.3390/audiolres14010002.

Biallelic variants in DNA2 cause poikiloderma with congenital cataracts and severe growth failure reminiscent of Rothmund-Thomson syndrome: We report on a novel gene (DNA2) associated with a phenotype reminiscent of Rothmund-Thomson syndrome in six Brazilian probands and two siblings of Swiss/Portuguese ancestry. Genomic and functional analysis revealed compound heterozygosis for a deep intronic splicing variant in trans with loss of function variants in DNA2, with reduction of the protein levels and impaired DNA double-strand break repair. The intronic variant is shared by all Brazilian patients, as well as the Portuguese father of the European siblings, indicating a probable founder effect. Biallelic variants in DNA2 were previously associated with microcephalic osteodysplastic primordial dwarfism. Although the individuals reported here present a similar growth pattern, the presence of poikiloderma and ocular anomalies is unique, suggestive of a Rothmund-Thomson phenotype.

PI: **Debora Bertola**
Publication: 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**. *Biallelic variants in DNA2 cause poikiloderma with congenital cataracts and severe growth failure reminiscent of Rothmund-Thomson syndrome.* J Med Genet. 2023 Nov;60(11):1127-1132. doi: 10.1136/jmg-2022-109119.

A1.2. Complex disorders

An evolutionary perspective on complex neuropsychiatric disease: The forces of evolution-mutation, selection, migration, and genetic drift-shape the genetic architecture of human traits, including the genetic architecture of complex neuropsychiatric illnesses.

Studying these illnesses in populations that are diverse in genetic ancestry, historical demography, and cultural history can reveal how evolutionary forces have guided adaptation over time and place. A fundamental truth of shared human biology is that an allele responsible for a disease in anyone, anywhere, reveals a gene critical to the normal biology underlying that condition in everyone, everywhere. Understanding the genetic causes of neuropsychiatric disease in the widest possible range of human populations thus yields the greatest possible range of insight into genes critical to human brain development. In this perspective, we explore some of the relationships between genes, adaptation, and history that can be illuminated by an evolutionary perspective on studies of complex neuropsychiatric disease in diverse populations.

PI: **Maria Rita Passos Bueno**
Publication: McClellan JM, Zoghbi AW, Buxbaum JD, Cappi C, Crowley JJ, Flint J, Grice DE, Gulsuner S, Iyegbe C, Jain S, Kuo PH, Lattig MC, **Passos-Bueno MR**, Purushottam M, Stein DJ, Sunshine AB, Susser ES, Walsh CA, Wootton O, King MC. *An evolutionary perspective on complex neuropsychiatric disease.* Neuron. 2024 Jan 3;112(1):7-24. doi: 10.1016/j.neuron.2023.10.037. Epub 2023 Nov 27.PMID: 38016473 Review.

Unraveling the Pivotal Role of Noncoding RNAs and Metabolic Pathways in hepatoblastomas: Hepatoblastoma stands as the most prevalent liver cancer in the pediatric population. Characterized by a low mutational burden, chromosomal and epigenetic alterations are key drivers of its tumorigenesis. In this study conducted in Brazilian patients, an in-depth whole transcriptome analysis was performed on 14 primary hepatoblastomas, compared to control liver tissues. Upregulated biological processes were linked to cell differentiation, signaling, morphogenesis, and development, involving known hepatoblastoma-associated genes (*DLK1, MEG3, HDAC2, TET1, HMGA2, DKK1, DKK4*), alongside with novel findings (*GYNG4, CDH3, and TNFRSF19*). Downregulated processes predominantly centered around oxidation and metabolism, affecting amines, nicotinamides, and lipids, featuring novel discoveries like the repression of *SYT7, TTC36, THRSP, CCND1, GCK and CAMK2B*. Two genes, which displayed a concordant pattern of DNA methylation alteration in their promoter regions and dysregulation in the transcriptome, were further validated by RT-qPCR: the upregulated *TNFRSF19*, a key gene in the embryonic development, and the repressed *THRSP*, connected to lipid metabolism. Furthermore, based on protein-protein interaction analysis, we identified genes holding central positions in the network, such as *HDAC2, CCND1, GCK, and CAMK2B*, among others, that emerged as prime candidates warranting functional validation in future studies. Notably, a significant dysregulation of non-coding RNAs (ncRNAs), predominantly upregulated transcripts, was observed, with 42% of the top 50 highly expressed genes being ncRNAs. An integrative miRNA-mRNA analysis revealed crucial biological processes associated with metabolism, oxidation reactions of lipids and carbohydrates, and methylation-dependent chromatin silencing. In particular, four upregulated miRNAs (miR-186, miR-214, miR-377, and miR-494) played a pivotal role in the network,

potentially targeting multiple protein-coding transcripts, including *CCND1* and *CAMK2B*. These findings provide insights into the complexity of the hepatoblastoma transcriptome and identify potential targets for future therapeutic interventions.

PI: **Ana Krepischi**
PhD: Sara Pires and Gustavo Dangoni

Publication: Aguiar TFM, Rivas MP, de Andrade Silva EM, **Pires SF**, **Dangoni GD**, Macedo TC, Defelicibus A, Barros BDF, Novak E, Cristofani LM, Odone V, Cypriano M, de Toledo SRC, da Cunha IW, da Costa CML, Carraro DM, Tojal I, de Oliveira Mendes TA, **Krepischi ACV**. *First Transcriptome Analysis of Hepatoblastoma in Brazil: Unraveling the Pivotal Role of Noncoding RNAs and Metabolic Pathways*. Biochem Genet. 2024 Apr 22. doi: 10.1007/s10528-024-10764-y. Epub ahead of print. PMID: 38649558.

HLA-worldwide Genetic diversity: SNP-based GWASs cannot capture the intense polymorphism of *HLA* genes, highly associated with disease susceptibility. There are methods to statistically impute *HLA* genotypes from SNP-genotypes data, but lack of diversity in reference panels hinders their performance. We evaluated the accuracy of the 1000 Genomes data as a reference panel for imputing HLA from admixed individuals of African and European ancestries, focusing on (a) the full dataset, (b) 10 replications from 6 populations, and (c) 19 conditions for the custom reference panels. The full dataset outperformed smaller models, with a good F1-score of 0.66 for *HLA-B*. However, custom models outperformed the multiethnic or population models of similar size (F1-scores up to 0.53, against up to 0.42). We demonstrated the importance of using genetically specific models for imputing populations, which are currently underrepresented in public datasets, opening the door to HLA imputation for every genetic population.

PIs: **Michel Naslavsky** and **Mayana Zatz**
This study is a collaboration between the group of Prof. Erick Castelli and our group.

Publications: **1)** Douillard V, Dos Santos Brito Silva N, Bourguiba-Hachemi S, **Naslavsky MS**, Scliar MO, Duarte YAO, **Zatz M**, Passos-Bueno MR, Limou S, Gourraud PA, Launay É, **Castelli EC**, Vince N; SNP-HLA Reference Consortium (SHLARC). *Optimal population-specific HLA imputation with dimension reduction*. HLA. 2024 Jan;103(1):e15282. doi: 10.1111/tan.15282. Epub 2023 Nov 11. PMID: 37950640.

2) Silva NSB, Bourguiba-Hachemi S, Ciriaco VAO, Knorst SHY, Carmo RT, Masotti C, Meyer D, **Naslavsky MS**, Duarte YAO, **Zatz M**, Pierre-Antoine Gourraud, Limou S, **Castelli EC**, Nicolas Vince N. *A multi-ethnic reference panel to impute HLA classical and non-classical class I alleles in admixed samples: Testing imputation accuracy in an admixed sample from Brazil*. HLA. 2024 Jun;103(6):e15543. doi: 10.1111/tan.15543.

A2. Investigation of mechanisms underlying clinical variability, and non-penetrance in genetic disorders

A2.1. Neuromuscular disorders

Telethoninopathy: Histological and ultrastructural findings in genetically proven TCAP gene-related limb girdle muscular dystrophy: Telethoninopathy or *TCAP*-gene related limb girdle muscular dystrophy is a rare genetic disease that was first described in Brazil. There are less than 60 reported families worldwide. Due to its rarity, detailed information on muscle biopsy light and electron microscopic features are lacking. A retrospective study of consecutive muscle biopsies was performed in patients from a Neuromuscular Outpatient Clinic between 2011 and 2023. Inclusion criteria included telethoninopathy diagnosed by both immunohistochemistry and molecular studies. Seven patients (0,7% or 7/953) were found: five male and two female, admitted from 6 to 54 years old. Detailed light and electron microscopy findings are illustrated. Muscle imaging is presented along with disease duration. A review of published cases is provided. In conclusion, a dystrophic pattern on muscle biopsy was found in 57% (4/7) of the patients. Other 43% (3/7) presented myopathic features such as variation in fibre calibre, nuclear internalization, rimmed vacuoles, and oxidative irregularities. Morphometry disclosed, in three patients, respectively, type 1 lobulated fibres that were 34%, 52%, and 57% smaller than type 2 fibres, without type 1 fibre predominance. Electron microscopy demonstrated nuclear pseudoinclusions, pyknosis, multifocal loss of the sarcolemma, and 17 nanometres intrasarcoplasmic filamentous inclusions. All patients presented: (1) complete absence of the immunohistochemical expression of telethonin, and (2) the homozygous c.157C>T, p.(Gln53*) pathogenic variant in exon 2 of the *TCAP* gene. Anti-telethonin immunohistochemistry may be helpful in unsolved cases with nonspecific myopathic abnormalities, specially with small type 1 lobulated fibres. Appropriate diagnosis is important for adequate genetic counselling.

PI: **Mariz Vainzof**
PhD: Lucas Santos Souza.

Publication: Cotta A, Carvalho E, Cunha-Jr. A, da Silveira EB, Cordeiro BA, Lima MI, Navarro MM, Godinho F, Valicek J; Miriam Melo Menezes, Nunes-Neves SV, Vargas AP, Xavier Neto R, Costa-e-Silva C, Takata RI, Cauhi AF, Paim JF, **Vainzof M**. *Light and electron microscopy findings in genetically proven TCAP gene-related limb girdle muscular dystrophy*. Surg Exp Pathol (in press, 2024).

Malignant hyperthermia phenotype-genotype correlations:
PI: **Mariz Vainzof** (geneticist responsible for the MH group)
Students: Lucas Santos Souza (Ph.D.) and Brandow Willis (MSc student)
Collaboration: Dr. Helga Cristina Almeida da Silva, Malignant Hyperthermia Unit - Discipline of Anesthesiology, Pain and Intensive Care - Federal University of Sao Paulo and Prof. Susan Treves of the Department of Biomedicine, Basel University Hospital.

Hypermobility is the capacity to perform joint movements in amplitudes greater than normal. Hypermobility is present in nearly 100% of congenital myopathy central core disease (CCD) patients but is sporadically described in the allelic disease malignant hyperthermia (MH). Our objective was to investigate the frequency/characteristics of hypermobility in MH susceptible patients as compared to a control group, aiming the identification of correlations between hypermobility and demographic/clinical findings in MH patients. We recruited 26 MH patients (MH history, positive in vitro contracture test (IVCT), no muscle weakness, no cores in muscle biopsy) and 23 controls (no MH/myopathy history). Patients/medical records were evaluated for obtaining demographic/clinical data. Hypermobility was assessed in all patients and controls with Bulbena score. Goniometry was performed in a subset of 11 patients and 11 controls. Bulbena score indicative of hypermobility was significantly more frequent in MH than in the control group (50% versus 13%, relative risk 2.06 (95%CI 1.27-3.35), chi-square test, p<.01). Goniometric assessment revealed significantly greater range of motion of mostly proximal movements in MH versus control groups. In the MH group, there was no correlation of the Bulbena score with age, sex, clinical complaints of myalgia/cramps, CK levels, IVCT result, or degree of contracture after caffeine or halothane. In conclusion, it is possible that predominantly proximal hypermobility is part of a clinical spectrum associated with RYR1 gene mutations, as it was present even when associated muscle weakness was not present. More studies are necessary to measure evolution and long-term impact of hypermobility in MH patients.

PI: **Mariz Vainzof**

Publication: Santos RCCS, Lima LFCDMS, Andrade PV, Santos JM, Galleni L, Ribeiro-Jr AF, Souza LS, Schmidt B, Oliveira ASB, Amaral JLG, **Vainzof M**, Silva HCA. *Report of Joint hypermobility in malignant hyperthermia susceptible patients: Observational study with a case-control descriptive design*. Brazilian Journal of Physical Therapy (in press, 2024)

Functional studies in dysferlinopathies: Tetraspanins organize protein complexes at the cell membrane and are responsible for assembling diverse binding partners in changing cellular states. Tetraspanin CD82 is a useful cell surface marker for prospective isolation of human myogenic progenitors and its expression is decreased in Duchenne muscular dystrophy (DMD) cell lines. The function of CD82 in skeletal muscle remains elusive, partly because the binding partners of this tetraspanin in muscle cells have not been identified. CD82-associated proteins are sought to be identified in human myotubes via mass spectrometry proteomics, which identifies dysferlin and myoferlin as CD82-binding partners. In human dysferlinopathy (Limb girdle muscular dystrophy R2, LGMDR2) myogenic cell lines, expression of CD82 protein is near absent in two of four patient samples. In the cell lines where CD82 protein levels are unaffected, increased expression of the ≈72 kDa mini-dysferlin product is identified using an antibody recognizing the dysferlin C-terminus. These data demonstrate that CD82 binds dysferlin/myoferlin in

differentiating muscle cells and its expression can be affected by loss of dysferlin in human myogenic cells.

PIs: **Mariz Vainzof** and **Mayana Zatz**
International collaboration: Emanuella Gussoni

Publication: Fontelonga T, Hall AJ, Brown JL, Jung YL, Alexander MS, Dominov JA, Mouly V, Vieira N, **Zatz M, Vainzof M**, **Gussoni E**. *Tetraspanin CD82 Associates with Trafficking Vesicle in Muscle Cells and Binds to Dysferlin and Myoferlin.* Adv Biol (Weinh). 2023 Jul 12:e2300157. doi: 10.1002/adbi.202300157. Online ahead of print. PMID: 37434585

Functional studies in Hearing Loss: We are currently investigating the functional effect of the genetic variants causative of hearing loss using as a model stem cells. Publications: **1) GJB2 c.35del variant up-regulates GJA1 gene expression and affects differentiation of human stem cells**: We have established stem cells lineages obtained from human exfoliated deciduous teeth (SHEDs) from patients with c.35delG variant in homozygosis, in order to investigate cell compensation mechanisms to the lack of functional Connexin 26 protein. The c.35delG variant in homozygosis is the most frequent cause of hereditary hearing loss in many populations. We observed that the variant up-regulates *GJA1* (encoding Connexin 43) RNA expression. The cells presented higher induced differentiation to adipocytes and osteocytes but lower chondrocyte differentiation. Our results suggest that *GJA1* increased expression may be involved in functional compensation for *GJB2* loss of function and it may explain changes in differentiation properties.

