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

Universidade de São Paulo

Instituto de Biociências

Departamento de Genética e Biologia Evolutiva

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REPORT

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ABSTRACT

During this last year, our group has published 70 journal articles (all listed below), 9 books or book chapters, 11 abstracts in National meetings, and 28 abstracts in International meetings. During this period, our graduate students submitted 6 Master Theses and 8 Doctoral Dissertations. About 16 conferences, lectures and symposia were done by our team.

Most of the articles were published as a result of our students' projects and involved the collaboration of several PIs from Hug-Cell . We also increased the interchange between groups, as suggested by our reviewers, as illustrated in figure 1.

In addition to the ongoing projects we have also embarked in a new project related to zika virus infection and the role of the host genome in the development of microcephaly and/or other associated malformations, namely, zika congenital syndrome. This project is involving several Hug-Cell members as well as other groups of researchers.

It is also noteworthy that the number of citations of our group is increasing every year, in particular since the approval of our first CEPID in 2000, which reinforces the importance of long term support from FAPESP (Figure 2).

The applications of technology transfer included genetic counseling for about1500families, 2640 genetic tests, production of a website for our laboratory of genetic tests and of variants of the Brazilian population,, maitenance of new multiuser equipment, and new partnerships.

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 is now extended to other CEPIDS, under the coordination of Eliana Dessen.

Furthermore, we had a 3-days meeting with our advisory committee, Prof. NissimBenvenisty, Prof. Gert-Jan van Ommen and Prof. Julio Licinio , last March. During this meeting we presented the main achievements from our

CEPID and the students presented their work orally or in posters. The committee had the opportunity to talk to all students and their evaluation and suggestions were summarized in a report (see enclosed)

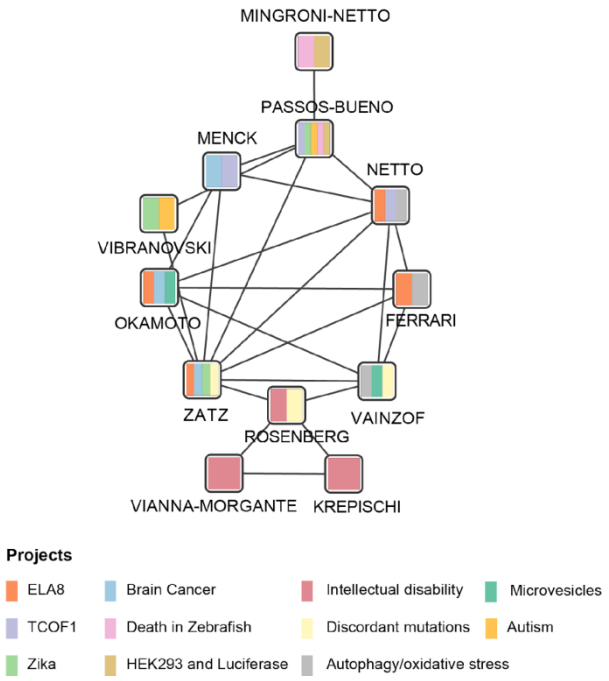

Figure 1*.Interaction network of CEPID researchers in terms of publications and projects. Projects are represented by colors.*

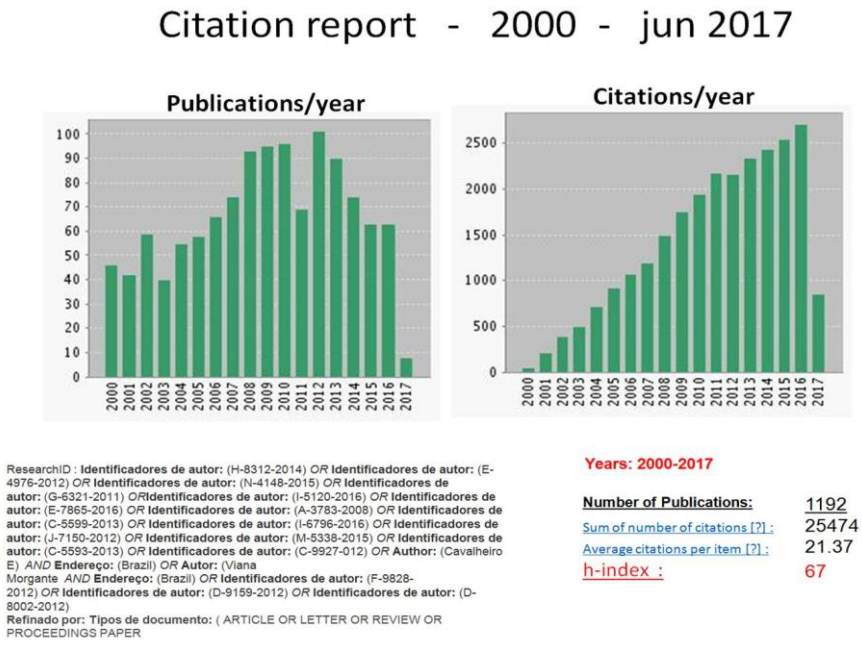

Figure 1. *Number of publications and citations per year, according to the Web of Science*

PART 1 – RESEARCH

Our main research results from July 2016 to June 2017, ordered by our main objectives and revised according to the advisory committee's recommendations are presented below.

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, non-penetrance in genetic disorders

A2.1. Neuromuscular disorders

A2.2. Craniofacial disorders

A2.3 .Neurodegeneration

A3. Epigenetics and diseases

A3.1. DNA methylation in congenital disorders

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

A3.3. Exploring the role of DNA methylation in cancer

B) The 80plus Project

C) Therapies in genetic disorders

D) Next Goals

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

During this period we have identified 2 new genes and one variant, as summarized below:

IMPA1 and severe intellectual disability

Intellectual disability (ID) is extremely heterogeneous and relatively little is known about the role of autosomal recessive traits. In a field study performed in a highly inbred area of Northeastern Brazil, we identified and investigated a large consanguineous family with nine adult members affected by severe ID associated with disruptive behavior. WES identified a homozygous deleterious variant in inositol monophosphatase 1 (IMPA1) (NM_005536), consisting of a 5-bp duplication (c.489_493dupGGGCT; chr8: 82,583,247; GRCh37/hg19) leading to a frameshift and a premature stop codon (p.Ser165Trpfs*10) that co-segregated with the disease in 26 genotyped family members. The IMPA1 gene product isresponsible for the final step of biotransformation of inositol triphosphate and diacylglycerol, two second messengers. Despite its many physiological functions, no clinical phenotype has been assigned to this gene dysfunction to date. Interestingly, IMPA1 is the main target of lithium, a drug that is at the forefront of treatment for bipolar disorder. Functional studies with neurons derived from patients IPS cells is currently being performed by ThalitaFigueiredo as a pos-doc from FAPESP (MayanaZatz supervision).

Xeroderma Pigmentosum patients in a small community and two founder effects: In this part of the project we basically investigate human diseases, which are due to defects in the maintenance of genome stability. The main disease investigated is xeroderma pigmentosum (XP), where patients have high frequency of skin tumors in the area exposed to sunlight, mainly due to genetic damage induced by the ultraviolet (UV) light. Defects on nucleotide excision repair (NER) or translesion synthesis (TLS) are responsible for increased frequency of mutagenesis after UV exposure and, consequently, skin cancer formation. Although this is a rare disease, we have identified an isolated community in the center of Brazil (Faina, Goiás- a very sunny place), where there is a high frequency of XP patients, due to consanguineous marriages. Interestingly, contrary to expected, two pathogenic mutations were found in the *XPV/POLH* gene. The families were investigated and the data revealed two founder mutations in that community *(Munford, Castro et al, 2017).*

Mutations in MAP3K7 causes frontometaphyseal dysplasia:

Frontometaphyseal dysplasia is a progressive sclerosing skeletal dysplasia associated with facial dysmorphisms, including ocular hypertelorism, a clinical feature commonly seen in Noonan syndrome. Mutations in FLNA are responsible for 50% of the cases. We evaluated a patient showing features compatible with a mild form of FMD. In collaboration with Stephen Robertson from New Zealand, our patient did not harbor mutations in FLNA. Instead, he presented a mutation in a novel gene, MAP3K7. Of note, our patient did not present a recurrent mutation found in several individuals, but a missense mutation affecting the kinase domain of the protein. Individuals with mutations in this domain showed a milder phenotype.

A1.2. Complex disorders

Copy number alterations in congenital disorders

CNVs are known to contribute to human normal variation and disease. Genomic imbalances have been investigated in several cohorts to identify genes or chromosomal regions involved in: hearing impairment, autism and syndromic intellectual disability *(De Souza Reis et a, 2017*; *Gamba et al, 2016*; *Linhares et al, 2016*;; *Machado et al, 2016*).

Copy number alterations in cancer

While isolated genes can account for selection of specific chromosome imbalances (drivers), another alternative theory, applying an evolutionary perspective, hypothesizes that the different karyotypes with specific combinations of chromosome alterations could result in slightly different tumor subtypes, and progression. We investigated the role of copy number alterations in different cancer types, identifying genes and chromosome regions associated with tumor development and progression as well as clinical features *(Ferreira et al., 2016; Mariano et al., 2016).*

Mechanisms of cancer aggressiveness

Pre-clinical studies are valuable to develop new drugs and treatment protocols for cancer and they invariably employ cell lines. Compared to other types of

cancer, there are relatively few cell lines of medulloblastoma available in central repositories, in part due to intrinsic difficulties in establishing continuous cell lines from pediatric brain tumors. Given that medulloblastoma are highly heterogeneous at the molecular, histological, and clinical levels, novel cell lines are instrumental for studying medulloblastoma biology. We have reported the establishment and characterization of a new cell line derived from a medulloblastoma patient with advantageous features for pre-clinical studies, namely enhanced aggressive traits, stem cell properties, increased chemoresistance, tumorigenicity in an orthotopic metastatic model, and resemblance of original medulloblastoma behavior (Silva et al. 2016). Employing this novel cell line, in addition other classic cell lines available in central repositories, in functional studies, we found a specific correlation between OCT4A expression and poor survival, as well as a potent oncogenic activity for OCT4A, which enhanced metastatic spreading of tumor cells within the neural-axis. OCT4A expression also contributed to acquisition of heterogeneous chromosomal aberrations and aberrant expression of non-coding RNAs in stem-like cancer cells*(Silva et al. 2017).* These findings highlight the involvement of OCT4A in a mechanism driving aggressiveness of medulloblastoma, which could be further explored not only as a prognostic indicator, but also as a therapeutic target for a precision medicine approach in neuro-oncology.

Rare variants in craniofacial complex disorders

Non-syndromic cleft lip and palate (NSCLP) is a common complex disorder (incidence 1: 600 births) with still unsolved genetic architecture. Using exome and candidate gene analyses, we showed that rare loss-of-function (LoF) but not missense variants in *ARHGAP29* (Savastano et al., 2016) are relevant to NSCLP, but with incomplete penetrance (<60%). We have hypothesized that the penetrance of NSCLP in patients with rare LoF variants depends on a second hit. Our results suggest that epigenetics is a possible mechanism involved as a second hit (details in Epigenetics' topic).

Autism spectrum disorders: In a collaborative study leaded by Dr. Brentani, through the study of a family segregating the ASD phenotype, it was shown that

mutations in genes mapped outside of the CNV region also contribute to the phenotype, further confirming the complex genetic basis of ASD *(Reis et al., 2017).*

Congenital zika syndrome susceptibility: what did we learn from twin studies?

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. However, no study has reported the outcome of NPC derived from CZS affected and non-affected babies exposed to ZIKV. Reports on discordant dizygotic twins (DZ) whose mothers were infected by ZIKV during pregnancy suggest that host genomic variants may contribute to the development of CZS. We have investigated eight pairs of twins born from mothers with gestational ZIKV infection: five are discordant (affected and non-affected), all dizygotic (DZ) while three are concordant (both affected), one DZ and two monozygotic (MZ). Human induced pluripotent stem cells (hiPSC)-derived NPC from three pairs of dizygotic/discordant twins for CZS were infected with Brazilian ZIKV ($ZIKV^{BR}$). We demonstrate for the first time that NPCs from the affected twins had a significantly higher viral release, reduction of cell proliferation and impaired mTOR signaling as compared to their respective non-affected siblings. Whole-exome sequencing analysis revealed an enrichment of mutations in a set of genes in the affected individuals. These results support the hypothesis that the host individual genetic background may play a critical role in CZS development. This work involved many students from our CEPID and several groups of investigatorsfrom different Brazilian states. It received an award from ISSCR and was submitted to publication.

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

A2.1. Neuromuscular disorders

- Human genes

DMD, caused by the absence of muscle dystrophin, is a severe lethal

neuromuscular disorder with onset in early childhood and leading to premature death. We have identified two Duchenne muscular dystrophy (DMD) patients with nonsense mutations in the dystrophin gene that had a milder course despite the complete absence of muscle dystrophin. Exome sequencing had previously failed to identify any reported polymorphisms which could explain the milder phenotype in these two patients *(Zatz., 2015).* We have now shown that an up-regulation in utrophin expression, which has been suggested as a potential therapeutic approach for DMD, could not explain the milder phenotype either *(Vainzof et al., 2016)*.

