

# **Molecular Targets For Therapy In Acute Leukemia**

***Essay***

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***By***

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## **DEDICATION**

To .....

**My Mother,**

**My Father,**

**My Husband,**

**My Children**

**And**

**My Friends**

**Neven & Iman**

## List of Abbreviations

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

## **List of Abbreviations (Cont.)**

|                  |                                                         |
|------------------|---------------------------------------------------------|
| <b>CSF-I</b>     | : Colon Stimulating Factor –I                           |
| <b>DAC</b>       | : Deoxy Azacytidine                                     |
| <b>DAPK</b>      | : Death-associated protein kinase                       |
| <b>DDX10</b>     | : DEAD box proteins                                     |
| <b>DEK gene</b>  | : Dog Embryo Kidney gene                                |
| <b>Del</b>       | : Deletion                                              |
| <b>DFS</b>       | : Disease Free Survival                                 |
| <b>Diablo</b>    | : Direct IAP binding with low PI                        |
| <b>DIC</b>       | : Disseminated Intravascular Coagulopathy               |
| <b>DNA</b>       | : Deoxyribonucleic Acid                                 |
| <b>E2F</b>       | : Transcription factor family inducing E <sub>2</sub> F |
| <b>EBV</b>       | : Epstein Barr Virus                                    |
| <b>ECOG</b>      | : Eastern Co-operative Oncology Group                   |
| <b>EGIL</b>      | : European Group for the Immunological                  |
| <b>ERK</b>       | : Extracellular Signal Regulated Kinase                 |
| <b>ETO</b>       | : Eight Twenty-One gene                                 |
| <b>EVI1</b>      | : Ecotropic Viral Integration site 1                    |
| <b>FAB</b>       | : French–American–British                               |
| <b>FC</b>        | : Flow Cytometry                                        |
| <b>FDA</b>       | : Food and Drug Administration                          |
| <b>FISH</b>      | : Fluorescence In Situ Hybridization                    |
| <b>FLT3</b>      | : FMS-Like Tyrosine Kinase 3                            |
| <b>FOX</b>       | : Forkhead-box gene                                     |
| <b>FTI</b>       | : Farnesyl Transferase Inhibitors                       |
| <b>GIMEMA</b>    | : Gruppo Italiano Malattie Ematologiche Maligne dell'   |
| <b>GO</b>        | : Gemtuzumab Ozogamicin                                 |
| <b>HDACs</b>     | : Histone Deacetylases                                  |
| <b>HIV</b>       | : Human Immune Deficiency Virus                         |
| <b>HLA</b>       | : Human Leucocyte Antigens                              |
| <b>HMBA</b>      | : Hexamethylene Bisacetamide                            |
| <b>HOX genes</b> | : Homeobox Genes                                        |
| <b>HSV</b>       | : Herpes Simplex Virus                                  |
| <b>HTLV-I</b>    | : Human T-cell Leukemia Virus type –I                   |
| <b>Htr A2</b>    | : High temperature requirement serine protease A2       |
| <b>Ig</b>        | : Immunoglobulin                                        |
| <b>IGH</b>       | : Immunoglobulin Heavy Chain Gene                       |
| <b>Ins</b>       | : Insertions                                            |
| <b>Inv</b>       | : Inversions                                            |
| <b>ISSR</b>      | : Intersequence-Specific PCR                            |
| <b>ITD</b>       | : Internal Tandem Duplications                          |

## **List of Abbreviations (Cont.)**

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

## **List of Abbreviations (Cont.)**

|                               |                                                                |
|-------------------------------|----------------------------------------------------------------|
| <b>PKC<math>\alpha</math></b> | : Protein Kinase $\alpha$                                      |
| <b>PLZF</b>                   | : Promyelocytic Leukemia Zinc Finger                           |
| <b>PT</b>                     | : Prothrombin Time                                             |
| <b>q</b>                      | : Long Arm Of Chromosome                                       |
| <b>Q-PCR</b>                  | : Quantitative PCR                                             |
| <b>RAR<math>\alpha</math></b> | : Retinoic Acid Receptor- $\alpha$                             |
| <b>RAS</b>                    | : Retinoic Acid Syndrome                                       |
| <b>RB1</b>                    | : Retinoblastoma Gene                                          |
| <b>RISC</b>                   | : RNA-induced silencing complex                                |
| <b>RITS</b>                   | : RNA-induced transcriptional silencing                        |
| <b>RNA</b>                    | : Ribonucleic Acid                                             |
| <b>RQ-PCR</b>                 | : Real-Time PCR                                                |
| <b>RTK</b>                    | : Receptor Tyrosine Kinase                                     |
| <b>RT-PCR</b>                 | : Reverse Transcriptase                                        |
| <b>RUNX1</b>                  | : Runt-related transcription factor 1<br>(Synonyms: AML,CBFA2) |
| <b>SAHA</b>                   | : Suberoylanilide Hydroxamic Acid                              |
| <b>SBB</b>                    | : Sudan black B                                                |
| <b>SCT</b>                    | : Autologous Stem Cell Transplantation                         |
| <b>shRNA</b>                  | : Short Hairpin RNA                                            |
| <b>siRNA</b>                  | : Interference RNA                                             |
| <b>SKY</b>                    | : Spectral Karyotyping                                         |
| <b>Sm</b>                     | : Surface Membrane                                             |
| <b>SMAC</b>                   | : Second mitochondria derived activator of<br>caspase          |
| <b>SMMHC</b>                  | : Smooth Muscle Myosin Heavy Chain<br>gene(MYH 11)             |
| <b>SNP</b>                    | : Single Nucleotide Polymorphism                               |
| <b>STAT</b>                   | : Signal Transducer and Activator of<br>Transcription proteins |
| <b>t</b>                      | : Translocations                                               |
| <b>TCR</b>                    | : T-Cell Receptor Gene Rearrangements                          |
| <b>TCRB</b>                   | : T-cell receptor B gene                                       |
| <b>TdT</b>                    | : Terminal Deoxynucleotidyl Transferase                        |
| <b>TGFB1</b>                  | : Fibroblast Growth Factors                                    |
| <b>TNF<math>\alpha</math></b> | : Tumor Necrosis Factor Alpha                                  |
| <b>trx</b>                    | : Drosophila Trithorax                                         |
| <b>VDR</b>                    | : Vitamin D receptor                                           |
| <b>WCPs</b>                   | : Whole Chromosome Probes                                      |
| <b>WHO</b>                    | : World Health Organization                                    |
| <b>WT1</b>                    | : 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**).