THE ROLE OF FLT3 IN HEMOPOIESIS AND LEUKEMIA

Essay

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Submitted by

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List of abbreviation

AKT	**Protein kinase B**
ALL	**Acute lymphocytic leukemia**
ALM	**Activation loop mutation**
AML	**Acute myeloid leukemia**
ANOVA	**Analysis of variance**
APL	**Acute promyelocytic leukemia**
AR	**Autosomal recessive**
ATP	**Adenosine triphosphate**
ATRA	**All *trans*-retinoic acid**
BCR	**Breakpoint cluster region**
BM	**Bone marrow**
BMT	**Bone marrow transplantation**
CCG	**Children's cooperative group**
CML	**Chronic myeloid leukemia**
CR	**Complete remission**
DC	**Dendritic cells**
DFS	**Disease free survival**
DIC	**Disseminated intravascular Coagulopathy**
ECD	**Extracellular domain**
EFS	**Event free survival**
EGF	**Epidermal growth factor**
EPH B2	**Type of receptor**
ERK 1/2	**Extracellular signal regulated kinase1 and 2**
FAB	**French American British**
FGFR1	**Fibroblast growth factor 1 receptor**
FISH	**Fluorescence insitu hypridization**
FLK	**Fetal liver kinase**
FLT3	**Fetal liver tyrosine kinase 3** **Fms-like tyrosine kinase 3**
G-CSF	**Granulocyte colony stimulating factor**
GM-CSF	**Granulocyte-Macrophage colony stimulating factor**

List of abbreviation

GVL	**Graft versus leukemia**
IGFIR	**Insulin like growth factor 1 receptor**
ITD	**Internal tandem duplication**
JM	**Juxtamembrane domain**
KD	**Kinase domain**
KI	**Kinase insert**
LDH	**Lactate dehydrogenase**
LOH	**Loss of heterozygosity**
LSC	**Leukemic stem cell**
MAPK	**Mitogen activated protein kinase**
MDS	**Myelodysplastic syndrome**
MLL	**Mixed lineage leukemia**
MPD	**Myeloproliferative disorders**
MRD	**Minimal residual disease**
MS	**Myeloid sarcoma**
NK	**Natural killer cells**
OS	**Overall survival**
PB	**Peripheral blood**
PCA	**Principle component analysis**
PDGF	**Platelet derived growth factor**
PFS	**Progression free survival**
PI 3K	**Phosphoinositide-3-kinase**
RARα	**Type of gene**
RR	**Relative risk**
RTK	**Receptor tyrosine kinase**
SCT	**Stemcell transplantation**
SCTK-1	**Stemcell tyrosine kinase-1**
STAT5	**Signal transducer and activator of transcript**
TK	**Tyrosine kinase**
TKD	**Tyrosine kinase domain**
TM	**Transmembrane domain**
UK MRC	**United Kingdom medical research council**

List of abbreviation

UPN	**Unique patient numbers**
VEGF-R2	**Vascular endothelial growth factor receptor 2**
WnT	**Wingless type**
WT	**Wild type**

INTRODUCTION

FLT3 (Fms-like tyrosine kinase 3) is a receptor tyrosine kinase expressed in a variety of human cell line of both myeloid and B lymphoid lineage **(Brasel *et al.*, 1995; Turner *et al.*, 1996; Gilliland and Griffin, 2002; Steven Knapper, 2007).**

It is also expressed at high levels in a spectrum of hematological malignancies including 70%-100% of AML (acute myeloid leukemia) of FAB (French-American-British) subtypes, B precursor cell of ALL (Acute Lymphocytic Leukemia), a fraction of T cell ALL & CML (Chronic Myeloid Leukemia) in lymphoid blast crisis as well as myeloid sarcoma **(Rasko *et al.*, 1995; Rosnet *et al.*, 1996; Steven Knapper, 2007).**

FLT3 gene encodes a 993 amino acid protein in humans and is expressed in hemopoeitic cells, placenta, gonads and brain **(Rosnet *et al.*, 1993; Ana Marcovic et al., 2005; Steven Knapper, 2007).**

