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

Universidade de São Paulo

Instituto de Biociências

Departamento de Genética e Biologia Evolutiva

FAPESP/CEPID 2013/08028-1

Coordinator: MayanaZatz

REPORT

July 2019 to June 2020

SUMMARY

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Coordination

Mayana Zatz - General coordinator

Maria Rita Passos-Bueno - Transfer of Technology

Eliana M. Belluzzo Dessen - Education/Public

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ABSTRACT

Since July 2019 ,our group published 60 articles in peer-review journals,3 book chapters, 12 Abstracts in National meetings and 21 in international meetings. Our collaborators were co-authors in additional 17 publications. Our students presented 5 MSc Dissertations and 10 PhD Theses . Most of the articles involved the collaboration of students and PIs from HUG-CELL. About 34 conferences, lectures and symposia were presented by our team.

The continuation of our research on Zika virus revealed that zika virus can be a potent oncolytic agent against brain tumors, which can open new avenues for therapies. These results were published and were the cover of the journal Cancer Research *(Kaid et al., June 2018).* More recently, this study was expanded and we have shown the potential of zika virus injections for treatment of dogs with brain tumors *(Kaid et al., Molecular therapy, 2020)*. This finding illustrates how basic research can lead to a highly relevant therapeutic application. Another important paper on autism that called the attention of the media was published in the high impact journal Molecular Psychiatry *(Griesi et al., 2020)*. Our google scholar citation index per year continues to increase as observed in <https://scholar.google.com.br/citations?user=CH1QvYIAAAAJ&hl=pt-BR>.

The applications of technology transfer included genetic counseling for about 1,653 families. Despite the interruption of activities during the coronavirus pandemia, a total of 13,064 genetic tests and 10,711 sanger sequencing reactions, were performed at HUG-CELL EMU for 9 CEPID researchers, more than 400 external users, as detailed in the report. We also acquired and installed a next generation Ilumina NovaSeq 6000^{TM} with Federal Funds (transfer of “verba parlamentar” from Senator Mara Gabrilli). This equipment, the only one available in a public institution will allow us to increase significantly our genome testing capacity.

Our education program included several projects such as laboratory classes at public schools, the Giant Cell project, educational leaflets, TV programs, among others. Furthermore, the **Sowing the seed of knowledge Project**, which aims to disseminate science knowledge and curiosity in subways and other public spaces, which was started in HUG-CELL was extended to other CEPIDS, under the coordination of Eliana Belluzzo Dessen. We also gave hundreds of interviews about our projects, new scientific publications or ethical issues associated to the application of novel genetic technologies.

PART 1

RESEARCH

Our main research results from July 2019 to June 2020, classified by our main objectives are

A. GENE IDENTIFICATION AND MECHANISMS IN GENETIC DISORDERS

A1. Identification of new human genes in both simple (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

A2.2. Craniofacial disorders

A2.3. Neurodegeneration

A2.4. Neurodevelopmental

A3. Epigenetics and diseases

A3.1. DNA methylation in congenital disorders

A3.2. Epigenetics in disorders of multifactorial inheritance: NSCLP

A3.3. How DNA damage and Genome Instability can be implicated in human diseases?

B. THE 80plus PROJECT

C. THERAPIES IN GENETIC DISORDERS

C1. Pre-Clinical studies with murine stem cells

C2. Safety-related concerns in cell therapy

C3. Other therapeutic approaches

C4. Tissue engineering

A. GENE IDENTIFICATION AND MECHANISMS IN GENETIC DISORDERS

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

A1.1. Mendelian Disorders

Expanding the role of *SETD5* haploinsufficiency in neurodevelopment and neuroblastoma

Despite the well-known intersection between biological pathways of cancer and development, such as cell growth and division, the etiology of most of these associations remains unexplored. The genomic study of rare patients presenting both conditions can allow the identification of the underlying genes, as well as contribute to our understanding of the disease development. Our findings suggest an association of the germline *SETD5* deletion to a shared susceptibility to neurodevelopmental disorders and cancer, which may expand the spectrum of clinical signs associated with this condition *(Pires et al.; accepted in Pediatric Blood and Cancer, may 2020).* Given the rarity of both neuroblastomas and *SETD5* deletion, this association may go unnoticed, and thus more studies are needed to evaluate its strength.

PIs: Ana Krepischi and Carla Rosenberg - Graduate students and postdocs: Sara Pires and Anne Barbosa.

Syndromic and non-syndromic hearing loss

In 2009, our group mapped a novel locus of autosomal dominant hearing loss in the chromosomal region 2p14, which was named as DFNA58 *(Lezirovitz et al. 2009).* Since then, exome sequencing and array genotyping allowed the identification of a genomic duplication in the mapped region comprising three protein coding genes (*PLEK*, *CNRIP1* and *PP3R1*) and other non-coding RNA genes. The duplication segregated perfectly with the phenotype, allowing us to consider it as causative. Our studies showed the expression of the three proteins in murine cochlea and increased expression of the RNAs in blood of the duplication carriers, mainly of the transcript of *CNRIP1,* suggesting changes in the expression levels of these genes in the hearing organs underlies the DFNA58 form of deafness

(Lezirovitz et al., 2020). More recently, other students of the group, Andre Silva Bueno and Larissa Nascimento, are undertaking the analysis of Brazilian families with hearing loss searching for novel genes or mechanisms of mutation.

PI: Regina Mingroni-Neto – Msc studests: Andre Silva Bueno and Larissa Nascimento.

Skeletal Dysplasias

We evaluated an individual presenting low bone mineral density with recurrent fractures and deformities, compatible with the diagnosis of osteogenesis imperfecta (OI), besides oligodontia. Exome sequencing of the index individual was performed in our Center and did not reveal any variant in known genes associated with OI. In our analysis to identify variants in a novel gene, we prioritize the homozygous variants. Among them, this individual harbored a homozygous loss of function variant in *MESD*, whose product exerts a chaperone activity in WNT signaling, a pathway involved in skeletal development. We collaborated with groups in the US and Germany in order to collect a large number of patients. In total, four other individuals were included and functional analysis was performed in order to prove that *MESD* is a novel gene associated with autosomal recessive OI.*(Moosa et al., 2019)*. During the period we have also co-authored 5 additional papers. *(Uchiyama et al., 2019), (Saida et al., 2019), (Aoi et al., 2019), (Homma et AL., 2019); (Aguiar et AL, 2020*).

PI: Debora Bertola – MSc students Raíssa Modaffore Dandalo Girardi and Leticia Alves da Rocha.

A1.2. Complex disorders

Copy number alterations in genetic disorders

CNVs are known to contribute to human normal variation and disease. Genomic imbalances have been investigated in different cohorts to identify genes or chromosomal regions involved in stature *(Albuquerque et al . 2020)*, *(Funari et al, 2019),* and cancer *(Aguiar et al. 2020), (Mariano et al 2019).*

We have also characterized a cohort of 34 Brazilian patients with Phelan-McDermid syndrome (PMS), a recurrent syndromic form of autism, mostly caused by CNVs of variable size at 22q13.33. Notably, an atypical case diagnosed with PMS at 18 years old and IQ within the normal range was identified, suggesting that resilience to such mutations occurs. This case expands the clinical spectrum of variability in PMS and opens perspectives to identify protective mechanisms that can minimize the severity of this condition. *(Samogy-Costa et al., 2020).*

We also improved the copy number determination from sequencing data, in collaborative work with the Center for Human Genetics, University Hospitals Leuven, (Belgium); this work resulted from a BEPE exchange project (FAPESP 2017/23448-8). The data show the use of new algorithms to improve copy number determination from mosaic situations *(Brison et al. 2019)*, *(Villela et al. 2019)*, New approach also directed to mosaic situation shows that, together with copy-number profiling, accurate haplotyping can be reconstructed *(Che et al. 2020)*.

PIs- Ana Krepischi and Carla Rosenberg; Graduate students and postdocs: Juliana Sobral, Talita Aguiar, Maria Rivas, Darine Villela.(Villela et al., 2020)

PIs-Maria Rita Passos-Bueno, Maria Vibranovski, Ana Krepischi, Carla Rosenberg. Graduate students: Claudia Samogy-Costa (Master), Elisa Varella-Branco (Master), Frederico Monfardini (PhD). (Samogy-Costa et al., 2020)

Genetic alterations affecting cancer development and aggressiveness

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 represents 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. Nuclear magnetic resonance (NMR) is one of the main methods used in metabolomics studies and different types of samples can be analyzed to detect and identify cancer metabolic signatures as well as to validate biomarkers using enlarged group of samples. We

have produced a review article regarding data on metabolomic findings and differences in pediatric cancers *(Escobar et al. 2020),* Literature search for biomarkers points to around 20–30 compounds that could be associated with pediatric cancer as well as metastasis. Currently, our group is using NMR to study serum and tumor samples from patients with osteosarcomas or hepatoblastomas.

Hepatoblastoma is a very rare embryonal liver cancer supposed to arise from the impairment of hepatocyte differentiation during embryogenesis. We investigated by exome sequencing the burden of somatic mutations in a cohort of 10 hepatoblastomas, including a congenital case *(Aguiar et al. 2020)*. Our data disclosed a low mutational background and pointed out to a novel set of candidate genes for hepatoblastoma biology, which were shown to impact gene expression levels. Our data provided evidence that *CX3CL1/CX3CR1* chemokine signaling pathway is likely involved with hepatoblastoma progression, besides reporting specific tumor mutational signatures. Additionally, we explored the underlying mechanisms related to aberrant epigenetic modifications in hepatoblastomas that we have previously identified, a general disrupted expression of the DNA methylation machinery, in association with an enrichment of 5hmC content. Our findings support a model of active demethylation by TETs in hepatoblastoma, which in combination with *UHRF1* overexpression would lead to DNA hypomethylation and an increase in overall 5hmC content. Furthermore, our data suggest that decreased 5hmC content might be associated with poor survival rate, highlighting a pivotal role of epigenetics in hepatoblastoma development and progression (Rivas et al. 2019).

PIs: Ana Krepischi and Carla Rosenberg - Graduate students and postdocs: Juliana Sobral, Talita Aguiar, Maria Rivas, Anne Barbosa.

miR-367 as a therapeutic target in stem-like cells from embryonal central nervous system tumors

Aberrant expression of the pluripotency factor OCT4A in embryonal tumors of the central nervous system (CNS) is a key factor that contributes to tumor aggressiveness and correlates with poor patient survival. OCT4A overexpression has been shown to up-regulate miR-367, a microRNA (miRNA) that regulates

pluripotency in embryonic stem cells and stem-like aggressive traits in cancer cells. Here, we show that (a) miR-367 is carried in microvesicles derived from embryonal CNS tumor cells expressing OCT4A; and (b) inhibition of miR-367 in these cells attenuates their aggressive traits. miR-367 silencing in OCT4A-overexpressing tumor cells significantly reduced their proliferative and invasive behavior, clonogenic activity, and tumorsphere generation capability. In vivo, targeting of miR-367 through direct injections of a specific inhibitor into the cerebrospinal fluid of Balb/C nude mice bearing OCT4A-overexpressing tumor xenografts inhibited tumor development and improved overall survival. miR-367 was also shown to target SUZ12, one of the core components of the polycomb repressive complex 2 known to be involved in epigenetic silencing of pluripotency-related genes, including POU5F1, which encodes OCT4A. Our findings reveal possible clinical applications of a cancer stemness pathway, highlighting miR-367 as a putative liquid biopsy biomarker that could be further explored to improve early diagnosis and prognosis prediction, and potentially serve as a therapeutic target in aggressive embryonal CNS tumors *(Kaid et al., 2019).*

PI: Oswaldo Keith Okamoto - students Carolini Kaid Davila (PhD) , Amanda Assoni (PhD) and Dione Jordan (IC). Collaboration: postdocs: Heloisa Maria de Siqueira Bueno and Bruno Henrique Silva Araujo.