PI: **Regina Mingroni-Netto**
Student: Dayane Bernardino Cruz (Msc)

Publication: Batissoco AC, **Cruz DB**, Alegria TGP, Kobayashi G, Oiticica J, Soares Netto LE, Passos-Bueno MR, Haddad LA, **Mingroni Netto RC**. *GJB2 c.35del variant up-regulates GJA1 gene expression and affects differentiation of human stem cells*. Genet Mol Biol. 2024 Apr 15;47(2):e20230170. doi: 10.1590/1678-4685-GMB-2023-0170. eCollection 2024

2) Generation of four induced pluripotent stem cells lines from PBMC of the DFNA58 family members: Two hearing-impaired duplication carriers (USPi006-A e USPi007-A) and two normal-hearing noncarriers (USPi004-A and USPi005-A): We have recently obtained induced pluripotent stem cell lines from patients of the original family who allowed mapping and identification for the first time of DFNA58 locus as causative of autosomal dominant hearing loss. The cells are under investigation regarding RNA expression changes

caused by the genomic duplication previously described in *Lezirovitz et al. Hum Mol Genet. 2020 Jun 3;29(9):1520-1536*

PI: **Regina Mingroni Netto**
Researcher CEGH-CEL: Gerson Kobayashi

Publication: **Kobayashi GS**, Vieira-Silva GA, Varella-Branco E, Moreira DP, Kitajima JPFW, Hemza CRML, **Mingroni-Netto RC**, Lojudice FH, Oiticica J, Bento RF, Batissoco AC, Lezirovitz K. *Generation of four induced pluripotent stem cells lines from PBMC of the DFNA58 family members: Two hearing-impaired duplication carriers (USPi006-A e USPi007-A) and two normal-hearing noncarriers (USPi004-A and USPi005-A)*. Stem Cell Res. 2023 Sep;71:103181. doi: 10.1016/j.scr.2023.103181. Epub 2023 Aug 9

3) Ca2+-binding to the C2E domain of otoferlin is required for hair cell exocytosis and hearing: In a detailed functional study about the effect of the missense variant on the otoferlin (*OTOF*) gene, the authors introduced a human mutation (I1573T, *OtofI1573T*/*I1573T* mice) in the immediate proximity of the Ca2+ binding top loop aspartates that was expected to affect Ca2+/phospholipid binding. The effect of the variant was disruption of Ca2+ binding of the C2E domain revealing a lack of Ca2+ influx-triggered exocytosis in the inner hair cells of the mice, explaining the synapse alterations in *OTOF* related hearing loss. Clinical data of a Brazilian individual with a homozygous *OTOFI1573T* variant were presented in the paper and hearing alterations were compared to the effects of the variant in the mouse model.

PI: **Regina Célia Mingroni-Netto**
International Collaboration: Dr. Barbara Vona

Publication: Chen H, Mehar Monga M, Fang Q, Slitin L, Neef J, Chepurwar SS, **Mingroni Netto RC**, Lezirovitz K, Tabith Jr A, Benseler F, Brose N, Kusch K, Wichmann C, Nicola Strenzke N, **Vona B**, Preobraschenski J, Tobias Moser T. *Ca2+ binding to the C2E domain of otoferlin is required for hair cell exocytosis and hearing*. Protein Cell. 2024 Apr 1;15(4):305-312. doi: 10.1093/procel/pwad058

A2.2. Structural Variation in Genetic Disorders

A germline chimeric *KANK1-DMRT1* transcript derived from a complex structural variant is associated with a congenital heart defect segregating across five generations: Structural variants (SVs) pose a challenge to detect and interpret, but their study provides novel biological insights and molecular diagnosis underlying rare diseases. The aim of this study was to resolve a 9p24 rearrangement segregating in a family through five generations with a congenital heart defect (congenital pulmonary and aortic valvular stenosis and

pulmonary artery stenosis), by applying a combined genomic analysis. The analysis involved multiple techniques, including karyotype, chromosomal microarray analysis (CMA), FISH, genome sequencing (GS), RNA-seq, and optical genome mapping (OGM). A complex 9p24 SV was hinted at by CMA results, showing three interspersed duplicated segments. Combined GS and OGM analyses revealed that the 9p24 duplications constitute a complex SV, on which a set of breakpoints matches the boundaries of the CMA duplicated sequences. The proposed structure for this complex rearrangement implies three duplications associated with an inversion of ~ 2 Mb region on chromosome 9 and a SINE element insertion at the more distal breakpoint. Interestingly, this genomic structure of rearrangement forms a chimeric transcript of the KANK1/DMRT1 loci, which was confirmed by both RNA-seq and Sanger sequencing on blood samples from 9p24 rearrangement carriers. Altogether with breakpoint amplification and FISH analysis, this combined approach allowed a deep characterization of this complex rearrangement. Although the genotype-phenotype correlation remains elusive from the molecular mechanism point of view, this study identified a large genomic rearrangement at 9p24 segregating with a familial congenital heart defect, revealing a genetic biomarker that was successfully applied for embryo selection, changing the reproductive perspective of affected individuals.

PIs: **Ana Krepischi** and **Carla Rosenberg**
Visiting professor: Veniamin Fishman

Publications: da Costa SS, **Fishman V,** Pinheiro M, Rodrigueiro A, Sanseverino MT, Zielinsky P, Carvalho CMB, **Rosenberg C, Krepischi ACV**. *A germline chimeric KANK1-DMRT1 transcript derived from a complex structural variant is associated with a congenital heart defect segregating across five generations*. Chromosome Res. 2024 Mar 19;32(2):6. doi: 10.1007/s10577-024-09750-2. PMID: 38504027.

Low-pass whole genome sequencing is a reliable and cost-effective approach for copy number variant analysis in the clinical setting: Next generation sequencing technology has greatly reduced the cost and time required for sequencing a genome. An approach that is rapidly being adopted as an alternative method for CNV analysis is the low-pass whole genome sequencing (LP-WGS). Here, we evaluated the performance of LP-WGS to detect copy number variants (CNVs) in clinical cytogenetics. Known CNVs detected by chromosomal microarray analyses (CMA) were selected for comparison and used as positive controls; our panel included 44 DNA samples (12 prenatal and 32 postnatal), comprising a total of 55 chromosome imbalances. The selected cases were chosen to provide a wide range of clinically relevant CNVs, the vast majority being associated with intellectual disability or recognizable syndromes. The chromosome imbalances ranged in size from 75 kb to 90.3 Mb, including aneuploidies and two cases of mosaicism. All CNVs were successfully detected by LP-WGS, showing a high level of consistency and robust performance of the sequencing method. Notably, the size of chromosome imbalances detected by CMA and LP-WGS were compatible

between the two different platforms, which indicates that the resolution and sensitivity of the LP-WGS approach are at least similar to those provided by CMA. Our data show the potential use of LP-WGS to detect CNVs in clinical diagnosis and confirm the method as an alternative for chromosome imbalances detection.

PIs: **Ana Krepischi** and **Carla Rosenberg**
Pos-doc: Patricia Mazzonetto

Publications: **Mazzonetto PC**, Villela D, da Costa SS, **Krepischi ACV**, Milanezi F, Migliavacca MP, Pierry PM, Bonaldi A, Almeida LGD, De Souza CA, Kroll JE, Paula MG, Guarischi-Sousa R, Scapulatempo-Neto C, **Rosenberg C**. *Low-pass whole genome sequencing is a reliable and cost-effective approach for copy number variant analysis in the clinical setting*. Ann Hum Genet. 2024 Mar;88(2):113-125. doi: 10.1111/ahg.12532. Epub 2023 Oct 9. PMID: 37807935.

A2.3. Neurodegeneration

Intracellular dynamics in neurodegeneration: Vaccinia-related kinase 1 (*VRK1*) is a gene which has been implicated in the pathological process of a broad range of neurodevelopmental disorders as well as neuropathies, such as Amyotrophic Lateral Sclerosis (ALS). Here we report a family presenting ALS in an autosomal recessive mode of inheritance, segregating with a homozygous missense mutation located in *VRK1* gene (p.R321C; Arg321Cys). Proteomic analyses from iPSC-derived motor neurons identified 720 proteins eligible for subsequent investigation, and our exploration of protein profiles revealed significant enrichments in pathways such as mTOR signaling, E2F, MYC targets, DNA repair response, cell proliferation and energetic metabolism. Functional studies further validated such alterations, showing that affected motor neurons presented decreased levels of global protein output, ER stress and downregulation of mTOR signaling. Mitochondrial alterations also pointed to decreased reserve capacity and increased non-mitochondrial oxygen consumption. Taken together, our results present the main pathological alterations associated with *VRK1* mutation in ALS.

PIs: **Mayana Zatz** and **Merari de Fátima Ramires Ferrari**
Pos-doc student: Danyllo Oliveira, Amanda Assoni

Publication: **Oliveira D**, **Assoni AF**, Alves LM, Sakugawa A, Melo US, Teles E Silva AL, Sertie AL, Caires LC, Goulart E, Ghirotto B, Carvalho VM, **Ferrari MR**, **Zatz M**. *ALS-associated VRK1 R321C mutation causes proteostatic imbalance and mitochondrial defects in iPSC-derived motor neurons*. Neurobiol Dis. 2024 May 26;198:106540. doi: 10.1016/j.nbd.2024.106540.

Mechanisms underlying neurodegeneration in ALS: Amyotrophic lateral sclerosis type 6 (ALS6) is a familial subtype of ALS linked to Fused in Sarcoma (FUS) gene mutation. FUS mutations lead to decreased global protein synthesis, but the mechanism that drives this has not been established. Here, we used ALS6 patient-derived induced pluripotent stem cells (hIPSCs) to study the effect of the ALS6 FUSR521H mutation on the translation machinery in motor neurons (MNs). We find, in agreement with findings of others, that protein synthesis is decreased in FUSR521H MNs. Furthermore, FUSR521H MNs are more sensitive to oxidative stress and display reduced expression of TGF-β and mTORC gene pathways when stressed. Finally, we show that IFNγ treatment reduces apoptosis of FUSR521H MNs exposed to oxidative stress and partially restores the translation rates in FUSR521H MNs. Overall, these findings suggest that a functional IFNγ response is important for FUS-mediated protein synthesis, possibly by FUS nuclear translocation in ALS6. Interestingly, in another study, we found that vesicle-associated membrane protein-associated protein B and C (VAPB), mutated in familial ALS type 8, is also implicated CNS cancer. Studying medulloblastoma, a common childhood brain malignancy, we found that high VAPB expression correlates with reduced patient survival. VAPB was essential for medulloblastoma cell proliferation in vitro and in vivo, with VAPB knockout delaying cell cycle progression and reducing WNT-related protein transcript levels. Our findings highlight VAPB as a clinical modifier and potential therapeutic target for medulloblastoma treatment.

PIs: **Mayana Zatz** and **Oswaldo Keith Okamoto**
Pos-doc student: Amanda Assoni and Danyllo Oliveira
Collaboration: Prof. Floris Foijer

Publication: **Assoni AF**, Guerrero EN, Wardenaar R, **Oliveira D**, Bakker PL, Alves LM, Carvalho VM, **Okamoto OK**, **Zatz M**, **Foijer F**. *IFNγ protects motor neurons from oxidative stress via enhanced global protein synthesis in FUS-associated amyotrophic lateral sclerosis*. Brain Pathol. 2024 Jan;34(1):e13206. doi: 10.1111/bpa.13206. Epub 2023 Aug 15. PMID: 37582053; PMCID: PMC10711262.

Mitochondrial dysfunction and ALS pathogenesis: Vesicle-associated membrane protein-associated protein-B (VAPB) is an ER membrane bound protein. VAPB P56S causes a dominant, familial form of amyotrophic lateral sclerosis (ALS), however, the mechanism through which this mutation causes motor neuron (MN) disease remains unknown. Using inducible wild type (WT) and VAPB P56S expressing iPSC-derived MNs we show that VAPB P56S, but not WT, protein decreased neuronal firing and mitochondrial-ER contact (MERC) with an associated age-dependent decrease in mitochondrial membrane potential (MMP); all typical characteristics of MN-disease. We further show that VAPB P56S expressing iPSC-derived MNs have enhanced age-dependent sensitivity to ER stress. We identified elevated expression of the master regulator of the Integrated Stress Response (ISR) marker ATF4 and decreased protein synthesis in the VAPB P56S iPSC-derived MNs. Chemical inhibition of ISR with the compound, ISRIB, rescued all MN disease phenotype in VAPB P56S MNs. Thus, our

results not only support ISR inhibition as a potential therapeutic target for ALS patients, but also provides evidence to pathogenesis.

PI: **Mayana Zatz**
Collaboration with the group of Helen Cristina Miranda

Publication: Landry C, Costanzo J, Mitne-Neto M, **Zatz M**, Schaffer A, Hatzoglou M, Muotri A, **Miranda HC**. *Mitochondrial dysfunction heightens the integrated stress response to drive ALS pathogenesis*. bioRxiv [Preprint]. 2024 May 14:2024.05.13.594000. doi: 10.1101/2024.05.13.594000. PMID: 38798645; PMCID: PMC11118434.

Neurological disease modeling: Amyotrophic lateral sclerosis type 6 (ALS6) is a familial subtype of ALS linked to mutations in the Fused in Sarcoma (FUS) gene, leading to decreased global protein synthesis. Using ALS6 patient-derived induced pluripotent stem cells (hIPSCs), we studied the FUSR521H mutation's effect on the translation machinery in motor neurons (MNs). We confirmed that protein synthesis is reduced in FUSR521H MNs and found these MNs are more sensitive to oxidative stress, displaying reduced expression of TGF-β and mTORC pathways under stress. Treatment with IFNγ reduced apoptosis and partially restored translation rates in FUSR521H MNs, suggesting that a functional IFNγ response is crucial for FUS-mediated protein synthesis, potentially through FUS nuclear translocation in ALS6. Interestingly, in another study, we found that vesicle-associated membrane protein-associated protein B and C (VAPB), mutated in familial ALS type 8, is also implicated CNS cancer. Studying medulloblastoma, a common childhood brain malignancy, we found that high VAPB expression correlates with reduced patient survival. VAPB was essential for medulloblastoma cell proliferation in vitro and in vivo, with VAPB knockout delaying cell cycle progression and reducing WNT-related protein transcript levels. Our findings highlight VAPB as a potential therapeutic target for medulloblastoma treatment.

PIs: **Oswaldo Keith Okamoto** and **Mayana Zatz**
Pos-doc: Elisa H. Jandrey, PhD and MSc students: Amanda Assoni (currently pos-doc), Gabriela M. Novaes, Rayane O. Ferreira, Thiago G. Mitsugi, Isabela Granha
Collaborations: Dr. Floris Foijer (European Research Institute for the Biology of A.geing (ERIBA), Medical Center University of Groningen, The Netherlands), Dra. Carolini Kaid (Vyro bio Inc), Dr. Valdemir Carvalho (Fleury Group)

Publication: **Assoni AF**, **Giove Mitsugi T**, Wardenaar R, **Ferreira RO**, **Jandrey EH**, **Machado Novaes G**, **Granha IFO**, Bakker P, **Kaid C**, **Zatz M**, **Keith Okamoto O**. *Neurodegeneration-associated protein VAPB regulates proliferation in medulloblastoma*. Sci Rep. 2023 Nov 9;13(1): 19481. doi: 10.1038/s41598-023-45319-5.

A3. Epigenetics and diseases

How DNA damage and Genome Instability can be implicated in human disease? Human syndromes with DNA repair deficiencies are often linked to symptoms of tumorigenesis and/or neurodegeneration and premature ageing. We have been investigating the syndrome xeroderma pigmentosum (XP), who present increased frequency of skin tumors and, depending on the mutation and mutated gene, effects on neurological problems. During this period, we succeed to complete work focused on DNA replication processes, related or not to the presence of DNA damage. After the identification of a few Brazilian patients with neurological problems, a novel mutation was detected in the gene that encodes PCNA, an essential protein necessary for DNA synthesis. This was only the second different mutation detected in this gene in humans. Structural in vitro analyses indicated that this mutation leads to a protein with thermosensitivity, a feature confirmed with cells from one of the patients (*Magrino et al., 2023*). We also investigated detailed roles of DNA translesion synthesis (TLS) polymerases, especially Pol eta (defective in XP variant patients), Pol iota and Pol kappa. For these studies, cells defective in the removal of lesions by nucleotide excision repair (NER) due to mutation in the XPC protein, were depleted of Pol eta and/or Pol iota. After UV-irradiation, we detected that Pol iota has an important role in Pol eta defective cells. Several endpoints were analyzed, and the results clearly indicated that Pol iota act as a backup for Pol eta in the replication of damaged DNA (*Martins et al, 2024*). Moreover, working with 3D spheroids glioblastoma human cells, we detected that knock out for the Pol kappa lead the cells to be sensitive to temozolomide (TMZ), a first line pharmaceutical drug for this tumor. The results confirm this TLS polymerase plays a role providing the tumor cells with a tool to became resistant to TMZ (*Ribeiro et al. 2024*). We also concluded a thematic review where we summarize evidence for a paradoxical phenomenon: Pol eta, an error prone DNA TLS polymerase, bypasses cyclobutane pyrimidine dimers (CPDs) reading accurately the bases contained within the dimer, after Watson & Crick base pairing. On the other hand, the fast deamination that occurs in cytosines within the CPDs is the main reason for these lesions to generate C>T mutations in human skin (*Menck et al., 2024*). Collaboration works with medical doctors helping directly the XP-patients led to a better understanding of this syndrome (*Rocha et al, 2023; Marcos et al, 2024*). Finally, in collaboration with other groups working with bacteria or bacterial protein, we obtained information that helps to understand better how these organisms use DNA repair mechanisms to protect from the UV component of sunlight (*Fuentes-Leon et al, 2024; Torres-Obreque et al, 2024*).