- Murine models

We transferred the mdx mutation from the C57Bl to the 129/Sv strain to investigate how this would affect the phenotype of mdx mutation in a different genetic background. Functional analysis of mdx129 showed a progressive amelioration of the phenotype. Transcriptome comparative analysis showed involvement of immune system genes and a decreased participation of the endo/exocytic pathway and homeostasis categories, and an increased participation of the extracellular matrix and enzymatic activity categories. *(Comim et al., 2016)*.The most significant differentially expressed genes (DEGs) exclusively expressed in mdx129, were the upregulated *Spp1* and *Il1rn* genes. *Spp1* is a known DMD prognostic biomarker, and our data indicate that its upregulation can ameliorate the mdx phenotype. Modeling the expression of the DEGs involved with the milder course of mdx mutants should be tested as a possible therapeutic strategy for the dystrophic process *(Calyjur et al, 2016*).

A model for muscle degeneration/regeneration in murine models

A new study, using electroporation as a model of degeneration/regeneration to investigate the regenerative potential in neuromuscular disorders, has been introduced. Animals' calves were electroporated and analyzed after 3, 5, 10, 15, 21 and 30 days. Normal mice and two mouse models with mutations in the dysferlin (Dysf) and the dynamin-2 (Dnm2) genes, respectively (in collaboration with the Institute of Myology of Paris) are being analyzed. The aim is to investigate the pattern of alterations along time, both through histological

analysis and quantitative mRNA expression of genes involved in the degeneration/regeneration pathways.

The autophagic pathway in X-linked myopathy with excessive autophagy (XMEA)

X-linked myopathy with excessive autophagy (XMEA) is an inherited, slowly progressive myopathy, characterized by sarcoplasmic vacuoles in muscle fibers. XMEA is caused by mutations in the vacuolar membrane ATPase 21 gene (Vma21), resulting in a reduction of both mRNA and protein VMA21 levels, elevating lysosomal pH, blocking partially the final degradation step of autophagy and increasing the formation of autolysosomes. We recently identified a Brazilian family with XMEA caused by a unique small insertion-deletion in the Vma21 gene.Here, we studied immortalized myoblasts, isolated from muscle biopsies from one XMEA patient and one control. Through qPCR, the relative expression of autophagy-related genes was evaluated, and Myog analysis confirmed myotube formation. In controls, the autophagy genes Lc3b, Vps34 and Atg12 showed a similar pattern of expression in undifferentiated cells as well as after myotube differentiation. Interestingly, in the XMEA patient, these genes showed a lower expression in myoblasts, but a higher expression after myotube formation, suggesting a more activated autophagic gene induction. Immunofluorescence analysis using anti-LC3 antibody confirmed at the protein level the gene expression data. Our results show that the increase in autophagy that characterizes XMEA may arise after cells start to differentiate, and that in progenitor cells such as myoblasts, the signaling may be affected in a distinct way.

- *Canine models*: The search for protective genes/variants

Jagged 1 overexpression and Pitpna decreased expression Rescues the Duchenne Muscular Dystrophy Phenotype.

Duchenne muscular dystrophy (DMD), caused by mutations at the dystrophin gene, is the most common form of muscular dystrophy. There is no cure for DMD and current therapeutic approaches to restore dystrophin expression are only partially effective. The severely affected golden-retriever muscular dystrophy (GRMD) dogs are the best model to recapitulate the DMD

phenotype.. Previously, we identified two exceptional GRMD dogs that are mildly affected, have functional muscle, and normal lifespan despite the complete absence of dystrophin. *(Zatz et al., 2015*) . Next, our data on microarray and linkage analysis, whole-genome sequencing, and transcriptome analyses of these dogs compared to severely affected GRMD and control animals reveals that increased expression of Jagged1 gene, a known regulator of the Notch signaling pathway, is a hallmark of the mild phenotype. Functional analyses demonstrate that Jagged1 overexpression ameliorates the dystrophic phenotype, suggesting that Jagged1 may represent a target for DMD therapy in a dystrophin-independent manner *(Vieira et al., 2015, Cell)* . Interestingly, it was reported by another group of investigators that jagged-1 is decreased in serum of DMD patients which reinforce our findings.

Furthermore, microarray analysis of these “escaper” dogs revealed reduced expression of phosphatidylinositol transfer protein alpha (*PITPNA*) in escaper versus severely affected GRMD dogs. Based on these findings, we decided to pursue investigation of modulation of *PITPNA* expression on dystrophic pathology in GRMD dogs, dystrophin-deficient *sapje* zebrafish, and human DMD myogenic cells. In GRMD dogs, decreased expression of *Pitpna* was associated with increased phosphorylated Akt (pAkt) expression and decreased PTEN levels. Our findings suggest *PIPTNA* as a novel disease modifier that accords benefits to the abnormal signaling, morphology, and function of dystrophic skeletal muscle, and may be a new target for DMD and related neuromuscular diseases.

These two papers first authored by the pos-doc student Natassia Vieira were the results of a collaboration between our CEPID, Harvard medical center at Boston, Ma (Prof. Lou Kunkel) and Broad Institute (Prof. K lindblad-Toh).

These results which were published in Cell and PNAS , presenting Jagged-1 and *PITPNA* as genetic modifiers of DMD are of great interest as potential novel target for future therapies.

This work is currently being continued byNatassia Vieira who returned to our laboratory after her pos-doc. Aiming to understand how overexpression of *Jagged1* can modify the dystrophic phenotype, she is now working on lentivirus and adeno-associated virus (AAV) to overexpress the proteinin muscle cells and mouse models.

A2.2. Craniofacial disorders

Migration and osteogenic differentiation in Richieri-Costa-Pereira syndrome (RCPS)

In 2014, we demonstrated that loss-of-function variants in EIF4A3, a gene involved in the basic cell control of splicing and translation, cause a rare craniofacial disorder *(Favaro et al., 2014).* In order to understand how EIF4A3 dysregulation causes a specific phenotype, we recapitulated " in vitro" craniofacial development by differentiating iPSC from 3 RCPS patients and 3 controls into neural crest cells (iNCCs) and in turn, these cells were induced to mesenchymal stem cells (nMSC). Analysis of basic cellular process in iNCCs, revealed that the EIF4A3 depleted cells compromised cell migration while premature ossification was observed upon osteogenic induction of nMSC. These findings were also observed in mouse eif4a3 knockout models *(Miller, Kobayashi et al., 2017).* In summary, this study contribute to the understanding of cellular processes involved in this disorder. It also led to the establishment of a*in vitro* model to study the basic mechanisms leading to craniofacial disorders and open the perspective to test for drugs or molecules that could ameliorate the phenotype.

Dysregulation of ROS inTreacher Collins Syndrome

Treacher Collins Syndrome (TCS) is a rare congenital disease (1:50 000 live births) characterized by craniofacial defects, including hypoplasia of facial bones, cleft palate and palpebral fissures. Over 90% of the cases are due to mutations in the TCOF1 gene, which codifies the nucleolar protein Treacle. In a study leaded by Dr. Calcaterra (Universidade de Rosario, Argentina), it was established a novel TCS-like zebrafish model displaying features that fully recapitulate the spectrum of craniofacial abnormalities in patients as well as the main molecular alterations already characterized in mouse knockout models. The study of this new model showed that there is an increase of ROS along with the overexpression of redox-responsive genes and treatment with antioxidants ameliorated the phenotypic defects of craniofacial anomalies in TCS-like larvae. This study opens new avenues to explore molecules to recover the craniofacial alterations due to depletion of treacle *(de Peralta et al., 2016).*

FGF19 as a potential molecule to ameliorate craniosynostosis

Apert syndrome is one of the most severe forms of cranioysnostosis and patients are submitted for several surgeries during early infancy throughout adolescence in order to allow brain development. The causative mechanisms are gain-of-function mutations in *FGFR2*, which lead to loss of specificity for the ligands. Using fibroblast and stem cells of Apert patients and controls, we recently showed that FGF19, a ligand for the FGFR2 mutated protein, reduces osteogenese in cells of these patients, an information that can be used in the future for a better management of Apert patients *(Yeh et al.,2016).*

A2.3. Neurodegeneration

Intracellular trafficking and protein aggregation in neurodegeneration

Cell physiology is impaired before protein aggregation and this may be more relevant than inclusions themselves for neurodegeneration. During the last year we characterized an animal model to enable the analysis of the cell biology before and after protein aggregation *(Almeida et al, 2016a).* The model of early neurodegeneration employed low concentrations of rotenone that resembled protein aggregation and cell impairment characteristics of neurodegeneration *(Chaves et al, 2016)*. It was described for the first time that autophagy impairment during early neurodegeneration is rescued after protein aggregation. Neurotrophic factors signaling was also impaired before protein aggregation, although moderate physical activity prevents the impairment of neurotrophin signaling in the hippocampus of aged rats *(Almeida et al., 2016b).* In another study, we unveiled the intracellular signaling of nicotinic receptors, that culminates with protein aggregation associated with Alzheimer's disease*(Oliveira et al, 2016).* Protein aggregation associated with Parkinson's disease was also a matter of investigation, we demonstrated that alpha-synuclein A53T inhibits mitochondrial trafficking, probably by microtubule disruption *(Mello et al., 2016).*

A3. Epigenetics and diseases

A3.1. DNA methylation in congenital disorders

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

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

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. The CNVs detected affect several currently known candidate genes, such as *HDAC4*, *MYT1L*, *SIM1*, *POU3F2*, *EHMT1*, *SH2B1*, and *RAI1*. We also propose 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 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. Our next step will be whole-exome sequencing analyses of the unresolved cases.

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

Epigenetic studies allow the investigation of the impact of environmental factors in the human genome and its correlation with disease susceptibility. In this context, we considered important to evaluate if NSCLP, a complex disorder with high heritability but still with non-understood genetic contribution in its etiology, has an epigenetic signature. We, therefore, performed methylome-wide association study in Brazilian NSCLP (n=67) and controls (n=59), using DNA from peripheral blood. This study revealed 578 methylation variable positions significantly associated with NSCLP, further validated in a different population of European ancestry and in different tissues.. We next tested if methylation could contribute to penetrance of the phenotype in individuals heterozygous forLoF variants in CDH1. We observed that methylation levels were significantly higher in penetrant *CDH1*LoF NSCLP individuals as compared to non-affected individuals as well as non-affected individuals carriers of CDH1 LoF variants *(Alvizi et al., 2017).* In summary, epigenetics play a role in NSCLP and in a

proportion of cases, the penetrance of the NSCLP is the result of pathogenic rare LoF variants combined with epigenetic changes, which in turn, were possibly triggered by environmental factors that the fetus were exposed during pregnancy.

Alzheimer disease

We investigated for the first time the genomewide DNA methylation changes of noncoding RNA genes in the temporal cortex samples from individuals with Alzheimer's disease (AD). The methylome of 10 AD individuals and 10 age-matched controls were obtained using Illumina 450 K methylation array. A total of 2,095 among the 15,258 interrogated noncoding RNA CpG sites presented differential methylation, 161 of which were associated with miRNA genes. In particular, 10 miRNA CpG sites that were found to be hypermethylated in AD compared to control brains represent transcripts that have been previously associated with the disease. This miRNA set is predicted to target 33 coding genes from the neuregulin receptor complex (ErbB) signaling pathway, which is required for the neurons myelination process. For 6 of these miRNA genes (MIR9-1, MIR9-3, MIR181C, MIR124-1, MIR146B, and MIR451), the hypermethylation pattern is in agreement with previous results from literature that shows downregulation of miR-9, miR-181c, miR-124, miR-146b, and miR-451 in the AD brain. Our data implicate dysregulation of miRNA methylation as contributor to the pathogenesis of AD *(Villela et al, 2016).*

A3.3. Exploring the role of DNA methylation in cancer

Epigenetic dysregulation is an important emerging hallmark of cancer origin and development. The role of DNA methylation has been investigated by us in tumoral genomes and as a predisposing factor for cancer development. Our results in hepatoblastomas suggest an arrest at early stages of liver cell differentiation, in line with the hypothesis that hepatoblastoma ontogeny involves the disruption of liver development (Maschietto et al., 2016).

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

The XPV protein (also known as Pol eta) participates in the bypass of DNA damage induced by UV-light. Working with primary human fibroblasts we were able to detect that this protein is induced after irradiation, and the increased levels of XPV is an important contribution to cell capacity to survive UV, and this was demonstrated to be due to faster bypass of DNA lesions. These data unravel why this TLS pathway is so important for cellular resistance to UV, even in patients deficient in NER, such as XP-C, and contribute to understand the clinical phenotypes of XP-V patients *(Lerner et al, 2017).*

Another point of interest is how UV damages DNA, and how these damages contribute to skin tumor formation in XP patients, and, normal population. The sunlight that reaches Earth surface is mainly UVA wavelengths (320-400 nm), and some UVB (280-320 nm). The impact of UVB in DNA is clearly due to a direct mechanism generating pyrimidine dimers, but how UVA damages DNA is still a matter of debate. UVA certainly have also a direct effect generating pyrimidine dimers, but it is believed that an indirect effect, having chromophores as intermediates, generate oxidative radicals (such as singlet oxygen) that damage DNA. However, by investigating the mechanisms of in vitro DNA damage formation by UVA, we were able to detect the generation of singlet oxygen (and the consequent DNA damage) in a cell free system. The conclusion is that the DNA molecule by itself is sufficient to absorb UVA, and generate this oxidative radical, with no need of external chromophores. The implication is that the formation of singlet oxygen by and close to DNA may be an important physiological pathway of DNA damage formation within the cell, after UVA irradiation *(Yagura et al, 2017).* Moreover, we also have reviewed the implication of oxdative stress after UV light irradiation and how these DNA damage and their potential consequences *(Schuch et al, 2017).* Another genetic disease related to DNA repair which is of our interest is Fanconi anemia, where a defect on homologous recombination pathway may have severe consequences, and the genetic mechanisms involved in this disease was reviewed *(Renaudin et al, 2016).*

In collaboration with Dr. Alberto Kornblihtt, the role of DNA damage (mainly pyrimidine dimers) in the induction of changes in alternative splicing pathways was demonstrated. Basically, the participation of ATR kinase and XPE proteins were revealed *(Muñoz et al, 2017)***.**

Genetic mechanisms involved in cancer resistance to genotoxic agents.

