

# Promising Combinatorial Therapeutic Approach for Neural Repair and Recovery of Voluntary Control of Locomotion: Neural Pluripotent Cells and CPG Activators?

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## Short Communication

Neural stem cells are self-renewing cells that can become, mainly during embryonic development, different types of cells including neurons, astrocytes and oligodendrocytes [1]. After embryonic development, some neural stem cells localized in a few specific areas of the central nervous system remain capable of producing neurons throughout life.

In adults suffering of acute neurological disorders or neurodegenerative diseases, one emerging approach being explored by scientists is the use stem cell replacement therapy-neural stem cells are cultured *in vitro* as neurospheres with growth factors such as EGF and FGF. Withdrawal of these growth factors activates differentiation into neurons, astrocytes, or oligodendrocytes which can be transplanted in the central nervous system affected by the lesion or the disease. However, significant efficacy issues remain prior the transfer of this experimental approach into the clinic.

On the other hand, central pattern generator (CPG) neurons have recently been found to serve as key control systems underlying the expression of several motor functions [2]. CPGs are biological neural circuits that can produce the basic rhythmic motor outputs sent to muscles even in the absence of cortical control or sensory inputs. They are the source of the tightly coupled patterns of neural activity that generate rhythmic and stereotyped motor patterns of activity such as locomotion, breathing, defecation, urination, or ejaculation. Flexibility in response to sensory input is a fundamental quality of CPG driven behavior. CPGs have been found in practically all vertebrate species including human. Pharmacological approach aimed at modulating or reactivating CPGs are currently in development to improve the recovery of functions following acute neurological trauma or neurodegenerative diseases.

Research into stem cells grew out of findings made 50 y ago in mice by the Canadians, McCulloch and Till [1]. Giant steps have been made since then. Nowadays, adult stem cells are routinely used as treatment against cancer [3]. For neurological problems such as Alzheimer's disease, Parkinson's disease and brain or spinal cord injury (SCI), other types of stem cell approaches are currently being explored. Among them, embryonic stem cell technology (ES cells) was approved 9 y ago by the US Food and Drug Administration for a first clinical study in volunteers with SCI. However, that trial sponsored by Geron failed to show signs of efficacy because of financial problems (e.g., 2008 financial crisis) [4,5].

In fact, Geron Corporation originally launched a phase I clinical trial of a human embryonic stem cell (hESC)-based therapy for SCI. The company enrolled the first patient in 2010 but stopped the trial in 2011 after transplanting only 4 volunteers. Geron announced that it was discontinuing all of its stem cell research programs (i.e., neural, cardiac, and pancreatic). Geron's president justified that abrupt change in their research activity by stating that this would save the company at least \$25 million dollars annually. The chief executive officer of Geron stated that remaining resources would be used instead for its cancer programs.

However, since then the real problems Geron has had to face have come up. Ethical, regulatory and technical problems have largely prevented that trial as well as other trials with ES cells to be undertaken or completed [6]. To circumvent these problems, neural stem cells also called neural pluripotent cells (NPCs) have been proposed. Although NPCs can specifically generate all brain cell types (i.e., and not undesired cell types) [7], limited availability and immunologic complications have remained problematic. In order to find innovative approach capable of increasing survival rates, differentiation and integration of transplanted cells [8], combinatorial therapies could be explored. Felhings and colleagues recently began to explore NPCs [9] and chondroitinase (ChABC) for enhanced NPC survival [10]. Another type of approach that could also be explored is the combination of drugs and biologics potentially capable of boosting and enhancing NPCs survival, integration, tissue repair and functional recovery after SCI. Specifically, one promising avenue could thus be the combination of NPCs with a tritherapy called Spinalon.

The latter is a CPG-activating drug in clinical development (completed phase I/IIa trial in SCI patients [11,12]) for pharmacological reactivation of sublesional spinal locomotor neurons after chronic SCI [12].

In the first clinical trial in patients with SCI, single administration of buspirone/levodopa/carbidopa (Spinalon), levodopa/carbidopa (ratio 4: 1), and buspirone or placebo was performed using a dose-escalation design in 45 subjects placed in supine position. Blood samples before and at regular intervals (15, 30, 60, 120, 240 min) after treatment were collected whereas electromyographic (EMG) activity of eight muscles (four per leg) was monitored prior to and at several time points after drug administration. Spinalon was found in that study to display no sign of safety concerns-only mild nausea was found in 3 cases. At higher doses, Spinalon was considered to have reached maximum tolerated dose (MTD) since 3 out of 4 subjects' experienced related adverse events including vomiting. PK analyses showed comparable data between groups suggesting no significant drug interaction with Spinalon. Only the Spinalon treated groups displayed significant EMG activity accompanied by locomotor like characteristics that is with rhythmic

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and bilaterally alternating bursts. Therefore, that first study in patients with SCI provided evidence of safety and preliminary efficacy following a single administration of Spinalon [13-15].

Prior to that, Spinalon had been found to trigger within minutes post administration orally 'on-demand' temporary induction of locomotor like contractions and movements in the legs of completely paraplegic mice [12]. Therefore, building upon recent evidence showing that induced-neural activity below injury level (sublesionally) in the spinal cord of thoracically-injured rats can stimulate regrowth and functional repair through the epicenter [16], one could argue that Spinalon combined with human NPCs would provide a potent environment for stem cell differentiation, integration and repair capable, in turn, of significant recovery of voluntary ambulation in paraplegic subjects. Proof-of-concept data should be sought for additional intellectual property and the conduct of additional clinical trials with such as first-in-class drugs/biologics combinatorial approach for SCI.

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