Human Myeloid Inhibitory C-Lectin (hMICL): A Novel Acute Myeloid Leukemia Marker

Thesis
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سي- ليكتين المثبط النقوي البشري (hMICL) :

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List of Abbreviations

ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
APL	Acute Promyelocytic Leukemia
ATRA	All-Trans-Retinoic Acid
BAALC	Brain And Acute Leukemia Cytoplasmic Gene
BM	Bone Marrow
BSA	Bovine Serum Albumin
CAE	Chloroacetate Esterase
CBC	Complete Blood Count
CCR7	Chemokine (C-C Motif) Receptor 7
CD	Cluster of Differentiation
CEBPA	CCAAT/Enhancer Binding Protein
CLEC	C-Type Lectin-Like Receptor
CLEC12A	C-Type Lectin Domain Family 12 MemberA
CLL-1	C-Type Lectin-Like Molecule-1
CLR	C-Type Lectin-Like Receptor
CML	Chronic Myeloid Leukemia
CNS	Central Nervous System
CR	Complete Remission
CTLDs	C-Type Lectin-Like Domains
Cy5	Cyanin 5
DC	Dendritic Cells
DCAL-2	Dendritic Cell-Associated Lectin 2
DIC	Disseminated Intravascular Coagulopathy
EDTA	Ethylene Diamine Tetra-Acetic Acid
ELISA	Enzyme Linked Immunosorbent Assay
EM	Electron Microscopy
ERG	Erythroblastosis Virus E26 Oncogene-Like (Avian)
FAB	French-American-British
FAV	Favorable
FCM	Flowcytometry
Fig	Figure

FISH	Fluorescence In Situ Hybridization
FITC	Fluorescein Isothiocyanate
FLT-3	Fms-Related Tyrosine Kinase3
Hb	Hemoglobin
HLA	Human leukocyte antigen
hMICL	Human Myeloid Inhibitory C-Lectin
HS	Highly Significant
IP	Immunophenotyping
ITIM	Immunotyrosine-Based Inhibition Motif
KLRL1	Killer Lectin Like Receptor 1
LAIPs	Leukemia-Associated Immunophenotypes
LM	Light Microscopy
LOX-1	Low Density Lipoprotein-1
MFI	Mean Fluorescence Intensity
MLL	Myeloid Lymphoid Or Mixed Lineage Leukemia
MoAb	Monoclonal Antibody
MPAL	Mixed Phenotype Acute Leukemias
MPO	Myeloperoxidase
MRD	Minimal Residual Disease
NA	Sodium
NEC	Nonerythroid Cells
NKC	Natural Killer Complex
NKCL	NK-Like C-Type Lectin-Like Receptors
NPM-1	Nucleophosmin-1
NS	Non Significant
NSE	Nonspecific Esterase
p	Probability Of Chance
PAS	Periodic Acid Schiff
PB	Peripheral Blood
PBS	Phosphate Buffered Saline
PE	Phycoerythrin
PLT	Platelets
PT	Prothrombin Time
PTT	Partial Thrompoblastin Time
ROC	Receiver Operating Characteristic

RT-PCR	Reverse Transcription Polymerase Chain Reaction
S	Significant
SBB	Sudan Black B
SCT	Stem Cell Transplantation
SHIP	Src Homology-2 Domain-Containing Inositol Phosphatase
SHP	Src Homology-2 Domain-Containing Tyrosine Phosphatase
SPSS	Statistical Package For Social Science
TdT	Terminal Deoxynucleotidyl Transferase
TLC	Total Leukocytic Count
TSG	Tumor Suppressor Genes
WHO	World Health Organization

Introduction

Acute myeloid leukemia (AML) is the most common acute leukemia affecting adults and its incidence increases with age. The prognosis of AML is poor, primarily because of the relapses occurring on conventional chemotherapy regimens. The overall 5-year leukemia-free survival rate is only 25-35% and even lower in patients over 60 years old **(Zhao et al., 2010).** Therefore, alternative strategies are needed to complement the currently used chemotherapy treatment protocols **(Bakker et al., 2004).**

In the absence of leukemia specific markers, the distinction between leukemic and normal immature cells relies on the expression of antigen combinations defining leukemia-associated immunophenotypes (LAIPs), which are absent or extremely infrequent in normal bone marrow **(Al-Mawali et al., 2008).** However, evidence in the literature has outlined that these LAIPs are very different from patient to patient and they are not necessarily stable over the course of the disease **(Voskova et al., 2004).** Consequently, there is still a need for the identification of new antigens contributing to diagnostic and prognostic information, improving relapse detection, identification and ideally eradication of leukemic stem cells through antibody mediated therapy **(Larsen et al., 2012).**

The Human Myeloid Inhibitory C-Lectin (hMICL) also known as Human C-type lectin-like molecule-1 (CLL-1), or C-type lectin domain family 12 member A (CLEC12A), is a type II transmembrane glycoprotein and member of the large family of C-type lectin-like receptors involved in immune regulation **(Zhao et al., 2010).** The hMICL is a pan-myeloid antigen that is absent on normal uncommitted primitive $CD34^{+}$ $CD38^{-}$ or $CD34^{+}$ $CD33^{-}$ stem cells; which aids the discrimination between normal and leukemic stem cells, as well as introduces hMICL as a promising therapeutic target for eradication of antigen-bearing leukemic cells and the subsequent re-establishment of normal hematopoiesis through the remaining normal stem cells **(Bakker et al., 2004).**

Aim of Work

The aim of this work is to determine the diagnostic impact and the applicability of the Human Myeloid Inhibitory C-Lectin (hMICL) in routine clinical flowcytometry for the diagnosis of Acute Myeloid Leukemia (AML).

Chapter 1

ACUTE MYELOID LEUKEMIA

A) DEFINITION:

Acute myeloid leukemia (AML, also known as acute myelogenous leukemia and, less commonly, as acute non-lymphocytic leukemia) consists of a group of relatively well-defined hematopoietic neoplasms involving precursor cells committed to the myeloid line of cellular development (i.e., those giving rise to granulocytic, monocytic, erythroid, or megakaryocytic elements) **(Schiffer et al., 2010).**

B) EPIDIMIOLOGY:

AML is a highly malignant neoplasm responsible for a large number of cancer-related deaths **(Deschler and Lübbert, 2006)**.

1) *Incidence:* AML counts for 15 to 20 percent of the acute leukemias in children and 80 percent of acute leukemias in adults **(Lichtman and Liesveld, 2006).**

2) *Age:* The AML is the predominant form of leukemia during the neonatal period, but it represents < 15% of cases of leukemia in children under 10 years and 25 to 35% between ages 10 and 15 years. While in adults it represents