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

Universidade de São Paulo

Instituto de Biociências

Departamento de Genética e Biologia Evolutiva

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Coordinator: MayanaZatz

REPORT

July 2020 to June 2021

SUMMARY

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ABSTRACT

Since July 2020 our group published 86 articles in peer-review journals. Most of the articles involved the collaboration of students and PIs from HUG-CELL. On line activities included about 24 conferences, lectures and symposia which were presented by our team as well as 161 interviews.

In addition to our regular projects, we were involved in new projects related to the coronavirus pandemic. We established a new rapid diagnostic test (LAMP-RT) which can be done in saliva with a much lower cost. Besides the identification of SARS-Cov-2, this test showed interesting results which are detailed in the present report. In collaboration with the group of immunologists from FMUSP we are investigating possible genetic variants associated to COVID-19 resistance and reinfection.

The applications of technology transfer included genetic counseling for about 330 families. Despite the interruption of activities during the coronavirus pandemia, a total of 1372 genetic tests and more than 6000 Sanger sequencing reactions, were performed at HUG-CELL EMU for 9 CEPID researchers, 120 external users, as detailed in the report. All the NGS is being performed in the Ilumina NovaSeq 6000™ , acquired in December of 2019 with Federal Funds (transfer of “verba parlamentar” from Senator Mara Gabrilli).

The COVID-19 pandemic affected HUG-CELL activities targeting high school teachers and students. With the suspension of classroom classes in High Schools, both the mobile laboratory and the centers that lend teaching materials to teachers were also interrupted. During the period of this report, dissemination HUG-CELL’s activities focused on the online world. The team produced scientific dissemination content for the general public, but remained attentive to teachers, producing part of the posts on Instagram and Facebook focusing basic genetics and the SARS-CoV-2’s genetics.

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PART 1- RESEARCH

Our main research results from **July 2020 to June 2021**, classified by our main objectives are:

A. Gene Identification and Mechanisms in Genetic Disorders

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

A1.1. Mendelian Disorders

A1.2. Complex disorders

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

A2.1. Neuromuscular disorders

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C3. Other therapeutic approaches

C4. Tissue engineering

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A. Gene Identification and Mechanisms in Genetic Disorders

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

A1.1. Mendelian Disorders

Genetic etiology of Mendelian syndromic obesity

Syndromic obesity is an umbrella term used to describe cases of obesity occurring with additional phenotypes, including intellectual disability, dysmorphic features, or organ-specific developmental abnormalities. These conditions are rare and highly variable. In a significant number of patients, syndromic obesity follows a Mendelian pattern of inheritance and may occur by the altered expression of genes with pleiotropic effects. Pathogenic variants involving the *MYT1L* gene lead to an autosomal dominant form of syndromic obesity, characterized by polyphagia, intellectual disability/developmental delay, and behavioral problems, and that a characteristic facial phenotype does not seem to be recognizable. Trio whole exome sequencing was performed in a 10-year-old Brazilian male presenting polyphagia, severe early-onset obesity, intellectual disability, speech delay, macrocephaly, frontal bossing, telecanthus, strabismus, and hypogenitalism (*Obes Res Clin Pract15(2):124-132. doi: 10.1016/j.orcp.2021.01.001*). Additionally, we performed a literature review of patients carrying non-copy number *MYT1L* variants. A de novo genetic variant not previously reported in *MYT1L* (NM_015025.4:c.2990C>A) was identified in the proband and classified as pathogenic. From a literature search, 22 further patients carrying non-copy number *MYT1L* variants were identified, evidencing that although the associated phenotype is quite variable, intellectual disability/developmental and speech delays are always present. Further, most patients have obesity or overweight due to polyphagia. Macrocephaly, strabismus, behavioral problems, and hand/feet malformations are also recurrent features. We described the first Brazilian case of *MYT1L* related syndrome and highlighted clinical characteristics based on the literature. Further, although obesity is frequent, it is not an obligatory feature of all carriers of *MYT1L* mutations.

PIs: Carla Rosenberg, Célia Koiffmann and Ana Krepischi
Graduate student: Laura Carvalho
Publication: Carvalho *et a*l, 2021. *Obes Res Clin Pract*

Syndromic and non-syndromic hearing loss

In the last period, we described a novel gene, *NCOA3,* as a candidate to explain autosomal dominant hearing loss in a Brazilian pedigree. The candidate variant in *NCOA3* gene was found after linkage studies and exome sequencing. Its possible implication in hearing was confirmed after expression studies and genomic edition of the gene using zebrafish as an animal model. (Salazar-Silva *et al.,* 2020.)

After its first description in two large Brazilian pedigrees with autosomal dominant hearing loss (Dantas *et al.,* 2018. *Scientific Reports*), the variant c;2090T>G in the *MYO3A* gene was detected in further three Brazilian pedigrees, after screening of a collection of samples from our own laboratories. The investigation of the five pedigrees allowed to infer that the mutation occurred in a chromosomal segment of European ancestry and the time since the most common ancestor was estimated in 1100 years. This variant was also reported in a Dutch family, which shares a haplotype with the Brazilian samples, suggesting that Dutch colonists may have brought it to Northeastern Brazil in the 17th century (Bueno *et al*., 2021).

PI: Regina Mingroni-Netto
Msc students: Andre Silva Bueno, Larissa Nascimento and Beatriz Schiavo..
Publications: Salazar-Silva, *et al*., 2020. *Human Molecular Genetics*; Bueno *et al*., 2021. *European Journal of Human Genetics*

Skeletal Disorders

We evaluated and followed a patient, born from a consanguineous marriage, with an unrecognizable phenotype characterized by short stature, craniofacial dysmorphisms and skeletal anomalies. An International collaboration gathered the clinical and molecular data of nine probands presenting biallelic inactivating variants in *SCUBE3*, a gene not previously associated with a Mendelian phenotype. Functional analysis showed that SCUBE3 plays a role in bone morphogenic protein signaling and knockout mice recapitulate the phenotype observed in these individuals (Lin *et al.,* 2021). During the period we have co-authored one additional manuscript (Calpena *et al.,* 2021).

AI: Debora Bertola
Msc students: Raíssa Modaffore Dandalo Girardi and Leticia Alves da Rocha.
Publication: Lin *et al*. 2021. *Am J Hum Genet*; Calpena *et a*l., 2021. *J Med Genet.*

Craniosynostosis and SIX pathogenic variants: Craniosynostosis, premature fusion of cranial sutures, is a common birth defect (1:2,000). It is a heterogenous group of disorders. The genetic mechanism of most of the cases with craniosynostosis is still uncertain. Through whole exome sequencing we identified a family with two affected sibs with cranioysnostosis of coronal and lambdoid sutures as the main clinical findings with a pathogenic variant in SIX1. This was an unexpected finding, as pathogenic variants in SIX1 cause branchio-otic syndrome (BOS; MIM 608389), which does not include craniosynostosis in the phenotype.Our Brazilian family was important to strength the first association of pathogenic variants in SIX1 with the craniosynostosis phenotype (Calpena *et al.,* 2020*, J Med Genet*).

PIs: Maria Rita Passos Bueno and Debora Bertola
PhD student: Rodrigo Atique

A1.2. Complex disorders

Structural variation in genetic disorders

CNVs are known to contribute to human normal variation and disease. We have investigated during the past two decades the causal association of rare genomic imbalances with several phenotypes. Recently, CNVs were also found to contribute to the pathology of central precocious puberty cases (Canton *et al* 2021 - *10.1093/humrep/deaa306*). In 12 out of 36 selected patients (33%), rare genetic abnormalities were identified, including seven patients with pathogenic CNVs: three with *de novo* 7q11.23 deletions (Williams-Beuren syndrome), three with inherited Xp22.33 deletions, and one with *de novo* 1p31.3 duplication.

PIs: Ana Krepischi and Carla Rosenberg
Student master: Juliana Sobral
Publication: Canton *et al.,* 2021 *, Hum Reprod.*

Detection of mosaicism for segmental and whole chromosome imbalances by targeted sequencing

Mosaic segmental and whole chromosome copy number alterations are postzygotic variations known to be associated with several disorders. We have previously presented an efficient targeted sequencing approach to simultaneously detect point mutations and copy number variations (CNVs). In this study, we evaluated the efficiency of this approach to detect mosaic CNVs, using seven postnatal and 19 tumor samples, previously characterized by chromosomal microarray analyses (CMA)(*doi 10.1111/ahg.12402*). These samples harbored a total of 28 genomic imbalances ranging in size from 0.68 to 171 Mb, and present in 10-80% of the cells. All CNV regions covered by the platform were correctly identified in postnatal samples, and only seven out of 19 CNVs from tumor samples were not identified either because of a lack of target probes in the affected genomic regions or an absence of minimum reads for an alteration call. These results demonstrate that, in a research setting, this is a robust approach for detecting mosaicism in cases of segmental and whole chromosome alterations.

Congenital chromoanagenesis in the routine postnatal chromosomal microarray analyses

Chromosomal microarray analyses (CMA) have greatly increased both the yield and diagnostic accuracy of postnatal analysis; it has been used as a first-tier cytogenetic test in patients with intellectual disability, autism spectrum disorder, and multiple congenital abnormalities. During the last 15 years, we performed CMA in approximately 8,000 patients with neurodevelopmental and/or congenital disorders. ,In 13 (0.16%) genetically catastrophic complex chromosomal rearrangements were identified (doi 10.1002/ajmg.a.62237). These ultrarare rearrangements showed clustering of breakpoints, characteristic of chromoanagenesis events. All 13 complex events display underlying formation mechanisms, originating either by a synchronization of the shattering of clustered chromosome regions in which regional asynchrony of DNA replication may be one of the main causes of disruption. We provide an overview of the copy number profiling in these patients. Several previous studies have suggested that

chromoanagenesis is often a genetic disease source in postnatal diagnostic screening, but due to either the challenge of clinical interpretation or the limitation of resolution relative to the small size and complexity of chromogenic induced chromosome abnormalities, bringing further attention and to study its occurrence in the clinical setting is extremely important.

> PIs: Ana Krepischi and Carla Rosenberg
> Students: Juliana Sobral, posdoc Darine Villela
> Publication: Villela *et al.* 2020. *Hum Genet*

Cytogenetically visible inversions are formed by multiple molecular mechanisms

Cytogenetically detected inversions are generally assumed to be copy number and phenotypically neutral events. While nonallelic homologous recombination is thought to play a major role, recent data suggest the involvement of other molecular mechanisms in inversion formation. Using a combination of short-read whole-genome sequencing (WGS), 10X Genomics Chromium WGS, droplet digital polymerase chain reaction and array comparative genomic hybridization we investigated the genomic structure of 18 large unique cytogenetically detected chromosomal inversions and achieved nucleotide resolution of at least one chromosomal inversion junction for 13/18 (72%)(doi 10.1002/humu.24106). Surprisingly, we observed that seemingly copy number neutral inversions can be accompanied by a copy-number gain of up to 350 kb and local genomic complexities (3/18, 17%). In the resolved inversions, the mutational signatures are consistent with nonhomologous end-joining (8/13, 62%) or microhomology-mediated break-induced replication (5/13, 38%). Our study indicates that short-read 30x coverage WGS can detect a substantial fraction of chromosomal inversions. Moreover, replication-based mechanisms are responsible for approximately 38% of those events leading to a significant proportion of inversions that are actually accompanied by additional copy-number variation potentially contributing to the overall phenotypic presentation of those patients.

> PIs: Ana Krepischi anda Carla Rosenberg
> Master and postdocs: Juliana Sobral, Talita Aguiar and Darine Villela
> Publication: Pettersson *et al*., 2020, *Hum Mutat*.

Genetic and epigenetic alterations affecting cancer development and aggressiveness of embryonal cancers

Several lines of evidence indicate that childhood and adult cancers are distinct entities. Despite intensive efforts, genetic factors remain difficult to be captured in rare cancers, mainly embryonal tumors, which represent a heterogeneous group supposedly derived from undifferentiated cells, with histological features that resemble tissues of origin during embryogenesis. This key observation suggests that pediatric tumorigenesis might begin during early fetal or child life due to the errors in growth or pathways differentiation.

Hepatoblastoma, the embryonal cancer of liver

Hepatoblastoma is a very rare embryonal liver cancer supposed to arise from the impairment of hepatocyte differentiation during embryogenesis. We have previously shown a low mutational background, and a novel set of candidate genes for hepatoblastoma biology, including involvement of the *CX3CL1/CX3CR1* chemokine signaling pathway in progression. Additionally, we have been exploring the underlying epigenetic mechanisms, previously identifying a general disrupted expression of the DNA methylation machinery and enrichment of the 5hmC content. Our data have revealed that *NNMT*, a highly expressed gene in adipocytes and hepatocytes, presents promoter hypermethylation in hepatoblastomas. Significant *NNMT* downregulation was revealed in hepatoblastomas, with two orders of magnitude lower expression in tumor samples and hepatoblastoma cell lines than in hepatocellular carcinoma cell lines (Rivas *et al,* 2021*. 10.1177/1010428320977124*). A specific TSS1500 CpG site (cg02094283) hypermethylated in tumors exhibited inverse correlation between its methylation level and *NNMT* expression. A marked global reduction of the NNMT protein was validated in tumors, with strong correlation between gene and protein expression. Higher NNMT expression was statistically associated with late hepatoblastoma diagnosis, a known clinical variable of worse prognosis. In addition, untargeted metabolomics analysis detected aberrant lipid metabolism. We showed the first evidence that *NNMT* reduction occurs in hepatoblastomas, providing support to a potential effect of this reduction in the metabolism of tumors.

