



Universidad de Salamanca

Instituto de Biología Molecular y Celular del Cáncer

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Targeting the mTOR and TRAIL Pathways in Multiple Myeloma

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CERTIFICA,

Que Xi Chen, licenciado en Ingeniería Biológica, ha realizado bajo su dirección la Tesis Doctoral “Targeting the mTOR and TRAIL pathways in multiple myeloma” en el Instituto de Biología Molecular y Celular del Cáncer y reúne, a su juicio, originalidad y contenidos suficientes para que sea presentada ante el tribunal correspondiente y optar al grado de Doctor por la Universidad de Salamanca.

Y para que así conste, a efectos legales, expide el presente certificado en Salamanca, a 18 de Octubre de 2012.

Fdo. Atanasio Pandiella Alonso

Abbreviations

Abbreviations

4E-BP	eIF4E-binding protein
5'-TOP	5'-terminal oligopyrimidine
7-AAD	7-amino-actinomycin D
aCGH	array Comparative Genomic Hybridization
ADCC	Antibody-Dependent Cellular Cytotoxicity
AID	Activation-Induced Deaminase
AIF	Apoptosis-Inducing Factor
AMPK	Adenosine Monophosphate-activated Protein Kinase
ANOVA	Analysis of variance
APAF1	Apoptotic Protease-Activating Factor 1
APC	Allophycocyanin
ATP	Adenosine triphosphate
Bcl-2	B-cell lymphoma 2
Bcl-X_L	B-cell lymphoma-extra large
BH3	Bcl-2 Homology domain 3
BID	BH3 interacting domain death agonist
BIR	Baculoviral IAP Repeat
BMP-2	Bone Morphogenic Protein-2
BMSCs	Bone Marrow Stromal Cells
BRAF	v-raf murine sarcoma viral oncogene homolog B1
BrdU	Bromodeoxyuridine
BSA	Bovine Serum Albumin
CARD15	Caspase recruitment domain family, member 15
CCND1	Cyclin D1
CCT3	Chaperonin Containing TCP1, subunit 3
CD	Cluster of Differentiation
CDC	Complement-Dependent Cytotoxicity
CDK	Cyclin Dependent Kinase
cDNA	complement DNA
c-FLIP	cellular FLICE-Like Inhibitory Protein
CFSE	Carboxyfluorescein Diacetate Succinimidyl Ester
CHAPS	3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate
CNA	Copy Number Alteration
CNBr	Cyanogen bromide
CS1	CD2 Subset-1

Abbreviations

CSC	Cancer Stem Cell
CXCR4	chemokine (C-X-C motif) receptor 4
DeR1/2	Decoy Receptor 1/2
DEPTOR	DEP domain containing mTOR-interacting protein
DISC	Death Inducing Signaling Complex
DKK1	Dickkopf 1
DMEM	Dulbecco's Modified Eagle Medium
DMSO	Dimethyl sulfoxide
DR4	Death Receptor 4
DR5	Death Receptor 5
ECM	Extracellular matrix
EDTA	Ethylenediaminetetraacetic acid
eIF4E	Eukaryotic translation Initiation Factor 4E
ERK	Extracellular signal-regulated kinase
FADD	Fas-associated protein with death domain
FASL	FAS Ligand
FBS	Fetal Bovine Serum
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factor
FGFR3	Fibroblast Growth Factor Receptor 3
FISH	Fluorescence <i>In Situ</i> Hybridization
FITC	Fluorescein isothiocyanate
FKBP12	FK506-binding protein of 12 kDa
FRB	FKBP12-Rapamycin Binding
FTI	Farnesyltransferase inhibitor
GAP	GTPase-activating protein
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GDP	Guanosine diphosphate
GEF	Guanine nucleotide Exchange Factor
Grb10	Growth factor receptor-bound protein 10
GSEA	Gene-Set Enrichment Analysis
GST	Glutathione S-transferase
GTP	Guanosine Triphosphate
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid
HMCLs	Human Myeloma Cell Lines

