

Sadegh Babashah *Editor*

Cancer Stem Cells: Emerging Concepts and Future Perspectives in Translational Oncology

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I would like to dedicate this book to my dear wife for her patience, intellect and adventurous spirit. Her continued support and ongoing encouragement were great sources of inspiration when I spent time working on this project.

I also dedicate this book to my invaluable teachers and advisors Prof. Majid Sadeghizadeh and Prof. Sirous Zeinali, the pioneers of molecular biology and medicine in Iran.

And finally, I dedicate this book to those who pursue their dreams with passion and determination despite the many daunting hurdles and pressures they face.

Preface

The CSC theory posits tumor development might arise from a rare population of cells that show the stem cell-like properties. This theory was initially formulated approximately 150 years ago. The recent decade studies have tremendously advanced our understanding of the molecular pathogenesis of cancer. CSCs have been demonstrated to underlie resistance to conventional chemotherapeutics resulting in tumor recurrence and poor prognosis. In this context, the need to develop novel approaches for eradicating CSCs in order to inhibit tumor recurrence is considered as a major challenge in cancer treatment. Novel compounds precisely designed to eliminate CSCs or affect their microenvironment, and administered in concert with conventional chemotherapy, can lead to tumor bulk shrinkage and ablate resistance and relapse. Importantly, the number of preclinical investigations and clinical trials examining the potential use of anti-CSC drugs has grown exponentially in recent years. Despite all efforts made to develop CSC-targeted therapy, further investigations to identify the specific biological characteristics of CSCs could help us in better understanding the origin and molecular behavior of cancer. This lays a solid foundation to program and perform a more specific, safe, effective, “personalized,” and “targeted” therapeutic plan.

This book *Cancer Stem Cells: Emerging Concepts and Future Perspectives in Translational Oncology* aims to offer a broad framework for obtaining insight into the state-of-the-art knowledge of CSC biology and function and outline novel approaches for targeting CSCs. These revelations highlight the therapeutic implications of these cells in the future of clinical oncology. This book was scrupulously designed and explicitly written being well suited for graduate students, postdoctoral fellows, and all researchers who are studying different aspects of experimental oncology. Ranging from the fundamental concepts to clinical implications, this book is composed of nineteen chapters organized in three parts. The first part is devoted to delving deep into the biology of CSCs. Chapter 1 serves as an emblem of the whole book and presents a quick walk through the concepts. This chapter deals exclusively with CSC hypothesis and tumor heterogeneity models and highlights the importance of targeting CSCs for cancer therapy. Chapter 2 describes the principal mechanisms of tumor progression and metastasis, focusing in particular

on contribution of defined molecular constituents of metastatic niche to CSC physiology. Given that a link has been established between cytokine networks and cancer development, Chap. 3 aims to explore the contribution of key cytokines to the CSC phenotype in terms of survival and maintenance. By delineating the importance of chemokines as major modulators of tumor microenvironment, Chap. 4 details recent findings on the roles of CXCR4/CXCL12 chemokine axis for tumor progression, CSC maintenance, and its potential translation into therapeutic targeting. In Chap. 5, the general features of CSCs and the roles of noncoding RNAs, especially microRNAs and long noncoding RNAs, in the regulation of CSC properties are discussed. In addition, current therapeutic strategies aimed at regulating noncoding RNAs for the purpose of CSC therapy are summarized. As stem cells might be the targets of transformation during carcinogenesis, Chap. 6 provides evidence that stemness pathways are dysregulated due to accumulated mutations and epigenetic alterations. This chapter lends support to the concept that breast carcinogenesis results from dysregulation of self-renewal pathways of normal mammary stem cells. The second part of the book summarizes recent advances in the study of CSCs in different types of solid tumors and hematological malignancies. In Chaps. 7, 8, 9, 10, 11, and 12, authors effectively cover possible mechanisms involved in CSC theory, its markers, and their potential as prognostic or predictive molecules in terms of survival and treatment of selected cancers. Also, Chaps. 13 and 14 explain the importance of leukemic and lymphoid stem cells. Chapter 13 delineates the role played by malignant stem cells in myeloid and B-cell malignancies, and Chap. 14 provides an in-depth analysis to leukemic stem cells in acute lymphoblastic leukemia (ALL). The latter chapter particularizes that identification and characterization of leukemic stem cells and their integration with molecular studies have served as a basis for understanding the early stages of ALL development, identification of putative leukemia-initiating cells, and definition of their heterogeneity and changes during tumor development/progression. The third part of the book aims to offer novel approaches for targeting CSCs. In Chap. 15, authors discuss the signaling paradigm for stemness pathways, identify druggable targets, and present selected preclinical and clinical findings with agents targeting each pathway. Importantly, this chapter considers other disease-specific targeted agents to uncover roadblocks to the success of these anti-stemness agents including financial considerations, development of Multidrug resistance, and on-target adverse effects. Consistent with the notion that targeting the interplay between paracrine signals arising in the tumor stromal and the nearby cancerous cells holds promise for the successful elimination of CSCs, Chap. 16 offers a precise description to the latest findings in the optimization and tailoring of novel strategies designed for eliminating CSCs or affecting their microenvironment and administered in concert with conventional chemotherapy which can lead to tumor bulk shrinkage and ablate resistance and relapse. As chemoresistance is one of the most important hurdles to be overcome for improving long-term cancer patient survival, Chap. 17 discusses multiple mechanisms identified for CSC-associated chemoresistance and introduces epigenetic-modifying drugs and inhibitors designed for resensitizing CSCs to chemotherapeutics. In line with this, Chap. 18 outlines mechanisms that CSCs employ to resist ionizing radia-