Given the increased evidence of differentiation disruption and epigenetic changes in the genesis and progression of hepatoblastomas, we evaluated the expression of 24 genes associated with DNA methylation as well as different stages of hepatocyte differentiation and global DNA methylation (*Rivas et al - doi: 10.1016/j.clinre.2021.101684*). A panel of 13 genes was able to stratify tumors (*TET1, TET2, TET3, DNMT1, DNMT3A, UHRF1, ALB, CYP3A4, TDO2, UGT1A1, AFP, HNF4A,* and *FOXA2*). We proposed a stratification model for HB, with three groups that presented specific gene expression profiles of the panel of DNA methylation enzymes and hepatocyte differentiation markers. The data suggested that a subset of HBs were similar to differentiated livers, with upregulation of mature hepatocyte markers, decreased expression of DNA methylation enzymes, and higher global methylation levels; these findings might predict worse outcomes. This analysis reinforces that DNA methylation is a robust biomarker for this tumor type.

PIs: Ana Krepischi and Carla Rosenberg
Graduate students and post-docs: Talita Aguiar, Maria Prates Rivas and Juliana Sobral
Publications: Rivas *et al.,* 2021. *Clin Res Hepatol Gastroenterol;* Rivas *et al.* 2020. *Tumour Biol.*

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

A2.1. Neuromuscular disorders

Association of three different mutations in the CLCN1 gene modulating the phenotype in a consanguineous family with myotonia congenita

Myotonia congenita is a genetic disease caused by mutations in the CLCN1 gene, which encodes for the major chloride skeletal channel ClC-1, involved in the normal repolarization of muscle action potentials and consequent relaxation of the muscle after contraction. Two allelic forms are recognized, depending on the phenotype and the inheritance pattern: the autosomal dominant Thomsen disease with milder symptoms and the autosomal recessive Becker disorder with a severe phenotype. Before the recent

advances of molecular testing, the diagnosis and genetic counseling of families was a challenge due to the large number of mutations in the CLCN1 gene, found both in homozygous or in heterozygous state. Here, we studied a consanguineous family in which three members presented a variable phenotype of myotonia, associated to a combination of three different mutations in the CLCN1 gene. A pathogenic splicing site mutation which causes the skipping of exon 17 was present in homozygosis in one very severely affected son. This mutation was present in compound heterozygosis in the consanguineous parents, but interestingly it was associated to a different second variant in the other allele: c.1453 A > G in the mother and c.1842 G > C in the father. Both displayed variable, but less severe phenotypes than their homozygous son. These results highlight the importance of analyzing the combination of different variants in the same gene in particular in families with patients displaying different phenotypes. This approach may improve the diagnosis, prognosis, and genetic counseling of the involved families.

PI: Mariz Vainzof
Master student: Lucas Santos e Souza, PhD. And the clinical group of the HUG-CEL.
Publication: Souza *et al.,* 2021, *J Mol Neurosci*.

Dominant or recessive mutations in the *RYR1* gene causing central core myopathy in Brazilian patients

Central Core Disease (CCD) is an inherited neuromuscular disorder characterized by the presence of cores in muscle biopsy. CCD is caused by mutations in the RYR1 gene. This gene encodes the ryanodine receptor 1, which is an intracellular calcium release channel from the sarcoplasmic reticulum to the cytosol in response to depolarization of the plasma membrane. Mutations in this gene are also associated with susceptibility to Malignant Hyperthermia (MHS). In this study, we evaluated 20 families with clinical and histological characteristics of CCD to identify primary mutations in patients, for diagnosis and genetic counseling of the families. We identified variants in the RYR1 gene in 19/20 families. The molecular pathogenicity was confirmed in 16 of them. Most of these variants (22/23) are missense and unique in the families. Two variants were recurrent in two different families. We identified six families with biallelic mutations, five compound heterozygotes with no consanguinity, and one homozygous, with consanguineous parents, resulting in 30% of cases with possible autosomal recessive

inheritance. We identified seven novel variants, four of them classified as pathogenic. In one family, we identified two mutations in exon 102, segregating in cis, suggesting an additive effect of two mutations in the same allele. This work highlights the importance of using Next-Generation Sequencing technology for the molecular diagnosis of genetic diseases when a very large gene is involved, associated to a broad distribution of the mutations along it. These data also influence the prevention through adequate genetic counseling for the families and cautions against malignant hyperthermia susceptibility. The manuscript was published. (Galleni *et al.,* 2020)

PI: Mariz Vainzof
Students: Master students Leonardo Galeni and Lucas Santos e Souza, PhD.
And the clinical group of the HUG-CELL.
Publication: Galleni *et al*., *Acta Miopat.*

Muscle regeneration in spastic muscles of children with cerebral palsy

After early brain injury, patients with Cerebral Palsy (CP) experience several musculoskeletal changes including contractures and reduced force, secondary to both central and peripheral factors. Four mechanical/structural reasons for this force reduction are suggested: (1) reduced muscle size; (2) reduced contractile tissue, with replacement by fibrosis and/or fat; (3) over-stretched sarcomeres, associated with a great loss of isometric force; and (4) loss of sarcomeric titin, resulting in a decreased passive force. Epigenetic factors related to impaired muscle growth and production of sarcomeres in CP were also proposed, based on DNA hypermethylation of myoblast gene promotor regions.

The decreased muscle volumes have been associated with several causative factors, including impaired muscle growth and regeneration. Also, muscle contractures in CP were associated with a decrease in the number and the loss satellite cell myogenic potential. However, it is still not known if the reduced number of satellite cells is the cause or a consequence of the inhibited muscle structural proteins production. In this respect, muscle impairment and muscle regeneration processes, and the role of satellite cells in spastic CP, have received increased attention, as this knowledge could be used as strategies for treatment of spastic muscles. An invited commentary about this topic has been published in the Journal Development Medicina e Child Neurology.

PIs: Mariz Vainzof and Juliana Gurgel Giannetti
Publication: Vainzof and Gurgel-Giannetti 2021, *J Dev Med Child Neurol.*

A2.2. Craniofacial development

Modelling Craniofacial syndromes in a dish

In the previous report, we have described the establishment of a protocol that *in vitro* recapitules human neural crest cell development from neural plate border (NPB), which corresponds to early stages of the embryonic development (between Carnegie stage 11 to 13 in week 4). After extensive revision with inclusion of several new experiments to address the reviewers questions this protocol was published This protocol is currently being used in two undergoing projects of this CEPID, being an important asset of our laboratory to investigate the molecular mechanisms of genetic disorders caused by mutated genes that compromise neural crest cell function.

PI: Maria Rita Passos-Bueno
Postdoctoral and undergraduate students: Gerson Kobayashi, Danielle Moreira, Camila Musso and Gabriella Hsia.
Publication: Gobayashi *et al.,* 2020. *Stem Cell Reports.*

A2.3. Neurodegeneration

Intracellular dynamics and protein aggregation in neurodegeneration

Organelles juxtaposition has been detected for decades, although only recently gained importance due to a pivotal role in the regulation of cellular processes dependent on membrane contact sites. Endoplasmic reticulum (ER) and mitochondria interaction is a prime example of organelles contact sites. Mitochondria-associated membranes (MAM) are proposed to harbor ER-mitochondria tether complexes, mainly when these organelles are less than 30 nm apart. Dysfunctions of proteins located at the MAM are associated with neurodegenerative diseases such as Parkinson's, Alzheimer's and amyotrophic

lateral sclerosis, as well as neurodevelopmental disorders; hence any malfunction in MAM can potentially trigger cell death. During the last year we focused on the role of ER-mitochondria contact sites, regarding calcium homeostasis, lipid metabolism, autophagy, morphology and dynamics of mitochondria,in the context of neurodegenerative diseases. We have observed that mutant alpha-synuclein promoted an increase in ER area, as well as differences in mitochondria morphology in this cellular model of Parkinson's disease. A review on this topic was published recently by our group.

PI: Merari Ferrari
Postdoc: Seyed Reza Raeisossadati, Students: Isabela Geacomini Rocha, Caio José Machado da Veiga and the Lab Technician: Andressa Yurie Silvestre Sakugawa.
Publication: Raeisossadati and Ferrari 2020. *Cell Mol Neurobiol*.

A2.4. The search for modifier variant

Different gene expression profiles in iPSC-derived motor neurons from ALS8 patients with variable clinical courses suggest mitigating pathways for neurodegeneration

One of the Center's main objectives is to identify mitigating mechanisms of genetic diseases, through the study of patients carrying discordant phenotypes. With this aim we studied five Amyotrophic Lateral Sclerosis type 8 (ALS8) patients presenting different clinical profiles.

Aiming to search for potential pathways associated with phenotypic discordance, induced pluripotent stem cell (iPSCs) lineages were derived for each patient and three controls. Then, motor neurons (MNs) were differentiated for the three experimental groups, namely, ALS8 "severe", ALS8 "mild" and controls. A whole transcriptome assay through RNA Sequencing was performed, and, in parallel, functional studies on cell death and energetic metabolism were carried out Pooled together, our results suggest the differentially expressed genes in the mild ALS8 patients might be attenuating the pathological effects of VAPB mutation, through protein translation enhancing. As a result, such neurons presented lower cell death rates and better mitochondrial activity. We intend now to study how the identified genes interfere with the pathological process,

aiming to identify druggable targets. The present work was part of the PhD thesis of Danyllo Oliveira presented in 2020 and the results were published in two papers.

PI: Mayana Zatz
Student: Danyllo Oliveira, PhD.
Collaboration: Sergio Verkovsy-Almeida and Oswaldo Keith Okamoto.
Publications: Oliveira *et al*., 2020. *Human Molecular Genetics*; Oliveira *et al*., 2021. *Neural Regeneration Research*.

Manifesting carriers of X-linked myotubular myopathy: Genetic modifiers modulating the phenotype

Myotubular myopathy is a rare genetic disease which affects skeletal and respiratory muscles, and is caused by mutations in the *MTM1* gene. The disease is classified as recessive X-linked. Women carrying the mutations are usually asymptomatic, but many symptomatic heterozygous females have been reported, as compared with the lower frequency of manifesting carriers in other X-linked recessive diseases. In two families, we identified 4/8 and 2/4 female carriers presenting some degree of clinical manifestation. XCI was random in three of four informative manifesting carriers. The disease penetrance rate was estimated to be 30%, compatible with incomplete penetrance. Exome comparative analyses identified variants within a segment of 4.2 Mb on chromosome 19, containing the KIR (killer cell immunoglobulin-like receptors) cluster of genes, that were present in all non-manifesting carriers and absent in all manifesting carriers. We hypothesized that this KIR variants may modulate the phenotype, acting as a protective factor in the non-manifesting carriers. In conclusions, affected XLMTM females carriers have been described with a surprisingly high frequency for a recessive X-linked disease, raising the question about the pattern of inheritance or the role of modifier factors acting on the disease phenotype.

PI: Mariz Vainzof
Student: Master student Lucas Santos e Souza, PhD. student Camila de Freitas Almeida.
Collaboration: Erick C. Castelli.
Publication: Souza LS *et al.,* 2020*. Neurology Genet.*

What is the role of IMPA1 enzyme in familial intellectual disability?

We described, for the first time, a homozygous mutation in the inositol monophosphatase 1 (*IMPA1*) gene in nine individuals with severe intellectual disability (ID) and disruptive behavior (Figueiredo *et al.,* 2016). These individuals belong to the same family from Northeastern Brazil, which has 28 consanguineous marriages and 59 genotyped family members. IMPA1 is responsible for the generation of free inositol from *de novo* biosynthesis and recycling from inositol polyphosphates and participates in the phosphatidylinositol signaling pathway. Aiming to understand the role of IMPA1 deficiency in ID, we generated induced pluripotent stem cells (iPSCs) from patients and neurotypical controls and differentiated these into hippocampal dentate gyrus-like neurons and astrocytes. IMPA1-deficient neuronal progenitor cells (NPCs) revealed substantial deficits in proliferation and neurogenic potential. At low passage NPCs (P1 to P3), we observed cell cycle arrest, apoptosis, progressive change to a glial morphology and reduction in neuronal differentiation. These observations were validated by rescuing the phenotype with *myo*-inositol supplemented media during differentiation of patient derived-iPSCs into neurons and by the reduction of neurogenic potential in control NPCs expressing shIMPA1. Transcriptome analysis showed that NPCs and neurons derived from ID patients have extensive deregulation of gene expression affecting pathways necessary for neurogenesis and upregulation of gliogenic genes. IMPA1 deficiency did not affect cell cycle progression or survival in iPSCs and glial progenitor cells or astrocyte differentiation. Therefore, this study showed that the *IMPA1* mutation specifically affects NPC survival and neuronal differentiation.

> PI: Mayana Zatz
> Postdoc student: Thalita Figueiredo
> Collaboration: Group of Prof. Fred Gage from Salk Institute, La Jolla, USA .
> Publication: Figueiredo *et al*., 2020. *Molecular Psychiatry*.

Germline variants of Brazilian women with breast cancer and detection of a novel pathogenic ATM deletion in early-onset breast cancer

Currently, more than 25 genes have been associated with breast cancer predisposition, conferring different cancer risks. However, only 4–5% of the hereditary cases are caused by highly penetrant mutations in genes such as BRCA1 and BRCA2

(BRCA1/2), and genomic studies continue to uncover new genes supposedly related to this phenotype through a polygenic/oligogenic model. Studies in ethnically admixed Latin American populations have identified regions with increased frequency of deleterious variants in breast cancer predisposing genes. In this context, the Brazilian population exhibits great genetic heterogeneity, and is not well represented in international databases, which makes it difficult to interpret the clinical relevance of germline variants. In a recent study (Bandeira et al. Breast Cancer. 2021), we evaluated the frequency of pathogenic/likely pathogenic (P/LP) germline variants in up to 37 breast cancer predisposing genes, in a cohort of 105 breast and/or ovarian cancer Brazilian women referred to two research centers between 2014 and 2019. A total of 22 patients (21%) were found to carry P/LP variants, and 16 VUS were detected in 15 patients (14.3%). Additionally, a novel pathogenic ATM intragenic deletion was identified in an early-onset breast cancer. We also detected a BRCA1 pathogenic variant (c.5074+2T>C) in higher frequency (10×) than in other studies with similar cohorts. Our findings contribute to the characterization of the genetic background of breast cancer predisposition in the Brazilian population as a useful resource to discriminate between deleterious variants and VUS, thus enabling improvement in the preventive health care and clinical management of carriers.

