

tezomib, 4 Hoi	tezomib, 24 Hc	tezomib, 72 Hc	<p>Autophagy</p> <ul style="list-style-type: none"> Eukaryotic Mediated Autophagy Late endosomal microautophagy <p>Macroautophagy</p> <ul style="list-style-type: none"> Selective autophagy Mitophagy <ul style="list-style-type: none"> PINK1–PRKN Mediated Mitophagy Aggrephagy Pexophagy <p>Cell Cycle</p> <ul style="list-style-type: none"> Cell Cycle Checkpoints <ul style="list-style-type: none"> G2/M Checkpoints G1/S DNA Damage Checkpoints <ul style="list-style-type: none"> p53–Dependent G1/S DNA damage checkpoint p53–Dependent G1 DNA Damage Response p53–Independent G1/S DNA damage checkpoint p53–Independent DNA Damage Response Cell Cycle, Mitotic <ul style="list-style-type: none"> Mitotic G2–G2/M phases G2/M Transition <ul style="list-style-type: none"> Regulation of PLK1 Activity at G2/M Transition Centrosome maturation <ul style="list-style-type: none"> The role of GTSE1 in G2/M progression after G2 checkpoint FBXL7 down–regulates AURKA during mitotic entry and in early mitosis AURKA Activation by TPX2 Regulation of mitotic cell cycle <ul style="list-style-type: none"> APC/C–mediated degradation of cell cycle proteins Autodegradation of Cdh1 by Cdh1/APC/C APC/C:Cdh1 mediated degradation of Cdc20 and other APC/C:Cdh1 targeted proteins Regulation of APC/C activators between G1/S and early anaphase Activation of APC/C and APC/C:Cdc20 mediated degradation of mitotic proteins Mitotic G1 phase and G1/S transition G1/S Transition <ul style="list-style-type: none"> E2F mediated regulation of DNA replication Cyclin E associated events during G1/S transition G1/S–Specific Transcription M Phase <ul style="list-style-type: none"> Mitotic Metaphase and Anaphase Mitotic Anaphase Mitotic Prometaphase Recruitment of NuMA to mitotic centrosomes S Phase <ul style="list-style-type: none"> Cyclin A:Cdk2–associated events at S phase entry SCF/Skp2–mediated degradation of p27/p21 Ubiquitin–dependent degradation of Cyclin D <p>Cell–Cell communication</p> <ul style="list-style-type: none"> Cell junction organization Cell–extracellular matrix interactions <p>Cellular responses to stimuli</p> <ul style="list-style-type: none"> Cellular responses to stress <ul style="list-style-type: none"> Cellular response to hypoxia <ul style="list-style-type: none"> Oxygen–dependent proline hydroxylation of Hypoxia–inducible Factor Alpha Cellular Senescence Induced Senescence HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of lig Cellular response to heat stress <ul style="list-style-type: none"> Regulation of HSF1–mediated heat shock response HSF1 activation HSF1–dependent transactivation Attenuation phase Unfolded Protein Response (UPR) <ul style="list-style-type: none"> IRE1alpha activates chaperones XBP1(S) activates chaperone genes Heme signaling Cellular response to starvation <ul style="list-style-type: none"> Response of EIF2AK4 (GCN2) to amino acid deficiency Amino acids regulate mTORC1 Cellular response to chemical stress <ul style="list-style-type: none"> Detoxification of Reactive Oxygen Species Cytoprotection by HMOX1 KEAP1–NFE2L2 pathway <ul style="list-style-type: none"> Regulation of BACH1 activity Nuclear events mediated by NFE2L2 <p>Chromatin organization</p> <ul style="list-style-type: none"> Chromatin modifying enzymes RMTs methylate histone arginines <p>DNA Repair</p> <ul style="list-style-type: none"> DNA Damage Bypass <ul style="list-style-type: none"> Translesion synthesis by Y family DNA polymerases bypasses lesions on DNA templa Translesion synthesis by REV1 Translesion Synthesis by POLH Translesion synthesis by POLK Translesion synthesis by POLI Recognition of DNA damage by PCNA–containing replication complex <p>DNA Double–Strand Break Repair</p> <ul style="list-style-type: none"> Homology Directed Repair <ul