Proteome and miRNome profiling of microvesicles derived from medulloblastoma cell lines with stem-like properties reveals biomarkers of poor prognosis

Primary central nervous system (CNS) tumors are the most common deadly childhood cancer. Several patients with medulloblastoma experience local or metastatic recurrences after standard treatment, a condition associated with very poor prognosis. Current neuroimaging techniques do not accurately detect residual stem-like medulloblastoma cells promoting tumor relapses. In attempt to identify candidate tumor markers that could be circulating in blood or cerebrospinal (CSF) fluid of patients, we evaluated the proteome and miRNome content of extracellular microvesicles (MVs) released by highly-aggressive stem-like medulloblastoma cells

overexpressing the pluripotent factor OCT4A. These cells display enhanced tumor initiating capability and resistance to chemotherapeutic agents. A common set of 464 proteins and 10 microRNAs were exclusively detected in MVs of OCT4A-overexpressing cells from four distinct medulloblastoma cell lines, DAOY, CHLA-01-MED, D283-MED, and USP13-MED. The interactome mapping of these exclusive proteins and miRNAs revealed ERK, PI3K/AKT/mTOR, EGF/EGFR, and stem cell self-renewal as the main oncogenic signaling pathways altered in these aggressive medulloblastoma cells. Of these MV cargos, four proteins (UBE2M, HNRNPCL2, HNRNPCL3, HNRNPCL4) and five miRNAs (miR-4449, miR-500b, miR-3648, miR-1291, miR-3607) have not been previously reported in MVs from normal tissues and in CSF. These proteins and miRNAs carried within MVs might serve as biomarkers of aggressive stem-like medulloblastoma cells to improve clinical benefit by helping refining diagnosis, patient stratification, and early detection of relapsed disease *(Kaid et al., 2020).*

PI: Oswaldo Keith Okamoto - students and collaborators: Carolini Kaid Davila (PhD) Amanda Assoni (PhD), Marina Marçola (postdoc), Patricia Semedo-Kuriki (technician), Raul Hernandes Bortolin (postdoc), Valdemir Melechco Carvalho (research collaborator - Grupo Fleury),

Novel candidate genes in craniofacial complex disorders

Cleft lip with or without cleft palate (CL/P) is a common complex disorder. Up to now, there are 4 genes that when mutated cause CL/P. We have sequenced 30 genes within the Wnt pathway in 300 CL/P patients. Three novel candidate genes not yet associated with CL/P have been identified. The functional characterization of mutations at these novel candidate genes is currently being conducted. *(Brito et al., 2019, ASHG meeting)*.

PI: Maria Rita Passos-Bueno; postdoc: Luciano Brito.

Novel candidate genes in Autism spectrum disorder (ASD): ASD is a genetic heterogeneous complex disorder. Despite the great advance in the understanding of the genetic architecture of ASD in the last years, identification of truly pathogenic variants and the associated genes still represent a challenge. Recently, we suggested two novel candidate ASD genes (*PRPF8* and *RBM14*) by combining the data of whole exome sequencing of 30 Brazilian ASD probands and their parents (ASD trios) with data of the MSSNG database (about 5,000 ASD trios) (Montenegro et al., 2020). As part of the Autism Sequencing Consortium *(Satterstrom et al., 2020)*, we have now nearly 300 ASD trios in our database, which will be used in new research projects of our group.

PI: Maria Rita Passos-Bueno - Collaborators: Guilherme Yamamoto, Stephen Scherer (University of Toronto, Canada); undergraduate students: Eduarda M. da Silva Montenegro (PhD); Claudia I.Samogi Costa, Master; Tatiana F. de Almeida (PhD).

CONGENITAL ZIKA SYNDROME SUSCEPTIBILITY: WHAT DID WE LEARN FROM TWIN STUDIES?

Differential gene expression elicited by ZIKV infection in trophoblasts from discordant congenital Zika syndrome twins

Congenital Zika syndrome (CZS), caused by Zika virus (ZIKV) infection, has been associated to impairment of early brain development, particularly related to neural progenitor cells (NPC) survival and growth. We have previously shown that discordant CZS twins show differential *in vitro* viral susceptibility of neural progenitor cells (NPCs). Subsequently, we analyzed hiPSC-derived trophoblasts from the same three pairs of dizygotic twins discordant for CZS. We compared by RNA-Seq the hiPSC-derived trophoblasts from CZS-affected and CZS-non-affected twins. Following $ZIKV^{BR}$ *in vitro* exposure, we show that trophoblasts from CZS-affected twins are significantly more susceptible to $ZIKV^{BR}$ infection when compared with trophoblasts from CZS-non-affected twins. Most importantly, $ZIKV^{BR}$ infection causes the downregulation of genes related to the extracellular matrix organization and to leukocyte activation, which are important for trophoblast adhesion as well as

innate immune response activation, only in the hiPSC-derived trophoblasts from CZS-affected twins. Overall, our results show that trophoblasts from CZS-non-affected twins have the ability to respond more efficiently to ZIKV infection in the placenta, and this may be a key parameter to predict protection from ZIKV dissemination into fetuses' tissues. This work is a continuation of our publication in NPC, performed by the posdoc students Luiz Carlos Caires-Junior and Ernesto Goulart (supervision Mayana Zatz) in collaboration with the group of Sergio Verjovsky-Almeida *(Amaral MS, et al., PLos neglected diseases, 2020)*.

PIs: Sergio Verjovsky-Almeida and Mayana Zatz- postdoc students: Luiz Carlos Caires-Junior and Ernesto Goulart.

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

A2.1. Neuromuscular disorders

Manifesting carriers in recessive X-linked myotubular myopathy

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, i and manifests in living born males with an estimated incidence of 1/50,000. Myotubular myopathy is characteristic and very severe, including hypotonia and generalized muscle weakness since birth. Most patients die in the first year of life due to respiratory failure. However, many patient with a more benign phenotype have been recently identified through molecular analysis. 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. Mutations in the *MTM1* gene were identified in patients from twelve different families, using a NGS panel for neuromuscular disorders. Seven among these mutations were novel. 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. We demonstrated the possible existence of genetic mechanisms and variants accountable for the clinical manifestation in these women, which can become future targets for therapies. The manuscript "Manifesting carriers of X-linked Myotubular Myopathy: genetic modifiers modulating the phenotype" is under revision.

PI: Mariz Vainzof - Master student Lucas Santos e Souza, PhD. student Camila de Freitas Almeida. Collaboration: Erick C. Castelli.

X-linked myopathy with excessive autophagy (XMEA)

X-linked myopathy with excessive autophagy (XMEA) is a genetic disease associated with weakness of the proximal muscles. It is caused by mutations in the VMA21 gene, coding for a chaperone that functions in the vacuolar ATPase (v-ATPase) assembly. Mutations associated with lower content of assembled v-ATPases lead to an increase in lysosomal pH, culminating in partial blockage of macroautophagy, with accumulation of vacuoles of undigested content. Here, we studied a 5-year-old boy affected by XMEA, caused by a small indel in the VMA21 gene. Detection of sarcoplasmic Lc3 (also known as MAP1LC3B)-positive vacuoles in his muscle biopsy confirmed an autophagy defect. To understand how autophagy is regulated in XMEA myogenesis, we used patient-derived muscle cells to evaluate autophagy during in vitro muscle differentiation. An increase in lysosomal pH was observed in the patient's cells, compatible with predicted functional defect of his

mutation. Additionally, there was an increase in autophagic flux in XMEA myotubes. Interestingly, we observed that differentiation of XMEA myoblasts was altered, with increased myotube formation observed through a higher fusion index, which was not dependent on lysosomal acidification. Moreover, no variation in the expression of myogenic factors nor the presence of regenerating fibers in the patient's muscle were observed. Myoblast fusion is a tightly regulated process; therefore, the uncontrolled fusion of XMEA myoblasts might generate cells that are not as functional as normal muscle cells. Our data provide new evidence on the reason for predominant muscle involvement in the context of the XMEA phenotype. A new manuscript was published with these results in the journal Disease Models and Mechanisms *(Fernandes et al, 2020).*

PI: Mariz Vainzof - collaboration of the PI Merari Ramires Ferrari - Master student Stephanie de Alcantara Machado, and PhD. student Lucas de Santos Souza. International collaboration: Dr. Vincent Mouly (Institute of Myology, Paris).

A.2.2. Craniofacial development

Modelling Craniofacial syndromes in a dish: Due to the inherent difficulties to study human embryos, we have been establishing a protocol using induced pluripotent stem cells (iPSC) to model very early human craniofacial development, particularly at the embryonic stage that will give rise to neural crest cells. Neural crest cells (NCCs) contribute to the morphogenesis of several cell types and tissues during vertebrate embryonic development, including those of the craniofacial region. NCCs are originated from the neural plate border (NPB), undergoing a series of tightly regulated cellular events, such as epithelial-mesenchymal transition (EMT), migration, and differentiation. Disturbances in these processes are associated with several disorders, such as Treacher Collins and Richieri-Costa-Pereira syndromes, which are topics of study of our group. These observations highlight the importance of establishing experimental frameworks that recapitulate human NCC development. Here, we report that the E6 neural induction method transiently produces neural plate border-like cells (NBCs), which can be efficiently converted into NCCs. We show that NBC-to-NCC induction elicits a shift of cellular states

showing sequential molecular and cellular hallmarks of NCC specification and EMT, including downregulation of NPB factors and upregulation of NCC specifiers and EMT inducers, coupled with EMT-associated cadherin modulation. Investigation of these early NCC developmental steps *in vitro* will be useful in future research focusing on human development and disease *(in review in Stem Cell Reports).*

PI: Maria Rita Passos-Bueno - postdoctoral and undergraduate students: Gerson Kobayashi, Danielle Moreira, Camila Munso, Gabriella Hsia.

A.2.3. Neurodegeneration

Intracellular trafficking and protein aggregation in neurodegeneration

Disrupted neuronal intracellular trafficking is often related with protein aggregates present in the brain during neurodegenerative diseases such as Alzheimer's. Impairment of intracellular transport may be related to Rab proteins, a class of small GTPases responsible for trafficking of organelles and vesicles. Deficit in trafficking between the endoplasmic reticulum (ER) and Golgi apparatus mediated by Rab1 and 6 may lead to increased unfolded protein response (UPR) and ER stress and remodeling. In the study carried by Lima et al (2019) we analyzed the levels of Rabs 1 and 6 in the hippocampus of aged rats and in vitro during protein aggregation promoted by exposure to rotenone. Rab1 levels and cell viability decreased, whereas Rab6, UPR proteins and ER remodeling increased during protein aggregation, which were restored to normal levels after exogenous expression of Rab1.These results suggest that decrease of Rab1 levels contributes to ER stress and remodeling, while maintaining the elevated expression of Rab1 prevented impairment of cell viability during protein aggregation. In conclusion, Rab1 is a significant player to maintain intracellular homeostasis and its expression may mitigate ER dysfunction in the context of neurodegeneration-related protein inclusion.

PI: Merari Ferrari - students Nathan C.R. Lima, Thaiany Q. Melo, Karla Pacheco de Melo and the Lab Techinician Andressa Yurie Silvestre Sakugawa.