PI: Oswaldo Keith Okamoto
PhD student: Gabriel Bandeira
Collaboration: Groups of Prof. Thomaz Gollop, Mayana Zatz, Maria Rita Passos-Bueno and Ana Krepischi.
Publication: Bandeira *et al*., 2021. *Breast Cancer*.

A2.5. Genetic modifiers in CNV syndromes associated with incomplete penetrance

Investigating Genetic Factors Contributing to Variable Expressivity of Class I 17p13.3 Microduplication

Typically, when a recognized pathogenic CNV is identified, other genetic factors are not considered. 17p13.3 microduplications are rare copy number variations (CNVs) associated with variable phenotypes, including facial dysmorphism, developmental delay, intellectual disability, and autism. We investigated via whole-exome sequencing the

presence of additional variants in four carriers of class I 17p13.3 microduplications. A 730 kb 17p13.3 microduplication was identified in two half-brothers with intellectual disability, but not in a third affected half-brother or blood cells from their normal mother (Family A), thus leading to the hypothesis of maternal germline mosaicism. No additional pathogenic variants were detected in Family A. Two affected siblings carried maternally inherited 450 kb 17p13.3 microduplication (Family B); the three carriers of the microduplication exhibited microcephaly and learning disability/speech impairment of variable degrees. Exome analysis revealed a variant of uncertain significance in RORA, a gene already linked to autism, in the autistic boy; his sister was heterozygous for a CYP1B1 pathogenic variant that could be related to her congenital glaucoma. Besides, both siblings carried a loss-of-function variant in DIP2B, a candidate gene for intellectual disability, which was inherited from their father, who also exhibited learning disability in childhood. In conclusion, additional pathogenic variants were revealed in two affected carriers of class I 17p13.3 microduplication, probably adding to their phenotypes. These results provided new evidence regarding the contribution of RORA and DIP2B to neurocognitive deficits, and highlighted the importance of full genetic investigation in carriers of CNV syndromes with variable expressivity. Finally, we suggest that microcephaly may be a rare clinical feature also related to the presence of the class I 17p13.3 microduplication.

> PIs: Ana Krepischi, Angela Morgante, Débora Bertola and Carla Rosenberg
> Graduate Student: Giovanna Tolezano
> Publication: Tolezano *et al.,* 2020*. Int J Mol Cell Med.*

A3. Epigenetics and diseases

A3.1. How DNA damage and Genome Instability can be implicated in human disease?

This part of the project is related to repair of DNA damage and their consequences. This includes human syndromes with defects in DNA repair, such as xeroderma pigmentosum (XP). XP patients present a high frequency of skin tumors in regions exposed to sunlight, due to their deficiency in nucleotide excision repair (NER). We are involved in the molecular diagnosis (mutation identification) in XP patients in Brazil, and soon we will be presenting a distribution of the mutated genes and mutations

in this country. Recently, in collaboration with Dr. Ricardo S Gomez (UFMG) a case report of a novel mutation in the XPV protein (*POLH* gene) was described. Curiously, the patient have a tumor in the lip, what is not so frequent, although we propose this is related to the habit of chewing tobacco, and XP-V patients are specially susceptible (Pereira *et al.,* 2021).

We also concluded the work in collaboration with Dr. Paulo Saldiva (FM, USP), where XPC deficient mice (that simulate the phenotype of XP patients in many aspects) were exposed to air pollution. The results indicated a high sensitivity of these mice to this exposure, inducing increased genotoxic stress and inflammation (de Oliveira Alves *et al.,* 2020). Also, the interface of DNA repair processes and immunological responses, including inflammation was reviewed in collaboration of Dr. Niels O Camara (ICB, USP) (Marconi *et al.,* 2021). Part of the XP patients and other human syndromes deficient in NER develop neurodegenerative development problems and premature aging phenotypes. This is most certainly due to problems on the transcription of damaged templates. We reviewed the role of the transcription blockage by DNA damage in neurological tissues (Kajitani, Nascimento *et al.,* 2021). And due to our interest in sunlight effects in human skin, we also collaborated with Dr. Ana Maria Castrucci (IB-USP) and identified a novel role for melanopsin, as a protein that participates in the responses to UVA-light in skin cells (Assis *et al.,* 2020). We were also able to measure DNA damage induced directly in the environment, at the Brazilian base in the Antarctic continent. Interestingly, our measures indicate that the number of pyrimidine dimers induced by DNA exposure is very high in that continent, and inversely proportional to the thickness of the ozone layer. These results confirm the need of sunlight protection for the researchers and personnel that work in that continent, as well as recall the impact of ozone layer reduction in UV incidence in the Earth surface (Fuentes-Leon *et al.,* 2021). We are also interested to identify mechanisms of tumor resistance to chemotherapeutic drugs that work by damaging DNA. During this last period, we concluded our work on a screening of pathways glioma cell use to achieve resistance to temozolomide (TMZ). For this work, two CRISPR/Cas genome wide libraries were used to explore knocked out or activated genes enriched in glioma cells that survived TMZ treatment. Several pathways were identified in this work, including those that were already known to act in TMZ resistance, such as NRF2- pathway and mismatch repair. Other pathways were also revealed and are being investigated (Rocha *et al.,* 2020).

PI: Carlos F. Menck
Post docs: Andre Uchimura Bastos, Giovana Leantro
PhD students: Matheus Molina Silva, Livia Luz Nascimento, Davi Jardim Martins, Davi Mendes, Marcela Latância.
Collaboration: Dr. Clarissa RR Rocha (UNIFESP), Dr. Gustavo Satoru Kajitani (UFOP), Dr. Ana Maria Castrucci (IB,USP), Dr. Paulo Saldiva (FMUSP), Dr. Niels O. Camara (ICB,USP), Dr. Ricardo S. Gomez (UFMG), Dr. Angel Sanchez - Lamar-Universidad de Habana, Cuba.
Publications: (*Assis et al, 2020*); (*Rocha et al., 2020*); (*Pereira et al, 2021*); (*Marconi et al, 2021*); (*Kajitani, Nascimento et al, 2021)* and (*Fuentes-Leon et al., 2021)*

B.The 80plus Project

Whole-genome sequencing (WGS) of a large number of individuals can reveal rare variants in known disease genes, improve identification of novel genes and pathways associated with phenotypes and identify genomic regions not represented on reference genomes. Most importantly, ancestry diversity is critical to elucidate differences in disease's genomic architecture and improve signals detected by previous studies, since non-European and admixed populations harbor specific variants, which are still vastly underrepresented in genomic studies. The lack of diversity leads to a significant bias on the primary resource for precision medicine and consequently less accurate tests on non-European descent individuals, potentially increasing health disparities.

Knowledge about allelic frequencies from multiple populations is also crucial when prioritizing candidate clinical variants. For rare Mendelian disorders, the frequency in any given population cannot be higher than expected for disease incidence. Moreover, the penetrance of variants may vary across backgrounds. For variants associated with monogenic late-onset disorders, unaffected elderly individuals serve as a proper control

group to improve diagnosis accuracy. This rationale was previously explored by us using whole-exome sequencing of elderly Brazilians, and by others using a European-descent whole-genome dataset of Australian elderly.

Here we present the first high-coverage WGS of a Latin American census-based cohort composed of 1,171 unrelated elderly from São Paulo, Brazil's largest metropolis, which includes immigrant descendants from different continents and individuals from various Brazilian states. These individuals aged 60 or older have been comprehensively phenotyped by the longitudinal Health, Well-Being, and Aging (SABE - *Saúde, Bem-estar e Envelhecimento*) study. By carrying out WGS on this population-based cohort, we identified genomic variation absent from public databases, including single nucleotide substitutions, insertion/deletion variants (indels), chromosomal haplotypes, accurate HLA variant calls, mobile element insertions, and non-reference sequences (NRS). Additionally, we explored pathogenicity assertions in disease-related genes of clinical relevance and GWAS performance for selected phenotypes. We also created new reference imputation panels for the whole-genome and HLA alleles, which improved imputation accuracy. Lastly, we provide variants and respective allelic frequencies in a public resource, ABraOM <http://abraom.ib.usp.br>.

These results were presented as a preprint article sent to MedXriv (Naslavsky *et al.,* 2020).

PIs: Mayana Zatz and Michel S. Naslavsky
The following groups are participating in this multicenter effort : Pedro Galante and Thiago Miller (Instituto de Pesquisa Sírio-Libanês), Victor Guryev and Stepanka Zverinova (ERIBA, Groningen), Erick Castelli (UNESP Botucatu), Diogo Meyer and Kelly Nunes (IBUSP), Eduardo Tarazona, Wagner Magalhães, Nathalia Matta, Victor Borda (UFMG).
Data collaborators: Heinner Guio (Instituto Nacional de Salud, Lima, Peru and Universidad de Huánuco, Huánuco, Peru), Mauricio L. Barreto (UFBA and Center for Data and Knowledge Integration for Health, Institute Gonçalo Muniz, Fundação Oswaldo Cruz, Salvador, Brazil), Maria Fernanda Lima-Costa (Instituto de Pesquisas René Rachou, Fundação Oswaldo Cruz and UFMG, Belo Horizonte, MG, Brazil), Bernardo L Horta (UFPel, Pelotas, Brazil).

Biased pathogenic assertions of loss of function variants challenge molecular diagnosis of admixed individuals

Diagnosis of individuals affected by monogenic disorders was significantly improved by next-generation sequencing targeting clinically relevant genes. Whole exomes yield a large number of variants that require several filtering steps, prioritization, and pathogenicity classification. Among the criteria recommended by ACMG, those that rely on population databases critically affect analyses of individuals with underrepresented ancestries. Population-specific allelic frequencies need consideration when characterizing potential deleteriousness of variants. An orthogonal input for classification is annotation of variants previously classified as pathogenic as a criterion that provide supporting evidence widely sourced at ClinVar. We used a whole-genome dataset from a census-based cohort of 1,171 elderly individuals from São Paulo, Brazil, highly admixed and unaffected by severe monogenic disorders, to investigate if pathogenic assertions in ClinVar are enriched with higher proportions of European ancestry, indicating bias. Potential loss of function (pLOF) variants were filtered from 4,250 genes associated with Mendelian disorders and annotated with ClinVar assertions. Over 1,800 single nucleotide pLOF variants were included, 381 had non-Benign assertions. Among carriers (N=463), average European ancestry was significantly higher than non-carriers (N=708; p=0.011). pLOFs in genomic contexts of non-European local ancestries were nearly three times less likely to have any ClinVar entry (OR=0.353;p<0.0001). Independent pathogenicity assertions are useful for variant classification in molecular diagnosis. However, European overrepresentation of assertions can promote distortions when classifying variants in non-European individuals, even in admixed samples with a relatively high proportion of European ancestry. The investigation and deposit of clinically relevant findings of diverse populations is fundamental to improve this scenario.

Publication: Naslavsky *et al., Am Journal of Medical Genetics*-Part C, in press

TCF7L2 rs7903146 polymorphism association with diabetes and obesity in an elderly cohort from Brazil

Type 2 diabetes mellitus (T2DM) and obesity are complex pandemic diseases in the 21st century. Worldwide, the T allele rs7903146 in the TCF7L2 gene is recognized as a strong GWAS signal associated with T2DM. However, the association between the C allele and obesity is still poorly explored and needs to be replicated in other populations. Thus, the primary objectives of this study were to evaluate the TCF7L2 rs7903146 association with T2DM according to BMI status and to determine if this variant is related to obesity and BMI variation in a cohort of elderly Brazilians.

A total of 1,023 participants from an elderly census-based cohort called SABE (Saúde, Bem Estar e Envelhecimento—Health, Well-Being and Aging) were stratified by BMI status and type 2 diabetes presence. The TCF7L2 genotypes were filtered from the Online Archive of Brazilian Mutations (ABraOM—Online Archive of Brazilian Mutations) database, a web-based public database with sequencing data of samples of the SABE's participants. Logistic regression models and interaction analyses were performed. The BMI variation (∆ BMI) was calculated from anthropometric data collected in up to two time-points with a ten-year-assessment interval.

We confirmed that the rs7903146 is both associated with T2DM and obesity. The *TCF7L2* rs7903146 T allele increased T2DM risk in the normal weight group and interacted with sex, age and BMI, while the C allele increased obesity risk. The TT genotype was associated with a lesser extent of BMI variation over the SABE study's 10-year period.

> PI: This was a collaboration between our group and the group of Prof. Flavia Errera from the University Federal of Espírito Santo in collaboration with the CEGH-CEL team.
> Publication: Bride *et al*., 2021. *Peer J*.

Socioeconomic factors and health status disparities associated with difficulty in ADLs and IADLs among long-lived populations in Brazil: a cross-sectional study

The aims of this study was to evaluate the association between socioeconomic factors, health status, and Functional Capacity (FC) in the oldest senior citizens in a metropolis and a poor rural region of Brazil.

Cross-sectional study of 417 seniors aged ≥80 years, data collected through Brazil's Health, Well-being and Aging survey. FC assessed by self-reporting of difficulties in Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs). Chi-square tests and multiple logistic regression analyses were performed using "R" statistical software.