HRP	Horseradish peroxidase
HSCs	Hemotapoietic stem cells
IAP	Inhibitor of Apoptosis Protein
IC50	50% Inhibition Concentration
ICAM-1	Intracellular adhesion molecular-1
IGF-1	Insulin-like Growth Factor 1
IgG	Immunoglobulin G
IgH	Immunoglobulin Heavy-chain
IHC	Immunohistochemistry
IKK	I κ B Kinase
IL-3/6/7	Interleukin-3/6/7
IMiDs	Immunomodulatory drugs
IPTG	Isopropyl β -D-1-thiogalactopyranoside
ISS	International Staging System
IκB	Inhibitors of NF- κ B
JAK	Janus kinase
KLH	Keyhole Limpet Hemocyanin
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LFA-1	Lymphocyte Function-associated Antigen-1
LPS	Lipopolysaccharide
MAF	v-maf musculoaponeurotic fibrosarcoma oncogene homolog (avian)
MAPK	Mitogen Activated Protein Kinase
MAPKK	MAPK Kinase
MAPKKK	MAPK Kinase Kinase
MBS	3-maleimidobenzoic acid N-hydroxysuccinimide ester
Mcl-1	Myeloid Cell Leukemia sequence 1
MEK	MAPK/ERK Kinase
MEKK	MEK Kinase
MGUS	Monoclonal Gammopathy of Undetermined Significance
MIP1α	Macrophage Inflammatory Protein 1 α
MKK	MAP Kinase Kinase
mLST8	mammalian Lethal with sec-13 protein 8
MM	Multiple Myeloma
MMGP	Multiple Myeloma Genomics Portal

Abbreviations

MMSET	Multiple Myeloma SET domain
MRD	Minimal Residual Disease
mSIN1	mammalian Stress-activated map kinase-interacting protein 1
mTOR	mechanistic Target of Rapamycin
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MUC1	Mucin 1, cell surface associated
Myc	v-myc myelocytomatosis viral oncogene homolog (avian)
NF-κB	Nuclear Factor of kappa light polypeptide gene enhancer in B-cells 1
NHS	N-hydroxysuccinimide ester
NIK	NF- κ B-Inducing Kinase
NOD	Nonobese diabetic
NRAS	Neuroblastoma RAS viral (v-ras) oncogene homolog
OD	Optical Density
OPG	Osteoprotegerin
PAGE	Polyacrylamide gel electrophoresis
PARP	Poly(ADP-ribose) Polymerase
PBS	Phosphate Buffered Saline
PCs	Plasma Cells
PE	Phycoerythrin
PEI	Polyethylenimide
PFA	Paraformaldehyde
PI	Propidium Iodide
PI3K	Phosphoinositide-3 Kinase
PIAS	Protein Inhibitors of Activated Stats
PIP₂	phosphatidylinositol-4,5-bisphosphate
PIP₃	phosphatidylinositol- 3,4,5 trisphosphate
PKB	Protein Kinase B
PKC-α	Protein Kinase C- α
PMSF	Phenylmethanesulfonylfluoride
PRAS40	Proline-Rich Akt Substrate 40 kDa
Protor1/2	Protein observed with Rictor 1/2
PSGL-1	P-selectin Glycoprotein Ligand-1
PTEN	Phosphatase and tensin homolog
qWB	quantitative Western Blot

Raf	Rapidly Accelerated Fibrosarcoma
RANKL	Receptor Activator of NF- κ B Ligand
Raptor	Regulatory-associated protein of mTOR
RAS	Rat sarcoma
Rb	Retinoblastoma
RelA/B	v-rel reticuloendotheliosis viral oncogene homolog A/B
Rheb	Ras homolog enriched in brain
rhTRAIL	recombinant human TRAIL
Rictor	Rapamycin-insensitive companion of mTOR
RMA	Robust Multi-array Average
RNAi	RNA interference
RT	Reversed Transcription
RTK	Receptor Tyrosine Kinase
RUNX2	Runt-related transcription factor 2
S6K	S6 Kinase
SCID	Severe Combined ImmunoDeficiency
SD	Standard Deviation
SDF-1α	Stromal Cell-derived Factor-1 α
SDS	Sodium Dodecyl Sulfate
SGK1	Serum- and Glucocorticoid-regulated Kinase 1
SHP	SH2-containing Phosphatase
shRNA	short-hairpin RNA
SMAC	Second Mitochondria-derived Activator of Caspase
SMM	Smoldering Multiple Myeloma
SNP	Single Nucleotide Polymorphism
SOCS	Suppressors of cytokine signaling
STAT	Signal Transducer and Activator of Transcription
tBID	truncated BID
TMRE	Tetramethyl-rhodamine ethyl ester
TNF	Tumor Necrosis Factor
TNFRSF10A/B/C/D	Tumor Necrosis Factor Receptor Superfamily, member 10A/B/C/D
TRAIL	TNF-related apoptosis-inducing ligand
TRAILR1/2/3/4	TRAIL Receptor 1/2/3/4
Tris	Tris(hydroxymethyl)aminomethane

Abbreviations

TSC1/2	Tuberous Sclerosis Protein 1/2
VCAM-1	Vascular Cell Adhesion Molecule-1
VEGF	Vascular Endothelial Growth Factor
VLA-4	Very Late Antigen-4
WB	Western Blot
XIAP	X-linked Inhibitor of Apoptosis
β--ME	β-mercaptoethanol

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