



## Ruben Dagda Pittsburgh Medical Technology Examiner

# Scientists extract pluripotent stem cells for medical use from an unexpected source: hair

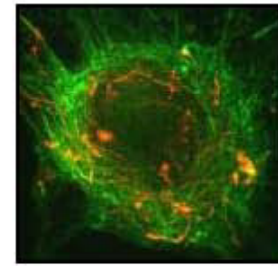
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If there was anything good that came from banning embryonic stem cell research during the Bush administration, is that it forced scientists to find more creative alternative solutions for acquiring other sources of stem cells for therapeutic use. Certainly, the clinical or biomedical use of either embryonic stem cells generates a lot of controversy with ethical and moral dimensions. Although the Obama administration lifted an [eight year federal ban](#) that prohibits the use of federal money to fund embryonic stem cell research, novel techniques such as [single blastomere transfer](#) and the ability to reprogram adult somatic cells to an "embryonic-like" state may show similar or better therapeutic potential compared to embryonic stem cells. Thus, these techniques may preclude the use embryonic stem cells altogether in the near future.

The reprogramming of adult somatic tissues to pluripotent stem cells or also known as induced pluripotent stem cells, opened the possibility for treating neurodegenerative and other devastating chronic diseases without the use of embryonic stem cells. The therapeutic potential of induced pluripotent stem cells include their use for replenishing neurons that are lost in chronic neurodegenerative diseases such as Parkinsons disease, disease characterized by the progressive loss of dopaminergic neurons or Amyotrophic lateral sclerosis (Lou Gehrig's disease). This technique was developed several years ago and it involves a tedious, expensive and time-consuming protocol but never-the-less it has spurred a high level of excitement and interest among the scientific community to further develop, refine and exploit these methods for therapeutic use. In brief, this technique involves the ability to turn somatic cells (terminally differentiated cells) into "embryonic-like" stem cells by exposing adult somatic cells (ie., fibroblasts or skin cells derived from patients) to different growth factors or infecting somatic cells with viruses that carry certain "pluripotent" genes such as homeobox or oncogenic genes OCT4, KLF4, SOX2, and c-MYC. Clearly, the plasticity and flexibility of this technique for transforming adult somatic cells into pluripotent cells is amazing. For instance, scientists have been able to successfully reprogram fibroblasts from old patients into pluripotent stem cells and differentiate them into dopaminergic neurons (Soldner et al., 2009). Moreover, several cell lines derived from induced pluripotent stem cells can be used to model these devastating chronic diseases *in vitro* (Soldner et al., 2009; Dimos et al., 2008).

However, there are some caveats associated with the use of induced pluripotent stem cell technology. Although, patients transplanted with tissue derived from pluripotent stem cells do not face the problem of immunological rejection, there is still a high risk for developing [teratomas](#), rare neoplasms (tumors) containing multiple layers of normal tissue, since not all stem cells become fully differentiated. Moreover, a major caveat of using viruses to infect and transform somatic cells into pluripotent stem cells is the fact that these genes are stably integrated into the genome of cells. Particularly, the leaky expression of c-MYC oncogene can induce differentiated cells to revert back to an embryonic state and thus form teratomas in patients. In order to circumvent this problem, adult somatic cells are transduced with viruses that carry excisable versions of these genes. In other words, once incorporated onto the genomes of somatic cells, these genes can be later biochemically excised from the genome; thus creating terminally differentiated cell lines that are free of oncogenic or embryonic genes (Soldner et al., 2009). Another problem with this technique is the extremely low efficiency of adult somatic cells that are successfully converted into pluripotent stem cells which severely limits the potential of this technique for obtaining pluripotent stem cells in a large scale basis (about 100 cells out of 1 million are successfully reprogrammed or about a 0.005% reprogramming efficiency).

