HUMAN GENOME RESEARCH CENTER (HGRC)

Departamento de Genética e Biologia Evolutiva
Instituto de Biociências
Universidade de São Paulo

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Coordinator: Mayana Zatz

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Group members

Coordination

Mayana Zatz - General Coordinator
Maria Rita Passos-Bueno - Transfer of Technology
Eliana M. Belluzzo Dessen - Education/Public Information

Principal Investigators

Angela M. Vianna-Morgante
Célia P. Koiffmann
Mariz Vainzof
Regina Célia Mingroni-Netto
Carla Rosenberg

Associate Investigators

Carlos F. Menck
Fernando Kok
Luciana Haddad
Luis Eduardo Netto

PART 1 - RESEARCH

GENOME RESEARCH

I- Neuromuscular and Neurodegenerative Disorders

a) Identification of new genes

We were able to refine the region where the SPOAN (spastic paraplegia, optic atrophy and neuropathy) is mapped and exclude more candidate genes. This work was part of the Ph.D. thesis of Lucia Inês Macedo-Souza and was published in Annals of Human Genetics (Macedo-Souza et al.2009)

b) **Identification of new mutations**

We collaborated with two multicenter researches on spastic paraplegia (Denora et al., 2009) and osteogeneseis imperfecta imperfecta (Barbirato et al., 2009)

c) Mechanisms underlying phenotypic variability in facioscapulohumeral muscular dystrophy

This work was done by the Ph.D. student Patricia Arashiro. Through microarray analysis we observed a different expression profile in affected patients as compared to asymptomatic carriers of the FSHD deletion. This work was done in collaboration with Prof. Louis Kunkel from Boston and was published in PNAS (Arashiro et al., 2009)

d) Association studies

We collaborated with a multicenter association study on Alzheimer disease and a polymorphism in the *BDNF* gene (Fukumoto et al., 2009).

In addition we published a short report suggesting an association between a polymorphism in the serotonin transporter genes and optimism in the Brazilian population (Nishimura et al., 2009)

e) Insights from exceptional cases

Patients with atypical phenotypes may contribute to our comprehension on the mechanisms underlying phenotypic variability. A boy with a nonsense mutation in the dystrophin gene who is still asymptomatic at age 7 was recently reported (Dubowitz, 2006). We have observed a comparable situation in Ringo, a golden retriever muscular dystrophy dog, who is almost asymptomatic at age 6 and 5 months. Several parameters were investigated in this dog in an attempt at explaining his mild course (Zucconi et al., 2009), as part of an ongoing study.

f) Phenotypic variability

The possible modifier effect of the myostatin gene modulation, in the hypermusculature phenotype of patients with congenital myotonia was evaluated and excluded (Muniz et al., 2009).Mitochondrial alterations in patients with centronuclear myopathy due to mutations in the Dynamin 2 gene were described (Zanoteli et al., 2009).

Additionaly, our group participated in complementary studies on the mdx mouse, which demonstrated alteration of neurotrophic factors in the brain (Comim et al., 2009A), as well as oxidative variability, in this murine model with dystrophin deficiency (Comim e col, 2009b)

The pattern of expression of genes related to the degeneration and regeneration cascates were evaluated in the mouse models for muscular dystrophies (Paula Onofre, MSc Thesis and a manuscript is in preparation).

The analysis of the protein FKRP in the mouse models, using two antibodies developed in our labs are showing a specific perinuclear distribution of this protein in the dystrophic muscle, mainly in the centronucleated regenerating fibers, suggesting a role in this process. This work was presented and received a prize in the 14th Meeting of WMS by the Ph.D. student Poliana Martins.

Redox states characterization: Thiols (molecules containing -SH groups) are main players in redox signaling that can undergo various reversible redox processes such as oxidation to disulfide bonds (RSSR). As a consequence, thiols can function as redox switches in signal transduction pathways and can underlie phenotypic variability in genetic diseases. In this context, it was relevant to characterize in detail how redox switches of glutaredoxin (Discola et al., 2009) and peroxiredoxin (Ogusucu et al., 2009) operate in the model organism: *Saccharomyces cerevisiae.* We also characterize a 1-Cys Prx redox switch from bacteria (Martin et al., 2009).

II- Developmental Disorders: Craniofacial defects, neurodevelopmental disorders, mental retardation associated or not with malformation, obesity and deafness

a) Identification of candidate genes for autism.

We have shown that SNPs at HTR1B but not at HTR1C might contribute to the occurrence of autism in the Brazilian population (Orabona et al., 2009). The publication of this paper represented an important achievement for our group, as it was our first publication on this subject. We are currently cloning a chromosome breakpoint from a patient with autism. The result of this analysis might contribute to the identification of a new locus for autism.

b)**Spectrum of clinical variability associated with *IRF6* mutations.**

Based on a study of 100 familial cases with non syndromic cleft lip or cleft palate we have established the minimum clinical and genetic parameter to indicate genetic testing of this gene (Jehee et al., 2009). We are currently testing *IRF6* as a candidate for non syndromic forms of cleft lip associated or not with cleft palate (NSCL/P), and developing new strategies to identify genes for NSCL/P.

c)Mutations and functional analysis of *COL18A1*.

Novel mutations in the COL18A1 gene in patients with Knobloch syndrome were identified and the functional analysis of those with an unknown functional effect were performed (Suzuki et al., 2009). In addition, we have concluded a first characterization of the promoter 1 of *COL18A1* with the identification of enhancer elements (Kague et al., 2009)**.**

d) ***NSD1* mutations.**

Two partial deletions not previously reported for the *NSD1* gene responsible for Sotos syndrome were reported (Fagali et al.,2009).

e) Craniofacial syndromes.

We have collaborated with the molecular characterization of a new form of mandibulofacial syndrome (Guion-Almeida et al., 2009). Besides, we were invited to write a review of the syndromes of the first and second pharyngeal arches by the American Journal of Medical Genetics (Passos-Bueno et al., 2009).

f) Limb defects.