Although the maintenance of genetic instability is important to prevent consequences as cancer, tumor cells use these mechanisms to survive DNA damage induced by many of the main chemotherapeutic agents. Investigating the mechanisms by which glioblastoma cells resist to cisplatine and temozolomide (TMZ) (two important drugs in the treatment of this type of cancer), we have previously found that glutathione can provide protection, by avoiding DNA to be damaged. By further studying this mechanism we found that NRF2, one of the most important transcription factors related to oxidative stress, is induced after TMZ treatment in glioma cells. This induction is highly relevant for cell protection to TMZ and is one of the main regulation mechanisms responsible for TMZ resistance. We found that monitoring this pathway may be highly relevant for improve therapy to this devastating disease *(Rocha et al, 2016).*

B) THE 80plus PROJECT

This project was initiated aiming to have a database from a cohort of elderly individuals from the Brazilian population. Brazilians are highly admixed with ancestry from Europe, Africa, America, and Asia and yet still underrepresented in genomic databanks. Population representative phenotype and genotype repositories are essential for variant interpretation through allele frequency filtering since elderly individuals are less likely to harbor pathogenic mutations for early- and adult-onset diseases. We started recruiting healthy subjects over 80, who were ascertained based on preserved cognitive capacity and ability to live independently. Subsequently, in a collaboration with Prof. Maria Lucia Lebrão (deceased in 2016) and Yeda Duarte (from Faculdade de SaúdePública) we included a cohort of over 1000 individuals older than 60 who had been followed since year 2000. We also established a collaboration with Prof. Edson Amaro Jr. (from Instituto de Pesquisas Hospital Albert Einstein) which allowed to perform brain MRI in 580 subjects and with Human Longevity Inc. from S. Diego (California) where whole genome sequencing in 1320 subjects, all older than 60, was performed.

Whole exome analysis

A first exome analysis of 609 subjects from this cohort was recently published *(Naslavsky et al., 2017)* and deposited in a web-based public database ABraOM (Online Archive of Brazilian Mutations). We found 9,791 potential loss-of-function variants with about 300 mutations per individual. Pathogenic variants on clinically relevant genes (ACMG) were observed in 1.15% of the individuals and were correlated with clinical phenotype. We conducted incidence estimation for prevalent recessive disorders based upon heterozygous frequency and concluded that it relies on appropriate pathogenicity assertion. Most importantly, 207,621 variants were absent from major public databases and it is expected that many others will be identified with further WGS analysis of the entire cohort. These observations illustrate the relevance of collecting demographic data from diverse, poorly characterized populations.

Whole genome sequences from the 1320 subjects, which represent the largest cohort of Latin America, were recently transferred to the our CEPID high performance computers. This data is opening the possibility of several collaborations with different groups such as:

a) identification of retroelements (RNA retrocopies, mRNAs, L1, Alus and LTRs) with Pedro Galante (from Hospital sirio-libanês) ,

b) mitochondrial genome variation and nuclear covariants with the group of Marcelo Briones from UNIFESP

c) analysis of DNA repair in healthy nonagenarians as compared to patients with conditions caused by defective DNA repair , Prof. CF Menck from ICB

d) analysis of local ancestry with Diogo Meyer and Regina Mingroni-Netto

C) THERAPIES IN GENETIC DISORDERS

Adult human mesenchymal stem-cells: protein profile characterization and pre-clinical studies

MSCS secretome characterization: Different Donors Mesenchymal Stromal Cells Secretomes Reveal Heterogeneous Profile of Relevance for

Therapeutic Use.

Despite several advances, there is still no effective therapy for Duchenne muscular dystrophy (DMD). Therefore, the potential regenerative capacities, and immune-privileged properties of mesenchymal stromal cells (MSCs), have been the focus of intense investigation in different animal models aiming the treatment of these disorders. However, these studies have shown different outcomes according to the sources from which MSCs were obtained, which raise the question whether stem cells from distinct sources have comparable clinical effects. We analyzed the protein content of the secretome of MSCs, isolated from three different sources (adipose tissue, skeletal muscle, and uterine tubes), obtained from five donors and evaluated their in vitro properties when cocultured with DMD myoblasts. All MSC lineages showed pathways enrichment related to protein metabolic process, oxidation-reduction process, cell proliferation, and regulation of apoptosis. We found that MSCs secretome proteins and their effect *in vitro* vary significantly according to the tissue and donors, indicating the importance of characterizing MSC secretome profile before its use in animal and clinical trials. Despite the individual differences a pool of conditioned media from all MSCs lineages was able to delay apoptosis and enhance migration when in contact with DMD myoblasts. Interestingly, inthe co-culture of one donor's secretome where we observed a more significant delayed apoptosis in contact with DMD myoblasts there was an increased expression of several proteins including jagged-1. This finding called our attention since over expression of jagged-1 was identified as responsible for the mild phenotype and normal life reported in two golden-retriever (GRMD) dogs from our colony. This work was the MSc thesis of Amanda Assoni (MayanaZatz, supervision) and was published in stem cells dev *(Assoni et al., 2017).*

Pre-clinical studies: Transplantation of Human Adipose Mesenchymal Stem Cells in Non-Immunosuppressed GRMD Dogs is a Safe Procedure.

The possibility to treat DMD through cell therapy with mesenchymal stromal cells (MSCs) has been widely investigated in different animal models. However, some crucial questions need to be addressed before starting human therapeutic

trials, particularly regarding its use for genetic disorders. How safe is the procedure? Are there any side effects following mesenchymal stem cell transplantation? To address these questions for DMD the best model is the golden retriever muscular dystrophy dog (GRMD), which is the closest model to the human condition displaying a much longer lifespan than other models. We have investigated and followed 5 GRMD dogs, which were repeatedly transplanted with human adipose-derived mesenchymal stromal cells (hASC), derived from different donors. Xenogeneic cell transplantation, which was done without immunosuppression, was well tolerated in all animals with no apparent long-term adverse effect. We show that repeated heterologous stem-cell injection is a safe procedure, which is fundamental before starting human clinical trials. (Pelatti et al., 2016). The follow-up of these dogs is continuing. One of the injected dogs was born September 2008 which also represents an exceptional longer survival.

Pre-Clinical studies with murine stem cells

Muscle stem cells for murine muscle regeneration.

We are investigating stem cells from distinct sources and their extracellular vesicles in attempt to find a cellular type and/or factors that promotes muscle regeneration. A review article about muscle stem cells was recently published *(Almeida et al., 2016 a)*

Study of myogenic potential of extracellular vesicles in murine models for muscular dystrophies:

Some recent studies have shown the potential of extracellular vesicles (EVs) in muscular regeneration, and here, we are testing which cell type would contain the best information of this regenerative potential. Firstly, we are using EVs isolated from C2C12 cells, because of their good muscle proliferation and differentiation capacity. We concluded that the incorporation of EVs in the cells can occurs quickly but gradually. For the observation in vivo of EVs effect on muscle regeneration, EVs were injected directly into the gastrocnemius muscle of normal (C57black) and dystrophic mice (Dmdmdx and Largemyd), and the

muscles were analyzed after 2 and 10 days. In order to verify if EVs could contribute with functional benefit, other animals were monthly injected with EVs, and functional analyzes are being performed in blind test. In the next step, the same experiments will be performed with EVs isolated from diverse lineages of mesenchymal stem cells and muscle progenitor cells. Better understanding the mechanisms of generation and operation of these vesicles would be crucial in order to verify their myogenic potential.

D) NEXT GOALS - (2017-2018)

The Human Genome Center was initiated in 2000 with the aim of improving our basic knowledge and diagnosis of prevalent genetic diseases in the Brazilian population, mainly neuromuscular, craniofacial, and mental disability. The activities were expanded in 2005, by introducing stem-cell research to understand gene expression and differentiation in complex genetic disorders and to evaluate stem cell based disease therapy. In 2013, the Human Genome and Stem-cell research center (HUG-CELL) was started and further expanded to include research on the genetics and genomic instability associated with aging and degenerative diseases, epigenetic mechanisms involved in disease manifestation, phenotypic variability between individuals with identical Mendelian disease mutations, and the 80 plus project, aimed at comparing the genome variation and brain function (MRI) of healthy Brazilian individuals older than 80 to a cohort older than 60 that has been followed since 2000. Our goals for the first four years were accomplished and resulted in several peer-reviewed publications.

In the next years, we will focus on the search for variants or mechanisms responsible for modulating the severity of the phenotype and to molecularly investigate how variants lead to disease. Among these projects, we would like to highlight our investment of the mechanistic response of inflammation in the etiology of neuromuscular and craniofacial disorders, that can be in some cases be mediated by epigenetic changes in the individual at risk for developing the disease. We expect to contribute to a better understanding of neuromuscular, neurodegenerative, craniofacial and autism/intellectual disability disorders. In order to achieve these goals, we will use *in vitro* and *in vivo* models - from yeast

in ALS to canine models for muscular dystrophy. These models have already been standardized in HUG-CELL. We also will continue to search for novel disease-gene identification associated with rare and common disorders, particularly associated with intellectual disability (ID), autism (ASD) and syndromic obesity.

Healthy human aging is a growing topic of interest and understanding the complexity of the nature versus nurture balance is one of the greatest challenges. The establishment of a collaboration project between three Brazilian groups (HUG-CELL, Faculty of SaudePública and Hospital Albert Einstein) and the Human Longevity Institute in S. Diego allowed us to perform whole genome sequencing (WGS) in a cohort of 1320 individuals older than 60. This databank, the largest one in Latin America, opened several questions to be addressed in collaboration with other groups with expertise in bioinformatic. Amongthem are Dr. Pedro Galante from Instituto Sírio libanês de ensino e pesquisa,Dr. Marcelo Brionesfrom Unifesp and Dr. João Setubalfrom IQUSP. We hope that this collaborative study will contribute to enhance our understanding of the genetic and environmental mechanisms involved in aging as well as constitute an important databank for our population. It is also our expectation that a better characterization of the variants of Brazilian exomes can provide estimates of incidence and prevalence of some rare diseases. Additionally, analysis of the microbiome offers new possibilities for understanding human diseases, particularly the complex ones. In addition to genomic analysis of multifactorial diseases, we will invest in the analysis of the mouth microbiome to evaluate its contribution to the etiology of non syndromic cleft lip and palate.

Our pre-clinical studies on stem-cell therapy in different animal models have shown that the clinical benefits from mesenchymal stem-cells (MSCs) are based on their immunomodulatory and anti-inflammatory properties and not due to stem-cell differentiation. Based on these results , we have started a pre-clinical therapeutic trial with human immunoglobulin (IG) in severely affected mdx/utr- mice model since IG is known to have important anti-inflammatory properties. This project is being carried out by the IC student

Bruno Ghirotto, with a FAPESP fellowship (MayanaZatz supervision);. It was selected by USP-PRP to be presented internationally. It is also our plan to start a cell therapy clinical trial in two groups of patients: a) a small group of Duchenne muscular dystrophy patients ; b) osteoarthritis. This project, which was planned to start in 2017, in collaboration with AACD (Associação de assistência a criançadefeituosa) was delayed due to bureaucratic problems. This Project will be supported by a Grant of R$16.000.000,00 from a federal initiative of PRONAS.

We had also started a collaborative project on regenerative medicine where our first goal was to compare the potential of different stem cells to differentiate in hepatocyes. This project , named CIPETRO, is a collaboration with Prof. SilvanoRaia from FMUSP and partially funded by the MInistry of Health (Ministério da Saúde). During last year this project which is undertaken by two students, Luiz Carlos Caires (pos-doc) and Ernesto Goulart (PhD, FAPESP) and one IC student (Kayque Silva, FAPESP) has advanced during this year. The preliminary results showed the potential of IPS derived human cells to differentiate in various cell lines (hepatocyte, hepatoblasts, endothelial and mesenchymal cells) and reconstitute a liver in a rat model. The next step will be to evaluate whether it will be functional.

Furthermore, due to Zika epidemic we have started a new project aimed at contributing *to our understanding of the mechanisms underlying the development of microcephaly associated or not with other malformations (Zika congenital syndrome) in fetuses exposed to Zika virus during gestation.*The main questions we wanted to address are: a) Is there genetic predisposition for acquiring the infection and for the development of microcephaly associated or not to other malformations in fetuses exposed to the Zika virus? b) In affected babies, is there altered expression of genes responsible for the genetic forms of microcephaly? In order to address these questions we performed first functional studies comparing discordant dizygotic twins (one affected and one normal) born to mothers infected by Zika virus during pregnancy. We were able to obtain samples from 8 pairs of twins (5 discordant all DZ and 3 concordant for ZCS, 2 MZ and one DZ) and compared IPS derived neuroprogenitor cells (NPC) from three sets of discordant twins (one affected and one normal). We

observed that NPC from the affected twins differed significantly from the normal twin regarding cell death, virus replication and mTor pathway. These results support the hypothesis of a genetic susceptibility to acquire CZS. Exome analysis of 18 affected babies allowed us to exclude previous genes involved in microcephaly and revealed enrichment of some other genes. Our next plan is to derive trophoblasts from these twins and investigate the outcome after “in vitro” infection with zika virus. Next we will perform RNAseq analysis in these samples in an attempt to identify genes/variants involved in this process. This study will be done in collaboration with the group of Prof. Sergio Verjovski-Almeida from Butantan institute.