style="list-style-type: none"> HDR through Homologous Recombination (HRR) or Single Strand Annealing (SSA) HDR through Homologous Recombination (HRR) Processing of DNA double–strand break ends DNA Double Strand Break Response <ul style="list-style-type: none"> Recruitment and ATM–mediated phosphorylation of repair and signaling proteins at Fanconi Anemia Pathway Nucleotide Excision Repair <ul style="list-style-type: none"> Global Genome Nucleotide Excision Repair (GG–NER) DNA Damage Recognition in GG–NER Formation of Incision Complex in GG–NER Gap–filling DNA repair synthesis and ligation in GG–NER <p>DNA Replication</p> <ul style="list-style-type: none"> DNA Replication Pre–Initiation <ul style="list-style-type: none"> Assembly of the pre–replicative complex Synthesis of DNA <ul style="list-style-type: none"> Switching of origins to a post–replicative state Orc1 removal from chromatin CDK–mediated phosphorylation and removal of Cdc6 <p>Developmental Biology</p> <ul style="list-style-type: none"> Gastrulation <ul style="list-style-type: none"> Formation of paraxial mesoderm Somitogenesis Nervous system development <ul style="list-style-type: none"> Axon guidance <ul style="list-style-type: none"> EPH–Ephrin signaling EPH–ephrin mediated repulsion of cells Semaphorin interactions Sema3A PAK dependent Axon repulsion Signaling by ROBO receptors <ul style="list-style-type: none"> Regulation of expression of SLITs and ROBOs <p>Disease</p> <ul style="list-style-type: none"> Diseases of DNA repair <ul style="list-style-type: none"> Diseases of DNA Double–Strand Break Repair <ul style="list-style-type: none"> Defective homologous recombination repair (HRR) due to BRCA1 loss of function Defective homologous recombination repair (HRR) due to PALB2 loss of function Defective HDR through Homologous Recombination Repair (HRR) due to PALB2 loss of Defective HDR through Homologous Recombination Repair (HRR) due to PALB2 loss of Diseases of metabolism <ul style="list-style-type: none"> Defects in vitamin and cofactor metabolism <ul style="list-style-type: none"> Defects in cobalamin (B12) metabolism Diseases of carbohydrate metabolism Diseases of signal transduction by growth factor receptors and second messengers <ul style="list-style-type: none"> Signaling by ERBB2 in Cancer <ul style="list-style-type: none"> Constitutive Signaling by Overexpressed ERBB2 Signaling by ERBB2 KD Mutants Signaling by ERBB2 ECD mutants Signaling by ERBB2 TMD/JMD mutants Signaling by EGFR in Cancer <ul style="list-style-type: none"> Signaling by EGFRvIII in Cancer Constitutive Signaling by EGFRvIII Signaling by Ligand–Responsive EGFR Variants in Cancer Constitutive Signaling by Ligand–Responsive EGFR Cancer Variants Hh mutants abrogate ligand secretion Hh mutants are degraded by ERAD Signaling by KIT in disease <ul style="list-style-type: none"> Signaling by phosphorylated juxtamembrane, extracellular and kinase domain KIT m Signaling by PDGFR in disease <ul style="list-style-type: none"> Signaling by PDGFRA transmembrane, juxtamembrane and kinase domain mutants Signaling by PDGFR extracellular domain mutants Signaling by ALK in cancer <ul style="list-style-type: none"> Signaling by ALK fusions and activated point mutants Disorders of transmembrane transporters <ul style="list-style-type: none"> ABC transporter disorders <ul style="list-style-type: none"> Defective CFTR causes cystic fibrosis Infectious disease <ul style="list-style-type: none"> Bacterial Infection Pathways <ul style="list-style-type: none"> Uptake and actions of bacterial toxins Listeria monocytogenes entry into host cells INB–mediated entry of Listeria monocytogenes into host cell Parasitic Infection Pathways <ul style="list-style-type: none"> Leishmania infection <ul style="list-style-type: none"> Leishmania parasite