A.2.4. Autism Spectrum Disorder (ASD): pathophysiological mechanisms

Dysregulation of gene modules in early neurodevelopment in ASD: In addition to contributing to the identification of novel locus and to understand molecular mechanisms leading to clinical variability in ASD syndromes, we also have been interested in understanding the pathophysiology of ASD. In this context, we have analysed the transcriptome of iPSC-derived neuronal cells (neuroprogenitor cells, NPC and neurons) from an ASD cohort composed mostly of high-functioning individuals and from non-ASD individuals. None of the ASD patients carried variants of larger effect and monogenic inheritance was excluded. The transcriptome profiles from NPC best reflects in vivo neuronal tissue from fetal brains at 4–10 post-conception weeks (pcw) and are most likely to be of cortical identity, the neurons, after 4 weeks of differentiation from NPC, best reflect a mid-fetal period (16–24 pcw) and have an expression profile more similar to cerebellar cortex, evidencing a temporal progression of neuronal differentiation. We observed that ASD patients presented expression dysregulation of a module of co-expressed genes involved in protein synthesis in neuronal progenitor cells (NPC), and a module of genes related to synapse/neurotransmission and a module related to translation in neurons.The module related to synapse has been consistently found as upregulated in other transcriptome of ASD iPSC-derived neurons and has an expression profile more closely related to fetal brain while downregulated in postmortem brain tissue of ASD individuals. Also, the genes within this module are enriched by known ASD candidate genes. These results indicate a reliable association of this network to ASD and suggest that its dysregulation might occur in different directions across brain development in ASD individuals. Therefore, the expression pattern of this network might be used as a biomarker for non-monogenic forms ASD and should be experimentally explored as a therapeutic target *(Griesi-Oliveira et al., 2020).*

PI: Maria Rita Passos-Bueno - collaborators: Andréa Sertie; postdocs and students: Karina Griesi-Oliveira* and Angela May Suzuki. *Currently, a researcher at Instituto Einstein de Pesquisa

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. They were classified as ALS8 "severe" and "mild". The three "severe" individuals exhibited a typical progression of this disease, with onset around their 50's, and being more affected than the mild group at the time of physical evaluation. The "milds" consisted of two individuals that, in spite of being at the eighth decade of life, presented an ALS8 manifestation of very slow progression. Exome sequencing for all five patients identified only the ALS8 causing mutation, localized at *VAPB* gene (*VAPB* p.P56S).

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. Initially, were also able to rule out potential differences in clinical outcomes due to overexpression of VAPB, as in all ALS8 patients this gene was downregulated, both at RNA and protein levels, as previously reported. Surprisingly, we observed that the MN lineages from the "mild" presented cell death and energetic metabolism patterns similar to the controls, and different from the "severe" patients. The protein synthesis assay showed that the ALS8 milds had increased levels of pmTOR, 4EBP1 and RPS6, when compared to controls and the "severe" group. Additionally, the whole transcriptome revealed that both "mild patients" presented in common 43 upregulated genes and 66 downregulated, in comparison to the other two groups. Gene Ontology analysis showed that such differentially expressed genes converged for pathways associated with protein synthesis and protein addressing to endoplasmic reticulum.

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 (supervision, Mayana Zatz) and has recently been published in *Human Molecular Genetics*. *(Oliveira D, et al., 2020).*

PI: Mayana Zatz - students and collaborators: Danyllo OIiveira, PhD student; collaborator: Sergio Verkovsy-Almeida.

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. The manuscript is under review at Molecular Psychiatry.

PI: Mayana Zatz - Postdoc student : Thalita Figueiredo. Collaboration with the group of Prof. Fred Gage from Salk Institute, La Jolla, USA .

Mitigating variants in Duchenne muscular dystrophy

DMD is a X-linked disease affecting 1 in 3500-5000 boys worldwide. Muscle dystrophin absence leads to muscle degeneration, progressive weakness, loss of ambulation and death. Restoration of muscle dystrophin has been shown modest functional results, highlighting the need to find alternative therapies. On this respect, the study of genetic modifiers is of utmost interest. In 2015, our group described that Jagged1 upregulation on dystrophic dog's muscles *(Vieira et al., 2015)* lead to a mild phenotype through a dystrophin-independent mechanism. Since Jagged1 is a Notch ligand, this work opened new questions about Notch pathway modulation and its functional role in DMD pathology. Recently, we found that two mildly affected unrelated patients (one Brazilian and one Spanish) share a similar very rare variant in the *NOTCH* gene that leads to an amino acid change in the same domain of the Notch protein.This finding turned this genetic variant an important candidate for modulating DMD. Aiming to understand the underlying mechanism we undertook several experiments summarized below:

We generated iPSCs from these 2 unique unrelated mild DMD patients with as compared to IPSc from 2 unaffected relatives that carry the same *NOTCH* variant and 5 severely affected DMD patients. We performed and analyzed whole-exome sequencing (WES) of these two cases as compared with ~50 DMD patients, including the mild patients. We successfully differentiated all patient's iPSCs and 5 controls into skeletal muscle cells (SkM). Our preliminary results showed that *in vitro* muscle phenotype is concordant with the patient's clinical progression. We observed that canonical genes of the notch pathway are overexpressed in iPSCs-derived SkM as compared to severe patients and myogenic markers expression is higher in mild

patients iPSCs-derived SkM than in severe patients. We are currently using gene editing technique, CRISPR Cas9, to create isogenic lineages with or without specific variants.

This study is undertaken by a group of students under Mayana Zatz supervision and collaboration with two different labs of Harvard Medical School. Currently, the pos-doc student Felipe de Souza Leite is spending one year at Dr. Louis Kunkel and Dr. Olivier Pourquié with a BEPE fellowship from FAPESP. He plans to generate Pax7-reporter lines from our patients and to test the modulation of the notch pathway in muscles of two dystrophic models of zebrafish, named Sapje and Sapje-like.

This project is also partially funded by another grant: Muscular Dystrophies: New therapeutic strategies based on protective mechanisms, approved by Brazilian Health Ministry, CNPq process number: 40416120197.

PI: Mayana Zatz - Felipe de Souza Leite (postdoc), Joyce Esposito (PhD student); Igor Neves (Msc student), Raul Bortolin (postdoc), Danyllo Oliveira (PhD student) Carolini Kaid (postdoc), Vanessa Romanelli (postdoc), Claudia Ismania (PhD student), Danielle Moreira (postdoc), Bruno Torres (postdoc)
Collaborators: Dr. Louis Kunkel – Boston Children's Hospital, Boston, USA; Dr. Olivier Pourquié – Brigham and Women's Hospital, Boston, USA; Dr. Sergio Verjovski Almeida – Instituto Butantan, São Paulo, BRA.

A3. Epigenetics and diseases

A3.1. DNA methylation in congenital disorders

Prader-Willi and syndromes associated with obesity (syndromic obesity)

Chromosomal microarray analysis in 279 patients with syndromic obesity (obesity with additional phenotypes) was performed and reveals multiple recurring disease-causing CNVs and novel obesity-risk loci *(D'Angelo et al., 2018).* Whole-exome sequencing analyses of the unresolved cases are in progress.

Twin girls with an atypically severe PWS phenotype were reported on whom combined analysis of the clinical features and molecular studies identified a blended phenotype likely explained by a dual molecular diagnosis of Prader-Willi and Pitt-Hopkins syndrome *(Jehee et al. 2017).*

Chromosomal microarray analysis in 279 patients with syndromic obesity (obesity with additional phenotypes) was performed and revealed multiple recurring disease-causing CNVs and novel obesity-risk loci. The CNVs detected affect several currently known candidate genes, such as *HDAC4*, *MYT1L*, *SIM1*, *POU3F2*, *EHMT1*, *SH2B1*, and *RAI1*. We also proposed novel candidates, for instance *TAS1R3*, *GAS6*, *ALOX5AP*, and *SGCG*/*MIPEP*. In addition, three relatively small CNVs with uncertain significance affected genes previously mapped to CNV loci detected in patients with syndromic obesity (*PLIN2*, *LINGO2* and *MACROD2*). These results underscore that the locus heterogeneity in syndromic obesity due to diagnosis for patients can be challenging. CMA provides an important diagnostic value and may help defining new rare genetic forms of obesity . We are now analyzing by whole-exome sequencing the unresolved cases in collaboration with.

PI: Celia P. Koiffman- collaboration Prof Dr Carla Rosenberg

Epigenetics in NSCLP

We have recently initiated epigenetic studies in non-syndromic cleft lip and palate (NSCLP), a complex disorder with unexplained high heritability. In our previous report, we have shown that NSCLP individuals present an epigenetic signature, a finding that was validated in different and independent populations *(*Alvizi et al., 2017*).* We have now found a differentially hypomethylated region in mir132 after reanalysis of the Brazilian NSCLP methylome using a different pipeline. Notably, altered epigenetic marks in this locus were found in 21-26% of the affected individuals as compared to only 10% of the control population. We have shown that *mir132* hypomethylation leads to *mir152* upregulation. *In vivo* analysis using zebrafish embryos revealed that *mir152* upregulation leads to craniofacial impairment affecting analogue structures to mammalian palatal defects. Also, we demonstrated that zebrafish embryonic hypoxia leads to *mir152* upregulation

combined with *mir152* hypomethylation and also analogue palatal alterations. By sequencing strategies, we found no obvious genetic variation associated to *mir152* epivariation. We therefore suggest that hypomethylation of mir152, which can be induced by hypoxia in early pregnancy, is a novel and frequent predisposing factor to NSCLP. This paper is being evaluated at eLife and published in bioRxiv *(preprint first posted online Nov. 22, 2019)*.doi:http://dx.doi.org/10.1101/850016

PI: Maria Rita Passos-Bueno - postdocs, graduate and undergraduate students: Lucas Alvizi, Gerson Kobayashi, Luciano A. Brito, Sofia L. Ramos, Camila B.F. da Silva, Barbara Bischain.

DNA Methylation in KDM5C -Intellectual Disability

Mutations in *KDM5C* (lysine (K)-specific demethylase 5C) were causally associated with up to 3% of X-linked intellectual disability (ID) in males. By exome and Sanger sequencing, a novel frameshift *KDM5C* variant was identified in two monozygotic twins and their older brother, which was inherited from their clinically normal mother, who had completely skewed X-inactivation. DNA methylation (DNAm) data were evaluated using the Illumina 450K Methylation Beadchip arrays. Comparison of methylation levels between the three patients and male controls identified 399 differentially methylated CpG sites, which were enriched among those CpG sites modulated during brain development. The DNAm changes did not differ between the monozygotic twins nor between them and their older sibling, all presenting a global hypomethylation, similar to other studies that associated DNA methylation changes to different *KDM5C* mutations. The remarkable similarity between the methylation changes in the monozygotic twins and their older brother is indicative that these epigenetic changes were mostly driven by the *KDM5C* mutation *(Guerra et al. 2019)*.

PIs: Ana Krepischi and Angela Morgante; graduate student: Silvia Costa.

A.3.3. How DNA damage and Genome Instability can be implicated in human disease?