Socioeconomic and demographic inequalities in Brazil can influence FC in seniors aged 80 years and older. Comparatively, urban long-lived people had a higher prevalence of difficulties for ADLs and rural ones showed more difficulties for IADLs. Among urban oldest seniors, female gender and lower-income were correlated with difficulties for IADLs. Among rural oldest seniors, female gender, stroke, joint disease, and inadequate weight independently were correlated with difficulties for ADLs, while the number of chronic diseases was associated with difficulties for IADLs.

Financial constraints may favor the development of functional limitations among older seniors in large urban centers. In poor rural areas, inadequate nutritional status and chronic diseases may increase their susceptibility to functional decline.

> This was a collaboration between our group and the group of Silvana Santos from the University of Paraiba.
> Publication: Matheson *et al*., *The Journal of Health Care Organization*, Provision, and Financing, 2021.

Admixture/fine-mapping in Brazilians reveals a West African associated potential regulatory variant (rs114066381) with a strong female-specific effect on body mass and fat mass indexes

Admixed populations are a resource to study the global genetic architecture of complex phenotypes, which is critical, considering that non-European populations are severely underrepresented in genomic studies. Here, we study the genetic architecture of BMI in children, young adults, and elderly individuals from the admixed population of Brazil.Leveraging admixture in Brazilians, whose chromosomes are mosaics of fragments of Native American, European, and African origins, we used genome-wide data to perform admixture mapping/fine-mapping of body mass index (BMI) in three Brazilian population-based cohorts from Northeast (Salvador), Southeast (Bambuí), and South (Pelotas).

We found significant associations with African-associated alleles in children from Salvador (*PALD1* and *ZMIZ1* genes), and in young adults from Pelotas (*NOD2* and *MTUS2* genes). More importantly, in Pelotas, rs114066381, mapped in a potential regulatory region, is significantly associated only in females ($p = 2.76e{-}06$). This variant is rare in Europeans but with frequencies of ~3% in West Africa and has a strong female-specific effect (95% CI: 2.32–5.65 kg/m2 per each A allele). We confirmed this sex-specific association and replicated its strong effect for an adjusted fat mass index in the same Pelotas cohort, and for BMI in another Brazilian cohort from São Paulo (Southeast Brazil). A meta-analysis confirmed the significant association. Remarkably, we observed that while the frequency of rs114066381-A allele ranges from 0.8 to 2.1% in the studied populations, it attains ~9% among women with morbid obesity from Pelotas, São Paulo, and Bambuí. The effect size of rs114066381 is at least five times higher than the *FTO* SNPs rs9939609 and rs1558902, already emblematic for their high effects.

We identified six candidate SNPs associated with BMI. rs114066381 stands out for its high effect that was replicated and its high frequency in women with morbid obesity. We demonstrate how admixed populations are a source of new relevant phenotype-associated genetic variants.

> This study is a collaboration between the HUG-CELL team and Eduardo Tarazona from Universidade Federal of Minas Gerais . Marilia Scliar, the first author of the paper is a posdoc at HUG-Cell
> Publication: Scliar *et al*., 2021. *International Journal of Obesity*.

Exploring a Region on Chromosome 8p23.1 Displaying Positive Selection Signals in Brazilian Admixed Populations: Additional Insights Into Predisposition to Obesity and Related Disorders

This publication aimed to extend the previous work by studying additional Brazilian admixed individuals and examining DNA sequencing data from the ch 8p23.1 candidate region. Thus, we inferred the local ancestry of 125 exomes from individuals born in five towns within the Southeast region of Brazil (São Paulo, Campinas, Barretos, and Ribeirão Preto located in the state of São Paulo and Belo Horizonte, the capital of the state of Minas Gerais), and compared to data from two public Brazilian reference genomic

databases, BIPMed and ABraOM, and with information from the 1000 Genomes Project phase 3 and gnomAD databases. Our results revealed that ancestry is similar among individuals born in the five Brazilian towns assessed; however, an increased proportion of sub-Saharan African ancestry was observed in individuals from Belo Horizonte. In addition, individuals from the five towns considered, as well as those from the ABRAOM dataset, had the same overrepresentation of Native-American ancestry on the ch 8p23.1 locus that was previously reported for the BIPMed reference sample. Sequencing analysis of ch 8p23.1 revealed the presence of 442 non-synonymous variants, including frameshift, inframe deletion, start loss, stop gain, stop loss, and splicing site variants, which occurred in 24 genes. Among these genes, 13 were associated with obesity, type II diabetes, lipid levels, and waist circumference. These results strengthen the hypothesis that a set of variants located on ch 8p23.1 that result from positive selection during early admixture events may influence obesity-related disease predisposition in admixed individuals of the Brazilian population. Furthermore, we present evidence that the exploration of local ancestry deviation in admixed individuals may provide information with the potential to be translated into health care improvement.

> This project is a collaboration between our group and the Group of Prof. Iscia Lopes Cendes from UNICAMP.
> Publication: Secolin *et al.,* 2021*. Front Genet.*

C. Therapies in Genetic Disorders

C1. Pre-Clinical studies with murine stem cells

Cochear gene expression patterns are consistent with regeneration of hair cells after knock-down of the *Hes* gene in postnatal mice: one step towards gene therapy in hearing loss

We investigated gene expression effects in hair cells and supporting cells after Hes1-shRNA lentivirus transduction in organotypic cultures of the organ of Corti from postnatal-day-3 mice. Myo7a (hair cell marker) and Sox2 (progenitor cell marker) mRNA levels significantly increased. The modulation of gene expression in the organ of Corti upon Hes1 knockdown is consistent with cell phenotypes related to lateral inhibition mechanism in the inner ear. The lentivirus-based expression of Hes1-shRNA is a valuable strategy for genetic interference in the organ of Corti and for future in protocols aiming at the regeneration of hair cells in vivo.

> PI: Regina Mingroni-Netto
> Publication: Batissoco *et al*., 2021. *Braz J Med Biol.*

Skeletal muscle injury by electroporation – a model to study degeneration/regeneration pathways in muscle – post-injury muscle regeneration in the elderly

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, either by exercise or disease. 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 is an easy and simple alternative to induce muscle lesion. It 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).* This methodology is being used now for the study of muscle regeneration with age. The process of muscle degeneration with subsequent poor regeneration is the primary cause of muscle loss and weakness seen in dystrophies muscle. Recent studies have identified tubular aggregates (ATs) in muscle fibers of elderly male mice, in an event dependent on the age of the animal. In human ATs have been observed in some types of dystrophic muscles, but with evidence of a relation with senescence. Myogranules are another type of myo-aggregate that has been currently related to muscle regeneration. In a pathological situation, however, an abnormal accumulation of this type of aggregate was observed, which remains accumulated in the fibers, impacting the regeneration. 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 PhD: Felipe Tadeu Galante Rocha de Vasconcelos

Satellite cells deficiency and defective regeneration in dynamin2-related centro nuclear myopathy

Dynamin 2 (DNM2) is a ubiquitously expressed protein involved in many functions related to trafficking and remodeling of membranes, and cytoskeleton dynamics. Mutations in the *DNM2* gene cause the autosomal dominant centronuclear myopathy

(AD-CNM), characterized mainly by muscle weakness and central nuclei. Several hypotheses and mechanisms have been proposed to explain the disease, but the muscle-specific impact of the mutations still needs to be further investigated. Satellite cells (SC) are the main source for muscle growth and regeneration of mature tissue. Here, we investigated these cells and muscle regeneration in the KI-*Dnm2*$^{R465W/+}$ mouse model for AD-CNM. We found reduced number of PAX7-positive SCs, which were also less activated after induced muscle injury. The muscles of the KI-*Dnm2*$^{R465W/+}$ mouse regenerated more slowly and less efficiently than wild-type ones, formed less new myofibers, and did not recover its normal mass 15 days after injury. Moreover, we also observed downregulation of myogenic regulatory factors. Altogether, our data provide evidence that the muscle regeneration is impaired in the KI-*Dnm2*$^{R465W/+}$ mouse due to SC deficiency. Thus, our findings contribute with one more layer to the comprehension of the disease, especially to the understanding of the regenerative process that has not been previously addressed in AD-CNM.

PI: Mariz Vainzof
PhD student: Camila F Almeida
International collaboration: Marc Bitoun, Sorbonne Université, INSERM, Institute of Myology, Centre of Research in Myology, Paris.
Publication: Almeida *et al.,* 021. *FASEB J.*

C2. Safety-related concerns in cell therapy

C2.1. Clinical Application of Human Induced Pluripotent Stem Cell-Derived Organoids as an Alternative to Organ Transplantation

Many clinically oriented cell therapy studies have reported controversial results about therapeutic evidence and adverse events. Most early studies rely on two-dimensional cultures, which fail to replicate biological interactions among cells and between cells and the extracellular matrix (ECM), occuring in native tissues. Conversely, tridimensional (3D) cell culture systems can mimic *in vivo* conditions involving cell-cell and cell-matrix interactions, such as dynamic regulation of signaling pathways and paracrine signals. With the advent of induced pluripotent stem cells (iPSCs) and the emergence of other new technologies, such as 3D bioprinting and organoid development,

the production of organ-like structures in the laboratory is a reality. In a new study (Hsia *et al.,* 2021*. Stem Cells Int.*), we discussed the therapeutic and safety issues regarding the use of organoids to treat individuals suffering from end-stage organ failure diseases. This could be an alternative approach to organ transplantation, due to high rates of organ rejection, shortage of organ donors, and long waiting lines. Investments and efforts to develop laboratory-grown organs have increased over the past years, and with the recent progress in regenerative medicine, growing organ-like structures *in vitro* might be a reality within the next decades. In our study, we address recent preclinical progress on transplantation of intestine, retina, kidney, liver, pancreas, brain, lung, and heart organoids. Also, we discuss the main outcomes after organoid transplantation, common challenges faced by these promising regenerative medicine approaches, and future perspectives on the field.

PI: Oswaldo Keith Okamoto
Collaboration: PhD students Gabriella Shih Ping Hsia, Joyce Esposito, Letícia Alves da Rocha, and Sofia Lígia Guimarães Ramos.
Publication: Hsia *et al., 2021. Stem Cells Int.*

C3. Other therapeutic approaches

Clinical impact of Zika Virus injection in dogs with Advanced-Stage brain tumors

Malignant brain tumors are among the most aggressive cancers with poor prognosis and no effective treatment. Recently, we reported the oncolytic potential of Zika virus infecting and destroying the human central nervous system (CNS) tumors in vitro and in immunodeficient mice model. Subsequently, we analyzed the safety of Brazilian Zika virus (ZIKVBR) intrathecal injections in three dogs bearing spontaneous CNS tumors aiming an anti-tumoral therapy. We further assessed some aspects of the innate immune and inflammatory response that triggers the anti-tumoral response observed during the ZIKVBR administration in vivo and in vitro. For the first time, we showed that there were no negative clinical side effects following ZIKVBR CNS injections in dogs, confirming the safety of the procedure. Furthermore, the intrathecal ZIKVBR injections reduced tumor size in immunocompetent dogs bearing spontaneous intracranial tumors, improved their neurological clinical symptoms significantly, and

extended their survival by inducing the destruction specifically of tumor cells, sparing normal neurons, and activating an immune response. These results open new perspectives for upcoming virotherapy using ZIKV to destroy and induce an anti-tumoral immune response in CNS tumors for which there are currently no effective treatments.In the last year we have established a new partnership with the veterinarian clinic PetCare and we hope that soon we will be able to start new trials.

The paper was recently published in Molecular Therapy *(*Kaid *et al., 2020) and a* second paper was published addressing some questions about this approach in dogs. (Kaid and Zatz*, 2020*).

PI: Mayana Zatz and Oswaldo Keith Okamoto, pos-doc Carolini Kaid Davila
Publication: Kaid and Zatz, 2020. *Molecular therapy*.

Host genetic susceptibility to ZIKV congenital syndrome: A tale of twins

Zika virus (ZIKV) is a skillful neural progenitor cells (NPCs) pathogen. Aiming to enhance our comprehension of the underlying mechanisms and to understand the role of host genetic background causing ZIKV neuronal pathology, we focused our investigation in pairs of twins. We ascertained 9 pairs and obtained samples from 8. Among them, 6 pairs were dizygotic (DZ) and 2 were monozygotic (MZ). The two MZ were both affected, but five of the 6 DZ were discordant (i.e. one affected and one normal) for CZS. These 6 NPCs samples were then infected in vitro with ZIKV. Surprisingly, the results clearly indicated that affected babies cells were much more efficient in replicating ZIKV once infected, therefore developing associated severe cellular pathology. RNA sequencing (RNA-Seq) highlighted a differential neurodevelopmental program that involves Wnt and mTOR signaling. Further analysis showed that mTOR was one of the main drivers of the discordancy observed in the twins` cohort. Overall, our results indicate that CZS is not a stochastic event and depends on NPCs intrinsic susceptibility, possibly related to epigenetic and/or oligogenic mechanisms. This pioneer study shed light into ZIKV molecular infection mechanism and into how genetics can enhance our understanding on clinical relevant findings and individual-specific response to pathogens. This study paved the way to the new ongoing project where we are investigating the oncolytic effect of zika virus against brain tumors.

