National Science and Technology Institute for Translational Medicine (INCT-TM): advancing the field of translational medicine and mental health

Instituto Nacional de Ciência e Tecnologia em Medicina Translacional (INCT-TM): abordagens metodológicas

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Abstract

Objective: Translational medicine has been described as the integrated application of innovative pharmacology tools, biomarkers, clinical methods, clinical technologies and study designs to improve the understanding of medical disorders. In medicine, translational research offers an opportunity for applying the findings obtained from basic research to every-day clinical applications. The National Science and Technology Institute for Translational Medicine is comprised of six member institutions (Universidade Federal do Rio Grande do Sul, Universidade de São Paulo-Ribeirão Preto, Universidade Federal do Rio de Janeiro, Pontifícia Universidade Católica do Rio Grande do Sul, Universidade Estadual de Santa Catarina and a core facility that serves all centers). The objectives of the project are divided into four areas: Institutional, Research, Human Resources and Technology for the Community and Productive Sector. **Method:** In this manuscript, we describe some of the approaches used to attain the main objectives of the National Science and Technology Institute for Translational Medicine, which include the development of 1) animal models for bipolar disorder; 2) strategies to investigate neurobehavioral function and cognitive dysfunction associated with brain disorders; 3) experimental models of brain function and behavior, neuropsychiatric disorders, cell proliferation, and cancer; 4) Simulated Public Speaking and 5) Virtual reality simulation for inducing panic disorder and agoraphobia. **Conclusion:** The main focus of the National Science and Technology Institute for Translational Medicine is the development of more useful methods that allow for a better application of basic research-based knowledge to the medical field.

Descriptors: Mental health; Biomedical research; Innovation; Biomarkers, pharmacological; Technological development

Resumo

Objetivo: *Medicina translacional pode ser descrita como a aplicação integrada de ferramentas farmacológicas inovadoras, biomarcadores, métodos e tecnologias clínicas e delineamentos de pesquisa para aumentar o conhecimento a respeito das doenças. A pesquisa translacional oferece uma oportunidade para aplicar os achados de pesquisa básica na clínica cotidiana. O Instituto Nacional de Ciência e Tecnologia – Medicina Translacional foi criado com seis centros (Universidade Federal do Rio Grande do Sul, Universidade de São Paulo-Ribeirão Preto, Universidade Federal do Rio de Janeiro, Pontifícia Universidade Católica do Rio Grande do Sul, Universidade Estadual de Santa Catarina e uma core facility que serve a todos os centros). Os objetivos deste projeto são divididos em quatro dimensões: institucional, pesquisa, formação de recursos humanos e transferência de tecnologia para a comunidade e setor produtivo.* ***Método:*** *Neste artigo, são apresentadas algumas das estratégias utilizadas para atingir os objetivos do Instituto Nacional de Ciência e Tecnologia – Medicina Translacional: 1) Desenvolvimento de modelos animais para o transtorno bipolar; 2) Estratégias de investigação neurocomportamental e disfunções cognitivas dos transtornos cerebrais; 3) Modelos experimentais de funcionamento cerebral e comportamento, proliferação celular e câncer; 4) Teste de Simulação de Falar em Público e 5) Realidade Virtual para indução de Pânico e Agorafobia.* ***Conclusão:*** *O Instituto Nacional de Ciência e Tecnologia – Medicina Translacional possui como foco principal o desenvolvimento de metodologias mais úteis para aumentar a aplicabilidade dos conhecimentos da pesquisa básica em medicina.*

Descritores: *Saúde mental; Pesquisa biomédica; Inovação; Biomarcadores farmacológicos; Desenvolvimento tecnológico*

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Introduction

In medicine, translational research offers an opportunity for applying the findings obtained from basic research to every-day clinical applications. Given its importance and fast growth, in 2003, this field earned the right to have a journal of its own. The Journal of Translational Medicine is an open access journal that publishes articles focusing on human experimentation-derived information to optimize communication between basic and clinical science.

According to Marincola,[1] the purpose of translational research is to test new therapeutic strategies to be developed in humans through experimentation. Translational research should be regarded as a two-way road i.e., Bench to Bedside and Bedside to Bench. However, Bedside to Bench efforts have regrettably been rather limited, mainly because scientific aspects have been poorly understood by full time clinicians, and also because basic scientists have difficulty in appreciating how hard it is to deal with human beings.

