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NATIONAL INSTITUTES OF SCIENCE AND TECHNOLOGY

TRANSLATIONAL MEDICINE RESEARCH INSTITUTE

Partial results

Flávio Kapczinski

Porto Alegre, February 2010
First report of the National Institute of Science and Technology for Translational Medicine (INCT-TM)

Presentation:

The present report concerns the activities developed within the scope of INCT-TM during 2009. During this period, activities focused on the development of the Institute's infrastructure, with acquisition of sequencers and real-time PCR targeting the analysis of gene transcription (USP-Ribeirão Preto and UFRGS-Porto Alegre), as well as on cost estimation and starting the process to purchase other equipments listed in the original proposal. Activities in proteomics began in collaboration with the INCT for Tuberculosis (INCT-TB, PUCRS). We observed a quality-upgrade effect on innovation and an impact on productivity levels in the associate centers (as described later). The associate centers altogether published a total of 160 articles. Of these, 67 articles were developed specifically within INCT-TM projects, in collaboration with different centers (as described later). About one third of the whole 2009 production, developed specifically within the scope of INCT-TM, has already been submitted or is in process, and the center’s total scientific production is estimated at 100 articles published in international journals in 2009. During 2009, novel biomarkers, particularly in the field of oncology (cofilin as a marker of lung cancer), and psychiatric disorders were identified (as described later).

Aiming at technology transfer to the production sector and patenting, NeuroAssay Ltd, a university-based business incubator and INCT-TM partner, initiated a project to develop new epigenetic modulators, and FK Biotechnology, in partnership with NeuroAssay Ltd, initiated a project to develop therapeutic peptides. UFRGS patent division has started the application process for the grant of a patent for the systemic toxicity index, originally proposed by this group. The collaborating centers have also received important institutional improvements, such as a 100-square-meter area specially designed for INCT-TM research activities within Hospital de Clínicas de Porto Alegre (HCPA), institution where the INCT-TM central laboratory is located. Therefore, the objectives for 2009 were fully achieved. Over the coming years, we should ensure continuity of ongoing activities with fully installed equipments and operating physical infrastructure, as stated in our original project.

1) Management Committee – meetings and decisions

- The 1st Meeting of the National Institute of Science and Technology for Translational Medicine was held in Florianópolis (SC), Brazil, March 04-08, 2009, attracting Brazilian INCT-TM participants and international referees: Prof. Trevor Young (Canada) and Prof. Robert Post (USA).

At this occasion, each group delivered a presentation, followed by a discussion about research progress, with the participation of international guests.

Main decisions:

a) Resources should be used in accordance with INCT-TM guidelines, so that the Institute is able to fulfill its duty. Groups should be aware of the allocation of funds to each center and plan the use of resources according to the assigned budget. For example: If, at first, the center uses more financial resources, later it might only use resources for partial funding, or vice-versa, according to the assigned budget.

b) CNPq requires at least 3 estimates for each purchase. If the most expensive estimate is chosen, a technical explanation must be provided. Alternatively, a single estimate may be presented, with an accompanying exclusively declaration by the supplier, stating that this is the only company supplying such equipment.

c) Estimates should be sent to Rafael Gelpi (rafaelgelpi@gmail.com). Every Thursday, weekly (except holidays), purchase requests are approved by the general coordinator (F Kapczinski) or, in his absence, by the vice-coordinator (J Crippa). All other coordinators will receive an email message with approval of purchase orders.

d) Resources are available exclusively as an order check, signed by the coordinator (F Kapczinski). For this purpose, full company details are requested and the receipt should bear the name of Flávio Kapczinski and INCT process number (579671/2008-7).

e) Financial resources should follow property procedures within the target institution, issuing a document for filing purposes.
f) Whenever possible, expenses should be summed together to a larger amount to facilitate management of resources and reduce the number of checks issued. Worth noting that the administrative secretary, Carolina Smaniotto, is being paid from the general coordinator's own research grants, since the INCT order did not include grants for technical support.

g) Each coordinator is in charge of screening and managing requests from groups collaborating with their institution and submitting those purchase requests that they believe to be relevant.

h) Special situations are yet to be clarified with CNPq, such as other forms of purchasing, and should be handled on a case-by-case basis (such situations can be emailed to Carolina). To date, CNPq instructions indicate the need for the above steps.