Part of our work deals with the mechanisms of DNA damage and mutagenesis in xeroderma pigmentosum (XP) cells. Xeroderma pigmentosum is a human syndrome with high frequency (2000 times increased compared to normal people) of skin tumor due to sunlight damage. Recent work have revealed how XP cells from the variant type (XP-V: deficient in DNA polymerase eta, a translesion polymerase) respond to UVA-light, with special attention on how oxidative stress are high on these cells *(Moreno et al, 2019).* Also an exome sequencing project was applied to understand the mutagenesis induced by UVA-light in XP-V cells. Mutation signatures have revealed interesting features for these cells *(Moreno, de Souza et al, 2020)*. We have also observed that nucleotide excision repair (NER) ERCC2/XPD protein is important in cells' resistance responses to oxidative stress induced DNA damage *(Lerner et al, 2019).*

Also the molecular diagnosis of XP patients in Brazil allowed us to present the first profile of mutations affected in the XP genes in this country, with clear prevalence of mutations in *XPC* and *XPV/POLH* genes. Interestingly, many not previously mutations were detected in these families *(Santiago et al, 2020)*; in collaboration with Dr. Maria Isabel Achatz, HAC Camargo, SP. Moreover, ancestry studies of two mutations in the *XPV/POLH* gene previously detected in a Brazilian genetic cluster, identified that at least one of them has familial links with patients previously described in Spain *(Castro et al, 2020).*

In collaboration with Dr. Alain Sarasin (IGR, Villejuif, France), we have also identified large deletions in immunoglobulin genes, when XP-V patients were studied *(Lerner et al, 2020)* and a predisposition of XP-C patients to leukemia, associated with p53 polymorphism (Sarasin et al, 2020). Also with Dr. Sarasin and Dr. Januário Bispo Cabral-Neto (UFRJ, RJ), we presented a review on the XP patients' phenotype and social behavior *(Cabral-Neto et al, 2019).* Another review describing the interface of NER and base excision repair (BER) mechanisms *(Kumar, Moreno et al, 2020)* was written in collaboration with Dr. Bennet Van Houten (Pittsburgh, USA).

DNA repair mechanisms are also associated with tumor resistance to genotoxic chemotherapeutic drugs. In the last period, we have investigated how 3-

D cultures of breast cancer cells respond to cisplatin treatment. Interestingly, we found that translesion synthesis (DNA polymerase zeta) and ATR kinase are associated with cells resistance to this drug, enlightening potential targets that could potentiate therapy *(Gomes et al, 2019).* Also, a detailed study with lung tumor cells revealed a balance of DNA repair (ERCC1 protein) and oxidative stress (NRF2/GSH) responses in the resistance to cisplatin treatment *(Silva et al, 2019).*

Finally, the exome sequencing of mutated mice of the animal facility of the Institute of Biomedical Sciences, USP, revealed significant phenotypes association with mutated genes, as well as identified mice models related to human diseases *(Mazzoneto et al, 2019), (Yamamoto et al, 2019)*; and the relation of NEK kinases with DNA repair processes was investigated in collaboration with Dr. Jorg Kobarg-UNICAMP, SP *(Melo-Hanchuk et al, 2019), (Peres de Oliveira et al, 2020).*

PI: Carlos F. Menck - Postdoc student: Clarissa R. Ribeiro Rocha, Luciana Rodrigues Gomes, Natalia Cesar Moreno; PhD studest: Matheus Molina Silva, Tiago Antonio de Souza, Davi Jardim Martins. Collaboration: Dr. Maria Isabel Achatz, HAC Camargo, Dr. Alain Sarasin (IGR, Villejuif, France), Dr. Januário Bispo Cabral-Neto (UFRJ, RJ) Dr. Bennet Van Houten (University of Pittsburgh, USA), Dr. Jorg Kobarg (UNICAMP, SP).

B. THE 80plus PROJECT

SABE and 80plus whole genome sequence dataset

The ongoing analyses of the whole-genome sequencing dataset of the elderly cohorts (SABE and 80+), two challenges were faced: selecting a set of clinically relevant genes to identify pathogenic variants associated to monogenic diseases and integration of the available clinical phenotypes to support interpretation. We have found 32 variants with potential loss of function and classified as pathogenic and of monoallelic inheritance, in 924 genes associated to

paediatric disorders, carried by forty individuals of SABE cohort. These results were presented in the 2018 ASHG. This study was expanded to analyze over 4 thousand genes associated to Mendelian disorders (OMIM). This ongoing project includes manual curation for pathogenicity reclassification and cross referencing with clinical phenotypes. A PhD project is being conducted to characterize pharmacogenomics variants, allelic and haplotypic distribution in genomic segments with local ancestry inference (SABE and 80+ cohorts), in collaboration with University of Toronto. Following up elderly ascertained in 80+ cohort is being performed to improve interpretation of secondary findings in actionable genes (ACMG-59 list). We have published the neuroimaging evaluation of SABE and 80+ cohorts with Dr. Edson Amaro's team (Albert Einstein Hospital). The data derived from whole-genome sequencing of the elderly were also helpful for identification of novel loci associated to body mass index and structural variant in glycoforin gene family, both studies submitted for peer-reviewed journals and currently available as pre-prints (bioRXiv). In collaboration with the reproductive genetics group (Prof. Bianca Bianco, FMABC), the analyses of variants found in women that were refractory to in vitro fertilization treatment were recently published after contribution of HUG-CELL databases and bioinformatics pipelines. This project represents a multicenter project with the involvement of Brazilian and international collaborators. A manuscript with the genome data of this cohort will be submitted soon to publication.

PI - Mayana Zatz and Michel N. Naslavasky

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 (UFMG); Esteban Parra (University of Toronto); Stephen Scherer (Sick Kids Hospital, Toronto).

C. THERAPIES IN GENETIC DISORDERS

C1. Pre-Clinical studies with murine stem cells

Muscle satellite cells and impaired late stage regeneration in different murine models of muscular dystrophies

Satellite cells (SCs) are the main muscle stem cells responsible for its regenerative capacity. In muscular dystrophies, however, a failure of the regenerative process results in muscle degeneration and weakness. To analyze the effect of different degrees of muscle degeneration in SCs behavior, we studied adult muscle of the dystrophic strains: *DMD*^{mdx}, *Large*^{myd}, *DMD*^{mdx}/*Large*^{myd} with variable histopathological alterations. Similar results were observed in the dystrophic models, which maintained normal levels of PAX7 expression, retained the Pax7-positive SCs pool, and their proliferation capacity. Moreover, an elevated expression of MYOG, an important myogenic factor, was also observed. The ability to form new fibers was proved through the presence of dMyHC positive regenerating fibers. However, those fibers had incomplete maturation characteristics, such as small and homogenous fiber caliber, which could contribute to their dysfunction. We concluded that dystrophic muscles, independently of their degeneration degree, retain their SCs pool with proliferating and regenerative capacities. Nonetheless, the maturation of these new fibers is incomplete and do not prevent muscle degeneration. Taken together, these results suggest that improvement of late muscle regeneration should better contribute to therapeutic approaches.

The manuscript “A Muscle satellite cells and impaired late stage regeneration in different murine models for muscular dystrophies” was published in Scientific Reports *(Ribeiro et al., 2019).*

PI: Mariz Vainzof - Master student Antonio F. Ribeiro Junior, Master student Lucas S. e Souza and PhD Camila F. Almeida.

Skeletal muscle injury by electroporation – a model to study degeneration/regeneration pathways in muscle

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

Here we proposed 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. Three days after electroporation, the muscle shows prominent signals of degeneration, like areas of necrosis and infiltration of macrophages, followed by regeneration, observed by the presence of centrally nucleated myofibers. After five days the regeneration is very active, with small dMyHC positive fibers. Fifteen days later, we observe a general regeneration of the muscle, with normal sized fibers after 60 days. 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. This data was published in Methods in Molecular Biology *(Almeida and Vainzof, 2020).*

PI: Mariz Vainzof - PhD student Camila de Freitas Almeida.

Faster regeneration associated to high expression of Fam65b and Hdac6 in dysferlin-deficient mouse

Dysferlin is a sarcolemmal muscle protein associated with the processes of membrane repair, trafficking, and fusion of intracellular vesicles and muscle regeneration. Mutations in the DYSF gene cause clinically distinct forms of muscular

dystrophies. The dysferlin-deficient SJL/J mouse model presents a reduction of 85% of the protein but shows mild weakness and discrete histopathological alterations. To study the effect of dysferlin deficiency in the muscle regenerative process, we used a model of electrical injury by electroporation to induce muscle degeneration/regeneration in the SJL/J mouse. The relative expression of the genes Pax7, MyoD, Myf5, and Myog was accompanied by the histopathological evaluation during muscle recovery at different time points after injury. We also investigated the effects of dysferlin deficiency in the expression of genes encoding FAM65B and HDAC6 proteins, recently described as forming a tricomplex with dysferlin at the beginning of myoblast differentiation. We observed an altered time course through the process of degeneration and regeneration in dysferlin-deficient mice, with remarkable regenerative capacity characterized by a faster and effective response in the first days after injury, as compared to the WT mice. Also, dysferlin deficiency seems to significantly alter the gene expression of Fam65b and Hdac6 during regeneration, since higher levels of expression of both genes were observed in dysferlin-deficient mice. These results need further attention to define their relevance in the disease mechanism. This data were published in Journal of Molecular Histology *(Ishiba et al. 2019).*

PI: Mariz Vainzof - Master student Renata Ishiba and students from the lab.

Satellite cells deficiency and defective regeneration in dynamin2-related centronuclear 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. A manuscript has been submitted for publication.

PI: Mariz Vainzof - PhD student Camila F Almeida. International collaboration: Marc Bitoun, Sorbonne Université, INSERM, Institute of Myology, Centre of Research in Myology, Paris.

C2. Safety-related concerns in cell therapy

Clinical Translation of Mesenchymal Stromal Cell Therapy for Graft Versus Host Disease

We have previously reported that mesenchymal stromal cells (MSC) may exert pro-tumorigenic effects when in close contact with tumor cells, an issue that must be carefully considered when employing these cells in cancer therapy protocols. In a new study (Godoy et al. Frontiers Cell & Dev. Biol. 2019), we discussed the immunomodulatory properties that support the therapeutic use of MSCs for the treatment of graft versus host disease (GVHD) in cancer patients and contextualized the main clinical findings of recent clinical trials using these cells. Hematopoietic stem cell (HSC) transplantation is the paradigm of stem cell therapy for the treatment of cancer patients. However, GVHD is a complication commonly seen in patients undergoing allogeneic HSC transplantation. The immune cells derived from the grafted stem cells attack the tissues of the recipient patients, including those of the skin, liver, eyes, mouth, lungs, gastrointestinal tract, neuromuscular system and genitourinary tract, which can lead to severe morbidity and mortality. Although treatable by systemic administration of corticosteroids, effective responses are not

achieved for a significant proportion of patients, a condition associated with a poor prognosis. The use of MSCs as an alternative to steroid-refractory GVHD has improved in the past decade, but the results are still controversial. Some studies have shown improvement in patients' quality of life after treatment with MSC, while others have found no significant benefits. In addition to variations in the study design, discrepancies in the protocols for isolation, characterization and *ex vivo* manipulation of MSCs are responsible for inconsistent therapeutic results. Safety and tolerability of MSC infusions, however, has been attested in the vast majority of these trials, with no significant complications reported. Critical parameters for the clinical translation of CTM were also highlighted, including the consistent production of CTM according to Good Manufacturing Practices (GMPs) and informative potency tests for product quality control *(Godoy et al. 2019).*

PI: Oswaldo Keith Okamoto - collaboration with the clinical researchers Juliana A. P. Godoy, Raquel M. A. Paiva, Aline M. Souza, Andrea T. Kondo, Jose M. Kutner (Hosp. Israelita Albert Einstein).

C3. Other therapeutic approaches

Safety, Tumor Reduction, and 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. However, translating this approach to humans requires pre-clinical trials in another immunocompetent animal model. Here, 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. The paper was recently published *(Kaid et al., 2020 Molecular therapy, May 6;28(5):1276-1286).*

PI: Mayana Zatz - students and collaborators: Carolini Kaid (postdoc), Raquel Azevedo dos Santos Madi, Renato Astray, Ernesto Goulart (postdoc), Luiz Carlos Caires-Junior (postdoc), with the collaboration of Oswaldo Keith Okamoto and students at different levels from different centers.

