HAEMATOPOIETICALLY ACTIVE CYTOKINES

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MOHAMED ALI MOHAMED EID
M.B., B.Ch [1988]

SUPERVISORS

Prof. Dr. OSAIMA EL-SAID SELIM
Professor of Clinical Pathology
Faculty of Medicine
Ain-Shams University

Dr. HALA MAHMOUD HAMDY ABAZA
Lecturer of Clinical Haematology
Faculty of Medicine
Ain-Shams University

Faculty of Medicine
Ain-Shams University
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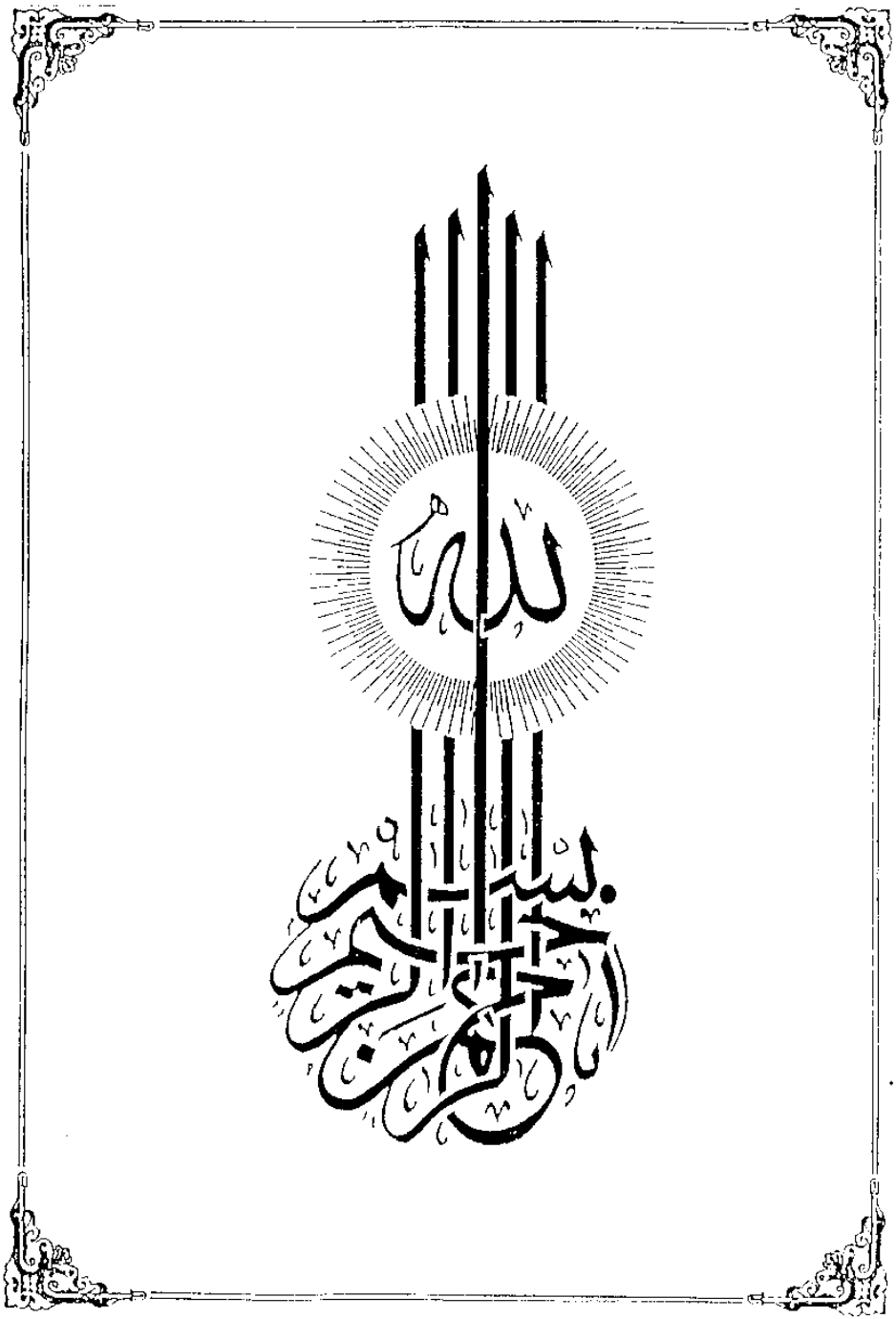

