Molecular Targets For Therapy In Acute Leukemia

Essay

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In Clinical Pathology

By

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DEDICATION

To …….

My Mother,

My Father,

My Husband,

My Children

And

My Friends

Neven & Iman

List of Abbreviations

(-)	**:** Loss of chromosome
(+)	**:** Gain of chromosome
ABL	**:** Ableson Tyrosine Kinase Gene
AL	**:** Acute Leukemia
ALL	**:** Acute Lymphoblastic Leukemia
AML	**:** Acute Myeloid Leukemia
AP	**:** Acid phosphatase
APaF-1	: Apoptotic protease activating factor 1
APL	**:** Acute promyelocytic leukemia
aPTT	**:** Activated partial thromboplastin time
ATM gene	**:** Ataxia Teleangiectasia Mutated gene
ATP	**:** Adenosine Triphosphate
ATRA	**:** All Trans Retinoic Acid
BA	**:** Break-Apart Probe
BCL	**:** B-cell lymphoma/leukemia
BCR	**:** Breakpoint Cluster Region
BCRP	**:** Breast Cancer Resistance Protein
BCSH	**:** British Committee for Standards in Haematology
BFM group	**:** Berlin–Frankfurt–Münster group
CAN	**:** Candida gene
CBF	**:** Core Binding Factor
CBFα	**:** Core Binding Factor Alpha Subunit
CBFβ	**:** Core Binding Factor Beta Subunit
CC	**:** Conventional Cytogenetics
CD	**:** Cluster Of Differentiation
CDKs	**:** Cyclin-Dependent Kinases
cDNA	**:**Complementary deoxyribonucleic acid
CEBP (CBP)	**:** CCAAT-Enhancer-Binding-Protein
CEPs	**:** Centromere-Enumerating Probes
CESH	**:** Comparative Expressed Sequence Hybridization
CGH	**:** Comparative Genomic Hybridization
CKIs	**:** Cyclin-Dependent Kinases Inhibitors
CMV	**:** Cytomegalo Virus
CNS	**:** Central Nervous System
CR	**:** Complete Remission
CRBP	**:** Cellular Retinol-Binding Protein-I Gene
CSF	**:** Cerebro Spinal Fluid

List of Abbreviations (Cont.)

CSF-I	**:** Colon Stimulating Factor –I
DAC	**:** Deoxy Azacytidine
DAPK	**:** Death-associated protein kinase
DDX10	**:** DEAD box proteins
DEK gene	**:** Dog Embryo Kidney gene
Del	: Deletion
DFS	: Disease Free Survival
Diablo	: Direct IAP binding with low PI
DIC	**:** Disseminated Intravascular Coagulopathy
DNA	**:** Deoxyribonucleic Acid
E2F	**:** Transcription factor family inducing E_2F
EBV	**:** Epstein Barr Virus
ECOG	: Eastern Co-operative Oncology Group
EGIL	**:** European Group for the Immunological
ERK	**:** Extracellular Signal Regulated Kinase
ETO	**:** Eight Twenty-One gene
EVI1	**:** Ecotropic Viral Integration site 1
FAB	**:** French–American–British
FC	: Flow Cytometry
FDA	**:** Food and Drug Administration
FISH	**:** Fluorescence In Situ Hybridization
FLT3	**:** FMS-Like Tyrosine Kinase 3
FOX	**:** Forkhead-box gene
FTI	**:** Farynesyl Transferase Inhibitors
GIMEMA	: Gruppo Italiano Malattie Ematologiche Maligne dell'
GO	**:** Gemtuzumab Ozogamicin
HDACs	**:** Histone Deacetylases
HIV	**:** Human Immune Deficiency Virus
HLA	**:** Human Leucocyte Antigens
HMBA	**:** Hexamethylene Bisacetamide
HOX genes	**:** Homeobox Genes
HSV	**:** Herpes Simplex Virus
HTLV-I	**:** Human T-cell Leukemia Virus type –I
Htr A2	: High temperature requirement serine protease A2
Ig	**:** Immunoglobulin
IGH	**:** Immunoglobulin Heavy Chain Gene
Ins	**:** Insertions
Inv	**:** Inversions
ISSR	**:** Intersequence-Specific PCR
ITD	**:** Internal Tandem Duplications

List of Abbreviations (Cont.)

