STEM CELLS AND TISSUE ENGINEERING IN TREATMENT OF PEDIATRIC GASTROINTESTINAL DISORDERS

Essay
Submitted for Partial Fulfillment of Master Degree In pediatrics

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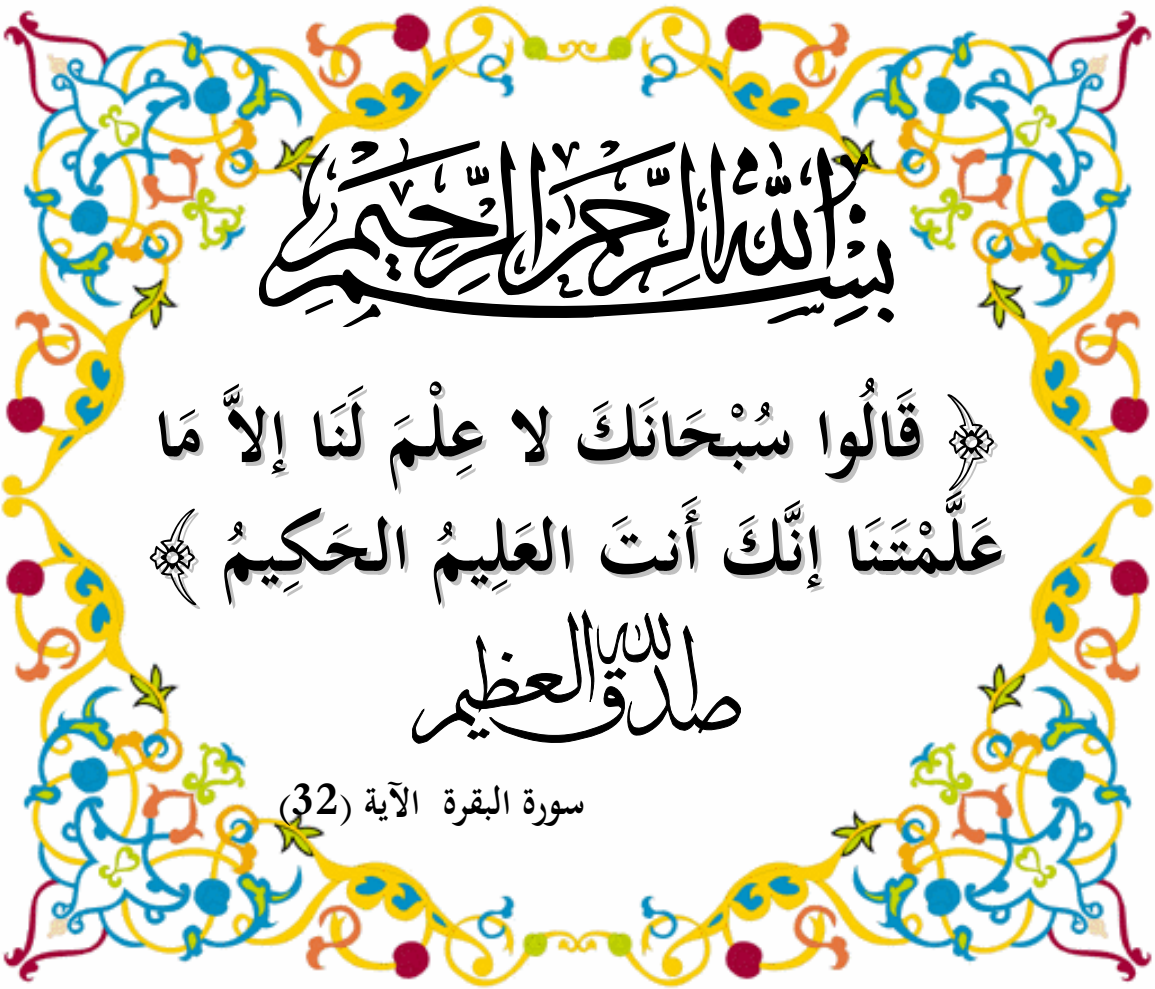
بسم الله الرحمن الرحيم
﴿ قَالُوا سُبْحَانَكَ لا عِلْمَ لَنَا إلاَّ مَا
عَلَّمْتَنَا إنَّكَ أَنتَ العَلِيمُ الحَكِيمُ ﴾
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AEA	**Anti-endomysial.**
AFS	**Amniotic fluid stem.**
AGA	**Antigliadin antibodies.**
APC	**Adenomatous polyposis coli**
ASC	**Adult stem cell.**
ASCs	**Adult stem cells.**
ASCA	**Anti-Saccharomyces cerevisiae antibody**
bFGF	**Basic fibroblast growth factor.**
BM	**Bone marrow.**
BM-SC	**Bone marrow-derived stem cell.**
BMP	**Bone morphogenic protein.**
CD	**Cluster of differentiation.**
CDAI	**Chrohn's Disease Activity Index.**
CNS	**Central nervous system.**
CD	**Crohn's disease**
Cy	**Cyclophosphamide**
DCAMKL-1	**Doublecortin and Ca M kinase-like-1**
EB	**Embryoid body.**
ECL	**Entero-chromaffin-like**
EG	**Embryonic germ**
EGF	**Epidermal growth factor.**
EGFR	**Epidermal growth factor receptor.**
ENS	**Enteric nervous system.**
ENSC	**Enteric neural stem cell.**
ES	**Embryonic stem**
ESC	**Embryonic stem cell.**
ESCs	**Embryonic stem cells.**
epiSC	**Epiblast stem cell.**
FACS	**Fluorescent activated cell sorting**

