



**Karolinska  
Institutet**

**Institutionen för Klinisk Neurovetenskap**

# **On Endovascular Methods for Cell Transplantation**

**AKADEMISK AVHANDLING**

som för avläggande av medicine doktorsexamen vid Karolinska  
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## ABSTRACT

*Background:* Cell based transplantation methods are a pivotal part of the emerging field of regenerative medicine. These transplantation methods could possibly produce curative treatments where, previously, expectations of such feats were low. Diseases for which treatments are evaluated are in such diverging physiological systems as e.g. the CNS with ischemic or traumatic injuries, the endocrine system with type I diabetes mellitus, or musculo-skeletal system with dystrophies, hematological system with leukemia and cardiovascular system with ischemic heart disease among others. Transplantation methods for cells span from open surgical/percutaneous, over intravenous, to specific intra-arterial methods. The method for delivery of cells is in fact an important part of the translation of cell based therapies to clinical practice. With that said, the use of endovascular techniques opens attractive routes of transplantation that needs to be thoroughly studied in order to achieve maximum efficacy.

*Methods:* We have utilized a model of traumatic brain injury in the rat where cell transplantations have been performed by selective intra-arterial methods and compared to intravenous administration. Analysis of engraftment has been performed by immunohistochemistry and cell characterization has been performed by microarray and RT-qPCR. Further, we have developed the Extroducer catheter system, a “nano”-catheter aimed for trans-vessel wall technique passage, in simulator, ex vivo, in vivo in rat and with full clinical integration in rabbit and swine. Long term follow-up studies have been performed both in rat (14 days) and rabbit (5, 30 and 80 days).

*Results and Conclusions:* We first show that selective intra-arterial methods increase engraftment levels up to fifteen-folds higher compared to intravenous controls. However, not all cell systems are found to be optimal for intra-luminal transplantation methods. Some of the factors limiting engraftment were thus explored within the cell systems themselves. These findings indicated that lack of engraftment might be dependent on integrin expression and endothelial interactions. For cells that lack the capacity of diapedesis and especially for more specific niche cell systems, such as insulin producing cells in the pancreas, the Extroducer can create direct parenchymal access via the endovascular route. Thus, the Extroducer system, developed within this thesis, offers a working channel between the proximal end of an endovascular catheter and the parenchyma of any organ of the body. Development and testing verified integration with clinical routine catheters. No long term adverse events were observed in the rat or the rabbit following the trans-vessel wall passage. In conclusion, endovascular intervention can provide a number of conceptually different methods for cell transplantation.

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