Translational medicine has been described as the integrated application of innovative pharmacology tools, biomarkers, clinical methods, clinical technologies and study designs to improve disease understanding, and confidence in human drug targets, and to increase confidence in drug candidates, understand the therapeutic index in humans, enhance cost-effective decision-making in exploratory development and increase rates of phase II success.[2]

Translational research can be defined as one of the most important activities in translational medicine because as it underpins predictions about possible drug activities across species, which is particularly important when compounds with unprecedented drug targets are administered to humans for the first time.[2] To be successful, translational researchers need to identify scientific, financial, ethical, regulatory, legislative and operational hurdles and provide creative solutions to facilitate this process.[2]

To achieve this goal, however, there are a number of obstacles that need to be overcome. Main obstacles include lack of funding, the high cost and slow-appearing results, inadequate samples, conflict of interest, regulatory burdens, right to privacy, fragmented infrastructure, shortage of qualified investigators, inadequate rewarding, shortage of experts willing to participate, incompatible databases and lack of congressional and public support.[2]

The Brazilian Ministry of Science and Technology and *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq) decided to fund the INCT-TM, which includes four areas of interest: I) Institutional development; II) Research; III) Human resources; and IV) Transfer of technology to the community and the productive sector.

INCT-TM's mission is to apply basic research findings to the clinical context, emphasizing the search for patents and new product development. In this context, the critical transduction point is to identify the basic research findings that are relevant enough to make such achievement either desirable or rewarding. To identify new molecular targets as candidates for translational action, we will evaluate the effects of pharmacological intervention while using experimental models. With this, a target protein profile will be obtained which will, in turn, be studied according to its possible mechanism of action after the use of pharmacological inhibitors or the super-expression or under-expression of the molecule has taken place. We will then validate this target protein's action based on the pharmacological agent under study. Each validation of a hypothetical target creates an opportunity for translational research, thus moving from a basic research finding to a clinical setting application. This process can be defined as a qualified search for therapeutic targets guided by the identification of target proteins.

In this manuscript, we describe some of the approaches that we are going to use to reach the main objectives of INCT (Table 1).

Method

To achieve these objectives, the procedures described in Table 2 will be used.

Examples of the methodologies to be used are outlined below.

I - Development of animal models for bipolar disorder

Bipolar disorder (BD) is a prevalent, chronic and life-threatening illness characterized by altering episodes of mania and depression.[3] Although little is known about the precise neurobiological underpinnings of BD, this knowledge is critical for the development of specific-targeted therapies that are more effective, work rapidly, and are better tolerated than existing therapies.[4]

The development of animal models has been an important tool in investigating new intracellular systems that may be involved in BD[5,6] and new pharmacological approaches.[4,7,8] Ellenbroek and Cools have proposed that the validity of animal models in psychiatric disorders should demonstrate the following three major criteria: face, construct and predictive validity.[9] Face validity represents how similar the model can mimic the symptoms of a specific illness, whereas construct validity relates to the model's ability to reproduce certain pathophysiological aspects of the illness. Finally, the predictive validity evaluates if the therapeutic agents used in the treatment of an illness can reverse the symptoms induced in the animal model.

According to Belmaker, since the unique hallmark of the illness is mania, an appropriate animal model of BD should show certain features typical of a manic episode such as euphoria, irritability, aggressiveness, hyperactivity, insomnia or increased sexual drive.[10] Repeated injections of d-amphetamine (d-AMPH) induced hyperactivity in animals[8] by elevating extracellular dopamine, and it has been suggested as a relevant animal model of mania.[11-17]

There is an emerging body of data suggesting that BD is associated with decreased neurotrophins (BDNF, NGF and NT-3),[18,19] an increased oxidative[20,21] and DNA damage.[22]

The group that is leading the INCT-TM has proposed a new animal model of mania, focusing on both acute and prophylactic