DEDICATED TO

MY

LOVELY PARENTS

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CONTENTS

LIST OF ABBREVIATIONS

BFU-E	Burst Forming Unit-Erythroid
BFU-MK	Burst Forming Unit-Megakaryocyte
BMT	Bone Marrow Transplantation
CFU-E	Colony Forming Unit-Erythroid
CFU-MK	Colony Forming Unit-Megakaryocyte
CFU-SA	Colony Forming Unit-Stimulating Activity
CR	Complete Remission
DBA	Diamond-Blackfan Anaemia
Ds RNA	Double stranded Ribonucleic Acid
ECEF	Eosinophil Cytotoxicity Enhancing Factor
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme Linked Immunosorbent Assay
EPO	Erythropoietin
G-CSF	Granulocyte-Colony Stimulating Factor
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factor
IFN	Interferon
IL	Interleukin
M-CSF	Macrophage-Colony Stimulating Factor
MDS	Myelodysplastic Syndromes
MK-CSA	Megakaryocyte-Colony Stimulating Activity
MO-ABs	Monoclonal Antibodies
PBM	Peripheral Blood Mononuclear Cells
PGE	Prostaglandin E
R hu	Recombinant human
TNF	Tumor Necrosis Factor

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

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AIM OF THE WORK

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INTRODUCTION

Cytokines are naturally occurring molecules that are produced in the body constitutively or after induction. The cytokines play a key role in the complex network of cell interactions that keep blood cell production within a normal range. The activities of natural cytokines are mimicked by recombinantly produced molecules. Both forms have been characterized as regard to their cellular production and their in-vitro and in-vivo action on normal hematopoietic cell population. (Brazmeyer et al., 1992)

Some cytokines, especially the myeloid growth factors [e.g.; granulocyte-macrophage colony stimulating factor (GM-CSF), granulocyte-CSF (G-CSF), macrophage-CSF (CSF-1), interleukin-3 (IL-3), (multi-CSF) and erythropoietin (EPO)], have multiple therapeutic potentials for the correction of breakdown in hematological control mechanisms and abnormalities in cytokine-cell interactions encountered with in many hematological disorders. Recombinant human (R hu) GM-CSF and G-CSF have been successfully used in myelodysplastic syndromes (MDS), chronic and idiopathic neutropenia, aplastic anaemia, malignancies, hairy cell

leukemia, chronic lymphocytic leukemia and other lymphoproliferative disorders (**Broxmeyer et al., 1992**). Additionally, R hu-IL-3 therapy enhances the proliferation of multi-potential and lineage-restricted progenitors when used in aplastic anaemia, MDS and bone marrow failure (**Ottmann et al., 1990**). Meanwhile, R hu-EPO is efficacious in correcting anaemia of end-stage renal disease, in preventing chemotherapy-induced anaemia and in improving anaemia of MDS, aplastic anaemia and anaemia of malignancy (**Pippard et al., 1992**).

In autologous and allogenic stem cell transplantation, R hu growth factors may be used either to expand stem/progenitor cells *in-vitro*, or to accelerate delayed engraftment (**Masaoka et al., 1990**). Moreover, the CSFs are being used to accelerate recovery of blood cells after high-dose chemotherapy (**Gianni et al., 1990**), to shorten the time intervals between chemotherapy administration to patients (**Vadhan-Raj et al., 1990**) or to enhance the proliferation of leukemic cells increasing their susceptibility to cycle-active cytotoxic agents and reducing their drug resistance (**Cannistra et al., 1991**). Additionally, the metastatic spread of tumor cells in certain animal models can be dampened by the administration of cytokines, especially when used in

conjunction with other forms of therapy. Therefore, singly or in combination with other cytokines, or with the more standard treatments of chemotherapy, irradiation or bone marrow transplantation, cytokines are beginning to make their mark as important adjunct to therapy (**Broxmeyer et al., 1992**).

AIM OF THE WORK

The aim of the present work is to review and evaluate the clinical applications of available hematopoietically active cytokines, both in-vivo and in-vitro.

REVIEW OF LITERATURE

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HEMATOPOIETICALLY ACTIVE CYTOKINES

Cytokines are naturally occurring molecules that are produced in the body constitutively or after induction. The cytokines have many biological activities on cell processes, as they stimulate, enhance or suppress the proliferation and differentiation of hematopoietic stem and progenitor cells (**Broxmeyer, 1990**). The effects of cytokines can be mediated through specific cytokine receptors on stem cells or through receptors on non-stem/progenitor accessory cells (**Broxmeyer et al., 1992**). The preparation of large quantities of highly purified recombinant cytokines has provided a basis for their biological and physico-chemical characterization. Although they are different in amino acids sequence, cytokines have a number of biological and physicochemical properties in common (**Trotta, 1991**).

Cytokine receptors:

There is a family of cytokine receptors [G-CSF, GM-CSF, EPO, IL-3, IL-4, IL-6 and the ß-chain of IL-2] that is characterized by certain structural features including four conserved cysteine residues and a double tryptophane-serine in their extracellular domains. This hematopoietic receptor