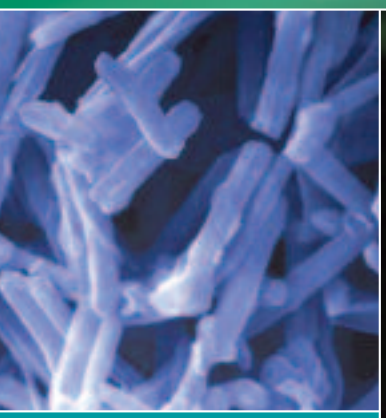
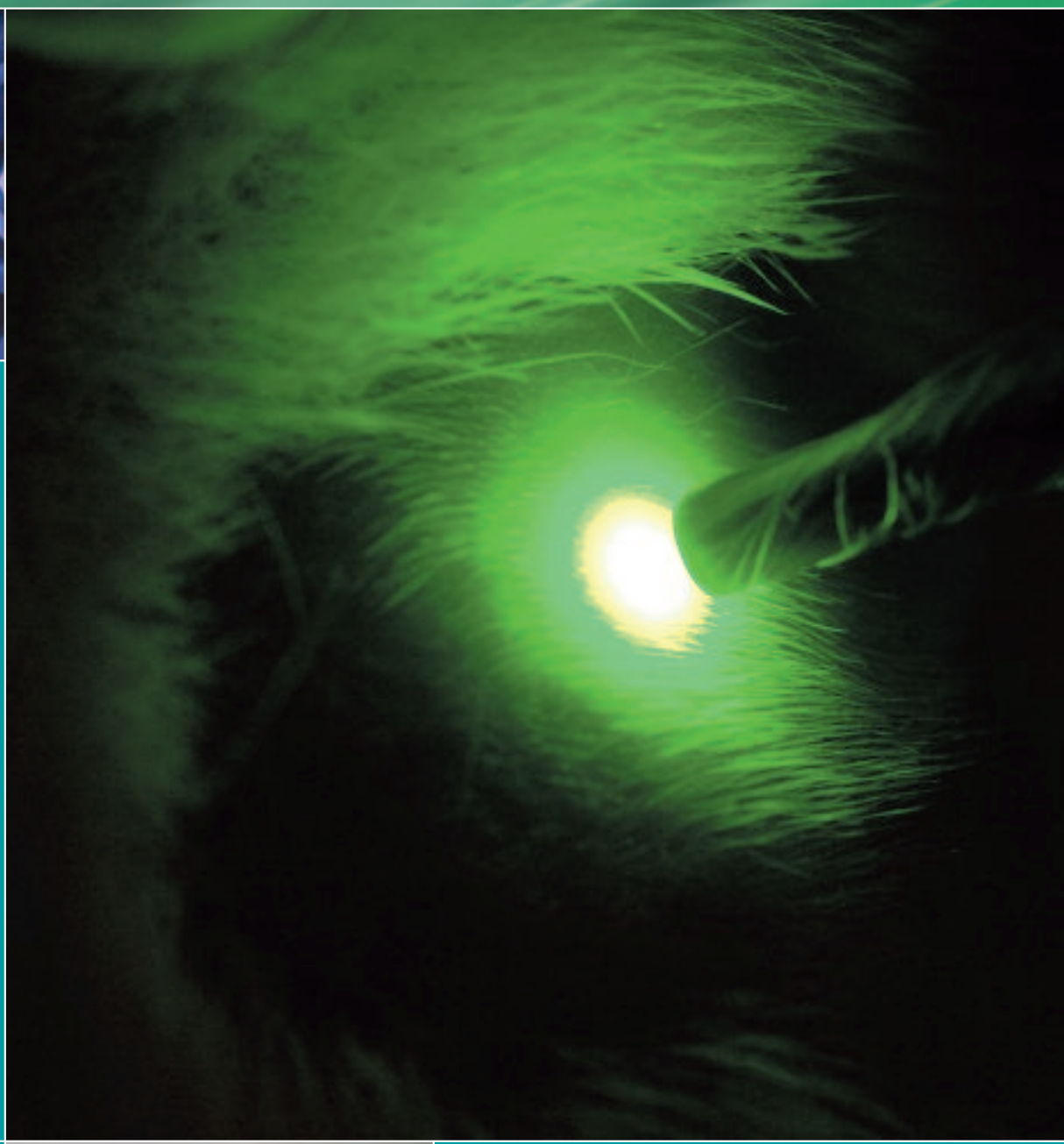
RESEARCH, INNOVATION AND DISSEMINATION CENTERS (RIDC)

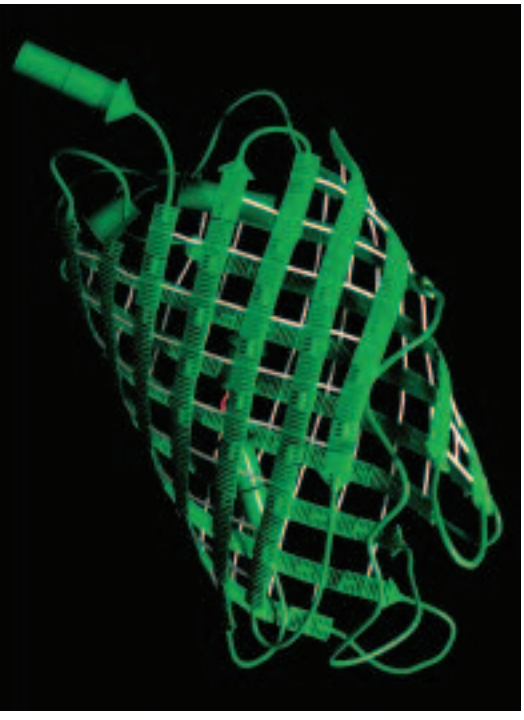
FAPESP
THE STATE OF SÃO PAULO RESEARCH FOUNDATION

MULTIDISCIPLINARY, HIGH IMPACT SCIENCE





RESEARCH IN THE CUTTING EDGE OF KNOWLEDGE



FAPESP supports eleven RIDC's (Research, Innovation and Dissemination Centers) producing scientific knowledge in areas such as cell therapy, the human genome, molecular biotechnology, cancer research and treatment, applied toxinology, sleep disturbance, optics and photonics, atomic and molecular physics, ceramic materials, violence, and studies of metropolitan areas.

The Centers are located in the state of São Paulo and are financed by the State of São Paulo Research Foundation (FAPESP), one of the main Brazilian agencies for promoting scientific research.

In addition to carrying out scientific research, all the Centers develop activities related to the application of their results, creating innovation and disseminating knowledge to various sectors of society.

SCIENTIFIC OPPORTUNITIES IN SÃO PAULO, BRAZIL

Brazil is one of the four main emerging nations. More than ten thousand doctorate level scientists are formed yearly and the country ranks 15th in the number of scientific papers published.

The State of São Paulo, with 40 million people and 34% of Brazil's GNP responds for 53% of the science created in Brazil. The state hosts the University of São Paulo (USP) and the State University of Campinas (Unicamp) , both classified among the 200 best in the world by the Times Higher Education Suplement (THES), and the growing University of The State of São Paulo (UNESP), Federal University of ABC (a metropolitan region), Federal University of São Carlos, the Aeronautics Technology Institute (ITA) and the National Space Research Institute (INPE).

Universities in the state of São Paulo have strong graduate programs: the University of São Paulo forms two thousand doctorates every year, the State University of Campinas forms eight hundred and the University of the State of São Paulo six hundred.

In addition to the three state universities the state has 19 research institutes, three federal universities of international research level and most of Brazilian industrial R&D. The state houses more than 10 thousand fulltime faculty and 130 thousand students. São Paulo alone, produces more scientific papers than any country in Latin America, except for Brazil.

FAPESP: SUPPORT FOR RESEARCH IN SÃO PAULO

The State of São Paulo Research Foundation (FAPESP) promotes scientific research in the State of São Paulo, Brazil. Through a robust program of fellowships and research grants it supports fundamental and applied research.

Created in 1962, the foundation is entitled by the State Constitution to 1 per cent of the tax revenues of the state of São Paulo. FAPESP has a sizable endowment and has already supported, over these 46 years, 89,000 fellowships and 80,000 research awards.

In 2008 FAPESP will invest US$ 388 million in fellowships and research grants. The success rate for proposals in the fellowship programs ranges from 40 per cent to 63 per cent. In the grants programs the proposal success rate ranges from 40 per cent to 60 per cent, depending on the particular type of grant.

OPPORTUNITIES AND CHALLENGES

One of FAPESP's goals is the broadening and diversification of the research system in the state of São Paulo, strengthening the existing centers of excellence, by supporting their research, and stimulating the creation of new centers or research groups tackling new lines of activity.

This is achieved mainly by funding Thematic Projects, Young Researchers Awards, the Biota-FAPESP Program and the RIDC (Research, Innovation and Dissemination Centers) Program. All of these have in their teams, in addition to experienced scientists, young researchers as post-doctoral fellows, from Brazil and from abroad. FAPESP supports more than one thousand post-doctoral fellowships.

Contact FAPESP (www.oportunidades.fapesp.br) or a coordinator from the Center which interests you to find out about post-doctoral opportunities.

A MODEL ORGANIZATION FOR ACADEMIC RESEARCH

The Research, Innovation and Dissemination Centers (RIDC) integrate basic multidisciplinary research, the transfer of technology through collaboration with industry and government, and extension activities in scientific education. Created in 2000 by FAPESP, the eleven Centers perform world class research in medicine, immunology, sociology, urbanism, physics and biotechnology.

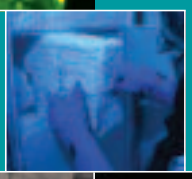
The research groups that make up the Centers are dedicated to lines of research linked to a central theme. Expert researchers train new professionals and produce results internationally recognized such as the use of stem cells for the treatment for juvenile diabetes, and a report on violence against children in the world, commissioned at the end of 2006 by the United Nations.

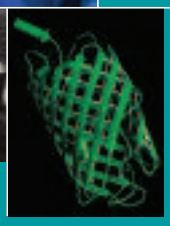
The RIDC's study problems relevant to the country and to the world. Their objectives also include the creation of research partnerships with industry and with institutions capable of putting public policies into practice, the stimulus for the creation of spin-offs based on the results of research. They also offer short courses and workshops for the training of high school teachers.

Each RIDC periodically undergoes an in-depth assessment by international ad-hoc committees invited by FAPESP. Additionally, each RDIC has an International Advisory Board composed by scientists invited by the researchers who lead each center

THE ELEVEN CENTERS ARE

- Center for Structural Molecular Biotechnology, at the University of São Paulo (USP)
- Center for Research and Treatment of Cancer, at the Antonio Prudente Cancer Hospital
- Center Human Genome Studies, at the University of São Paulo (USP)
- Center for Cell Therapy Research, at the University of São Paulo (USP)
- Center for Applied Toxinology, at the Butantan Research Institute
- Center for Sleep Studies, at the Federal University of São Paulo (Unifesp)
- Center for Research into Optics and Photonics, at the University of São Paulo (USP)
- Center for Research into Optics and Photonics, at the State University of Campinas (Unicamp)
- Center for Metropolitan Studies
- Center for the Study of Violence, at the University of São Paulo (USP)
- Multidisciplinary Center for Development of Ceramic Materials, at University of São Paulo (USP)





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MAIN PUBLICATIONS

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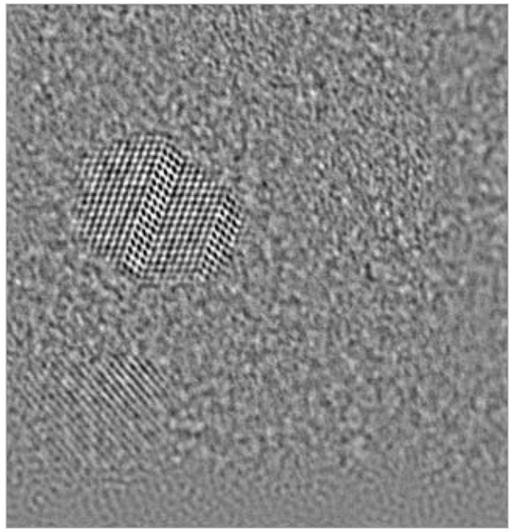

HRTEM image of a Si substract prepared at CePOF, showing the atom's chemical interactions

Optics and Photonics Research Center at Unicamp

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OPTICS AND PHOTONICS RESEARCH CENTER AT UNICAMP

CEPOF-UNICAMP

RESEARCH, INNOVATION AND DISSEMINATION CENTERS (RIDC)

FAPESP

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- Exploratory Photonics
Carlos Lenz César

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Confocal laser scanning biological microscope at the biophotonics lab

CePOF-Unicamp is a multidisciplinary center for research, technology transfer, and education and dissemination of optics and photonics. The center gathers researchers from the Physics Institute, Electrical and Computing Engineering School, Chemistry Institute, Biology Institute, and School of Medical Sciences at the State University of Campinas (Unicamp), the Energetic and Nuclear Research Institute (IPEN), and the Special Laboratory for Lasers in Dentistry (LEO, University of São Paulo).[1]

The center congregates expertise in optical fibers, glass materials, nonlinear fiber optics, femtosecond physics, optical metrology, quantum optics, waveguide modeling, and optical communication systems and devices.

