Stem Cells for Brain Diseases – **New Life & Targeted Death**

By A/Prof Wong Meng Cheong

Our brains are the seat of our memories, emotions, thought and actions. A complex, richly interconnected and delicate organ indeed. Brain diseases are ranked third or fourth, as a cause of death. But for paralysis, incoordination, sensory loss, speech difficulties, insight and memory loss, judgement lapse and cognitive impairment, and as a cause of long term, serious disability in adult Singaporeans, brain diseases are number one.

This essay is about a local personal journey, with crucial collaborators, seeking stem/progenitor cells to repair a neurodegenerative disease and to target a malignant brain disease. The journey is not halfway and many difficulties lie ahead for the use of cell therapies for degenerative diseases and destroying brain tumours.

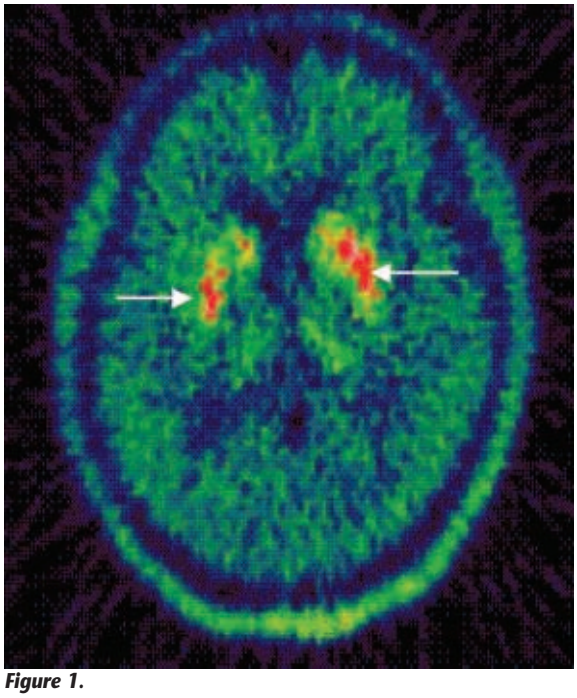

Figure 1.

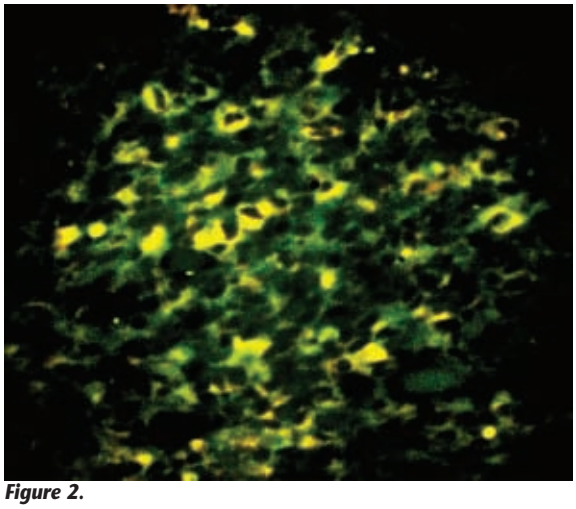

Figure 2.

About the author:
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In Parkinson's Disease, progressive degeneration of neuronal systems, particularly dopaminergic, results in steady decline with gait impairment, rigidity, tremor and slowed movements. An eventual bed-bound state with pneumonia or other complications is common.

In 1990, a Lund University, Sweden group published how fetal dopamine neuron grafts can survive and improve motor function in the prestigious journal *Science*. Our group's work to develop neurotransplantation for severe cases started in 1993. By 1995, we had only accomplished meetings and written proposals to authorities. During this time, the first two prospective patients had died of their disease. Work began in earnest, when neurologists Dr Erle Lim and Dr Tan Eng King, neurosurgeon Dr Thomas John, obstetricians Dr Yeo Seow Heong and Dr Ann Tan, and scientist Dr Li Yongbiao formed our team. Not to "reinvent the wheel", we sought collaboration with world leaders in the field, our Swedish colleagues. In 1997, at 2-month intervals, one team member after another, made the trip to the Wallenberg Neuroscience Center in Lund, Sweden. Our Swedish colleagues, persuaded of our seriousness, were generous. We learnt enormously, obtained equipment, refined techniques and successfully performed rodent neurotransplants.

In July 1999, we performed the region's first neuro-transplantation, using cells grafted from multiple fetal ventral mesencephalon for a patient with severe Parkinson's Disease. Six to nine months post-transplant, the patient was significantly better, but by 24 months, initial improvement was lost, and steady, progressive deterioration set in. MRC Center, Hammersmith Hospital, London, performed the Positron Emission Tomography scans, pre-transplant and 18 months post-transplant *(Figure 1)*, revealing 57% ^{18}F-dopa signal improvement in the transplanted putamen *(see arrows)*, but relentless 15% signal decline in the non-transplanted regions.

Gliomas are the most common type of primary brain tumours. They cause much suffering and many patients suffer seizures, headache, paralysis, cognitive impairment and other problems. Despite modern treatment with surgery, radiation therapy and chemotherapy, Glioblastoma Multiforme (high grade or malignant glioma) has a median survival of about 12 months. Better therapies are sorely needed.

Our group and others have had success killing glioma cells with biological strategies such as gene therapy. But these are confined to tumour cells in vitro and in animal systems. One crucial hurdle has been the issue of delivery of these biological therapies to the brain tumour. We need "missiles" which will go where we target, with only a minimum of the specific "genetic payload" going astray. And we need sufficient numbers of these genes reaching their target and to be adequately expressed. Such a targeted

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"missile" system could potentially and significantly advance delivery of biological therapies.

Using blood stem cells, we have derived cells that "home" to an animal model of brain tumours. Essentially human malignant glioma tumour cells are grown in the brain of an immunocompromised mouse. After deriving the cells with the characteristics that we want, we label these cells with a fluorescent marker so that we can easily identify them later. We inject our stem cell derived "homing" cells intravenously into the mice, and later sacrifice the mice, examining their brain tumours for fluores-cent "missiles" that have hit the target and we examine other organs also, for "missiles" which have gone elsewhere. Two types of "smart bombs" have been developed to arm the missiles. *Figure 2* shows a microscopic section of fluorescent cells which have "homed" to the brain tumour.

In conclusion, many diseases of the brain cause terrible morbidity, followed by death. Stem cell therapies bring hope to patients with Parkinson's Disease, Huntington's Disease, Multiple Sclerosis, Stroke and Brain Tumours. Scientific advances will continue to underpin and advance medicine. Our patients await, impatiently. ■

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