FGF	**Fibroblast growth factor.**
FSCs	**Fetal stem cells.**
G-CSF	**Granulocyte- colony stimulating factor**
GISCs	**Gastrointestinal stem cells.**
GLP-2	**Glucagon-like peptide-2**
GM-CSF	**Granulocyte-macrophage- colony stimulating factor.**
G-MRI	**Gadolinium-enhanced magnetic resonance imaging**
GVHD	**Graft-versus-host-disease.**
GVL	**Graft versus leukemia.**
HGF	**Hepatocyte growth factor.**
HLA	**Human leukocytic antigen.**
HSC	**Hematopoietic stem cell.**
HSCs	**Hematopoietic stem cells.**
HSCR	**Hirschsprung disease.**
HSCT	**Hematopoietic stem cell transplantation.**
IBD	**Inflammatory bowel disease.**
ICM	**Inner cell mass.**
I-FABP	**Fatty acid binding protein in the intestine.**
IGF	**Insulin like growth factor.**
IGFBPs	**Insulin like growth factor binding proteins.**
Ihh	**Indian hedgehog.**
IL-3	**Interleukin-3.**
IL-6	**Interleukin-6.**
IL-8	**Interleukin-8.**
iPS	**Induced pluripotent stem.**
ISCs	**Intestinal stem cells.**
IVF	**In vitro fertilization.**
KGF	**Keratinocyte growth factor.**
L-FABP	**Fatty acid binding protein in the liver.**
Lgr5	**Leucine-rich-repeat-containing G-protein-coupled receptor 5.**

LIF	**Leukemia inhibitory factor.**
ME	**Middle Eastern.**
MEF	**Mouse embryonic fibroblast.**
MEFs	**Mouse embryonic fibroblasts.**
MHC	**Major histocompatibility antigens.**
MNCF	**Mononuclear cell fraction.**
MSC	**Mesenchymal stem cell.**
MSCs	**Mesenchymal stem cells.**
NA	**North African.**
NC	**Nack cell.**
NEC	**Necrotizing enterocolitis.**
NESC	**Neuroepithelial stem cells.**
NK	**Natural killer.**
NLB	**Neurosphere like body.**
NSC	**Neural stem cell.**
OmpC	**Escherichia coli outer membrane-porin.**
pANCA	**perinuclear antineutrophil cytoplasmic antibodies**
PBSC	**Peripheral blood stem cells.**
PC	**Parietal cell.**
PN	**Parenteral nutrition.**
PSC	**Pluripotent stem cell.**
PTEN	**P-phosphatase and tensin homologue.**
RCD	**Refractory Celiac Disease.**
SC	**Stem cell.**
SBS	**Short bowel syndrome.**
SCNT	**Somatic cell nuclear transfer.**
SCT	**Stem cell transplantation.**
SIS	**Small intestinal submucosa.**
TBI	**Total body irradiation.**
TGF-β	**Transforming growth factor – β.**
Th1	**T helper cell 1**