- A meeting with the management committee was held in Ribeirão Preto (SP), Brazil, May 30, 2009:

  a) At this occasion, INCT strategic objectives were outlined.

  b) Molecular candidates for new drugs were as follows: 1. Tianeptine as a bipolar disorder stabilizer; 2. GRPR as a tumor growth modulator; 3. Cannabidiol as a hypnotic; and 4. Ayahuasca as an antidepressant. Testing these prototypes in animal models and cell cultures was established as the primary action.

  c) In the case of UFRJ Center, the physical infrastructure was seriously deficient, preventing the optimal functioning of the center. It was established that the manager of INCTs should be then consulted about the feasibility of an infrastructure work of R$ 160,000.00 within the scope of INCT-TM.

  d) It was established that each center’s individual purchases would not be dispersed into small expenditure items, so that expenses over R$ 10,000.00 should be discussed weekly at the INCT-TM Center for Expenditure Budget in the city of Porto Alegre, in the presence of the general coordinator, who will sign the checks.

  e) It was established that all studies using animal models should be conducted in the city of Criciúma (SC) in order to optimize the use of resources, and experiments with cell cultures should be conducted at UFRGS Center.

  f) The Ribeirão Preto Center (USP-RP) was acknowledged to be the main center in the identification of new psychoactive compounds based on natural compounds with psychotropic characteristics.

2) Collaborative activities among INCT participating groups

The interaction between INCT research groups has been positive and, in addition to intellectual interaction, there has been mutual action to improve experimental procedures, concerning both the acquisition of reagents for pilot studies and training programs to use new equipment. Some examples of such interaction are given below:

  a) The supply of psychotropic substances and biological material (including plasma and blood) for INCT-related research projects.

  b) Sending participants to other centers to learn techniques related to our research projects (including image analysis techniques).

  c) Receiving participants from other centers to enhance knowledge-sharing, focusing on the implementation of techniques currently not available at their centers.

  d) Intellectual collaboration with studies developed in other centers.

  e) Discussion of molecules common to the mechanisms of neurodegenerative diseases and cancer, for example.

  f) Owing to the graduate courses offered at the proposing Institutions, professors could deliver lectures and/or be a member of the examining committee at a thesis and/or dissertation defense in different centers.

  g) Scientific works in partnership with other research groups, such as the synthesis and supply of Cannabidiol from USP-RP group (Prof. José Crippa) to UNESC group (Prof. João Quevedo); measurement of neurotrophin levels (BDNF, NGF, NT-3, and NT-4) from UFRGS group (Prof. Flávio Kapczinski) to UNESC group (Prof. João Quevedo); biochemical measurements (respiratory chain and oxidative stress) from UNESC Laboratory for Experimental Pathophysiology (Prof. Emilio Luiz Streck and Prof. Felipe Dal-Pizzol) to UNESC group (Prof. João Quevedo).
3) Collaborative activities between INCT groups and other institutions (private companies, governmental and non-governmental organizations, etc.)

INCT-TM carries out activities in collaboration with the following institutions:

**Private non-profit organizations**

- SOAD Cancer Research Foundation
- Children’s Cancer Institute of Rio Grande do Sul

**Biotechnology companies**

- FK Biotechnology (Department of Biophysics, UFRGS)
- NeuroAssay Research and Development (Center for Biotechnology, UFRGS)

4) Main technical and scientific results

Throughout this first year, we published *67 articles with acknowledged support from CNPq/INCT, as follows:

* the actual number of published articles is higher, but several 2009 publications were submitted in 2008 and, therefore, did not acknowledge the affiliation with INCT (see subheading Other papers).


**Effects of mood stabilizers on hippocampus and amygdala BDNF levels in an animal model of mania induced by ouabain**

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Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Research report

Neurochemical and behavioural effects of acute and chronic memantine administration in rats: Further support for NMDA as a new pharmacological target for the treatment of depression?

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Original Paper

Effects of cannabidiol on amphetamine-induced oxidative stress generation in an animal model of mania

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BDNF and PDE4, but not the GRPR, Regulate Viability of Human Medulloblastoma Cells

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**Brain-derived neurotrophic factor gene val66met polymorphism and executive functioning in patients with bipolar disorder**

Polimorfismo do gene do fator neurotrófico derivado do cérebro val66met e função executiva em pacientes com transtorno bipolar

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18. Decreased brain-derived neurotrophic factor in medicated and drug-free bipolar patients

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Ketamine treatment reverses behavioral and physiological alterations induced by chronic mild stress in rats

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Serum brain-derived neurotrophic factor (BDNF) is not associated with response to electroconvulsive therapy (ECT): A pilot study in drug resistant depressed patients

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Brain-derived neurotrophic factor serum levels before and after treatment for acute mania

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(Fundo de Incentivo a Pesquisa de Hospital de Clínicas de Porto Alegre) and AstraZeneca.


Research report

Development and use of a biological rhythm interview

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Bipolar disorder and age-related functional impairment
Prejuízo funcional associado à idade e transtorno bipolar

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Ataques de pânico são realmente inofensivos? O impacto cardiovascular do transtorno de pânico
Are panic attacks really harmless? The cardiovascular impact of panic disorder

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The fear circuitry in panic disorder and its modulation by cognitive-behaviour therapy interventions.