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). This is a result of a 2016 expansion, with the acquisition of a storage server with 480 TB partially financed by USP. Use of Bravo robot (located at FMUSP, Dr. Marie) was validated and it is scheduled to be used routinely for exome library preparations next year. The *managing committee* is meeting once a year, while the *User committee* constantlyprovides suggestions to improve organization(http://genoma.ib.usp.br/servicos/sequenciamento-de-nova-geracao-ngs/comite).A total of 900 NGS tests (350 research; 550 paid) and ~ 48,632 sanger sequencing reactions(13,632 research; 35,000 paid) were performed at HUGH-CEL EMU for 9 researchers, 260 external users and samples for genetic diagnosis from our non-profit laboratory (detail in b). In addition, 95 samples for NGS from non-CEPID researchers were run in the EMU HighSeq equipment.

b) 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 established induced pluripotent stem cells (iPSC) of 72 patients with different genetic disorders and 14 controls (267 clones) in the last 5 years

c) Genetic counseling service: About 1500 families were attended by our team (about 60% 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. Written reports were provided to all attending individuals.

d) GeneticTests: We set up a web page of the non-profit laboratory for genetic tests (http://laboratorio.genoma.usp.br). During the last two years, we performed 1140 paid genetic tests (MLPA/disease specific CNVs, Triple/PCR for expansion, NGS panels, NGS exome). The number of paid tests have significantly increased in the last year (from 400 to 740), with a predominance of NGS-based tests **(Figure 1)**. NGS panels showed a high sensitivity, particularly for metabolic and neuromuscular disorders **(Figure 2).** The quality and reliability of our genetic tests have been certified yearly by the European Molecular Genetics Quality Netwok (EMQN). Additionally, about 1900 tests (Sanger sequencing, MLPA, NGS, Cytogenetics- karyotype, array-comparative genomic hybridization) related to research projects were also perfomed by HUG-CEL. The sequencing reactions of these tests were performed by the EMU facility.

e)Website of Brazilian Genetic Variation: We have developed, and hosted in our servers, a public access website (http://abraom.ib.usp.br) to provide information on the frequency of variants in 609 Brazilian healthy individuals that are parto f the Sao Paulo city elderly cohort studied at our cente (SABE cohort). The data was also published in Human Mutation and provides valuable information for the interpretation of pathogenicity of variants identified in genetic tests in Brazil and around the world.

e) Income resources administration: The income of the genetic tests and services are being used to pay for activities not supported by our current grants or university, such as payment of technicians **(Figure 3),** equipment maintenance and reagents for the genetic tests. This income isbeingadministratedatthe fundação Faculdade de Medicina USP and Fundação Universidade de São Paulo.

f) Partnership with AACD: A partnership with AACD has been established

since 2015, which supports salary of two medical doctors, two physiotherapists and two secretaries.

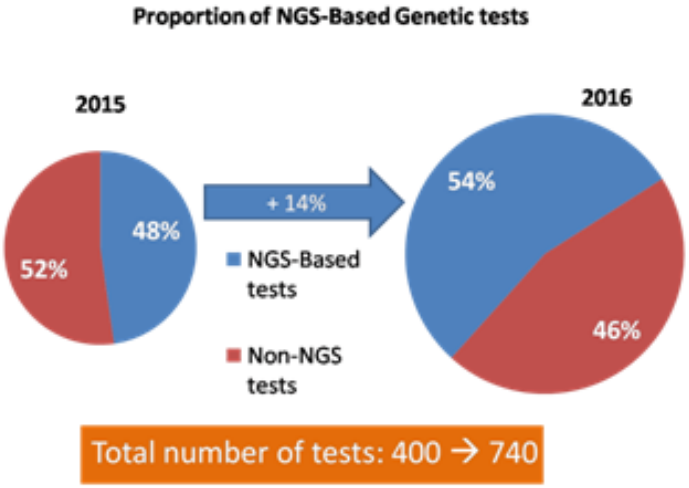

Figure 1: *Proportion of NGS-based genetic tests in the last two years.*

	2015 - 2017		
	Patients (N)	Positive detection	SENSITIVITY (%)
EXOME sequencing	61	21	**34,4**
PANEL sequencing			
Cancer (diagnostic testing)	42	14	33,3
Connective tissue disorders	8	2	25,0
Craniosynostosis / Craniofacial disorders	19	7	36,8
Developmental disorders	42	22	52,4
Metabolic disorders	18	12	66,7
Neurodegenerative disorders	19	10	52,6
Neuromuscular disorders	132	86	65,2
Skeletal disorders	26	12	46,2
TOTAL (PANEL sequencing)	306	165	**53,9**

Figure 2: *Sensitivity of genetic tests.*

Figure 3*:Proportion of technicians supported (total or partial salary) by the income from HUG-CEL services. About 30% of the technicians from USP are shared with other non-researchers at the Department or Institute of Biosciences.*

PART 3 - EDUCATION/ OUT REACH

A) High School Support Program

1. Project: Laboratory classes at school

http://www.genoma.ib.usp.br/pt-br/educacao-e-difusao/nossos-projetos/parcerias-com-diretorias-de-ensino/aulas-praticas-nas-escolas

We establish 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 **(annexes 4.1 to 4.3)**. 16 hours of technical and pedagogical support to 50 High School teachers were delivered; 39 students were trained to act as monitors during the time the laboratory is installed in their schools; 52 High Schools were assisted (8 of them twice in the period), from July/2016 to June/2017 and nearly 35,000 students were benefited.

2. Instructional support project

http://www.genoma.ib.usp.br/educacao-e-difusao/nossos-projetos/parcerias-com-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 centers, which currently provide instructional material to more than 100 teachers each year. 32 hours of technical and pedagogical support to 144 High School teachers were delivered for teachers of Biology, Sciences and Physics **(annex 4.4).**

3. The **Giant Cell Project**

http://www.genoma.ib.usp.br/pt-br/educacao-e-difusao/nossos-projetos/celula-gigante , a scenic cell amplified 130,000 times and a set of complementary activities designed to facilitate the understanding of cell concepts and a Scientific exhibition **"Light and Life" (USP goes to your school project**

http://www.genoma.ib.usp.br/pt-br/educacao-e-difusao/nossos-projetos/parcerias-com-diretorias-de-ensino/usp-vai-a-sua-escolawere visited

by 12 thousand people in this period **(annex 4.5)**.

4. First art competition for high school students on “DNA and biological heritage” http://www.genoma.ib.usp.br/pt-br/concurso-artistico - 108 participants presented videos, animations, drawings, sculptures, poems and songs.

B) Project having patients and their families as target

1. **Educational leaflets** –three more leaflets of a series of 12 educational leaflets were produced in the period.
http://www.genoma.ib.usp.br/educacao-e-difusao/materiais-didaticos/folhetos

2. TV Genoma indoor - The idea behind “TV Genoma” is to produce an information stream to allow otherwise largely redundant basic genetic information to be displayed in a more dynamic and instructive way. A variety of snippets of genetic information are shown interleaved with short videos about more general aspects.

C) Projects having the general public as target – The Sowing the seed of knowledge project – Metric of the second campaign “Is it at the DNA?”

http://www.ib.usp.br/biologia/projetosemear/estanodna/: The audience of 25 thousand users made more than 82 thousand page hits during one and a half years, with the majority concentrated in the first 8 months. HUGH-CELL coordinated, at the Metro, the campaign of the following Cepids: Centro de Pesquisa em Alimentos, Centro de Pesquisa em Processos Redox em Biomedicina and Centro de Pesquisa em Obesidade e Comorbidades.

D) Interviews to the Media and Science Dissemination Articles

The interaction with the media to discuss, translate and disseminate new scientific discoveries to lay people was achieved through 20 interviews and articles of science dissemination. **(annex 4.6)**

Annex 1
Publications in peer reviewed journals, books and patent

From July 2016 until June 2017, our group has published 71 journal articles (all listed below), 9 books or book chapters, 11 abstracts in National meetings, and 28 abstracts in International meetings. During this period, our graduate students submitted 6 Master Theses and 8 Doctoral Dissertations. About 15 conferences, lectures and symposia were done by our time.

1. Articles

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2. Patents

International patent filing:

Title: “Compositions and methods of treating muscular dystrophy”

Application No./ Patent No. PCT/US2015/056026

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Applicant: The Broad Institute, Inc., Children's Medical Center Corporation, University Of Sao Paulo.

Inventors: Kerstin Lindblad-Toh, Louis M. Kunkel, Natassia M. VIEIRA, Mayana ZATZ

Annex 2
Meetings, Conferences, Lectures

1. Abstracts: National Meetings

1. Aguiar TFM,Maschietto M, Carraro DM, Rosenberg C, Costa CM L, DA Cunha IW, Caminada TSR, Cypriano M, **Krepischi AC**. Estudo de mutações somáticas identificadas em Sequenciamento de Exoma de Hepatoblastomas. In: SOBOPE - XV Congresso Brasileiro de Oncologia Pediátrica, 2016, Rio de Janeiro. XV Congresso Brasileiro de Oncologia
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3. Barcelos IP,Paz J A, **Okamoto OK,** Matushita H, Bueno C. Matsui Junior C, Souza FAP, **Kok F**, Kubota GT, Lucato LT, Godoy LFS, Manreza MLG, Takahashi PG, Passalacqua PS, Cunha, PEL, Paolilo RB, Kaid C, Cortez BA, Reed, U.C. .Relato de caso de síndrome de MowatWinson e astrocitomapilocitico de mesencefalo e pedúnculo cerbelar superior . In: 11º Congresso Brasileiro de Neurologia Infantil e 2º Encontro das Sociedades de Neurologia Infantil do Cone Sul, 2016, Foz do Iguaçú. Cadrno de resumos, 2016
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23. Rivas MP, **Krepischi AC**. . Epigenetic mechanisms in liver tumors: Gene expression analysis of epigenetic machinery in hepatoblastomas. In: AACR International Conference on Translational Cancer Medicine, 2017, São Paulo.

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7. Conferences, Symposia, Round Tables, Lectures

1. **Krepischi ACV**. *Câncer pediátrico: como a genética pode contribuir*. 2016. (Apresentação de Trabalho/Conferência ou palestra). Instituto da Criança-FMUSP
2. **Mingroni-Netto RCA** contribuição do Laboratório de Genética Humana-IBUSP-ao aconselhamento genético da deficiência auditiva, 2016 durante o

Colóquio: conhecendo a USP: contribuições da pesquisa e da extensão no campo das deficiências. 5 de dezembro de 2016

3. **Mingroni-Netto R.C**. “Ampliação do diagnóstico molecular da surdez”, no painel “Avanços no diagnóstico molecular da surdez no Brasil” durante o congresso “Hearingand Balance” da Fundação Otorrinolaringologia, São Paulo, 6/4/2017
4. **Mingroni-Netto RC.** “Fundamentos da Genética, herança , genes, cromossomos e mutações”., durante o I Encontro do Departamento Científico de Neurogenética da Academia Brasileira de Neurologia, 3/6/2016. São Paulo
5. **Mingroni-Netto RC.**Moderadora da Mesa –redonda “ Como produzir novas células ciliadas” durante p XXVII Simpósio e XII Jornada de Fonoaudiologia, SIJO/UNIFESP, 15/09/2016, São Paulo.
6. **Okamoto OK**. Palestra: “As células-tronco tumorais”. AC Camargo Cancer Center. 2016.
7. **Okamoto OK**. Special seminar: “Stem cell self-renewal genes as drivers of brain tumor aggressiveness”. Universityof Southampton, 2017.
8. **Okamoto OK**. Palestra: “CRISPR-Cas9 e identificação de alvos terapêuticos em células-tronco tumorais”. SIMPÓSIO USP-DISCUTE “Impactos da nova técnica de edição de genomas CRISPR-Cas9 na ciência e na sociedade”. Pró-reitorias de Pesquisa e Pós-Graduação (USP) e ACIESP. ICB-USP, 2017.
9. **Passos-Bueno MR** . Apresentação de trabalho "Como interpretar funcionalmentenosso genoma". XXXI Reunião Anual da FeSBE . Foz do Iguaçu,, Brasil, 2016.
10. **Passos-Bueno MR** . Seminário "Como traduzir o significado funcional das variantes genéticas?" genoma". Departamento de Genética da Faculdade de Medicina de Ribeirão Preto, Ribeirão Preto, 2016
11. Sanchez SanchezSM, Oliveira K G O, Romariz SAA , Perez SCC - Zachi EC - Yamamoto GL -Sosa J - Reis EMR - **Passos-Bueno MR**, **Sertie AL** . "Estudo de mecanismos de epigenéticos em tumores de fígado: análise da expressão de genes reguladores da maquinaria epigenética em hepatoblastomas". VI Simpósio de atividades acadêmicas do Departamento de Genética e Biologia Evolutiva, USP, São Paulo, 2016.
12. **Vainzof M**. "Sequenciamento de nova geração na investigação das miopatias:

como interpretar?" XXVII Congresso Brasileiro de Neurologia-Mesa Redonda: Atualização no diagnóstico das miopatias. Belo Horizonte, 2016.

13. **Vainzof M** . "Células-tronco e medicina regenerativa" - Congresso Brasileiro de Genética - Genética na Praça, Caxambu, 2016
14. **Zatz M**. "Stem-Cells in Duchenne muscular dystrophy: myth or reality? " XX Congresso da SBTMO. Sociedade Brasileira de Transplante de Medula Óssea. Fortaleza, Brasil, 2016.
15. **Vianna-Morgante AM**, Lyon Mary F: *A história de uma hipótese* – Instituto de Biociências – USP, setembro 2016.