Table 1 - Goals and areas defining translational research in INCT-TM

1. Development of new therapeutic approaches for the treatment of schizophrenia and bipolar depression (e.g. the use of N-acetyl-cisteine). In the case of conducting a randomized clinical trial for schizophrenia, it will include before and after blood serum analysis.
2. Investigating the clinical use of tianeptin as a treatment for bipolar depression via a randomized clinical trial in humans, applying epigenomics analysis in blood serum before and after treatment.
3. Development of the therapeutic use of cannabidiol in social anxiety disorders via a randomized clinical trial in humans, applying epigenomics analysis in blood serum before and after treatment.
4. Prospective use of ayahuaska derivatives in an in vivo model for anxiety via animal blood serum and cerebral tissue epigenomics analysis.
5. Prospective use of therapeutic agonists and antagonists of neuropeptide receptors, focusing on the gastrin releasing peptide receptor (GRPR) as antitumor agents for colorrectal cancer by incubating tissue cultures with different agents that act on the GRPR.
6. Prospective clinical use of brain derived neurotrophic factor (BDNF) as a marker for activity, staging, and therapeutic response in the major psychiatric disorders (schizophrenia and bipolar disorder). In this case, there will be no pharmacological intervention, since each stage in the disease will function as interventions.
7. Propective clinical use of oxidative stress markers as markers for activity, staging, and therapeutic response in the major psychiatric disorders (schizophrenia and bipolar disorder). In this case, there will be no pharmacological intervention, since each stage in the disease will function as interventions.
8. Prospective therapeutic use of agents, such as histone deacetylase inhibitors, that affects epigenetic mechanisms by promoting chromatin unraveling as potential anti-tumor agents for colorrectal cancer.
9. Prospective therapeutic use of iron chelating agents as potential medication for cognitive enhancement via animal models that evaluate memory formation before and after the intervention.
10. Prospective therapeutic use of agents that alter signaling transduction, such as phosphodiesterase inhibitor type 4 and dopaminergic agonists as potential cognitive enhancers, via memory formation animal models as above.

treatments. The reversal model is designed to reproduce the management of an acute manic episode. Animals receive a daily intraperitoneal injection of either d-AMPH or saline for 14 days. Between the 8th and the 14th day, animals that received saline or d-AMPH are divided into 6 experimental groups of 6–8 animals per group: saline + saline (SAL), saline + lithium (Li), saline + valproate (VPA), AMPH + saline, AMPH + lithium (d-AMPH + Li) and d-AMPH + valproate (d-AMPH+VPA). Animals in the Li group receive intraperitoneal injections of lithium twice a day; those in the VPA group receive valproate twice a day. The locomotor activity is measured 2 hours after the last injection of d-AMPH or saline to assess whether hiperlocomotion was induced in the animals receiving d-AMPH+saline.

The prevention model is designed to mimic the maintenance phase of the treatment of BD. In this protocol, animals receive intraperitoneal injections of either lithium twice a day, valproate twice a day or saline for 14 days. Between the 8th and the 14th day, the animals that received lithium, valproate or saline are divided into 6 experimental groups of 6–8 animals per group: SAL, Li, VPA, d-AMPH, Li + d-AMPH and VPA + d-AMPH. The d-AMPH group receives 1 daily intraperitoneal injection of either d-AMPH or saline. The locomotor activity is measured 2 hours after the last injection.

The motor activity is assessed in the open-field task, which is performed in a 40 × 60 cm open field surrounded by 50 cm high walls made of brown plywood with a frontal glass wall. The floor of the open field is divided into 12 equal rectangles with black lines. The animals are placed on the left rear quadrant to freely explore the arena for 5 minutes. The number of crossings of the black lines is considered to be a measure of horizontal locomotor activity and the number of retreats is considered to be a measure of vertical locomotor activity.

II - Strategies to investigate neurobehavioral function and cognitive dysfunction associated with brain disorders

Neurobiological, neuropharmacological and biochemical techniques developed based on animals models of neurobehavioral function and cognitive dysfunction associated with brain disorders are used to identify potential therapeutic interventions.

Methods:

1) Animals

Five rats or mice are housed in a cage in a temperature-controlled colony room with food and water available *ad libitum* and are then maintained on a 12-h light/dark cycle. Behavioral procedures are conducted during the light phase of the cycle. All procedures are conducted in accordance with the NIH Guide for Care and Use of Laboratory Animals (NIH publication No. 80-23 revised 1996). Experimental protocols are approved by the institutional research ethics and animal care committee. All efforts are made to minimize the number of animals used and their suffering.