CePOF missions are:

- To develop fundamental and applied research, integrating cross-disciplinary expertise to explore advanced applications of optics and photonics;
- To disseminate optics and photonics to the general public, thus promoting science at all levels of education;
- To promote innovation in the industry through technology transfer, small business incubation, and continued education programs.

CePOF organizes R&D activities into well-defined projects that require the contributions from groups with complementary expertise. This teamwork and leadership development atmosphere stimulates our young researchers to go deeper into the theoretical details and measurement techniques that are necessary for technological developments. The center also encourages students and post-docs to travel abroad, thus strengthening external collaborations, bringing back new variants for research, and assimilating state-of-the-art methods and techniques.

1 Further information on the Center organization and participants is available from CePOF-Unicamp web pages: www.ifi.unicamp.br/foton

MAIN RESEARCH TOPICS

The research activities include fundamental studies in optical communication (devices and systems) and exploratory photonics (materials sciences, photonics in life sciences, optical metrology and quantum optics), as well as applied projects on industry's demand.

Research Topics
Biophotonics
Fiber Optics Parametric Amplifier (FOPA)
KyaTera Project
Optical Fibers
Optical Metrology
Photonic Waveguide Devices
Quantum Dots
Rare Earth Doped Fiber Optic Amplifier (REDFA)
Semiconductor Optical Amplifier(SOA)
Silicon Photonics

Optical Communication Laboratories
Non-linear optics and optical processing, high-capacity WDM systems, and advanced optical amplifiers.
- Laboratories and Research Activities
Optical Communication Lab
Fiber optics parametric devices
Stimulated Brillouin Scattering (SBS) in optical fibers
Photonic Crystal Fibers (PCFs)
Modeling waveguides using finite elements
WebLab on Optical Communication
- LapCom Prof. Atílio José Giarolla
Semiconductor Optical Amplifiers (SOAs)
Automatic gain control for Erbium Doped Fiber Amplifiers (EDFA)

Exploratory Photonics Laboratories
In this program we explore new and advanced applications for photonics. The research projects are divided in the areas:
- Advanced materials and structures
Researches on new materials and structures with applications in optical communication, sensors, and bio-photonics
- Photonics in life sciences:
Researches on new techniques using optical tweezers combined with micro-spectroscopy, nonlinear optics, and colloidal quantum dots; researches on lasers and materials with applications in dentistry and medicine
- Optical metrology:
Fundamental and applied research using femtosecond combs
- Quantum Optics:
Quantum processes for theoretical studies

Institutions connected at KyaTera Project


Optical Communications Lab

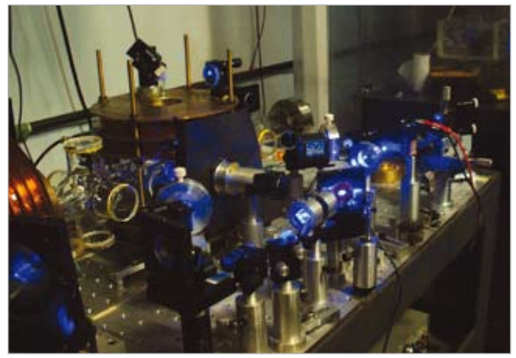
SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Our R&D projects are organized within two main Programs: Optical Communication and Exploratory Photonics.

The Optical Communication Program covers fundamental and applied aspects of materials, devices, and systems. In this program, we explore advances in physics that may lead to significant improvements in the transmission and networking capacity of optical communication. In order to explore the ultimate limits of fiber optic systems, new ultra-broadband optical amplifiers and all-optical optical routers are necessary. To this end, we investigate Fiber-Optic Parametric Devices (amplifiers, wavelength converters) Semiconductor Optical Amplifiers, and special Rare Earth Doped Fiber Amplifiers. Our program covers waveguide and fiber modeling and manufacturing, device development and system studies. In a special project within this program, called KyaTera[2], we developed a dark fiber optical testbed in the State of São Paulo (over 4,000 km of fibers, presently), with the fibers reaching directly the walls of every laboratory. This Fiber-to-the-Lab network is ideal for field trials of photonic devices and optical networks, and offers essentially unlimited bandwidth for the development of future Internet applications. Telefonica and Padtec are our main industrial partners in this project.

In the Exploratory Photonics Program we explore advanced applications of photonics, mainly in Life sciences, sensing and metrology. We develop new biophotonics techniques using optical tweezers combined with micro-spectroscopy, nonlinear optics, and colloidal quantum dots (home produced), optical coherent tomography, and photodynamic therapy. Most of the lasers that we use in our clinical dentistry studies are developed within the center, using crystals grown also in the center. For sensing applications we develop special Photonic Crystal Fibers (PCFs) and methods to laterally access the holes in these fibers. In Optical Metrology, we develop femtosecond frequency combs by using (home developed) Ti:Saphire lasers, and next generation atomic clocks with ultra-stabilized cw lasers and alkaline-earth atoms (Calcium or Ytterbium).

Our R&D facilities include: optical fiber drawing towers for Photonic Crystal Fiber and specialty fibers (e.g., erbium doped telluride fibers); micro fabrication facility (semiconductor amplifiers, micro-disk and stadium lasers, erbium-doped amorphous silicon waveguides, ion-exchange glass waveguides); laser ablation facilities – ns and fs; high-performance computer cluster facility for waveguide modeling; high-capacity DWDM systems; KyaTera dark fiber testbed facility; optical tweezers/micro-spectroscopy with CARS (Coherent anti-Stokes Raman Scattering), 6.7 fs laser with carrier-envelope-phase stabilization control, 0.5 TW 5 Hz 30 fs amplified system, crystal growth facility, diode pumped solid-state laser development facility, micro-FTIR spectroscopy, fast infrared thermography, optical coherent tomography systems; LELO – Special Laboratory on Lasers in Dentistry facility ; laser-cooled optical atomic clock system; and glass fabrication facility.


Ti:Se laser in operation at Lasers and Application Lab

2. The name KyaTera comes from "Kya" ("net" in Tupi-Guarani, the language of the native Brazilian people) and "Tera" ("monster, marvel" in Greek).

MAIN PUBLICATIONS

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Patent Deposit

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About 25,000 DNA samples from families with different genetic disorders are stored in the Human Genome Research Center

The Human Genome Research Center (HGRC)

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THE HUMAN GENOME RESEARCH CENTER
HGRC

RESEARCH, INNOVATION AND DISSEMINATION CENTERS (RIDC)

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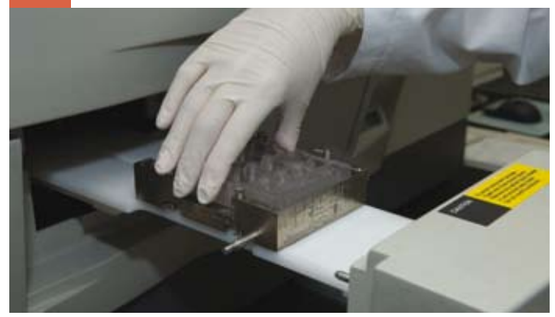

The Human Genome Research Center, in addition to genetic research and counseling, has set up and currently maintains a core facility for DNA sequencing, microsatellites analysis and diagnostic tests for genetic disorders

The Human Genome Research Center (HGRC) at the University of São Paulo is dedicated to the study of genetic disorders. Since its beginning, about 40 years ago, more than 100,000 patients have been referred and investigated by different groups of the Biosciences Institute always in a mutually beneficial interaction: patients generating research and research helping patients. The establishment of the HGRC enhanced integration between the Principal Investigators (PI) responsible for the different research groups, resulting in optimization of resources and know how for scientific investigation on the human genome and consequently a better service to patients as well.

The aim of the HGRC is to enhance comprehension of gene function with focus on neuromuscular, craniofacial and brain development mainly through the study of genetic disorders, which is the ultimate goal of the Human Genome Project. It is also our aim to contribute to the development of new approaches to treat genetic or acquired conditions. These are ambitious avenues of research, which draw upon the combined expertise of our research team. To achieve these goals, the identification of disease genes as well as studies on genotype-phenotype correlations through the analysis of the effect of different mutations on protein expression and phenotypic variability remain a major challenge behind all research on the Human Genome. In terms of pathological variation, recent molecular studies have shown for a great number of genetic disorders that patients, who present the same underlying mutations, may have strikingly different phenotypes. These observations highlight the importance of other genetic and/or non-genetic factors in determining phenotypic expression. The possibility to treat affected patients in the future, also one of our main goals, is being approached through cell and gene therapy investigations by using different animal models.

MAIN RESEARCH TOPICS

Molecular basis of genetic disorders through:

Identification of genes associated with human genetic disorders, particularly neuromuscular and developmental disorders.

Functional and protein analysis

Genotype-phenotype relationship

Association studies in complex disorders

Development of future therapeutic approaches to genetic diseases through research related to:

Analysis of stem-cells from different sources and therapeutic trials with animal models

Gene therapy based on RNA interference and on adenovirus

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Research
Identification of genes associated with human genetic disorders

Mapped disease genes:
- Amyotrophic lateral sclerosis, *Als*8
- A form of X-linked spinal muscular atrophy
- A new form of autosomal dominant *Lgmd-Lgmd*1G
- A new autosomal recessive syndrome, with spastic paraplegia, optic atrophy, and neuropathy –*Spoan*
- A form of X-linked spastic paraplegy
- Aurycular condylar syndrome
- Autosomal recessive form of craniometaphyseal dysplasia
- A new locus for deafnesss
- A new locus for ectrodactily/tibial hemimelia syndrome
- A new locus for Angelman-like syndrome

The genes involved in the pathogenesis of the following diseases were identified:
a) Limb-girdle muscular Dystropy 2G: telethonin
b) Knobloch syndrome: mutations in *Col*18A1
c) Amyotrophic lateral sclerosis: *Vap*-B
d) A new form of syndromic X-linked mental rertardation: *Ube*2A
e) Carpenter Syndrome: *Rab*23
f) Spastic paraplegia type 8: *Kiaao*196 gene

Functional and Protein analysis
For neuromuscular disorders, one important result was the observation that VAP-B (vesicle-associated membrane protein-associated protein b) involved in the fusion of membranes and the transport of intracellular proteins is responsible for ALS8, a dominant form of amyotrophic lateral sclerosis with great clinical variability. More recently it has been suggested by other groups that VAP-B is apparently also involved in sporadic forms of ALS, which opens new avenues of research of worldwide interest. This outlines the importance of investigating the cause of apparently rare disorders.

The analysis of more than 10 muscle proteins was done in about 600 patients affected by different forms of MD. We developed new methods for protein studies, and evaluated the interaction among several proteins of the muscle sarcolemma.

Genotype-phenotype relationship
Many important findings have been achieved through this approach as summarized below.

Screening of mutations for different disorders showed that a strict genotype-phenotype correlation is not the rule. For most disorders, patients with the same mutation may show discordant clinical courses. Identifying the responsible mechanisms, and particularly what "protects" some individuals from the deleterious effects of pathogenic mutations, remains a great challenge, still under investigation, which may have important impacts in future treatments.

The characterization of the most prevalent mutations in our population for some disorders allowed us to develop molecular tests extremely important for diagnosis and identification of asymptomatic carriers in "at-risk" families.

Function of different isoforms as well as identification of important protein functional domains have been identified for some genes involved in neuromuscular and developmental disorders.

The genetic studies of a large cohort of patients with Prader-Willi and Angelman syndromes (genomic diseases) pointed out that the phenotypic variability are due to the different mechanisms involved in the etiology of these syndromes (deletion, uniparental disomy) and that the most severe phenotype of AS results from larger deletions occurring in chromosome region 15q11-13.

The use of expression profile array in a Mendelian bone disorder led to the identification of new proteins involved in osteogenesis, which might provide new targets for the action of drugs that can accelerate bone ossification.

Complex disorders (unknown mechanisms and multifactorial inheritance)
In chromosomal studies, the introduction of the technique of comparative genomic hybridization based on arrays (array-CGH) allowed the detection of chromosomal losses and gains below the microscope resolution. This led to the identification of microrarrangements underlying the etiology of congenital malformations, unexplained mental retardation and deafness. We have shown that microchromosomal rearrangements are important mutational mechanisms in syndromic craniosynostosis and syndromic obesity associated with behavioral disturbances. New candidate gene regions have been identified for these phenotypes.