PI: Mayana Zatz
Posdocs: Luiz Carlos de Caires Junior and Ernesto Goulart
Publication: Book chapter: Zika virus< Biology, Transmission, and Pathology

Novel immunotherapy with CAR-like Natural Killer cells to treat Hematological Malignancies

Cancer progression is associated with an ineffective antitumor response, mediated by multiple mechanisms. Therefore, promising immunotherapy strategies have been developed to enhance the activity of T and NK cells against cancer targets. Natural killer (NK)-cell recognition and function against NK-resistant cancers remain substantial barriers to the broad application of NK-cell immunotherapy. Potential solutions include bispecific engagers that target NK-cell activity via an NK-activating receptor when simultaneously targeting a tumor-specific antigen, as well as enhancing functionality using IL12/15/18 cytokine pre-activation. In a novel study (Kerbauy et al. Clinical cancer Research, 2021), we assessed single-cell NK-cell responses stimulated by the tetravalent bispecific antibody AFM13 that binds CD30 on leukemia/lymphoma targets and CD16A on various types of NK cells using mass cytometry and cytotoxicity assays. The combination of AFM13 and IL12/15/18 pre-activation of blood and cord blood–derived NK cells was investigated in vitro and in vivo. We found heterogeneity within AFM13-directed conventional blood NK cell (cNK) responses, as well as consistent AFM13-directed polyfunctional activation of mature NK cells across donors. NK-cell source also impacted the AFM13 response, with cNK cells from healthy donors exhibiting superior responses to those from patients with Hodgkin lymphoma. IL12/15/18-induced memory-like NK cells from peripheral blood exhibited enhanced killing of CD30+ lymphoma targets directed by AFM13, compared with cNK cells. Cord-blood NK cells preactivated with IL12/15/18 and ex vivo expanded with K562-based feeders also exhibited enhanced killing with AFM13 stimulation via upregulation of signaling pathways related to NK-cell effector function. AFM13–NK complex cells exhibited enhanced responses to CD30+ lymphomas in vitro and in vivo. Our study identifies AFM13 as a promising combination with cytokine-activated adult blood or cord-blood NK cells to treat CD30+ hematologic malignancies, warranting clinical trials with these novel combinations.

PI: Oswaldo Keith Okamoto
PhD student: Lucila Kerbauy.
International collaboration: Groups of Dr. Elizabeth J Shpall and Dr. Katayoun Rezvani (Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA), and Dr. Todd A Fehniger
(Department of Medicine, Division of Oncology, Washington University School of Medicine,
St. Louis, Missouri, USA).
Publication: Kerbauy *et al., 2021. Clin Cancer Res.* Online ahead of print.

C4. Tissue engineering

Hepatic bioengineering technologies aiming the future of human organs transplantation

Liver transplantation from compatible donors has been the main therapy available for patients with irreversible hepatic injuries. Due to the increasing shortage of organs suitable for transplantation, tissue engineering technologies are important alternatives or surrogate approaches for the future of human organ transplantations. New bioengineering tools have been designed to produce decellularized organs (i.e. scaffolds) which could be recellularized with human cells. The aim of the present work was to investigate the possibility to improve liver scaffold recellularization by pre-coating decellularized tissue scaffolds with HepG2-conditioned medium (CM). Furthermore, we evaluated the capability of commercial human liver cells (HepG2) to adhere to several types of extracellular matrices (ECM) as well as CM components. Wistar rat livers were decellularized and analyzed by histology, scanning electron microscopy (SEM), immunohistochemistry and residual DNA-content analysis. Human induced pluripotent stem cells (hiPSCs)-derived mesenchymal cells (hiMSCs), and human commercial hepatic (HepG2) and endothelial (HAEC) cells were used for liver scaffold recellularization with or without CM pre-coating. Recellularization occurred for up to 5 weeks. Hepatic tissues and CM were analyzed by proteomic assays. We show that integrity and anatomical organization of the hepatic ECM were maintained after decellularization, and proteomic analysis suggested that pre-coating with CM enriched the decellularized liver ECM. Pre-coating with HepG2-CM highly improved liver recellularization and revealed the positive effects of liver ECM and CM components association.

PI: Mayana Zatz
Posdoc students: Luiz Caires-Junior and Ernesto Goulart
Publication: Caires-Junior *et al.,* 2021.*Mat. Sciences Eng. C.*

D.The Covid 19 Pandemic

Along the COVID-19 pandemic, several HUG-CELL principal investigators were directly involved in projects, or collaborated with other researchers, to tackle important problems involving SARS-CoV-2 infection and COVID-19 manifestations, such as host genomic variability in association with these phenotypes.

A sample collection was initiated in August 2020 targeting four main groups: recovered centenarians, young individuals deceased due to COVID-19, discordant couples and twins. This strategy of extreme phenotypes to increase the probability of association signal detection was published (Naslavsky *et al.,* 2021). First results were published as preprints. T cell mediated immune response in twins discordant for COVID-19 severity correlate with the manifestation phenotype regardless of the monozygotic sibship (Castro *et al.,* 2021). In discordant couples, genes involved in immune modulation located within the Major Histocompatibility Complex (MHC) and within the Leucocyte Receptor Complex (LRC) regions were found to harbor variants that were significantly associated with infection resistance (Castelli *et al.,* 2021). Finally, a description of variants in candidate COVID-19-related genes revealed rare variants that are predicted to be functional (Secolin *et al.,* 2021). Finally, a test for SARS-COV-2 detection by direct RT-LAMP in saliva was developed, as detailed in **Transfer of Technology session**. The protocol and analysis of clinical data of COVID-19 positive individuals have been submitted for publication and these data have already been published as preprint (Kobayashi *et al.,* 2021).

D1. Increased susceptibility or resistance to COVID-19

The great clinical variability ranging from severe lethal cases to asymptomatic individuals led us to investigate whether there is a genetic contribution underlying such variability. In order to address this question we decided to compare different groups: 1) young patients with a lethal outcome (collaboration with the group of Prof. Paulo Saldiva) ; 2) discordant couples; 3) Elderly individuals(older than 90) who were infected and cured or who remained asymptomatic; 4) twins. In addition to genetic studies we also investigated immunological parameters in collaboration with the group of Prof. Jorge Kalil, Edecio Cunha-Neto end Keity Santos, from INCOR/FMUSP. Until now, two papers were submitted . The preprints are in MedXriV.

D2. Immunogenetics of resistance to SARS-CoV-2 infection in discordant couples

Despite the high number of individuals infected by SARS-CoV-2 who develop COVID-19 symptoms worldwide, many exposed individuals remain asymptomatic and/or stay uninfected. This could be explained by a combination of environmental (exposure, previous infection), epigenetic, and genetic factors. Aiming to identify genetic variants involved in SARS-CoV-2 resistance, we analyzed 86 discordant Brazilian couples where one was infected and symptomatic while the partner remained asymptomatic and seronegative despite sharing the same bedroom during the infection. The discordant partners had comparable ages, and genetic ancestry proportions. Whole-exome sequencing followed by a state-of-the-art method to call genotypes and haplotypes across the highly polymorphic MHC and LRC. We observed a minor impact in antigen-presentation genes and KIR genes associated with resistance. Interestingly, genes related to immune modulation, mainly involved in NK cell killing activation/inhibition harbor variants potentially contributing to infection resistance. We hypothesize that individuals prone to produce higher amounts of MICA (possibly soluble), LILRB1, LILRB2, and low amounts of MICB, would be more susceptible to infection. According to this hypothesis, quantitative differences in these NK activity-related molecules could contribute to resistance to COVID-19 down regulating NK cell cytotoxic activity in infected individuals but not in resistant partners. The manuscript was submitted to MedXriV (Castelli *et al., 2021*).

PI: Mayana Zatz and Maria Rita Passos-Bueno
Posdoc student: Mateus Vidigal
Collaborators: Erick Castelli, Michel Naslavsky, Edecio Cunha-Neto and Keity Santos

D3. Monozygotic twins discordant for severe clinical recurrence of COVID-19 show drastically distinct T cell responses to SARS-Cov-2

Clinical recurrence of COVID-19 in convalescent patients has been reported, which immune mechanisms have not been thoroughly investigated. Presence of neutralizing antibodies suggests other types of immune response are involved.

We assessed the innate type I/III IFN response, T cell responses to SARS-CoV-2 with IFNγ ELISPOT, binding and neutralizing antibody assays, in two monozygotic twin pairs with one COVID-19 recurrence case.

In pair 1, four months after a first mild episode of infection for both siblings, one displayed severe clinical recurrence of COVID-19. Twin pair 2 of siblings underwent non-recurring asymptomatic infection. All fours individuals presented similar overall responses, except for remarkably difference found in specific cellular responses. Recurring sibling presented a reduced number of recognized T cell epitopes as compared to the other three including her non-recurring sibling.

Our results suggest that an effective SARS-CoV-2-specific T cell immune response is key for complete viral control and avoidance of clinical recurrence of COVID-19. Besides, adaptive immunity can be distinct in MZ twins. Given the rising concern about SARS-CoV-2 variants that evade neutralizing antibodies elicited by vaccination or infection, our study stresses the importance of T cell responses in protection against recurrence/reinfection. The paper was submitted to MedXriv, (Castro MV *et al.,* 2021).

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PART 2 - TRANSFER OF TECHNOLOGY/ TECHNOLOGY APPLICATIONS

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

a) Sequencing Facility (EMU/ Equipamento Multiusuário /Multiuser Equipment-FAPESP): HUG-CEL EMU <http://genoma.ib.usp.br/servicos> contains four sequencing apparatus: ABI 3730 DNA Analyser sequencer - (Applied Biosystems), NovaSeq, MiSeq and HiSeq 2500 (Illumina); and infrastructure for storage and data processing (total storage capacity of 660 TB with 60 TB allocated at USP Cloud and two processing servers with 512 GB RAM and 32 cores in total). In the end of the year of 2019, we acquired a NOVASeq-illumina equipment with federal resources. Due to the COVID19 pandemic, it was only installed in April of 2020 and the first validation sequencing occurred in August of the same year. Since that we have sequenced 1183 samples (507 private and 676 non-paid/research tests) including exome and customized panels The sequencing facility has been organized following the EMU/ FAPESP guidelines <http://genoma.ib.usp.br/servicos/sequenciamento -de-nova-geracao-ngs/comite>. However, since 2020 we are registered at the multi-user facility at USP (<http://uspmulti.prp.usp.br/index.php>, following the administrative terms of USP/FAPESP) our webpage at USP: <http://uspmulti.prp.usp.br/pagina_ result_detalhes.php?id=11&idServico=19>.

b) Genetic Tests and sequencing services: The web page of the non-profit laboratory for genetic tests <http://laboratorio.genoma.usp.br> is being constantly updated with the inclusion of new tests in order to provide new tests for physicians and their patients. For instance, we soon intend to make available the molecular testing for detection of pathogenic expansion in *C9orf72*, previously associated with amyotrophic lateral sclerosis and other phenotypes. Nowadays, most tests performed in our laboratory are NGS-based. In addition to WES, we offer around 18 small and medium-sized panels covering different disease groups, from cancer to developmental disorders. We also are constantly checking the quality of our pipelines and improving them as necessary, for example, we recently improved our pipeline for CNV detection. The incorporation of CNV

analysis from NGS-based data in our routine has improved our diagnosis yield in almost 10% (43,9% sequencing analysis only and 53,3% sequencing analysis plus CNV analysis).

Unfortunately, the favorable scenario we experienced during 2019 concerning the number of requests for genetic testing has changed by the current Covid-19 pandemic. Nevertheless, during the last year, we have performed 1372 genetic tests or NGS sequencing service (MLPA/disease specific CNVs, Triple/PCR for expansion, NGS panels, NGS exome, aCGH; 619 as paid test or service and 753 as research). The quality and reliability of our genetic tests have been certified yearly by the European Molecular Genetics Quality Netwok (EMQN). NGS Sequencing service has been requested by 5 non HUGH-CEL researchers.

Additionally, about 6,664 Sanger sequencing reaction tests were performed. These sequencing reactions were ordered by 120 researchers (63% from USP, 35% of other governmental universities; 2% private Institutions). Except for aCGH test, which is done in the cytogenetic facility coordinated by two of our PIs (C Rosenberg, AC Krepischi), all the others were performed at the CEGH-CEL facilities.

c) Genetic counseling service: Genetic counseling of families with affected patients includes diagnosis, identification and testing of “at-risk carriers”, orientation about prognosis and management and genetic counseling. About 322 consultations were performed by our team, most of them were virtual genetic counseling sessions. A written report, including results of genetic tests, were provided for most of the attended individuals.

d) Bio-repository: A collection of more than 20,000 DNA samples of patients with genetic disorders and their relatives has been established in the last 30 years. In addition to somatic cell cultures (fibroblast, myoblasts), we have established induced pluripotent stem cells (iPSC) of 80 patients with different genetic disorders and 14 controls in the last 6 years. This bio-repository has been maintained and modestly expanded in this last year due to COVID-19 pandemic.

e) DATABASES: We have developed, and hosted in our servers, a public access website <http://abraom.ib.usp.be> - ABraOM - Arquivo Brasileiro Online de Mutações) to provide information on the frequency of variants in 1171 Brazilian healthy

individuals that are part of the Sao Paulo city elderly cohort studied at our center (SABE cohort; data-set1 = 609 whole exome sequence; data-set 2 = 1171 whole genome sequencing). These datasets have provided valuable information for the interpretation of pathogenicity of variants identified in genetic tests in Brazil and around the world.