C.4 Tissue engineering

“Adult and iPS-derived non-parenchymal cells regulate liver organoid development through differential modulation of Wnt and TGF-β”

Liver organoid technology holds great promises to be used in large scale population-based drug screening and in future regenerative medicine strategies. Recently, some studies reported robust protocols for generating isogenic liver organoids using liver parenchymal and non-parenchymal cells derived from induced pluripotent stem cells (iPS) or using isogenic adult primary non-parenchymal cells. However, the use of whole iPS-derived cells could represent great challenges for a translational perspective. Here, we evaluated the influence of isogenic versus heterogenic non-parenchymal cells, using iPS-derived or adult primary cell lines, in the liver organoid development. We tested four groups comprised of all different combinations of non-parenchymal cells for the liver functionality in vitro. Gene expression and protein secretion of important hepatic function markers were evaluated. Additionally, liver development-associated signaling pathways were tested. Finally, organoid label-free proteomic analysis and non-parenchymal cell secretome were performed in all groups at day 12. We show that liver organoids generated using primary mesenchymal stromal cells and iPS-derived endothelial

cells expressed and produced significantly more albumin and showed increased expression of CYP1A1, CYP1A2, and TDO2 while presented reduced TGF-β and Wnt signaling activity. Proteomics analysis revealed that major shifts in protein expression induced by this specific combination of non-parenchymal cells are related to integrin profile and TGF-β/Wnt signaling activity. Aiming the translation of this technology bench-to-bedside, this work highlights the role of important developmental pathways that are modulated by non-parenchymal cells enhancing the liver organoid maturation. The results were published *(Goulart et al., Stem cell research therapy, 2019).*

PI: Mayana Zatz – students and collaboration: Ernesto Goulart PhD, Luiz Caires-Junior (postdoc) with the collaboration of Prof. Silvano Raia (FMUSP) and Prof. Dr. Peter I. Lelkes (Temple University).

“3D bioprinting of liver spheroids derived from human induced pluripotent stem cells sustain liver function and viability in vitro.”

“The liver is responsible for many metabolic, endocrine and exocrine functions. Approximately 2 million deaths per year are associated with liver failure. Modern 3D bioprinting technologies allied with autologous induced pluripotent stem cells (iPS)-derived grafts could represent a relevant tissue engineering approach to treat end stage liver disease patients. However, protocols that accurately recapitulates liver's epithelial parenchym*a* through bioprinting are still underdeveloped. Here we evaluated the impacts of using single cell dispersion (i.e. obtained from conventional bidimensional differentiation) of iPS-derived parenchymal (i.e. hepatocyte-like cells) versus using iPS-derived hepatocyte-like cells spheroids (i.e. three-dimensional cell culture), both in combination with non-parenchymal cells (e.g. mesenchymal and endothelial cells), into final liver tissue functionality. Single cell constructs showed reduced cell survival and hepatic function and unbalanced protein/amino acid metabolism when compared to spheroid printed constructs after 18 days in culture. In addition, single cell printed constructs revealed epithelial-mesenchymal transition, resulting in rapid loss of hepatocyte phenotype. These results indicate the advantage of using spheroid-based bioprinting, contributing to improve current liver bioprinting technology towards future regenerative medicine applications and liver

physiology and disease modeling". The results were published in Biofabrication *(Goulart et al., 2020).*

In the same period, Ernesto received the ISSCR honorable mention award at the annual meeting, held in July 2019 in Los Angeles - USA, for his abstract presented at the congress, entitled: DEVELOPMENT AND IN VITRO CHARACTERIZATION OF AN IPS-DERIVED FUNCTIONAL LIVER ACCESSORY VASCULAR SHUNT. Currently, Ernesto is developing his postdoctoral project at our CEPID in the project: Development of universal hepatic organoids derived from iPS cells (FAPESP 2019/18469-1).

PI: Mayana Zatz – students and collaboration: Ernesto Goulart PhD, Luiz Caires-Junior (postdoc) with the collaboration of Prof. Silvano Raia (FMUSP) and Prof. Dr. Peter I. Lelkes (Temple University).

Hepatic bioengineering technologies aiming the future of human organs transplantation

Hepatic bioengineering technologies have been developed aiming the future of human organs transplantation. New tissue engineering tools have been designed to produce decellularized organs (i.e. scaffolds) which could be recellularized with human cells. However, protocols for inducing better liver scaffolds recellularization need to be ameliorated. The aim of the present investigation is to improve the hepatic recellularization by coating liver scaffolds with HepG2-conditioned medium (HepG2-CM). Wistar rat livers were collected and cannulated by portal vein (PV) and vena cava (VC). They were decellularized by perfusion of 1% of Triton-X solution with 0.05% NaOH. The samples were analyzed by immunohistochemistry, scanning electronic microscopy (SEM), histology and proteomic assays. Human iPSCs and differentiated cells were characterized by immunofluorescence staining (IF), flow cytometry, RT-qPCR. The anatomical organization of hepatic extracellular matrices (ECM) was preserved after the decellularization procedure. The liver scaffolds had no nuclei and cellular residues. Proteomic analysis suggested that pre-coating liver scaffolds with HepG2-CM enriched acellular liver ECM. Pre-coated decellularized livers were recellularized with HepG2, hiPSCs-derived mesenchymal stem cells (hiMSCs) and human aortic endothelial cells (HAEC) for up to 5 weeks

and an improved liver recellularization was observed. Further studies are still needed but our preliminary results suggest that pre-coating of livers-ECM significantly improved recellularization, revealing the positive effects of liver ECM and CM components association.

PI: Mayana Zatz - This project is undertaken by the postdoc student Luiz Caires-Junior and will be submitted to publication soon.

Etoposide-induced hepatocyte-like cells maturation mechanisms

The investigation about the etoposide-induced hepatocyte-like cells maturation mechanisms was done within two stages: (i) determination of non-toxic concentrations of etoposide; and (ii) characterization of hepatic differentiation and maturation molecular markers.

The first stage was developed through a dose-response assay with HLCs and hepatocellular carcinoma cells (HepG2). The toxicity was evaluated using the Cell Proliferation Kit II (XTT) (Merck ®). Etoposide concentrations greater than 30 uM were toxic for both cell lines but more toxic for HepG2 cells (Figure 1), indicating that etoposide induces apoptosis mainly in proliferative cells, with poorly understood effects in non-proliferative cells as HLCs.

The second stage was developed with treated and non-treated HLCs in different timepoints after treatment. The gene expression of characteristic hepatocyte markers (*ALB*, *AHR*, *CYP1A2* e *CYP3A4*) was evaluated by RT-qPCR. Significant difference in *ALB* gene expression in treated HLCs *vs.* controls and enhancing significance over time indicates that the use of etoposide causes maturation, and that this maturation is progressive.

PI: Mayana Zatz - Kayque Alves Telles Silva (PhD student).

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 three sequencing apparatus (ABI 3730 DNA Analyser sequencer (Applied Biosystems), 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. We expect that competitive sequencing services will be possible to be offered with this new equipment. The sequencing facility has been organized following the EMU/FAPESP guidelines <http://genoma.ib.usp.br/servicos/sequenciamento -de-nova-geracao-ngs/comite>. However, in 2019-2020 we have been 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) Private Tests: 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. 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.

In order to expand the number of requests for genetic testing during 2019, we have launched an advertisement on 28th February, the Rare Disease Day, informing the people about the relevance of the ascertained diagnosis of rare

disorders and about the availability of NGS-based tests at a reasonable price. Several other educational advertisements were conducted thereafter. We observed a sustained increase of tests throughout the year, as observed by comparing the number of NGS-based tests performed by HUG-CELL in 2018 (n=359) and in 2019 (n=591). Unfortunately, this favorable scenario has been changed by the current Covid-19 pandemic, but we intend to use different strategies to recover the demand during the remaining months of 2020. Nevertheless, during the last year, we have performed 4,959 genetic tests (MLPA/disease specific CNVs, Triple/PCR for expansion, NGS panels, NGS exome, aCGH). The quality and reliability of our genetic tests have been certified yearly by the European Molecular Genetics Quality Netwok (EMQN). Additionally, about 10,711 Sanger sequencing reaction tests were performed. These sequencing reactions were ordered by 202 researchers (56% from USP, 39% of other governmental universities; 5% 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) Research/non-paid tests. A total of 8,105 research or non-paid tests (NSG, Sanger Sequencing, aCGH, MLPA, cytogenetics, methylation 15q) were performed at HUG-CEL for 9 researchers. Most of these samples (˜90%) were received by our non-profit laboratory and processed at CEGH-CEL sequencing facility, while the remaining 10% (cytogenetics and array-CGH) were performed in the lab of some of our PIs.

d) Genetic counseling service: About 1,653 consultations were performed by our team (277 paid, 1,376 non-paid). About 90% of them were offered at the HUG-CEL and the remaining ones in other hospitals in Sao Paulo or in other regions of Brazil. Genetic counseling of families with affected patients includes diagnosis, identification and testing of “at-risk carriers”, orientation about prognosis and management and genetic counseling. More than 1,300 written reports, including results of genetic tests, were provided to attending individuals. As a consequence of the pandemia and demand by the families, we have now systematically offered genetic counseling services online using Zoom platform. The experience has been very positive and we have received very good feedback from the families.

e) 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 77 patients with different genetic disorders and 14 controls (267 clones) in the last 5 years.

f) 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 609 Brazilian healthy individuals that are part of the Sao Paulo city elderly cohort studied at our center (SABE cohort). This data has provided valuable information for the interpretation of pathogenicity of variants identified in genetic tests in Brazil and around the world. Due to the benefit to the community, we will also include in the ABraOM website the SABE-WGS-1171 dataset. It comprehends whole genome sequencing variants of 1,171 unrelated individuals from SABE cohorts enrolled in 2010-2012, based on human reference hg38. Since this new cohort has partial overlap with the 609 exomes, but is larger than the previous one, we are going to implement new engines of searching data and a faster method for viewing variants.

DesBraVar is a software that is being developed 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 - ZEN). 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. In 2018, we started to develop the pipelines to process the sequencing data and the programs to display and analyze these data on a web interface. Since the first semester of 2019, bioinformatic processes are being validated and the web interface is being adjusted to perform more complex analyzes and facilitate usage. We forecast that in the second semester of 2020 the database will be put to use by the analysts of CEGH-CEL. At first, the use will be restricted to this group 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, in the first semester of 2021. We will use the database for sampling storage of the Brazilian population, the genomes of the SABE database, as well as cohorts of patients studied in the CEGH-CEL center. Subsequently, over the next semesters, new tools will be implemented such as trio analysis, and analysis based on a genetic inheritance pattern.

g) RT-LAMP for COVID-19: We are standardizing the amplification of SARS-COV-2 through the RT- LAMP (Reverse Transcription Loop-mediated Isothermal Amplification). Furthermore, we also have established a collaboration with Dr. Shaker Chuck Farah (Instituto de Quimica, USP) for the production of the RT-LAMP enzymes (reverse transcriptase III and Bst) as well as with Fleury laboratory, that will provide the tested RNAs of infected individuals by the standard gold RT-qPCR. Saliva has recently become an alternative sample source for SARS-COV-2 testing, which represents an excellent alternative for nasofaringe or orofaringe swabs, as auto-collection could be an easy option. With this aim, we are also standardizing a solution that inactivates saliva inhibitors to conserve the virus and its RNA to be tested.This project has been recently approved by FAPESP-COVID-19 initiative.

h) 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 is administered at Fundação Faculdade de Medicina USP and Fundação Universidade de São Paulo.

