

# **Expression of Chemokine Receptor “CXCR4” as a Prognostic Factor in Acute Myeloid Leukemia**

**Thesis**

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# LIST OF ABBREVIATIONS

<b>AIDS</b>	Acquired immunodeficiency syndrome
<b>ALL</b>	Acute lymphoblastic leukemia
<b>AML</b>	Acute myeloid leukemia
<b>ANLL</b>	Acute nonlymphocytic leukemia
<b>AP</b>	Acid phosphatase
<b>APL</b>	Acute promyelocytic leukemia
<b>APL-V</b>	Acute promyelocytic leukemia- variant
<b>ATRA</b>	All-trans-retinoic acid
<b>BFGF</b>	Basic fibroblast growth factor
<b>BM</b>	Bone marrow
<b>BRCP</b>	Breast cancer resistance protein
<b>C</b>	Single cysteine residue
<b>CAE</b>	Chloroacetate esterase
<b>CAM-DR</b>	Cell adhesion-mediated drug resistance
<b>CBC</b>	Complete blood count
<b>CC</b>	Cysteine-Cysteine
<b>CD</b>	Cluster of differentiation
<b>CEC</b>	Circulating endothelial cells
<b>CGH</b>	Comparative genomic hybridization
<b>CLL</b>	Chronic lymphocytic leukemia
<b>CML</b>	Chronic myeloid leukemia
<b>CNS</b>	Central nervous system
<b>CR</b>	Complete remission
<b>CRc</b>	Complete cytogenetic remission
<b>CSF</b>	Cerebrospinal fluid
<b>CX3C</b>	Cysteine-3aa-Cysteine
<b>CX3CR1</b>	Fractalkine receptor
<b>CXC</b>	Cysteine-aa-Cysteine
<b>CXCR4</b>	CXC Chemokine receptor-4
<b>DAG</b>	Diacyl-glycerol
<b>DARC</b>	Duffy antigen
<b>DC</b>	Dendritic cell
<b>del</b>	Deletion

<b>DFS</b>	Disease free survival
<b>DIC</b>	Disseminated intravascular coagulation
<b>DNA</b>	Deoxyribonucleic acid
<b>ECM</b>	Extracellular matrix
<b>EGF</b>	Epidermal growth factor
<b>EGIL</b>	European Group for the Immunological Characterization of Leukemias
<b>ELR</b>	Three amino acid motif “Glu-Leu-Arg”
<b>EM</b>	Electron microscopy
<b>FAB</b>	French-American-British
<b>FCM</b>	Flow cytometry
<b>FISH</b>	Fluorescence in-situ hybridization
<b>FLT-3</b>	Fms-like tyrosine kinase
<b>FN</b>	Fibronectin
<b>G-CSF</b>	Granulocyte colony-stimulating factor
<b>GDP</b>	Guanosine diphosphate
<b>GM-CSF</b>	Granulocyte Monocyte Colony stimulating factor
<b>Gp</b>	Glycoprotein
<b>GPCRs</b>	G protein-coupled receptors
<b>GTP</b>	Guanosine triphosphate
<b>GVL</b>	Graft-versus-leukemia
<b>Hb</b>	Hemoglobin
<b>HIF-1<math>\alpha</math></b>	Hypoxia-inducible factor-1 alpha
<b>HIV</b>	Human immunodeficiency virus
<b>HLA</b>	Human leucocyte antigen
<b>HSCS</b>	Hematopoietic stem cells
<b>IL</b>	Interleukin
<b>INFs</b>	Interferons
<b>INF-<math>\gamma</math></b>	Interferon- $\gamma$
<b>inv</b>	Inversion
<b>IPT</b>	Immunophenotyping
<b>K</b>	Potassium
<b>Kd</b>	Kilodalton
<b>LDH</b>	Lactate dehydrogenase
<b>LESTER</b>	Leukocyte-expressed seven-transmembrane receptor
<b>LFA-1</b>	Leukocyte function-associated antigen-1

