Cell therapy in management of type 1 diabetes,

An experimental animal trial

Thesis

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God bless you all

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List of Abbreviations

BM	Bone Marrow
BM-SC	Bone Marrow Stem Cells
BW	Bodyweight
CB	Cord Blood
CBE	Cord-Blood-Derived Embryonic-like Stem Cells.
CB-SC	Cord Blood-Derived Stem Cells
CJD	Creutzfeldt-Jakob disease
CMV	Cyto-Megalo Virus
EG	Embryonic Germ Cells
EPC	Endothelial Progenitor Cells
ES	Embryonic Stem
FBS	Fetal Bovine Serum
GDM	Gestational Diabetes Mellitus
HESC	Human Embryonic Stem

	Cells
HSC	Hematopoietic Stem Cells
HUCB	Human Umbilical Cord Blood
IAPP	Islet Amyloid Polypeptide
IDDM	Insulin-Dependent Diabetes Mellitus
IDF	International Diabetes Federation
IVF	In Vitro Fertilization
LCA	Human Leukocyte Antigens
MSC	Mesenchymal Stem Cells
NIDDM	Non-Insulin-Dependent Diabetes Mellitus
NO	Nitric Oxide
NOD	Non Obese Diabetic
NPH	Neutral Protamine Hagedorn
PBMC	Peripheral Blood

	Mononuclear Cells
PBS	Phosphate Buffer Saline
PD-L1	Program Death Ligand-1
PP	Pancreatic Polypeptide
RV	Right Ventricle
SCID	Severe Combined Immuno-Deficient
SS	Somatostatin
STZ	Streptozotocin
T1D	Type 1 Diabetes
TGF-B	Transforming Growth Factor-b
UCB	Umbilical Cord Blood
USSC	Unrestricted Somatic Stem Cell
VEGF-A	Vascular Endothelial Growth Factor-A

Introduction and Aim of Work

INTRODUCTION

In recent years, human umbilical cord blood (HUCB) has emerged as an attractive tool for cell-based therapy. Although, at present, the clinical application of HUCB is limited to the fields of hematology and oncology, a rising number of studies show potential for further application in the treatment of non-hematopoietic diseases **(Kogler *et al.*, 2004).**

Many reports have demonstrated a greater potential of cells present in HUCB. Umbilical cord blood is known as a rich source of hematopoietic stem cells (HSC) **(Broxmeyer *et al.*, 1989),** which makes it a valuable alternative to bone marrow (BM) transplantation in hematology and oncology **(Mayani and Lansdorp, 1998).**

In addition to the Human Stem Cells, a variety of different stem cell types have been identified within HUCB, Mesenchymal stem cells (MSC) **(Bieback *et al.*, 2004)**, endothelial stem cells (ESC) **(Murohara *et al.*, 2000)** and peripheral blood mononuclear cells (PBMC) **(Ende *et al.*, 2004).**

Although cord blood is mainly used for the treatment of malignant and genetic blood diseases, the therapeutic potential of HUCB cells can go beyond blood system therapy.

HUCB as a source of stem cells has a number of significant advantages over other stem cell sources. First of all, non-invasive collection without any risk for the donor and a real abundance. Last but not least, HUCB stem cells, unlike the more controversial embryonic stem cells, do not involve ethical issues **(Koblas *et al.*, 2005).**

In theory, pluripotent cells have the capacity to reprogram a hostile immune response to tolerate pancreatic β-cells and to regenerate pancreatic β-cell mass.

These two factors are the necessary ingredients for reversing type 1 diabetes. However, in practice there are many unanswered scientific questions that need clarification before we claim success.

In this issue, **Haller *et al.* (2009)** reported that autologous umbilical cord blood infusion into young children with type 1 diabetes. Children aged above one year old who were involved in the study were brought back for clinical, metabolic, and immunologic evaluation after umbilical cord blood transfusion. The results of this study were uniformly negative but demonstrated the safety of the procedure.

On the other hand, **Soria *et al.* (2000)** implanted one million mouse ES-derived insulin-secreting cells into the spleen of streptozotocin diabetic mice, and found normalization of blood glucose levels within a week and restoration of body weight in 4 weeks. Moreover, **Ende *et al.*, (2002)** demonstrated that transplantation of HUCB mononuclear cells into type 1 diabetic mice improved not only their glycemia but also their survival.

Aim of the work:

1. Is to study the clinical effect of injecting peripheral blood mononuclear cells (PBMC) derived from HUCB into diabetic rats.
2. To demonstrate the histological alterations of the pancreas before and after administration of the HUCB Mononuclear cells.
3. To follow immunologically the merging process of the injected cells process into the host pancreatic tissue.

Review of Literature

1- *Nomenclature of the pancreas*

The pancreas, the glucose regulating organ of the body, was first identified for western civilization by Herophilus (335–280 BC), a Greek anatomist and a surgeon. Only a few hundred years later, Rufus of Ephesus, another Greek anatomist, gave the pancreas its name. The term "pancreas" is derived from the Greek (Pan = "all", "whole"), and (creas = "flesh") it is presumed because of its fleshy consistency ***(Harper, 2007).***

Islet Formation during Embryonic Development

The involvement of islets in diabetes represented a critical discovery in pancreas physiology and naturally led investigators to study the origin of islets during pancreas embryogenesis.

In ***1895, Laguesse*** significantly contributed to this field with his work on the sheep embryo. He reported the existence of deeply stained eosinophilic cells containing granules, referred to as ‘cellules troubles’ (opaque cells). These cells, scattered within the ductal epithelium, appeared to bud from primitive tubules, proliferate and form the ‘primary islets’. According to ***Laguesse,*** primary islets were only transient and were replaced in older embryos by ‘secondary islets’ derived from secreting acini arising from the primitive tubules. ***Laguesse*** also described regression of these secondary islets and their transformation into acini, a