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JOHNS HOPKINS
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Dimas Tadeu Covas
Professor Titular
Faculdade de Medicina de Ribeirão Preto
Hemocentro de Ribeirão Preto
Universidade de São Paulo (USP),
Ribeirão Preto, São Paulo, Brasil

Dear Prof. Dr. Dimas Tadeu Covas,

I am delighted to collaborate on your grant application to establish a *Center for Cell-based Therapy*. I am happy to contribute as a scientific collaborator and for the training of the students and fellows involved in the project. I understand that this will be a grant application to FAPESP as part of Programa CEPID (Centros de Pesquisa, Inovação e Difusão). The work described in this grant is important for the advancement of cancer research and I am happy to help your laboratories and collaborators in this effort.

Your proposed center has as one of its main projects to study the Homeobox HOX genes and their transcriptional regulation under the direction of Dr. Aparecida Maria Fontes. We have already established collaboration with Dr. Fontes and pledged our support for this project, including the new work proposed as part of the center investigation.

Our laboratory also believes the HOX genes are very important for medulloblastoma development. We were the first to show in our laboratory that a developmentally related family of homeobox genes, in particular OTX2, is amplified and a likely oncogene for medulloblastoma (Boon K, Eberhart CG, Riggins GJ: **Genomic amplification of orthodenticle homologue 2 in medulloblastomas**. *Cancer Res* 2005, **65**(3):703-707.). Subsequently we have evaluated the molecular targeting potential of this homeobox gene in cancer (Bai R, Siu IM, Tyler BM, Staedtke V, Gallia GL, Riggins GJ: **Evaluation of retinoic acid therapy for OTX2-positive medulloblastomas**. *Neuro Oncol*. 2011). In addition we have contributed to the sequencing of medulloblastoma and the discovery of new driver genes, such as MLL2, that regulate the epigenetics of medulloblastoma formation (Parsons DW et al: **The genetic landscape of the childhood cancer medulloblastoma**. *Science*, **331**(6016):435-439. Components of these studies, and our on-going studies of medulloblastoma could help contribute significantly to the understanding the HOX genes play in the development of medulloblastoma.

Our laboratory has been employing cancer stem cell technology for the study of brain cancer. In particular we have developed cancer stem cell 'oncosphere' lines. We have established about 12 different glioblastoma oncosphere lines for in vitro and in vivo study of cancer. In particular we are using these oncosphere lines for translational development, because we believe the lines are more accurate in terms of cancer biology and response to therapy. We are happy to share this technology in any manner that would help your work.

I would also like to additionally offer to contribute to your project in the following ways. We can offer technical support, experience and protocols if there are methods that are not readily available for your work. My laboratory would be willing to host a PhD student from your laboratory to work on this program as part of a 'sandwich' PhD training program. I am also happy to participate in committee meetings, lab meetings and other scientific discussions either by teleconference and/or during my periodic visits to Brazil. Certainly, if you have an opportunity to visit our laboratory to discuss the project, I would be happy to assist in making a visit here possible. I hope that all these activities will help strengthen the ties between our institutions and lead to further productive interactions.

Thank you once again for inviting me to participate in this exciting project and I wish you the best for success in continuing this center.

Sincerely,

Gregory J. Riggins, M.D. Ph.D.
Professor of Neurosurgery & Oncology
Irving J. Sherman Research Professor in Neurosurgery
Director, Division of Neurosurgery Research