JAK	**:** Janus Family Of Cytosolic Tyrosine Kinases
lAPs	**:** Inhibitor Of Apoptosis Proteins
LATE-PCR	**:** Linear-After-The-Exponential-Pcr
LDH	**:** Lactate Dehydrogenase
LRP	**:** Lung Resist Protein
MAL	**:** Megakaryocytic Acute Leukemia
MDR1	**:** Multi- Drug Resistance Gene
MDS	**:** Myelodysplastic Syndrome
MEK	**:** Mitogen / Extracellular-Signal Regulated Kinase
M-FISH	**:** Multiplex Metaphase FISH
MGF	**:** Mast Cell Growth Factor
miRNA	**:** MicroRNA
MKK	**:** Map Kinase Kinase
MLL	**:** Mixed Lineage Leukemia or Myeloid/Lymphoid Leukemia Gene
MLPA	: Multiplex Ligation-Dependent Probe Amplification
moAbs	**:** Monoclonal Antibodies
MOZ	**:** Monocytic Leukemia Zinc Finger Protein Gene
MPO	**:** Myeloperoxidase
MRC	: Medical Research Council
MRP1	**:** Multi- drug resistance-associated protein 1
MSP	**:** Methylation-specific PCR
mTOR	**:** Mammalian target of rapamycin
MUM1 (IRF4)	: Multiple myeloma 1 or interferon regulatory factor 4
MYC	**:** Myelocytomatosis viral oncogene
NCI	**:** National Cancer Institute
NFkB	: Nuclear factor B
NPM	**:** Nucleophosmin
NSE	**:** Non specific esterase
NUP98	**:** Nucleoporin gene
OS	: Overall Survival
OTT	**:** One Twenty Two gene
P	**:** Short Arm Of Chromosome
P21	**:** Protein 21 kDa
P53	**:** Protein 53
PCM1	**:** Human Autoantigen Pericentriolar Material
PCR	**:** Polymerase Chain Reaction
PDGFA	**:** Platelet DERIVED Growth Factors Family
Pi3AKT	**:** Phosphoinositol Inositol 3-Kinase
PKC412	**:** Protein Tyrosine Kinase Inhibitor

List of Abbreviations (Cont.)

PKCα	**:** Protein Kinase α
PLZF	**:** Promyelocytic Leukemia Zinc Finger
PT	**:** Prothrombin Time
q	**:** Long Arm Of Chromosome
Q-PCR	**:** Quantitative PCR
RARa	**:** Retinoic Acid Receptor-**a**
RAS	**:** Retinoic Acid Syndrome
RB1	**:** Retinoblastoma Gene
RISC	**:** RNA-induced silencing complex
RITS	**:** RNA-induced transcriptional silencing
RNA	**:** Ribonucleic Acid
RQ-PCR	**:** Real-Time PCR
RTK	**:** Receptor Tyrosine Kinase
RT-PCR	**:** Reverse Transcriptase
RUNX1	**:** Runt-related transcription factor 1 (Synonyms: AML,CBFA2)
SAHA	**:** Suberoylanilide Hydroxamic Acid
SBB	**:** Sudan black B
SCT	**:** Autologous Stem Cell Transplantation
shRNA	**:** Short Hairpin RNA
siRNA	**:** Interference RNA
SKY	**:** Spectral Karyotyping
Sm	**:** Surface Membrane
SMAC	: Second mitochondria derived activator of caspase
SMMHC	: Smooth Muscle Myosin Heavy Chain gene(MYH 11)
SNP	**:** Single Nucleotide Polymorphism
STAT	**:** Signal Transducer and Activator of Transcription proteins
t	**:** Translocations
TCR	**:** T-Cell Receptor Gene Rearrangements
TCRB	**:** T-cell receptor B gene
TdT	**:** Terminal Deoxynucleotidyl Transferase
TGFB1	**:** Fibroblast Growth Factors
TNFalpha	**:** Tumor Necrosis Factor Alpha
trx	**:** Drosophilia Trithorax
VDR	: Vitamin D receptor
WCPs	**:** Whole Chromosome Probes
WHO	**:** World Health Organization
WT1	**:** Wilms' tumor gene

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INTRODUCTION

It's increasingly evident that molecular diagnostics will be pivotal in the delivery of safe and effective therapy for many diseases in the future. A huge body of new information on the genetic, genomic and proteomic profiles of different hematopoietic diseases is accumulating ***(Braziel et al., 2003)***.

In patients with acute leukemia there have been different risks groups identified, which are mainly based on molecular subtype (i.e., genetic subtype and immune phenotype); patients still relapse within these apparent homogeneous subgroups. Recent researches aimed to identify genes and proteins that improve risk group classification based on molecular subtype and risk to relapse as well as to identify causes of cellular drug resistance and therapy failures ***(Pieters et al., 2004)***.

The realization of molecular signaling pathways that ultimately lead to cell proliferation and growth were largely unrecognized, underscored the importance of identifying molecular target specific therapy that would provide the potential of maximal therapeutic benefit while minimizing toxicity to normal cells ***(Lander et al., 2001)***.

It has become evident that the new discovery and treatment paradigm oncology involves both the identification of critical genes and proteins involved in cell division and growth;

and the fully characterization of the micro environment in which these genes control molecular switches ***(Laheru, 2003)*.**

Several molecular targets for therapy were identified through research activities involving drug resistance profiles, collaborative gene expression profiling studies and others. The targets identified were varied e.g. the Tyrosine Kinase receptor, FLT3 ***(Pieters et al., 2004)***, molecular defect associated with the constitutively active Tyrosine Kinase fusion protein bcr/abl, the activating RAF mutations … and others ***(Liang et al., 2003)*.**