tion and therapeutic strategies that are currently being used in the clinic or are in various stages of development for overcoming CSC-associated radioresistance. Finally, Chap. 19 discusses the diagnostic and therapeutic potentials of CSCs and introduces biomarkers in preclinical models and clinical trials to evaluate the therapeutic effectiveness of CSCs.

This book would not have come to fruition without the continuous support and administrative assistance of Melania Ruiz, along with the additional administrative help by Marleen Moor and Ilse Hensen-Kooijman from Springer International Publishing Switzerland. I also want to thank Dr. Babak Bakhshinejad for his valuable comments during the editing process of the book. Ultimately, I would like to express my profound gratitude to all of the authors for their time and efforts in bringing this project to completion. I am truly honored to have the opportunity to work with such a prestigious team. It is hoped that this book will serve to encourage continued collaboration among its authors.

Tehran, Iran
October, 2015

Sadegh Babashah, Ph.D.

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Abbreviations

β APN	β -Aminopropionitrile
γ -IR	γ -Irradiation
ω -3 PUFA	Omega-3 polyunsaturated

A

ABC	ATP-binding cassette
ACKR3	Atypical chemokine receptor 3
ADAM	A disintegrin and a metalloprotease domain
ADCC	Antibody-dependent cellular cytotoxicity
ADT	Androgen-deprivation therapy
AFP	Alpha-fetoprotein
AhR	Aryl hydrocarbon receptor
AIDS	Acquired immunodeficiency syndrome
AJCC	American Joint Cancer Committee
ALDH	Aldehyde dehydrogenase
ALK	Activin receptor-like kinase
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
AMPK	Adenosine monophosphate-activated protein kinase
ANGPT1	Angiopoietin 1
ANKRD28	Ankyrin repeat domain 28
APC	Adenomatous polyposis coli
APH1	Anterior pharynx-defective 1
APL	Acute promyelocytic leukemia
AR	Androgen receptor
Arx	Aristaless-related homeobox
AT1	Alveolar type 1
ATM	Ataxia-telangiectasia mutated
ATO	Arsenic trioxide
ATRA	All-trans retinoic acid
A β PP	Amyloid beta-protein precursor

B

6-BG	O(6)-Benzylguanine
B-ALL	B-cell acute lymphoblastic leukemia
B-CLL	B-cell chronic lymphocytic leukemia
BAA	Bodipy-aminoacetate
BAAA	Bodipy-aminoacetaldehyde
BADJs	Bronchoalveolar duct junctions
BCC	Basal cell carcinoma
BCL-2	B-cell lymphoma protein 2
Bcl-XI	B-cell lymphoma-extra large
BCNU	Bis-chloroethylnitrosourea
BCRP	Breast cancer resistance protein
BCRP1	Breakpoint cluster region pseudogene 1
BCSC	Breast cancer stem cells
bFGF	Basic fibroblast growth factor
BiCNU	Bis-chloroethylnitrosourea
BiTEs	Bispecific T-cell engagers
BKCa	Calcium-dependent potassium channels
BM	Bone marrow
BMI1	B lymphoma Mo-MLV insertion region 1 homolog
BMDCs	Bone marrow-derived cells
BMP	Bone morphogenetic protein
BPH	Benign prostatic hyperplasia
bsAbs	Bispecific antibodies