PART 3

EDUCATION OUT REACH

A. High School Support Program

A.1. Project: Laboratory classes at school <http://www.genoma.ib.usp.br/pt-br/educacao-e-difusao/nossosprojetos/parcerias-com-diretorias-de-ensino/aulas-praticas-nas-escolas > We have established laboratory classes within individual schools for periods of 3 weeks, where teachers were assisted in leading laboratory classes related to the cellular basis of Genetics, including the use of microscopes and 6 different practical kits. 16 hours of technical and pedagogical support to 60 High School teachers were delivered **(annex 4.1);** 79 students were trained to act as monitors during the time the laboratory is installed in their schools **(annex 4.2);** 35 High Schools were assisted, from July/2019 to June/2020 **(annex 4.3)** and around 42 thousand students were benefited.

A.2. Instructional support project <http://www.genoma.ib.usp.br/educacao-e-difusao/nossos-projetos/parceriascom-diretorias-de-ensino/material-instrucional-nas-escolas > The objective of the project is to help teachers to over-come some of the teaching and learning difficulties presented by the abstract nature of some Genetics concepts. We provided instructional support material to facilitate the teaching and learning processes and established three loan centres, which currently provide instructional material to more than 100 teachers each year. In 2020 teachers' orientation didn't occur because of the Covid-19 pandemic disease.

A.3. Scientific Exhibitions

A.3.a. The "Giant Cell" <http://www.genoma.ib.usp.br/pt-br/educacao-e-difusao/nossosprojetos/celula-gigante> is a scenic cell amplified 130,000 times and a set of complementary activities designed to facilitate the understanding of cell concepts. It was exhibited in Osasco Plaza Shopping, São Paulo, on August, 12Th to 16th, from 9 a.m. to 7 p.m. (2,400 visitors) and on USP Profession Fair, Parque Cientec, São Paulo, on August, 22nd to 24th, 2019, from 9 a.m. to 5 p.m. (2,300 visitors).

A.3.b. The Scientific exhibition "Light and Life" (USP goes to your school project II) <http://www.genoma.ib.usp.br/pt-br/educacao-e-difusao/nossosprojetos/ parcerias-

com- diretorias-de-ensino/usp-vai-a-sua-escola> is an interdisciplinary exhibition of Biology and Physics that interrelates concepts from these two disciplines such as light and its importance for biological processes. The Luz e Vida Exhibition was exhibited at Osasco Plaza Shopping, Osasco, SP, on August 12nd to 16th, 2019, from 9 am to 7 pm – (2,400 visitors).

B. Projects having the general public as target

CEGH-CELL has a dissemination team that produces scientific dissemination content for the general public. **YouTube**, **Facebook** and **Instagram** are the main media where the content is served, under the name of **genomaUSP**. The objective is to satisfy people's hunger for quality knowledge and information, in addition to creating a proximity to the public's relationship with science and scientists. On YouTube <https://www.youtube.com/genomausp>, there are videos in 5 formats: "**ABC genoma**", with series of videos on a specific topic treated from different perspectives; "**Direct from the Genoma**", with news about CEGH-CELL research; "**Speech Geneticist**", with interviews by researchers on a variety of issues related to genetics; "**Specials**", with videos about projects and commemorative dates, and "**Courses**", where there are recordings of courses, workshops or lectures that took place at CEGH-CELL. On **Instagram**<https://www.instagram.com/genoma.usp/>, YouTube videos are released and posts are made on subjects related to CEGH-CELL activities, such as cancer, muscular dystrophies or even basic content on genetics. For Stories, there is the "**Laboratory Life**" format, which opens the doors of the laboratory to the public based on the explanation of a specific object by a scientific initiation or graduate student. Throughout the speech, he delves into the routine and research in which the young scientist is inserted, without losing lightness and good humor. On **Facebook** <https://www.facebook.com/pordentrodogenoma/> there is also the dissemination of YouTube videos and content about CEGH-CELL that appear in journalistic media, in addition to the reproduction of posts made for Instagram. The number of CEGH-CELL media followers continues to grow and, until May 2020, correspond to 11,251 on Facebook, 10,800 on Instagram and 1,440 on YouTube

Annex 1

Publications in peer reviewed journals, books and patent

From July 2019 until June 2020, our group has published **60** journal articles (all listed below), **3** books or book chapters, **12** abstracts in National meetings, and **21** abstracts in International meetings. During this period, our graduate students submitted **5** Master Theses and **10** Doctoral Dissertations. About **34** conferences, lectures and symposia were done by our time.

1. Articles

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2. Books and Book Chapters

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Annex 2
Meetings, Conferences, Lectures

1. Abstracts: National Meetings

1. Barros JS, Aguiar T, Costa SS, Barbosa AC, Rivas MP, Novak E, Odone Filho V, Toledo RC, Cypriano M, Carraro DM, Cunha IW, Costa CML, **Rosenberg C**, **Krepische ACV.** Insights into a rare embryonal liver cancer open novel avenues of study: Not all hepatoblastomas In: **65º Congresso Brasileiro de Genética**, 2019, Águas de Lindóia. 65º. Congresso Nacional de Genética - Abstracts. 2019, Sociedade Brasileira de Genética.

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65th Brazilian Congress of Genetics abstracts. , 2019. v.65. p.395

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2. Abstracts: International Meetings

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2. **Caires-Junior LC**. HEPG2 Conditioned Medium Improves Hepatic Scaffold Recellularization. **ISSCR 2019 - Annual Meeting** Congresso de Células Tronco -

International Society for Stem Cell Research . - Los Angeles, EUA, 2019.

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6. **Goulart E**. Development and *in vitro* characterization of a bioartificial hiPS-derived liver accessory vascular shunt (poster), **Congresso: ISSCR 2019** - Annual meeting - Los Angeles, EUA, 2019.

7. **Goulart E.** - 3D bioprinting liver organoid using hepatic spheroids derived from human induced pluripotent stem cells sustain liver function and viability in vitro (poster). **Congresso: ISSCR 2020** - Annual meeting – Online, 2020.

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12. Nascimento S, Castellar DCO, Alvarez KCA, Alves-Paiva RM, Godoy JAP, Bortolini MAT, Castro R, Kondo AT, **Okamoto OK**, Kutner JM. Patient Clonal Chromosomal Alterations during Human Multipotent Mesenchymal Stromal Cell Culture. In: **AABB Annual Meeting,** 2019, San Antonio. Abstract compilation book, 2019.

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20. Silva MC, Lago JH, Brocchi M, **Netto LES**, Oliveira MA. A new Prx inhibitor from Brazilian biodiversity with antibacterial properties In: 26th Annual Conference SfRBM, Las Vegas. Free Radical Biology and Medicine. Elsevier, 2019. v.145. p.S19 –

21. Tairum CA, Silva MC, Breyer CA, Gomes F, Oliveira MA; **Netto LES.** Analysis of the Role of Thr/Ser of Tsa1 Catalytic Triad in Hyperoxidation Process In: 26th Annual Conference SfRBM, 2019, Las Vegas. Free Radical Biology Medicne. , 2019. v.145. p.S40

3. Conferences, Symposia, Round Tables, Lectures

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2. Alvizi L, Brito LA, Bischain B, Silva CBF, Ramos SLG, Kobayashi GS, Wang J, **Maria Rita Passos-Bueno*** . mir152 hypomethylation, potentially triggered by embryonic hypoxia, as a mechanism for non-syndromic cleft lip/palate, In **Gordon Research Conference** on Craniofacial Morphogenesis and Tissue Regeneration, Lucca - Itália, Fevereiro 23 e 28, 2020. (* apresentação em forma de painel)

3. Brito LA, Musso CM, Hsia G, Kobayashi GS, Wang J, **Passos-Bueno M.R**. Contribution of rare variants in he noncanonical Wnt/planar cell polarity pathway genes to nonsyndromic cleft lip and/or palate, In **American Society of Human Genetics, 2019**, Houston- EUA, 15-19, outubro.

4. Dias IO, **Ferrari MFR**. Analysis of tau protein hyperphosphorylation in olfactory bulb of a mouse model of down syndrome: association with alzheimer´s disease. In: **27 Simpósio Internacional de Iniciação Científica da USP**, 2019, São Paulo. 27 SIICUSP.

5. Gianetti NG, **Ferrari MFR**. . Analysis of autophagy in a mouse model for alzheimer´s disease prior na during hyperphosphorylation of tau. In: **27 Simpósio Internacional de Iniciação Científica da USP**, 2019, São Paulo. 27 SIICUSP, 2019.

6. Henrique AM, **Ferrari MFR**. . Mitophagy- and autophagy-related proteins are reduced before protein aggregation in the hippocampus of a mouse model of Alzheimer?s diseaseed proteins are reduced before protein aggregation in the hippocampus of a mouse model of Alzheimer?s disease. In: **XXXIV Reunião Anual da FeSBE**, 2019, Campos do Jordão. 34 FeSBE, 2019.

7. Henrique AM, **Ferrari MFR.** Mitophagy – and autophagy related proteins are reduced before protein aggregation in the hippocampus of mouse model of alzheimer´s disease. In: **27 Simpósio Internacional de Iniciação Científica da USP**, 2019, São Paulo. 27 SIICUSP.

8. **Mingroni-Netto RC. The demographic history of Afro-descendant quilombo ´populations in the Vale do Ribeira Region (São Paulo, Brazil)**, 2019. Conference presented in the Seminars in Biodiversity and Evolution, University of Porto, Portugal, CIBIO - Research Center in Biodiversity and Genetic Resources - Campos de Vairão;

9. **Mingroni-Netto RC.** Experience of molecular studies with Brazilian families with hearing loss. Conference presented in the **Seminars of the Genetic** Unit of the Hospital Burlo Garofolo - Trieste - Italy - January 2020

10. **Mingroni-Netto RC.** Ensino de Genética e Doenças Raras. **Conference presented at the Senado Federal**, in the second meeting of the temporary committe about rare diseases, activity organized by the senators Mara Gabrilli and Romário, 2019.

11. Moreira DP, Suzuki AM, Varela E, Griesi-Oliveira K, Monfardin F, **Sertié A**, **Passos-Bueno MR.** Deficiency of TBCK leads to deregulation of TBR1: A gene associated to autism spectrum disorder. **INSAR - International Society for Autism Research**. (vitual presertatiom) junho, 2020.

12. **Naslavsky MS.** Arquivo Brasileiro Online de Mutações (ABraOM) can contribute to the neuromuscular genetics field? XVII Latin American Congress of Genetics (ALAG 2019), 6 a 9 de outubro 2019, Mendoza.

13. **Okamoto OK.** Vírus Zika; um potencial aliado no combate ao câncer cerebral. **Ciclo Virtual de Formação do Curso de Biomedicina**, FACTHUS, MG, 2020.

14. **Okamoto OK.** Desafios e oportunidades para desenvolvimento de novos negócios com terapia celular e gênica. **Biotech Day**, Eretz.bio, São Paulo, 2019.

15. **Okamoto OK.** Stem cell culture innovation in GMP Facility. XXVII Simpósio Internacional de Hemoterapia e Terapia Celular | **II Fórum Internacional de Terapia Celular**. Hosp. Albert Einstein, São Paulo, 2019.

16. **Okamoto OK.** A técnica do CRISPR na edição gênica. **71ª Reunião Anual da Sociedade Brasileira para o Progresso da Ciência** (SBPC),Campo Grande, 2019.

17. **Okamoto OK.** As células-tronco mesenquimais aumentam as propriedades tumorigênicas do glioblastoma humano através de mecanismos independentes de comunicação célula-célula. XXIII Congresso da Sociedade Brasileira de Transplante de Medula Óssea - SBTMO 2019 / **III Encontro da Sociedade Latino-Americana de**

18. **Passos-Bueno MR**. Estudos genéticos - conceitos éticos, abordagem de achados acidentais? In: II Curso Pré-congresso - Aplicação do Diagnóstico Genético-Molecular na Prática da Endocrinologia para **XV Curso de Atualização em Endocrinologia na Prática Ambulatorial** - Estudos genéticos - conceitos éticos, abordagem de achados acidentais? Faculdade de Medicina da USP, São Paulo , 6 de março de 2020.