In the family reported by Santos et al (2008), most of the known genes related to limb defects were excluded as candidates to explain the defects. Genomic scanning with Affimetrix SNP arrays is under way as the mapping strategy. Many genes in the candidate chromosomal region 17p13, mapped in the report by Lezirovitz et al.(2008) as explaining split hand/split foot malformation associated to tibial hemimelia, were excluded as harboring the causative mutation after sequencing. A collaborative study was established with Dr. Stefan Mundlos, Institut für Medizinische Genetik harité, Universitätsmedizin Berlin, Germany, where similar cases are under investigation.

g) **Syndromic obesity.**

We screened for 11p36 deletions a group of 154 hyperphagic and obese, PWS-negative patients. Our work reinforced the association between monosomy 1p36 and obesity and hyperphagia in addition to a submicroscopic deletion of ~2 to 3 Mb in size. Important nervous system and glucose or lipid metabolism genes are mapped to this region (D´Angelo,et al.,accepted for publication). The use of SNP-array to identify critical genomic regions involved in the manifestation of obesity, hyperphagia and behavioral disturbances detected patients with del 6q, dup 14q, del Xp22.12, del 2p25.3→pter, and del12q21.1.

h) **Prader-Willi and Angelman syndromes.**

In this ongoing project, the sample of PWS and AS patients was increased, and screening of *UBE3A* mutations in AS patients was performed. We are also screening patients with Angelman-like phenotypes for 22q13 deletions. In a collaborative study a rare case of trisomy 15pter-q21.2 due to a *de novo* marker chromosome was reported (Pacanaro et al., 2009, in press)

i) Robinow-syndrome.

In our search of the genetic causes of the dominant form of Robinow syndrome (RS), we described a second child with a de novo deletion encompassing 1q41q42.2. This deletion, however, was not found in a cohort of 24 other RS patients investigated by MLPA designed for genes mapped at the regions. The presence of agenesis of corpus callosum in the patient led us to suggest a gene at 1q41q42.2 might be involved in the defect. (Mazzeu et al., accepted for publication).

j) **Deafness.**

A new locus for autosomal dominant non-syndromic deafness was mapped and named DFNA58 (Lezirovitz et al., 2009). Sequencing of many candidate genes in the mapped chromosomal region was performed, but the gene has not been identified yet. Our work on the molecular diagnosis of deafness, mainly related to connexin genes, resulted in two publications, including the report of a novel Connexin 26 mutation (Batissoco et al, 2009a and Batissoco et al **,** 2009b)**.** Molecular analysis of selected patients, mainly presenting auditory neuropathy, revealed that mutations in the *OTOF* gene are an important cause of auditory neuropathy in Brazilian patients, and six novel mutations in this gene were reported (Romanos et al, 2009). The results of association studies in noise-induced hearing loss were presented in the 7th Molecular Biology of Hearing and Deafness Meeting, in Boston (USA) and the submitted manuscript is under review. The investigation of chromosomal imbalances by Array-CGH in a selected sample of individuals with syndromic deafness, presenting phenotypes that did allow classification into known syndromes, revealed a high number of patients with submicroscopic

rearrangements. Rare copy number changes were found in eight of 29 patients, and changes were *de novo* in four cases. (Catelani et al ,2009. The chromosomal regions involved in copy number changes were analyzed in order to select candidate genes for deafness. A MLPA kit was, then, developed to investigate copy number variation in those selected genes in a larger series of patients presenting with syndromic or non-syndromic deafness.

k) **Genetic factors associated with hypertension and obesity in Afro-Brazilian partially isolated populations:**

Genotyping of SNPs of candidate genes to explain hypertension in the African-derived populations proceeded last year and a manuscript on association studies regarding obesity-related phenotypes was submitted. A large sample of African-Brazilians from the same populations was genotyped with a set of 48 autosomal population-specific alleles, for ethnic admixture estimates. Results were used to control population stratification in the association studies. The Ms. Dissertation of Daniel Rincon, concluded in 2009, comprised the analysis of mitochondrial DNA polymorphisms in the same sample, which also allowed ethnic admixture estimates.

l) **Mental retardation.**

By array-CGH, we detected four mentally impaired individuals carrying de novo microdeletions that shared a common segment at 17p13.1, and encompassed 18 genes, including three involved in cancer (*KCTD11/REN, DLG4/PSD95,* and *GPS2*). In two patients, the deletions also included TP53, the most frequently inactivated gene in human cancers. The deleted tumor suppressor genes *KCTD11, DLG4*, and *GPS2*, as well as *GABARAP* gene, have a known or suspected function in neuronal development and haploinsufficiency for one or more of these genes may be causing mental impairment in our patients. This delelion occurred in ~1% of the mentally retarded Brazilian patients that we investigated by array CGH, and appears to be prone to rearrangements. The constitutive deletion of tumor suppressor genes in these patients, particularly *TP53*, probably confers a significantly increased lifetime risk for cancer and (Krepischi-Santos et al., 2009).

A collaborative study of research teams in USA, Europe, Australia and ours in Brazil showed that microrerrangements of *ZNF630* gene found in mentally retarded individuals is not the cause of mental impairment. Although we found a 1.6-fold higher frequency of this deletion in males with mental retardation as compared to controls, this increase was not statistically significant (*p*-value=0.174). Conversely, a 1.9-fold lower frequency of *ZNF630* duplications was observed in patients, which was not significant either (*p*-value=0.163). (Lugtenberg et al, accepted for publication)

III - CHROMOSOMAL STUDIES

a) Mechanisms originating chromosomal rearrangements.

In the above-referred study of microrrangements of *ZNF630* gene in mentally retarded individuals, the breakpoints were analyzed in ten families, including a Brazilian family, and in all cases they were located within two segmental duplications that share more than 99% sequence identity, indicating that the deletions resulted from non-allelic homologous recombination (Lugtenberg et al, accepted for publication).