PI: **Carlos Frederico Martins Menck**

Publications: **1)** Magrino J, Munford V, Martins DJ, Homma TK, Page B, Gaubitz C, Freire BL, Lerario AM, Vilar JB, Amorin A, Leão EKE, Kok F, **Menck CF**, Jorge AA, Kelch BA. *A thermosensitive PCNA allele underlies an ataxia-telangiectasia-like disorder*. J Biol Chem. 299(5):104656, 2023.

2) Martins DJ, Singh JK, Jahjah T, Vessoni AT, Leandro GDS, Silva MM, Biard DSF, Quinet A, **Menck CFM.** *Polymerase iota plays a key role during translesion synthesis of*

UV-induced lesions in the absence of polymerase eta. Photochem Photobiol. 100: 4-18. 2024.

3) Ribeiro DL, Latancia MT, de Souza I, Ariwoola AA, Mendes D, Rocha CRR, Lengert AVH, **Menck CFM.** *Temozolomide resistance mechanisms: unveiling the role of translesion DNA polymerase kappa in glioblastoma spheroids in vitro.* Biosci Rep. 44(5):BSR20230667. 2024.

4) Menck CFM, Galhardo RS, Quinet A. *The accurate bypass of pyrimidine dimers by DNA polymerase eta contributes to ultraviolet-induced mutagenesis.* Mutat Res/ Fundamental and Molecular Mechanisms of Mutagenesis. 828:111840. 2024.

5) Rocha LKFL, Ferreira P, Gianotti MA, Avancini J, **Menck CFM**, Castro LP, de Oliveira ZNP, Rivitti MC, Samorano LP, Pereira NV, Festa Neto C Australas J. *Imiquimod chemoprophylaxis for field cancerization in xeroderma pigmentosum patients-A prospective study.* Dermatol. 64(3):435-438. 2023.

6). Marcos AAA, Freitas D, Hazarbassanov RM, Fernandes AG, Castro LP, Melo DBV, **Menck CFM**, Morales MC, Gomes JÁP, Belfort Neto R, Singh AD. *Evaluation of Meibomian gland dysfunction using meibography in patients with xeroderma pigmentosum.* Arq Bras Oftalmol. 87(2): e20220319. 2024.

7) Fuentes-León F, Quintero-Ruiz N, Fernández-Silva FS, Munford V, Vernhes Tamayo M, **Menck CFM**, Galhardo RS, Sánchez-Lamar A. *Genotoxicity of ultraviolet light and sunlight in the bacterium Caulobacter crescentus: Wavelength-dependence.* Mutat Res Genet Toxicol Environ Mutagen. 894:503727. 2024.

8) Torres-Obreque K, Gonçalves FG, Ferraro RB, Fuentes-León F, **Menck CFM,** Costa-Silva TA, Monteiro G, Perego P, Rangel-Yagui CO. *Recombinant production of a highly efficient photolyase from Thermus thermophilus.* Biotechnol J. 19(2):e2300325. 2024.

B. The 80plus project and Aging

B1. Contributions of 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). Several studies are being conducted using SABE dataset as reference, controls or source of functional variation. Since SABE is highly admixed, several ancestry-specific analyses are being conducted. A recent example was on cardiomyopathies and Chagas disease (CD). A third of CD cases evolve into chronic chagas cardiomyopathy (CCC). Mitochondrial DNA haplogrouping has indicated that African haplogroups were over represented in the Chagas subject groups in comparison with healthy Brazilian individuals.

The European lineage is associated with protection against cardiomyopathy and the macro haplogroup H is associated with increased risk towards CCC. Using mitochondrial DNA sequencing, 84 mtDNA-encoded protein sequence pathogenic variants were associated with CCC. Among them, two variants were associated with left ventricular non-compaction and two to hypertrophic cardiomyopathy. The finding that mitochondrial protein-coding SNPs and mitochondrial haplogroups are associated with risk of evolving to CCC is consistent with a key role of mitochondrial DNA in the development of the CD-associated cardiomyopathy.

PIs (SABE dataset): **Mayana Zatz**, **Michel Naslavsky** and **Yeda Duarte**
Collaborators: Mario Hirata, Jorge Kalil, Edécio Cunha-Neto

Publication: Gallardo F, Pauline Brochet P, Goudenège D, Nunes JPS, Andrieux P, Ianni BM, Frade AF, Mady C, Santos RHB, Kuramoto A, Steffen S, Stolf AN, Pomerantzeff P, Fiorelli AI, Bocchi EA, Pissetti CW, Saba B, Dias FC, Sampaio MF, Gaiotto FA, Marin-Neto JA, Fragata A, Zaniratto RCF, Siqueira S, Peixoto GDL, Bacal F, Buck P, Almeida RR, Lin-Wang HT, Schmidt A, **Hirata MH**, Donadi EA, Pereira AC, Rodrigues Junior V, Martinelli M, **Naslavsky M**, **Kalil J**, Procaccio V, **Cunha-Neto E**, Chevillard C. *Mitochondrial DNA Haplogroups and Variants Predispose to Chagas Disease Cardiomyopathy*. Hearts 2023, 4(4), 97-117; https://doi.org/10.3390/hearts4040013

B.2. Genomic analyses of the BioBank for Aging Studies: 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. Apolipoprotein E ε4 allele (APOE-ε4) is the main genetic risk factor for late-onset Alzheimer's disease (AD) and may impact cognitive function also via other neuropathological lesions. However, there is limited evidence available from diverse populations, as APOE associations with dementia seem to differ by race. Therefore, we aimed to evaluate the pathways linking APOE-ε4 to cognitive abilities through AD and non-AD neuropathology in an autopsy study with an admixed sample. We included 648 participants (mean age 75 ± 12 years old, mean education 4.4 ± 3.7 years, 52% women, 69% White, and 28% APOE-ε4 carriers). The association between APOE-ε4 and cognitive abilities was mediated by neurofibrillary tangles ($\beta = 0.88$, 95% CI = 0.45; 1.38, $p < 0.001$) and neuritic plaques ($\beta = 1.36$, 95% CI = 0.86; 1.96, $p < 0.001$). Lacunar infarcts, hyaline arteriosclerosis, CAA, LBD, and TDP-43 were not mediators in the pathway from APOE-ε4 to cognition. The association between APOE-ε4 and cognitive abilities was partially mediated by AD-pathology. On the other hand, cerebrovascular lesions and other neurodegenerative diseases did not mediate the association between APOE-ε4 and cognition. Regarding other APOE alleles, APOE-ε2 seems to decrease carotid atherosclerosis risk. APOE-ε2 carriers had a lower percentage of carotid obstruction and less severe stenosis. APOE-ε4 was not related to a higher risk of carotid atherosclerosis in this cross-sectional population-based autopsy study.

PIs: Lea Grinberg and Claudia Suemoto.
Collaboration: **Michel Naslavsky** and **Mayana Zatz**

Publications: **1)** Paradela RS, Justo AFO, Paes VR, Leite REP, Pasqualucci CA, **Grinberg LT**, **Naslavsky MS**, **Zatz M**, Nitrini R, Jacob-Filho W, **Suemoto CK**. *Association between APOE-ε4 allele and cognitive function is mediated by Alzheimer's disease pathology: a population-based autopsy study in an admixed sample*. Acta Neuropathol Commun. 2023 Dec 19;11(1):205. doi: 10.1186/s40478-023-01681-z

2) Paradela, RS., Farias-Itao DS, Leite REP, Pasqualucci C A., **Grinberg LT, Naslavsky MS, Zatz M**, Nitrini, R., Jacob-Filho, W., & **Suemoto CK.** (2023). *Apolipoprotein E ε2 allele is associated with lower risk of carotid artery obstruction in a population-based autopsy study*. In Journal of Stroke and Cerebrovascular Diseases (Vol. 32, Issue 9, p. 107229). Elsevier BV. https://doi.org/10.1016/j.jstrokecerebrovasdis.2023.107229

B.3. The importance of older genomes: The difficulty in classifying a rare genetic variant as "likely pathogenic", "likely benign" or VUS (variant of unknown significance) represents a major challenge in genetic counseling (GC) when trying to establish a diagnosis or as a result of incidental findings. They may impact the prognosis in conditions of late onset as for example, neuromuscular disorders or the consultants` reproductive decision about future offspring. Here we report two unrelated families, one Brazilian and one of East/Asian ancestry, where a rare previously unreported deletion in the dystrophin gene was identified. In these two families the analysis of older male relatives (aged from 56 to 89 years-old) who were fully asymptomatic provided relevant information to the involved families about the potential pathogenicity of this dystrophin variant. They support our previous suggestion on the relevance of genome sequencing of older healthy individuals or family members as well as the importance of sharing new relevant information for decision-making to families previously submitted to Genetic counseling . Additionally, such case reports contribute to the classification of VUS enhancing our knowledge on the impact of specific mutations in functional studies.

PI: **Mayana Zatz**
Publication: **Zatz M**. The importance of elderly genomes. Genomic Psychiatry (2024) 1, 1–3. doi: https://doi.org/10.61373/gp024b.0019; Published online: 15 March 2024

B.4. Via de sinalização WNT na demência e sua relação com o diabetes tipo E: O envelhecimento é o principal fator de risco para a demência, que afeta cerca de 50 milhões de pessoas em todo o mundo, com 10 milhões de novos casos por ano, com destaque para a Doença de Alzheimer (DA), forma mais comum de demência (60-70% dos casos). A demência afeta a sociedade, a família e aos acometidos devido os sintomas que perpassam danos físicos, psicológicos, sociais e econômicos que podem atingir 2 trilhões de dólares,

tornando-se uma prioridade de saúde pública. Além disso, as terapias existentes têm sido em grande parte ineficazes e a compreensão dos mecanismos fisiopatológicos da doença ainda é limitada. Assim, a elucidação dos mecanismos do envelhecimento e da demência é indispensável para sua mitigação. Evidências estabelecem uma conexão entre demência e diabetes, destacando o impacto da homeostase da glicose na formação de proteínas anômalas.

PI: Flavia Herrera
Collaboration: **Michel Naslavsky, Maria Rita Passos-Bueno** and **Mayana Zatz**

Publication: Sossai P, Barcelos EC, Fernandes I, Rodrigues AS, **Naslavsky M**, Maranduba CM, de Paula F, **Passos-Bueno MR**, **Zatz M**, Errera F. Participação da via de sinalização WNT na demência e sua relação com diabetes tipo 3. In: Aragão JA, Dal Molin RS, Zago M (org.). *Envelhecimento Humano e Contemporaneidade: Tópicos atuais em Pesquisa.* Vol 3, ISBN 978-65-5360-524-4, Ano 2023, Editora Cientifica (e-book), p 106-126. Disponível em: https://www.editoracientifica.com.br/books/chapter/participacao-da-via-de-sinalizacao-wnt-na-demencia-e-sua-relacao-com-o-diabetes-tipo-3

B.5. Fragilidade: Evolução Conceitual, Epidemiologia e Fisiopatologia: O envelhecimento da população, em conjunto com o aumento da expectativa de vida, traz a necessidade de maior atenção quanto à saúde e qualidade de vida do idoso. Nesse contexto, a Síndrome da Fragilidade no Idoso, ou apenas Fragilidade, tem se tornado um grande desafio para as gerações atuais e futuras. A fragilidade é uma condição clínica caracterizada por uma vulnerabilidade excessiva do indivíduo a estressores endógenos e exógenos, expondo o indivíduo a um maior risco de resultados negativos relacionados à saúde. Indivíduos frágeis são mais suscetíveis à hospitalização, quedas e à morte devido a eventos estressores que, em indivíduos não-frágeis, não costumam ter resultados tão adversos. O conceito de fragilidade tem evoluído ao longo das últimas décadas e sua epidemiologia tem acompanhado as tendências da transição sócio-demográfica em diferentes populações mundiais.

PIs: **Michel Naslavsky**, **Maria Rita Passos-Bueno** and **Mayana Zatz**
Colaboração com o grupo da Prof. Flavia Valle Errera.

Publication: Barcelos EC, Barcelos DHF, Borges RR, Silveira IF, Errera LI, De Paula F, **Naslavsky M**, **Passos-Bueno MR**, **Zatz M**, Flávia Errera FIV. Fragilidade: Evolução Conceitual, Epidemiologia e Fisiopatologia. In: Aragão JA, Dal Molin RS, Zago M (org.). *Envelhecimento Humano e Contemporaneidade: Tópicos atuais em Pesquisa*. Vol 2, ISBN 978-65-5360-438-4, Ano 2023, Editora Cientifica (e-book), p.296-314. Disponível em: https://www.editoracientifica.com.br/books/chapter/fragilidade-evolucao-conceitual-epidemiologia-e-fisiopatologia

B.6. A multi-ethnic reference panel to impute HLA classical and non-classical class I alleles in admixed samples: Testing imputation accuracy in an admixed sample from Brazil: The MHC class I region contains crucial genes for the innate and adaptive immune response, playing a key role in susceptibility to many autoimmune and infectious diseases. Genome-wide association studies have identified numerous disease-associated SNPs within this region. However, these associations do not fully capture the immune-biological relevance of specific HLA alleles. HLA imputation techniques may leverage available SNP arrays by predicting allele genotypes based on the linkage disequilibrium between SNPs and specific HLA alleles. Successful imputation requires diverse and large reference panels, especially for admixed populations. This study employed a bioinformatics approach to call SNPs and HLA alleles in multi-ethnic samples from the 1000 genomes (1KG) dataset and admixed individuals from Brazil (SABE), utilising 30X whole-genome sequencing data. Using HIBAG, we created three reference panels: 1KG (n = 2504), SABE (n = 1171), and the full model (n = 3675) encompassing all samples. In extensive cross-validation of these reference panels, the multi-ethnic 1KG reference exhibited overall superior performance than the reference with only Brazilian samples. However, the best results were achieved with the full model. Additionally, we expanded the scope of imputation by developing reference panels for non-classical, MICA, MICB and HLA-H genes, previously unavailable for multi-ethnic populations. Validation in an independent Brazilian dataset showcased the superiority of our reference panels over the Michigan Imputation Server, particularly in predicting HLA-B alleles among Brazilians. Our investigations underscored the need to enhance or adapt reference panels to encompass the target population's genetic diversity, emphasising the significance of multiethnic references for accurate imputation across different populations.

PI: **Mayana Zatz**

Publication: Silva NSB, Bourguiba-Hachemi S, Ciriaco VAO, Knorst SHY, Carmo RT, Masotti C, Meyer D, Naslavsky MS, Duarte YAO, **Zatz M**, Gourraud PA, Limou S, Castelli EC, Vince N. *A multi-ethnic reference panel to impute HLA classical and non-classical class I alleles in admixed samples: Testing imputation accuracy in an admixed sample from Brazil*. HLA. 2024 Jun;103(6):e15543. doi: 10.1111/tan.15543. PMID: 38837862.