The Human Genome Center (HGRC) is the largest center for the study of genome disorders in Latin America and is an important contributor in stem cell research

In the group of multifactorial inheritance diseases of, one of our major contributions has been the finding that maternal and fetal genotypes might interact in the predisposition to cleft lip and/or palate.

We also showed that functional analysis of a gene can be achieved through case-control studies in common disorders for which a candidate gene might play a major causative role. For example, we showed that variations in *Col*18A1, in which null mutations cause Knobloch syndrome, is associated to common diseases, such as cancer and obesity. This once again shows that functional analysis of genes associated to rare Mendelian disorders can contribute to the understanding of the human genome.

Future Therapeutic approaches
a) Stem cells investigation
Our main results relate to the differentiation of human adult stem-cells from different sources and pre-clinical therapeutic trials in animal models. Our preliminary results showed the possibility to restore faulty muscle proteins in animal models with muscular dystrophy as well as bone reconstruction. We have also published a paper pointing out that the richest source of mesenchymal stem-cells in umbilical cord units is not the blood but rather the cord, which is usually discarded.

b) Gene therapy
In an effort to start work that may be related to gene therapy, we have been employing cell culture and animal models as recipients of gene transfer. For that we developed recombinant adenovirus vectors to transfer genetic information directly to cells that are from human patients and analyzed their ability to correct the cells' genetic defects. Our data achieved some success correcting the DNA repair deficiency in xeroderma pigmentosum cells, providing hope for these patients to face their skin problems when exposed to sunlight. Moreover, our studies have also been able to propose a new strategy, monitoring DNA repair of tumor cells, to battle aggressive tumors such as glioblastomas.

c) Transfer of technology and genetic counseling
Our results are critical in GC for the estimation of genetic risks, identification of "at-risk" carriers, management and follow-up of patients. Our Center also interacts with patients/parents associations such as the Brazilian Muscular Dystrophy Association (ABDIM), Fragile X Prader-Willi, Angelman associations and Cleft lip/palate Associations. Through ABDIM we established an important partnership with Secretaria da Saúde de São Paulo and more recently with Petrobras for diagnostic tests and management of patients with neuromuscular disorders. The Center also performs genetic services, sequencing and genetic tests, for other members of the scientific or medical community.

The HGCR is also involved in the identification of strategies to ameliorate the suffering of some genetic diseases, in particular neuromuscular, craniofacial and deafness. Recently, a patent application has been done regarding use of a new source of stem cells for bone reconstruction.

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Multidisciplinary Center for Development of Ceramic Materials

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MULTIDISCIPLINARY CENTER FOR DEVELOPMENT OF CERAMIC MATERIALS

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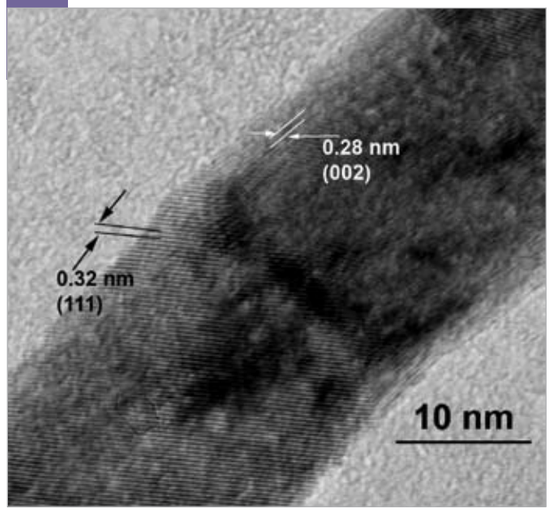

Synthesis of nanocrystalline ceramics: HRTEM image of CeO_2 nanobelts obtained by the oriented attachment (OA) mechanism

The Multidisciplinary Center for Development of Ceramic Materials was proposed by researchers of Paulista State University (Unesp), Federal University of São Carlos (UFSCar), University of São Paulo (USP) and Institute for Energetic and Nuclear Researches (IPEN). The activities of the proposed Center are totally focused on the enhancement of interdisciplinary and multidisciplinary research. The Center was constituted with the multifold mission of encouraging basic and applied research – so that new knowledge can be constantly generated – and promoting a systematic transfer of this knowledge for technological applications and educational purposes. This continuous process spreads knowledge, enlightens the society through instruction, and feeds back the cycle with more demands, that are ultimately satisfied with innovative approaches. To achieve these goals, the Center elects the industry and the schools of all levels as qualified partners for the task.

Our mission is to become formally estabilished as a reference center for ceramics research and development. For this, the Center consolidates an existing infrastructure and improves it to host, as a single and unique institution in science, engineering and education, basic and applied research, technology transfer and diffusion of knowledge. By hosting and encouraging interdisciplinary collaborations, the Center opens new means for research, both on campus and outside universities. The Center provides an intellectual atmosphere and physical means for scientists from different departments and institutions to meet and work together. Theoreticians and experimentalists, mathematicians, physicists, chemists and engineers will have the opportunity to discuss and argue in such a way that the ideas of each area of research will influence one another collectively, and thus new research themes will emerge.

MAIN RESEARCH TOPICS

Catalysis
Thin films
Nanotechnology
Theorical chemistry
Voltage-dependent resistors
Cosmetics
Luminescent materials
Ceramic pigments
Sensors
Art ceramics
Refractories

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Innovations: highlights Refractory
The innovations developed by the metallurgical sector with the CSN company consisted in advanced refractories that can be applied in order to assure high metal quality from economical and ecological aspects. During services, not only must refractories tolerate high temperature but also withstand stress (thermal and / or mechanical), as well as exhibit resistance to combined attack by liquids such as molten metals, slags and fluxes.

Catalyst Materials
The innovation contracted by Petrobras (Brazilian Petroleum Company) is the development of a new catalyst material based on Al_2O_3-ZrO_2 system. Basically, the innovation consists of modifying the Al_2O_3 surface by using a nanolayer of zirconia and analyzing the influence of the ZrO_2 layer on hydrogenation reactions. Figure 1 shows HRTEM image of the alumina with a ZrO_2 layer.

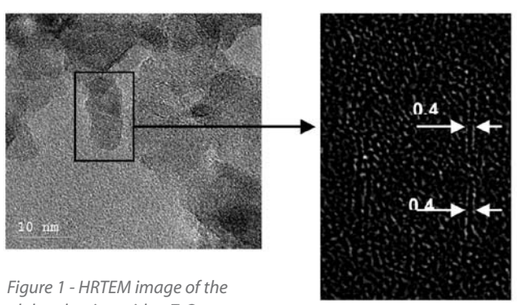

Figure 1 - HRTEM image of the alpha alumina with a ZrO_2 layer (HRTEM=High Resolution Transmission Electron Microscopy)

Development of automotive temperature sensors
Different kinds of perovskite-based NTC temperature sensors have been developed by the MCDCM which were synthesized by mixing, pressing and sintering Ni, Cu, Mn, and Co oxides aiming to apply such compositions as automotive temperature sensors. Some compositions have also been synthesized by a modified polymeric precursor technique. The electrical characterization was carried out by dc methods. An experimental sequence for producing large quantities of each composition was evaluated for the scaling up of the thermistor production by Metalúrgica Iguaçu Ltda. Therefore, the challenge posed by local industries looking for Brazilian-made temperature sensors for application in the automotive industry has been overcome: four out of six thermistors with behaviors similar to those exhibited by commercial thermistors have been successfully developed.

Spin-off Companies
Our students have nucleated two small companies, based on researches developed in our Center. The first one was Kosmo Science and the main purpose of this company is to develop analytical procedures to characterize cosmetic products, as well as the interaction of the cosmetics with hair and skin.

The second company nucleated in our Center was Nanox. The goal of this company is to develop nanostructured coating with functional properties such as bactericide and hard coatings. Figure 2 shows a nanostructured ZrO_2 coating on stainless steel developed by Nanox. This company is also working in the hydrothermal synthesis segment, developing small reactors for laboratories.

New product (Technological Innovation in Small Business - PIPE/FAPESP)
In this group of innovation, our main goal was the development of new products in collaboration with small companies and with the financial support of FAPESP through PIPE projects. An example of innovation was the development of translucent alumina pieces for dentistry applications. This innovation was contracted by Tecnident Ltda., from the dentistry sector that produces dental restoration 100% translucent alumina brackets.

The development of a dental restoration entirely comprised of ceramics, aiming to replace the traditional metal/ceramic dental restoration. This project was very complex and demanded the development of a porous ceramic matrix, and a glass to be infiltrated in the porous matrix. After the glass infiltration, a composite material was formed with excellent mechanical properties. Figure 3 shows an example of a ceramic dental restoration developed along with the EDG Company.

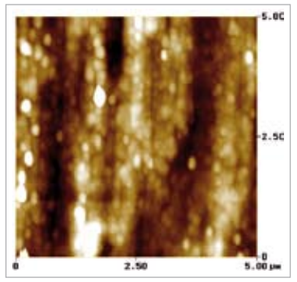

Figure 2 - AFM image of a nanostructured ZrO_2 coating on stainless steel

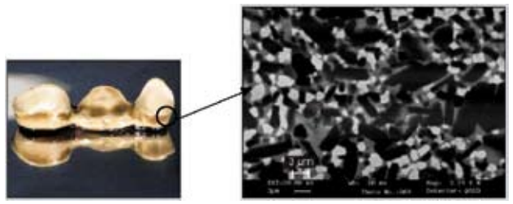

Figure 3 - Example of a ceramic dental restoration developed along with the EDG Company

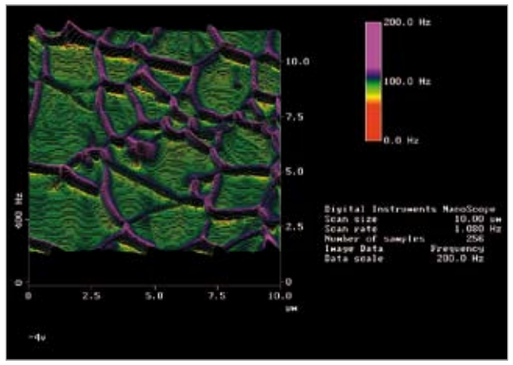

Figure 4 – EFM image of a polycrystalline SnO_2-based varistor

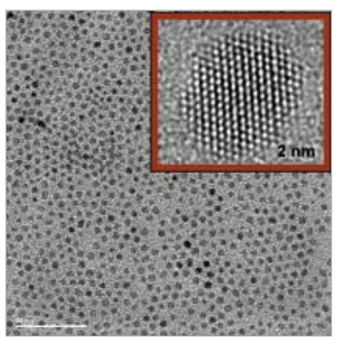

Figure 5 - HRTEM image of ZrO_2 nanocrystal processed by solvothermal process. The inset shows in detail the nanocrystal synthesized at our center

Polycrystalline Semiconductors
Concerning polyrcrystalline ceramic devices, the main development of our center was the SnO_2 based voltage-dependent resistors. We have shown the good electric performance of this device and its superior thermal conductivity and low degradation rate. The development performed by our group shows that the SnO_2-based voltage-dependent resistors presents properties similar or even superior to the ZnO-based voltage-dependent resistors, suggesting that this device is a good candidate for commercial production. An example of the work done on this device is illustrated in Figure 4. This figure shows an Electric Force Microscopy (EFM) image of a SnO_2-based varistor, where it is possible to see the voltage barriers at the grain boundary. In this image, noteworthy is the elevated number of voltage barriers in the grain boundary, which suggests an elevated number of effective barriers.

Synthesis of Nanocrystalline Ceramics
As to the synthesis of nanostructured metal oxides, the main result obtained by the MCDCM was the development of a kinetic model to describe the growth process of nanocrystals in colloidal dispersion, more specifically a statistic model to describe the oriented attachment (OA) mechanism. The OA mechanism originally proposed by Banfield and Penn (*Science.* 1998, **281**, 969) is a process involving the self-organization of adjacent nanocrystals and coalescence. The number of nanostructured materials obtained by the OA process is growing rapidly and has become an attractive form of processing nanomaterials with anisotropic structure. An in-depth understanding of this mechanism allowed for obtaining nanocrystals with controlled morphology, as illustrated in the HRTEM image in Figure 5.

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CENTER FOR METROPOLITAN STUDIES

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Using geo-referenced technologies such as satellite images, CEM developed a methodology for recognizing precarious settlements – which have sanitation, familiar income and other conditions similar to those of slums – and generated intra-urban cartographies of 371 municipalities in a study for Ministério das Cidades

The *Centro de Estudos da Metrópole* (Center for Metropolitan Studies) – CEM develops advanced studies on themes related to urban processes, with emphasis on the Brazilian context and in a dialogue with the world production in the area. Its central proposal is to investigate the reproduction mechanisms of social inequality in metropolitan environments. It is not the case of merely producing the mapping of these inequalities, but of carrying through an analytical effort in order to understand in depth the dynamics producing and reproducing them, so as to ascertain policies aimed at overcoming them.