We collaborated in the investigation of the mechanisms for the origin of *MECP2* non-recurrent duplications. The diversity and complexiy of the breakpoint regions were

demonstrated. This analysis led to the proposal that low-copy repeats in the vicinity of the *MECP2* gene might generate an unstable DNA structure that can induce DNA strand lesions, such as a collapsed fork, and facilitate a Fork Stalling and Template Switching (FoSTeS) event producing the complex rearrangements involving MECP2 (Carvalho et al., 2009).

b) Evolutionary studies

In order to study the intergeneric variability of the Y chromosome, we generated, by microdissection, a Y whole-chromosome probe from Brachytelesarachnoides, and hybridized to metaphases of Atelesbelzebuthmarginatus, Lagothrixlagothricha, and Alouatta male specimens. Our results supported a close phylogenetic relationship among *Brachyteles, Ateles*, and *Lagothrix* and their placement in the Atelinae subfamily, but excluded Alouatta from this group indicating its placement as basal to this group (Gifalli-Iughetti and Koiffmann, 2009). Also using in situ hybridization, we investigated the intraspecific and interspecific variability of the synteny of human chromosomes 14 and 15 in *Platyrrhini*, in 15 species from 13 genera; our data suggest that this association has been retained in most platyrrhines despite the occurrence of extensive inter and intrachromosomal rearrangements (Gifalli-Iughetti and Koiffmann, accepted for publication).

IV. INTERFERING IN THE HUMAN GENOME.

From the beginning of this Project, we have employed adenovirus derived recombinant vectors, able to complement DNA repair defects in human cells During this last period, the characterization of mutations in the gene XPC from three xeroderma pigmentosum patients (two families) was concluded. The identification of the mutated gene was initially performed using these adenovirus vectors, and the mutations included one that was still not described. This work was published in the Journal of Investigative Dermatology (Leite et al, 2009), and this was the first of this type for XP patients in this country.
We also developed recombinant adenovirus bearing specific photolyase genes,
Concerning the different strategies for gene therapy of XP patients we published recently a review in Drugs for the Future (Lima-Bessa et al, 2009).

Part of our work is to search for cell responses to DNA damage that lead to cell death, including apoptosis. In previous work, we proposed that the chlorethylating agents ACNU and BCNU need the p53 protein in order to repair the lesions induced in the DNA of glioma cells, so that p53 deficient cells are more sensitive to the treatment. Using UV as a model to induce DNA lesions, we demonstrate that this can be the case, as the glioma cells respond similarly to UV-induced and ACNU- induced lesions. In fact, the UV lesions are removed more slowly in glioma cells deficient for p53. These results were published in Molecular Cancer Research (Batista et al, 2009). We also published a review on the mechanisms for cell death induced by UV light, in the journal Mutation Research Reviews (Batista et al, 2009). Moreover, in collaboration with the group of Dr. Sarasin and Dr. JP Henriques (UFRGS, RS), we obtained evidences that link nucleotide excision repair in human cells and DNA lesions induced by the well known chemotherapeutic agent doxorubicin, accepted for publication in DNA Repair (Saffi et al, in press).

STEM CELLS

a) Human stem cells

We observed that stem cells from umbilical cord blood have myogenic potencial (Jazedje et al., 2009a). We also identified a new source of mesenchymal stem cells in the Fallopian tube (Jadezje et al., 2009b).

In a collaborative study with Dr. Sergio Verjovski-Almeida and his student Yuri Moreira from IQUSP we observed that mesenchymal stem-cells from umbilical cord tissue have an expression profile different from those obtained from umbilical cord blood (Secco et al., 2009). This work which was done by the Ph.D. students Mariane Secco and Eder Zucconi is the continuation of the work where we have shown that the cord is much richer in mesenchymal stem-cells than blood (Secco et al., 2008).

We have also shown that stem cells can be obtained from small fragments of orbicular oris muscle, which are regularly discarded in reconstruction surgeries of patients with cleft lip. Besides, we also showed the osteogenic potential of these cells both *in vitro* and in *vivo* (Bueno et al., 2009). These results also resulted in a patent deposit. Our main aims in this area are to identify novel biomaterials and markers that can identify those cells with the best osteogenic potentials.

b) Canine stem cells

We identified and characterized two new sources of canine stem-cells: from umbilical cord tissue (Zucconi et al., 2009) and adipose tissue (Vieira et al., 2009, in press).

c) Murine stem cells

A comparative study of the myogenic potential of embryonic stem cells (ESCs), versus bone marrow mesenchymal stem cells (bmMSCs), when locally injected in the muscle of mdx mice was performed. We verified that bmMSCs were eliminated from the injected muscle after 2-10 days, while the ESC were retained, originating a teratoma (Ayub-Guerrieri D, Martins PCM, Onofre-Oliveira PCG, Lopes VF, Vasconcelos M, Silvia M. G. Massironi SMG, Pereira LV, Xavier-Neto J, Vainzof M Mesenchymal versus Embryonic stem cells in the mdx mouse model for Duchenne Muscular Dystrophy. , (submitted for publication).

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a-) Articles

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3. Carvalho, Maria Denise - Estudo dos efeitos da inibição do hormônio do crescimento e de transplante celular em modelos animais de distrofia muscular progressiva-IB-USP, 2009
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6. Onofre, PC G . Estudo do padrão de degeneração regeneração em modelos murinos distróficos. MSc Dissertation, Instituto de Biociências USP. April 2009.

7. Rincon D. Estudos de Dna Mitocondrial em Populações Remanescentes de Quilombos do Vale do Ribeira. MSc Dissertation, Instituto de Biociências USP. October 2009
8. Zucconi, Eder- Avaliação acerca do uso potencial de células tronco para terapia celular no modelo canino de distrofia muscular GRMD- IB-USP, 2009.

AWARDS AND HONORS

Mayana Zatz - Premio México de Ciencia y Tecnología, Governo do México. Mexico City, December 2009.