Large-scale projects on genomics of Mendelian and complex disorders in Brazilians

Pilot project of genomic screening for couples: Rare genetic diseases (RGDs) require the Brazilian public universal healthcare system (SUS) to pay high-cost treatments, such as Spinal Amyotrophy (SMA) - R$6.4 million/patient. There are more than 2000 recessive RGDs, affecting up to 1 in every 100-200 Brazilians, impacting patients and families. Costly diagnosis and non-specific therapies burden the SUS and impact society. Without screening programs, couples carrying pathogenic genetic variants in genes associated with recessive conditions (at-risk couples - ARCs) only become aware of the risk after the birth of the first affected child. This project was approved by the Brazilian Ministry of Health (MS/DECIT/GenBR via CNPq)

and is under implementation by HUG-CELL with national partnerships (UFES, UFBA, UEPB) and aims to: (a) offer a pilot approach to screening ARCs, prior to conception, with the aim of reducing the incidence of births with RGDs; (b) recruit 5000 couples with and without a family history of RGDs, in public campaigns, to be ascertained in genetic centers in the Southeast and Northeast regions; (c) clinical, phenotypic and genealogical data will be collected from eligible volunteers; (d) offer genetic tests to detect pathogenic variants in the SMN1/SMN2 genes (MLPA), in FMR1 (expansions using TP-PCR), in addition to screening around 400 genes for recessive RGDs (whole-exome sequencing); produce individual reports to returned in Genetic Counseling (GC) sessions; (e) present reproductive options including referral to assisted reproduction and pre-implantation diagnosis of embryos for ACRs that opt-in; (f) train health services and professionals, test and provide GC to individuals at risk, calculate the incidence of carriers in the population, establish the cost-effectiveness of a screening program.

PIs: **Michel Naslavsky**, **Mayana Zatz** and **Maria Rita Passos-Bueno**
Researchers: **Regina Mingroni-Neto, Débora Bertola, Ana Krepischi, Eliana Dessen**, Silvana Santos (UEPB), Angelina Acosta (UFBA), Flávia Errera (UFES), Flávia Paula (UFES), Joanna Meira (UFBA)

Genomas SUS Network project: In order to advance Brazilian research on human genomics and build foundations for precision health applied in the Brazilian public universal healthcare system (SUS), researchers from several public academic institutions created a Network project to integrate experience, resources and samples involving five regions of the country. This project is currently funded by the Brazilian Ministry of Health (MS/DECIT/Genomas Brasil) and under implementation. Following standardized protocols shared by participating laboratories, this project unites eight anchor centers across the country and collaborating institutions to: (a) whole-genome sequencing 21,000 samples in 1 year (sourced from research cohorts), integrating genomic information with clinical and population data to characterize genetic mechanisms associated with disease phenotypes; (b) manage working groups for tackling and harmonizing data from the sequenced cohorts regarding diseases of relevance to SUS, such as cancer, infectious diseases, cardiovascular, neurological, endocrine-metabolic, autoimmune, hematological and rare diseases, as well as topics relevant to health care such as aging and response to pharmaceuticals; (c) create a network of laboratories with capacity and experience for genomic studies and exams in the context of SUS: five existing laboratories in the states of São Paulo (CEGH-CEL/IBUSP and LTO/FMRP), Rio de Janeiro (UFRJ) and Paraná (Fiocruz and IPEC Guarapuava), and three new laboratories in the states of Pará (UFPA), Pernambuco (Fiocruz), and Minas Gerais (UFMG). These laboratories will be available to support future projects and provide services to SUS genomic exams.

PIs: **Michel Naslavsky (HUG-CELL IBUSP),** Leandro Colli (Laboratory of Translational Oncology/FMRP USP), Adriana Carvalho (National Laboratory of Cardiology UFRJ), Fábio Passetti (Fiocruz-PR), David Livingstone

(IPEC Guarapuava), Ândrea Ribeiro (UFPA), Norma Lucena (Fiocruz-PE) and Eduardo Tarazona-Santos (UFMG)

Effects of miscegenation on the modulation of genomic risk in Alzheimer's disease: The *APOE* gene is recurrently associated with the risk of dementia, particularly Alzheimer's disease (AD), with allele 4 being the risk factor with the greatest effect attributed to the most prevalent form of multifactorial etiology. Recent studies have demonstrated that APOE4 contributes differently depending on the individual's global and local ancestry around the gene, with attenuated risk in Africans when compared to Europeans. The function of these genomic contexts in AD neuropathologies (NPs) is still an open problem. This study is currently funded by the Alzheimer's Association, Instituto Serrapilheira and FAPESP (PI: Michel Naslavsky) and proposes to: (a) dissect global (GA) and local (LA) ancestry patterns of the APOE gene and LA of genes involved in APOE and lipid metabolism regulatory pathways in brain samples; (b) evaluate the modulation of the effect of common APOE alleles and associated regulatory pathways on AD NPs and cognitive decline; (c) verify the association between GA and LA of APOE, its regulators and lipid metabolism genes and neuroimaging measurements of white matter and lipidomic profiles of tissue and plasma; (d) test the hypothesis of the involvement of APOE and ancestry in cognitive outcomes via lipid changes in myelination and white matter. Around 400 post-mortem cases with pathological series from the BAS population cohort (FMUSP) will be subjected to mid-coverage whole-genome sequencing (MC-WGS, 10-15X) where the aim is to initially describe common and rare variants, as well as GA and LA. At the moment, 135 samples have been sequenced.

PIs: **Michel Naslavsky** and **Mayana Zatz** (INCT Coordinator)
Collaborators: Lea Grinberg (UCSF and FMUSP), Renata Leite (FMUSP), Claudia Suemoto (FMUSP)

C.Therapies in Genetic Disorders

C1. Pre-Clinical studies with murine stem cells

C2. Safety-related concerns in cell therapy

MSC quality assessment for clinical applications: The limited proliferative lifespan of human mesenchymal stem cells (hMSCs) poses a challenge for clinical use. This study assessed hMSC proliferation from P0 to P16, examining differentiation capacity, immunophenotyping, immunomodulatory activity, and telomere length to determine their upper

cultivation limit. Cumulative doubling time increased until P5, remained stable between P5 and P8, and decreased after P8. Differentiation into adipocytes, chondrocytes, and osteoblasts significantly declined by P10. CD73 and CD105 expression decreased by P10, while CD90 expression remained high. Negative markers CD19, HLA-DR, and CD34 increased by P10. Significant telomere shortening was observed by P10. The ability to inhibit MNC proliferation decreased by P10. In conclusion, hMSCs are suitable for clinical use up to passages 7-8. Beyond passage 10, significant declines in potency, immunophenotyping profiles, proliferation rates, and telomere length indicate a transition towards senescence.

PI: **Oswaldo Keith Okamoto**

Publication: Sielski M, Andrade H, Alves Paiva RD, Coa L, Oliveira D, Kutner JM, Kondo AT, Kerbauy LN, Azevedo J, **Okamoto OK**, J.A. Godoy JA. *Aging of mesenchymal stem cells in vitro: implications in phenotype and differentiation capacity.* Cytotherapy. Volume 26, Issue 6, Supplement, June 2024, Page S46.

Embryos with genetic abnormalities as source of human embryonic stem cell lines: This study investigated whether discarded blastocyst-stage embryos with genetic abnormalities and poor morphology could be a reliable source of human embryonic stem cell (HESC) lines. Twenty-three embryos donated between February 2020 and April 2021 were evaluated using preimplantation genetic testing and then cultured to generate HESCs. Of the 23 embryos, 17 survived warming, with 16 remaining viable. Despite their poor quality, only one previously untested embryo generated a functional, euploid HESC line with preserved pluripotency. The study concluded that embryos with poor morphology and genetic abnormalities are unsuitable for generating pluripotent HESC lines, highlighting the importance of genetic counseling regarding their clinical use.

PI: **Oswaldo Keith Okamoto**
PhD and Master students: Lucila Kerbauy, Ianae Ceschin, Susana Joya,
Thiago G. Mitsugi.
Collaboration: Dr. J.M. Kutner (Albert Einstein Hospital)

Publications: **1)** M Sielski, H Andrade, RD Alves Paiva, L Coa, D Oliveira, JM Kutner, LN Kerbauy, J Azevedo, **OK Okamoto**, JA Godoy. *Aging of mesenchymal stem cells in vitro: implications in phenotype and differentiation capacity*. Cytotherapy, 26(S6): pS46, 2024.

2) Ceschin II, Ceschin AP, Joya MS, Mitsugi TG, Nishikawa LK, Krepischi AC, **Okamoto OK**. *Functional assessment of donated human embryos for the generation of pluripotent embryonic stem cell lines*. Reprod Biomed Online. 2023 Mar;46(3):491-501.

C3. Myogenesis and Muscle Regeneration mechanisms in aging and in dystrophic processes, aiming targets for therapies

Induced degeneration and regeneration in aged muscle reduce tubular aggregates but not muscle function: Tubular aggregates (TA) are skeletal muscle structures that arise from the progressive accumulation of sarcoplasmic reticulum proteins. Cytoplasmic aggregates in muscle fibers have already been observed in mice and humans, mainly during aging and muscle disease processes. However, the effects of muscle regeneration on TA formation have not yet been reported. This study aimed to investigate the relationship between degeneration/regeneration and TA in aged murine models. We investigated the presence and quantity of TA in old males from two murine models with intense muscle degeneration and regeneration. One was a *Dmd*^{mdx} model of Duchenne Muscular Dystrophy (n=6). In the other model, muscle damage was induced by electroporation in C57BL/6J wild-type mice, analyzed after 5, 15, and 30 days post-electroporation (dpe; n=15). Regeneration was evaluated based on the quantity of developmental myosin heavy chain (dMyHC)-positive fibers**.** The frequency of fibers containing TA was higher in aged C57BL/6J (26±8.3%) than in old dystrophic *Dmd*^{mdx} mice (2.4±2%). Comparing the data from induced degeneration/regeneration in normal mice revealed a reduced proportion of TA-containing fibers after 5 and 30 dpe. Normal aged muscle was able to regenerate and form dMyHC+ fibers, mainly at 5 dpe (0.1±0.1 vs 16.5±2.6%). However, there was no difference in force or resistance between normal and 30 dpe animals, except for the measurements by the Actimeter device, which showed the worst parameters in the second group. Our results suggest that TA also forms in the *Dmd*^{mdx} muscle but in smaller amounts. The intense degeneration and regeneration of the old dystrophic model resulted in the generation of new muscle fibers with a lower quantity of TA. Data from electroporated wild-type mice support the idea that muscle regeneration leads to a reduction in the amount of TA. We suggest that TA accumulates in muscle fibers throughout physiological aging and that regeneration leads to the formation of new fibers without these structures. In addition, these new fibers do not confer functional benefits to the muscle.

PIs: **Mariz Vainzof** and **Merari de Fátima Ramires Ferrari**
Students: Felipe Tadeu Galante Rocha de Vasconcelos (PhD. student), Lucas Santos Souza (PhD.) and Brandow willis (MSc)

Publication: Vasconcelos FTGR, Ribeiro Júnior AF, Souza BW, Zogbi IA, Carvalho LML , Feitosa LN, Souza LS, Saldys NG , **Ferrari MFR**, **Vainzof M**. *Induced degeneration and regeneration in aged muscle reduce tubular aggregates but not muscle function*. Front Neurol. 2024 Jan 26;15:1325222. doi: 10.3389/fneur.2024.1325222. eCollection 2024

C4. Advanced therapies for cancer

Adoptive cell therapies for cancer: BCMA-targeted CAR-T cell therapy has significantly improved Multiple Myeloma (MM) treatment but faces challenges like production shortages, high costs, and long waiting lists. Initiatives in Brazil aim to develop BCMA CAR-T products to enhance access for relapsed/refractory MM patients, potentially reducing disparities and costs. Our study explored second-generation anti-BCMA CAR and its fourth-generation version with Interleukin-15 (CAR-BCMA-IL15). Our CAR-BCMA-IL15 cells showed higher cytotoxicity and cytokine production against BCMA-positive cells, supporting further research for clinical use. Meanwhile, NK cells, crucial for antitumor responses and post-hematopoietic stem cell transplantation outcomes, require feeder cells for ex vivo expansion while maintaining cytotoxic properties. We developed a new K562.clone1 feeder cells by transducing mbIL-21 and 4-1BBL proteins, resulting in over 100-fold expansion of NK cells, compared to less than 10-fold with K562-WT. The NK cell frequency increased significantly with K562.clone1, and the expanded NK cells exhibited strong cytotoxicity against acute myeloid leukemia (AML) and tumor cell lines. Our K562.Clone1 feeder cell effectively enhances NK cell expansion and function.

PI: **Oswaldo Keith Okamoto**
PhD and Master students: Lucila Kerbauy, Thiago G. Mitsugi.
Collaboration: Dr. J.M. Kutner and Dr. N. Hamerschlak (Albert Einstein Hospital).

Publications: **1)** Mitsugi T, Suzuki C, Andrade GP, Vidal EKS, Barros CCC, Azevedo JTC, Melo RAP, **Okamoto OK**, Zanetti L, Hamerschlak N, Kerbauy LN. Enhancing Anti-BCMA CAR-T Cell Activity with sIL-15 Cytokine: Evaluation of Its Impact on in Vitro Cytotoxicity, Cytokine Production, and T Cell Exhaustion. Transplantation and Cellular Therapy, v30(2):S371-S372, 2024.

2) Watanabe CM, Suzuki CI, dos Santos AM, Aloia TP, Lee G, Wald D, **Okamoto OK**, de Azevedo JT, de Godoy JA, Santos FP, Weinlich R, Kerbauy LN, Kutner JM, Paiva RM, Hamerschlak N. Induction of expansion of ex vivo NK cells using a new feeder cell built in Brazil: An extended flow cytometry evaluation of K562.mbIL21.4BBL. bioRxiv, 2024.02. 23.581719.

Oncolytic virus therapy for pediatric cancer: we have reported a systematic analysis of the therapeutic use of different oncolytic viruses (OVs), addressing challenges in treating pediatric brain tumors and neuroblastoma. Our overview of preclinical studies provided detailed information of emerging OVs such as Zika virus (ZIKV), Measles virus, Reovirus, and Poliovirus, highlighting their infection mechanisms and in vitro and in vivo findings. In a novel study, we also developed a first-in-class microRNA-sensitive oncolytic ZIKV for virotherapy against CNS tumors. This modified ZIKV showed oncolytic effects in tumor cells while being safe for normal cells, including neural stem cells. Our study demonstrated total tumor remission in mice with human CNS tumors, confirming the potential of ZIKV virotherapy as a novel treatment for highly lethal brain tumors. Additionally,

in pediatric neuroblastoma, we identified the PRVABC59 ZIKV strain's as a promising oncolytic virus, enhancing our understanding of ZIKV infection in neuroblastoma cells and facilitating the development of ZIKV-based oncolytic virotherapy for further preclinical and clinical investigations.

PIs: **Oswaldo Keith okamoto** and **Mayana Zatz**
Pos-doc: Elisa H. Jandrey; Marcia C.L.Pereira
PhD and master students: Gabriela M. Novaes, Isabela Granha
Undergrad student: Gustavo Sartorelli
Collaborations: Dr. Rob Ewing (University of Southampton, UK); Dr. Harry Bulstrode (University of Cambridge, UK); Dr. David Lagares (Harvard Medical School, USA); Dr. Carolini Kaid (Vyro Bio Inc).

Publications: **1)** I Granha, G Sartorelli, **OK Okamoto**, EHF Jandrey. *Emergent and underexplored oncolytic viruses for treating pediatric central nervous system tumors*. EJC Paediatric Oncology, V3, p100151, 2024.

2) Novaes GM, Lima C, Longo C, Machado PH, Silva TP, Olberg GGO, Módolo DG, Pereira MCL, Santos TG, **Zatz M**, Lagares D, de Franco M, Ho PL, Bulstrode H, **Okamoto OK**, Kaid C. *Genetically modified ZIKA virus as a microRNA-sensitive oncolytic virus against central nervous system tumors*. Mol Ther. 2024 Feb 7;32(2):440-456.

3) Sherwood M, Zhou Y, Sui Y, Wang Y, Skipp P, Kaid C, Gray J, **Okamoto OK**, Ewing RM. *Integrative transcriptomic and proteomic study of Zika viral infection reveals potential mechanisms for oncolytic therapy in neuroblastoma*. *F1000 Research*, 719 (12), 2024.