Researches taken to effect in the first years of the CEM revealed a paradox: even with a negative scenario in the economy and the labor market, an improvement has been observed in several social indicators concerning health, education, housing, and the ownership of durable goods, even in the more vulnerable metropolitan areas. Such improvement has been associated with the existence of multiple survival and social integration strategies, only in part affected by the properly economic dynamics of the 1990's. From these findings, the present central working hypothesis was elaborated, based on the premise that the social reproduction in São Paulo, and in other similar places, results from the association between general processes inducing the maintenance or the growth of inequality, on one hand, and political and social mechanisms that lessen social vulnerability, on the other. The focuses of the CEM's studies are as much the reproduction of the inequality as the production of social welfare.

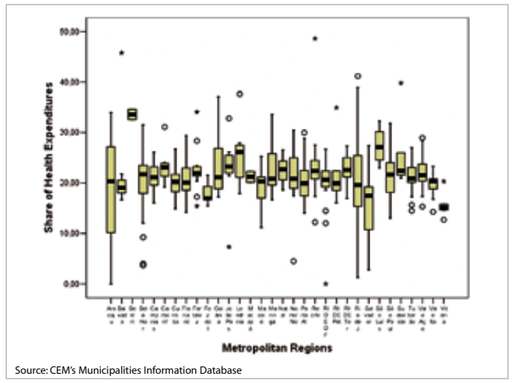
The researches developed by the CEM adopt an interdisciplinary approach, bringing together urbanists, sociologists, demographers, anthropologists, political scientists, and communicators. They also emphasize comparative analysis, involving metropolitan areas from different regions of Brazil and other countries. The main objects of study are the access to employment, social services, and social relations (associative movement, religion, and social networks).

MAIN RESEARCH TOPICS

Labor market, intermediation and social networks
This line of research approaches the labor market and its role in the reproduction of a determined pattern of inequality of opportunities. It is also dedicated to the mechanisms to which the individuals resort in order to face the vulnerability originating from the structure of occupational opportunities, based on intense transitions between situations in the market and in recurrent unemployment. This implies that the recent shifts in supply and demand for work force be investigated, considering the strong impact of structural changes in economic activity, such as the internationalization of enterprises and the displacement of occupations among the sectors of the economy. Studied in the same way are the formal – resulting from the system of intermediation – and informal – made available by the social networks – mechanisms providing access to occupations and the related transitional movements within the labor market.

Life conditions, State and public policies
This line of investigation examines the political institutions as explanatory factors of the access to social services – and, therefore, of life conditions of the poorer sections of the community – and the mechanisms through which they voice their interests. The axes of research intend to analyze the processes – collective and individual – of access to the State: (i) the policies themselves – their design and operational mechanisms; (ii) the networks of access to the State; (iii) the public expenditure and its determinants; (iv) the patterns of representation – representative or participative. This line of research includes comparative studies about localization and spatial dynamics involving shantytowns and precarious settlements, so as to subsidize State actions. In investigating the relationship between inequalities, social networks and spatial distribution, it opened new possibilities for studies on social segregation.

Sociability and urban life
This line of research examines the social relations and their impact on the experience of urban life and the opportunities of escaping from the situation of poverty. Two analytical dimensions are central to this line of investigation: (i) to analyze the effects of social networks upon the reproduction of poverty, based on the hypothesis that they can be a virtuous mechanism for reducing vulnerability, by providing access to the labor market and to public policies; (ii) to understand the role of family and migration in the reproduction of the religious sphere, starting from the hypothesis that new structures – not social, but rather communicational – would mold the foundations of contemporary urban experience.



Source: CEM's Municipalities Information Database

The boxplot shows the share of health expenditures on the total budget for the municipalities located in each of the 29 metropolitan areas in Brazil. It reveals they give high priority to this policy, since this expenditure median was around 20% in 2006, a rate which is quite representative of previous years. It is explained by policy-specific regulations of the central government over local governments spending decisions

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Research
- Brazilian municipalities give greater priority to redistributive than to developmental policies. Their participation in health and education programs has varied from 30% to 70% of total expenditures. In urban infrastructure and the public transportation, this proportion has varied from zero to 35%. Inequalities in expenditures are much higher in redistributive than in developmental policies. This outcome is explained by central government regulation.

- Surveys applied to the poor population in São Paulo (1991 and 2004) show that the employment situation has been deteriorating while social services have been considerably improved; they also show that the access to services relies mainly on institutional means and not on clientelistic practices. Research carried out in Salvador in 2006 arrived at similar findings.

- In a context of diminishing job opportunities, private services of job intermediation become more central, regardless of the governmental efforts for organizing a public system of employment allocation. However, the most important mechanism for the search for jobs in São Paulo, differently from Tokyo and Paris, is still the participation in personal networks, even for those who usually search through private institutions.

- Segregation has a strong effect on poverty, as well as on the access to public services.

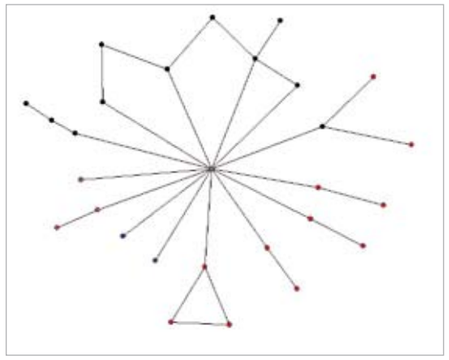
- Residential (income) segregation in São Paulo is similar to (racial) segregation in New York, and has increased between 1991 and 2000. However, the access of the poorer to social services is more related to policy design than to the patterns of intermediation or spatial segregation.

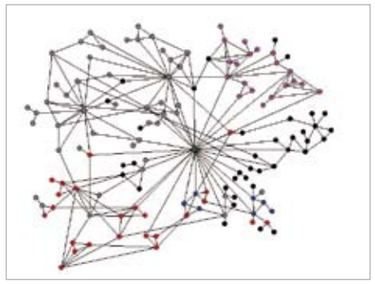
- The provision of infrastructure is strongly affected by networks linking bureaucracies within the State and private companies. Notwithstanding, the outcomes differ according to right and left wing administrations, as well as to the policies' institutions.

- The size of personal networks and the type and variability of the individual's sociability help to explain income, job status, and poverty. Variability in income is more extensively explained by networks than by traditional variables such as job status and schooling years.

- The strength of civil organizations does not affect their propensity to engage in the formulation of public policies. Such engagement is explained by the relationship with political parties and governmental agencies.

Technology transference
- Development of the software *TerraView Política Social*, in an agreement with the National Institute for Space Investigation, available for free download from the website.





CEM´s researches revealed that personal networks of the poorer (above) in Brazilian metropolitan regions tend to be smaller, more local, less heterogeneous and have less diversity of spheres than those of middle-class people (below). Quantitave analysis has added that relational indicators explain poverty conditions, measured by income, social precarity, job status and job tenure. The results suggest that these patterns of sociability must be taken into account by public policies designed to address social inequality and poverty

- GIS courses for habilitating professionals and researchers.

- Creation of a Geographic Information System with more than 140 layers of information for the metropolitan region of São Paulo. The most important databases are available for free download from the website.

- Studies directed to public policies, such as the Map of Vulnerability – which identified the spatial distribution of basic needs and has been used by the Municipality of São Paulo in formulating local policies – and the project for the *Ministério das Cidades* – which developed a methodology for recognizing precarious settlements, generated intra-urban cartographies of 371 municipalities, and undertook an extensive analysis on local governments' managerial capabilities concerning housing policies.

- Development and maintenance of Web Mapping servers the regions of São Paulo, Rio de Janeiro and Salvador, as well as about the municipalities of the State of São Paulo.

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Laser Capture Microdissection System Veritas™

The Antonio Prudente Cancer Care Center (APCCC), based at Cancer Hospital, in São Paulo, was approved by FAPESP in 2000. Its primary goal is to contribute to the advancement of cancer prevention, diagnosis and treatment. Following the best standards recognized worldwide, we aim to develop new tools to improve patient care. In 2000, research projects were primarily focused on gene discovery, mutation detection, differential expression between normal and tumor tissues, and epidemiology of HPV.

During its first five years, the APCCC got involved in a major sequencing effort, financed by FAPESP and the Ludwig Institute for Cancer Research (LICR), the Human Cancer Genome Project (HCGP). This project ended in 2001, with a significant contribution to the human transcriptome, producing an excess of 1 million ESTs generated from normal and tumor tissues. The APCCC contributed with more than 99% of tissue-derived RNA. Because of that, APCCC developed procedures and protocols for the creation of a tumor bank that allows the extraction of high quality DNA/RNA/protein.

At the same time, efforts were also dedicated to the establishment of cDNA microarray and tissue microarray platforms. Finally, we also invested heavily on bioinformatics in order to have these platforms integrated with our tumor bank and samples linked to clinical data, and acquired the expertise to analyze both platforms. This integrated effort for quantitative analysis of transcripts was the major achievement during that period and enabled us to identify new molecular markers for diagnosis and prognosis.

For the 2005-2008 period, we focused our research project on a small number of tumors (Head and neck, Sarcomas, Wilms' Tumor, and Breast). Thus, taking advantage of the previously built platforms, we were in a position to address clinically relevant questions: Can we improve diagnosis? Can we evaluate prognosis? Can we predict response to therapy? For the second period of RIDC (2005-2008) we succeeded in the identification of new diagnostic and prognostic markers for the proposed tumors.

MAIN RESEARCH TOPICS

During its existence, the APCCC has been characterized by the effort to bring together basic researchers and medical staff in order to produce new advances in tumor diagnosis and etiology, prognostic markers, and tools to predict response to therapy. It is a definition of translational research with the aim to benefit our patients.

APCCC has been working with gene expression transcriptomic studies. We participated in HCGP working with ORESTES and contributed with more than one million sequences of different tumors and their normal counterparts (Camargo AA et al. 2001. *Proc Natl Acad Sci USA*. **98(21)**:12103-8; Brentani H et al. 2003. *Proc Natl Acad Sci USA*. **100(23)**:13418-23). We worked with SAGE on establishing different mathematical models of analysis (Vêncio RZ et al. 2007. *BMC Bioinformatics*. **8**:246; Barrera J et al. 2007. *BMC Bioinformatics*. **8**:169), and have also been working with microarrays contributing with important classifiers that may help in clinical practice.

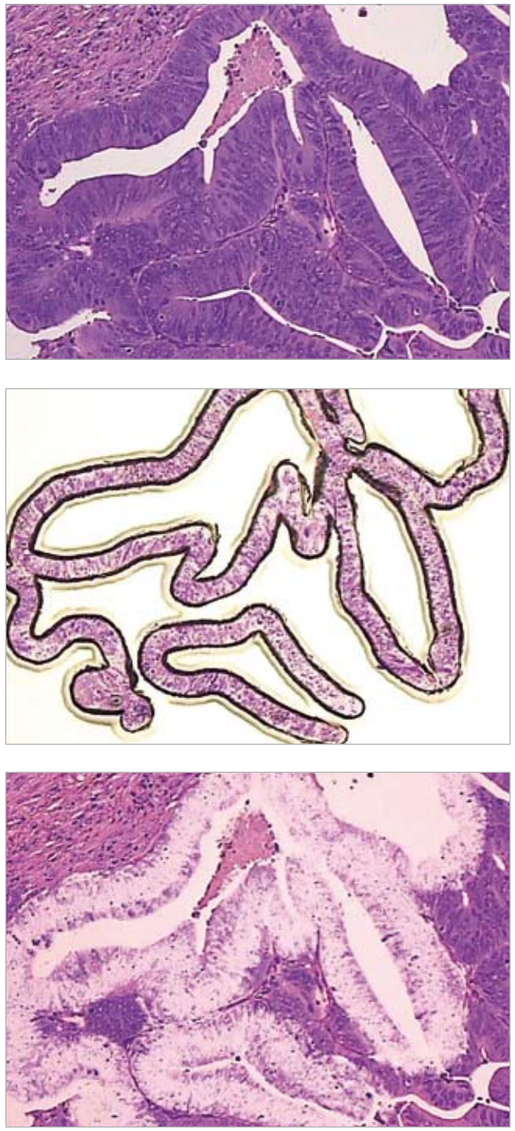
Several facilities have been organized as follows: tumor and DNA/RNA bank, DNA/RNA extraction facility, TMA facility, and gene expression facility. We them focused our efforts on four types of tumor: head and neck carcinomas, sarcomas, Wilms' tumor, and breast carcinomas.