DesBraVar is a software that is being developed since 2018 to provide integration between a public genomic database and a system that will allow the storage of processed NGS sequencing data and the analysis and visualization of results in a web interface. The primary objective of the project is to store genetic information so that it can be analyzed and compared with other databases (such as the individual's phenotype database: http://zen.genoma.ib.usp.br). In addition, another main objective is to enable students, teachers and researchers to be able to analyze genetic data promptly and without the need for constant bioinformatics support. We are starting to use this software to analyze individual exomes within a restricted group of analysts of HUGH-CEL, for testing and correcting any problems related to the user experience of the platform. After validation and enhancement of functions, the use will be extended to teachers, students and researchers. Subsequently, over the next semesters, new tools will be implemented such as trio analysis, and analysis based on a genetic inheritance pattern.

f) RT-LAMP for COVID-19: We have standardized the amplification of SARS-CoV-2 through RT- LAMP (Reverse Transcription Loop-mediated Isothermal Amplification) direct in saliva samples and have started to offer SARS-CoV2 testing as a service at CEGH-CEL in December 2020. Up to now, 3044 individuals were tested and a written report were sent to each tested individual less than 24 hs after saliva collection. The manuscript including the detailed protocol and the analysis of viral load of SARS-CoV-2 in 131 symptomatic COVID-19 individuals were submitted for publication. Of interest, we observed that males have 10 x higher viral load in saliva than in females, and that these differences is more pronounced when the individuals are less than 40 years old. These results suggest that young males are more likely to transmit the virus than females (Kobayashi *et al.,* https://medrxiv.org/cgi/content/short/2021.06.07.21258288v1). Furthermore, the collaboration with Dr. Shaker Chuck Farah and German Sgro (Instituto de Quimica, USP) for the production of the RT-LAMP enzymes (reverse transcriptase III and Bst) has also been successful and we expect to fully validate these products in the next month. Last year, we also established a collaboration with Dr. Silvia Figueiredo and

Ester Sabino, from Instituto de Medicina Tropical, USP, to transfer the RT-LAMP protocol to Universidade de São Caetano do Sul. Two technicians have already been trained by us and testing for SARS-CoV-2 of children and teachers are planned to start in a public school at São Caetano do Sul in August/2021. This project has been financed by FAPESP-COVID-19 initiative grant (FAPESP 20/05949-2), JBS and ITAU-Saude.

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

PART 3 - EDUCATION OUT REACH

The COVID-19 pandemic affected HUG-CELL activities targeting high school teachers and students. With the suspension of classroom classes in High Schools, both the mobile laboratory and the centers that lend teaching materials to teachers were also interrupted. During the period of this report, HUG-CELL's activities focused on the online world. The team produced scientific dissemination content for the general public, but remained attentive to teachers, producing part of the posts on Instagram and Facebook focusing basic genetics and the SARS-CoV-2's genetics. We received some testimonials from teachers who used the aforementioned posts as teaching material.

The main objective of HUG-CELL's science dissemination actions remained to satisfy people's hunger for knowledge and quality information, in addition to creating proximity between the public, science and scientists. On social networks, the HUG-CELL is known as **genomaUSP** and is present on **YouTube**, **Facebook** and **Instagram**.

On **YouTube** <https://www.youtube.com/genomausp>, the dissemination team conceived videos in 5 formats (**Annex 4.1**): "**CINEgenoma**" and "**Best moments | CINEgenoma**" present live streams of roundtable discussions with guests moderated by a member of HUG-CELL's science dissemination team about handpicked movies which spark a dialogue on genetics, science, medicine, society, ethics, education, and cinematography; "**ABC Genome**" has series of videos on a specific topics relevant to the public and unraveled by a HUG-CELL research team; "**Straight from Genome**" and "**Straight from Genome series**" reveal news about HUG-CELL's cutting edge research; "**Speak, geneticist!**", displays interviews by researchers on a variety of topics concerning genetics; "**Specials**", portrays videos about commemorative dates, projects in health and also student projects from university disciplines taught by our specialists; "**Courses**" exhibits recordings of courses, workshops or lectures that took place at HUG-CELL; and "**Decoding DNA - USP Radio**" reproduces our research coordinator's radio show streamed by **USP Radio**.

On **Instagram** <https://www.instagram.com/genoma.usp/>, the same YouTube videos are released and there are posts made on subjects related to HUG-CELL activities, for instance genetics, molecular biology, genetic diseases, genetic counseling. There are also current topics, such as genetics related to the COVID-19 pandemic and

gene editing. These posts have enlightening illustrations, several pages, adequate language for the general public (there is even a graphic novel), and popular culture references without giving up on scientific accuracy (**Annex 4.2**).

On **Facebook** <https://www. facebook.com/pordentrodogenoma/> there is also the dissemination of **YouTube** videos and content about HUG-CELL that appear in journalistic media, including the ones related to topics of Instagram posts.

The number of HUG-CELL media followers continues to grow and, until May 2021, corresponds to 11.978 on Facebook, 16.400 on Instagram and 4.000 on YouTube. Between June/2020 and May/2021, the Youtube Channel had 101.7k views, 5.5k hours watched and 2.6k new subscribers. Facebook page had 141k people reached, 29.6k actions of engagement as link clicks, comments, shares, reactions and views. For more statistics, check out **Annex 4.3**.

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

From July 2020 until June 2021, our group has published **85** journal articles (all listed below), **7** abstracts in National meetings, and **13** abstracts in International meetings. During this period, our graduate students submitted **6** Master Theses and **2** Doctoral Dissertations. About **24** conferences, lectures and symposia were presented done by our team.

1. Articles

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Annex 2 - Meetings, Conferences, Lectures

1. Abstract: National Meetings

1. Almeida AL, Castro MAA, Honjo R, Yamamoto GL, Oliveira LA, Kim CA, **Bertola DR**. Osteopatia estriada com esclerose craniana com expressividade variável intrafamilial: relato de caso. Poster. **Congresso Brasileiro de Genética Médica e Genômica.** 30/04 e 01/05/2021 online

2. Andrade PM, Souza JM, Teixeira ACB, Sogari VF, Callegari FM, **Krepischi ACV**, Oliveira ASB, **Vainzof M**, Silva HCA. RYR1 mutation associated with MH-cores rhabdomyosarcoma. 1o Simposio Brasileiro de Biologia Muscular. Virtual, 10-15 de maio de 2021.

3. Borges VM, Horimoto ARVR, Kimura L, Wijsman EM, **Mingroni-Netto RC.** Genome-wide mapping of essential hypertension in large pedigrees from African-derived quilombo populations of Vale do Ribeira (SP,Brazil) In: XXXII Congresso Brasileiro de Genética Médica, 2021. **Resumos do XXXII Congresso Brasileiro de Genética Médica**. Sociedade Brasileira de Genética Médica e Genômica, 2021.

4. Borges VM**, Mingroni-Netto RC.** Investigando genes relacionados à hipertensão essencial por abordagens in silico In: XXIII Encontro de Genética do Nordeste, 2021. **Resumos do XXIII Encontro de Genética do Nordeste**. Ribeirão Preto: Sociedade Brasileira de Genética, 2021.

5. Letícia A, Rocha LA, Yamamoto GL, Ceroni JR, Rachel S. Honjo RS, Bisneto EF, Oliveira LN, **Passos-Bueno MR**, Kim CA, **Bertola DR**. Congenital limb deficiency: clinical and genetic evaluation of a cohortof 41 individuals. Poster. **Congresso Brasileiro de Genética Médica e Genômica**. 30/04 e 01/05/2021 online

6. Linnenkamp BDW, Lazzaro Filho R; Rocha LA, Utagawa C, Kelmann S, Honjo R, Yamamoto GL,; KimCA, **Bertola DR**. Poster. Rothmund-Thomson syndrome: clinical and molecular analysis of a cohort of 11 individuals.

7. Rivadeneira MJ, Moraes MB, Rocha LA, YamamotoGL, Honjo R, Kim CA, Alexander AL. Jorge AAL, Santos ES, **Bertola DR**. Neurofibromatosis–Noonan Syndrome: Four Brazilian cases illustrating the heterogeneous etiological mechanism. Poster. **Congresso Brasileiro de Genética Médica e Genômica** 30/04 e 01/05/2021 online

2. Abstract: International Meetings

1. Andrade PV, Souza LS, Santos JM, Lutke C, Amaral JLG, **Vainzof M.** Silva HCA. Association of delayed Malignant Hyperthermia crisis with spinal cord injury. **Annual Meeting of the EMHG**, online, 13-15 may 2021.

2. Giovanna C Tolezano, Silvia Souza da Costa, Marília de O Scliar, Carolina F M de Souza, Hélio van der Linden Jr, Walter L M Fernandes, Paulo A Otto, **Vianna-Morgante AM**, **Rosenberg C**, **Bertola DR**, **Krepischi ACV** (2021) Genetic causes of microcephaly in a **Brazilian cohort**. Apresentação de pôster. Genomics of Rare Disease 2021. Online.

3. Godoy JAP, Paiva RMA, Oliveira DC, Coa LL, Alvarez KCA, **Okamoto OK**, Marti L C, Kondo AT, Bortolini MAT, Castro R, Kutner JM. Senescende State of Mesenchymal Stem Cells in Low Culture Passages: Implications for Clinical. USEps://doi.org/10.1016/j.jcyt.2021.02.097. In: **Congresso da Associação Brasileira de Terapia Celular e Gênica**, 2021, Curitiba. Cytotherapy, 2021. v. 23. p. 33-34.

4. Godoy JA.P, Alves-Paiva RM, Kondo AT, Kerbauy LN, Rodrigues M, **Okamoto OK**, Kutner J M. Detection of apoptosis in mesenchymal stromal cells ?in vitro? to predict their efficacy for treating graft versus host disease. In: **International Society for Cell Therapy Annual Meeting**, 2021, New Orleans. Cytotherapy, 2021. v. 23. p. s59-s59.

5. Latancia M, Bastos AU, Moreno NC, Jardim D, Rocha CRR; Leandro G, **Menck CFM**. Role of Error-Prone Polymerases on Glioma Cell Resistance to

Temozolomide. **AACR Virtual Annual Meeting**, April 10th – 15th and May 17th-21st, 2021. Virtual poster presentation.

6. Latancia M, André Uchimura Bastos, Natália C. Moreno, Davi Jardim, Clarissa RR Rocha, **Menck CFM**. The Role Of Error-Prone Polymerases On Tumor Cell Resistance To Temozolomide. Environmental Genomics: Mechanisms & Approaches for Genomic Integrity - The 51st **EMGS Virtual Meeting**, September 12th to 16th, 2021. Virtual poster presentation.

7. Kerbauy LL, Marin-Agudelo N, Kaplan A N, Banerjee M, Berrien-Elliott PP, Becker-Hapak MM, Basar M, Foster R, Melo M, Neal LG, Mcclain C, Daher E, Cortes M, A.Desai AKN, LIM S, Mendt FWI, Schappe MC, LI, Shaim LT, Sanabria H, Wong MH, LIU P, Ang E, CAI SO, Nandivada R, V. … **Okamoto OK**, et al. AFM13-loaded,blood and cord-blood-derived memory-like NK cells as therapy for CD30+ malignancies. In: **The Society for Immunotherapy of Cancer (SITC) Annual Meeting**, 2020, on line. Journal for ImmunoTherapy of Cancer, 2020. v. 8. p. A324-A325.

8. **Naslavsky MS, Yamamoto GL**, Ceroni JR, Scliar MO, Wang JYT, **Duarte YAO, Passos-Bueno MR, Zatz M.** Clinical findings from whole-genome sequencing in an admixed population-based sample of 1,171 aged individuals. In **2020 Annual Meeting of the American Society of Human Genetics**, October 2020.

9. Natália C Moreno, Tiago A Souza, Camila CM Garcia, Nathalia Quintero-Ruiz, Camila Corradi, Ligia P Castro, Veridiana Munford, Susan Ienne, Ludmil B Alexandrov, **Menck CFM**. UVA light induced mutagenesis in xeroderma pigmentosum variant cells after whole exome sequencing. Environmental Genomics: Mechanisms & Approaches for Genomic Integrity - **The 51st EMGS Virtual Meeting**, September 12th to 16th, 2021. Virtual in vivo Presentation at the Plataform 5: DNA repair.

10. Rivas MP, Johnston M, Kumbaji M, Cast A, Lee H, Gulati R, Bondoc A, Geller J, Tiao G, Aguiar T, Curdulino T, Maschietto M, **Krepischi ACV**, Timchenko N. Epigenetic Control of Gene Expression in Pediatric Liver Cancer - **3rd International Pediatric Liver Tumor Conference – Focus on High Risk Liver Cancers**. Feb 26th-Feb 27th, 2020. Cincinnati, Ohio, USA - Apresentação Oral.

11. Rivas MP, Johnston ME, Lee H, Gulati R, Bondoc A, Geller J, Tiao G, **Krepischi ACV**, Timchenko N. Epigenetic Control of Gene Expression in **Pediatric Liver Cancer - Digestive Health Center (DHC) Scientific Symposium**. Feb 25th, 2020. Cincinnati Children's Hospital Medical Center, Ohio, USA. Apresentação de Pôster.

12. Santos TR, Kaid C, Araujo DD, Neville IS, Uno M, **Zatz M**, **Okamoto OK**. **EX Vivo Expansion of Tumor Infiltrating Lymphocytes (TILS) and Cancer Stem Cells from Malignant Gliomas**. In: Congresso da Associação Brasileira de Terapia Celular e Gênica, 2021, Curitiba. Cytotherapy, 2021. v. 23. p. 15-16.

13. Souza JL, Gurgel-Giannetti G, Sampaio J, Wang M, Scliar M, **Zatz M**, **Vainzof M**. Clinical variability in LGMD2B: searching for modifier genes. **WMS 2020** – online. Neuromuscular Disorders, Vol. 30: S91–S92, October 2020.