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Research Article

FREEZING REACTION IN PANIC DISORDER PATIENTS ASSOCIATED WITH ANTICIPATORY ANXIETY

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The psychiatric side-effects of rimonabant
Os efeitos-colaterais psiquiátricos do rimonabanto

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27 October 2009

Anterior cingulate cortex activation as a trait of panic disorder in a patient with a temporal arachnoid cyst

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Glutamate-N-methyl-D-aspartate receptor modulation and minocycline for the treatment of patients with schizophrenia: an update

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Is the Fagerström Test for Nicotine Dependence a good instrument to assess tobacco use in patients with schizophrenia?

O Teste de Fagerström para Dependência de Nicotina é um bom instrumento para avaliar o uso de tabaco em pacientes com esquizofrenia?

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Systematic Review

Psychometric properties of the Fagerström Test for Nicotine Dependence*

As propriedades psicométricas do Teste de Fagerström para Dependência de Nicotina

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Carbon dioxide-induced panic attacks and quantitative electroencephalogram in panic disorder patients

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Cannabis and anxiety: a critical review of the evidence

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Modulation of effective connectivity during emotional processing by Δ9 tetrahydrocannabinol and cannabidiol

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Original Investigation

Psychometric qualities of the Brazilian versions of the Fagerström Test for Nicotine Dependence and the Heaviness of Smoking Index

Caroline de Meneses-Gaya, Antonio W. Zuardi, João Mazzocini de Azevedo Marques, Roberto M. Souza, Sonia R. Loureiro, & José Alexandre S. Crippa
Opposite Effects of Δ-9-Tetrahydrocannabinol and Cannabidiol on Human Brain Function and Psychopathology

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Social anxiety disorder: what are we losing with the current diagnostic criteria?

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Social anxiety disorder: what are we losing with the current diagnostic criteria?

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Study of the Discriminative Validity of the PHQ-9 and PHQ-2 in a Sample of Brazilian Women in the Context of Primary Health Care

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Flávia de Lima Osório, PhD, is a Research Assistant, José Alexandre S. Crippa, MD, PhD, is a Professor, Ana Villela Mendes, MSc, is a Postgraduate Student, Sonia Regina Loureiro, PhD, is a Professor; all are from the Department of Neurosciences and Behavior, Faculty of Medicine of Ribeirão Preto, University of São Paulo, and INCT Translational Medicine, São Paulo, Brazil.


Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder

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Effects of chronic mild stress on the oxidative parameters in the rat brain

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Review Article
The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders

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CASE REPORT

Nomophobia: The Mobile Phone in Panic Disorder With Agoraphobia
Reducing Phobias or Worsening of Dependence?

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Social anxiety disorder women easily recognize fearful, sad and happy faces: The influence of gender

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Chronic methylphenidate-effects over circadian cycle of young and adult rats submitted to open-field and object recognition tests.

Gomes KM, Souza RP, Valvassori SS, Réus GZ, Inácio CG, Martins MR, Comim CM, Quevedo J.
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In this study age-, circadian rhythm- and methylphenidate administration-effect on open-field habituation and object recognition were analyzed. Young and adult male Wistar rats were treated with saline or methylphenidate 2.0 mg/kg for 28 days. Experiments were performed during the light and the dark cycle. Locomotor activity was significantly altered by circadian cycle and methylphenidate treatment during the training session and by drug treatment during the testing session. Exploratory activity was significantly modulated by age during the training session and by age and drug treatment during the testing session. Object recognition memory was altered by cycle at the training session; by age 1.5 h later and by cycle and age 24 h after the training session. These results show that methylphenidate treatment was the major modulator factor on open-field test while cycle and age had an important effect on object recognition experiment.

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Study of killer immunoglobulin-like receptor genes and human leukocyte antigens class I ligands in a Caucasian Brazilian population with Crohn's disease and ulcerative colitis

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DNA damage after intracerebroventricular injection of ouabain in rats

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Short Reports

Mitochondrial respiratory chain and creatine kinase activities in mdx mouse brain

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Intracerebroventricular Ouabain Administration Induces Oxidative Stress in the Rat Brain

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Phosphoinositide 3-kinase is required for bombesin-induced enhancement of fear memory consolidation in the hippocampus

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Gastrin-releasing peptide receptor signaling in cancer

Review Article

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Rapid Report

**Retrieval mediated by hippocampal extracellular signal-regulated kinase/mitogen-activated protein kinase is required for memory strengthening**

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A systemic toxicity index developed to assess peripheral changes in mood episodes

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**CFL1 expression levels as a prognostic and drug resistance marker in non-small-cell lung cancer**


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**Financial support:** Brazilian MCT/CNPq Universal funds (479860/2006-8) and MCT/CNPq INCT-TM (573671/2008-7) funds and federal funds from the National Cancer Institute, National Institutes of Health (NO1-CO-12400). We would like to thank Dr Marcia Triunfol at Publicase for editing the article and for manuscript comments.
Other papers
(2009 publications that were submitted in 2008 and, therefore, do not acknowledge the affiliation with INCT).