The head and neck tumors front has been approached in order to recognize predictors of response for chemo/radiotherapy in larynx squamous cell carcinoma. By using biopsies taken before treatment, the gene expression profile of a group of 21 responders was compared with a second group of 14 non-responders. After mathematical analysis, four trios of genes were identified that could predict responsiveness to treatment.

We have also analyzed molecular signatures in sarcomas. Mesenchymal tumors are unusual, but they have significant morbidity and mortality. Our main effort in the last three years was to identify classifiers able to separate locally aggressive tumors but without ability to develop metastasis from potential metastatic sarcomas. We have used fibromatosis as a tumor model with high local aggressiveness and fibrosarcomas as a model of metastatic sarcomas.

The third branch of the Center is related to molecular markers as predictors of adverse outcome in Wilms' tumors. For this, we have tested blastemal predominant Wilms' tumors sensible and resistant to chemotherapy. By using SAGE, we have selected 14 differentially expressed genes.

Finally, the breast carcinoma front was approached by two different projects. One of them studied the validation of *Adam*23 hypermethylation (HyMe) as an independent prognostic factor, and the second aims to explore the transcriptional variability caused by alternative splicing to identify breast carcinoma-associated splicing variants.



Laser Capture Microdissection Procedure

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

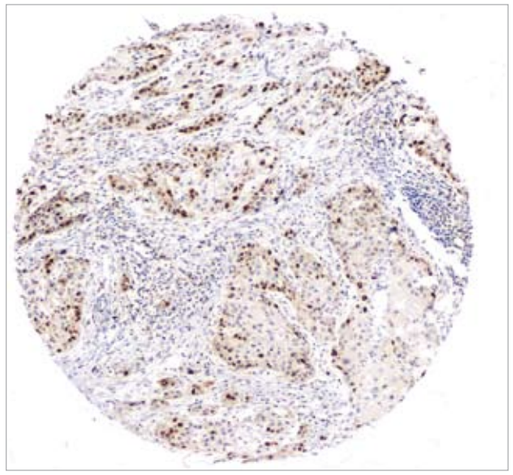
Our main research focus is on translation research in order to improve diagnosis and prognosis of the tumors, and identify predictors of treatment response. Nowadays our aims are concentrated on tumors of head and neck, soft tissues, breast and Wilms' tumor.

The breast carcinoma front was approached by two different projects. One of them studied the validation of *Adam*23 hypermethylation (HyMe) as an independent prognostic factor, and comprised three segments: *Adam*23 regulation of the activation of avb3 integrin; *Adam*23 HyMe in plasma samples from breast cancer patients; and *Adam*23 HyMe and detection of micrometastasis in sentinel lymph nodes. The second project in the breast carcinoma section aims to explore the transcriptional variability caused by alternative splicing to identify breast carcinoma-associated splicing variants.

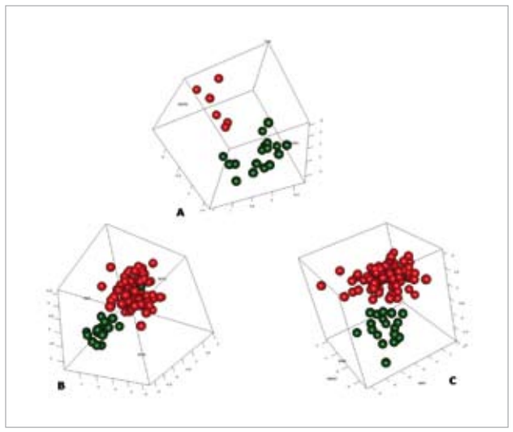
Also, we have analyzed molecular signatures in sarcomas. The main effort is to identify classifiers that are able to separate locally aggressive tumors, but without ability to develop metastasis from potential metastatic sarcomas.

A third segment of APCCC's proposal is related to predictors of response for chemo/radiotherapy in larynx squamous cell carcinoma. After mathematical analysis, four trios of genes were identified that could predict responsiveness to the treatment.

The last project is related to molecular markers as predictors of adverse outcome in Wilms' tumors. For this, we have tested blastemal predominant Wilms' tumors sensible and resistant to chemotherapy. Five genes showed a differential expression between relapsed and non-relapsed WT samples with statistical significance ($p<0.05$). All of them were over-expressed in nonrelapsed WT samples. Trios of classifiers were exhaustively searched among the 5 genes using the qRT-PCR data, and 2 trios were promising predictors of adverse outcome in WT, correctly separating 95% of the samples.



Topoisomerase positivity in squamous cell carcinoma



Scatter plot showing differences in gene expression between mesenchymal tumors

More than 10,000 samples in the Tissue Microarrays (TMA) of different organs and different tumors

MAIN PUBLICATIONS

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Studies conducted by CAT on rattlesnake venom may result in important pharmaceutical innovations

The Center for Applied Toxinology is a multi-institutional research organization based at Butantan Institute in São Paulo, Brazil, dedicated to the study of animal and microbial toxins. It was established in 2000 to stimulate research, disseminate knowledge, and foster interaction between science and industry. Laboratories from the University of São Paulo (USP), State University of São Paulo (Unesp), and Federal University of São Paulo (Unifesp) take part in CAT's activities.

Due to their high target selectivity, venom toxins have been used successfully as pharmacological tools and prototypes for drug development. While pharmaceutical companies spend billions of dollars searching for pharmacological compounds through extensive screening of chemical libraries, venomous animals, during millions of years, have designed their own "pharmacological" tools with the help of molecular evolution.

Acting as a whole, the large variety of toxins present in animal venoms impair the homeostasis of the cardiovascular, the nervous, and the defense systems of the animal, causing dysfunction of blood clotting and pressure, neurological responses to stimuli, cell secretion, migration and adhesion, ultimately resulting in the animal paralysis or death. At CAT, we take a multidisciplinary approach by investigating each particular toxin, which includes isolation, purification, studies of pharmacological actions, structure determination, and structure-function studies of the molecular and cell biology aspects.

CAT has established partnerships with Brazilian pharmaceutical enterprises for drug development. Research findings, obtained at CAT and protected by patents, have been transferred for drug development to some of the most important Brazilian pharmaceutical industries. Toxin based drugs affecting blood clotting, the cardiovascular system, pain perception, anti-proliferative compounds, and immune suppression are being subjected to pre-clinical trials.

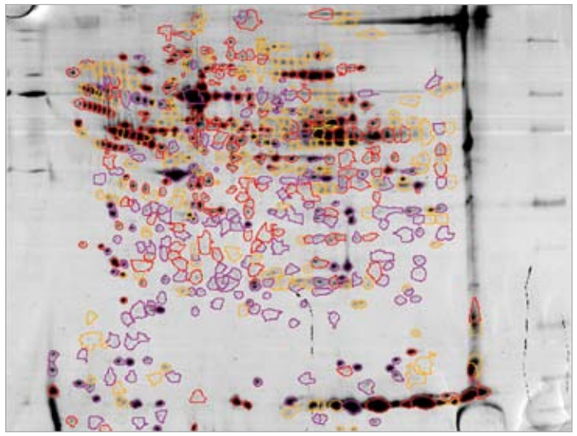
MAIN RESEARCH TOPICS

The toxins found in the venom of the snake *Bothrops jararaca* and their action on the cardiovascular system is one of the most advanced research areas of CAT, having already been studied since the late 1940's. It deals with the effects of the toxins on the control of blood pressure, coagulopathies, fibrinolysis, blood cell migration and adhesion. Involved in these studies are researchers working with proteomic techniques, synthesis of compounds derived from toxins, crystallography, molecular modeling, and a large number of biological assays. Molecular and cellular biology of these toxins, structure-activity relationship concerning their pathophysiological effects, their ability to identify pharmaceutical targets and/or biomarkers are also being investigated. Chemically modified snake venom toxins are being developed to treat dysfunctions of blood pressure regulation. Another research group is studying the toxins of a caterpillar, which have a strong action on coagulopathy processes.

Other research groups are devoted to the nociceptive effects of snake and fish toxins. These include: pain, analgesia, action on cell receptors and ion channels, cell migration and adhesion with special emphasis on neuronal and immune cells. Molecular and cellular mechanisms are under investigation, as well as their systemic action in animal models, both on isolated organs and cells. The main purpose is to use these toxins as lead molecules for the treatment of neuropathic pain and in inflammatory processes of the lung.

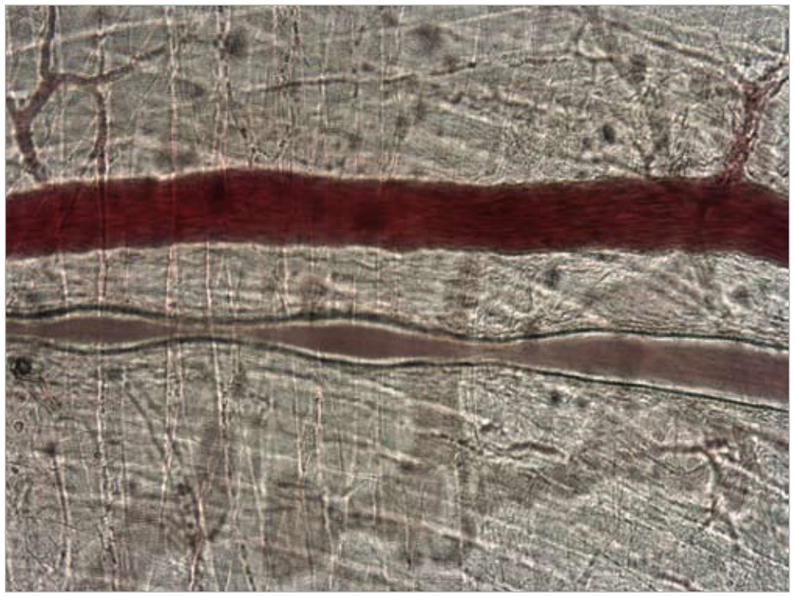
A third research area is concerned with arthropod toxins, which act on cellular proliferation and tumor growth, and are also being studied. Molecules have been isolated which have a strong effect on diverse tumor cells, and at present the mechanisms of action and the targets are being determined.

Finally, another group is investigating the embryogenesis of the central nervous system and the pathophysiological mechanisms related to neuronal migration, synaptogenesis, and neuritogenesis. A protein, fully characterized in our laboratory, was demonstrated to be essential for the cerebral cortex development. Several neuropathologies have been correlated to dysfunctions of this protein. It is thus being used as a target for drugs and toxin action.



2D Electrophoresis analysis of mouse skin proteins after injection of hemorrhagic toxin

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES



Fluorescence assisted cell sorter (FACS) at the Immunopharmacology Facility

Toxinology research projects have an obvious potential for pharmaceutical innovations and since its start in 2001, when CAT was created from scratch, the group efforts focused on basic research allied to protection of intellectual property, mobilization of additional funds for research (private sector investment), and the enhancement of partnerships with the industry.

The most representative publications reported findings on the following subjects: i) the cardiovascular effects of bradykinin potentiating peptides; ii) the antinociceptive effect of *Crotalus durissus terrificus* venom mediated by ions channels; iii) the structural basis for the activity of spider sphingomyelinases D; iv) sea anemone toxins activity on sodium channels; v) the gene delivery into cells by crotamine from *C. d. terrificus*; vi) the prothrombin activator from *Lonomia obliqua*; vi) the inhibition of NUDEL activity by disrupted-in-schizophrenia 1; vii) the function of non-catalytic domains of venom metalloproteinases.

Concerning the patents applied by CAT so far, we highlight the following pharmaceutical applications under development: 1) Evasin Project. We are finishing up the basic pre-clinical evaluation steps by using laboratory animals treated with various different synthetic peptides. Progress in the research with these molecules showed that the cardiovascular action of the peptides takes effect on a target different from the angiotensin-converting enzyme. 2) Enpak Project. A patent was filed concerning an analgesic compound, which is more potent than morphine and does not cause addiction. It is active, when taken orally, and shows long duration. This molecule, named Enpak (endogenous pain killer) was isolated and completely characterized and synthesized in our laboratories. 3) Lopap Project. Several aspects of the prothrombin activating activity of the bristles of the caterpillar *Lonomia obliqua*, assigned to a novel protease called Lopap, for *Lonomia obliqua* prothrombine activator protease. Recombinant Lopap, its use in diagnostic kits and as an agent causing fibrinogen depletion, are in basic pre-clinical evaluation steps 4) Amblyomin Project. A novel Kunitz-type protease inhibitor of factor FXa was identified in the salivary gland of the tick *Amblyoma cajennense*. Its therapeutic effect was shown on mice with dorsal melanomas and pulmonary metastasis.