C

CACs	Centroacinar cells
CAD	C-terminal activation domain
CAFC	Cobblestone area forming assay
CAFs	Cancer-associated fibroblasts
CAIX	Carbonic anhydrase isoform 9
CALLA	Common acute lymphoblastic leukemia antigen
cAMP	Cyclic adenosine monophosphate
CAN	Copy number alterations
CAPP-Seq	Cancer personalized profiling by deep sequencing
CAR	Chimeric antigen receptor
CARM1	Coactivator-associated arginine methyltransferase 1
CBCs	Crypt base columnar cells
CBP	CREB-binding protein
CCL2	C-C motif chemokine ligand 2
CCR	Chemokine receptor
CCSP	Clara cell secretory protein
CD	Cytosine deaminase
CD34	Cluster of differentiation protein 34
CD133	Cluster of differentiation protein 133

Cdc42	Cell division control protein 42 homolog
CDF	Difluorinated curcumin
CDK2	Cyclin-dependent kinase 2
CEA	Carcinoembryonic antigen
CGRP	Calcitonin gene-related peptide
Chk	Cell cycle checkpoint kinase
CK-20	Cytokeratin-20
CLL	Chronic lymphocytic leukemia
CLMP	Common lymphoid-myeloid progenitor
CLP	Common lymphoid progenitor
CML	Chronic myeloid leukemia
CMP	Common myeloid progenitor
CNAs	Copy number aberrations
CNS	Central nervous system
coA	Coactivator
coR	Corepressor
COX	Cyclooxygenase
CQ	Chloroquine
CRC	Colorectal cancer
CREB	cAMP response element-binding protein
CRLF2	Cytokine receptor-like factor 2
CRPC	Castrate-resistant prostate cancer
CSCs	Cancer stem cells
CSDC2	Cold-shock domain-containing protein C2
CSLCs	Cancer stem-like cells
CTCs	Circulating tumor cells
CTSD	Cathepsin D
CXCL	C-X-C motif chemokine ligand
CXCR	C-X-C motif chemokine receptor
CYP	P450 oxidase
D	
DAG	Diacylglycerol
DAPT	N-[N-(3,5-Difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester
DBH	Debromohymenialdisine
DC-TICs	Delayed contributing tumor-initiating cells
DCIS	Ductal carcinoma in situ
DCs	Dendritic cells
DGCR8	DiGeorge critical region 8
Dhh	Desert hedgehog
DLLs	Delta-like ligands
DMAG	Demethoxygeldanamycin hydrochloride
Dn	Dominant-negative
DNER	Delta and notch-like epidermal growth factor-related receptor
DNMT	DNA methyltransferase

DR	Death receptor
DSBs	Double-stranded breaks
Dsh	Dishevelled
dsRNA	Double-stranded RNA
DTCs	Disseminated tumor cells
Dvl	Dishevelled
E	
EBV	Epstein-Barr virus
EC	Endothelial cells
ECM	Extracellular matrix
EFNA1	Ephrin A1
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
ELAM1	Endothelial adhesion molecule 1
EMP	Erythro-myeloid progenitor
EMT	Epithelial to mesenchymal transition
EpCAM	Epithelial cell adhesion molecule
EPCs	Endothelial precursor cells
ER	Endoplasmic reticulum
ER	Estrogen receptor
ERBB2	Erythroblastic leukemia viral oncogene homolog 2
ERG	ETS-related gene
ERK	Extracellular signal-regulated kinases
ESA	Epithelial-specific antigen
ESCs	Embryonic stem cells
ESL-1	E-selectin ligand 1
ETPs	Early thymocyte progenitors
F	
FACS	Fluorescence-activated cell sorting
FADD	FAS-associating death domain
FAK	Focal adhesion kinase
FAL1	Focally amplified lncRNA on chromosome 1
FAP	Familial adenomatous polyposis
Fc	Fragment-crystallizable
FGF	Fibroblast growth factor
FIH-1	Factor-inhibiting hypoxia 1
Flt3	FMS-like tyrosine kinase 3
FKHR	Forkhead transcription factor Foxo1
FOX	Forkhead box protein
FOXO1	Forkhead box O1A
FRb	Folate receptor b
Fu	Fused
FU	Fluorouracil
FUOX	Fluorouracil and oxaliplatin
Fz	Frizzled