Student Awards:

1. Queren Correia de Carvalho: Menção Honrosa for the work: Seleçao genética e caracterização histopatológica de modelo murino para distrofia muscular congênita. 52º Concurso Cientistas do Amanha, 61ª Reunião Anual da SBPC, July 12 17 2009, Manaus,AM. for the work: Seleçao genética e caracterização histopatológica de modelo murino para distrofia muscular congênita.
2. Poliana Martins Machado - Elsevier WMS Membership Award for the presentation: Martins PCM; Ayub-Guerrieri D, Ferreira VL, Onofre-Oliveira P, Monteiro G, Zilbersztajn D, Yamamoto LU, Mor CMC, Netto LES, Vainzof M.. Fukutin related protein expression in murine dystrophic models carrying single and double mutations for Dystrophin and Large. 14th International Congress of the World Muscle Society, Geneva, Switzerland, 9-12 September 2009..
3. Nascimento RP – Prêmio Mauro Salzano de Genética Humana for the work: Análise funcional *in vivo* e *in vitro* das isoformas normal e mutada (Q128X) da proteína UBE2A humana revela possível mecanismo de auto-modulação por auto-ubiquitinação e degradação proteassômica. 55º Congresso Brasileiro de Genética, Águas de Lindóia, SP, September 2009.
4. Tatiana Jazedje, PREMIO SAÚDE, na categora SÁUDE DA MULHER. Para o trabalho: Jazedje T, Perin PM, Czeresnia CE, Maluf M, Halpern S, Secco M, Vieira NM, Zucconi E, Zatz M (2009). Human Fallopian Tube: A New Source of multipotent Adult Mesenchymal Stem Cells discarded in surgical procedures . J Transl Med. 2009 Jun 18;7(1):46J

PART 2. EDUCATION/PUBLIC INFORMATION

I. HIGH SCHOOL VISITING PROGRAM

1. **USP goes to your School** (A USP vai à sua Escola)

In a partnership action, the CEGH (Center of Human Genome Study) and CEPOF (Group of Optic from Physic Institute of São Paulo University, São Carlos) elaborated an itinerant exhibition focused on Stem Cell and Optics. In São Paulo, 19 schools were visited (**annex 1**), each of them during 2 to 5 days. The mediation was performed by 4 undergraduates or graduated students from USP, during 4.5 hours in the morning and 4 hours in the evening, 4 days a week (**annex 2)**. 30 biology and physics teachers were capacitated to be able to carry on activities related with the exhibited subjects, since we supplied educational material and follow-up. An evaluation of the exposition was performed and is published on line on magazine Genética na Escola http://www.geneticanaescola.com.br/ano4vol2/MS05_004.pdf.

2. **Partnership with Educational Directories North 2 and South 1**

b.1. Educational Directory North 2 – "Practical classes at school - The main objective of the partnership with the Educational Directory for the northern area of the city of São Paulo is to contribute to the improvement of teacher's competence and to stimulate the development of differentiated projects and activities in the classroom. During 2009, CEGH supplied microscopes and 5 different types of kits for practical classes for 13 schools. 16 teachers from these schools were previously capacitated do deal with the educational material. The equipment for the practical classes remains at each school during 2 weeks and two schools were attended at the same time (**annex 3**). 41 hours of teachers capacitating in using instructional material. **Instructional material -** 30 kits of instructional material were donated to 15 teachers that are participating in the program since 2006 (**annex 4**).

b.2. Educational Directory South 1 – 24 hours of actualization in Molecular Biology and Genetics basic concepts were given to (**annex 5**).

II. PARTNERSHIP WITH "ESTAÇÃO CIÊNCIA"

A Cell Biology Laboratory was constructed and equipped in a partnership action with Estação Ciência. The first program of this lab "Discovering the microscopic world" has as main objective to stimulate the innate curiosity and the research capacity of the public, allowing one to observe the invisible world. Groups of twenty people are attended twice a day, during sections of one hour, from Tuesday to Sunday, since June 24th (**annex 6**).

The table bellow summarizes the efforts of CEGH in improving the knowledge of genetics of high school students and their teachers, as well as professionals

Outreach work	**Number of hours of the activity**	**Audience (students)**	**Annex number**
Itinerant exposition USP goes to your school – August 17th to December 5th, 2009	**340**	**11.500**	**1 and 2**
Practical classes March 16th to June 29th, 2009	**1.040**	**8.000**	**3 and 4**

Cell Biology Laboratory	**204**	**4.080**	**6**
Teachers training	**64**	**59 teachers**	**1 to 5**

Annex 1 - USP goes to your School (A USP vai à sua Escola)
Visited High Schools and Capacitated teachers

Escolas	**Professores**
1. EE Alfredo Inácio Trindade	Maria Lúcia dos Santos (Biologia) **Maurício De Feo (Física)**
2. EE Arnaldo Barreto	Sônia Lúcia Costa Nogueira (Biologia) Robson Candeias Macedo (Física)
3. EE Profª. Cyrene de Oliveira Laet	Carla Josely Jurazecki (Biologia)
4. EE Francisco Voccio	Merita Paixão de Freitas Gregório (Biologia) Eduardo Arthur Becker (Física)
5. EE Gabriela Mistral	Aparecida Egracil Gonçalves Zaffarani (Biologia)
6. EE Guilherme de Almeida	**Vanderlei Ribeiro dos Santos (Biologia)** **Fátima Maria de Carvalho (Física)**
7. EE Gustavo Barroso	**Janethe Maria Santos (Biologia)** Allan de Almeida Silva (Física)
8. EE José do Amaral Mello	**Marilene Miranda da Silva (Biologia)** **Renata Marques Pereira (Física)**
9. EE Pedro Alexandrino	**Cleusa da Silva Trovão (Biologia)** **José Geraldo de Campos Sobrinho (Fìsica)**
10. EE Pedro de Moraes Victor	Simone Batista Vasconcelos (Biologia) Aparecida Gimenes Munhoz (Física)
11. EE Silva Jardim	**Ivonese Souza Mendes (Biologia)** Marinilse C. Sturla (Fìsica)
12. Colégio Drumont Villares	Sonia Machado Maluf Labate (Biologia) Claudemir Felix de Araujo (Física) Rafael Pereira de Gonzales (Física)
13. EE Elza Saraiva Monteiro	**Marly Martins Almeida da Silva (Física)**
14. EE Eurico Figueiredo	Fernando Barbosa Ferreira (Física)
15. EE Johann Gutenberg	Rosana Aparecida de Laurentis Pinheiro (Física)
16. Prof. Phylomena Baylão	Silvana dos Santos (Fìsica)
17. Rita Bicudo Pereira	Walkyria de Oliveira (Física)
18. EE Tito Prates da Fonseca	Alexandre M. Ferreira (Física)
19. EE Profª Veridiana C.C. Gomes	Carlos Felix C. Ardaya (Física)

Annex 2 - USP goes to your School – August 17th to December 5th.

