

## What's Hot in Parkinson's Disease?

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New iPS Stem Cells for Parkinson's Disease: What Does it Mean?

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One of the most recent and remarkable scientific developments has been the ability of scientists to manipulate somatic cells (e.g. skin cells) in such a way that they can be re-programmed to become pluripotent (they gain the ability to form multiple different cell types in the body). This ability is the result of inducing expression of several transcription factors (transcription factors encode the genetic maps in any individual person) and this induction results in the generation of what have been referred to as **induced pluripotent stem** (iPS) cells. In initial experiments, a combination of chemicals Oct4, Sox2, Klf4 and Myc were used to induce a transition of fibroblasts (e.g. parts of skin cells) into stable and self-renewing cells that very closely resembled embryonic stem cells (ES). Subsequently, this type of reprogramming has been demonstrated in a wide range of cell types.

Several techniques have been employed to achieve reprogramming of cells from various body tissues (somatic cells). These methods include nuclear transfer, cell fusion of somatic cells with ES cells, explantation of somatic cells in culture (from a dish in the lab), and the transduction of somatic cells with defined factors/chemicals. The exact molecular mechanism of this reprogramming however, is still uncertain. It will be necessary in the future to unlock the mystery behind why this reprogramming works, in order for us to understand why the process proceeds so slowly (often over a period of several weeks), and why only a small proportion of the infected fibroblasts (usually skin cells) achieve iPS cell status.

iPS cell possibilities precipitate the question that is on all Parkinson's disease patient's minds: would it be possible through cell reprogramming to generate tailor made cells as neurotherapeutics? Recent studies have shown the therapeutic application for the transplantation of iPS derived dopamine neurons (brain cells) in a rat model of Parkinson's disease. In these studies it was shown that dopamine neurons could be functionally integrated into the adult rat model of Parkinson's disease, and that this could lead to an improvement in the clinical symptoms of the disease. Similar experiments were also performed on hemophilia A mice (iPS derived endothelial cells into liver cells) and this also resulted in disease improvement (hemophilia is a blood disease). Hence, iPS cell-based strategies could become very important in the future treatment of Parkinson's disease.

Even though more work will be required before the generation of clinically applicable iPS cells, drug screening and disease modeling will be two potentially

immediately useable applications for this technology. Improvements in high throughput screening using iPS cells may allow for reductions in cost, and improvements in safety of drug screening (identifying new drugs to treat PD). Additionally the techniques may help us to understand the underlying pathophysiology of the disease.

There will be major challenges in the clinical implementation of therapeutic preparations derived from iPS cells. It is absolutely critical that these preparations be free of undifferentiated cells that may have the potential to form tumors. Further, the efficient purification of populations of disease-relevant cell types will be a major challenge. Finally, and perhaps most importantly, the development of techniques for the precise delivery of iPS cells into patients, and the functional engraftment of the cells into the appropriate and complex basal ganglia motor and nonmotor circuits in Parkinson's disease will provide the most formidable challenge. In summary, iPS cells should provide excitement for the Parkinson's disease patient, but we should also realize that a lot of the foundations for success still remain to be constructed and to be built upon.

\*The co-author of this month's What's Hot is Vinata Vedam-Mai who is a researcher working in the stem cell laboratory of Dr. Brent Reynolds at the University of Florida.

#### Selected References-

1. Forcing cells to change lineages. Grat, T. et al. Nature 2009. 462, 587-594.
2. Progress toward the clinical application of patient-specific pluripotent stem cells. Kiskinis, E. et al. J. Clin. Invest. 2010. 120 (1) 51-59.
3. Stem cells, the molecular circuitry of pluripotency and nuclear reprogramming. Jaenisch, R et. al. Cell, 2008. 132, 567-582.
4. Parkinson's disease patient-derived induced pluripotent stem cells free of viral reprogramming factors. Cell, 2009. 136 (5) 964-977.

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