<b>LIF</b>	Leukemia inhibitory factor
<b>LM</b>	Light microscopy
<b>LN</b>	Lymph node
<b>LRP</b>	Lung resistance protein
<b>MAP</b>	Mitogen activated protein
<b>M-CSF</b>	Macrophage- Colony stimulating factor
<b>MDR</b>	Multidrug resistance
<b>MDS</b>	Myelodysplastic syndrome
<b>MGSA</b>	Melanocyte growth stimulating activity
<b>MIC</b>	Morphologic-immunologic- cytogenetic
<b>MM</b>	Multiple myeloma
<b>MoAbs</b>	Monoclonal antibodies
<b>MPNS</b>	Myeloproliferative neoplasms
<b>MPO</b>	Myelo-peroxidase
<b>MRD</b>	Minimal residual disease
<b>MSC</b>	Mesenchymal stromal cells
<b>Na</b>	Sodium
<b>NF-<sup>κ</sup>b</b>	Nuclear factor- <sup>κ</sup> b
<b>NHL</b>	Non-Hodgkin lymphoma
<b>NK</b>	Natural killer
<b>NRF-1</b>	Nuclear Respiratory Factor-1
<b>NSE</b>	Non specific estrases
<b>OS</b>	Overall survival
<b>PAS</b>	Periodic acid Schiff
<b>PB</b>	Peripheral blood
<b>PBSC</b>	Peripheral blood stem cells
<b>PBSF</b>	Pre-B-cell growth-stimulating factor
<b>PCR</b>	Polymerase chain reaction
<b>PDGF-R</b>	Platelet derived growth factor receptor
<b>Pgp</b>	P-glycoprotein
<b>Ph+</b>	Malignant Philadelphia chromosome-positive
<b>PIP<sub>2</sub></b>	Phosphatidylinositol 4, 5-biphosphate
<b>PKC</b>	Protein kinase C
<b>PLC</b>	Phospholipase C
<b>PMPs</b>	Platelet-derived microparticles
<b>PR</b>	Partial remission

<b>PRS</b>	Post remission survivals
<b>PT</b>	Prothrombin time
<b>PTT</b>	Partial thrompoblastin time
<b>PTX</b>	Pertussis toxin
<b>RAR</b>	Retinoic acid receptor
<b>Rb</b>	Retinoblastoma
<b>RCC</b>	Renal cell carcinoma
<b>RGS</b>	Regulators of G-protein signaling
<b>RNA</b>	Ribonucleic acid
<b>RT-PCR</b>	Reverse transcriptase-polymerase chain reaction
<b>SBB</b>	Sudan black-B
<b>SC</b>	Stem cell
<b>SCID</b>	Severe combined immunodeficiency
<b>SCLC</b>	Small-cell lung cancer
<b>SCT</b>	Stem cell transplantation
<b>SD</b>	Standard deviation
<b>SDF-1</b>	Stromal cell derived factor-1
<b>SKY</b>	Specral karyotyping
<b>t</b>	Translocation
<b>TdT</b>	Terminal deoxynucleotidyl transferase
<b>TGF- <math>\beta</math></b>	Transforming growth factor beta
<b>TLC</b>	Total leukocytic count
<b>TNF-<math>\alpha</math></b>	Tumor necrosis factor- $\alpha$
<b>TP53</b>	Tumor suppressor gene p53
<b>TSG</b>	Tumor Suppressor Gene
<b>VEGF</b>	Vascular endothelial growth factor
<b>VHL</b>	Von Hippel-Lindau tumor suppressor gene
<b>VLA</b>	Very late antigen
<b>WBC</b>	White blood cell
<b>WHO</b>	World Health Organization
<b>Wt-1</b>	Wilms Tumor-1 Gene
<b>YY1</b>	Ying Yang 1

## **I) INTRODUCTION**

Acute myeloid leukemia (AML) is a heterogeneous group of diseases characterized by uncontrolled proliferation of myeloid progenitor cells (**Scott et al., 2005**). The AML is an aggressive malignancy with accumulation of blast cells in bone marrow. Myeloblasts can invade peripheral blood stream, and then localize in extramedullary sites. The regulation of this process has not been clearly explained so far. However, interactions between some chemokines and their specific receptors could be one of the mechanisms responsible for such kind of migration (**Mazur et al., 2007**).

Many critical interactions among cells of the immune system are controlled by soluble mediators called “cytokines”. The cytokines are a diverse group of intercellular signaling proteins that regulate, not only local and systemic immune and inflammatory responses, but also wound healing, haemopoiesis and many other biologic processes (**Le et al., 2004**). The chemotactic cytokines, called chemokines, are a super-family of small secreted cytokines that were initially characterized through their ability to prompt the migration of leucocytes (**Koizumi et al., 2007**). They are grouped into four classes based on the position of key cysteine residue: C, CC, CXC, and CX3C (**Barbero et al., 2002**).

The CXCR4 is a G protein-linked seven trans-membrane spanning chemokine receptor that binds stromal-cell derived factor-1 (SDF-1) (**Barretina et al., 2003**). Chemokine receptor (CXCR4) is essential for homing and maintenance of haematopoietic stem cells in distinct stromal cell niches within the marrow (**Burger and Burkle, 2007**).

Recent studies have reported that SDF-1 and functional CXCR4 microparticles are implicated in the pathogenesis and progression of AML. They also proposed that CXCR4 level is potentially valuable as an additional diagnostic AML variable (**Kalinkovich et al., 2006**). The CXCR4 expression in AML is a prognostic marker that can rapidly and easily be determined at disease presentation, **Spoo et al. (2007)**, suggested the incorporation of CXCR4 into the risk assessment of AML patients.