G

G proteins	Guanine nucleotide-binding proteins
G-6-PD	Glucose-6-phosphate dehydrogenase
G-CSF	Granulocyte colony-stimulating factor
GAGs	Glycosaminoglycans
GANT	Gli antagonist
GBM	Glioblastoma multiforme
GFAP	Glial fibrillary acidic protein
GM-CSF	Granulocyte macrophage colony-stimulating factor
GNA15	Guanine nucleotide-binding protein, alpha 15
GPCRs	G protein-coupled receptors
GRK	G protein-coupled receptor kinase
GSCs	Glioblastoma stem cells
GSEA	Gene set enrichment analysis
GSH	Glutathione
GSIs	γ -Secretase inhibitors
GSK3 β	Glycogen synthase kinase 3 β
GTP	Guanosine-5'-triphosphate
GTPase	Guanosine triphosphate hydrolase

H

HA	Hyaluronic acid
HB-EGF	Heparin-binding EGF-like growth factor
HCC	Hepatocellular carcinoma
HDAC	Histone deacetylase
HDACi	Histone deacetylase inhibitor
HER2	Human epidermal growth factor receptor 2
Hes1	Hairy enhancer of split 1
HGF	Hepatocyte growth factor
Hh	Hedgehog
HIF	Hypoxia inducible factors
Hip1	Hedgehog-interacting protein 1
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HNRNPK	Heterogeneous nuclear ribonucleoprotein K
HNSCC	Head and neck squamous cell carcinoma
HoxB	Homeobox protein
HOTAIR	HOX antisense intergenic RNA
HPCs	Hematopoietic progenitor cells
HPI	Hedgehog pathway inhibitor
HPV	Human papillomavirus
HR	Homologous recombination
HRE	Hypoxia response element
HSCs	Hematopoietic stem cells
HSP	Heat shock protein

HSPC Hematopoietic stem and progenitor cells
 HUVEC Human umbilical vein endothelial cells

I

IAP Inhibitor of apoptosis proteins
 IBC Inflammatory breast cancer
 IBD Irritable bowel disease
 ICAM1 Intracellular adhesion molecule 1
 ICD Intracellular domain
 ICL Idiopathic CD4⁺ T-cell lymphocytopenia
 IDH1 Isocitrate dehydrogenase 1
 IEX-1L Immediate early response gene X-1
 Ig Immunoglobulin
 IGF Insulin-like growth factor
 IGF-IR Insulin-like growth factor-I receptor
 Ihh Indian hedgehog
 IL Interleukin
 IL-1R1 IL-1 receptor 1
 IL-1Ra IL-1 receptor antagonist
 IL-1Rap IL-1 receptor accessory protein
 IM Imatinib mesylate
 iNOS Inducible nitric oxide synthase
 INXS Intronic BCL-XS-inducing lncRNA
 IP3 Inositoltrisphosphat
 iPSCs Induced pluripotent stem cells
 IR Ionizing radiation
 IRAK Interleukin-1 receptor-activated protein kinase
 ISCs Intestinal stem cells
 ITAC Interferon-inducible T-cell α -chemoattractant
 ITD Internal *tandem* duplication
 IWPs Inhibitors of Wnt production
 IWRs Inhibitors of Wnt response

J

JAGs Jagged ligands
 Jak Janus kinase
 JNK c-Jun N-terminal kinases

K

kDa Kilodalton
 KLF4 Kruppel-like factor 4

L

L1CAM L1 cell adhesion molecule
 LDA Limiting dilution analysis
 LDH L-Lactate dehydrogenase
 LEF Lymphoid enhancer factor

LGR5	Leucine-rich repeat-containing G protein-coupled receptor 5
lincRNAs	Long intergenic ncRNAs
LIP	Liver-enriched inhibitory protein
LMO	LIM-only domain
lncRNAs	Long noncoding RNAs
LOX	Lysyl oxidase
LRCs	Label-retaining intestinal stem cells
LRP	Lipoprotein receptor-related protein
LSCs	Leukemic stem cells
LTC-IC	Long-term culture-initiating cell assay
LTTICs	Long-term tumor-initiating cells