Th2	**T helper 2**
TNF	**Tumour necrosis factor.**
tTG	**Tissue transglutaminase.**
UC	**Ulcerative colitis.**
UCB	**Umbilical cord blood.**
VEGF	**Vascular endothelial growth factor.**
VLBW	**Very low birth weight.**
WJMSCs	**Wharton's jelly mesenchymal stem cells.**
ZCs	**Zymogenic cells.**

INTRODUCTION

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Introduction

The human body comprises over 200 different cell types that are organized into tissues and organs to provide all the functions required for viability and reproduction. Historically, biologists have been interested primarily in the events that occur prior to birth. The secgond half of the twentieth century was a golden era for developmental biology, since the key regulatory pathways that control specification and morphogenesis of tissues were defined at the molecular level **(Arias, 2008)**.

In recent years, there has been an explosion of interest in stem cells, not just within the scientific and medical communities but also among politicians, religious groups and ethicists. The origins of stem cell research lie in a desire to understand how tissues are maintained in adult life, rather than how different cell types arise in the embryo. An interest in adult tissues fell, historically, within the remit of pathologists and thus tended to be considered in the context of disease, particularly cancer **(Watt and Driskell, 2010)**.

It was appreciated long ago that within a given tissue there is cellular heterogeneity: in some tissues, such as the blood, skin and intestinal epithelium, the differentiated cells have a short lifespan and are unable to self-renew. This led to

the concept that such tissues are maintained by stem cells, defined as cells with extensive renewal capacity and the ability to generate daughter cells that undergo further differentiation. Such cells generate only the differentiated lineages appropriate for the tissue in which they reside and are thus referred to as multipotent or unipotent **(Watt and Driskell, 2010)**.

New therapies, based on stem cell transplantation or endogenous stem cells, are emerging areas, as is drug discovery. Haematopoietic stem cell transplantation is the oldest stem cell therapy and is the treatment that is most widely available **(Austin et al., 2008)**.

Also, the extensive proliferation and differentiation capacities of stem cells make them optimal for seeding tissue engineered grafts **(Satija et al., 2007)**.

Furthurmore, the release of protective factors (paracrine effects) has also been shown to be beneficial to ischemic tissues **(Wang et al., 2008)**.

Pediatric gastrointestinal disorders such as inflammatory bowel disease (IBD) and necrotizing enterocolitis (NEC) are concerning sources of patient morbidity and mortality within the pediatric community. Medical management of these diseases is often suboptimal, and surgical resection of the diseased intestine may be warranted **(Markel et al., 2006)**.

In any cases, however, surgical resection leaves the patient with an inadequate length of small intestine that precludes normal nutrient and fluid absorption. These patients may therefore require long term parenteral nutritional support due to short bowel syndrome (SBS) **(Goulet and Ruemmele, 2006)**.

Moreover, parenteral nutrition increases the risk for developing parenteral nutrition-associated liver failure **(Lloyd and Gabe, 2007)**.

Research is underway to understand the mechanisms associated with the intestinal ischemia and inflammation, bacterial translocation, sepsis, and organ failure that frequently go hand-in-hand with these disorders **(Markel et al., 2008)**.

Stem cell therapy might protect injured native intestine by promoting neovascularization, while also facilitating intestinal restitution following the removal of the injuring stimulus **(Aicher et al., 2007)**.

There were several reports indicated that bone marrow derived stem cells located in the injured gastrointestinal tract and contributed to its regeneration by differentiating into functional epithelia cells or infusing with the gastrointestinal stem cells. Although the concept of cell-based therapy for various diseases of the gastrointestinal tract is widely accepted,