MAIN PUBLICATIONS

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FAPESP

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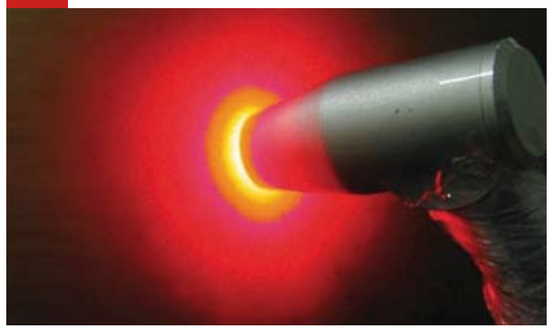

Laser and led therapy in bio-modulation

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- São Carlos School of Engineering
- Ribeirão Preto School of Medicine

Institute of Energy and Nuclear Research (Ipen)
- Laser and Applications Center

Other Institutions
EMBRAPA Instrumentation Center
Amaral Carvalho Hospital

Under the general rubric of Basic Research, the RIDC currently animates three major themes. In addition the Center supports eleven research partnerships with various dental, medical and veterinary schools pursuing research and treatment in medical dentistry, oncology and crop diseases.

Specific research programs in *Molecular and Optical* (AMO) *physics* concentrate on quantum condensed matter, cold atomic and molecular collisions as well as quantum atomic fluids like Bose-Einstein condensate, and the development of state-of-the-art time and frequency standards by using atomic clocks.

The *Photonic materials* program develops polymers and other organics, applies ultrashort light pulses for manufacturing and analysis, and characterizes optoelectronic thin films. *Biophotonics* investigates new noninvasive optics-based diagnostic tools, cancer therapies involving light (photodynamic therapy), early photodiagnosis of plant and crop diseases, and environmental issues such as pesticide degradation and pollution of ground waters.

These research programs are imbedded in partnering agreements with professional schools in the São Carlos region. Because of its unique expertise in optics, materials, and device development, the Center is planning a new basic research thrust into the multidisciplinary area of *plasmonics and nanophotonics*.

The Innovation axis develops new devices, interfaces with local high-technology enterprises, and creates spin-off companies to commercialize new applications developed at the Center. This activity is concentrated at the new LAT laboratory-Laboratory for Applied Technology and has resulted in the creation of thirty optics-based companies in São Carlos, three new spin-off companies alone in 2006.

The Outreach program involves educational activities at all levels from elementary school to post-graduate continuing education. The Week of Optics, SEMOPTICA, has become a major annual event in the school calendar all over the State of São Paulo. The Center broadcasts on Educational Television not only university level courses, but also programs popularizing important developments in optics-based science and technology. The Center has developed a Mobile Science Unit, a specially prepared bus to visit schools for the purpose of presenting scientific demonstration and expositions.

MAIN RESEARCH TOPICS

Atomic physics

Bose-Einstein condensate of rb and coherent modes

Cold atomic collisions

Time and frequency metrology

Photonic materials

Nonlinear spectroscopy in organic materials

Coherent control of light

Crystallization of a-Si

Opto eletronics of doped a-Si

Photo-structural changes in chalcogenides

Collaborative network

Clinical implementation of photodynamic therapy

In vivo studies to optimize PDT

Development of a real time dosimetry for photodynamic therapy

Microbial control using photodynamic reactions

Investigation of photobleaching in dental whitening

Optics applied to agriculture and enviroment

Ex vivo - determination of time of death by fluorescence spectroscopy

Fluorescence imaging and optical diagnostic tools

Optical fluorescence for diagnosing cancer and other lesions

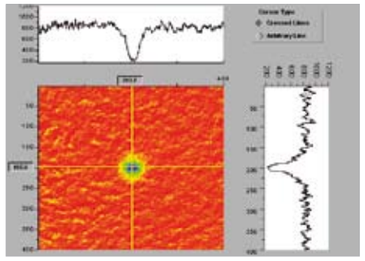
Photoprocessing of dental materials

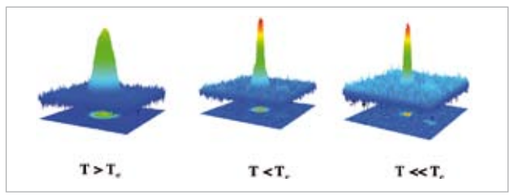
Laser ablation of hard dental tissues and materials – selective removal

Laser and LED therapy in bio-modulation

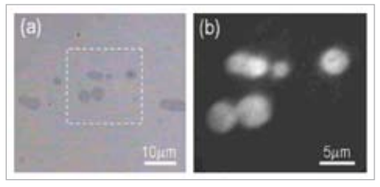
Development of a cylindrical symmetry wavefront sensor

Optical methods for evaluating organ conditions and transplant procedures

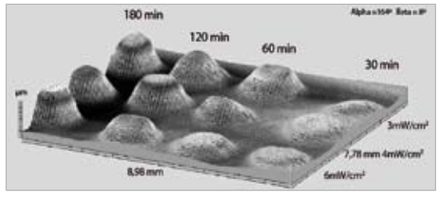




Time of flight image showing the Rb condensate with more that 100,000 atoms



Optical microscope image (a) and Raman imaging (b) of silicon micro-crystals that develop on the surface of amorphous Si films doped with approx. 0.1 at.% of Ni



Time and power density of irradiation on a GGS film sample

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

The photodynamic therapy and optimization projects of this procedure have obtained as a result an optimized dosimetry process that allows for the real time evaluation of the process. As a consequence of this, we have been successful in attaining a higher rate of success than usual in eliminating tumors. The development of new instruments based on LED and lasers have enabled us to perform superficial and interstitial procedures more efficiently.

The project Optical Fluorescence Diagnosis of Cancer and Other Lesions has developed both techniques and equipment that permit biopsy results with sensitivity higher than 94%. Still as far as determining UV-caused skin lesions is concerned, we are able to identify the onset of threatening lesions capable of evolving to tumors.

An optical fluorescence evaluation technique, such as the one we have developed, is used for assaying the viability of organs to be transplanted. Also finished are the methodology and clinical prototype, both of which have been successfully employed for clinical purposes for the first time. The project for optical detection of pathologic tissue conditions has achieved and precision levels higher than 90% in determining time of death.

We have also developed a new technology that conjugates both ultrasound and light for improving the cure efficiency of composite dental resins in more than 20%. Our work has also borne fruit in dental photobleaching, resulting in marketable systems, as well as the development of a new gel based on coal nanoparticles, which yields higher photobleaching efficiency. By using photodynamic therapy techniques, we have developed prototypes that are now being clinically employed in periodontics for mouth and dental prostheses disinfection. We have been able to attain up to nine logarithmic orders in bacterial and fungal reduction. The systems developed are being used in immunosuppressed, transplanted and elderly patients, who do not tolerate the aggressivity of most fungicidal agents.

Microbial control using photodynamic reaction

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THE CENTER FOR STRUCTURAL MOLECULAR BIOTECHNOLOGY

CBME

RESEARCH, INNOVATION
AND DISSEMINATION CENTERS (RIDC)

Crystal structure of the enzyme glyceraldehyde-3-phosphate dehydrogenase from Trypanosoma cruzi, one of the targets for anti-parasitic drug discovery at CBME

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Genetics and Evolution Departament / Federal University of São Carlos (DGE/UFSCar)

National Synchrotron Light Laboratory (LNLS)

State University of Campinas (Unicamp)

The major goal of the Center for Structural Molecular Biotechnology (CBME) is to perform both applied and basic research, as well as technological development in all areas that depend on Structure Based Molecular Design, specifically in the rational design of new structure-based compounds (drugs, vaccines, pesticides, herbicides) and in protein engineering. Our center promotes an integrated multidisciplinary approach including Molecular Biology, Biochemistry, Structural Biology, Medicinal Chemistry based on both Synthetic and Natural Product Chemistry, Molecular Immunology, Cell Biology and Pharmacology. Maximum integration and collaboration with the private sector is always sought, particularly with pharmaceutical and biotechnology companies and research institutes within the health and agricultural sectors. The integration of biological sciences with the facilities of the National Synchrotron Light Laboratory (LNLS) represents a major advantage for the center.

The research projects of CBME are selected by their focus on areas which are socially highly sensitive, such as human health, agriculture and the environment. The center aims to achieve maximum integration and partnership with both public and productive sectors, particularly national and international pharmaceutical companies, biotechnology industry, research institutions dedicated to human health and the agricultural sector. The large majority of the projects currently being developed are related to tropical parasitic diseases endemic in Brazil, as well as cancer, HIV and agricultural related diseases.

On the educational front, the center strongly invests in training programs for students and researchers in the area of Structural Biology in all institutions involved. Furthermore, the CBME will closely work with the Center for Scientific and Cultural Diffusion, which interacts with the community, through strong programs directed towards high school students, school teachers, libraries of experiments for school demonstrations, education at a distance via internet, videos, science fairs, lectures and so on.

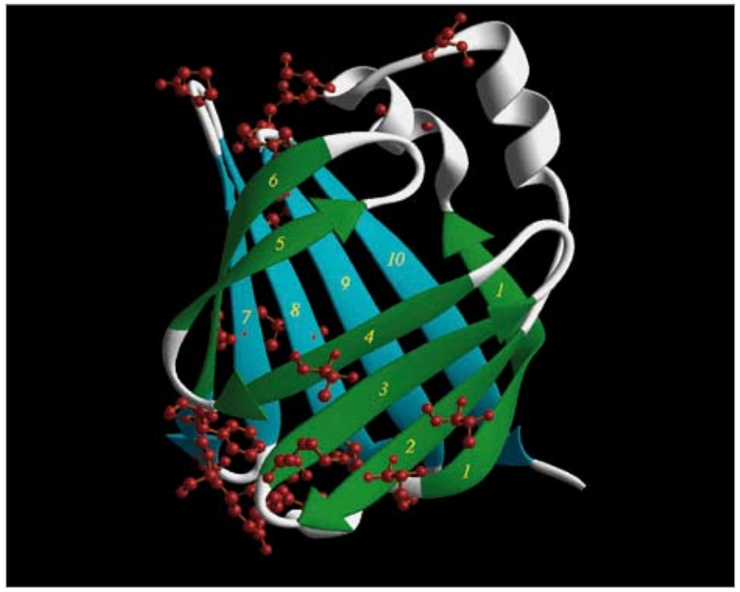
MAIN RESEARCH TOPICS

The laboratories of CBME integrate top technologies in molecular biology, biochemistry, protein crystallography and medicinal chemistry

The common issue on the research projects of CBME is the molecular approach, in atomic detail, of biological systems related to demanding areas of society, such as human health, agriculture, and environment. The team members are researchers with solid formation and background in different aspects of molecular and structural biology CBME's mission is to develop high-quality basic research in strategic areas for the country. The current main projects are related to endemic infectious diseases in Brazil, like Chagas' disease, leishmaniasis, schistosomiasis, yellow fever, malaria, and diarrhea. Other projects investigate proteins associated with cancer like septins, tubulin, Nek kinases and nuclear receptors; genetic diseases (Shwachman-Bondian-Diamond syndrome); anti-inflammatory drugs; plant-pathogen interactions; matrix metalloproteinases; disintegrins; myotoxins; and neurotoxins from Brazilian snake venoms; biological models of inflammation; and cellular signaling. The CBME research organization adopts a matrix arrangement, in which the heads of projects utilize all the available facilities, competences and skills, according to the projects' needs, thus optimizing the chances to achieve the established goals. These extensive external collaborations enable CBME to cover all the demanded methodologies and specialized techniques on developing projects.

By virtue of the strategic nature of CBME in pursuing partnerships with industry and research institutions, we are permanently open to set new challenges.

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES



The antigenic protein SM14 is a vaccine candidate for the treatment of schistosomiasis. A model for its three-dimensional structure, built by CBME researchers in collaborations with Fiocruz (RJ), has aided in better understanding its immunological properties, and the development of novel immunogenic peptides

During its existence CBME has contributed significantly to the current body of knowledge in structural biology of many different systems. These include studies on proteins from human parasites (such as *T. brucei, T. cruzi, P. falciparum, S. mansoni, L. major* among others) many of which are related to essential metabolic processes within the parasite and therefore potential targets for chemotherapy. Equally important have been studies on proteins related to non-infectious human diseases, such as nuclear receptors, where the classical methods of structural biology have been complemented by medicinal chemistry approaches towards the design of novel ligands with potential therapeutic benefit. Other projects have an alternative emphasis, for example on the design of peptides for vaccination trials or for diagnostic purposes or for better understanding of the molecular mechanisms behind the disease process itself. Overall, the research team of the CBME has solved tens of different protein structures and their complexes over the last seven years of existence.

Not all effort is devoted to research in human health. The discovery of a large number of cysteine protease inhibitors, coded by sugar cane has led to the development of transgenic plants resistant to common plagues that severely damage crops. Such experiments are currently ongoing involving researchers from the CBME together with studies aimed at better understanding the molecular mechanisms involved in plant/pathogen relationships.