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 -25

Autoantibodies against type I IFNs in humans with alternative NF-κB pathway deficiency: Patients with autoimmune polyendocrinopathy syndrome type 1 (APS-1) caused by autosomal recessive AIRE deficiency produce autoantibodies that neutralize type I interferons (IFNs)1,2, conferring a predisposition to life-threatening COVID-19 pneumonia3. Here we report that patients with autosomal recessive NIK or RELB deficiency, or a specific type of autosomal-dominant NF-κB2 deficiency, also have neutralizing autoantibodies against type I IFNs and are at higher risk of getting life-threatening COVID-19 pneumonia.

In patients with autosomal-dominant NF-κB2 deficiency, these autoantibodies are found only in individuals who are heterozygous for variants associated with both transcription (p52 activity) loss of function (LOF) due to impaired p100 processing to generate p52, and regulatory (IκBδ activity) gain of function (GOF) due to the accumulation of unprocessed p100, therefore increasing the inhibitory activity of IκBδ (hereafter, p52LOF/IκBδGOF). By contrast, neutralizing autoantibodies against type I IFNs are not found in individuals who are heterozygous for NFKB2 variants causing haploinsufficiency of p100 and p52 (hereafter, p52LOF/IκBδLOF) or gain-of-function of p52 (hereafter, p52GOF/IκBδLOF). In contrast to patients with APS-1, patients with disorders of NIK, RELB or NF-κB2 have very few tissue-specific autoantibodies. However, their thymuses have an abnormal structure, with few AIRE-expressing medullary thymic epithelial cells. Human inborn errors of the alternative NF-κB pathway impair the development of AIRE-expressing medullary thymic epithelial cells, thereby underlying the production of autoantibodies against type I IFNs and predisposition to viral diseases.

PI: **Mayana Zatz**
Pos-doc: Mateus Vidigal (PhD)

Publication: Le Voyer T, Parent AV, Liu X. et al. *Autoantibodies against type I IFNs in humans with alternative NF-κB pathway deficiency*. Nature 623, 803–813 (2023). https://doi.org/10.1038/s41586-023-06717-x

Lack of association between HLA and asymptomatic SARS-CoV-2 infection: Human genetic studies of critical COVID-19 pneumonia have revealed the essential role of type I interferon-dependent innate immunity to SARS-CoV-2 infection. Conversely, an association between the HLA-B*15:01 allele and asymptomatic SARS-CoV-2 infection in unvaccinated individuals was recently reported, suggesting a contribution of pre-existing T cell-dependent adaptive immunity. We report a lack of association of classical HLA alleles, including HLA-B*15:01, with pre-omicron asymptomatic SARS-CoV-2 infection in unvaccinated participants in a prospective population-based study in the US (191 asymptomatic vs. 945 symptomatic COVID-19 cases). Moreover, we found no such association in the international COVID Human Genetic Effort cohort (206 asymptomatic vs. 574 mild or moderate COVID-19 cases and 1,625 severe or critical COVID-19 cases). Finally, in the Human Challenge Characterisation study, the three HLA-B*15:01 individuals infected with SARS-CoV-2 developed symptoms. As with other acute primary infections, no classical HLA alleles favoring an asymptomatic course of SARS-CoV-2 infection were identified. These findings suggest that memory T-cell immunity to seasonal coronaviruses does not strongly influence the outcome of SARS-CoV-2 infection in unvaccinated individuals.

PI: **Mayana Zatz**
Pos-doc: Mateus Vidigal (PhD)

Publication: Marchal A, Cirulli ET, Neveux I, Bellos E, et.al. *Lack of association between HLA and asymptomatic SARS-CoV-2 infection*. medRxiv [Preprint]. 2023 Dec 8:2023.12.06.23299623. doi: 10.1101/2023.12.06.23299623. Update in: HGG Adv. 2024 Apr 26;:100300. PMID: 38168184; PMCID: PMC10760282.

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

Anti-RBD IgG antibodies from endemic coronaviruses do not protect against the acquisition of SARS-CoV-2 infection among exposed uninfected individuals: In this study, we investigated a cohort of 47 couples (N=94), where one partner tested positive for SARS-CoV-2 infection via real-time PCR while the other remained negative. Plasma samples, collected at least 30 days post-PCR reaction, were assessed using indirect ELISA and competition assays to measure specific antibodies against the receptor-binding domain (RBD) portion of the Spike (S) protein from SARS-CoV-2, HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1. IgG antibody levels against the four endemic coronavirus RBD proteins were similar between the PCR-positive and PCR-negative individuals, suggesting that IgG against endemic coronavirus RBD regions was not associated with protection from infection. Moreover, we found no significant IgG antibody cross-reactivity between endemic coronaviruses and SARS-CoV-2 RBDs. Taken together, results suggest that anti-RBD antibodies induced by a previous infection with endemic HCoVs do not protect against acquisition of COVID-19 among exposed uninfected individuals.

PIs: **Mayana Zatz** and **Michel Naslavsky**
Pos-doc: Mateus Vidigal (PhD)
Collaboration: Edecio Cunha-Neto and Jorge Kalil

Publication: Adami FL, **de Castro MV**, Almeida BS, Daher IP, Yamamoto MM, Santos KS, **Zatz M**, **Naslavsky MS**, Rosa DS, Cunha-Neto E, de Oliveira VL, **Kalil J**, Silvia Beatriz Boscardin SB. *Anti-RBD IgG antibodies from endemic coronaviruses do not protect against the acquisition of SARS-CoV-2 infection among exposed uninfected individuals.mong exposed uninfected individuals*. Sec. Viral Immunology, Volume 15 - 2024 | https://doi.org/10.3389/fimmu.2024.1396603

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 year, we have maintained the full operating capacity of 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). In the past year, we also maintained our infrastructure for storage by about ~1000 TB, which has been essential for whole-genome and whole-exome sequencing data, growing in scale. Even though we have an adequate infrastructure for both research and diagnosis purposes at our current demand, we are applying for an expansion given that this sequencing facility is registered at the multi-user facility at USP <https://uspmulti.prp.usp.br/public/centrais/11> and more collaborators and users could benefit from genomic analyses. Further, the introduction of long read sequencing will be an important task to be achieved in the near future, which will allow us to solve cases that present normal results in NGS or other genetic tests and open the possibilities to answer new research genomic questions.

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. The implemented test in 2023 for detection of pathogenic expansion at *C9orf72*, which is associated with neurodegenerative phenotypes, is currently being offered both as a standalone test and as part of a broader NGS panel for neurodegenerative disorders.
We are constantly updating our pipelines. In 2023-2024, we have been applying a CNV detection pipeline previously standardized by us for exome analysis. We have also tested several CNV callers for whole-genome sequencing analysis (WGS) and defined the Manta CNV caller as the best one, which has already been incorporated in our routine for research and services. We have also established and implemented a pipeline using ExpansionHunter (Illumina) to estimate repetition sizes in exomes and genomes to detect pathogenic expansions. 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. Furthermore, we have implemented a pipeline for transcriptome data analysis, including differential expression analysis and co-expression network analysis, which is being used on HUG-CELL research and also in bioinformatics consultation services.

We currently have a robust pipeline for variant discovery and interpretation for monogenic diseases that has been constantly updated. Our next goal is to improve the analysis of polygenic traits by the polygenic risk score (PRS) which will allow us to predict risk of developing or transmitting for several multifactorial conditions, such as autism spectrum disorder, cancer among others. The application of PRS represents a challenge in the genomics field, and most particularly for our ethnically admixed population due to lack of genomic data from Brazilian individuals with these conditions. We are thus validating different

pipelines for polygenic score (PGS) calculation on mid-pass WGS 10X data and developmental phenotypes, such as executive function. Our tests also include the comparison and validation of methods that are capable of performing adequately in admixed populations, such as the Brazilian.

During the last year (2023 to June 2024), we have performed about 17.200 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). A total of 453 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), UK. Furthermore, we have recently been approved by Anvisa (Agência Nacional de Vigilância Sanitária).

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 1330 consultations were performed by our team. A written report, including results of genetic tests, were provided for the attended individuals.
In this next year, it is expected a significant increase in the number of consultations for genetic counseling (at least 500 couples/year) associated with the recent approved project " Screening of young couples for mutations associated with autosomal recessive conditions"(details in **Pilot project of genomic screening for couples**).

c) **DATABASES:** We have maintained hosted in our servers the 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 .The individual-level data (BAM and gVCF files) from the 1171 WGS are also available for researchers who can access under request both datasets at the European Genome-phenome Archive <https://ega-archive.org/studies/EGAS00001005052>. We have recently opted to use Franklin Genoox <https://franklin.genoox.com/clinical-db/home> platform for analysis of the NGS tests, which is currently being used for the analysis of NGS tests. We have already uploaded 400 samples and one of the main advantages of using this platform is to centralize the samples and results**.**

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 an alternative source for human transplantation.

e) **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 66 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. 71 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**). 21 High school students were trained to act as monitors during the time the Itinerant Laboratory was in their schools (**Annex 4, Table 3**). On average, 700 students per school participate in laboratory classes, totaling 46,200 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.

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 (14th, 15th, 16th), during USP Professions Fair.

B. 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) **(Annex 4. Table 4**)

On YouTube https://www.youtube.com/genomausp between June/2023 and May 2024, the scientific dissemination team idealized and produced 28 videos that addressed different subjects. The total views in the last year, including old videos, was 155,1k.

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, 46 feed posts, 32 videos and 230 Stories were produced.

The number of followers on GenomaUSP media continues to grow and, by May 2022, corresponds to 12,000 on Facebook, 21,100 on Instagram and 11,010 on YouTube. Between June 2023 and May 2024, the YouTube channel had 155,011 views, 6,6 thousand hours watched and 2,010 new subscribers.

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

From July 2023 until June 2024, our group has published 81 journal articles (all listed below), 13 abstracts in National meetings, and 18 abstracts in International meetings. During this period, our graduate students submitted 4 Master Theses and 7 Doctoral Dissertations. About 40 conferences, lectures and symposia were presented done by our team

1.1. Book and book Chapters

1. Sossai P, Barcelos EC, Fernandes I, Rodrigues AS, **Naslavsky M**, Maranduba CM, de Paula F, **Passos-Bueno MR**, **Zatz M**, Errera F. Participação da via de sinalização WNT na demência e sua relação com diabetes tipo 3. In: Aragão JA, Dal Molin RS, Zago M (org.). Envelhecimento Humano e Contemporaneidade: Tópicos atuais em Pesquisa. Vol 3, ISBN 978-65-5360-524-4, Ano 2023, Editora Cientifica (e-book), p 106-126. Disponível em: https://www.editoracientifica.com.br/books/chapter/participacao-da-via-de-sinalizacao-wnt-na-demencia-e-sua-relacao-com-o-diabetes-tipo-3

2. Barcelos EC, Barcelos DHF, Borges RR, Silveira IF, Errera LI, De Paula F, **Naslavsky M**, **Passos-Bueno MR**, **Zatz M**, Flávia Errera FIV. Fragilidade: Evolução Conceitual, Epidemiologia e fisiopatologia. In: Aragão JA, Dal Molin RS, Zago M (org.). Envelhecimento Humano e Contemporaneidade: Tópicos atuais em Pesquisa. Vol 2, ISBN 978-65-5360-438-4, Ano 2023, Editora Cientifica (e-book), p.296-314. Disponível em: https://www.editoracientifica.com.br/books/chapter/fragilidade-evolucao-conceitual-epidemiologia-e-fisiopatologia

1.2 Articles

1. Adami FL, de Castro MV, Almeida BS, Daher IP, Yamamoto MM, Santos KS, **Zatz M**, **Naslavsky MS**, Rosa DS, Cunha-Neto E, de Oliveira VL, Kalil J, Silvia Beatriz BoscardinSB. Anti-RBD IgG antibodies from endemic coronaviruses do not protect against the acquisition of SARS-CoV-2 infection among exposed uninfected individuals.mong exposed uninfected individuals. Sec. Viral Immunology, Volume 15 - 2024 | https://doi.org/10.3389/fimmu.2024.1396603

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4. Assoni AF, Guerrero EN, Wardenaar R, Oliveira D, Bakker PL, Alves LM, Carvalho VM, **Okamoto OK**, **Zatz M**, Foijer F. IFNγ protects motor neurons from oxidative stress via enhanced global protein synthesis in FUS-associated amyotrophic lateral sclerosis. Brain Pathol. 2024 Jan;34(1):e13206. doi: 10.1111/bpa.13206. Epub 2023 Aug 15

5. Assoni AF, Giove Mitsugi T, Wardenaar R, Oliveira Ferreira R, Farias Jandrey EH, Machado Novaes G, Fonseca de Oliveira Granha I, Bakker P, Kaid C, **Zatz M**, Foijer F, **Keith Okamoto O**. Neurodegeneration-associated protein VAPB regulates proliferation in medulloblastoma. Sci Rep. 2023 Nov 9;13(1):19481. doi: 10.1038/s41598-023-45319-5.

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2.1. Abstract: International Meetings

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4. Endo AK, Granha IFO, Nomiyama PY, Silva LR, Sartorelli G, Novaes GM, Farias Jandrey EH, **Okamoto OK**. Synthetic LNCRNA With Therapeutic Approach In Medulloblastoma. In: The State of Art in Neuro Oncology - Society for Neuro-Oncology Latin America (SNOLA), 2024, São Paulo. Abstract compilation book, 2024.

5. Ferreira R, Andrade T, Landini V, Astray R, Lessa R, Madi R, Granato T, Kaid C, **Zatz M**. The safety and efficiency of serial ZIKV treatment in dogs bearing brain tumor. 16th Annual Meeting of the Korean Society of Medical Oncology & 2023 International Conference (KSMO 2023). Seoul, South Korea, September 7-8, 2023.

6. Ferreira R, Andrade T, Landini V, Astray R, Lessa R, Madi R, Granato T, Kaid C, **Zatz M**. The safety and efficiency of serial ZIKV treatment in dogs bearing brain tumor. Autumn Meeting of Korean Society for Neuro-Oncology. Seoul, South Korea, September 16th, 2023.

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12. Lima VA, Verhoeyen E, Giove Mitsugi T, **Okamoto O**K. Development of CAR (Chimeric Antigen Receptor) -NK Cells against Glioblastoma Stem Cells. In: The State of Art in Neuro Oncology - Society for Neuro-Oncology Latin America (SNOLA), 2024, São Paulo. Abstract compilation book, 2024.

13. Martins CCA, Maschietto M; Kimura L, Alvizi L, Borges VM, **Krepischi ACV**, **Mingroni Netto RC**. DNA methylation in blood and essential hypertension in African-Brazilian quilombo populations. European Society of Human Genetics Conference (ESHG 2024), 2024.

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16. Oliveira D, Alves LM, Nunes BG, Assoni AF, Teles K, **Sertie A**, Sakugawa A, **Ferrari MR**, **Zatz M**. Molecular characterization of VRK1 R321C mutation in autosamal recessive Amyotrophic Lateral Sclerosis using iPSC derived motor neurons. Conference for Neuroscience 2023. Washington, DC, United States, November 11-15th, 2023

17. Sielski M, Andrade H, Paiva RLMA, Coa L, Oliveira D, Kutner JM, Kondo AT, Kerbauy LN, Azevedo JTC, **Okamoto OK**, Godoy JAP. Aging of Mesenchymal Stem Cells In Vitro: Implicattions In Phenotype and Differentiation Capacity. In: Meeting of the American Society for Transplantation and Cellular Therapy, 2024, San Antonio. 30th ISCT annual meeting, 2024. v. 26. p. S46-S46.

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2.2. Abstract: National Meetings

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2. Barbosa IN, Souza Leite F, Esposito J, Pardo MCS, Jazedje T, **Zatz M**. Impact of DMD Correction on Myogenic Marker Expression in hiPSC-Derived Myoblasts. Frontiers in Myogenesis: Skeletal Muscle – Development, Regeneration and Disease, held at the Jequitimar Hotel, Guaruja, Brazil, on November 6-11, 2023.