However, scientists have found an alternative source of stem cells: hair. Hair constantly undergoes different cycles of regression, growth and rest. The regenerative process of hair is mediated by follicle stem cells located in the bulge area of hair follicles which have the capacity to differentiate to other cell types. Physiologically, [hair follicle](#) stem cells form a pool of cells that are involved in the regeneration of the anagen hair bulb and the sebaceous gland and the epidermis after injury or during hair loss. This is an infant and growing field with an enormous therapeutic potential. Several landmark research reports derived from a group of investigators led by Dr. Robert M. Hoffman of AntiCancer (San Diego, CA) initially described the presence of pluripotent stem cells in hair follicles. Dr. Robert M. Hoffman were is one of the first pioneers for developing techniques for growing hair follicle pluripotent stem cells in culture and differentiating these cells to other cell types (Arnoh et al., 2009; Arnoh et al., 2008; Arnoh et al., 2005a). In particular, nestin positive but keratin negative pluripotent follicle stem cells isolated from the hair follicle bulge area have the capacity to extensively differentiate into neurons and glia *in vitro* and *in vivo*. As described



Epifluorescent micrograph showing a group of embryonic cells (green) that have developed into neurons (red)

The image was taken in the lab of Guoping Fan at the [University of California, Los Angeles](#).

in their study, the procedure for extracting human pluripotent follicle stem cells involves isolating and dissecting hair follicles from human scalp skin samples. The dissected hair follicles are enzymatically dissociated and subsequently grown onto plastic tissue culture dishes for 4 weeks in a temperature controlled tissue culture incubator (Amoh et al., 2009). The cells can be exposed to certain growth factors and specialized conditioned media which allows them to differentiate into many different cell types including smooth muscle cells, neurons and glia.

The authors then wanted to investigate the therapeutic potential of human pluripotent hair follicle stem cells. Human hair follicle pluripotent stem cells were transplanted onto the severed sciatic nerves of nude mice or a control mice. Eight weeks following transplantation, histological analysis demonstrated that human hair follicle pluripotent stem cells formed colonies of Schwann cells that wrapped around the severed sciatic nerve. These new Schwann cells, support cells that maintain neuronal health and increase axonal electrical conductivity by forming myelin sheaths that wraps around the axon of neurons, apparently promoted the growth of pre-existing axons, resulting in functional regeneration and healing of the severed nerve. Thus the procedure allowed mice with sciatic nerve injury to complete regain mobility of their hind legs following transplantation. This exciting experimental result opens up the possibility of developing individualized therapies that utilize human hair follicle pluripotent stem cells to treat patients with neurodegenerative diseases or with spinal cord injury.

There are many advantages for using human follicle pluripotent stem cells:

- 1) Unlike adult somatic cells that can be transformed to pluripotent stem cells, human hair follicle pluripotent stem cells do not need genetic manipulation (viral mediated transduction of different pluripotent genes)
- 2) Human hair follicle pluripotent stem cells can be obtained and re-grown in large scale numbers that enhance their therapeutic potential
- 3) Although only a few of studies have described the biochemistry and cell biology of human hair follicle pluripotent stem cells, they do not appear to induce the formation of teratomas *in vivo*.
- 4) Since human hair follicle pluripotent stem cells can be differentiated to neurons, this technology offers the possibility for developing individual based therapies for patients and circumvents the problem of immunological rejection.

Overall, the authors of this paper provide a palpable alternative to the use of embryonic stem cells. Moreover, human follicles obtained from the scalp of patients may be an ideal and viable source for up-scaling production of stem cells for therapeutic use. Although human hair follicle pluripotent stem cells has been shown to be differentiated to neurons, it is not known whether these stem cells can be transformed to more specialized neuronal populations such as large peripheral motor neurons or dopaminergic neurons, which begs the question of whether this technique is useful for treating patients with ALS and Parkinson's disease respectively. Like anything else in biomedical research, there is no doubt that perseverance and discipline will yield the right answers in the near future. Apart from hair follicles, adult somatic cells (transformed by induced pluripotent stem cell techniques), and umbilical cord, will there be other sources of embryonic stem cells are waiting to be discovered in the future?

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