Such efforts in the research field have limited impact without corresponding attempts to make them relevant to the academic community and to society in general. The CBME has become renowned both nationally and internationally for its outreach department, which involves the development of novel teaching aids, games, videos as well as for running teacher-training courses and for motivating high school children towards a career in the biomolecular sciences. Furthermore, the Center has collaborated with many industrial partners over the years including well-known national pharmaceutical companies such as Eurofarma, Cristalia and EMS, and its members are always aware of potential patenting possibilities. Indeed, several patents have been filed both nationally and internationally over the last few years. Licensing of some of those to private partners is under advanced negotiations.

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CENTER FOR SLEEP STUDIES

RESEARCH, INNOVATION
AND DISSEMINATION CENTERS (RIDC)

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Association and Fund to Promotion of Psychopharmacology Research (AFIP)

Sleep laboratory: polysomnography recording

The Center for Sleep Studies is based at Federal University of São Paulo (Unifesp).

While the primary function of sleep remains unknown, the fact that prolonged sleep deprivation (SD) leads to death in humans and experimental animals indicates that sleep is essential for survival (*Perspect. Biol. Med*., **41(3)**:359-90, 1998). The biological significance of sleep is further signaled by the fact that it occurs in most species despite being apparently maladaptative with respect to other biological properties such as feeding, avoiding predators, and reproducing. Most organisms literally "fall asleep" as a normal behavior, and will experience an increasingly strong urge to do so if deprived of sleep. That the consequences of this overpowering urge to sleep may be disastrous in a number of situations is exemplified in accidents involving motor vehicles or heavy machinery.

The causes, mechanisms and consequences of SD and the physiological basis of the resulting need for sleep constitute the central focus of the research work proposed by our RIDC Center. Our goals are to expand scientific understanding of sleep functions by addressing the broad spectrum of consequences of sleep loss, and to develop and validate new diagnostic and therapeutic approaches to sleep-related conditions.

MAIN RESEARCH TOPICS

Effects of sleep deprivation on dopaminergic neurotransmission

Sleep and cognition

Circadian rhythms

Sleep, genital reflexes and hormones

Autoimmune diseases and sleep disorders

Sleep fragmentation and chronic pain

Breathing disorders related to sleep, with an emphasis on obstructive sleep apnea syndrome

Cardiovascular and metabolic alterations in sleep disorders

Relationship between physical activity and sleep

Sleep, somnolence, fatigue and accidents

Movement disorders during sleep

Cytotoxic effects of sleep deprivation

Sleep disorders resulting from malformations

Molecular and genetic mechanisms in sleep

Epidemiological genetics and phenotypes in sleep

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

The apnea-hypopnoea index is not enough to diagnose obstructive sleep apnea
There is a great individual variability in the stability of the apnea-hypopnoea index (AHI) from one night to another. Thus, for an adequate obstructive sleep apnea diagnosis, AHI should be used along with other clinical and polysomnographic parameters.

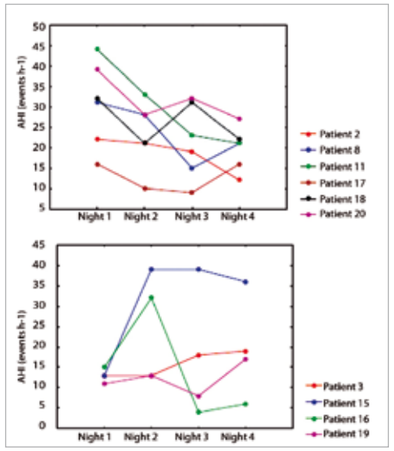

Figure 1: *Apnea-hypopnoea index (AHI) in the outpatients (50%) who had variable measures, and therefore would receive different obstructive sleep apnea diagnosis, during four consecutive nights (J.* Sleep Res. ***10****:245-51, 2001)*

Development of an animal model of Periodic Leg Movement (PLM)
Considering our observation that paraplegic individuals present frequent periodic leg movement (PLM), we proposed an animal model of PLM based on the higher incidence of limb movements during non-REM sleep in spinal cord injured (SCI) rats. Our model demonstrated that these movements may be generated in the spinal medulla without involvement of cortical structures (*Brain Res.* **1017**:32-8, 2004).

Mechanisms of paradoxical sleep deprivation-induced amnesia
We have demonstrated the involvement of oxidative stress in the amnesic effect of paradoxical sleep deprivation (PSD) in mice (*Neuropharmacology*, **46**:895-903, 2004), the anti-amnestic effect of antioxidant agents (*Neuropharmacology*, **46**:895-903, 2004) and the pro-amnesic effect of pro-oxidants (*Prog. Neuropsychopharmacol. Biol. Psychiatry*. **31**:65-70, 2007) in mice submitted to PSD. In addition, we have demonstrated that the amnesic effect of PSD in mice is also related to a concomitant anxiogenic effect of PSD (*Neurobiol. Learn. Mem*. **82**:90-8, 2004), is not related to modifications in GABAergic transmission, but is mediated by noradrenergic transmission (*Psychopharmacology*. **176**:115-22, 2004).

Mechanisms of sleep deprivation-induced facilitation of genital reflexes
The facilitatory effect of paradoxical sleep deprivation (PSD) on spontanelously genital reflexes in rats is associated with increased concentrations of progesterone and is dramatically potentiated by cocaine administration (*J. Neuroendocrinol*. **16**:154-9, 2004).

Anestrus in paradoxical sleep deprived female
Sleep deprivation presents distinct, long-lasting effects on estrous cycle (leading to a prolonged period of anestrus), and may modulate the ovarian hormone release through alterations in hormonal-neurochemical mechanisms (*Horm. Behav*. **49**:433-40, 2006).

The hyperfagia/weight loss paradox during sleep deprivation
The hyperfagia/weight loss paradox in sleep deprived rats results from difficulties in obtaining food to reach energetic needs especially during the first day of sleep deprivation, after which the animals adapt to the procedure (*Sleep*, **29**:1233-8, 2006).

A double-blind, placebo-controlled, crossover study of sildenafil in obstructive sleep apnea (OSA)
Sildenafil taken close to bedtime significantly worsens respiratory and oxygen saturation (SaO_2) variables during sleep in men, when compared to placebo.

Acupuncture is an effective treatment for moderate obstructive sleep apnea syndrome
Ten weekly sessions of acupuncture significantly improved the respiratory events of patients presenting with moderate OSAS in comparison to treatment with the sham procedure (needle insertion in non-acupoints) and to non-treated controls. Acupuncture also improved quality of life and decreased subjective sleepiness (*Sleep Med*. **8**:43-50, 2007).

Worsening of sleep complaints: an epidemiological study
We compared the prevalence of complaints of insomnia, excessive diurnal sleepiness, parasomnias, and sleep habits of the adult population in the city of São Paulo, Brazil, estimated in surveys carried out in 1987 and 1995 (1000 adult each; *Braz. J. Med. Biol. Res*. **40**:1505-15, 2007). Difficulty in maintaining sleep, initiating sleep and early morning awakening

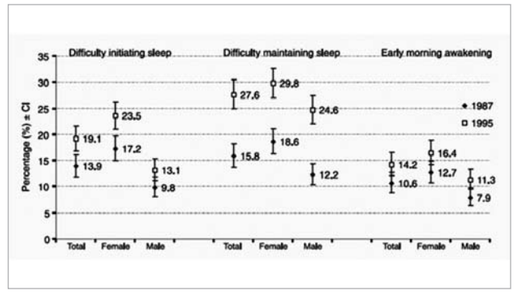

Figure 3: Insomnia complaints by gender in surveys carried out in 1987 and 1995 in the city of São Paulo (representative samples of 1000 adults per survey). Sleep complaints increased in 1995. Data are reported as percentages ± confidence interval (CI) at 95% (Z-test)

significantly increased throughout time, mainly in women. Besides sleeping slightly less, interviewees went to bed and woke up later in 1995. These major changes over a little less than a decade's time should be considered as an important public health issue.

Donepezil decreases apnea/hypopnoea in Alzheimer's patients
We found that donepezil improves apnea/hypopnoea index and oxygen saturation during sleep in Alzheimer disease patients with obstructive sleep apnea, despite REM sleep increase. This was the first controlled trial to show this magnitude of improvement of respiratory parameters, during sleep, with one drug (*Chest*. **133**:677–683, 2008).

Gene expression changes after sleep deprivation (unpublished data)
Paradoxical sleep deprivation promotes a number of behavioral, physiological, as well as cellular functioning alterations, including gene expression in specific brain regions. A total of 55 genes were found to be differently expressed in rats after 96 hours of sleep deprivation. Interestingly, after 24 hours of sleep recovery (rebound), approximately 50% (n=25) of the PSD genes had their expression returned to control levels. Also, 200 transcripts, such as Adenosine A2B receptor, Insulin receptor substrate2, Corticotropin releasing hormone, and Homer1, were specifically altered when compared to sleep deprivation condition. These data raise a number of potential candidates for the molecular basis of homeostatic mechanism of sleep regulation.

MAIN PUBLICATIONS

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Ruggero D, Grisendi S, Piazza F, et al. 2003. Dyskeratosis congenita and cancer in mice deficient in ribosomal RNA modification. *Science*. **299**:259-262.

Yoon A, Peng G, Brandenburger Y, et al. 2006. Impaired control of IRES-mediated translation in X-linked dyskeratosis congenita. *Science*. **312**:902-906.

Voltarelli JC, Couri CE, Stracieri AB, et al. 2007. Autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. *Jama*. **297**:1568-1576.

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CENTER FOR CELL-BASED THERAPY

RESEARCH, INNOVATION AND DISSEMINATION CENTERS (RIDC)

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All researchers belong to the Ribeirão Preto School of Medicine, University of S. Paulo, except for R. Chammas, who is from the Medicine School/USP – SP and M. Barbieri, who retired from Ribeirão Preto School of Philosophy, Sciences and Literature/USP.

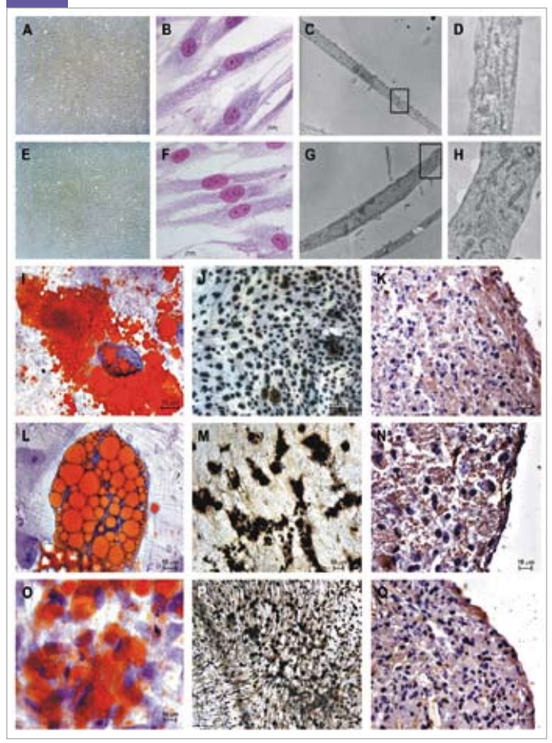


Figure 1. Morphology of human bone marrow-derived mesenchymal stromal cells (MSC) (A-D) and human foreskin-derived fibroblast (E-H). Phase contrast microscopy (A, E; magnification x40); Leishman staining (B, F); ultrastrucutre showing the nucleus with a spindle-shape fibroblastic morphology (C, G); higher magnification of the perinuclear region, showing the rough endoplasmic reticulum (D, H). Differentiation capacity of bone marrow MSC (I-K), pericytes (L-N) and skin fibroblast (O-Q) into adipocyte (I, L, O) (stained with Sudan II and scarlet), osteocytes (J, M, P) (von Kossa staining), and condrocytes (K, N, Q) (immunohistochemical demonstration of type II collagen)

The Center for Cell-Based Therapy was conceived based on the broad concept of using cells for therapy, under different conditions and from several sources. Our research has focused on areas considered essential for the understanding of the cellular mechanisms involved in regulation of stem cells activity, establishment of methods for stem cells isolation and *ex vivo* manipulation, and on the development of treatment strategies based on the use of stem cells to treat autoimmune diseases.

MAIN RESEARCH TOPICS

The project Stem cells for the treatment of neoplastic and inflammatory diseases aims to understand various aspects of Mesenchymal Stem Cells (MSC) biology that may be relevant for their use in medicine, including basic aspects and therapeutic applications in pre-clinical and clinical studies, and the pathways that control hematopoietic stem cell differentiation.