Table 2 - Main procedures of translational research in INCT-TM

1. To evaluate the pharmacological effect, the INCT-TM will utilize in vitro (cell culture) and *in vivo* (animal) models.
2. To search for biological markers it will be used epigenomics techniques.
3. To evaluate the biological effects of certain drugs in our animal models, the INCT-TM will:
a. Evaluate receptor activity in tissues via western blotting, *in vitro* kinase assays, ELISA and tissue microdissection.
b. Evaluate cellular viability for tissue culture models via MTT assays, clonogenic assays and apoptosis markers.
c. Evaluate cellular proliferation for tissue culture models via cell counting and flow citometry.
d. Identification of second messengers and transcription factors via immunoprecipitaion, EMSA and reporter assays.
e. Migration and invasion assays via growth in soft agar and transwell plate growth.
4. During the target validation phase we will use pharmacologic inhibitors for the protein targets identified in the different projects, besides using techniques such as gene silencing and super-expression.
5. During the clinical trials phase the INCT-TM will develop phase I, III, and IV trials to evaluate the therapeutic potential of each of the molecules previously identified.
6. Development of new human and experimental pharmacological and virtual models for neuropsychiatric disorders.

2) Experimental models of cognitive dysfunction and brain disorders: aging and brain iron overload

Neonatal iron administration to mice or rats produces brain iron accumulation that results in several features of dementia and neurodegenerative disorders. Twelve day-old rat pups receive a single oral daily dose of vehicle or 10.0mg/kg of body weight of Fe^{2+} via a metallic gastric tube for 3 days (postnatal days 12-14).[23-26] Aged rats and memory dysfunction induced by drug injections in rats are also used to investigate the biological basis of memory dysfunction and the effects of candidate therapeutic drugs.[25,27-29]

3) Pharmacological treatments

Animals are given systemic injections of appropriate agents that influence brain function by modulating neural transmission and display potential therapeutic or neurotoxic actions.[23-25,29]

4) Neurobehavioral procedures

Established animal models of learning and memory, particularly the novel object recognition memory task and other behavioral tests of brain function are used to investigate the neurobiological basis of memory dysfunction, brain disorders, and the possible therapeutic actions of candidate compounds.[23-25,29]

5) Neurochemical and molecular assays

Biochemical methods, including the measurement of acetylcholinesterase (AChE) activity, oxidative stress parameters, and the analysis of mRNA expression by reverse transcriptase polymerase chain reaction (RT-PCR) are used to examine alterations in the animals' brains related to iron accumulation, drug treatments or aging.[24,29]

III - Experimental models of brain function and behavior, neuropsychiatric disorders, cell proliferation, and cancer

Molecular and cell biology techniques and neuropharmacological assays are used to investigate molecular targets and candidate therapeutic compounds in experimental models of brain function and behavior, neuropsychiatric disorders, cell proliferation and cancer.

1. Molecular and cell biology

1) Cell culture and *in vitro* treatments

Human, rat, and mouse neural and cancer cell lines are grown and maintained as previously described.[30] Cultures are treated with agents that modulate membrane receptors, intracellular cell signaling pathways and epigenetic mechanisms.[30,31]

2) Cell proliferation and viability assays

Cell proliferation and viability are assessed by cell counting in a hemocytometer and the 3-(4,5 dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay.[30,31]

3) Reverse transcriptase polymerase chain reaction (RT-PCR)

The expression of mRNA for molecular targets in cultured cells is analyzed by RT-PCR using appropriate primers as previously described.[30,31]

4) Immunohistochemistry

The expression of proteins for molecular targets in cultured cells and biopsy samples from patients is examined by immunohistochemistry using appropriate antibodies as previously described.[30,31]

2. Molecular and behavioral neuropharmacology

1) Animals

Please, see item II.

2) Surgery

Animals are given intracerebral infusions through cannulae implanted under anesthesia and aimed at selective brain areas as described in previous studies.[32-34] Coordinates are obtained from the atlas of Paxinos and Watson.[35] Animals are allowed to recover at least 7 days after surgery.

3) Pharmacological procedures

Animals are given systemic injections or intracerebral microinfusions of appropriate agents that influence cell signaling mechanisms or induce features of brain disorders as previously described.[32-34]

4) Neurobehavioral procedures

Established animal models similar to those described in item

II are used to investigate the molecular mechanisms underlying synaptic plasticity, as well as the influence of candidate therapeutic and neurotoxic compounds on brain function in animals submitted to pharmacological or genetic interventions.[32-34]

5) Histology

After behavioral testing, animals given intracerebral treatments are put down and their brains are removed and stored in formalin before being sectioned and examined for cannulae placement.[32-34]

IV - Simulated Public Speaking Test

The Simulated Public Speaking Test (SPST) is an experimental model for the study of anxiety. The SPST was first proposed by McNair et al.[36] to investigate the effects of diazepam on anxiety.