3. Conferences, Symposia, Round Tables, Lectures

1. **Bertora DR.** Rasopatias. Webinar EducaGene, **Sociedade Brasileira de Genética Médica e Genômica**, 08/02/2021, transmissão via zoom. (Palestra)

2. **Duarte Y**, **Zatz M**, Covas DT, Fortes PJ, Precioso AR, Toledo K, Menezes PR Envelhecimento: Estudo para entender por que há idosos centenários que não têm sequer sintomas enquanto jovens morrem de Covid? In: **4o Webinar Agência Fapesp - Canal Butantan - COVID-19, 60+: que epidemia é essa?** Instituto Butantan, São Paulo, 24/09/2020 Transmissão pelo Canal do Instituo Butantan < https://www.youtube. com/watch?v=rt2RPUJJfxs> (Round Tables)

3. **Mingroni-Netto RC.** Genética da Deficiência auditiva: as contribuições do estudo das famílias brasileiras, *Data da* apresentação 25 de novembro de 2020; Local: Brasil; Cidade: São Paulo; Evento: **35o Congresso Internacional de Audiologia**; Inst.promotora/financiadora: Academia Brasileira de Audiologia. (Conferência ou palestra,Apresentação de Trabalho)

4. **Mingroni-Netto RC,** Visconti MA, Cortese JFN. Curso de Extensão: Bioética para pesquisa em ciências da vida, **Instituto de Biociências**, Universidade de São Paulo, 2020. (Organização)

5. **Mingroni-Netto RC.** Aspectos éticos do Aconselhamento Genético. Curso de Extensão: Bioética para pesquisa em ciências da vida - período 03/09/2020 até 23/10/2020, 32 horas. **Instituto de Biociências**, Universidade de São Paulo. (Palestra).

6. **Naslavsky M**, Rothbarth R, Cortese J. Mesa redonda: “De quem é o seu genoma?”. **Hospital Infantil Sabará**, Instituto Pensi e Núcleo de Bioética da Fundação José Luiz Egydio Setúbal. 24 de março de 2021.

7. **Naslavsky M**. Palestra: Como a genômica pode ajudar a medicina de precisão e a saúde dos brasileiros? Organizador**: Brasilien-Zentrum da Universidade de Tübingen**. 3 de março de 2021

8. **Naslavsky M**. Palestra: Clinically relevant findings from whole-genome sequencing over one thousand elderly admixed individuals from São Paulo, Brazil. **Sociedade Chilena de Genetica, SOCHIGEN**, 26 de novembro de 2020.

9. **Naslavsky M**. Apresentação para o laboratório clínico do **Hospital Israelita Albert Einstei**n. Como o projeto SABE será utilizado para a aplicação dos PRS no Brasil. Como o projeto SABE será utilizado para aplicação de riscos poligênicos no Brasil?. 24 de setembro de 2020

10. Sabino E, Calado R, **Zatz M.** Genômica – a Ciência da Vida In: **Ciclo ILP-FAPESP de Ciência e Inovação de 2020**, Instituto Butantan, São Paulo, 31/08/2020. – Transmissão pelo Canal Alesp < https://www.youtube.com/watch?v=O6S9RiH6dQk&t=64s> (Round Tables)

11. **Okamoto OK**. Tratamento com células CAR-T em tumores sólidos. 2021. **XXVIII Simpósio Internacional de Hemoterapia e Terapia Celular** e **III Fórum Internacional de Terapia Celular**. São Paulo. (Lectures)

12. **Okamoto OK**. Vírus Zika; um potencial aliado no combate ao câncer cerebral. 2020. **Ciclo Virtual de Formação do Curso de Biomedicina**. Facthus, MG. (Lectures)

13. **Okamoto OK**. Propriedades oncolíticas do Vírus Zika: um potencial aliado no combate ao câncer de SNC. 2020. **I Congresso do Triângulo Mineiro de Oncologia e Cirurgia Oncológica**, MG. (Lectures)

14. **Okamoto OK**. Edição de Genoma por CRISPR-CAS e Inovações na Terapia com Células CAR-T. 2020. **Hemato Innovation Day**. Eretz.bio, São Paulo.

15. **Okamoto OK**, Elvis Valera."Medicina de Precisão". In: **XXIV Congresso da Sociedade Brasileira de Transplante de Medula Óssea**, 2020. (Round Tables)

16. **Okamoto OK**, Rosalia Mendez Otero. "Neurological diseases". In: XI Congresso da Associação de Terapia Celular e Gênica – **Fórum Regional da ISCT SCA**, 2021. (Round Tables)

17. **Zatz M.** Novas abordagens em pesquisas visando terapias em distrofias musculares. In: **II Congresso Brasileiro de Neurogenética**, Academia Brasileira de Neurologia, 11-13 de março 2021. Evento online (Congresso)

18. **Zatz M** . SARS-Cov-2 and Genetics- Covid 19, **Covid Human Genetic Effort**, 31 de agosto, 2020. (Live - Lectures)

19. **Zatz M** . Resistance Against SARS-Cov-2 , **Covid Human Genetic Effort**, 16 de maio, 2021 (Live - Lectures)

20. **Zatz M** . Resistência ao SARS-COV-2. Canal Alesp, 31/09/2020,Transmissão por **Canal Alesp** < https://www.youtube.com/watch?v= O6S9RiH6dQk&t=64s>

21. **Zatz M.** GenÉTICA: como isso nos afeta? **Academia Sul-Rio-Grandense de Medicina**. 24/04/2021 – Transmissão via Zoom. (Palestra)

22. **Zatz M. Passos-Bueno MR.** Apresentação sobre Xenotranplante no Brasil ao **MCTI** – Ministério de Ciência e Tecnologia, setembro de 2021. Brasília. (Lectures)

23. **Zatz M.** Apresentação ao grupo do Prof. Stephens Blacklow, The Search for protective variants in Duchenne dystrophy-, **Harvard**, May, 2021, Evento online (Round Tables)

24. **Zatz M.** Variabilidade clínica na COVID-19: a genética explica? Instituto de Psiquiatria- **HCFMUSP** (Reunião geral) 5 de novembro, 2020 < https://www.youtube.com/watch?v= UhTiKrq1Sl4>

Annex 3 - Theses and Dissertations, Awards

1. PhD These

1.1. Danyllo Felipe de Oliveira

Título: Estudos genéticos e funcionais sobre os genes VAPB e VRK1 em duas famílias portadoras de Esclerose Lateral Amiotrófica". Doutorado, setembro de Área: Biologia - Genética

Orientadora: Mayana Zatz

Inst.Financiadora: CNPq

Defesa: 2020

1.2. Eduarda Morgana da Silva M.M. de Souza

Título: Investigação de variantes de novo e alterações no número de cópias na etiologia do transtorno do espectro autista

Área: Biologia - Genética

Orientadora: Maria Rita Passos Bueno

Defesa: agosto 2020

2. Master Degree

2.1. Gabriela Koch Alvarenga

Título: Estudos de correlação genótipo-fenótipo em pacientes com a síndrome de Hipotonia Infantil com Retardo Psicomotor e Fácies Características 3 (IHPRF3)
Área: Aconselhamento Genético e Genômica humana
Orientador: Maria Rita Passos Bueno
Defesa: Março 2021

2.2 Jáina Araújo Reis

Título: Distribuição celular e função da proteína C9ORF72 em modelos celulares de Esclerose Lateral Amiotrófica
Área: Biologia - Genética
Orientadora: Merari de Fátima. Ramires Ferrari
Inst. financiadora: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior

2.3. Larissa Nascimento Antunes

Título: Estudos moleculares na surdez de herança autossômica recesssiva. 2020. Área: Aconselhamento Genético e Genômica Humana (Mestrado profissional)
Orientadora: Regina Célia Mingroni Netto
Defesa: 2020

2.4. Leonardo Galleni Leão da Silva

Título: Caracterização molecular de pacientes brasileiros com Miopatia de Central Core, através de ferramentas de Sequenciamento de Nova Geração
Área: Biologia-Genética
Orientadora: Mariz Vainzof
Defesa: Fevereiro 2021
Inst. financiadora: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior

2.5. Leticia Alves da Rocha

Título da dissertação: Estudo genômico de indivíduos com deficiência congênita de membros.
Área Ciências - Programa de Pediatria – FMUSP

Orientadora: Débora Romeo Bertola

Defesa: Junho 2021

2.6. Raíssa Modaffore Dandalo Giradi

Título: Bases genéticas dos defeitos de segmentação vertebral: estudo genético-clínico focado em pacientes com disostose espondilocostal

Área: Aconselhamento Genético e Genômica humana

Orientadora: Debora Romeo Bertola

Defesa: março 2021

3. Awards

3.1. Carolini Kaid & **Oswaldo Keith Okamoto**. Prêmio Capes de Teses, Edição 2020 – área Ciências Biológicas I (Estudante e Orientador)

3.2. Marcela Latancia, André Uchimura Bastos, Natália C. Moreno, Davi Jardim, Clarissa RR Rocha, Giovana Leandro, **Carlos Menck FM**. Virtual poster presentation. This work received the "Global Scholar-in-Training Awards (GSITA)" at AACR's 2021 Annual Meeting – Role of Error-Prone Polymerases on Glioma Cell Resistance to Temozolomide.

3.3. Marcela Latancia; André Uchimura Bastos; Natália C. Moreno; Davi Jardim; Clarissa RR Rocha; **Carlos Menck FM**. The 51st EMGS Virtual Meeting, September 12th to 16th, 2021. Invited for an in vivo presentation at the DNA Repair Special Interest Group. And received the Award "EMGS Student and New Investigator Presentation Award", in this meeting!

Annex 4 - Tables Education /Out Reach

Annex 4.1. YouTube videos - CINE Genoma (started 9 months ago)

Film	Participants	Live transmission on	Views up to May 26, 2021
Jurassic Park: The Dinosaur Park	Adriano Garret - Film Critic Rodrigo Mendes – High School Biology Teacher Regina Mingroni-Netto – HUG-CELL Geneticist	August 5, 2020	7,085
Planet of the apes: the origin	Carlos Menck – HUG-CELL Geneticist Silvio Anaz – Film Critic Rodrigo Mendes – High School Biology Teacher	September 16, 2020	2,517
GATTACA	Sergio Rizzo – Film Critic Regina Mingroni Netto – HUG-CELL Geneticist Tatiana Nahas – High School Biology Teacher	October 14, 2020	16,752
Biohackers	João Cortese – Philosophy Teacher Ernesto Goulart – HUG-CELL Geneticist Paula Mello – High School Biology Teacher	December 10, 2020	732
Henrietta Lacks' Immortal Life	Merari Ferrari – HUG-CELL Cell Biologist Cristina Caldas – Serrapilheira Institut Director João Cortese – Philosophy teacher	March 17, 2021	1,27
The Island	Ernesto Goulart – HUG-CELL Geneticist Leonardo Lina – High School Biology Teacher Bruno Carmelo – Film Critic	April 14, 2021	625
Sankona - Brazilian Ancestry	Michel Naslavsky – HUG-CELL Geneticist Mônica Lima - LFÁfrica/UFRJ Daniel Munduruku – Writer	May 12, 2021	625

DIRETO DO GENOMA (Straight from Genome)	Post data	Views up to May 26, 2021
Zika virus: from enemy to ally	March 31, 2020	561
Diagnostic test for COVID-19	11 months	117
Why are there elderly people who do not show symptoms when exposed to SARS-CoV-2?	July 27, 2020	943
How do genes work in the neurons of autistic people?	August 13, 2020	392

Zika during twin pregnancy	September 26, 2020	64
The country's largest gene bank reflects the Brazilian's miscegenation	October 26, 2020	445
Early diagnosis of childhood cancer	December 22,2020	83
Laboratory raised liver	March 09, 2020	133

SÉRIES DO DIRETO DO GENOMA (Genome Direct Series)	**Post data**	**Views up to May 26, 2021**
Muscular dystrophy research (2 videos on playlist)		
I understand muscular dystrophies better	January 3, 2020	975
The mice that help research into muscular dystrophies	January 15, 2020	149
Tissue engineering (4 videos in playlist)		
Liver assembly for transplantation.	March 24, 2021	751
Organ production with 3D printer.	Nov 2, 2020	399
Organoids.	Dez 04, 2019	527
Organ Bioengineering	March 24, 2021	68
DNA Injuries in Antarctica (2 videos on playlist)		
Why go to Antarctica to study DNA damage?	April 05, 2021	70
Scientists have unforeseen events in the open-air laboratory	April 20, 2021	70

SÉRIE ABC DO GENOMA (ABC Genome Series)	**Post data**	**Views up to May 26, 2021**
ABC OF BREAST CANCER with 3 videos in the playlist:		
Hereditary breast cancer.	August 18, 2020	272
Hereditary breast cancer: from suspicion to clinical trials.	Sep 01, 2020	147
The search for new genetic causes for breast cancer.	Sep 08, 2020	167
ABC OF GENETIC COUNSELING with 2 videos in the playlist:		
Genetic counseling	May 19, 2021	94
Steps of Genetic Counseling	May 26, 2021	44

ESPECIAIS (Specials)	Post data	Views up to May 26, 2021
DECODING DNA - RADIO USP		
Need to sleep during the day can be explained by genetics?	April 15, 2021	149
Chinese and American scientists create embryos from ape and human cells.	April 26, 2021	105
CRISPR technique still brings ethical questions	April 13, 2021	255
Challenging questions raised by genome editing.	April 25, 2021	41
BEST MOMENTS OF CINE GENOME		
Is it possible to generate an adult clone?	April 21, 2021	45
Are human clones a reality?	April 23, 2021	60
Goals of creating human clones.	April 27, 2021	35
Human cloning in China and audiovisual imagery about biotechnology.	April 30, 2021	54
How art impacts the view of scientists	April 10, 2021	22
How Brazilian ancestry is present in the transmission of chromosomes.	April 21, 2021	65
Search for ancestry	April 26, 2021	40

Annex 4.2. - Post examples

Example A

1

2

Os cientistas verificaram que nos primeiros meses na EE1, 1.400 genes do Scott passaram a funcionar de forma diferente.

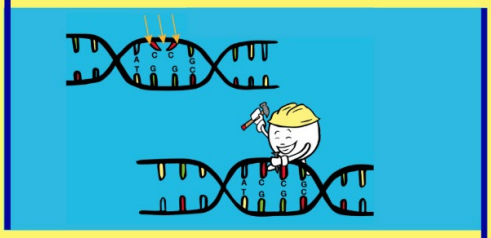
Estação Espacial Internacional Imagem: Nasa

É possível que esses genes sejam os responsáveis pelas alterações do organismo para viver na ausência de gravidade.

genoma

3

Um estudo com nemátodos, um tipo de vermes, sugere que a taxa de mutação é 8 vezes maior no espaço. Isso porque na Terra a radiação é bloqueada pelo campo magnético e pela atmosfera.



