

FULL SPEAKER BIOGRAPHY and ABSTRACT

Ernest Arenas, MD, PhD
Karolinska Institute

Ernest Arenas is Professor in Stem Cell Neurobiology and Program Director at the Division of Molecular Neurobiology. His laboratory is part of three European stem cell networks, including the Neurostemcell Project.

The main current goal of his laboratory understanding the development of midbrain dopaminergic neurons and the differentiation of stem cells in order to develop regenerative therapies for Parkinson's disease. The effort of the lab is thus devoted to:

- 1) Understanding the development of midbrain dopaminergic neurons, with particular focus to the function of Wnts and glia-derived diffusible factors.
- 2) The development of protocols and tools to improve the dopaminergic differentiation of human embryonic and neural stem cells.
- 3) The development of stem cell therapies and Regenerative Medicine for Parkinson's disease.

Function of Wnt5a in dopaminergic neuron development and its application to stem cell therapies for Parkinson's disease

Wnt5a is a morphogen that activates the Wnt/planar cell polarity pathway (PCP) and serves multiple functions during development. We previously found that Wnt5a promotes differentiation of ventral midbrain (VM) dopaminergic (DA) precursors in vitro. More recently, we found that Wnt-5a activates Wnt/PCP signaling in DA cells. Moreover, analysis of the developing VM of Wnt5a^{-/-} mice revealed that Wnt5a regulates VM morphogenesis, inhibits DA progenitor proliferation, and promotes differentiation of Nurr1⁺ DA precursors in vivo. These results suggested that Wnt5a could contribute to improve current protocols for the DA differentiation of stem cells and lead us to investigate whether Wnt5a could be used to develop stem cell replacement therapies for Parkinson's Disease (PD). We first examined VM neural stem cells grown as neurospheres (VMN), expanded with basic fibroblast growth factor (bFGF), and patterned with sonic hedgehog and FGF8. These preparations generated 7-fold more DA neurons compared to conventional bFGF-treated VMNs. Similar responses have been obtained for human VMN or ES cells. Interestingly, grafting of pre-differentiated mouse VMNs revealed that Wnt5a improved the number of surviving DA neurons in vivo, the expression of Mid DA genes, and the functional recovery of parkinsonian mice. Importantly, the number of undifferentiated progenitor cells was dramatically reduced two months after grafting and no tumors were detected. Thus, our findings show that Wnt5a not only improves the efficiency of neural stem cell-derived DA neurons in vivo, but also their safety. Based on these results, we propose that Wnt5a may significantly contribute to enhance the development of stem cell replacement therapies for PD.

What is the central hypothesis of your presentation?

Wnt5a is a morphogen that is expressed in the developing ventral midbrain and, as dopamine neuron development proceeds, restricts its expression in the ventral midline. We hypothesized that Wnt5a may serve an important function in midbrain DA neuron development.

What is the most important observation you will discuss?

Our findings show that Wnt5a decreases the proliferation of dopaminergic progenitors and enhances their differentiation in development and in human ES cultures. We conclude that the knowledge gained from the function of Wnt5a during mouse development can be used to improve protocols for the dopaminergic differentiation of human embryonic stem cells.

What is the translational significance?

The translational significance is that improvements in the dopaminergic differentiation of pluripotent stem cells, may allow to improve assays for drug development and modeling of diseases involving dopamine neurons, as well as cell replacement therapies for Parkinson's disease.