Annex 3
Theses and Dissertations, Awards

1. Ph.D.

1. **Fernando Gomes**. "Caracterização funcional da peroxirredoxina mitocondrial (mTPx1) na fisiologia redox de Saccharomyces cerevisiae". 2016. Ciências Biológicas (Genética)) - Universidade de São Paulo. Supervisor:Luis Netto
2. **FlávioRomero Palma**. "Investigação comparativa de modelos de FALS1 e FALS8 e de possíveis interações entre SOD1 e VAPB em Saccharomycescerevisiae". 2016. (Ciências Biológicas (Genética)) - Universidade de São Paulo. Supervisor:Luis Netto
3. **Leandro Ucela Alves**. “Estudos Genéticos e Moleculares em famílias com defeitos de membros”. Ciências BiológicasIBUSP Supervisor : Regina Mingroni Netto .
4. **Ligia Pereira Castro**. “Caracterização Genotípica de pacientes brasileiros com deficiência em processos de reparo de DNA”, 2016. PhD on Biotechnology, Universidade de São Paulo, SP, November 9th, 2016. Fellowship FAPESP.
5. **Thaiany Quevedo Melo**, “Overexpression of alpha-synuclein and its effects on mitochondria trafficking and autophagy in yeast, SH-SY5Y cells and hiPSC- derived dopaminergic eurons of patients with Parkinson´s disease”. Faculdade de Medicina da USP, December 2016. Supervisora: Merari Ferrari
6. **ValescaAnschau**. "Caracterização cinética da redução de 1-Cys Peroxirredoxinas por ascorbato". 2017. (Ciências Biológicas (Biologia Genética)) - Universidade de São Paulo. Supervisor:Luis Netto
7. **Patrícia Benites Gonçalves da Silva**. Fator de transcrição OCT4A e agressividade de meduloblastoma. 2016. Tese (Doutorado em Ciências Biológicas (Genética)) - Universidade de São Paulo, Fundação de Amparo à Pesquisa do Estado de São Paulo. Orientador: Oswaldo Keith Okamoto.
8. **Carolina de Oliveira Rodini**. Contribuição das células-tronco mesenquimais ao desenvolvimento tumoral. 2016. Tese (Doutorado em Biologia (genética)) - Universidade de São Paulo, Fundação de Amparo à Pesquisa do Estado de São Paulo. Orientador: Oswaldo Keith Okamoto.

2. Master

1. **Aline Lopes Ribeiro**. Lisil oxidase e propriedades pró-tumorigênicas de pericitos. 2016. Dissertação (Mestrado em Ciências Biológicas (Biologia Genética)) - Universidade de São Paulo, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior. Orientador: Oswaldo Keith Okamoto
2. **Dayane Bernardino da Cruz**. Expressão de conexinas em células-tronco da polpa dentária. 2016. Orientador: Regina Célia Mingroni Netto Dissertação Mestrado (Biologia/Genética) – 2016 Instituto de Biociências da Universidade de São Paulo
3. **Francisco Ivânio Arruda Alves**. "Análise de transcriptomas de células de pacientes xerodermapigmentosum após irradiação com luz UVA e estudo de retrocópias de genes de reparo." Orientador: Carlos Frederico Menckel. Master onBioinformatics, Universidade de São Paulo, SP, em 21 de fevereiro de 2017. Fellowship FAPESP.
4. **Julia Beck Raices**. “Modelo de seleção haploide para evolução de genes novos”. Orientadora. Maria DulcettiVibranovski. 21/06/2017.
5. **Juliana Emília Prior Carnavalli**. Obesidade e genes candidatos: estudo de associação em populações quilobolas do Vale do Ribeira**.** Orientador: Regina Célia Mingroni Netto. Dissertação Mestrado (Biologia/Genética) – 2016
6. **Renata Ishiba**. “Degeneração e regeneração muscular em modelos murinos com deficiência de disferlina”. Orientadora:Mariz Vainzof. Defesa: 07/04/2017. Bolsa CAPES.

3. Awards

1. **Bruno Ghirotto**, prêmio de Menção Honrosa pelo seu trabalho*Avaliação do potencial terapêutico de imunoglobulina G humana em modelo murino duplo knock-out para distrofia muscular de Duchenne.,* apresentado na Etapa Internacional do 24º SIICUSP, evento promovido pela Pró-reitoria de Pesquisa da USP, 2016. (MayanaZatz)
2. **Danielle Ayub-Guerrieri**. PrêmioElsevier no *International Congresso f the World Musclesociety*, Granada, Espanha, 4-8/10/2016,

http://www.worldmusclesociety.org/news/view/129 (Mariz Vainzof)

3. **Eduardo TassoniTsuchida**,aluno de iniciação científica. 6º Prêmio Oswaldo Frota-Pessoa de Incentivo à Pesquisa Científica (Modalidade Iniciação Científica), 2015.
4. **Eduardo TassoniTsuchida.** Menção Honrosa no 7º Prêmio Oswaldo Frota-Pessoa de Incentivo à Pesquisa Científica (Modalidade Iniciação Científica), 2016. (Luis Eduardo Soares Netto)
5. **Luiz Caires.** Prêmio da ISSCR para o trabalho Discordanttwins for congenital zikasyndrome show differentialzika viral infection in(HIPSC)-NPCS", junho de 2017
6. **Vanessa Simões**, aluna de mestrado. Prêmio de melhorpôsterapresentado no *23rd Congress of the International Union for Biochemistry and Molecular Biology* - 44th Annual Meeting of the Brazilian Society for Biochemistry and Molecular Biology, Simões V, Bueno MRSEP, Netto LES. Redox process canmediateosteogenic differentiation**.**

Annex 4
Tables Education /Out Reach

Annex 4.1

Laboratory Class Project - Training of 50 High School teachers

Educational Directory of Center-West Region, February, 2nd, 2017

Educational Directory of Osasco Region, March, 4th, 2017.

Educational Directory	Teacher	High School
Center-West	MordechajGrinbaun	EducationalDirectory
Center-West	Luciane Pereira Colares	EducationalDirectory
Center-West	Denise Ribeiro Rezende dos Santos	EducationalDirectory - supervisor
Center-West	Sandro Pereira de Novaes	DE Centro-Oeste
Center-West	Solange Aparecida Fatorelli	EE Alexandre Von Humboldt
Center-West	Léo Marcos Ortiz Credídio	EE Anhanguera
Center-West	Rubens Pimenta Maciel	EE Dona Ana Rosa de Araújo
Center-West	Jose Alves Mendes Filho	EE Emiliano Augusto Cavalcanti de A e Melo
Center-West	Fernanda M. C. Freitas	EE Guiomar Rocha Rinaldi
Center-West	Mychelle Teotônio Salgado	EE João XXIII
Center-West	Claudia Danieli Gil	EE Martim Francisco
Center-West	Antonio da Silva Sobrinho	EE Ministro Costa Manso
Center-West	Jacqueline C.N. Contreiras	EE Ministro Costa Manso
Center-West	Rosana Laranjeira dos Santos	EE Odair Martiniano da Silva – Mandela
Center-West	Wagner Junior	EE Oswado Aranha
Center-West	Moisés Rizzo	EE Pedro Fonseca
Center-West	Ana Claudia da Cunha	EE Pereira Barreto

	Mattos	
Center-West	Claudia Gil	EE Prof. Alberto Levy
Center-West	Angélica Cristine G. de Almeida Campos	EE Prof. Almeida Junior
Center-West	Vasco Degani	EE Prof. Andronico de Mello
Center-West	Raquel Maria Rodrigues	EE Prof. Antonio Alves Cruz
Center-West	Jéssica Bogna	EE Prof. Architiclino Santos
Center-West	Larissa Caroline Meneghin Vieira	EE Prof. Emygdio de Barros
Center-West	José Guilherme Andrade Filho	EE Prof. Lourival Gomes Machado
Center-West	Cecília Vaz Castro	EE Prof. Manuel Ciridião Buarque
Center-West	Helena Maria B. Francini	EE Prof.ª Lygia de Azevedo Souza e Sá
Center-West	Leandro de Souza Antonio	EE Prof.ª Maria Ribeiro Guimarães Bueno
Center-West	Lisandra Camila Oliveira	EE Romeu de Moraes
Center-West	Chandra Blanc M. Goes	EE Senador Adolfo Gordo
Center-West	Vanderson Cristiano de Souza	EE Solon Borges dos Reis
Center-West	Angela Maria Ventura	EE Virgília Rodrigues A. de Carvalho Pinto
Osasco	AngelaCarvalho Oliveira	EE Dr. Américo Marco Antonio
Osasco	Katia Cristina Guerreiro Carraro	EE Antonio Carlos da Trindade
Osasco	Karine Pereira	EE Cel. Antonio Paiva de Sampaio
Osasco	Marilin Fernandes Brandão	E E Prof. Armando Gaban
Osasco	UlimaRomina Alves	EE Dr. Aureliano Leite
Osasco	Jupciana Martins	EE Prof. Fanny Monzoni Santos

	Figueiredo	
Osasco	Denise Aparecida Miguel Silva	EEProf. Francisco Casabona
Osasco	Valquíria F.Cruz	EE Irmã Gabriela Maria Elizabeth Wienkem
Osasco	Josilaine Ribeiro de Barros	EE Prof. Gastão Ramos
Osasco	Cícero Prospero da Silva Correa	EE Dep. Guilherme de Oliveira Gomes
Osasco	Patricia do Carmo Lopes Barreto	EE Jardim Santa Maria
Osasco	Renata Osório Rosa Zanetti	EE Prof. José Jorge
Osasco	Danielle Monique do Nascimento Amaral	EE Prof.José Maria Rodrigues Leite
Osasco	Amanda Gouveia da Silva	EE Julia Lopes de Almeida
Osasco	Viviane dos Reis Silva	EE Prof. Dr. Luiz Lustosa da Silva
Osasco	Viviane dos Reis Silva	EE Neusa de Oliveira Prévide
Osasco	Angélica M. Fernandes	EE Prof.Newton Espirito Santo Ayres
Osasco	Vlademir Alves Miriam Santana Silva Aparecida	EE OguiomarRuggieri
Osasco	Cintia Maria Ferreira Carossa	EE Rosa Bonfiglioli

Annex4.2

Training of 39 High School students to act as monitors at their schools.LaboratoryClass Project, Osasco EducationalDirectory, March, 17th, 2017.

EducationalDirectory	Teacher	High School
Osasco	Maria Isabel M. P. de Araujo Kauan A. C. Soares Eduarda Gomes de Oliveira	EE Dr. Américo Marco Antonio
Osasco	Eduarda H.Avelino Mariana Remigio Rafael	EE Cel. Antonio Paiva de Sampaio
Osasco	Lais de Brito Silva Ronded Bispo Almeida dos Santos	E E Prof. Armando Gaban
Osasco	Alex Gomes Bianca da Silva dos Santos	EE Irmã Gabriela Maria Elizabeth Wienkem
Osasco	Mariana Vieira das Chagas Alessandra Brandão Giovanna G. A. Costa	EE Graciliano Ramos
Osasco	Franciele C.de O. Barros Tiago dos SantosTeixeira Samantha de Oliveira Tejada	EE Jose Geraldo Vieira
Osasco	Vivian Almeida da Silva Gabriel Augusto Justo Motta Andreyama Aparecida de Souza	EE Prof. José Jorge
Osasco	Julia Rutizat Nascimento Raissa Andrade do Nascimento Matheus Alves Landini	EE Julia Lopes de Almeida
Osasco	Giovanna Cavalcante Rocha Pamela Viana Fernandes Wanderson Gabriel	EE Leonardo Vilas Boas

Osasco	Fabiano Brito de Souza Giovanna Souza Costa Gabriela Taina Monteiro	EE Prof. Lucy Anna Latorre
Osasco	Cesar dos Santos Ferreira Jaqueline Santos de Amaral Kayque Ribeiro de Souza	EE Prof. Dr. Luiz Lustosa da Silva
Osasco	Julio Cesar Antoniassi Beatriz Vitoria Fonte Ingrid Vitoria Campos	EE Maria Augusta Siqueira
Osasco	Giovana Koper	EE OguiomarRuggieri
Osasco	Jorge Washington A Liriel Almeida Coelho	Educador Paulo Freire
Osasco	Kauê da Silva Teles Livia Lemes Letycia Vitória	E E São Paulo da Cruz

Annex4.3

Laboratory at School Project -School were attended from July, 2017 to June, 2017 - *Schools attended twice in this period

EducationalDirectory	High School
Osasco	EE Almeida Junior
Osasco	EE OguiomarRuggeri*
Osasco	EE Neuza de Oliveira Prévide
Osasco	EE Dr Luiz Lustosa
Osasco	EE Americo Marco Antonio
Osasco	EE Jose M. Rodrigues Leite
Osasco	EE Tarsila do Amaral*
Osasco	EE Prof. José Jorge*