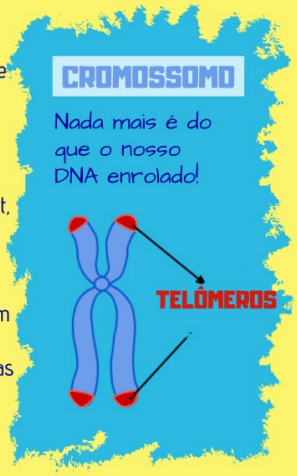
Por isso, na segunda metade da viagem espacial houve outra mudança. **Genes relacionados ao reparo do DNA foram ativados de forma mais intensa.**

genoma

4

Para fechar com chave de ouro, os cientistas verificaram que, na viagem espacial, as extremidades dos cromossomos de Scott, chamadas telômeros, cresceram.

Os telômeros protegem as regiões terminais dos cromossomos, mas não se sabe ainda o motivo da mudança.



genoma

5

Na volta, a atividade de mais de 91% dos genes de Scott que mudaram durante a viagem voltou ao normal. Para entender melhor os efeitos das alterações no organismo, será necessário fazer mais estudos no espaço!

genoma

6

7

"Ao contrário do que diz a história do incrível Hulk, a radiação não transforma ninguém em super-herói. Ela causa mutações no DNA! E radiação é o que mais tem no espaço! Mas não é só isso. Na ausência de gravidade, toda a regulação gênica é alterada para o organismo se acomodar às mudanças espaciais.

Se você já teve vontade de viajar no espaço, então é melhor entender antes o que vai acontecer com o seu DNA... Feliz dia do Astronauta!

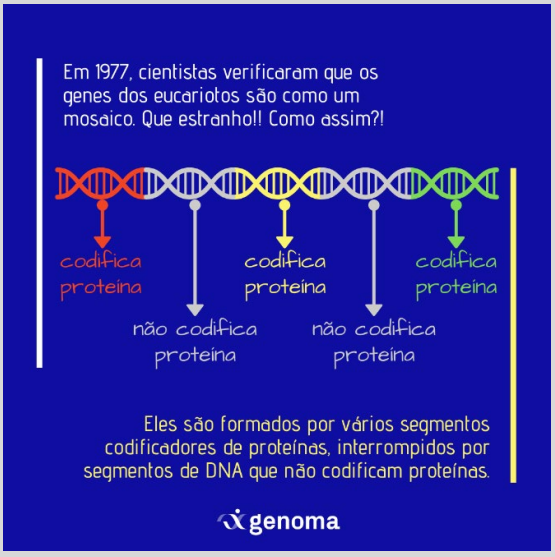
Se você pudesse morar em qualquer planeta, qual seria ele? Aproveita para compartilhar esse post com aqueles amigos que curtem muito entender o universo, a vida e tudo o mais! "

#diadoastronauta #astronauta

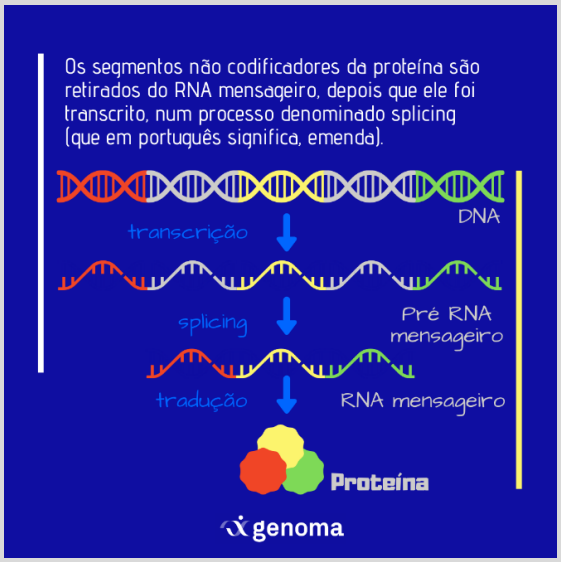
#dna #dnanoespaço #genetica

Example B

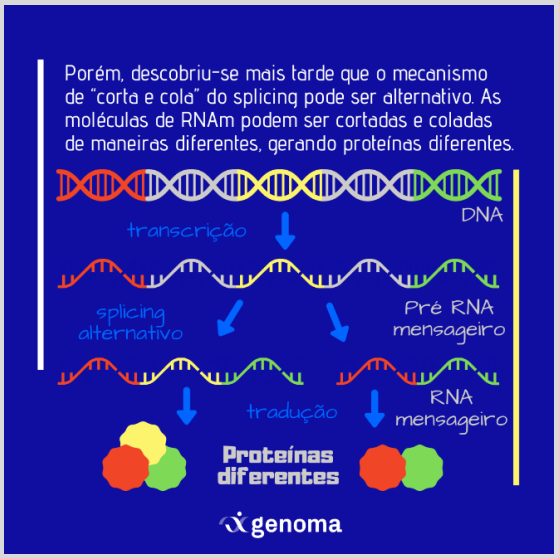
1



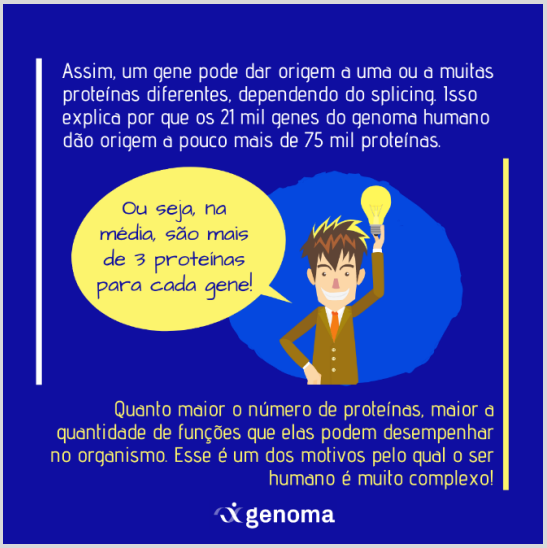
2



3



4



5

6

"Você aprendeu na escola que um gene dá origem a uma proteína? Antes de mais nada, se você lembra disso, já está de parabéns!!! 🎉🎉🎉 Mas tem um detalhe incrível: a natureza criou formas de produzir várias novas proteínas a partir do com o mesmo gene, o que permite aumentar a complexidade dos organismos. Por isso, um grande número de genes, por si só, não é garantia de complexidade. Entenda melhor nesse post!
E se gostou, volte 22 casinhas até o post "Tamanho não é documento 1!", e entenda por que um genoma grandão também não significa muita coisa em termos de complexidade dos seres vivos.
#tamanhonaoedocumento #genes #numerodegenes

Annex 4.3. - Published posts on GenomaUSP social media from June/2020 to May/2021

YouTube (57 posted videos)

Theme	Number of videos
Genetic tests	9
Coronavirus	2
Cancer	6
News - PL 529	1
Zika vírus	1
CRISPR-Cas9	2
Genetic Bank	1
Epigenetics	1
Genetic deseases	3
Institucional	2
Organ Bioengineering	2
DNA at the south pole	2
Decoding DNA - Participation by Mayana Zatz at Radio USP	4
CINEgenoma	8
Best moments of CINEgenoma	8
Genetic counseling	2

Instagram

(158 feed posts, 40 videos on IGTV/Reels and 444 Stories posted)

Topic	Number of posts	Videos on IGTV/ Reels
COVID-19	14	2
Genetic Tests	5	10
Commemorative dates	28	-

Vaccines	4	1
Announcement of grants, events, calls for volunteers and petitions	14	-
Foot Test	-	1
Virus an e cancer	2	-
Basic Genetics	5	-
Scientific trivia	11	-
CINEgenoma	34	5
Parthenogenesis	2	-
Autism	-	1
Cancer	4	3
Dieseases	1	1
Genetic editing	3	1
Transgenics	5	-
Zika virus	-	1
Fires	1	-
Chimeras	2	-
Twins	2	-
Genetic Bank	-	1
Steam cells	2	-
Albinism	3	-
Bacteria	5	-
Cloning	1	1
Organ Bioengineering	2	2
Institutional	1	1
HeLa Cells	-	1
DNA at the south pole	1	2
Xenotransplantation	1	-

Decoding DNA - Radio USP Program	-	4
Comic	3	-
Genetic counseling	2	2

Facebook (179 posts)

Content	Number of posts
Videos from the GenomaUSP channel on YouTube	45
Links to journalistic content in the HUG-CELL area of operation Published in the media	68
Instagram posts	61
CINEgenome Live Streams	5

Annex 4.4. Interviews to the Media and Science Dissemination Articles

1. **Krepischi A.** Participação como autora do editorial “Desafios do diagnóstico molecular da deficiência intelectual”. **Revista DI**, Ano 10, n.18, p. 2. São Paulo,. Disponível em < https://www.ijc.org.br/pt-br/sobre-deficiencia-intelectual/publicacoes/Paginas/revista-di.aspx > Acesso em 09/06/2021.

2. **Mingroni-Netto RC**. Entrevista: “Ciência versus fake news: como diferenciar pesquisas sérias de informações mentirosas”, 2020. **Jornal do Campus** - USP *Home page:* http://www.jornaldocampus.usp.br/index.php/2020/07/ciencia-versus-fake-news-como-diferenciar-pesquisas-serias-de-informacoes-mentirosas/

3. **Mingroni-Netto RC,** Silveira RVM, Grieco A, Garrett A.CINEGENOMA: "Live" Jurassic Park, Parque dos Dinossauros, 2020. Disponível em <https://www.youtube.com/watch?v=1ByDeEVjb14&t=3014s

4. **Mingroni-Netto RC**. Navas T, Grieco A, Rizzo S."Live" CINEGENOMA: GATTACA, a Experiência Genética, 2020. Disponível em <https://www.youtube.com/watch?v=jujxZuMgEck&t=3554s> Acesso em 09/06/2021.

5. **Mingroni-Netto RC.**; DIANESI, M. 'Live' sobre Aconselhamento Genético: O que é e qual a sua importância?, 2020. Disponível em < https://www.instagram.com/tv/CBgpivin_7t/?igshid=hs4ubougenks> Acesso em 09/06/2021.

6. **Mingroni-Netto RC -** Aconselhamento Genético - vídeo de divulgação disponibilizado no **Canal do Youtube do Genoma USP**. 19/05/2021. Disponível em < https://www.youtube.com/ watch?v=Sg7FKimK4Bo> Acesso em 09/06/2021.

7. **Mingroni-Netto RC**. Etapas do Aconselhamento Genético - video disponibilizado no **Canal do Youtube do Genoma USP**. 26/05/2021. Disponível em https://www.youtube.com/ watch?v=qfszqBnvUKE> Acesso em 09/06/2021.

8. **Naslavsky M.** Entrevista **para Rede Minas**. Série "Demência: mais perto de nós". Data da veiculação: 26/11/2020. Disponível em <https://fb.watch/4X12j7BIpq/> Acesso em 23/06/2021.

9. **Naslavsky M.**. Comentários sobre medicina de precisão e genomas brasileiros. **Revista Aptare.** Disponível em <http://revistaaptare.com.br/2020/11/10/riqueza-genetica/> Acesso em 23/06/2021.

10. **Naslavsky M.**. Matéria sobre SABE, medicina de precisão e bancos de dados genômicos de brasileiros. **Valor Econômico**. Disponível em <https://valor.globo.com/eu-e/noticia/2020/10/23/as-mutacoes-do-brasileiro.ghtml> Acesso em 23/06/2021.

11. **Naslavsky M.** Comentário sobre o papel da ciência na pandemia de Covid-19. **TV Aparecida**.Disponível em <https://www.youtube.com/watch?v=w1XbNXbbG08> Acesso em 23/06/2021.

12. **Naslavsky M**.. Entrevista sobre pré-publicação genomas brasileiros e ABraOM v2. **Rádio CBN.** Disponível em <https://cbn.globoradio.globo.com/media/audio/15802/usp-conclui-maior-banco-de-dados-geneticos-de-pess.htm> Acesso em 23/06/2021> Acesso em 23/06/2021.

13. Rocha IG; Veiga CJM, **Ferrari MFR.** Autoria do texto "Proteínas Mediadoras dos Sítios de Contato Mitocôndria-Retículo Endoplasmático na Doença de Parkinson" publicado para o Jornal de Divulgação Científica **Nanocell News**. **Edição Vol. 7, N. 6, 26 de Outubro de 2020**. Disponível em https://www.nanocell.org.br/proteinas-mediadoras-dos-sitios-de-contato-mitocondria-reticulo-endoplasmatico-na-doenca-de-parkinson/ Acesso em 09/06/2020.

14. Tolezano GC, Carvalho LML, **Krepischi ACV**, **Rosenberg C.** Autoria do texto "Inteligência e deficiência intelectual: bases genéticas e fatores ambientais". **Revista Genética na Escola**, v. 15, n.1, p. 18-25, 2020. Disponível < https://www.flipsnack.com/Eveli/revista-gen-tica-na-escola-vol-15-n-1.html> Acesso em 09/06/2020.

15. **Zatz M.** Entrevista para o Jornal da CBN sobre "Liberação de verbas públicas e investimentos privados melhoram expectativas na área da ciência". **Rádio CBN**,

São Paulo, 02.01.2020. Disponível em < https://m.cbn.globoradio.globo.com/media/audio/286929/liberacao-de-verbas-publicas-e-investimentos-priva.htm > Acesso em 03/06/2021.

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Annex 5 – Personnel\

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	Maria Carolina Boer
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