3. Batista MTO, Fernandes RB, Ferrer-Sueta G, Malavazi I, **Netto LES**. Biochemical and Structural Characterization of two 1-CYS Peroredoxins from Aspergillus Fumigatus. In: 68th Brazilian congress genetics, 2023, ouro preto. anais SBG. 2023, p.499

4. Castro MV, Oliveira, DF, Assoni AF, Da Silva MVR, **Zatz M**. Comparative Analysis of SARS-CoV-2 infection in induced pluripotent stem cell-derived astrocytes and neurons from recovered centenarians and severe cases. ISSCR 2023 São Paulo International Symposium In Person Meeting held 22-24 September 2023 in Ribeirão Preto, Brazil.

5. Castro MV, Da Silva MVR, Soares FB, Quiñones-Veja M, Sosa-Acosta P, Nogueira FCS, Domont GB, **Naslavsky MS**, **Zatz M**. Investigating Immune Proteins Linked to Natural Resistance to COVID-19 in Highly Exposed Individuals. XLVII Congress of the Brazilian Society of Immunology. October 02nd to 06th, 2023, in Ouro Preto, Minas Gerais, Brazil.

6. Da Silva MVR, De Castro MV, Soares FB, Cariste LM, Sasahara GL, Almeida RR, Santos KS, Cunha Neto E, Oliveira LD, Sato MN, **Naslavsky MS**, **Zatz M**. Unraveling COVID-19 Resistance: Distinct Immune Profile in Uninfected Women highly Exposed to SARS-CoV-2. XLVII Congress of the Brazilian Society of Immunology. October 02nd to 06th, 2023, in Ouro Preto, Minas Gerais, Brazil.

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9. Jazedje T, Coria VR, **Zatz M**. Jagged-1 haploinsufficiency does not exacerbate the clinical severity in a DMD patient. Frontiers in Myogenesis: Skeletal Muscle – Development, Regeneration and Disease, held at the Jequitimar Hotel, Guaruja, Brazil, on November 6-11, 2023.

10. Komatsu S, Pacheco L, Chianca F, Telles-Silva K, **Goulart E**, **Zatz M**. Topoisomerase 1 inhibition increases the expression of cardiac markers in IPSC-

CMS. ISSCR 2023 São Paulo International Symposium In Person Meeting held 22-24 September 2023 in Ribeirão Preto, Brazil.

11. Kobayashi GS, Vieira-Silva GA, Varella-Branco, Danielle P, Danielle P,Kitajima JPFW, **Mingroni-Netto RC**, Lojudice FH, Oiticica J, Batissoco AC, Lezirovitz K. Generation of induced pluripotent stem cells line from PBMC of DFNA58 family members In: 34 Congresso Brasileiro de Genética Médica, 2023, São Paulo. 34 Congresso Brasileiro de Genética Médica. , 2023. v.34.

12. Pacheco L, Komatsu S, Telles-Silva K, **Goulart E**, Caires L, **Zatz M**. Analysis of the effects of topoisomerase 2 inhibitors on in vitro hepatic differentiation. ISSCR 2023 São Paulo International Symposium In Person Meeting held 22-24 September 2023 in Ribeirão Preto, Brazil.

13. **Passos-Bueno.** Apresentação de pôster no evento científico. Neurodevelopmental disorders: genetic testing and counseling in a Brazilian cohort. GENÉTICA 2023 - 68th Brazilian Congress of Genetics, ocorrido de 2/09/2023 a 15/09/2023 em Ouro Preto/MG.

2.3. Conferences, Symposia, Round Tables, Lectures

1. Batista MTO, Bannitz-Fernandes R, Ferrer-Sueta G, Malavazi I, **Netto LES**. Biochemical and Structural Analysis of Peroxiredoxins from Aspergillus fumigatus In: **SfRBM - SFRRI 2023 Conference**, 2023, Punta del Este. Free Radical Biology Medicine. 2023, v.213,

2. Fiuza M, Cabreira I. Organization of Scientific Events: **IV Simpósio de Genética do TEA** (October/2023) and **I Conferência Nacional sobre a Síndrome de Phelan-McDermid** (October/2023).

3. Fiuza M. Attendance to Scientific Events: **Genetics and Genomics Scientific Retreat** (via Zoom) - Boston Children's Hospital / Harvard Medical Schoo. May/2024 and **Simpósio do Departamento de genética e Biologia Evolutiva**, March/2024.

4. Fiuza M**.** Lectures: Ensaios Pedagógicos para o Ensino em Biologia, March-June/2024. IB-USP.

5. Girardi AC**.** Aconselhamento genético a partir dos resultados da pesquisa genética sobre apraxia de fala na infância – **IX conferência nacional sobre apraxia de fala na infância**. A genética do autismo - Como os genes contribuem para o autismo. Seminário “O espectro como você nunca viu” CEMPA (Centro Multiprofissional de Potencialização da Aprendizagem) Petrolina PE 22/23 September 2023.

6. **Mingroni-Netto RC.** Genética molecular e o resgate da ancestralidade de habitantes de remanescentes de quilombos (Lecture), 2023. Universidade Federal de São Carlos - Campus de Araras. Evento: **X Semana dos Estudantes de Biologia** - Inst.promotora/financiadora: Universidade Federal de São Carlos

7. **Mingroni-Netto RC.** Apresentação de resultados com o poster Maternal inflammation drives cleft lip/palate via CDH1 epigenetic modulation. In**: 68º Congresso Brasileiro de Genética da Sociedade Brasileira de Genética**, em Ouro Preto, Minas Gerais, entre os dias 12 e 15 de setembro de 2023.

8. **Okamoto OK**. Solid tumors: how are advanced therapies working? **- XXI Simpósio Internacional de Hemoterapia e Terapia Celular | VI Fórum Internacional de Terapia Celular**, 2024.

9. **Okamoto OK**. Terapia celular em oncologia: estudos atuais e perspectivas.In: **XXX Simpósio Internacional de Hemoterapia e Terapia Celular | V Fórum Internacional de Terapia Celular** Einstein,2023.

10. **Passos-Bueno MR.** IV Simpósio de Genética do Autismo e **I Conferência Nacional sobre a Síndrome de Phelan-McDermid**, realizado nos dias 14 e 13 de Outubro de 2023 oferecido pelo grupo de pesquisa em genética do TEA do CEGH-CEL, Instituto de Biociências da USP em cooperação com a equipe do PROGENE e Associação Amigos e Familiares da Síndrome de Phelan-McDermid

11. **Passos-Bueno MR.** October/2023: IV Simpósio de Genética do TEA. October/2023: I Conferência Nacional sobre a Síndrome de Phelan-McDermid

12. **Passos-Bueno MR.** Attendance to Scientific Events**:** March-May/2023: Psiquiatria Social, March-May/2023: Psicopatologia da Criança: Abordagens psicanalíticas

13. **Passos-Bueno MR.** Leitura no Programa de Aperfeiçoamento de Ensino – Monitoria PAE da disciplina de Genética Humana e Médica e Oncogenética, para os alunos de graduação em Medicina (FMUSP) July-December/2023

14. Nani DA. Apresentação de resultados com o pôster Maternal inflammation drives cleft lip/palate via CDH1 epigenetic modulation: In: **68º Congresso Brasileiro de Genética da Sociedade Brasileira de Genética**, em Ouro Preto, Minas Gerais, entre os dias 12 e 15 de setembro de 2023.

15. **Naslavsky MS.** Apresentação Genética populacional e Score de risco poligênico. In: **Ciclo de palestras do grupo de laboratório de diagnóstico molecular do Hospital Israelita Albert Einstein**. 23 de junho de 2023

16. **Naslavsky MS** Curso de especialização “Programa de Diplomado en Bioinformática y Biología Computacional” Módulo: Medicina Genómica (12h). Realizado virtualmente pela Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile. 25 de setembro a 2 de outubro de 2023.

17. **Naslavsky MS.** Participação em evento Workshop sobre Construção de Repositório e Plataforma de Dados Genômicos no âmbito do Programa Genomas Brasil, Brasília, período de 9 a 11 de outubro de 2023.

18. **Naslavsky MS.** Participação no **Encontros Serrapilheira 2023**. Tibau do Sul – Rio Grande do Norte, 19 a 22 de outubro de 2023.

19. **Naslavsky MS.** Participação na reunião anual 2023 da **American Society of Human Genetics**, Washington, DC, Estados Unidos da América, 1 a 5 de novembro de 2023.

20. **Naslavsky MS.** Participação de Reunião para ajustes à resolução de atuação de biólogos em aconselhamento genético, pelo Conselho Federal de Biologia. Brasília – DF. Em 22 de novembro de 2023.

21. **Naslavsky MS.** Organização de Mesas Redondas para discussão sobre genética, bancos de dados e raças para publicação no periódico Frontiers in Genetics. 24 de novembro e 13 de dezembro de 2023.

22. **Naslavsky MS.** Participação e palestra no Illumina Clinical Summit. Título: Painel Projetos de PopGen no Brasil. Realizado em São Paulo-SP. 11 de dezembro de 2023.

23. **Naslavsky MS.** Apresentação de seminário Genomic analyses on two Brazilian admixed cohorts: novel variants, effect size modulation and PRS transferability. In: **Integrative Center For Neurobehavioral Genetics** (ICNG) da University of California Los Angeles. Em 29 de Janeiro de 2024.

24. **Naslavsky MS.** Participação no Debate Ciência no Cinema, projeto do ICTP-SAIFR em parceria com o Reag Belas Artes. Painel de discussão sobre o filme Pobres Criaturas. Em 2 de abril de 2024.

25. **Naslavsky MS.** Palestra Bioinformática aplicada para genômica populacional e saúde. In: **1º Simpósio de Genética Humana da Liga de Genética Humana** da Universidade Federal de Pernambuco. Realizado online em 9 de abril de 2024.

26. **Naslavsky MS.**Participação no **Workshop Regional** para promover a geração e uso equitativo do conhecimento em genômica humana nas Américas", organizada pela Organização Pan-Americana da Saúde/Organização Mundial da Saúde (OPAS/OMS) e pelo Ministério da Saúde (MS). Em Brasília, DF, de 15 a 16 de maio de 2024.

27. **Naslavsky MS.** Participação no evento **Seminário Marco Zero da Chamada MS-SECTICS-Decit/CNPq n° 16/2023** – Saúde de Precisão, o qual ocorrerá nos dias 10, 11 e 12 de junho de 2024 em Brasília DF.

28. **Netto LES**. Palestra Inhibiing Ohr (Organic Hydroperoxide Resistance protein): A unique antioxidant protein from pathogens, 2023. Evento: **SfRBM - SFRRI 2023 Conference**;

Inst.promotora/financiadora: Society for Redox Biology and Medicine. Uruguai; Cidade: Punta del Este.

29. **Vainzof M**. Palestra Regeneraao muscular visando alvos terapêuticos para doenças neuromusculares. In: **Simpósio de Depto. De Genetica e Biologia evolutiva do IBUSP**. . São Paulo, 25/3/2024

30. **Zatz. M.** Keynote sepaker: Os 90+: Longevidade e sobrevivência na COVID-19. In: **Congresso da SBG**, 14/09/2023, Ouro Preto, Brasil.

31. **Zatz M.** Keynote speaker: Como ser um centenário saudável. In: **Congresso Gero de Gerontologia**, SC HCFMUSP, 21/09/2023, São Paulo, Brasil. < https://lets.4.events/congresso-gero-2023-C14251E207?autoopen>

32. **Zatz M**. Keynote speaker: GenÉTICA **- Jornada do Programa de Oncologia** da Universidade de São Paulo, FMUSP/ICESP, Novembro 2023

33. **Zatz M**.. Palestra A medicina do futuro. In: **Congresso de pós-graduação**. 21/10/2023, Cidade universitária, São Paulo, Brasil.

34. **Zatz M** . Keynote speaker: Our contribution to neuromuscular disorders: from gene identification to novel therapeutic approaches. In**: Frontiers in Myogenesis Conference**. 17/11/2023, Guarujá, São Paulo, Brasil..

35. **Zatz M** . Keynote speaker: How to be a healthy centenarian. In: **1st Symposium on Skeletal Muscle Physiology and Pathology**, ICB, Novembro 2023. < https://ww3.icb.usp.br/eventos/1st-symposium-on-skeletal-muscle-physiology-and-pathology/>

36. **Zatz M** . Participação debate Os INCTs e o enfrentamento aos desafios do Brasil atual. In: **5ª Conferência Nacional de Ciência, Tecnologia e Inovação atual**- fevereiro 2024, Brasília

37. **Zatz M** Palestra A genetica dos grandes longevos. In: **Congresso da Sociedade Brasileira de geriatria e gerontologia**, GERP, março 2024

38. **Zatz M** . Participação collaborative workshop. What are the centenarians secrets ? Evento University of Birmingham/fapesp, Abril 2024, São Paulo, Brasil

39. **Zatz M** . Palestra A genética revolucionária a Saúde- Novas Fronteiras no tratamento de Saúde. In: **Health Week** – 3 edição, Faculdade Unimed, São Paulo, Junho 2024,

40. **Zatz M** .Palestra O futuro da medicina: da pesquisa básica ao tratamento. Universidade federal do Rio Grande do Sul, Junho 2024.

Annex 3 - Theses and Dissertations, Awards

3.1. PhD Theses

1. Name: Angélica Ramos
Title: Functions of 1-Cys Peroxiredoxin (Prx1) dual localization in Saccharomyces cerevisiae mitochondria
Orientador: **Luis Eduardo Soares Netto**
Doutorado: Biologicas (Genética) IB- USP
Defesa: 2024

2. Name: Camila Corradini
Title: Mutagenesis and mutational signature analysis in fibroblasts and tumors of xeroderma pigmentosum variant patients
Orientador: **Carlos Frederico Martins Menck**
Doutorado: Interunidades em Bioinformática- USP
Defesa: 2023

2. Name: Claudia Ismania Samogy Costa
Title: Alternative approachesto characterizing the genetic architecture of autism spectrum disorder
Orientador: **Maria Rita Passos Bueno**
Doutorado: Biologicas (Genética) IB- USP
Defesa: 2024

4. Name: Gabriel Bandeira do Carmo
Title: Estudo de mutações germinativas em famílias com predisposição hereditária ao câncer de mama.
Orientador: **Oswaldo Keith Okamoto**
Co-orientadora: **Ana Cristina V. Krepischi**
Doutorado: Biologicas (Genética) - USP
Defesa: 2024

5. Name: Ricardo Di Lazzaro Filho
Title: Genetic study of patients with Rothmund-Thomson syndrome
Orientador: **Débora Romeo Bertola**
Doutorado: Biologicas (Genética) IB- USP
Defesa: 2023

6. Name: Rogério Luis Aleixo Silva
Title: Unraveling the biological role of LsfA, a 1-Cys Prx involved in the Pseudomonas aeruginosa virulence
Orientador: **Luis Eduardo Soares Netto**
Doutorado: Biologicas (Genética) IB- USP
Defesa: 2024

7. Name: Vinícius Magalhães Borges

Title: Investigação genômica da hipertensão essencial em populações afro-brasileiras.
Orientador: **Regina Mingroni Netto**
Doutorado: Biologicas (Genética) IB- USP
Financiadora: CNPq.
Defesa: 2023

3.2. Master Degree

1. Name: **Lucas Carvalho Price.**
Title: Estudo da regulação de OCT4 pelo efetor da via Hippo, YAP, e seu efeito sobre células-tronco tumorais de meduloblastoma.
Orientador: **Oswaldo Keith Okamoto**
Mestrado: Biológicas (Genética) - USP
Defesa: 2023

2. Name: Taccyanna Mikulski Ali
Title: Monogenic diseases with low bone mineral density: clinical and genetic evaluation focused on patients with osteogenesis imperfecta
Orientador: **Débora Romeo Bertola**
Mestrado: Aconselhamento genético e Genômica Humana- IB-USP.
Defesa: 2023

3. Name: Thais Regina dos Santos
Title: Isolamento e Caracterização de Tumor-Infiltrating Lymphocytes (TILs) de Gliomas para Terapia Celular no Câncer.
Orientador: **Oswaldo Keith Okamoto**
Mestrado: Biotecnologia - USP
Defesa: 2023.