M

M-CSF	Macrophage colony-stimulating factor
mAb	Monoclonal antibody
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1
MAML	Mastermind-like
MAPK	Mitogen-activated protein kinases
MaSCs	Mammary stem cells
MCAo	Middle cerebral artery suture occlusion
MCP2	Monocyte chemoattractant protein 2
MDR	Multidrug resistance
MDR-1	Multidrug resistance protein 1
MDS	Myelodysplastic syndrome
MDSCs	Myeloid-derived suppressor cells
MECP2	Methyl-CpG-binding protein 2
MEK	Mitogen-activated protein <i>kinase</i>
MET	Mesenchymal to epithelial transition
MetSCs	Metastatic stem cells
MGMT	Methylguanine-DNA methyltransferase
MGUS	Monoclonal gammopathy of undetermined significance
MHC	Major histocompatibility complex
MI	Myocardial ischemia
MIB	Mindbomb
MIP	Macrophage inflammatory protein
miRNA	MicroRNA
MM	Multiple myeloma
MMP	Matrix metalloproteinase
MnSOD	Manganese superoxide dismutase
MPPs	Multipotent progenitors
MRD	Minimal residual disease
MRP	Multidrug resistance proteins
MSCs	Mesenchymal stem cells
Msi-1	Musashi 1
mTOR	Mammalian target of rapamycin

MTX	Methotrexate
MUC1	Mucin-1
Myc	v-Myc avian myelocytomatosis viral oncogene homolog
N	
N-Cor	Nuclear receptor corepressor
NATs	Natural antisense transcripts
NBD	Nucleotide-binding domain
NCSTN	Nicastrin
NEBs	Neuroepithelial bodies
NETs	Neuroendocrine tumors
NEURL	Neuralized
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B-cells
NF1	Neurofibromin 1
Ngn3	Neurogenin 3
NHEJ	Nonhomologous end-joining
NHL	Non-Hodgkin lymphoma
NICD	Notch intracellular domain
NK	Natural killer
NMRI	Naval Medical Research Institute, Lynch et al. (1937)
NO	Nitric oxide
NOD	Nonobese diabetic
NOG	NOD/Shi-scid/IL-2R γ ^{null}
NRF1	Nuclear respiratory factor 1
NRPs	Neuropilins
NSAID	Nonsteroidal antiinflammatory drug
NSC	Neural stem cells
NSCLC	Non-small cell lung cancer
nu/nu	Nude <i>mouse</i> (Foxn1 ^{nu} /Foxn1 ^{nu})
O	
OCT	Octamer-binding transcription factor
OPN	Osteopontin
OS	Overall survival
OVV	Oncolytic vaccine virus
OX	Oxaliplatin
P	
P-CYP	Copolymer-cycloamine conjugate
P-DTX	Copolymer-docetaxel conjugate
P-gp	P-glycoprotein
PACT	Protein activator of PKR
PanIN	Pancreatic intraepithelial lesion
PARP	Poly-ADP-ribose polymerase
PAUF	Pancreatic adenocarcinoma upregulated factor
PAX	Paired box gene

PBMC	Peripheral blood mononuclear cells
PCa	Prostate cancer
PcG	Polycomb group
PCGF4	Polycomb group RING finger protein 4
PCSC	Prostate cancer stem cells
PDAC	Pancreatic ductal adenocarcinoma
PDGF	Platelet-derived growth factor
PDGFRA	Platelet-derived growth factor receptor A
PDH	Prolyl hydroxylases
PK1	Phosphoinositide-dependent kinase 1
Pdx1	Pancreatic and duodenal homeobox 1
PEN2	Presenilin enhancer 2
PF	Platelet factor
PG	Prostaglandin
Ph	Philadelphia
PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase
PIP2	Phosphatidylinositol bisphosphate
PKA	Protein kinase A
PKC	Protein kinase C
PKR	Protein kinase R
PLC	Phospholipase C
PIGF	Placental growth factor
PMA	Phorbol-12-myristat-13-acetate
PORCN	Porcupine
PPAR	Peroxisome proliferator-activated receptor
PR	Progesterone receptor
Pre-miRNAs	Precursor microRNAs
Pri-miRNAs	Primary microRNAs
PRC2	Polycomb repressive complex 2
PROM1	Prominin 1
PSA	Prostate-specific antigen
PSC	Prostate stem cells
PSEN	Presenilin
Ptch	Patched
PTEN	Phosphatase and tensin homolog
Ptf1	Pancreas-specific transcription factor 1
pTHRp	Parathyroid hormone-related protein
PTP1B	Protein tyrosine phosphatase 1 B
PYK2	Protein tyrosine kinase FAK2
Q	
Q-PCR	Quantitative polymerase chain reaction
R	
RA	Retinoic acid
RA	Rheumatoid arthritis