FL is a type I transmembrane (TM) protein that can be released as a soluble homodimeric protein **(Gilliland and Griffin, 2002).** It encodes a 235 amino acid. FL is expressed in cells of hemopoeitic bone marrow microenvironment including bone marrow fibroblasts as well as hemopoeitic cell lines of myeloid and B and T cell lineage **(Gilliland and Griffin,**

2002). FL acts in synergy with other cytokines to promote expansion of hematopoeitic precursors **(Levis *et al*., 2003).**

FLT3 ligand was found to have several functions includes activation of FLT3, it has a role in immune response and it has an antitumor effect.

Mutations of FLT3 have been detected in about 30% of patients with AML and might play an important role in pathogenesis of AML. Again it is detected in a small number of patients with ALL and MDS and those patients' tend to have poor prognosis in both pediatrics and adults **(Frohling *et al*., 2001).**

The expression of mutant FLT3 receptor in marrow cells result in a lethal myeloproliferative syndrome and preliminary studies suggest that mutant FLT3 cooperates with other leukemia oncogenes to confer a more aggressive phenotype **(Levis *et al*., 2002).**

These results suggest that FLT3is an attractive therapeutic target for kinase inhibitors or other approaches for patients with mutations of this gene.

Mutations in two hot spots of the FLT3 gene lead to autoactivation of the receptor. First, internal tandem duplications in the juxtamembrane region of the receptor **(FLT3/ITD)**. Second, mutations is the activation loop, which is

located in the second kinase domain. Point mutations, deletions or small insertions are found at Asp835 **(Dirk *et al*., 2004; Steven Knapper, 2007).**

It have been demonstrated that FLT3/ITD mutations occur in a subset of patients with myeloid sarcoma. This is of potential importance because several small molecule inhibitors of FLT3 have been developed and are currently in early clinical trials as potential therapeutic agents for AML with FLT3 mutations. **(Levis *et al*., 2003).**

FLT3-specific antibodies may be useful not only in treating leukemia patients with FLT3/ITD mutations but also in treating those with associated overexpression of the wild-type FLT3 allele. IMC-EB10, as an efficacious and apparently nontoxic FLT3 inhibitor, especially those for whom cytotoxic chemotherapy has failed or those who are too old for more intensive treatment regimens, such as bone marrow transplantation.

Moreover, anti-FLT3 antibody-based therapy may have synergistic effects when combined with other therapies, such as cytotoxic chemotherapy **(Prewett *et al*., 2002; Yiwen *et al*., 2004)**.

Aim of work

The aim of this work is to elucidate the role of FLT3 mutation in hemopoeisis and leukemia regarding pathogenesis, prognosis and treatment.

THE ROLE OF FLT3 IN HEMOPOEISIS AND LEUKEMIA

FLT3 (FMS-like tyrosine kinase 3) is a Receptor Tyrosine Kinase (RTK) which is expressed by immature hemopoeitic cells and is important for the normal development of stem cells and the immune system**.** FLT3 is also known as FLK-2 (Fetal liver kinase-2) and STK-1 (Human stem cell kinase-1), FLT3 was cloned independently by 2 groups in 1991 **(Mathews *et al*., 1991; Rosnet *et al*.,1991a; Rosnet *et al*., 1991b; Gilliland and Griffin, 2002; Steven Knapper, 2007; Kyu-Tae Kim *et al*., 2007)**.

FLT3 has a strong sequence similarities with other members of class III receptor tyrosine kinase (RTKIII), a receptor family including FMS, FLT3 PDGFR, KIT which are characterized by an extracellular domain comprised of 5 immunoglobulin like (Ig-like) domains, a juxtamembrane domain and 2 kinase domain (KD5) interrupted by a kinase insert **(Rosnet *et al*., 1993; Agnes *et al*., 1994; Gilliland and Griffin, 2002; Steven Knapper, 2007).**