Annex 3 – USP goes to your School Under graduated and graduated students that act as mediators in the exposition August 11th to December 5th, 2009

Nome	**Disciplina**
Arthur Guimarães Carvalho Porto	Biologia
Danielle L M Coelho	Biologia
Fernando Jose da S. Abrahão	Física
John Herbert Maia de Sales	Física
Karla de Oliveira Pelegrino	Biologia
Marcel Valentino Bozzo	Biologia/Física
Ricardo Alho de Almeida Arruda	Biologia/Física
Roberto Pereira de Oliveira	Física
Sergio Cândido de Oliveira Jr	Biologia e Física
Sonia Liamara Martins	Biologia
Vinicius Félix Pacheco	Biologia

Annex 4 – Practical classes in public high schools –
Schools and teachers attended in 2009 – Directory North 2

High School	Teachers
EE Alberto Cardoso de Mello	Andréa Valete Machado
EE Albino César	Cristina Marçal da Silva Braga
EE Alfredo Inácio Trindade	Maria Lúcia dos Santos
EE Amenaíde Braga de Queiroz	Hosana Corrêa Luz Pastore
EE Antonio José Leite	Andrea dos Santos Garcia
EE Arnaldo Barreto	Sônia Lúcia Costa Nogueira
EE Carlos de Laet	Luciana Lucas de Almeida
EE Carmosina Monteiro Vianna	Maria da Graça Sapage Estácio
EE Dilson Funaro	Ana Maria Rodrigues Lima dos Santos Thaís Ferreira Lebrão
EE José do Amaral Mello	Marilene Miranda da Silva
EE Pedro de Moraes Victor	Nímia Esther C. Couso Forst Simone Batista Vasconcelos
EE Raquel de Assis Barreiros	Daiane Danielle Bastos
EE Pedro Alexandrino	Priscila Marasse de Araujo
EE Veridiana Camacho Gomes	Cleusa da Silva Trovão

Annex 5 – Practical Classes - March 16th to June 26th, 2009.

Annex 6
Instrucional Kits:"Família Silva e seus Genes" e "Filho de Scoiso, scoisinho é" donated to teacher/schools.

Escola	Professor(a)
EE Alberto Cardoso de Mello	Andréa Valete machado
EE Albino César	Cristina Marçal da Silva Braga Márcia Herrera Garcia Antonio
EE Buenos Aires	Leonardo Peres Cardoso de Andrade
EE Carlos de Laet	Luciana Lucas de Almeida
EE Dilson Funaro, Ministro	Ana Maria Rodrigues Lima dos Santos Aline Cristina L. Santos
EE Amenaíde B Queiroz	Hosana Costa Luz Pastore
EE Arnaldo Barreto	Sônia Lúcia Costa Nogueira
EE Carmosina Monteiro Vianna	Maria da Graça Sapage Estácio
EE Alfredo Inácio Trindade	Maria Lúcia dos Santos
EE Gustavo Barroso	Maria Ivaneide de Almeida Neves
EE Veridiana Camacho Gomes	Cleusa da Silva Trovão
EE Raquel de Assis Barreiros	Daiane Danielle Bastos
Diretoria Norte 2	Vera Lúcia Pirrè de Castro

Annex 7 - **Schools and teachers attended in 2009 – Directory South 1**

High Schools	**Teachers**
E E Angelo Mendes	Joana D'arc Pereira Souza
E E Francisco de Paula	Inês Cristina Paes de A. Pinto Lucy Souza Cerqueira de Oliveira
E E Hugo Lacorte	Adriana da Silva Norberto Bruno Tomas Paukert
E E Ibrahim Nobre	Ivonilda de Almeida Das Mercês Santos
E E Isaltino de Mello	Ione Ishii
E E Joaquim Adolfo Araújo	Vanessa Sobral Amboni
EE João Ernesto Faggin	Luanda Cristina dos Santos Luana Cristina dos Santos
E E Lais Amaral	Helena Maria Bucchianeri Fran
E E Sabóia de Medeiros	Margarida Pereira Claro
E E M Pena	Josiane S M Barbosa

Annex 8 – Cellular Biology Laboratory in Estação Ciência

Inauguration of the Laboratory in Estação Ciência
June 24th, 2009

III. OTHER ACTIVITIES

a-) Courses

Genetics for Neurologists – 8 hours – Audience of 110 neurologists

“ Aconselhamento Genético”, 19º Congresso de Biólogos do CRBio-01, Sâo Pedro, SP, July 27 2009.

8:30-9:10 hs - Quase tudo o que você queria saber sobre genética e tinha vergonha de perguntar Prof. Dr. Fernando Kok (CEGH e HC-USP)
9:10-10:40 hs - Distúrbios cognitivos e comportamentais
1. Transtorno global do desenvolvimento: tirando o autismo das sombras - Profa. Dra. Maria Rita Passos Bueno (CEGH)
2. Passo a passo na investigação da deficiência mental: um novo olhar sobre os cromossomos - Dra. Carla Rosemberg (CEGH)
3. Síndromes neurocomportamentais
Angelman e Prader Willi: tudo e nada em comum - Dra. Célia Koiffmann (CEGH)
Síndrome de Rett: desvendando o fenótipo – Prof. Dr. Fernando Kok (CEGH e HC-USP)
Deficiência mental: o X da questão - Dra. Angela M. Vianna-Morgante (CEGH)
10:40-11:00 hs – Coffee-break
11:00 – 12:30 hs Problemas específicos: genético ou ambiental?
1. Lactente com Malformações Múltiplas - Dra. Fernanda Jehee (CEGH)
2. Surdez - Dra. Regina Mingroni (CEGH)
3. Epilepsia – Profa. Dra. Iscia Lopes-Cendes (Unicamp)
12:30 – 13:30 hs - Almoço
13:30 – 14:30 hs Doenças neuromusculares
1. Distrofias musculares – Profa. Dra. Mariz Vainzof (CEGH)
2. Ataxias hereditárias – Dra. Emilia Embiruçu Leão (HC-USP)
14:30: 15:20 Discussão de casos clínicos: qual o seu diagnóstico?
15:20-15:40 Coffee-break
15:40-17:00 Terapêutica: o que temos e o que queremos
1. Enquanto o tratamento não chega, o que fazer? Dr. Jorge Forbes (CEGH)
2. Células-tronco e a esperança renovada Profa. Dra. Mayana Zatz (CEGH)
Encerramento