5) National and international events: presentation of papers, organization of courses, seminars, lectures, panels

1. March 13, 2009: Event to commemorate the launch of INCT-TM, with the Seminar: Epigenetics as a research tool in translational medicine (Prof. Robert Post, Pennsylvania State University, USA).

2. Poster presentation at the XXIV Annual Meeting of the Federation of Societies of Experimental Biology (FeSBE), 2009. Chronic harmine administration induces antidepressant-like effects and increases BDNF levels in the rat hippocampus.

3. Poster presentation at FeSBE, 2009. Chronic memantine administration induces antidepressant-like effects with no change in BDNF levels in the rat hippocampus.


6. Poster presentation at the **29th Scientific Week of Hospital de Clínicas de Porto Alegre**, 2009. Decreased serum BDNF levels in medicated and drug-free bipolar patients.


12. Oral presentation at the **II UFSCPA Scientific Week**, 2009. Increased neurotrophin-3 levels in medicated and drug-free bipolar patients during manic and depressive episodes.

13. Poster presentation at **FeSBE**, 2009. Decreased brain-derived neurotrophic factor (BDNF) levels in medicated and drug-free bipolar patients.

14. Poster presentation at **FeSBE**, 2009. Serum brain-derived neurotrophic factor (BDNF) levels are not associated with response to electroconvulsive therapy (ECT): a pilot study in drug-resistant depressed patients.


17. Roesler R. The gastrin-releasing peptide receptor as a therapeutic target in cancer and neurological disorders. Lecture on Experimental Pharmacology and Oncology, Max Delbrück Center for Molecular Medicine, Berlin, Germany. 2009.


70. Souza B, Petronilho F, Vuolo F, Felisberto F, Mina FG, Constantino LS, Comim CM, Barichello T, Dal-Pizzol F, Quevedo J. Effects of acute treatment with amphetamine on


84. Cassol Jr OJ, Comim CM, Petronilho F, Hermani F, Constantino LC, Quevedo J, Dal-Pizzol F. Effects of treatment with dexamethasone on depressive-like parameters in sepsis survivor...


6) Activities for human resources development and training

- The discipline “Translational Medicine” was offered in the Graduate Program in Medical Sciences – UFRGS in the second semester of 2009.
- The discipline “From the laboratory to clinical practice: Translational Medicine in the development of diagnostic tests in psychiatry” was offered in the Graduate Program in Medicine: Psychiatry – UFRGS in the second semester of 2009.
- The discipline “Investigation Methods in Translational Medicine” was framed to be offered in the Graduate Program in Neurosciences – USP-RP Medical School.
- Undergraduate scientific initiation students; master’s, doctoral and post-doctoral students; industrial and technological development (DTI) scholarship holders.

7) Future perspectives and outgrowth

INCT-TM accomplished its full implementation through operating equipment and physical infrastructure during this first year, which did not hinder the rapid progress of our research line: 67 studies including different INCT groups were published in 2009; and over 30 articles are in process to be published in 2010 (regarding the work developed throughout 2009). Therefore, INCT-TM has proved to be a very productive group, which, according to its mission, aims at the transposition of basic science data to the clinical context. Furthermore, the main INCT-TM perspectives include the synthesis of novel molecules (at least two compounds obtained from the modification of existing drugs and one compound obtained from natural extracts). Thus, our 2010 goals include both the synthesis and patenting of these compounds, with the possibility of their transfer to the production sector in 2011.
The main outgrowths of INCT-TM actions in 2009 were:
1) physical infrastructure improvements in all participating centers;
2) improvements in laboratory equipment;
3) qualification of human resources through the available grants;
4) increase in formal collaboration among the involved centers.

Thus, a solid platform was created for the development of research in translational medicine. These outgrowths may assist us in integrating the science produced in university centers with technological innovation, which, in its final version, should occur in the production sector of biotechnology and the Brazilian pharmaceutical industry. As attested by the high scientific production of INCT-TM, Brazilian science has advanced considerably concerning productivity and impact. A closer connection with the production sector has been established so that academic knowledge can be transformed into productive knowledge. INCT-TM has an active role in this focus shift within the Brazilian scientific community.