4. Name: Thiago Giove Mitsugi
Title: Desenvolvimento de receptor quimérico de antígeno tumoral com aplicação no tratamento de glioblastoma.
Orientador: **Oswaldo Keith Okamoto**
Mestrado: Biológicas (Genética) – IB-USP
Defesa: 2023

3.3 Awards

1. **Best Poster**: Branco EV; Kobayashi GS; Lacerda ECM; Toledo, VHC; Ramos I; Fiuza, MA; Carvalho LML; Costa CIS, Girardi ACS; **Krepischi ACV**, Casella EB; **Passos-Bueno MR**. Unveiling SHANK3: Illuminating Pathways for Precision Interventions in Phelan-McDermid

Syndrome". Poster Session Phelan-McDermid Conference, Phelan-McDermid Syndrome Foundation, 2024.

2. **Best Poster**: Lima VA, Verhoeyen E, Giove Mitsugi T, **Okamoto OK**. Development of CAR-NK Cells against Glioblastoma Stem Cells"). The State of Art in Neuro Oncology - Society for Neuro-Oncology Latin America (SNOLA), 2024.

3. **Honorable Mention**: Silva LR, Farias Jandrey EH, Rego GSC, Endo AK, **Okamoto OK**. The role of the EZH2 protein in CNS Tumor development. The State of Art in Neuro Oncology, Society for Neuro-Oncology Latin America (SNOLA), 2024.

4. **Honorable Mention:** Endo AK, Granha IFO, Nomiyama PY, Silva LR, Sartorelli G, Novaes GM, Farias Jandrey EH, **Okamoto OK**. Synthetic lncRNA with therapeutic approach in Medulloblastoma. The State of Art in Neuro Oncology - Society for Neuro-Oncology Latin America (SNOLA), 2024.

5. **Awarded as the best post-doc from USP in the field of "Biological Sciences "**De Castro MV. Candidate genes for natural resistance to COVID-19 in the Brazilian admixed population. Supervisor: **Mayana Zatz**. Presented at the Congresso de Pós-Doutorandos da USP, São Paulo, October 17-19, 2023.

6. **Travel award** para aluna de doutorado Angelica Ramos, SfRBM, 2023.

7. **Travel award** para aluna de doutorado Maria Tereza Oliveira Batista, SfRBM, 2023

8. **Travel award** para aluno de doutorado Rogério Aleixo Silva, SfRBM, 2023.

Annex 4 - Education Out Reach

4.1. Interviews to the Media

1. Assoni AF, **Okamoto OK**. Entrevista: Proteína ligada a doenças neurodegenerativas pode ser caminho para apontar gravidade de câncer no cérebro. 08/12/2023, **Agência FAPESP**, São Paulo <https://agencia.fapesp.br/proteina-ligada-a-doencas-neurodegenerativas-pode-ser-caminho-para-apontar-gravidade-de-cancer-no-cerebro/50418>

2. **Okamoto OK**. Entrevista: Os caminhos para o futuro Terapias avançadas e medicamentos biológicos apontam para tratamentos mais eficazes e com menos efeitos colaterais. 24/07/2023 , **Jornal O Estado SPaulo** (Estadão). <https://www.estadao.com.br/saude/os-caminhos-para-o-futuro/

3. **Zatz M**. Radio columnist Decodificando o DNA “No reino animal, quanto do comportamento depende da genética e do ambiente?” **Rádio USP**, 14/12/2023. < https://jornal.usp.br/radio-usp/no-reino-animal-quanto-do-comportamento-depende-da-genetica-e-do-ambiente/ >

4. **Zatz M**. Radio columnist Decodificando o DNA “Reino Unido aprova terapia gênica para anemia falciforme e talassemia” **Rádio USP**, 30/11/2023. < https://jornal.usp.br/radio-usp/reino-unido-aprova-terapia-genica-para-anemia-falciforme-e-talassemia/ >

5. **Zatz M**, D'Avila, R. Interview Programa Roberto D’Avila. Globoplay. 21/11/2023 <https://globoplay.globo.com/v/12133632/>

6. **Zatz M**. Radio columnist Decodificando o DNA “Como o ChatGPT pode influenciar na medicina?” **Rádio USP**, 16/11/2023. < https://jornal.usp.br/radio-usp/como-o-chatgpt-pode-influenciar-a-medicina/ >

7. **Zatz M**. Radio columnist Decodificando o DNA “Descriminalização do aborto volta a ser pauta no Supremo Tribunal Federal” **Rádio USP**, 02/11/2023. < https://jornal.usp.br/radio-usp/descriminalizacao-do-aborto-volta-a-ser-pauta-no-supremo-tribunal-federal/ >

8. **Zatz M**. Radio columnist Decodificando o DNA “Genes sem função conhecida são investigados por pesquisadores ingleses” **Rádio USP**, 19/10/2023. < https://jornal.usp.br/radio-usp/genes-sem-funcao-conhecida-sao-investigados-por-pesquisadores-ingleses/ >

9. **Zatz M**. Radio columnist Decodificando o DNA “Criação de órgãos humanos em suínos é a nova aposta da ciência para evitar rejeição em transplantes” **Rádio USP**,05/10/2023. < https://jornal.usp.br/radio-usp/criacao-de-orgaos-humanos-em-suinos-e-a-nova-aposta-da-ciencia-para-evitar-rejeicao-em-transplantes/ >

10. **Zatz M**. Report comment “Quando o ativismo judicial do STF fica obsoleto”. **Crusué**, edição 317, 03/09/2023.< https://crusoe.com.br/diario/quando-o-ativismo-judicial-do-stf-fica-obsoleto>

11. **Zatz M**. Radio columnist Decodificando o DNA “O “pai” da ovelha Dolly morre aos 79 anos” **Rádio USP**, 21/09/2023. < https://jornal.usp.br/radio-usp/pai-da-ovelha-dolly-morre-aos-79-anos/ >

12. **Zatz M**, Assis T, Beltrão M . Report comment “Dona Lucinda conta seus segredos para chegar aos 101 anos com saúde e disposição”. **TV Globo**, Globoplay, 30/09/2023 < https://globoplay.globo.com/v/11989244/>

13. **Zatz M**. Report comment “Sete hábitos apoiados pela ciência que aumentam a longevidade”. **Portal UOL**, 01/09/2023. < https://www.uol.com.br/vivabem/colunas/ageless/2023/09/01/sete-habitos-apoiados-pela-ciencia-que-aumentam-a-longevidade.htm >

14. **Zatz M**. Radio columnist Decodificando o DNA “Cientistas alteram genoma das moscas-da-fruta para que sejam capazes de se reproduzirem sem machos” **Rádio USP**,

07/09/2023. < https://jornal.usp.br/radio-usp/rim-de-porco-transplantado-para-homem-com-morte-cerebral-funciona-bem-apos-32-dias-da-cirurgia/ >

15. **Zatz M**. Radio columnist Decodificando o DNA “Rim de porco transplantado para homem com morte cerebral funciona bem após 32 dias da cirurgia” **Rádio USP**, 24/08/2023. < https://jornal.usp.br/radio-usp/rim-de-porco-transplantado-para-homem-com-morte-cerebral-funciona-bem-apos-32-dias-da-cirurgia/ >

16. **Zatz M**, Kalache A , Motta Z . Report comment “Pessoas com 80+ anos mantêm rotina criativa de descobertas e recomeços”. **Portal SESC**, 31/08/2023. < https://www.sescsp.org.br/pessoas-com-mais-de-80-anos-mantem-rotina-criativa-de-descobertas-e-recomecos/ >

17. **Zatz M**. Radio columnist Decodificando o DNA “Risco de demência pode estar associada a desregulação de proteínas do sangue” **Rádio USP**, 10/08/2023. <https://jornal.usp.br/radio-usp/risco-de-demencia-pode-estar-associado-a-desregulacao-de-proteinas-do-sangue/>

18. **Zatz M**. Radio columnist Decodificando o DNA “Como ser um centenário saudável?” **Rádio USP**, 28/07/2023. <https://jornal.usp.br/radio-usp/como -ser-um-centenario-saudavel/>

19. **Zatz M**. Radio columnist Decodificando o DNA “Proteína antienvelhecimento melhora cognição e memória de macacos rhesus”. **Rádio USP**, 13/07/2023. <https://jornal.usp.br/radio-usp/proteina-antienvelhecimento-melhora-cognicao-e-memoria-de-macacos-rhesus/>

20. Bustamante M, **Zatz M.** Interview , Mulheres na Ciências: “Premio da Unesco reconhece pesquisas lideradas por mulheres. **TV Brasil**, 15/07/2023. < https://tvbrasil.ebc.com.br/reporter-brasil/2023/07/premio-da-unesco-reconhece-pesquisas-lideradas-por-mulheres>

21. **Zatz M**. Radio columnist Decodificando o DNA. “Pesquisadores criam o primeiro embrião sintético sem óvulo e espermatozoide”, **Rádio USP**, 29/06/2023. <https://jornal.usp.br/radio-usp/pesquisadores-criam-o-primeiro-embriao-sintetico-sem-ovulo-ou-espermatozoide/>

22. **Zatz M**. Report comment “Você diz que sou velho? Eu digo: sou sábio”. **Revista Época – Negócios**, 08/06/2023 <https://epocanegocios.globo.com/colunas/50-vida-e-trabalho/coluna/2023/06/voce-diz-que-sou-velho-eu-digo-sou-sabio.ghtml >

23. **Zatz M**, Vieira I. Criação de embrião humano ‘sintético’ sem espermatozoide ou óvulo é realizada por cientistas. **Canal Consulta Pública**, 27/06/2023. < https://canalconsultapublica.com.br/2023/06/26/noticias/criacao-de-embriao-humano-sintetico-sem-espermatozoide-ou-ovulo-e-realizada-por-cientistas/>

24. **Zatz M**. Newspaper comment “De bezerro clonado a miniporco transgênico: como a USP ajuda a revolucionar a pesquisa genética”, **Estadão**. 21/01/2024.

25. **Zatz M**. Radio columnist Decodificando o DNA “Nova abordagem terapêutica usa organoides celulares para tratar ratos com síndrome de Timothy” **Rádio USP**, 16/05/2024

< https://jornal.usp.br/radio-usp/nova-abordagem-terapeutica-usa-organoides-celulares-para-tratar-ratos-com-sindrome-de-timothy/ >

26. **Zatz M**. Radio columnist Decodificando o DNA "Programa do CNPq quer repatriar cientistas brasileiros que atuam no exterior" **Rádio USP**, 02/05/2024 < https://jornal.usp.br/radio-usp/programa-do-cnpq-quer-repatriar-cientistas-brasileiros-que-atuam-no-exterior/ >

27. **Zatz M**. Radio columnist Decodificando o DNA "Pesquisadores holandeses descobrem novo gene associado aos canhotos" **Rádio USP**, 18/04/2024 < https://jornal.usp.br/radio-usp/pesquisadores-holandeses-descobrem-novo-gene-associado-aos-canhotos/ >

28. **Zatz M**. Radio columnist Decodificando o DNA "Americanos realizam o primeiro xenotransplante de rim em paciente vivo" **Rádio USP**, 04/04/2024 < https://jornal.usp.br/radio-usp/mayana-3-4americanos-realizam-o-primeiro-xenotransplante-de-rim-em-paciente-vivo/ >

29. **Zatz M**. Radio columnist Decodificando o DNA "A possível associação entre o desequilíbrio da microbiota intestinal e a susceptibilidade a vícios" **Rádio USP**, 21/03/2024 < https://jornal.usp.br/radio-usp/a-possivel-associacao-entre-o-desequilibrio-da-microbiota-intestinal-e-a-susceptibilidade-a-vicios/ >

30. **Zatz M**. Radio columnist Decodificando o DNA "Programa do CNPq produziu conhecimentos importantes em diversas áreas, afirma Mayana Zatz" **Rádio USP**, 07/03/2024 < https://jornal.usp.br/radio-usp/programa-do-cnpq-produziu-conhecimentos-importantes-em-diversas-areas-afirma-mayana-zatz/ >

31. **Zatz M**. Radio columnist Decodificando o DNA "Programa do CNPq produziu conhecimentos importantes em diversas áreas, afirma Mayana Zatz" **Rádio USP**, 07/03/2024 < https://jornal.usp.br/radio-usp/programa-do-cnpq-produziu-conhecimentos-importantes-em-diversas-areas-afirma-mayana-zatz/ >

32. **Zatz M**. Radio columnist Decodificando o DNA "Estudar o genoma de idosos saudáveis ajuda a entender as variantes genéticas que causam doenças" **Rádio USP**, 22/02/2024.< https://jornal.usp.br/radio-usp/estudar-o-genoma-de-idosos-saudaveis-ajuda-a-entender-quais-variantes-geneticas-causam-doencas/ >

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4.2. Science Dissemination

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4.3. Tables

Table 1 - 66 schools were assisted by the Laboratory Classes at Schools project from July to November 2023 and from February to June 2024.

July to November, 2023

Schools	Educational Directory
EE Glória Azedia Bonetti	Osasco
EE José Geraldo Vieira	Osasco
EE Rosa Bonfiglioli	Osasco
EE Prof.Elói Lacerda	Osasco
EE Educador Paulo Freire	Osasco
EE Walter Negrelli	Osasco
EE Prof. Newton Espírito Santo Ayres	Osasco
EE São Paulo da Cruz	Osasco
EE Prof. Fanny Monzoni Santos	Osasco
EE Dep. Guilherme de Oliveira	Osasco
EE Américo Marco Antonio	Osasco
EE Prof. José Jorge	Osasco
EE Alice Velho Teixeira	Osasco
EE Antonio Raposo Tavares/CENEART	Osasco
EE Prof José Liberatti	Osasco
EE Prof Vicente Peixoto	Osasco
EE CEL Antonio Paiva de Sampaio	Osasco
EE Irmã Gabriela Maria Elizabeth Wienkem	Osasco
EE Graciliano Ramos	Osasco
EE José Maria Rodrigues Leite	Osasco
EE Prof João Baptista de Brito	Osasco
EE Lourival Gomes Machado	Centro-Oeste
EE Lygia de Azevedo Souza e Sá	Centro-Oeste
EE Guiomar Rocha Rinaldi	Centro- Oeste
EE Prof. Thomázia Montoro	Centro- Oeste
EE Pedro Fonseca	Centro-Oeste
EE Pereira Barreto	Centro-Oeste
EE Paulo Rossi	Centro-Oeste
EE Anhanguera	Centro-Oeste
EE Dona Ana Rosa de Araújo	Centro-Oeste
EE Prof Martim Francisco	Centro-Oeste
EE Prof Keizo Ishihara	Centro-Oeste
EE Prof Virgília Rodrigues A. de Carvalho Pinto	Centro-Oeste
EE Prof Manuel Ciridião Buarque	Centro-Oeste
EE Profa Flávia Vizibeli Pirró	Centro-Oeste
EE Dep. Augusto do Amaral	Centro-Oeste

February to May, 2024

Schools	Educational Directory
EE Prof. Architiclino Santos	Centro-Oeste
EE Prof.Maria Eugênia Martins	Centro-Oeste
EE Prof Ennio Voss	Centro-Oeste
EE Oswaldo Aranha	Centro-Oeste
EE Pereira Barreto	Centro-Oeste
EE Dr.Reinaldo Ribeiro da Silva	Centro-Oeste
EE Aristides de Castro	Centro-Oeste
EE Samuel Klabin	Centro-Oeste
EE Maria Augusta Siqueira	Osasco
EE Alcyr de Oliveira Porciuncula	Osasco
EE José Geraldo Vieira	Osasco
EE José Maria Rodrigues Leite	Osasco
EE Francisco Casabona	Osasco
EE Antônio Carlos da Trindade	Osasco
EE Eloi Lacerda	Osasco
EE Walter Negreli	Osasco
EE Lucy Anna Carroso Latorrre	Osasco
EE Major Telmo Coelho Filho	Osasco
EE Leonardo Vilas Boas	Osasco
EE Américo Marco Antonio	Osasco
EE Oguiomar Ruggeri	Osasco
EE Antônio Brás Gambarini	Osasco
EE Vicente Peixoto	Osasco
EE José Liberatti	Osasco
EE Educador Paulo	Osasco
EE Neuza de Oliveira Prévide	Osasco
EE José Edson	Osasco
EE Francisca Lisboa Peralta	Osasco
EE Cel. Antonio de Paiva Sampaio	Osasco
EE José Jorge	Osasco

Table 2 - 71 High School Teachers were trained to work in the Laboratory Classes at School Project, belonging to the Teaching Boards of the Osasco Region (02/272024) and Midwest (03/27/2024).

