A STUDY OF FETAL NEURONAL TISSUE GRAFT IN A HETEROTOPIC TRANSPLANTATION SITE AND ITS IMPLICATIONS

BY

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Thesis submitted for the degree of Doctor of Philosophy (Science)

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Certificate from the Supervisors

This is to certify that the thesis entitled “A Study of Fetal Neuronal Tissue Graft in a Heterotopic Transplantation Site and its Implications” submitted by Bimal Krishna Samanta, who got his name registered on 22.12.03 for the award of Ph.D. (Science) degree of Jadavpur University, is absolutely based upon his own work under the supervision of Dr Niranjan Bhattacharya and Prof Malay Chatterjee and that neither this thesis nor any part of its has been submitted for any degree / diploma or any other academic award anywhere before.

1. …….

2. …….

(Signature of the supervisors & date with official seal)

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Kolkata, the , 2008. (BIMAL KRISHNA SAMANTA)

DEDICATION

To

The memory of my departed father Late Lalit mohan Samanta.

List of Publications and Conferences Attended

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1. Samanta, B. K., Chandra, N. C., Ghosh, S. and Mukherjee, K. L. (1984). Aldose metabolism in developing human fetal brain and liver. Experientia. 40, 1420-1422.

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CONFERENCES ATTENDED FOR THE LAST 11 YEARS
(poster presentation / oral presentation / as delegates):

1. XXIVth Annual Conference of the Association of Clinical Biochemists of India, 12-14 December, 1997, Science City, Kolkata.

2. 13th Annual Meeting of the Society of Biomaterials & Artificial Organs, India, 20-21 December, 2002, J.U., Kolkata.

3. 49th Annual Conference of the International College of Surgeons (Indian Section), 4-7 September, 2003, Chennai.

4. 63rd Annual Conference of the Association of Surgeons of India, 25-30 December, 2003, Pune.

5. 6th Annual Conference of the Association of Clinical Biochemists of India (West Bengal Chapter), 29th February, 2004, Institute of Child Health, Kolkata.

6. International Symposium on Advanced Materials and Processing, 6-8 December, 2004, IIT, Kharagpur.

7. 50th Annual Conference of the International College of Surgeons (Indian Section), 28-31 December, 2004, New Delhi.

8. Conference on Current Trends in Clinical Biochemistry and Workshop on Application of HPLC in the diagnosis of Thalassaemia and Haemoglobinopathies of Eastern Zone Association of Clinical Biochemists of India, 29-30 April and May 1, 2005, Vivekananda Institute of Medical Sciences, Kolkata.

9. Conference on Stress 2006 of National Referal Centre for the Prevention of Lead Absorption in India (West Bengal), 10-11 June, 2006, Vivekananda Institute of Medical Sciences, Kolkata.

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Preface

The most advanced research on the use of human fetal tissue has been done in Parkinson's disease, which affects about 1.5 million people in the U.S only. Patients with Parkinson's disease experience tremors, slurred speed and slowness of movement that eventually progresses to total paralysis. In this progressive, debilitating illness, the cells in a small part of the brain called the substantia nigra are destroyed, depriving the striatum (the part of the brain that controls movement) of a critical molecule called dopamine. Despite devastating loss of motor control, mental faculties in Parkinson's patients remain intact, and while the disease is in itself not fatal, patients often succumb to complications such as injuries from falls or pneumonia.

During brain development, one of the most important structures is the subventricular zone (SVZ), from which most neurons are generated. In adulthood the SVZ maintains a pool of progenitor cells that continuously replace neurons in the olfactory bulb. Neurodegenerative diseases induce a substantial upregulation or downregulation of SVZ progenitor cell proliferation, depending on the type of disorder. Far from being a dormant layer, the SVZ responds to neurodegenerative disease in a way that makes it a potential target for therapeutic intervention (1).

One of the most promising areas in medical research today is fetal tissue transplantation. At stake is a source for stem cells, progenitor cells harvested from human fetuses that can differentiate into any cell in the adult human body. This chameleon-like ability of stem cells makes them potentially useful in replacing critical cells in the adult human body that have been ravaged by injury or disease.

Fetal tissue transplants, in which such organ specific and nonspecific stem cells live in their natural environment, and are injected into the failing organs of patients, work on the premise that placed in the right environment, the

transplanted cells take their cues from their surroundings and develop into the needed tissue. Inject them into the brain, they become brain cells. Inject them into the pancreas, and they develop into pancreatic cells. Stem cells seem adaptable to such procedures, growing rapidly after transplantation, and secreting hormones and other chemicals that promote tissue growth. As an added bonus, these “master” cells are too undeveloped to be detected by the recipient’s immune system, and thus often avoid the rejection that plagues normal organ transplant procedures.

Fetal Tissue Used to Treat Diseases and Defects

Fetal tissue transplants are being investigated as treatments for a wide range of debilitating human conditions. Researchers hope to cure diabetes by regenerating insulin-producing pancreatic cells in diabetics, and blindness by regrowing retinal tissue in the eye. Scientists hope to develop better treatments for heart attack victims with fetal tissue used to regrow damaged heart muscle. Fetal tissue transplants also look promising for a variety of problems caused by destroyed nerve cells, such as Parkinson’s disease, Huntington’s Chorea, and even spinal cord injuries.

The crux of the method is the use of fetal stem cells to replace damaged tissue that the body itself cannot repair. For instance, paralysis is currently incurable because, once destroyed, the nerve cells of the spinal cord are not able to grow back. Researchers hope that stem cells can be used to bridge a spinal cord injury in much the same way as skin cells grow back to cover a cut. Although not ready to be tried in people, procedures that inject fetal tissue cells at spinal cord breaks have shown encouraging results in small animals, as in one study where scientists were able to get partially paralyzed cats to walk again. Similar experiments to regenerate nerve cells of the brain are also being investigated as cures for Huntington’s Chorea and Parkinson’s Disease, two diseases caused when specialized nerve cells in the brain begin to die off.

The first line of treatment for Parkinson's disease is drug therapy. Unfortunately, L-dopa, a precursor of dopamine which can be absorbed by the brain, helps only as long as there are some substantia nigra cells still alive to absorb the drug. Once that area of the brain is destroyed, L-dopa becomes ineffective, which until recently left the patient without any available treatment for this disorder. Now, in certain centres of excellence, pioneering fetal tissue transplants into the brain of Parkinson's patients show promise in slowing or even reversing symptoms of the disease. In this treatment, cells from the pre-brain structures of 6-8 week old fetuses are injected into the patient's striatum, where if all goes well they grow into a bundle of nerve cells that produce the needed dopamine. Patients with successful fetal tissue transplants have shown remarkable improvement in the severity of tremors and in their ability to move.

With such exciting results and millions of people in this country alone suffering from Parkinson's and other diseases that may be helped by fetal tissue transplants, patients and their advocates are urging further research into the use of stem cells. However, currently the only reliable source of fetal stem cells is selectively aborted human fetuses, collected from abortion clinics with the permission of the mother.

The present thesis examined the safety aspects of fetal neuronal tissue transplantation at a subcutaneous heterotopic site under local anaesthesia in different patients with severe idiopathic Parkinsonism, not responding to conventional drugs. All the cases passed through the voluntary consent protocol and were cleared by the Institutional ethical committee of the hospital.

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