Osasco	EE Lucy Anna Latorre
Osasco	EE Fanny Monsoni
Osasco	EE Gastão Ramos*
Osasco	EE Antonio Raposo Tavares
Osasco	EE Julia Lopes
Osasco	EE José Edson M. Gomes
Osasco	EE Walter Negrelli*
Osasco	EE Irmã Gabriela
Osasco	EE Alice Velho Teixeira*
Osasco	EE Major Telmo Coelho*
Osasco	EE Armando Gaban
Osasco	EE Francisco Matarazo
Itapecerica da Serra	EE Carlos Alberto Pereira
Itapecerica da Serra	EE Jardim Montesano
Itapecerica da Serra	EE Gertrudes Eder
Itapecerica da Serra	EE Sebastião de M. Cardoso
Itapecerica da Serra	EE Maria Olimpia de S. Q. Maciel
Itapecerica da Serra	EE Jardim do Carmo
Itapecerica da Serra	EE Donizetti Aparecido Leite
Itapecerica da Serra	EE Eduardo Roberto Daher
Itapecerica da Serra	EE Jornalista Paulo de Castro Junior
Itapecerica da Serra	EE Joaquim Fernando Paes de Barros Neto
Osasco	EE Benedicto Caldeira
Osasco	EE Antonio Carlos da Trindade
Centro-Oeste	EE Prof. Emygdio de Barros
Centro-Oeste	EE Prof. Almeida Junior*

Centro-Oeste	EE Solon Borges dos Reis
Centro-Oeste	EE Prof. Architiclino Santos
Osasco	EE Eloi Lacerda
Osasco	EE Francisco Casabona
Centro-Oeste	EE Emiliano Augusto Cavalcante de A. e Melo
Centro-Oeste	EE Virgilia Rodrigues A de Carvalho
Osasco	EE Josué Benedicto Lopes
Osasco	EE Luiz Lustosa da Silva
Osasco	EE Jardim Santa Maria
Centro-Oeste	EE João XXIII
Centro-Oeste	EE Profa. Guiomar Rocha Rinaldi
Osasco	EE José Ribeiro de Souza
Osasco	EE Francisco Buonaduce
Centro-Oeste	EE Prof. Lygia de Azevedo Souza e Sá
Centro-Oeste	EE Prof. Pedro Fonseca
Osasco	EE Leonardo Vilas Boas
Osasco	EE Fundação Casa
Osasco	EE São Paulo Cruz

Annex4.4

Training of 31 Biology High School teachers to work on the Project "Instructional Material"; Educational Directory from Osasco: August, 31st, 2016

Teacher	High School
Eunice Hoffman Macedo	EE Prof. Alice Velho Teixeira
Beatriz Ribeiro Zanon	EE Dr. Américo Marco Antonio

Fernanda GagetiColepicolo	EE Dr. Antonio Braz Gambarini
José Carlos de Oliveira Junior	EE Antonio de Almeida Junior
Hayrton Avelino Monteiro	EE Antonio Raposo Tavares
Cintia Rossini	EE Prof. Benedito Caldeira
Denise Eduarda R.F de Santana	EE Jardim Cipava II
Marcos Viana da Silva	EE Prof. Ernesto Thenn de Barros
Jair Gonçalves da Rocha	EE Prof. Fanny Monzoni Santos
Reginaldo dos Santos	EE Prof. Francisca Lisboa Peralta
Roseli Cristina Laranjeira	EE Francisco Matarazzo Sobrinho
ValquiriaFornarollii da Cruz	EE Irmã Gabriela Maria Elizabeth Wienkem
Alessandra Brito Santos Freitas	EE Prof. Gastão Ramos
Rosemary Vale	EE Dep. Guilherme de Oliveira Gomes
Carolina Assaf	EE Prof. Heloisa de Assunpção
Ronaldo Adriano de Faria	EE Jardim Santa Maria III
Mirian Alves Aversa	EE José Edson Martins Gomes
Carmen Cinira Teixeira	EE José Geraldo Vieira
Miriam Lúcia de Oliveira	EE Prof. José Jorge
Lucilene Costa de Souza	EE Prof. Jose Liberatti
Nilda Aparecida Maximode Matos	EE Prof. Josué Benedito Mendes
Maria Angela S Gomes	EE Leonardo Vilas Boas
Marcos Viana da Silva	EE Prof.Lucy Anna Latorre
Luciana Cardoso Romeiko	EE Prof. Maria augusta Siqueira
Iraci Vieira de Araujo	EE Prof. Neuza de Oliveira Prévide
Mirian Santana Silva Aparecida	EE Prof. OguiomarRuggieri
Flávia Garcia Borges	EE Educador Paulo Freire

Cintia Rocini	EE Rosa Bonfiglioli
Aline Ribeiro Del Negro	E E São Paulo da Cruz
Divina Maria de Camargo	E E Tarsila do Amaral
Rosemary Valli	Fundação Casa I

Training of 44 Biology High School teachers to work on the Project "Instructional Material"; Educational Directory from Osasco: April, 18th, 2017

Teacher	High School
Andre Ribeiro Lopes da Sé	EE Prof. Alcyr de Oliveira Porciuncula
Eunice Hoffman Macedo	EE Prof. Alice Velho Teixeira
Fernanda Ferreira de Almeida	EE Dr. Américo Marco Antonio
Fernanda GagetiColepicolo	EE Dr. Antônio Braz Gambarini
Kátia Cristina Guerreiro Carraro	EE Antonio Carlos de Trindade
Luciana Aparecida Monteiro Paiva	EE Antonio de Almeida Junior
Karine Pereira	EE Cel. Antonio Paiva Sampaio
Maria Helena Fernandes Damasceno	EE Antonio Raposo Tavares
Marilin Fernandes Brandão	EE Prof.ArmandoGaban
UlimaRolima Alves	EE Dr. Aureliano Leite
Cintia Rocini	EE Prof. Benedicto Caldeira
Maria Neuza de Souza Carvalho	EE Prof. Claudinei Garcia
Andrea Barbieri Rezende	EE Prof. Eloi Lacerda
Maria de Lurdes Mesquita O. Sepriano	EE Prof. Ernesto Then de Barros
Simone Alvarenga Cunha	EE Prof. Fanny Monzoni Santos
Patricia R Santos	EE Prof. Fernando Buonaduce
Marcela Alves	EE Prof. Francisca Lisboa Peralta

Karina da Silva Almeida	EE Francisco Matarazzo Sobrinho
Valquíria Fornarolli da Cruz	EE Irmã Gabriela Maria Wienkem
Josilaine Ribeiro de Barros	EE Prof. Gastão Ramos
Daniela Camargo da Palma	EE Glória Azedia Bonetti
Carlos Alberto Ramos	EE Graciliano Ramos
Cícero Próspero da Silva Correia	EE Dep. Guilherme de O. Gomes
Sergio Seixas de Barros	EE Profa. Heloisa de Assumpção
Ezilda Oliveira Alves	EE Prof. João Baptista de Brito
Mirian Alves Aversa	EE José Edson Martins Gomes
Renato Policarpo da Silva	EE Prof. Jose Jorge
Danielle Monique do Nascimento	EE Prof. Jose Maria Rodrigues Leite
SoniaRegina Silverio Monteiro	EE Jose Ribeiro de Souza
Maira Figueiredo Nunes	EE Prof. JosueBenedicto Mendes
Silvana P Santos Gonçalves	EE Julia Lopes de Almeida
Maria Ângela da S. Gomes	EE Leonardo Vilas Boas
Bruno Henrique Cohenh	EE Profa. Lucy Anna Latorre
Viviane dos Reis Silva	EE Prof. Dr. Luiz Lustosa da Silva
Luciana Cardoso Romeiko	EE Prof. Maria Augusta Siqueira
Guilherme Thiago Brandt Mazinni	EE Prof. Neusa de Oliveira Prévide
Angelica Maria Fernandes	EE Prof. Newton do E. Santo Ayres
Bruno Henrique Coventi	EE Prof. OguiomarRuggeri
Elaine Dias dos Santos	EE Prof. Orlando Geríbola
Gislene Mariano Costa	Educador Paulo Freire
Denise Fernandes	EE Dr. Ricardo Genesio da Silva
Cintia Rocini	EERosa Bonfiglioli
Denise Fernandes	EE Tarsila do Amaral

Suelen Ribeiro Borde	EE Major Telmo Coelho Filho

Training of 32 Biology High School teachers to work on the Project "Instructional Material"; Educational Directory of Catanduva: May, 4th, 2017

Teacher	**High School**
Rômulo SensulineValaretto	EE Prof. Dinorah Silveira Borges
Katia Maria de Almeida	EE Barão do Rio Branco
José Luis Dotto	EE Joaquim Alves Figueiredo
Maria de Fatima Menésio Santos	EE Saturnino Antonio Rosa
Rubens Avelino Neto	EE Isabel LerroOrtenblad
Fabiana Aparecida dos Santos	EE Carolina de Quadros Toledo
Juliana Frenkelis de Oliveira	EE Gabriel Hernandes
Lucia Aparecida Zoli de Souza	EE Dr.Carlos Augusto Froelich
Elaine Parra Martins	EE Antonio Carlos
Tadeu Francisco de Tadei	EE Prof Ruth Dalva Ferraz Farão
Evelise B. Ravazi	EE Nicola Mastrocola
Nadia Perpetua RosanteLucheti Rosiane Cristina de Lima Lorenceti	EE Prof. Bento de Siqueira
Camila B. Zanetti Priscila da Silva Fernandes Helena Ribeiro Souza	EE Joao Gomieri Sobrinho
Roseli Perpétua Bordenalli	EE Antonio Maximiano Rodrigues
Valentim Apdo. Garum	EE Prof. Vitorino Pereira
Giuliano Peres	EE Jardim Imperial
Antonio Marcos Torres Sueli M.G. Carvalho	EE Capitão HoracioAntonio do Nascimento

Katiuscia P. Belotti C. Costa	EE GiusepeFormigoni
Adriana Prado	EE Dr Nestor Sampaio Bittencourt
Thais Aparecida Aessemi	EE Benedito Borges da Silveira
Joice Matture	EE Prof. Elmira Goulart Pereira
Samira Macedo	EE Paulo de Lima
Julice Lute Boque Marco Antonio Teotônio de Castro	EE Prof. Mario Florence
Adriana Mara Trovo Rota Solange de Oliveira Neves Turchieri	EE Prof. Shirlei Camargo Von Zubem
IveliseTereza de Castro Sachi	EE Pedro Teixeira de Queiroz
Natalia Estevam Gomes Mamede	EE Alfredo Minervino

Training of 37 Physics and Sciences High School teachers to work on the Project "Instructional Material"; Partnership with Instituto de Física-IF-USP/SP

Educational Directory of Catanduva: May, 5th, 2017

Teacher	High School
Renan M C Attab Ana Paula RossetoCorsatti	EE João Gomieri Sobrinho
Josiane Cristina de Lima Lorenceti Nadia Perpetua RosanteLucheti	EE Prof. Bento de Siqueira
Lucas Gustavo pires Barlza Claudia Maria da S. Esparza	EE Nicola Mastrocola
Elisangela Ap. R .de Assis Tobochi Anderson Cardoso	EE Gabriel Hernandez Ferreira
Evelise B. Ravazi	EE Barão do Rio Branco
Glauciê Garrafa Berto de Moraes	EE Paulo de Lima Correa
Wanda Mineiro	EE Benedito Borges da Silveira

Margie de L. Oliveira	EE Dinorah Silveira Borges
Denise SisdeliDocci	EE Alfredo Minervino
Maria José BernardesFernandes Elaine Parra Martins	EE Antonio Carlos
Carlos Henrique Cagnassi	EE Giuseppe Formigoni
Lea Aparecida de Almeida Edilamar Aparecida Zanqueta	EE Antonio Maximiano Rodrigues
Renato Pardi Diegues	EE Capitão HoracioAntonio do Nascimento
Valentim Aparecido Garcia Giuliano Peres	EE Vitorino Pereira
Vlademir J. Toneto Miriam Palotta Lima	EE Pedro Teixeira de Queiroz
José Luis Dotto	EE Joaquim Alves Figueira
Gesiane G. Magalhães	EE Isabel Lima
Thais de Fátima Piovesano Lucinéia Cristina da Silva	EE Dr.Carlos Augusto Froelich
Tânia R. VendraquiniCarvalho MauricioRibeiro	EE Jardim Imperial
Edimara Cristina Ferraz	EE Carolina de QuadrosToledo
Gislene Rocha Fulas	EE Saturnino Antonio Rosa
Edson F. de Aguiar	EE Prof. Shirlei Camargo Von Zubem
Celi C. BortolucciAssolini Enicélia da G. Castelhandro	EE Prof. Mario Florence
Alessandro T Chaves	EE Dr Nestor Sampaio Bittencourt
Silverlaine G. M. Santos	EE Prof Ruth Dalva Ferraz Farão
Lourdes Aparecida Souza Santos	EE Elmira Goulart

Annex4.5

EXHBITIONS OF THE "GIANT CELL" AND THE SCIENTIFIC EXHBITION "LIGHT AND LIFE"

GiantCell

- 18 a 20/08/2016 – 10ª. Feira USP e as Profissões, Parque Cientec. 2,550 visitors

Giant Cell and Light and Life

- August, 17th to 21th , 2015 – Osasco Plaza Shopping, Osasco, SP - 2,780 visitors
- October, 17th and 18th, 2015 – ViradaCientífica da USP – 600 visitors
- August, 09thto 13th, 2016 – EE Barão de Rio Branco, Catanduva, SP – 3093 visitors
- September, 05th to 09th, 2016 – Osasco Plaza Shopping, Osasco, SP – 2,500 visitors
- September, 11th to 14th , 2016 – Brazilian-International Congress of Genetics, Caxambu, MG – 600 visitors