School	Student	Educational Directory
EE José Ribeiro de Souza	Raquel Aparecida Marques da Silva	Osasco
EE Francisco Casabona	Victoria do Nascimento Meira	Osasco
EE Antônio de Almeida Junior	Maria Eduarda de Paula	Osasco
EE José Maria Rodrigues Leite	Isabelly Rosa de Souza	Osasco
EE Educador Paulo Freire	Laura França Carneiro	Osasco
EE Eloi Lacerda	Kleber Rodrigues	Osasco
EE Francisco Matarazzo Sobrinho	Ana Clara Cavalcanti Novais	Osasco

EE Neusa de Oliveira Previde	Lucas Henrique M Silva	Osasco
EE José Edson Martins Gomes	Marina B M Martins	Osasco
EE Ana Carrozo Latorre	Kauan Ronaldo Vasconcelos	Osasco
EE Alcyr Oliveira Porciuncula	Queren Hapuke Barbosa da Cruz	Osasco
EE José Geraldo Vieira	Maria Luiza A Nakajda	Osasco
	Pedro Mantovani Munis Guimarães	
EE Jose Liberatt	Emilie Cardoso	Osasco
	Isabela de Souza Coelho	
	Barbara dos Santos	
EE Leonardo Villas Boas	Emilly Conceição Silva	Osasco
EE Orlando Geribola	Iguel Mantoan Santos	Osasco
EE Prof. Alice Velho Teixeira	Gabriel Willian Rodrigues da Silva	Osasco
EE Prof. José Jorge	Robson Martins	Osasco
EE Walter Negreli	Natan Paulo Silva	Osasco

Table 3 – 21 High School Students from the Osasco Educational Directory were trained to work on the Didactical Material Project (02/27/2024)

School	Student	Educational Directory
EE José Ribeiro de Souza	Raquel Aparecida Marques da Silva	Osasco
EE Francisco Casabona	Victoria do Nascimento Meira	Osasco
EE Antônio de Almeida Junior	Maria Eduarda de Paula	Osasco
EE José Maria Rodrigues Leite	Isabelly Rosa de Souza	Osasco
EE Educador Paulo Freire	Laura França Carneiro	Osasco
EE Eloi Lacerda	Kleber Rodrigues	Osasco
EE Francisco Matarazzo Sobrinho	Ana Clara Cavalcanti Novais	Osasco
EE Neusa de Oliveira Previde	Lucas Henrique M Silva	Osasco
EE José Edson Martins Gomes	Marina B M Martins	Osasco
EE Ana Carrozo Latorre	Kauan Ronaldo Vasconcelos	Osasco
EE Alcyr Oliveira Porciuncula	Queren Hapuke Barbosa da Cruz	Osasco
EE José Geraldo Vieira	Maria Luiza A Nakajda	Osasco
	Pedro Mantovani Munis Guimarães	
EE Jose Liberatt	Emilie Cardoso	Osasco
	Isabela de Souza Coelho	
	Barbara dos Santos	
EE Leonardo Villas Boas	Emilly Conceição Silva	Osasco
EE Orlando Geribola	Iguel Mantoan Santos	Osasco
EE Prof. Alice Velho Teixeira	Gabriel Willian Rodrigues da Silva	Osasco
EE Prof. José Jorge	Robson Martins	Osasco
EE Walter Negreli	Natan Paulo Silva	Osasco

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 (28 videos)

Youtube (28 vídeos postados; 155,1 mil views no período)

Subjects	Number of videos	Views
ABC Epigenetics	6	4.950
Decoding DNA - Mayana Zatz Programm on Rádio USP	18	2.946
Podcast CEPODE	2	668
Divulgation of HUG-CELL Research from HUG-CELL divulgation Divulgação de pesquisas do centro (teste de Covid-19, envelhecimento saudável)	2	230

4.B. Instagram (46 Posts, 32 Reels, 230 stories)

Subjects	Posts	Stories	Reels/Videos
ABC Epigenetics	7	7	6
Health in summer	2	2	
Alzheimer	1		
Parkinson's disease	1		
Genetics of Obsessive Compulsive Disorder	2	2	
Genetics of Autism Spectrum Disorder	1	1	2
Gene Edition	1		
Vacines	3	3	
Cancer/Therapies	5	3	1
Healthy aging	2	1	
Organ transplantation	2	2	
Felowships available	3	1	
Notable women scientists	3	3	
Decoding DNA			18
News, current scientific news and commemorative dates	8	6	1
Nobel Prizes	1	1	
CEPODE	3	3	
Dissemination of HUG-CELL research and services	1	6	3

Teacher training and Giant Cell exhibition	1	5	1

4.C. Facebook (19 videos, 17 posts, 230 stories)

Conteúdo	Postagens
Videos from the GenomaUSP channel on Youtube	19
Posts on Instagram	17

Annex 5 – Personnel

Scientific Initiation - IS	
Supervisor	**Student**
Ana Cristina V. Krepischi	Davi Mendes Campos Fialho
	Bianca Kurashima
	Larissa Moreira
	Maisa Ganz Sanchez Sennes
Carlos Frederico Martins Menck	Vitoria Rezende Goll
	Alissa Ukei
	Raphael Gesini Scaramal Pires
Luis Eduardo Soares Netto	Laura Maria Batista Leal
	Milene Feitosa de Araujo Martins
	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
	Luan Fávero Montes
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	Ruan Carlos Salvador
	Ana Julia Natucci Mergulhão
	Thais Palio de Carvalho
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
Luis Eduardo Soares Netto	
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
Mariz Vainzof	Brandow Willy Souza.
	Isabela de Aquino Zogbi
Michel Naslavsky	Airi Carvalho
	Gabriel do Nascimento Santos
	Gustavo Pukar Augusto (1)
	Leonardo Carvalheira (1)
	Mariana Bardella
	Thiago Pires (1)

Regina Célia Mingroni Netto	Sophia Lincoln Cardoso de Azevedo
	Beatriz Cetalle Schiavo
Oswaldo Keith Okamoto	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**
Ana Cristina V. Krepischi	Sara Ferreira Pires
Carlos Frederico Martins Menck	Camila Corradi
	Davi Jardim Martins.
	Davi Mendes
	Maira Rodrigues de Camargo Neves
	Gabrielly Cristine Martins
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	Rebeca Bandeira Candia
	Maria Tereza Oliveira Batista.
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	Camila Cristina Ávila Martins

Pos Doctorate/Visiting Researcher	
Supervisor	**Name**
Ana Cristina V. Krepischi	Veniamin Fishman (*)
	Laura Cardoso
Carla Rosenberg	Darine Vilella
Carlos Frederico Martins Menck	Diego Luis Ribeiro
	Fernanda Sodré
	Giovana da Silva Leandro
	Orlando Louzada Neto
	James Londero
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
	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

Laboratory Technicians and Assistants		
Supervisor	**Funding Source**	**Name**
Ana Cristina V. Krepischi	USP	Maria Raimunda L. S. Pinheiro
	USP	Silvia Souza da Costa
Celia Koiffmann	USP	Cláudia I. Emilio de Castro Fabris
Eliana Maria B. Dessen	HUG-CELL/FUSP	Andrea Grieco
	CEPID/IB-USP	Marici Leite Salviano
Luis Eduardo Soares Netto	USP	Simone Vidigal Alves
	USP	Thiago Geronimo Alegria
Maria Rita Passos Bueno	HUG-CELL/FFM	Ana Girardi
	HUG-CELL/FFM	Bruno de Oliviera Stephan
	HUG-CELL/FFM	Carolina Régoli Dias
	HUG-CELL/Fapesp	Daiane Gil Franco
	HUG-CELL/FUSP	Guilherme Lopes Yamamoto
	HUG-CELL/FUSP	Jaqueline Yu Ting Wang
	USP	Kátia Maria da Rocha
	HUG-CELL/FFM	Kelly Bagatini
	INCT	Bruno Guimarães Macarini
	HUG-CELL/FFM	Monica C. V. Rodrigues da Silva
	USP	Monize Lazar Magalhães
	USP	Naila Cristina V. Lourenço
	USP	Roberto Rivelino de Camargo
	USP	Simone Gomes Ferreira
	HUG-CELL/FUSP	Fabiane Felisberto
	USP	Vanessa Naomi V. O. Takahashi
Mariz Vainzof	INCT/FUSP	Letícia Nogueira Feitosa
	USP	Job Carvalho Bezerra
Mayana Zatz	HUG-CELL/FUSP	Heloísa Maria de Siqueira Bueno
	USP	Marta Canovas
	HUG-CELL/Fapesp	Tatiana Jazedje
	HUG-CELL/FFM	Thais Oliveira de Andrade
	HUG-CELL/FFM	Vivian Landini

	HUG-CELL/Fapesp	Fernanda Chianca
	HUG-CELL/Fapesp	Maria Fernanda Amarante
	HUG-CELL/Fapesp	Mayana Pardo
Merari R. F. Ferrari	USP	Andressa Y. Silvestre Sakugawa
Regina Célia Mingroni Netto	USP	Israel Rubio

Bioinformatics Support / Information Technology		
Supervisor	**Funding Source**	**Name**
Maria Rita Passos Bueno	HUG-CELL/FAPESP	Carlos Eduardo da Silva Simões
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Eliana M.B. Dessen	USP	Luciana Cristina A.Oliveira
Maria Rita Passos-Bueno	HUG-CELL/FUSP	Caissa Santos C. da Silva
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	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 (pos-doc), Michelle Araujo pos-doc 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** and **Michel Naslavsky**
Team: Felipe Leite (pos-doc), Joyce Esposito (PhD student), Igor Neves (PhD student), Mariana Bardella (MSc 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 with 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** and **Maria Rita Passos-Bueno**
Team: Mateus Vidigal (posdoc), Amanda Fassoni (pos-doc), Danyllo Oliveira (pos-doc), Vivian Romanholi Cória (MSc), Monize Silva (PhD student), 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).

Screening pilot project for couples: Rare genetic diseases (RGDs) require the Brazilian public universal healthcare system (SUS) to pay high-cost treatments, such as Spinal Amyotrophy (SMA) - R$6.4 million/patient. There are more than 2000 recessive RGDs, affecting up to 1 in every 100-200 Brazilians, impacting patients and families. Costly diagnosis and non-specific therapies burden the SUS and impact society. Without screening programs, couples carrying pathogenic genetic variants in genes associated with recessive conditions (at-risk couples - ARCs) only become aware of the risk after the birth of the first affected child. This project was approved by the Brazilian Ministry of Health (MS/DECIT/GenBR via CNPq) and is under implementation by HUG-CELL with national partnerships (UFES, UFBA, UEPB) and aims to: (a) offer a pilot approach to screening ARCs, prior to conception, with the aim of reducing the incidence of births with RGDs; (b) recruit 5000 couples with and without a family history of RGDs, in public campaigns, to be ascertained in genetic centers in the Southeast and Northeast regions; (c) clinical, phenotypic and genealogical data will be collected from eligible volunteers; (d) offer genetic tests to detect pathogenic variants in the SMN1/SMN2 genes (MLPA), in FMR1 (expansions using TP-PCR), in addition to screening around 400 genes for recessive RGDs (whole-exome sequencing); produce individual reports to returned

in Genetic Counseling (GC) sessions; (e) present reproductive options including referral to assisted reproduction and pre-implantation diagnosis of embryos for ACRs that opt-in; (f) train health services and professionals, test and provide GC to individuals at risk, calculate the incidence of carriers in the population, establish the cost-effectiveness of a screening program.

PIs: **Michel Naslavsky**, **Mayana Zatz** and **Maria Rita Passos-Bueno**
Researchers: **Regina Mingroni-Neto, Débora Bertona, Ana Krepischi, Eliana Dessen**, Silvana Santos (UEPB), Angelina Acosta (UFBA), Flávia Errera (UFES), Flávia Paula (UFES), Joanna Meira (UFBA)

Genomas SUS Network project: in order to advance Brazilian research on human genomics and build foundations for precision health applied in the Brazilian public universal healthcare system (SUS), researchers from several public academic institutions created a Network project to integrate experience, resources and samples involving five regions of the country. This project is currently funded by the Brazilian Ministry of Health (MS/DECIT/Genomas Brasil) and under implementation. Following standardized protocols shared by participating laboratories, this project unites eight anchor centers across the country and collaborating institutions to: (a) whole-genome sequencing 21,000 samples in 1 year (sourced from research cohorts), integrating genomic information with clinical and population data to characterize genetic mechanisms associated with disease phenotypes; (b) manage working groups for tackling and harmonizing data from the sequenced cohorts regarding diseases of relevance to SUS, such as cancer, infectious diseases, cardiovascular, neurological, endocrine-metabolic, autoimmune, hematological and rare diseases, as well as topics relevant to health care such as aging and response to pharmaceuticals; (c) create a network of laboratories with capacity and experience for genomic studies and exams in the context of SUS: five existing laboratories in the states of São Paulo (CEGH-CEL/IBUSP and LTO/FMRP), Rio de Janeiro (UFRJ) and Paraná (Fiocruz and IPEC Guarapuava), and three new laboratories in the states of Pará (UFPA), Pernambuco (Fiocruz), and Minas Gerais (UFMG). These laboratories will be available to support future projects and provide services to SUS genomic exams.

PIs: **Michel Naslavsky** (HUG-CELL IBUSP)**,** Leandro Colli (Laboratory of Translational Oncology/FMRP USP), Adriana Carvalho (National Laboratory of Cardiology UFRJ), Fábio Passetti (Fiocruz-PR), David Livingstone (IPEC Guarapuava), Ândrea Ribeiro (UFPA), Norma Lucena (Fiocruz-PE) and Eduardo Tarazona-Santos (UFMG)

Effects of miscegenation on the modulation of genomic risk in Alzheimer's disease: The *APOE* gene is recurrently associated with the risk of dementia, particularly Alzheimer's disease (AD), with allele 4 being the risk factor with the greatest effect attributed to the most prevalent form of multifactorial etiology. Recent studies have demonstrated that APOE4 contributes

differently depending on the individual's global and local ancestry around the gene, with attenuated risk in Africans when compared to Europeans. The function of these genomic contexts in AD neuropathologies (NPs) is still an open problem. This study is currently funded by the Alzheimer's Association, Instituto Serrapilheira and FAPESP (PI: Michel Naslavsky) and proposes to: (a) dissect global (GA) and local (LA) ancestry patterns of the APOE gene and LA of genes involved in APOE and lipid metabolism regulatory pathways in brain samples; (b) evaluate the modulation of the effect of common APOE alleles and associated regulatory pathways on AD NPs and cognitive decline; (c) verify the association between GA and LA of APOE, its regulators and lipid metabolism genes and neuroimaging measurements of white matter and lipidomic profiles of tissue and plasma; (d) test the hypothesis of the involvement of APOE and ancestry in cognitive outcomes via lipid changes in myelination and white matter. Around 400 post-mortem cases with pathological series from the BAS population cohort (FMUSP) will be subjected to mid-coverage whole-genome sequencing (MC-WGS, 10-15X) where the aim is to initially describe common and rare variants, as well as GA and LA. At the moment, 135 samples have been sequenced.

PIs: **Michel Naslavsky** and **Mayana Zatz** (INCT Coordinator)
Collaborators: Lea Grinberg (UCSF and FMUSP), Renata Leite (FMUSP), Claudia Suemoto (FMUSP)

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 (pos-doc), 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 (MSc), 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 (MSc), 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 Naslavsky**
National Collaboration: Dr. Diogo Meyer
International Collaboration: University of Marshall, WV, EUA, with a team coordinated by Dr. Alejandro Nato Jr.