19. **Passos-Bueno MR**.. Minicurso: Genética das Doenças Complexas: Nossa Experiência com Transtornos do Espectro Autista. **22º. Encontro Nacional de Biomedicina** Novembro de 2019, Botucatu, UNESP-Botucatu.

20. **Passos-Bueno MR**. Genes e Mecanismos de doenças complexas. **9 th Seminar Series of Scientific Research** of the Institute of Biology. 2019.

21. **Passos-Bueno MR**. Patient's Cells or CRISPR-Cas9 edited cells for modeling human diseases? In **65th Brazilian Congress of Genetics.** Águas de Lindóia, SP, 2019 setembro.

22. **Passos-Bueno MR.** Autism spectrum disorder: our contribution In **I Workshop.Molecular and cellular mechanisms**. Instituto de Ciências Biomédicas, São Paulo, novembro 2019. (Oficina).

23. **Passos-Bueno MR**. Doenças Genéticas para entender o Genoma Humano: Nossa contribuição. **Departamento de Imunologia da Universidade de São Paulo** Instituto de Ciências Biomédicas, USP.. 2019. (Seminário).

24. Pettersson M, Grochowski CM, Wincent J, Eisfeldt J, Cheung SW, **Krepische ACV**, **Rosenberg C**, Lupski JR, Ottosson J, Lovmar L, Gacic J, Lundberg ES, Nilsson D, Carvalho C, Lindstrand A. Cytogenetically visible inversions are formed by multiple molecular mechanisms. **Molecular Cytogenetics** 12, 2019

25. Queiroz EO, Sakugawa AYS, **Ferrari MFR**.. Clusterin prevents Endoplasmic Reticulum stress during overexpression and aggregation of α-synuclein in dopaminergic neurons. In: **XXXIV Reunião Anual da FeSBE**, 2019, Campos do Jordão. 34 FeSBE, 2019.

26. Reis JA , **Ferrari MFR**. . The presence of mutant hSOD1 leads to nuclear translocation of the C9orf72 protein. In: **XIII Reunião Regional da FeSBE**, 2019, Belém. 13 FeSBE Regional, 2019.

27. Stephan BO, Castro MAA, Toledo RAF, **Passos-Bueno MR**, Yamamoto GL, Kim CA, **Bertola DR**.. Apresentation Poster - Intracranial calcifications associated with rare monogenic disorders with skeletal involvement. **XXXI Congresso Brasileiro de Genética Médica** , Salvador, Bahia, 01 a 05 julho de 2019.

28. Yamamoto GL, Rocha L, Ceroni JR, Honjo R, Bisneto EF, Oliveira L, Lopes MA, **Passos-Bueno MR**, Kim CA, **Bertola DR**. **14º Congresso da Sociedade Internacional de Displasias Esqueléticas**. Congenital limb deficiency: clinical and genetic evaluation of a cohort of 37 individuals. Oslo, Noruega, 11 a 14 de setembro de 2019.

29. **Zatz M**. Palestra “Zika vírus como aliado do combate ao câncer”. Ministrada para o programa Fronteiras na Saúde, promovido pelo curso de Medicina da UniMAX. **Centro Universitário Max Planck**. Indaiatuba, 07.09.2019

30. **Zatz M**, Einsten A, Morgadinho F. Palestra no Painel "Criatividade em saúde: busca por novos modelos - avanços da Medicina” In: **8º Fórum LIDE da Saúde e Bem-Estar- Avanços da Medicina e longevidade**. São Paulo, 18 de julho de 2019.

31. **Zatz M**. Palestra " Zika virus: from enemy to ally” In: **VII International Symposium on Translational Oncology**. The Institute of Research of Education of Barretos Cancer Hospital, Barretos, 14 de setembro de 2019.

32. **Zatz M**. Apresentação - Envelhecimento e doenças genéticas: genômica e metagenômica In: **III Seminário de Avaliação dos Institutos Nacionais de Ciência e Tecnologia**. INCT e CNPq, Brasília, 19 a 21 de novembro de 2019.

33. **Zatz M**, Soares AS, Vaz J, Carvalho M, Torga E, Salles T. Painel : Liderança de um mundo em transformação. **8 º Semana do Conhecimento -** Anvisa**,** Brasília, 20 a 22 de novembro de 2019.

34. **Zatz M**. When being Just a scientist is not enough In: **6th TREAT-NMD International Conference,** Leiden, December 10 to 11, 2019

Annex 3

Theses and Dissertations, Awards

1. PhD

1. **Aureliano Torquato Brandão**. A contribuição da ultrassonografia na avaliação dos ligamentos do cotovelo: estudo comparativo com ressonância magnética.
   Tese (Doutorado em Medicina) - Universidade de São Paulo - 2019.
   Orientador: Edson Amaro Junior.

2. **Camila de Freitas Almeida**. Skeletal muscle regeneration in DNM2-related centronuclear myopathy.
   Tese (Doutorado em Genética) -Instituto de Biociência, USP – 2019.
   Orientador: Mariz Vainzof

3. **Camila Manso Musso**. Investigating the pathogenic mechanism underlying Richieri-Costa-Pereira syndrome
   Tese (Doutorado em Genética) -Instituto de Biociência, USP – 2019.
   Orientador: Maria Rita Passos Bueno

4. **Ernesto da Silveira Goulart Guimarães**. Engenharia tecidual hepática utilizando células tronco pluripotentes induzidas
   Tese (Doutorado em Genética) -Instituto de Biociência, USP – 2019.
   Orientador: Mayana Zatz

5. **Liliana Lourenço Jorge**. Controlabilidade e coping em lombalgia crônica (LMC): um estudo com ressonância magnética funcional (fMRI)
   Tese (Doutorado em Radiologia) - Universidade de São Paulo – 2019.
   Orientador: Edson Amaro Junior.

6. **Lucas Ávila Lessa Garcia**. Convergência multimodal em neurorradiologia: aplicações na epilepsia generalizada idiopática.
   Tese (Doutorado em Radiologia) - Universidade de São Paulo – 2019.
   Orientador: Edson Amaro Junior.

7. **Lucas Zoppi Campane**. Diferenças funcionais e estruturais encefálicas entre consumidores regulares de vinho tinto e abstêmios: análise por imagem de ressonância magnética.
   Tese (Doutorado em Radiologia) - Universidade de São Paulo, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – 2019
   Orientador: Edson Amaro Junior

8. **Luiz Gustavo Dufner de Almeida**. Mutational and functional study of Tuberous Sclerosis Complex 1 and 2 genes (TSC1 and TSC2).
   Tese (Doutorado em Genética) -Instituto de Biociência, USP – 2019.
   Orientador: Luciana Haddad

9. **Nathalia Quintero-Ruiz**. Mutagenesis profile incued by UVA and UVB light in human cells from xeroderma pigmentosum group C.
   Tese (Doutorado em Microbiologia) -Instituto de Ciências Biomédicas, USP – 2020.
   Orientador: Carlos Frederico Menckel

10. **Michelle Buscarilli de Moraes**. Estudo clínico e molecular de pacientes com síndrome de Noonan e síndromes relacionadas à síndrome de Noonan pelo sequenciamento de nova geração. 2019
    Tese (Doutorado Pediatria) Faculdade de Medicina – USP
    Orientador: Débora Romeo Bertola

2. Master

1. **André Silva Bueno**. Identificação de variantes patogênicas em famílias com perda auditiva de herança autossômica dominante.
   Dissertação (Mestrado em Biologia/Genética) - Instituto de Biociências, USP – 2020.
   Orientador: Regina Célia Mingroni-Netto
   Inst. financiadora: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior

2. **Elisa Varella Branco**. Caracterização genótipo-fenótipo em novas síndromes associadas ao Transtorno do Espectro Autista.
   Dissertação (Mestrado em Genética) – Instituto de Biociências) – USP, 2019.
   Orientador Maria Rita dos Santos e Passos Bueno

3. **Raquel de Souza Lima**. Efeito das chaperonas BAG2 e DNAJB6 na degradação proteica em modelos celulares de doenças neurodegenerativas.
   Dissertação (Mestrado em genética) – Instituto de Biociências – USP, 2019.
   Orientador: Merari de Fatima Ramires Ferrari

4. **Valdemir Pereira de Sousa**. Associação do SNP Gln27Glu do gene ADRB2 com parâmetros clínicos, de função pulmonar e de gravidade da asma. 2019.
   Dissertação (Mestrado em Biotecnologia) - Universidade Federal do Espírito Santo.
   Orientador: Flavia Imbroisi Valle Errera.

5. **William Bertani Torres**. Sequenciamento de nova geração e sua aplicação no estudo genético da síndrome de Waardenburg.
   Dissertação (Mestrado Conhecimento Aconselhamento Genético e Genômica

Humana) – Instituto de Biociências – USP, 2019.
Orientador: Regina Célia Mingroni Netto

3. Awards

1. Prêmio “Jovem Investigador” para **Guilherme L. Yamamoto**. Presentation pôster a Congenital limb deficiency: clinical and genetic evaluation of a cohort of 37 individuals no **14º Encontro da International Skeletal Dysplasia Society (Sociedade Internacional de Displasias**, Oslo, Noruega, setembro de 2019.

2. **Mayana Zatz** - Honorable Mention for poster of Human Genetics at the **65th Congress of Genetics**, Brazilian Society of Genetics, 2019.

Annex 4

Tables Education /Out Reach

Annex 4.1 - Practical Classes at School Project - Training of 35 teachers from schools of the Educational Directory of Osasco, on 02/18/2020 and of 25 teachers from schools of the Educational Directory Midwest, on 2/21/2020

High Schools	Teachers	Educational Directory
EE Prof. Alcyr Oliveira Porciuncula	Antonio Pedro de Castro	Osasco
EE Prof. Alice Velho Teixeira	Elen Gonçalves dos Santos	Osasco
EE Antônio de Almeida Junior	Izilda Aparecida da Silva	Osasco
E EDr Américo Marco Antonio	Alvanira A. Nascimento	Osasco
EE DrAntonioBrasGambarini	Raael Menezes Silva	Osasco
EE CelAntonio Paiva Sampaio	Marcel Yuki Fujita	Osasco
EE Antônio Raposo Tavares	Rafael Barros Novaes	Osasco
EE Armando Gaban	Marina Santos Barbosa	Osasco
EE Dr. Aureliano Leite*	Antonio Pedro de Castro	Osasco
EE Prof. Benedito Caldeira	Rômulo de Carvalho	Osasco
EE Prof. Eloi Lacerda	Nill Allan Nunes Antunes	Osasco
EE Prof. Ernesto Then de Barros	YoshikoWakabayashiRebolças	Osasco
EE Profa. Fanny Monzoni Santos	Jasiel Canuto Almeida	Osasco
EE Profa. Francisca Lisboa Peralta	Valdir Salatino	Osasco
EE Francisco Matarazzo Sobrinho	Lieda Rodrigues	Osasco
EE Graciliano Ramos	Maria de Lourdes de MendonçaMiwa	Osasco
EE Deputado Guilherme de Oliveira	Keila Soares Lima	Osasco
EE Heloisa de Assumpção	Elivelton dos Santos Alves	Osasco
EE Jardim Santa Maria III	Ester Alves Correa	Osasco
EE Prof. João Batista de Brito	Wilson Domingues	Osasco
EE José Geraldo Vieira	Carmen Cinira Teixeira	Osasco
EE Prof. José Jorge	Benedita de Souza	Osasco
EE Prof. José Maria Rodrigues Leite	Denise Schwartz do Amaral Martins	Osasco
EE Prof. José Liberatti	Lucilene da Costa de Souza	Osasco
EE Prof. Josué Benedito Mendes	Guilherme Thiago Brandt Mazini	Osasco
EE Prof. Dr. Luiz Lustosa	Lieda Rodrigues	Osasco
EE Maria Augusta Siqueira	Luciana Cardoso Romeiko	Osasco
EE Prof. Newton do Espirito Santo Ayres	William de Campos	Osasco
EE Neusa de Oliveira Prévide	Alessandra Paula de Andrade Luz	Osasco
EE Prof. Oguiomar Ruggieri	Renata Aparecida de Oliveira Maino	Osasco
EE Educador Paulo Freire	Vitor Manuel da Conceição Cabeleira	Osasco
EE Ricardo Genésio da Silva	Etiene Alencar Ferreira	Osasco
EE São Paulo Da Cruz	Cristiane Ferreira Gomes	Osasco
EE Major Temo Coelho Filho	Vanderlei Leite de Matos	Osasco
EE Prof Vicente Peixoto	Mara Regina Senna	Osasco
EE Ana Rosa de Araujo	Tatiana de Fatima ReisPaulinetti	Midwest
EE Emiliano Augusto Cavalcanti de Albuquerque E Melo	Elizabeth Mendes Martins de Moura	Midwest
EE Godofredo Furtado	Eliana OrquizaPescuma Bruno Z.Garzoni	Midwest