Annex 4.6

Interviews to the Media and Science Dissemination

1. Uma lição de futuro - *Época negócios*, **MayanaZatz**,janeiro de 2017
2. Em time que está ganhando não se mexe- *Veja* online, janeiro de 2017http://veja.abril.com.br/complemento/pagina-aberta/fapesp-em-time-que-esta-ganhando-nao-se-mexe.html
3. Novas perspectivas para o transplante de órgãos -**MayanaZatz-***O Estado de S. Paulo* , 3 de fevereiro
4. Atritos entre governadores e FAPESP- **MayanaZatz -** entrevista a Gabriel Alves, *Folha de S*. *Paulo*, 4 de fevereiro
5. Filhos se parecem mais com os pais? **MayanaZatz -**Entrevista ao Fantástico, *Rede Globo* 5 de fevereiro
6. Queremos viver mil anos? **MayanaZatz**participaçãoDebate com Felipe

Pondé, *Jornal da Cultura*, 16 de fevereiro

7. Projeto Genocão, **MayanaZatz,** *Rádio Jovem Pan*, 17 de fevereiro
8. A importância das agências financiadoras para pesquisa científica, **MayanaZatz,** *Radio USP*, 20 de fevereiro
9. Gemelos, clave para entender cómoelzika provoca malformaciones congénitas, Global - Auclic de lainformación, **MayanaZatz,** 27 de fevereiro http://www.unamglobal.unam.mx/?p=11674
10. A importância da FAPESP para as pesquisas.**MayanaZatz,***Jornal da USP*, 6 de março https://jornal.usp.br/atualidades/mayana-zatz-comenta-em-entrevista-corte-de-recursos-da-fapesp/
11. Mulheres na ciência. **MayanaZatz***Jornal da Cultura*, 8 de marçohttps://www.youtube.com/watch?v=THL2cfsojp4
12. Mulheres já produzem metade da ciência do Brasil, diz levantamento .**MayanaZatz,***Folha de S. Paulo,*http://www1.folha.uol.com.br/sobretudo/carreiras/2017/03/1864542-mulheres-ja-produzem-metade-da-ciencia-do-brasil-diz-levantamento.shtml?cmpid=compw
13. Dia internacional da mulher, **MayanaZatz,** *Jornal do Brasil*5.http://www.educacao.sp.gov.br/noticias/de-marie-curie-a-mayana-zatz-conheca-mulheres-destaques-em-seis-areas-do-conhecimento
14. Pesquisas com CRISPR-cas9 devem ser realizadas em embriões? **MayanaZatz,** *Rádio USP,* 12 de abril
15. Instituto Serrapilheira- A importância do investimento na iniciativa privada- J*ornal da Band*, **MayanaZatz,** 12 de abril
16. *Revista NEXO*: **MayanaZatz**:https://www.nexojornal.com.br/expresso/2017/04/18/Como-os-cientistas-reagem-ao-menor-or%C3%A7amento-federal-para-a-%C3%A1rea-em-12-anos, 18 de abril
17. Clues to zika damage might lie in cases of twins- NY times, **MayanaZatz,** 2 de maio
18. Entrevista com **Regina CéliaMingroni Netto** para a Revista *O Biólogo*, tema “Mendel e o nascimento da Genética”, 2016.
19. Entrevista à Rádio USP. Professor explica como erros aleatórios do DNA

podem causar câncer.**O Keith Okamoto,** (24/05/2017). http://jornal.usp.br/atualidades/professor-explica-como-erros-aleatorios-do-dna-podem-causar-cancer/

20. Participação em mesa redonda sobre prevenção do câncer no Fórum "A Jornada do Paciente com Câncer", promovido pela Folha. **O Keith Okamoto,** (24-25 de Abril). http://www1.folha.uol.com.br/seminariosfolha/2017/04/1874385-veja-a-programacao-do-forum-a-jornada-do-paciente-com-cancer.shtml

Annex 5
Personal

Students IC

NAME	SUPERVISOR
André Silva Bueno	Regina C.Mingroni-Netto
Artur Berselle	Maria Rita Passos-Bueno
Barbara Santos de Oliveira	Merari F. R. Ferrari
Camila Corradi	Carlos F M Menck
Camila Lovaglio Santos	Maria Rita Passos-Bueno
Carolina de Seixas Couto Leite	Oswaldo Keith Okamoto
Daniel Fredy Vargas Teran	Mariz Vainzof
Eduardo Tsuchida	Luis Eduardo Soares Netto
Erika Ramos	Maria Rita Passos-Bueno
Gabriel Monteiro do Carmo	MayanaZatz
Gabriela Furukawa	Oswaldo Keith Okamoto
Gabriella Hsiya	Maria Rita Passos-Bueno
Joana Guiro Carvalho da Rocha	Oswaldo Keith Okamoto
João Vicente Malvezzi	Ana C V Krepischi
Karla Pacheco Melo	Merari F. R. Ferrari
Kayque Alves Telles Silva	Mayana Zatz
Letícia Yumi Takasi	Mariz Vainzof
Lucas Vecchiato de Melo	Maria Rita Passos-Bueno
Maíra Fessardi	Luis Eduardo Soares Netto
Marina Garcia Ribeiro	Mariz Vainzof
Matheus Molina	Carlos F M Menck
Natália Fagundes Borges Teruel	Merari F. R. Ferrari
Niara Régia F. de Souza	Angela M. Vianna-Morgante
Rafaela Regina Cardoso	Merari F. R. Ferrari

Rosanna Miki Kimura Cerioni	Oswaldo Keith Okamoto

Students Master

NAME	SUPERVISOR
Alexsandro Santos	Carla Rosenberg
Aline Lopes Ribeiro	Oswaldo Keith Okamoto
Antonio Fernando Ribeiro Junior	Mariz Vainzof
Claudia Ismania Samogy Costa	Maria Rita Passos Bueno
Dayane Bernardino da Cruz	Regina C.Mingroni-Netto
Ricardo di Lazzaro Filho	Debora Romeo Bertola
Humberto Cezar Marcolino	Regina C.Mingroni-Netto
Isabela Mayá Wayhs Silva	Maria Rita Passos-Bueno
Juliana Plat de Aguiar Gomes	MayanaZatz
Juliana Sobral de Barros	Ana C V Krepischi
Leonardo Galleni Leão da SIlva	Mariz Vainzof
Livia Luz Souza Nascimento	Carlos F M Menck
Mariana Soares Fogo	Celia Koiffmann
Mayra Pelatti	MayanaZatz
Raquel de Souza Lima	Merari F. R. Ferrari
Renata Ishiba	Mariz Vainzof
Rodrigo Salazar da Silva	Regina C.Mingroni-Netto
Rogério Luis Aleixo Silva	Luis Eduardo Soares Netto
Sandra Mabel Sánchez Sánchez	Andrea Sertie
Stephanie de Alcântara Fernandes	Mariz Vainzof
Thaise Carneiro	Carla Rosenberg
Thaise Nayane	Carla Rosenberg
Thiago Rosa Olávio	Mayana Zatz
Vanessa Simões	Luis Eduardo Soares Netto

Students Doctorate

NAME	SUPERVISOR
Ágatha Cristhina Oliveira Faria	Maria Rita Passos Bueno
Allysson Allan De Farias	Fernando Kok
Amanda Faria Assoni	Mayana Zatz
Angela May Suzuki	Maria Rita Passos Bueno
Anita Martins Fontes Del Guercio	Luis Eduardo Soares Netto
Camila de Freitas Almeida	Mariz Vainzof
Camila Manso Musso	Maria Rita Passos Bueno
Carolina de Oliveira Rodini	Oswaldo Keith Okamoto
Carolina Malcher	Maria Rita Passos-Bueno
Carolini Kaid Dávila	Oswaldo Keith Okamoto
Danielle de Paula Moreira	Maria Rita Passos-Bueno
Danyllo Felipe de Oliveira	Mayana Zatz
Davi Mendes	Carlos F M Menck
Davi Jardim Martins	Carlos F M Menck
Eduarda Morgana da Silva M. M. de Souza	Maria Rita Passos Bueno
Ernesto Goulart	Mayana Zatz
Estela Mitie Cruvinel	Célia P. Koiffmann
Felipe Augusto André Ishiy	Maria Rita Passos-Bueno
Fernando Gomes	Luis Eduardo Soares Netto
Flávio Romero Palma	Luis Eduardo Soares Netto
Francine Campagnari	Carla Rosenberg
Gabriel Nassar Reich Goldstein	Maria D. Vibranovski
Guilherme Lopes Yamamoto	Debora Romeo Bertola
Gustavo Satoru Kajitani	Carlos F M Menck
Juliana Emilia Prior Carnavalli	Carla Rosenberg

Leandro Ucela Alves	Regina C.Mingroni-Netto
Lucas Alvizi Cruz	Maria Rita Passos-Bueno
Luciano Abreu Brito	Maria Rita Passos-Bueno
Luiz Gustavo Dufner De Almeida	Luciana Haddad
Maria Prates Rivas	Ana C V Krepischi
Michel Satya Naslavsky	Mayana Zatz
Michelle Buscarilli de Moraes	Debora Romeo Bertola
Natalia Cestari Moreno	Carlos F M Menck
Nathalia Quinteros	Carlos F M Menck
Patrícia Benites Gonçalves da Silva	Oswaldo Keith Okamoto
Renata Bannitz Fernandes	Luis Eduardo Soares Netto
Renato Domingos	Luis Eduardo Soares Netto
Renato Mateus Domingos	Luis Eduardo Soares Netto
Rodrigo Atique Ferraz de Toledo	Maria Rita Passos Bueno
Silvia Costa	Carla Rosenberg
Talita Aguiar	Ana C V Krepischi
Tatiana Ferreira de Almeida	Maria Rita Passos-Bueno
Thaiany Quevedo Melo	Merari F. R. Ferrari
Tiago Antonio de Souza	Carlos F M Menck
Valesca Anschau	Luis Eduardo Soares Netto
Vanessa Luiza Romanelli	Maria Rita Passos-Bueno
Wagner Antonio da Rosa Baratela	Debora Romeo Bertola

Students Pos Doctorate /Visiting Researcher

NAME	SUPERVISOR
Alexandra Pelegrini	Carlos F M Menck
Amajad Iqbal Kazi	Merari F. R. Ferrari
André Luis Fernandes dos Santos	Mariz Vainzof

Beatriz de Araujo Cortez	Oswaldo Keith Okamoto
Bruno Henrique Silva Araujo Torres	Esper Abrão Cavalheiro
Carla Sustek D'Angelo	Célia P. Koiffmann
Clarice Savastano	Maria Rita Passos-Bueno
Clarissa R. Ribeiro Rocha	Carlos F M Menck
Danielle Ayub-Guerrieri	Mariz Vainzof
Darine Villela	Carla Rosenberg
Diogo de Abreu Meireles	Luis Eduardo Soares Netto
Eder Zucconi	Mayana Zatz
Gerson Shigeru Kobayashi	Maria Rita Passos Bueno
Giovana Leandro da Silva	Carlos F M Menck
Giuliana Castello Coatti	Mayana Zatz
Karina Griesi Oliveira	Maria Rita Passos-Bueno
Kelly Nunes	Regina C.Mingroni-Netto
Ligia Pereira de Castro	Carlos F M Menck
Lúcia Inês Macedo de Souza	Mayana Zatz
Luciana RodriguesGomes	Carlos F M Menck
Luciane Portas Capelo	Maria Rita Passos-Bueno
Luiz Carlos de Caires Júnior	Mayana Zatz
Márcia Cristina Teixeira dos Santos	Oswaldo Keith Okamoto
Maria Cristina Mingues Spinola	Luis Eduardo Soares Netto
Mariane Secco	MayanaZatz
Monica Castro Varela	Célia P. Koiffmann
Natassia Vieira	Mayana Zatz
Roberto Dalto Fanganillo	Maria Rita Passos-Bueno
Uirá Souto Melo	Mayana Zatz
Valquíria Santos	Carlos F M Menck

Laboratory Technicians and Assistants

NAME	FUNDING SOURCE	SUPERVISOR
Andressa Yurie Sakugawa	USP	Luis Eduardo Soares Netto
Antonia Cerqueira	USP	Mayana Zatz
Cláudia Irene Emilio de Castro Fabris	USP	Celia Koiffmann
Erica Baroni Cangusu	FUSP-AACD	Mayana Zatz
Guilherme Lopes Yamamoto	CEGH-CELL-FUSP	Maria Rita Passos-Bueno
Heloísa Maria de Siqueira Bueno	FUSP	Mayana Zatz
Job Carvalho Bezerra	USP	Eliana M B. Dessen
Kátia Maria da Rocha	CEPID-USP	Maria Rita Passos-Bueno
Laurinda de Fátima P. Cally Baptista	USP	Angela M.Vianna-Morgante
Letícia Nogueira Feitosa	CEGH-CELL-FUSP	MarizVainzof
Maria Raimunda L. Santana Pinheiro	USP	Ana Krepischi
Maria Teresa B. de Mello Auricchio	USP	Regina C.Mingroni-Netto
Marta Canovas	CEPID-USP	Mayana Zatz
Meire Aguena	CEGH-CELL-FUSP	Maria Rita Passos-Bueno
Monica Castro V. Rodrigues da Silva	CEGH-CELL-FUSP	Maria Rita Passos-Bueno
Monize Lazar Magalhães	CEPID-USP	Maria Rita Passos-Bueno
Naila Cristina V. Lourenço	INCT-USP	Maria Rita Passos-Bueno
Patricia Semedo Kuriki	INCT-USP	Oswaldo Keith Okamoto
Paulo Rogério de Souza	USP	Regina C.Mingroni-Netto
Roberto Rivelino de Camargo	CEPID-USP	Maria Rita Passos-Bueno
Silvia Costa	USP	Carla Rosenberg
Simone Gomes Ferreira	USP	Maria Rita Passos-Bueno
Simone Vidigal Alves	USP	Luis Eduardo Soares Netto
Suzana Andreoli Marques Ezquina	FUSP	Maria Rita Passos-Bueno

Tatiana Rodrigues Nahas	FUSP	Eliana M B. Dessen
Thais Oliveira deAndrade	FUSP-AACD	Mayana Zatz
Tatiane Viana	CEGH-CELL-FUSP	Maria Rita Passos-Bueno
Thiago Geronimo Alegria	USP	Luis Eduardo Soares Netto
Vanessa Naomi	CEPID-USP	Maria Rita Passos-Bueno
Vivian Palmeira Landini e Silva	FUSP-AACD	Mayana Zatz

Administrative

NAME	FUNDING SOURCE	SUPERVISOR
Bernadete Morelli Soares	AACD	Mayana Zatz
Constancia Urbani Gotto	AACD	Mayana Zatz
Luceleni da Silva	USP	Celia P. Koiffmann
Luciana Cristina A.Oliveira	CEPID-USP	Mayana Zatz
Luciano Cabral da Silva Costa	USP	Mayana Zatz
Maraisa de Castro Sebastião	USP	Ana Krepischi
Márcia Góes Teixeira	AACD	Mayana Zatz
Marta Rita Celestino de Macedo	CEPID-USP	Eliana M B. Dessen
Vanessa Yumiko Sato de Jesus	AACD-CEGH-CELL	Mayana Zatz
Wagner Falciano	CEPID-I-USP	Mayana Zatz

IT - Information Technology

Fernando Luis Molina	CEGH-CELL-FUSP	Mayana Zatz
Daniel Bozoklian do Amaral	AACD-CEGH-FUSP	Mayana Zatz

2nd Evaluation Report

March 23, 2017

We are delighted to submit this 2017 report on the activities of the Human Genome and Stem Cell Research Center at USP funded by CEPID.