b-) Science Divulgation Articles

Zatz M. Ciência e religião nas escolas brasileiras. Veja.com. 01 de janeiro

Zatz M. O porque do sexo. Veja.com. 08 de janeiro

Zatz M. Homossexualidade: genético ou ambiental? Veja.com. 15 de janeiro

Zatz M. DPI para câncer de mama. Você faria? Veja.com. 22 de janeiro

Zatz M. Contra o corte de verbas para ciência. Veja.com. 29 de janeiro

Zatz M. Pesquisa com células-tronco para derrame. Veja.com. 05 de fevereiro

Zatz M. Drogas para turbinar o cérebro. Veja.com. 12 de fevereiro
Zatz M. Um alerta contra clínicas não credenciadas. Veja.com. 21 de fevereiro
Zatz M. Genes de atletas. Você gostaria de ser testado/. Veja.com. 27 de fevereiro
Zatz M. Esclerose-lateral amiotrófica: o que há de novo? Veja.com. 6 de março
Zatz M. Fátima e Diogo-desautorizando o sofrimento. Veja.com. 12 de março
Zatz M. Células-tronco e AIDS . Veja.com. 19 de março
Zatz M. As surpresas depois do projeto genoma humano. Veja.com. 26 de março
Zatz M. Proibido de trabalhar - Veja.com. 2 de abril
Zatz M. Exames genéticos- Veja.com. 9 de abril
Zatz M. Sangue do cordão umbilical: quando guardar? Veja.com. 16 de abril
Zatz M. Cordão umbilical – utilização - Veja.com. 24 de abril
Zatz M. Gene do otimismo- Veja.com. 30-abril
Zatz M. SP: um importante fator de atração- Veja.com. 7 de maio
Zatz M. Laminina e distrofias- Veja.com. 15 de maio
Zatz M. Hemofilia- Veja.com. 22 de maio
Zatz M. Correções necessárias- Veja.com. 29 de maio
Zatz M. Diagnóstico pré-natal para hemofilia **-** Veja.com. 4 de junho
Zatz M. Hemofilia e o dilema ético- Veja.com. 11 de junho
Zatz M. Ética e hemofilia - Qual foi a decisão- Veja.com. 18 de junho
Zatz M. A história de uma pesquisa salva- Veja.com. 24 de junho
Zatz M. Mais uma fonte de células-tronco - Veja.com .30 de junho
Zatz M. Diabetes nos filhos- Veja. Com. 2 de julho
Zatz M. A vida reprodutiva da mulher é limitada ou não? Veja. Com. 9 de julho
Zatz M. Mais uma questão ética- Veja. Com. 16 de julho
Zatz M. O caso da índia: testar ou não testar?- Veja. Com. 23 de julho
Zatz M. Estamos mais próximos de produzir um clone humano - Veja. Com. 30 de julho
Zatz M. Síndrome de Prader-Willi – Veja.com. 6 de agosto
Zatz M. Síndrome de Down- Veja.com. 13 de agosto
Zatz M. Diferenciação celular- Veja.com. 20 de agosto
Zatz M. A versão roedora de Dolly- Estado de S.Paulo, Caderno Aliás, 23 de agosto

Zatz M. Debate-já – Veja.com. 27 de agosto

Zatz M. Experiência em macacos traz esperança para portadoras de doenças mitocondriais- Veja.com. 3 de setembro

Zatz M. Novos genes de risco para doença de Alzheimer- Veja.com.10 de setembro

Zatz M. Testes para doença de Alzheimer – Veja. com.17 de setembro

Zatz M. Quanto você precisa dormir? – Veja.com.24 de setembro

Zatz M. Profissão, prazer e retorno financeiro. Veja.com.1 de outubro

Zatz M. Um brasileiro explica o Nobel de Medicina – Veja.com.8 de outubro

Zatz M. Quebra de sigilo: do Enem ao nosso genoma – Veja.com. 15 de outubro

Zatz M. Células-tronco de cordão umbilical: novas descobertas – Veja.com. 22 de outubro

Zatz M. Os primeiros formandos de pré-iniciação científica da USP – Veja.com. 29 de outubro

Zatz M. Células-tronco em doenças neuromusculares – Veja.com. 5 de novembro

Zatz M. Tratamento na China: depoimento de um paciente- Veja.com. 12 de novembro

Zatz M. Xampus, DNA, células-tronco - Veja. Com. 19 de novembro

Zatz M. A competição entre as células-tronco . Veja. Com. 24 de novembro

Zatz M. CTE: enfim liberadas com suporte. Veja. Com. 3 de dezembro

Zatz M. Os avanços da terapia gênica. Veja. Com. 10 de dezembro

Passos-Bueno MR. “Encarei meu DNA”, Revista Epoca. 20/04/2009

c-) Lectures

3. Dessen, EMB “Avaliação da Exposição a USP Vai a sua Escola como instrumento motivacional para o ensino formal. Congresso de Microbiologia, Porto de Galinhas, PE, November 11, 2009
4. Koiffmann,CP Ética em Pesquisa em Seres Humanos: sequenciamento do Genoma Humana e Terapia Celular.”Termo de Consentimento em Pesquisa em Doenças Genéticas”. São Paulo, 21/05/2009.
5. Koiffmann,CP Ética em Pesquisa em Seres Humanos: sequenciamento do Genoma Humana e Terapia Celular.”Termo de Consentimento em Pesquisa em Doenças Genéticas”. São Paulo, 21/05/2009.
6. Mingroni-Netto RC “ Avaliação Genética da Surdez” , no Complexo Hospitalar Edmundo Vasconcelos, 9 de novembro de 2009.
7. Mingroni-Netto RC “ Herança Citoplasmática”, na 12 a Semana Temática da Biologia, September 12, 2009