Rac	Ras-related C3 botulinum toxin substrate
RANKL	Receptor activator of NF- κ B ligand
RAR	Retinoic acid receptor
Ras	Rat sarcoma protein family
RCC	Renal cell carcinoma
RFS	Relapse-free survival
Rho	Ras homolog gene family
RNAi	RNA interference
RNF51	RING finger protein 51
RONS	Reactive oxygen and nitrogen species
ROS	Reactive oxygen species
RT-PCR	Reverse transcriptase polymerase chain reaction
RTKs	Receptor tyrosine kinases
S	
SABR	Stereotactic ablative radiotherapy
SAHA	Suberoylanilide hydroxamic acid
SALL4	Sal-like protein 4
SCC	Squamous cell carcinoma
SCDSF	Stem cells differentiation stage factors
SCID	Severe combined immunodeficiency
SCLC	Small cell lung cancer
SCs	Stem cells
SDF-1	Stromal cell-derived factor 1
SDH	Succinate dehydrogenase
SETDB1	SET domain bifurcated 1
SFN	Sulforaphane
SFRPs	Secreted frizzled-related proteins
SGZ	Subgranular zone
SH	Src homology
Shh	Sonic hedgehog
SHIP	Src homology 2-containing inositol-5'-phosphatase
siRNA	Small interfering RNA
SIRP	Signal regulatory protein
SL-IC	SCID leukemia-initiating cells
SLE	Systemic lupus erythematosus
SLGCs	Stem-like glioma cells
Smo	Smoothed
SMRT	Silencing mediator of retinoic acid and thyroid hormone receptor
SOCE	Store-operated Ca ²⁺ entry
SP	Side population
SP-C	Surfactant protein C
SPNs	Solid pseudopapillary neoplasms
SPPs	Signal peptide peptidases
SRS	Stereotactic radiosurgery

SSBs	Single-stranded breaks
SSEA-1	Stage-specific embryonic antigen 1
STAT	Signal transducer and activator of transcription
Stat5-CA	Stat5 constitutively active
SuFu	Suppressor of fused
SVZ	Sub-ventricular zone

T

T-ALLs	T-cell acute lymphoblastic leukemias
T-TACs	Tumor transient amplifying cells
T-UCRs	Transcribed ultraconserved regions
TAAAs	Tumor-associated antigens
TACE	Tumor necrosis factor- α -converting enzyme
TAMs	Tumor-associated macrophages
TBI	Total body irradiation
TCF	T-cell factor
TCGA	The Cancer Genome Atlas
TDECs	Tumor-derived endothelial cells
TET2	Ten-eleven-translocation gene 2 tumor suppressor
TGF- β	Transforming growth factor- β
TGF- β R	Transforming growth factor- β receptor
Th1	T-cell helper type 1
TIMP-2	Tissue inhibitor of metalloproteinase 2
TK	Thymidine kinase
TKIs	Tyrosine kinase inhibitors
TMD	Transmembrane domain
TMZ	Temozolomide
TNC	Tenascin C
TNF- α	Tumor necrosis factor- α
TR4	Testicular nuclear receptor 4
TRAF	TNF receptor-associated factor
TRAIL	TNF-related apoptosis-inducing ligand
TRBP	Transactivation response RNA-binding protein
TS	Thymidylate synthase
TSGs	Tumor suppressor genes
TSLP	Thymic stromal-derived lymphopoietin
TTL	Time to development of leukemia

U

3'UTRs	3'-Untranslated region
5'UTRs	5'-Untranslated region
UGP2	UDP-glucose pyrophosphorylase 2
uPA	Urokinase-type plasminogen activator
uPAR	Urokinase-type plasminogen activator receptor
UPR	Unfolded protein response
UPRT	Uracil phosphoribosyltransferase