The center has three major goals:
A. Research
B. Promotion of genomic science at the community level through education and science dissemination
C. Technology transfer.

Research:

The Human Genome and Stem Cell Research Center conducts genetic research that is applied to clinical settings. Major foci and expertise of the center include (i) the analysis of genetic diseases that have Mendelian inheritance, (ii) the genetic basis of common and complex disorders, and (iii) chromosomal aberrations.

The center has been particularly productive since the last review. The center's groups, most often in collaboration with international scientists, who recognize the center's many strengths, have published their innovative findings in leading international journals.

Complex disorders represent a challenge for genetics. The center has approached this challenging topic with studies on the genetics of hypertension and obesity, and also by highly interesting study of a unique cohort of individuals over 80 years old, with a focus on the genetic factors associated with longevity and health. The third topic addresses chromosomal aberrations, with contributions to small chromosomal aberrations and translocations and their impact on intellectual impairment.

Key strengths of the research include the richness of clinical cases that the center diagnoses and whenever possible treats, and the outstanding expertise of the investigators. In addition, the center has state of the art equipment, including sequencing facilities that enable in-depth analysis of genetic material.

As the research aims to elucidate both mechanisms of disease, and the genotype-phenotype relationship, animal models have been used with great success. The investigators use not only mammals such as rodents and dogs, but also other vertebrates, such as zebra fish. Moreover, the researchers are using stem cells, particularly human induced pluripotent stem cells (iPSC) to model and study various diseases for which they have access to clinical samples. The review panel was impressed by their ability to combine animal and state-of-the-art cellular models.

The excellence of their research is reflected by the fact that CEPID has had a superior level of scientific impact in the past two years, since our last evaluation. Briefly, the center has published over 100 manuscripts in 2015-2016, and during this period received over 4,000 citations. Some of the papers were published in the world's most prestigious journals such as *Cell* (the best journal in cell biology), PNAS (an outstanding journal that covers all aspects of science), and the American Journal of Human Genetics (the best journal in the field of human genetics). It is evident that the combination of the outstanding scientific community at CEPID, enabling unique collaboration among the various scientists, together with the state of the art facilities and a wide breadth of different topics related to human disorders, makes this center the best human genetic center in South America.

Education/science dissemination:

The educational community engagement program, led by Eliana Dessen, is a major highlight of the CEPID program. It can be considered as world leading, positioned at the same level and in some respects exceeding the success of similar efforts by NIH (USA), the Max-Plank Institute (Germany) and the Wellcome Trust (UK). It has amazing breadth spanning covering biology and genetics/life sciences, and in collaboration with the Physics center, it has expanded into other beta-science.

The formats used to engage the community were particularly impressive. They provide classes and kits for high school, (identifying the need to "train the trainer," and thereby teaching the teachers, using the interesting approach of enlisting interested students for monitoring this. Their

comprehensive approach to this area had several complementary elements, including a high school support program, programs targeting patients and their families as well as well as separate programs for the general public, and liaison with the press and news media.

The High School Support Program is particularly innovative. It has been structured as follows:

1. Laboratory: This consists of laboratory classes at individual schools for periods of 3 weeks. Teachers were assisted in leading laboratory classes related to the cellular basis of Genetics, including the use of microscopes and 6 practical kits. They delivered 40 hours of educational support to 134 High School teachers; 86 students were trained as teaching assistants. This covered 47 High Schools (7 of them twice), from July 2015 to June 2016, with a student base of 35,000 students.
2. Instructional support project: This helps teachers overcome the teaching and learning difficulties presented by genetics concepts. They provided instructional support material to facilitate the teaching and learning processes and established three loan centers that support 100 teachers each year.
3. Active Methods in the teaching: 4 Pedagogical workshops of 5 hours each to 87 high school biology teachers
4. The Giant Cell Project: A model cell was amplified 130,000 times and a set of complementary activities designed to facilitate the understanding of cell concepts in conjunction with a scientific exhibition “Light and Life,” visited by nearly 5 thousand people.

Technology transfer:

The bioinformatics and genetic sequencing capacity and outcomes have improved substantially since the last review, in great part thanks to great strides in the area of technology transfer. The AbraOM cohort resource provided the basis for an extraordinary collaboration with the Human Longevity Institute in San Diego, California, USA that resulted in whole genome sequencing provided by Human Longevity at a cost exceeding USD$5 million. The progress in the area of technology transfer has been considerable and should be seen as model of what a public university can

achieve in partnership with the private sector.

Other highlights of their technology transfer program include the following:

· Genetic counseling service: 2551 families in the last year.

· Genetic Tests: 1660 genetic tests using techniques, such as karyotype, aCGH, MLPA, Triple (TP)-PCR, microsatellite analysis, Sanger Sequencing and Next Generation Sequencing. Of the 1660 genetic tests, 455 were private tests (most NGS target sequence), while the remaining were related to research projects or were performed for patients who could not afford them. The income of the genetic tests is being used for equipment maintenance, purchase of reagents and payment of technician's salary.

· Establishment of an EMU (EquipamentoMultiusuário / Multi-user Equipment)-FAPESP for Next-Generation Sequencing (NGS).

· Partnership with OMINT.

Scientific meeting:

Over three days (March 21-23, 2017), the evaluation of the progress of the project took place at CEPID facilities at USP, taking advance of their newly renovated space for general discussion and poster presentations. We had numerous formal presentations along with many informal discussions. At the beginning of the three-day brainstorming, Prof. MayanaZatz gave an overview on the outstanding research and innovations that were made in the past two years. Then, Prof. Maria Rita Passos-Bueno discussed the transfer of technology, giving special attention to the new state of the art genomic facilities, and their use within the center. Lastly, Prof. Eliana Dessen discussed the educational part of the project and the outreach for students, teachers and the general population. This part of the center is even more impressive than what we found in 2014. It is a fair judgment that this program is unparalleled elsewhere in the world, both in depth of information generated and in the breadth of leverage, with inquisitive

posters in the Sao Paulo underground, reaching out to millions of people. Following these three general presentations, we had the unique opportunity to attend 14 presentations given by students and post-docs on their outstanding scientific activities during the past two years. In addition to the oral presentations there were 30 poster presentations, which enabled one-on-one discussions with the students. We were extremely impressed by the level of the research and the quality of the students and post-docs. Clearly CEPID is a hub of excellent science that enables young scientists to be exposed to cutting edge research.

Examples of CEPID Research Highlights:

Zika virus research

A prime example of the unique and major value of the investment in CEPID is the amazing advances made with the Zika virus research. Precipitated by a specific, urgent question from FAPESP and given the timeliness of the Zika health threat this research was started only in April 2016. Nonetheless, just less that a year later several major findings have already been made, which received a commentary in the international top journal *Nature* by Declan Butler. This rapid progress is based on the innovative idea of professor Zatz and her team to look for concordant and discordant Zika-infected twins to uncover genetic components of susceptibility, if present. This was found to be the case, and in our opinion the ability of so rapidly answering this question and quickly focusing on follow-up questions is exclusively due to the possibility of combining the existing technological infrastructure with the long standing genetic and biological expertise present in the institute.

AbraOM cohort resource

Great strides were also made with the study of the healthy aging cohort. In our previous report this promising resource had just been generated. Today, the first analysis, by 'Whole Exome Analysis' (WES), has been completed, and the data resource submitted and accepted for publication in Human Mutation (the top journal in the field of the study and reporting of

human genetic variation).

In total, 2.4 million variants were found, reduced after stringent quality control to 1.3 million variants relative to the reference genome. Strikingly, ca. 200.000 new variants were found (~15%) not present in the current genome databases. This high yield of new variants clearly indicates that this novel Brazilian resource highlights new genetic variability which has thus far not been explored by genome sequencing efforts ongoing elsewhere. This resource is especially invaluable because of the parallel availability of extensive environmental, health, lifestyle and medication information, collected through a 150-page questionnaire, as well as the full brain MRI scan dataset of the entire cohort. This type of 'deep-phenotyping' makes this resource an invaluable asset in future studies on healthy aging, mental and physical resilience and common diseases like cancer, cardiovascular disease and obesity/type2 diabetes. Consequently, this project constitutes a powerful jumping board for worldwide collaborations with academic institutions, but also with industry, who finds itself increasingly reliant on these rich resources combining clinical, molecular and lifestyle data.

Indeed, just prior to our visit, the next, far more comprehensive dataset was received, the 'Whole Genome Sequencing' (WGS) of this in collaboration with the Human Longevity Institute of Craig Venter at San Diego (USA). Having 1300 complete human genome sequences, covered at 30x depth, is truly a major next step. In order to house this in CEPID, a new datacenter has been established – dedicated to the recently deceased founder of the AbraOM resource Maria Lebrão and inaugurated during our visit. While the aim is to make all these data openly available internationally – and this has already been done for the first wave of WES data of AbraOM - the local availability of these data (and the attraction emanating from this to visiting scientists), will further augment the bioinformatics skills of the center, which have made remarkable strides in comparison with our previous visit. Typically the PhD students in their discussions at the poster sessions demonstrated extensive hands-on experience with the current analytical algorithms of state-of-the arts genetics analysis. In view of the great attention, after the genome project,

not for the similarity but the difference of genomes worldwide, the ability of the current students, to use molecular genetic analysis to identify and study cytogenetic and subchromosomal copy number differences, it is likely that the AbraOM resource will yield many major surprises and new insights.

Research on animal model

A good example of fruitful model animal research is that into the dog model for Duchenne Muscular Dystrophy. In the Brazilian Golden Retriever Muscular Dystrophy colony, one dog, Ringo, seemed to escape the severe presentation leading to early death. Ringo was then bred and another dog was found in the progeny, Suflair, with the same unexpected phenotype. Using GWAS, family genetic study and whole genome analysis, the escape ability was traced back to a mutation in the promoter of the transcription factor Jagged 1, causing a binding site for a myogenic factor. This doubles Jag1 expression specifically in early muscle development and apparently protects against the disease severity. This increase in Jag1 was proven to be the protective mechanism by showing that the same mutation in the DMD Zebra fish model Sapje also allowed the fish to escape severe disease. Further ongoing research has identified more factors with similar properties. A plausible hope is that further studies may lead to ways to interfere mechanistically with the disease severity in human Duchenne patients as well. This work is also exemplary for the value of international collaboration, in this case with the group of Prof Lou Kunkel in Boston USA, and the Brazilian scientist involved in this study, Dr. Natassa Vieira, now has a joint position at CEPID and in Boston.

Discussion and recommendations:

CEPID is performing very advanced research on the identification of genetic disorders, and modifiers in human diseases. Moreover, for many of the disorders studied, the investigators are uncovering disease mechanism using animal models (fish, mice and dogs) or human pluripotent stem cell models. In addition, they have generated an outstanding genetic cohort of elderly Brazilians that will represent the basis

for many future studies.

We recommend that in selecting main research topics involving this cohort, priority be given to the Brazilian uniqueness, which will increase global interest and complementarity. Examples could be (1) overall resilience due to judicious combination of available clinical, imaging and genetic information, and (2) study of the population evolution in Brazil, with emphasis on the origins and unique properties of the indigenous genomic component.

In line with our previous recommendation, we envision that in the future the center will focus more on therapy for human disorders and we recommend that additional budget will be allocated for medium scale drug screening facilities.

We furthermore recommend that the center continues to build on existing international collaborations and forges new ones based on the increased strength of the resources. It has been one of the strong points of this center to collaborate with many major research institutions, while maintaining their own identity.

In conclusion, CEPID is a hub of excellent science related to the human diseases, with a special focus on the disorders of the Brazilian population. The center is the best of its type in South America. Its productivity is comparable to best programs in this area worldwide. We therefore recommend with the highest level of enthusiasm the continuation and increase of the funding of the center in order to support the maintenance and expansion of its activities.

Sincerely,

Prof. Gert-Jan van Ommen
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