8. Mingroni-Netto RC “Diagnóstico Molecular na Neuropatia auditiva”, 1 Simpósio de Estudos Avançados em Audição, Latin Ear, Campinas, December 10, 2009.
9. Mingroni-Netto RC “Genética de Populações de Remanescentes de Quilombos”, 19º Congresso de Biólogos do CRBio-01, São Pedro, July 28 2009.
10. Mingroni-Netto RC “Genética e Neuropatia auditiva”, III Seminário Internacional em Saúde Auditiva, PUC, São Paulo, August 13 2009,
11. Mingroni-Netto RC “Heterogeneity of genes and mutations related to hearing loss: A Brazilian experience”, Unidade de Genética Molecular do Hospital Ramon Y Cajal, Madrid, Espanha, October 20, 2009;
12. Mingroni-Netto RC “O Conselho Regional de Biologia e a profissão de Biólogo”, Comemorações do Dia do Biólogo, IB-USP, September 4 2009.
13. Passos-Bueno MR Symposium – Velocardiofacial syndrome, 11th International Congress on Cleft lip and Palate and related craniofacial anomalies, Fortaleza 10-13 setembro, 2009
14. Passos-Bueno MR , Depto. Microbiologia, Imunologia e Parasitologia e da Sociedade de pesquisa em Biologia Celular, 14/04/2009
15. Passos-Bueno MR Bioinformática e Doenças Genéticas. IME-USP, São Paulo, SP, November 13, 2009.
16. Passos-Bueno MR Células Tronco Mesenquimais para a Compreensão de Doenças Genéticas. Sociedade de Pesquisa em Biologia Celular, São Paulo, SP April 14, 2009
17. Passos-Bueno MR Células tronco na regeneração de defeitos craniofaciais. IOT, FMUSP, São Paulo, SP, November 13, 2009.
18. Passos-Bueno MR Genes e Doenças Humanas, Hospital A.C. Camargo, São Paulo, SP, May 5, 2009.
19. Passos-Bueno MR Vias de Sinalização em doenças craniofaciais,10o. Simpósio Nacional de Biologia Molecular Aplicada à Medicina, Ribeirão Preto, November 6, 2009.
20. Passos-Bueno MR, Craniofacial Genetics Symposium –,11th International Congress on Cleft lip and Palate and related craniofacial anomalies, Fortaleza 10-13 setembro, 2009.
21. Passos-Bueno MR. Transtorno global do desenvolvimento: tirando o autismo das sombras. curso pré-congressso: Genética para Neurologistas, CEGH, USP, 19/11/2009.
22. Vainzof M “Genética da Hipertermia Maligna”, curso de Extensão “Hotline de Hipertermia Maligna, UNIFESP. São Paulo, SP, March 20, 2009.
23. Vainzof M “Genética da Hipertermia Maligna”. 55º Congresso Brasileiro de Anestesiologia, São Paulo, SP, November 7 2009.
24. Vainzof M “Muscular dystrophy and protein analysis in Brazil”. Pediatric Neurology, Children's Medical Center, University of Texas Southwestern Medical Center, Texas, USA. October 26, 2009.
25. Vainzof M “Neuromuiscular Disease in Brazil”, Workshop “Neuromuscular Diseases” , 9o Congresso Internacional de Reabilitação Infantil da ORITEL – Network of Latin America, São Paulo SP, August 2009
26. Vainzof M “Terapia Celular em Doenças Neurmusculares” III Semana de Pós-Graduação de Bioquímica Médica, Centro de Ciencias da Saúde, UFRJ, Rio de Janeiro, RJ, September 17, 2009.
27. Vainzof M Diagnóstico Imuohistoquímico e por Western blotting nas miopatias.Curso de Atualizaçao em Doenças Neuromusculares, FMUSP, São Paulo, SP, June 26 2009
28. Vainzof M Estudo de Proteinas musculares e sua relação com o processo de degeneraçao muscular em pacientes e modelos animais para distrofias musculares progressiva. Seminários do Departamento de Fisiologia, IBUSP, São Paulo, SP,

June 2, 2009.

29. Vianna-Morgante AM “Alterações estruturais do cromossomo X e deficiência mental” 10º Simpósio Nacional de Biologia Molecular Aplicada à Medicina, Ribeirão Preto, SP, November 6, 2009
30. Vianna-Morgante AM “Imprinting genômico e doenças genéticas”, Workshop A Evolução do Genoma Humano, Instituto Sírio-Libanês de Ensino e Pesquisa, São Paulo, SP, October 9, 2009.
31. Vianna-Morgante AM “O cromossomo X humano e a deficiência mental”, IB-USP, São Paulo, SP October 23, 2009
32. Vianna-Morgante AM “Retardo mental ligado ao cromossomo X”, IB-USP, São Paulo, SP, June 2, 2009.
33. Zatz M. Stem-cells: Fiction, reality and ethic- International meeting on stem-cells- Centro Brasileiro Britânico, São Paulo, February 11
34. Zatz M Stem-cells and muscle regeneration- International meeting on stem-cells- Centro Brasileiro Britânico, São Paulo, February 17
35. Zatz M Stem cells and muscular disorders- Centro do Genoma Humano, April 8
36. Zatz M O que significa sequenciar o nosso genoma? Centro do Genoma Humano, April 21
37. Zatz M Células-tronco: Pesquisas,política e ética. Curso de Medicina da USP, May 8
38. Zatz M Stem cells and muscular disorders- Congresso internacional da Faculdade de Odontologia, May, 14
39. Zatz M Genética: o admirável medo do futuro- V Congresso Interamericano de Psicologia da Saúde- HC/FMUSP, May, 22
40. Zatz M Stem cells in the Human Genome Center- Grupo Santander, May 19
41. Zatz M Dysferlinopathies: from gene mapping to preclinical studies- Boston, June 2
42. Zatz M Groningen and São Paulo University- Holland, June 5,
43. Zatz M Discoveries in muscles from FSHD patients and animal models- Boston, June
44. 16
45. Zatz M Células-tronco: pesquisas e novos desafios éticos, São Carlos, August 18
46. Zatz M Células-tronco em doença neuromusculares. Congresso da AACD, August 20
47. Zatz M Perspectivas terapêuticas das células-tronco, Sbg Meeting, September 2
48. Zatz M Stem-cells in neuromuscular disorders- Ribeirão Preto, September 25
49. Zatz M Encerramento do primeiro programa de pré-iniciação científica da USP- Centro Rebouças,October 29
50. Zatz M Células-tronco: esperança renovada- Pré-Congresso de Neurologia, November 19

d-) Meeting Organization

Vianna-Morgante AM, Pearson PL - 14th International Workshop on Fragile X and X-linked Mental Retardation, Praia do Forte, Bahia, September 2009.

e-) Training courses and exchange research experiences among labs:

Zucconi E. attend the course HYDRA V EUROPEAN SUMMER SCHOOL, STEM CELLS & REGENERATIVE MEDICINE, September, 19 to 25th, 2009, Hydra, Greece

Karina G. Oliveira: is doing part of her doctorate at University of California, at Dr. A. Muotri's laboratory September 2009-march 2010.