1. Protocol

The whole experimental session takes place in a room at a controlled temperature and with sound attenuation to minimize environmental interference. The procedure consists of the following steps:

1) The activity starts with the establishment of rapport and a briefing on the aims of the test to be performed. The subject then reads and decides whether or not to sign the first of two informed consents.

2) The self-rating scales VAMS, ESS, and SSPS-E are completed, in this sequence, and physiological recordings are made: blood pressure (BP), heart rate (HR), pulse width (PW), and skin conductance level (SC). BP, HR, and PW are recorded using a digital monitor. SC is recorded by a computer at a constant voltage (0.6 V) controlled by a psychophysiological system (Contact Precision Instruments, United Kingdom). Two electrodes are fixated onto the middle portion of the right hand index and middle fingers using adhesive tape (Beckman, United Kingdom), and contact with the skin is ensured with the use of conductive gel (KY, Johnson & Johnson, Brazil). The number of spontaneous fluctuations in SC (SF) and the mean SC level are recorded. This phase is called Baseline Measure (BM).

3) In the experiment room, the subject is instructed to relax for 30 minutes in the horizontal position. The examiner offers the subject some reading material with neutral contents and then leaves the room. The three self-rating scales are again completed and physiological recordings are made in this phase, which is termed Pre-stress Measure (PreSM).

4) The second informed consent, describing the remaining of the experimental session is presented to the patient. The test can only be carried on provided the informed consent is signed.

5) The subject is asked to sit down in front of a TV set and a video camera, and to watch a previously recorded video with verbal instructions on the task to be performed. The subject is informed that he/she will have two minutes to prepare a four-minute speech about his/her city's public transportation system and that the speech will be recorded and analyzed by a psychologist.

6) The subject starts preparing the speech. After two minutes, a new assessment is made using the scales and physiological recordings, described as Anticipatory Anxiety Measure (AAM).

7) The examiner leaves the room and the subject is instructed to start his/her speech, which is captured by the camera and displayed on the TV screen so that the participant sees him/herself while performing the activity.

8) Two minutes after the beginning of the speech, the examiner interrupts it so that new measures can be taken. This phase is called Perfomance Anxiety Measure (PAM).

9) Following the completion of the scales, the subject resumes the speech for another two minutes, after which a new evaluation is made. This is considered to be the first Post-stress Anxiety Measure (F0).

10) The participant is asked to remain in the room, lying on the chair while trying to relax. New post-stress measures are recorded as Post-stress Anxiety 1 (F1).

11) Thirty minutes after F1, the participant is once more asked to complete the scales and physiological recordings are made. This set of recordings is called Post-stress Anxiety 2 (F2), after which the experimental session is over.

V. Virtual reality simulation for patients with panic disorder and agoraphobia

The term "virtual reality" is usually applied to real time interaction with three-dimensional (3D) computer-generated environments.[37] VR can be defined as a dynamic and reactive set-up with a computer-generated environment that is used for different purposes of human interaction.[38]

The objective is to verify if patients with panic disorder and agoraphobia have similar reactions to normal controls when exposed to an agoraphobia-related virtual environment. The targets are anxiety, somatic sensations, autonomic arousal, and modifications in cardiac rhythm and respiratory alterations.

1. Procedure

The following scales are used at the initial evaluation: Panic Disorder Severity Scale, Beck Anxiety Index, Beck Depression Index, Agoraphobic Cognitions Questionnaire and the Mobility Inventory. During the experiment, the scales and questionnaires used are the Subjective Units of Distress Scale (SUDS), the Panic Disorder Questionnaire and the Igroup Presence Questionnaire.

The equipment used to measure physiologic variables is the Biopac MP100 with AcqKnowledge software, a respiratory effort transducer, EKG electrodes and skin conductance electrodes. The simulation was displayed in a regular computer screen and headphones were used.

The procedure goes as described below:

1) Instructions to subjects.