We are also focusing on separating the most primitive MSC from the remaining differentiated cellular population, by using specific markers such as STRO1, CD146, CD106, CD73 and CD63, by flow sorting or by purification with magnetic beads labeled with the specific antibodies. Animal models suitable for MSC transplant, to perform *in vivo* studies are under development. We are currently studying the behavior of MSC *in vivo*, by using animal models of various diseases, including post bone marrow transplantation graft versus host disease (GVHD), acute liver injury induced by carbon tetrachloride, chronic cardiac insufficiency induced by adriamycin, and in acute radiation disease.

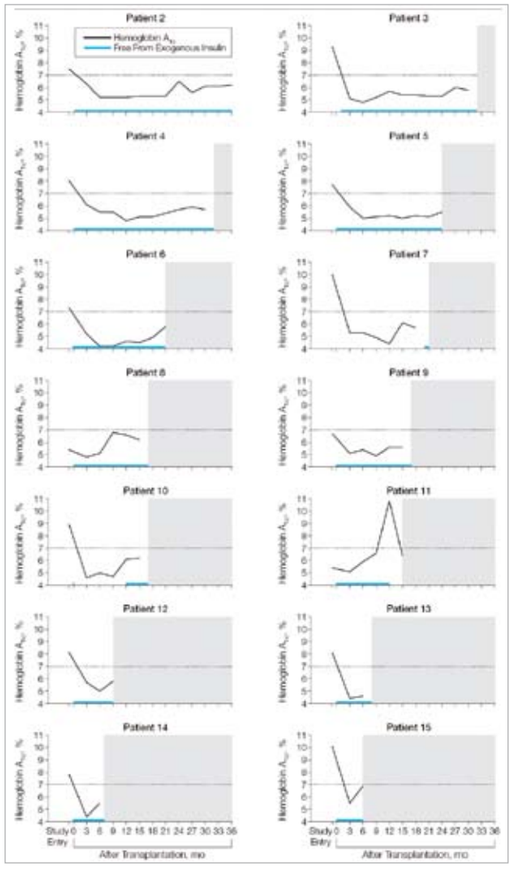
One of our projects uses an experimental model in rats to evaluate the potential impact of human mesenchymal bone marrow stem cells (hMSC) transplantation in chronic heart failure.

The Hematopoietic progenitors study compares the functional properties and gene expression profiles of pure populations of bone marrow, peripheral blood, and umbilical cord blood CD133+, CD34+, CD34+KDR+, CD133+KDR+, CD34-CD133+, CD34+CD133+ cells to study their capacity to form hematopoietic colonies in long term-culture (LTC-IC), and endothelial colonies in matrigel plaques.

We are starting to study biological characteristics of donated Embryonic Stem Cells (ES) lines to: 1. evaluate the ES gene expression profiles by quantitative and qualitative methods; 2. compare the ES gene expression profile with the gene expression profile of adult stem cells including hematopoietic stem cells (CD34+, CD133+) and mesenchymal stem cells from bone marrow and umbilical cord blood; and 3. understand the genetic and molecular mechanisms involved in the initial phase of ES differentiation.

We are currently in the phase I/II trial of hematopoietic stem cell transplantation (HSCT) for early-onset type I diabetes mellitus.

In searching for new therapeutic targets in cancer, two groups of diseases were selected for further analysis: lymphoproliferative disorders and acute myelogenous leukemia.



Hemoglobin A_{1c} Levels and Periods Free From Exogenous Insulin Requirement

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

We have characterized the transcriptome of mesenchymal stem cells (MSCs) and hematopoetic stem cells (HSCs), and determined whether their source affected gene expression profile. In addition, we have succeeded in isolating MSCs from several tissues. Recently, we have compared three cell types: MSCs, fibroblasts and pericytes. Our results showed that pericytes and fibroblasts could be induced to differentiate and presented morphologic and immunophenotypic features similar to MSCs. In agreement, the gene expression profile of these cells were similar. This was the first study to prove that human MSC and pericytes are similar cells located in the wall of the vasculature, where they are involved in tissue repair.

Animal models have been instrumental to our studies on leukemogenesis and HSC function. Regarding leukemogenesis, we have selected acute promyelocytic leukemia (APL) as a model. We have characterized three transgenic mouse models (TM) expressing distinct fusion genes associated with APL. All of them developed a form of leukemia after a long latency, but their leukemic cells displayed distinct morphologic features and response to treatment. Our results indicate that these fusion proteins are necessary but not sufficient to cause leukemia, and that they are relevant for leukemia phenotype. On a different line, our studies involving Dkc1m mice (mutants that express low levels of a pseudouridine synthase) were the first to prove that the impairment of ribosome biogenesis may affect stem cells.

CTC performed the first clinical trial evaluating the safety and metabolic effects of high-dose immunosuppression followed by autologous nonmyeloablative hematopoietic stem cell transplantation (AHST) in newly diagnosed type 1 diabetes mellitus (DM). This is a phase 1/2 prospective study involving 15 patients. During a 7-36-month follow-up, 14 patients became insulin-free and the C-peptide response curve was significantly greater than the pretreatment values. There was no mortality. We concluded that AHST has acceptable toxicity and has benefited patients with newly diagnosed type 1 DM.

Regarding technological innovation, our main project is focused on the development and production of recombinant factor VIII to be used in the treatment of type A hemophiliacs. We have generated 41 transgenic cell lines expressing more than 100 IU/mL of FVIII, of which two were chosen for industrial process escalation.

Finally, the CTC activities of diffusion are focused on the improvement of science teaching in public schools. These activities have the participation of teachers, and students can attend at two facilities created by CTC: House of Sciences and in the Museum and Laboratory for Science Teaching (MuLEC). Finally, the book "Células-tronco: a Nova Fronteira da Medicina" published by CTC investigators won the 2007 Jaboti Award.

MAIN PUBLICATIONS

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Center for the Study of Violence

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CENTER FOR THE STUDY OF VIOLENCE

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RESEARCH, INNOVATION AND DISSEMINATION CENTERS (RIDC)

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The Center for the Study of Violence (NEV/USP) was created during the Brazilian democratic transition, in 1987, and it is one of the Support Centers for Research of the Unversity of São Paulo.

The aim of NEV´s research program is to analyze the obstacles to the implementation of democratic rule of law, identifying what has changed, as well as what has not, both in society and in the justice system, in the realm of ideas, values and norms towards human rights, law, justice and the institutions that should enforce them and unravel the connections between permanence and change in an authoritarian culture through the process of democratization in Brazil. The key question is: what kind of democracy prospers, in an environment of continued violation of human rights, and how change can take place so that a 'good' democracy can develop. Continued human rights violations, though no longer a state policy, result from the endemic omission of the State to punish state agents involved in such violations, and to effectively implement social and economic rights. Our challenges are multiple but a key one resides in that gross human rights violations, combined with the violation of social, economic and cultural rights converge to feed the powerlessness of citizens in relation to the state, and this in turn affects their trust in the efficacy of democracy moreover in beliefs about human rights as universal rights. This continued presence of gross human rights violations, and of profound inequalities in the access to rights, prevents cooperation and solidarity among the needy sectors of the society, and generates powerful obstacles for the re-socialization of authoritarian beliefs and values into democratic ones.

Nowadays the team is formed by researchers of the areas of social sciences, law, history, psychology, public health, statistics and literature.

MAIN RESEARCH TOPICS

Democracy, rule of law and human rights
Monitoring Human Rights Violations
The analysis of the democratic rule of law entails the examination of the legal system; the state and the government; courts, law enforcement and prisons; rules that govern state institutions; rights and guarantees for social participation and access to civil and human rights. This is what the two main research lines of the NEV aim to do: assess the functioning of the justice system (the rule of law) and democracy while monitoring access to human rights and societal reactions. The major actor here is the state, but not the only one. Focus is also placed on society for if the state has legitimacy this emanates from the people.

The two research lines, together, measure quality of democracy at different levels:
1- at a broader level, by monitoring the access to rights by the population. We try to identify the degree of protection enjoyed by the population to exercise participation and competition, and moreover to demand responses from authorities, i.e. exercise vertical accountability. These demand that people do not feel fear, enjoy civil and political freedom, have access to information and are not coerced by living in extreme conditions of economic need;
2 - at the institutional level, by investigating how successful the criminal justice system is to secure the right to life and thus to prevent fear, in particular assessing how far the criminal justice system is capable of guaranteeing the equality of citizens before the law, and what the system reveals about the application of the rule of law in the public security area;
3 - at societal level by following the impact on individuals of the continued exposure to violence on their trust in democracy and its institutions and in their attitudes and values toward human rights.

The following post-doctoral opportunities are envisaged for the next three year-period:

Socioeconomic Development and Human Rights
This project will explore the relations between socioeconomic development and human rights, with focus on questions about employment, unemployment and labor market. The project will contribute to the development of worthy labor concept, which is present in some specialized literature analysies.

Economic Cost of Human Rights Violations
This theme has been imposed on academic debate and it needs a sophisticated methodological treatment. Applicants should have a PhD degree in Economy Science and be expert on the themes, as proved by publications in international journals.

Social Communication
There is yet strong resistance to recognize the respect for human rights as a basis for a peaceful society, which in some social groups are identified as bandit rights. To overcome this resistance through a deliberate programme of information dissemination for strengthening the political, socialeconomic and civil rights, we need previous scientific knowledge about how to set up ties between transmitter and receptor of messages in specific social contexts that are usually ways of violence, crime and gross human rights violations.

The extra-judicial mechanisms of reparation for the victims of violations of human rights: the Latin-American experiences/ Truth Commissions in Latin-American States: a Comparative Study
The project shall comprehend a comparative study concerning the most representative Truth Commissions in Latin-American States such as: Argentina, Chile, Peru and Uruguay. The analysis shall comprise: (i) historical aspects; (ii) legitimacy and popular representation, and (iii) application of the mechanisms of truth, justice, reconciliation and reparations.

The extra-judicial mechanisms of reparation for the victims of violations of human rights: the Latin-American experiences/ Truth Commission in Peru and South Africa: a Comparative Study
The main purpose of this research is to evaluate the models of Truth Commissions that were adopted in Peru and South Africa, since both have been defined as successful experiences regarding the reconciliation process and the right to memory. After a comparative study, the elaboration of a critical analysis concerning both mechanisms is expected, in order to contribute to the democracy and construction of the Rule of Law in the Brazilian context.

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Monitoring human rights violations
This research has allowed us to follow how access to human rights change through time across the national territory. Data from the databases have resulted in analysis of the relation between civil rights/socio-economic rights and homicide/gross human rights violations. The databases have been used to inform the UN Special Reporter, and have also been used to monitor the implementation of recommendations to reduce torture in Brazil.

Democracy, rule of law and human rights
In Brazil public policies in the area of security are historically authoritarian. There is intense bureaucratic resistance in governmental agencies to external analysis of their actions. There is also an enduring disjunction between the normative-institutional scenario and the results of governmental actions and this cannot be solely attributed to the elites. The policies for the area of criminal law were not able to establish a new paradigm for the organization or functioning of the police and prison apparatuses, in accordance with democratic principles and with constitutional norms. This, combined with the growth of the prison population, has created fertile ground for prison rebellions and riots.

Exposure to violence and socially shared representations and attitudes to justice, rights and punishment and human rights.
This research combines quantitative (survey) and qualitative sources (focus groups discussions) and reveals that exposure to violence increases fear, reduce the rejection of gross human rights violations and increase the calls for more severe forms of punishment. Feelings of fear and insecurity, as shown by the survey data analysis, is supported by the raise in violent criminal offenses observed in São Paulo since the beginning of the 1980´s, including gross human rights violations. This growth was not followed by a proportional increase in the number of inquests and penal processes. The data collected by the project suggests that the rates of impunity for these crimes are higher than in other countries such as the United States.

The poor results of the law enforcement agencies to prevent and to punish violence, coupled with the obstacles that citizens find in having access to justice, could well encourage private forms of "justice" (lynching and executions). They also foster collective fear and insecurity, resulting in a vicious cycle in which poor performance further reduces public trust in the justice system as well as in the agents of the system. How can political trust of citizens in democratic institutions be improved, in particular in the institutions that detain the monopoly of use of physical force to contain violence and crime? Many believe that the more severe the punishment, the greater is citizens' trust in law enforcement agencies, thus ensuring the respect for and the internal cohesion of the public order.

Integrated Theory on Human Rights
This project is to analyze the relations between the international legal system of human rights and Brazilian laws, as well as the role of agents and institutions in the implementation of a human rights regime. A key innovation is the experience of the Network of Youth Human Rights Observatories. These observatories were established in underprivileged communities in Brazil. They enabled youth to report the Human Rights situation in their communities, to raise authorities' and society's awareness about the problems, evaluate the local impact of public policies and identify possible local measures to solve the problems and finally to build up an enabling environment for more effective and efficacious forms of interventions by youth.