Roberto Fanganiello has done part of his doctorate at University of Yale, at Dr. Eswarakamur's laboratory, march2008 to fev 2009

Shannon Fisher , a researcher from the Pensivalnia University has visited our laboratory for 2 days.

D. Bueno attend the course EMBRIONIC STEM CELLS (ES) AS A MODEL SYSTEM FOR EMBRYONIC DEVELOPMENT, February 06 to 21, 2009, São Paulo,SP.

Alexander Kneppers, from Leiden University, spend 5 days at Genoma Center to audit the laboratory for genetic testing

Prof. Vincenzo Nigro from Napoli, Italy visited our Center between November 22-28, to discuss collaborative projects, and gave two lectures.

PART 3. TRANSFER OF TECHNOLOGY/ TECHNOLOGY APPLICATIONS

This section will include the main activities done in the last year regarding genetic counseling, genetic testing, sequencing and microsatellite services. These activities involve the participation of all the seven main researchers of the CEPID project, as follows: Angela Vianna-Morgante, Carla Rosenberg, Célia Koiffmann, Maria Rita Passos-Bueno, Mariz Vainzof, Regina C. Mingroni-Netto, and Mayana Zatz. Also, the neurologist Fernando Kok, and clinical geneticists Rita de Cassia Pavanello and Debora Bertola, all collaborators of CEPID, contribute to these activities. Prof. Paulo A. Otto, from the Department of Genetics and Evolutionary Biology, also collaborates to the Genetic Counseling service.

Genetic Counseling at CEGH: We offer this service for 6 main group of disorders: neuromuscular (M. Zatz, M. Vainzof, F. Kok. RC Pavanello), mental retardation, syndromic and non syndromic forms (A Vianna-Morgante, C. Rosenberg, P A Otto), Developmental disorders associated with behavior disturbances and/or obesity (C. Koiffmann), Hearing diseases (R. C. MingroniNetto), Craniofacial syndromes (M.R. Passos-Bueno) and Autism (M.R. Passos-Bueno). About 2000 families (neuromuscular, ~800; craniofacial + autism, 1200 families; hearing disorders, 116 families, mental retardation, 400 families) were seen during 2009 and received Genetic Counseling (GC). Genetic testing was offered in all necessary cases, as their results are critical for estimation of genetic recurrence risks, management and follow up of patients.

Genetic Counseling at other regions of the country: As a partner of operation smile, who offers surgery repair for clefting patients, we have evaluated and offered GC for more than 400 families with cleft lip and palate patients ascertained in 4 different regions of the country (Maceio, Rio de Janeiro, Fortaleza, Barbalha and Santarém).

Database of the Genome Center: The use of the software developed by IME-USP to input clinical data has been initiated in August/09 (http: zen.genoma.ib.usp.br). The efforts will now be concentrated in the set up of the control of exams, workflow of DNA genetic tests and cell bank. This software is being developed by Dr. João E. Ferreira and his team, at the Institute of Mathematics/USP in collaboration with CEPID/CEGH-USP.

Other activities and interactions: Our Center also interacts with patients/parents associations such as the Brazilian Muscular Dystrophy Association (ABDIM), Fragile X, Prader-Willi, Angelman, and Cleft lip/palate Associations. Through ABDIM we established an important partnership with the Secretaria da Saúde de São Paulo to support genetic tests aiming diagnosis and genetic counseling as well as management to families with affected members by neuromuscular disorders. Through this program we evaluated 500 patients from the state of Sao Paulo, and performed about 300 molecular tests for the diagnosis of NMD. Additionally, a second partnership with AACD-ABDIM, consisting in the PAF-GEN project, allowed us to evaluate patients from other states of Brazil, including clinical, physiotherapy and diagnosis of neuromuscular disorders (about 80 molecular tests and 20 muscle biopsies per year).

We also have established a collaboration since 2007 with the Institute of Lacanian psychoanalysis (IPLA-Instituto de PsicoanáliseLacaniana) directed by the psychoanalyst Jorge Forbes, in order to evaluate the effect of a novel psychoanalytic approach and treatment to families with affected members by neuromuscular disorders. The team which includes 21 psychoanalists performs about 30 consultations per week.

We have introduced this year a support to the families with autism, which is leaded by a research group of the Psychology Institute (Dr. M. Hubner).

At last, we have a significant interchange of information about genetic tests and genetic counseling with the general public through e-mails.

Sequencing service and diagnostic tests for the general community: In 2009, we obtained an income of R$200.000,00 (about US$100.000,0/ ~16.000 reactions) with the sequencing service, which is comparable to the income of the previous years. About 300 genetic tests ordered by clinicians outside the CEGH were performed resulting in an income of R$110.000 (~US$55.000,00). Three additional tests were routinely included, MLPA subtelomeric and microdeletion syndromes and array CGH, as planned in 2008. This income has been used to pay salaries for technicians and secretary, and equipment maintenance.

Audit in the DNA diagnostic lab: A second technical audit was performed in our Molecular Genetics Laboratory by Alexander Kneppers (Leiden University, Department of Human Genetics, Netherlands), who is an expert in this field. He considered that we have done a great improvement since last year and our main goal for the year of 2010 will be to write all the necessary documentations and start to ask an external audit for evaluation of the protocols.

Main Proposals for 2010

a) Maintenance of the three mains services: genetic counseling, genetic testing and sequencing/microsatelitte services.

b) Set up the control of exams and cell bank through the software being developed

c) Write the documentation to get audit evaluation