2) Positioning of electrodes and respiratory effort transducer.

3) Anxiety rating – SUDS.

4) Exposure to a neutral stimulus (gray screen) for 30 sec. Applied in concurrence with the physiologic measurements.

5) Exposure to a virtual environment for 3 minutes.

6) Exposure to neutral stimulus.

7) Rating of anxiety and panic disorder symptoms as determined by the SUDS and PSQ scales.

8) Answering the Igroup Presence Questionnaire.

Discussion

We have described above five methodologies that will be used in translational research. Although some of these methodologies have been in use for quite some time, the INCT-TM was created with the intention of placing them in a more systematic approach which will result in their enhancement, thus expanding their applicability. It will also allow for these specific research fields to grow faster than they would have had this specific funding project not existed.

At present, the INCT-TM contributes with innovations to the area of biological markers in psychiatry, and this recognition is seen in the ability to capture international financial support. One of the biological markers is the brain-derived neurotrophic factor (BDNF), a marker for central nervous system neuroplasticity.[39] This marker is associated with the effect of therapeutic molecules and it is utilized as a guide for indentifying new treatments. Considering the importance of growth factors in inflammation and oncology, the effects of BDNF are also being evaluated for use in such medical fields. As a result, the first international patent deposit utilizing gastrin releasing peptide receptor (GRPR) antagonists, which increase BDNF expression, for therapeutic use in neurological, psychiatric, and inflammatory diseases arose in collaboration with the international biotechnology company AEterna Zentaris.

It is important to highlight that, since 2006, Brasil ranks 15th among the countries with the most intense documented scientific production measured in terms of the number of articles published in indexed peer-reviewed journals. However, since there has been a major gap between Brazil's scientific production and its ability to generate new scientific knowledge, which accounts for 2% of the worlds' total academic production, only 0.1% of the international patents were registered by either Brazilian researchers or institutions. Moreover, compared to its ability to publish scientific articles, Brazil's ability to generate scientific knowledge is twenty times smaller.

Translational research in medicine offers an opportunity to apply the findings obtained in basic research to every-day clinical applications. The INCT-TM group's recent history suggests that basic research applied towards medicine represents not only an opportunity to generate new products and patents, but also a chance to obtain international funding.[40] The main focus of this group is the development of a more applicable interface between basic research and its use in medicine. With this purpose in mind, it has joined six different groups that have also shaped their lines of research around this goal, focusing primarily on translating the data obtained from in vitro and in vivo models to its clinical counterparts in the areas of psychiatry, neurology, oncology and inflammation/rheumatology.

We also propose to unify our methodologies for the systematic study of the interaction of pharmacological intervention and target proteins. This research institute aims at implementing the first research group specifically conceived and accordingly equipped with state of the art techniques to identify molecular targets for pharmacological intervention. Moreover, the Institute will interact with innovation technology cores at both universities and pharmaceutical companies.

Based on the aforementioned facts, we believe that the creation of opportunities for patent deposits and technology transfer in industry should be a priority for INCT-TM. Results will be analyzed in partnership with the technology transfer offices of each participating institution with regards to their potential to generate patents before their submission and publication. Partnerships to set the appropriate guidelines and procedures for intellectual property development will be established among the participating institutions and industry collaborators.

Since INCT-TM already has biotechnology departments as part of its member universities and that the team has already established partnerships with pharmaceutical companies and privates institutions that support research, it is evident that this institute finds itself in a privileged position to transfer the results of this enterprise, which is geared towards the development of high technology industry.

Disclosures

Writing group member	Employment	Research grant[1]	Other research grant or medical continuous education[2]	Speaker's honoraria	Ownership interest	Consultant/ advisory board	Other[3]
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** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
Note: FMRP-USP = Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo; UNESC = Universidade do Extremo Sul Catarinense; UFRGS = Universidade federal do Rio Grande do Sul; PUC-RS = Pontifícia Universidade Católica do Rio Grande do Sul; UFRJ = Universidade federal do Rio de Janeiro; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; CAPES = Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; FAPESP = Fundação de Amparo à Pesquisa do Estado de São Paulo; FAEPA = Fundação de Apoio ao Ensino, Pesquisa e Assistência do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto; FIPE-HCPA = Fundo de Incentivo à Pesquisa do Hospital de Clínicas de Porto Alegre.
For more information, see Instructions for authors.

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