EE João XXIII	Cecília Elizabete Batista	Midwest
EE Odair Martiniano da Silva Mandela	Arnaldo Jr. M. Nunes Jessé Sabino Cardoso	Midwest
EE Prof. Alberto Levy	Heitor de Jesus eMartins de Amorim	Midwest
EE Prof. Almeida Junior	Diego Arruda Filgueira	Midwest
EE Prof. Aristides de CasTro	Paulo Batista Agante	Midwest
EE Prof. Daniel Paulo Verano Pontes	Clélia Maria de Sá Wernz Rosa	Midwest
EE Prof. Oswaldo Walder	Lilian ColombiniEtchebehere Amanda Cristina Teixeira Ferreira da Silva*	Midwest
Fundação Casa	Amanda Cristina Teixeira Ferreira da Silva*	Midwest
EE Prof. Manuel Ciridião Buarque	Cecília Vaz Castro Vivian Alexandre de Oliveira	Midwest
EE Prof. Maria Eugênia Martins	Maria Tereza Osório Mallman Franco	Midwest
EE Prof. Napoleão de Carvalho Freire	Adriana Alexandre de Amorim	Midwest
EE Raul Cortez	Marcos Vinicius da Silva Santos	Midwest
E E Romeu de Moraes	Lisandra Camila de Oliveira	Midwest
EE Samuel Klabin	Madalena Rosa chaves	Midwest
EE Senador Adolfo Gordo	Andrea Cardoso De Moraes	Midwest
EE Solon Borges dos Reis	Bruno Kestutis de Alvarenga	Midwest
EE Thomázia Montoro	Juliana Cristian PariseGobbo	Midwest
EE Virgílio Rodrigues de A. Carvalho Pinto	Orlando Luiz Amado Gianetti	Midwest
EE. Prof. Emygdio de Barros	Rosana Aparecida Dias	Midwest

**Prof. Leciona em 02 escolas*

Annex 4.2 - Practical Classes at School Project - Training of high school students to act as monitors during the period of 3 weeks that the mobile laboratory visits their schools. 51 students from the Osasco Educational Directory were trained on 02/18/2020 and 28 students Midwest

High Schools	Studentes	Educational Directory
EE Prof. Alcyr Oliveira Porciuncula	Kayky de Oliveira Pontes Luiz Eduardo do Nascimento Hemares Nayara Rayane Freires	Osasco
EE Prof. Alice Velho Teixeira	Gabriel Nelson Silva Vivian Pereira Gomes	Osasco
EE Antônio de Almeida Junior	Giovana Madureira de Paula Julia Santos Kathlen Cerqueira de Freitas	Osasco
EE CelAntonio Paiva Sampaio	Camila Borba Bernadino Dayane Silva Rocha	Osasco
EE Antônio Raposo Tavares	Angélica Mariane Dias Leite Julia Pontes de Carvalho Sarah Assis de Oliveira	Osasco
EE Armando Gaban	Ana Luiza Oliveira Paloma Ariel de Oliveira Besse	Osasco

	Vanessa SeibelRasera	
EE Prof. Ernesto Then de Barros	Gabriele Oliveira dos Santos Ana Beatriz AkemiSumiya Stheffany Alberto Ribeiro	Osasco
EE Profa. Francisca Lisboa Peralta	Ana Claudia Guedes de Lima Isabela Rodrigues de Carvalho Samuel Henrique Palhoto Lima Bento	Osasco
EE Francisco Matarazzo Sobrinho	Guilherme de Moura Holanda Tiago Rocha de Souza	Osasco
EE Graciliano Ramos	Fabricio de Araujo Santana Jheniffer Alves Ferreira Leandro Coelho	Osasco
EE Heloisa de Assumpção	Jonas Antony Santana de Paula Nicolas Rodrigues Cardoso	Osasco
EE Jardim Santa Maria III	Isaque Fernandes Abel S	Osasco
EE Prof. João Batista de Brito	Matheus Martins Rodrigues	Osasco
EE José Geraldo Vieira	CristhoferHupalo dos Santos Melissa Marinho Guimarães	Osasco
EE Prof. José Jorge	Gabriela de Roco Souza Lorena Pereira Bernardo Thauany Molina Tomaz	Osasco
EE Prof. José Maria Rodrigues Leite	Vitória Martins Yasmin Soares Ana LiviaSombreiraBonagio	Osasco
EE Maria Augusta Siqueira	Alice Mota da Silva Carlos Eduardo Pontes Ruiz Gabriela Filgueira Santos	Osasco
EE Neusa de Oliveira Prévide	Isabelly Lima Alves Kauê Renato Pereira Nathalia de Cassia Ferreira da Silva	Osasco
EE Prof. OguiomarRuggieri	Heitor Lessi Tomé	Osasco
EE Educador Paulo Freire	Geovana de Sá Costa Nathanael Ferreira NeliseLorraira Carvalho do Nascimento	Osasco
EE Major Telmo Coelho Filho	Gabrielly Ferreira da Silva Ramos Ingrid laurano Fernandes	Osasco
EE Emiliano Augusto Cavalcanti de Albuquerque E Melo	Emily Mariane Silva Gevana Moraes da Costa	Midwest
EE Godofredo Furtado	Ana Carolina dos Santos Lorenzo Christie dos Reis Saladino Richard BrunelliKeeim Cezar Julia Pedroso dos Santos	Midwest
EE Odair Martiniano da Silva Mandela	José Vilela Nunes Netto Lincoln Souza Bernardes	Midwest
EE Prof. Alberto Levy	Larissa Lisandra Kato San'tana Lucas Martins Santos	Midwest
EE Prof. Daniel Paulo Verano Pontes	Talita Pereira Silva Roberta Silva Santos Vanessa Maria Soares de Souza	Midwest
EE Prof. Maria Eugênia Martins	Nicole de Santana Vilaça	Midwest
EE Samuel Klabin	Beatriz Ribeiro Bitencourt	Midwest

	Ana Carolina da Silva Calixto	
EE Solon Borges dos Reis	Julia Sarha de Oliveira Kawakami Gabrielle Alves Ferreira Alyson Pereira de Jesus	Midwest
EE Tomazia Montoro	ThawaniCristina Mendes da Costa Silva Murilo da Silva Costa Gabriela Felipe Medeiro Santos	Midwest
School names were not provided	Guilherme Nunes Machado Katrryna Rosa de A Soares Manuela Freire da Silva Maria Eduarda Vieira Rodrigues Kauan da Silva Staniseaw Matheus Konrad da Silva	Midwest

Annex 4.3 - Practical Lessons at School Project - 25 Schools administrated by Educational Directories from Osasco and Midwest region were attended, from June 2019 to June 2020

EE Elói Lacerda	Osasco
EENeuza de Oliveira Prévide	Osasco
EE Aureliano Leite	Osasco
EE Gastão Ramos	Osasco
EE Antônio Carlos da Trindade	Osasco
EE Maria Augusta Siqueira	Osasco
EE São Paulo da Cruz	Osasco
EE Newton Espirito Santo Ayres	Osasco
EE Tarsila do Amaral	Osasco
EE Ricardo Genésio da Silva	Osasco
EE João Baptista de Brito	Osasco
EE Maria Rodrigues Leite	Osasco
EE Armando Gaban	Osasco
EE Fanny Monzoni Santos	Osasco
EE Alice Velho Teixeira	Osasco
EE Educador Paulo Freire	Osasco
EE Alcyr Oliveira Porciúncula	Osasco
EE Claudinei Garcia	Osasco
EE Dona Ana Rosa de Araújo	Midwest
EE Prof. Almeida Júnior	Midwest
EE Tomazia Montoro	Midwest
EE Godofredo Furtado	Midwest

EE Paulo Ross	Midwest
EE Prof.Daniel Paulo Verano Pontes	Midwest
EE Emiliano de Carvalho	Midwest
EE Prof. Architiclino Santos	Midwest
EE João XXIII	Midwest
EE Dr.Kyrilos	Midwest
EE Odair Martiniano da Silva Mandela	Midwest

Projeto Aulas Práticas na Escola – 25 Escolas atendidas, pertencentes às Diretorias de Ensino de Osasco de Centro-oeste, de junho de 2019 a junho de 2020

EE Jose Maria Rodrigues Leite	Osasco
EE José Geraldo Vieira	Osasco
EE José Liberatti	Osasco
EE Antônio Raposo Tavares	Osasco
EE Godofredo Furtado	Midwest
EE Emiliano de Carvalho	Midwest

Annex 4.4 - Interviews to the Media and Science Dissemination Articles

1. **Denssen BEM**, Grieco A, Stam G, Ventura M. Vídeos de educação e divulgação científica à comunidade no canal do CEPID-Centro de Pesquisa sobre o Genoma Humano e Células-tronco no Youtube – **Canal Genoma USP** (produção 2019/2020) . Disponível em <https://www.youtube.com/c/GenomaUSP?reload=9> Acesso em 08/06/2020.

2. **Mingroni-Netto RC**. Aconselhamento Genético: resolução organiza a atividade. Revista **O Biólogo** - produção regular do Conselho Regional de Biologia . Ed. 51 jul/ago/set 2019, p 20-21.

3. **Zatz M.** Entrevista concedida ao Programa Matéria de Capa. Título “Viver para sempre”. **TV Cultura**, 07.07.2019. Disponível em < https://tvcultura.com.br/videos/70027_materia-de-capa-viver-para-sempre-07-07-2019.html > Acesso em 28/05/2020.

4. **Zatz M.** Entrevista sobre o Dia Nacional da Ciência**. Rádio CBN**, 08.07.2019. Podcast disponível em < http://cbn.globoradio.globo.com/media/audio/266718/se-nao-investirmos-em-ciencia-nunca-vamos-sair-da-.htm> Acesso em 28/05/2020.

5. **Zatz M.** Participação na coluna radiofônica Decodificando o DNA – defende “incentivos fiscais para aumentar investimentos em ciências e tecnologia”. **Rádio USP**, 10.07.2019. Disponível em < https://jornal.usp.br/atualidades/brasil-precisa-aumentar-os-investimentos-em-ciencia-e-tecnologia/ > Acesso em 28/05/2020.

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Annex 5

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