growth and survival Viral Infection Pathways <ul style="list-style-type: none"> HIV Infection <ul style="list-style-type: none"> HIV Life Cycle <ul style="list-style-type: none"> Host Interactions of HIV factors Influenza Infection <ul style="list-style-type: none"> Influenza Viral RNA Transcription and Replication SARS–CoV Infections <ul style="list-style-type: none"> SARS–CoV–1 Infection <ul style="list-style-type: none"> Potential therapeutics for SARS SARS–CoV–2 Infection <ul style="list-style-type: none"> Respiratory Syncytial Virus (RSV) genome replication, transcription and translat <p>Extracellular matrix organization</p> <ul style="list-style-type: none"> Integrin cell surface interactions Non–integrin membrane–ECM interactions <p>Gene expression (Transcription)</p> <ul style="list-style-type: none"> Epigenetic regulation of gene expression <ul style="list-style-type: none"> Positive epigenetic regulation of rRNA expression ERCC6 (CSB) and EHM12 (G9a) positively regulate rRNA expression <p>Gene Silencing by RNA</p> <ul style="list-style-type: none"> PIWI–interacting RNA (piRNA) biogenesis <p>RNA Polymerase II Transcription</p> <ul style="list-style-type: none"> Generic Transcription Pathway <ul style="list-style-type: none"> Transcriptional Regulation by TP53 <ul style="list-style-type: none"> TP53 Regulates Metabolic Genes Regulation of TP53 Activity TP53 Regulates Transcription of Cell Cycle Genes Transcriptional regulation by RUNX3 <ul style="list-style-type: none"> Regulation of RUNX3 expression and activity Transcriptional regulation by RUNX2 <ul style="list-style-type: none"> Regulation of RUNX2 expression and activity Transcriptional regulation by RUNX1 <ul style="list-style-type: none"> Regulation of RUNX1 Expression and Activity RUNX1 regulates transcription of genes involved in differentiation of HSCs FOXO–mediated transcription <p>Hemostasis</p> <ul style="list-style-type: none"> Cell surface interactions at the vascular wall Factors involved in megakaryocyte development and platelet production Kinesins Platelet activation, signaling and aggregation <ul style="list-style-type: none"> GPVI–mediated activation cascade Response to elevated platelet cytosolic Ca2+ Platelet degranulation <p>Immune System</p> <ul style="list-style-type: none"> Adaptive Immune System <ul style="list-style-type: none"> Immunoregulatory interactions between a Lymphoid and a non–Lymphoid cell TCR signaling <ul style="list-style-type: none"> Downstream TCR signaling <ul style="list-style-type: none"> Phosphorylation of CD3 and TCR zeta chains Translocation of ZAP–70 to Immunological synapse Generation of second messenger molecules Costimulation by the CD28 family <ul style="list-style-type: none"> PD–1 signaling Class I MHC mediated antigen processing & presentation <ul style="list-style-type: none"> Antigen processing–Cross presentation ER–Phagosome pathway <ul style="list-style-type: none"> Cross–presentation of soluble exogenous antigens (endosomes) Antigen processing: Ubiquitination & Proteasome degradation Antigen Presentation: Folding, assembly and peptide loading of class I MHC Signaling by the B Cell Receptor (BCR) <ul style="list-style-type: none"> Downstream signaling events of B Cell Receptor (BCR) <ul style="list-style-type: none"> Activation of NF–kappaB in B cells Antigen activates B Cell Receptor (BCR) leading to generation of second messenge Cytokine Signaling in Immune system <ul style="list-style-type: none"> Signaling by Interleukins <ul style="list-style-type: none"> Interleukin–7 signaling Interleukin–1 family signaling <ul style="list-style-type: none"> Interleukin–1 signaling Interleukin–12 family signaling Interleukin–35 Signalling Interleukin–2 family signaling Interleukin–3, Interleukin–5 and GM–CSF signaling Interleukin–4 and Interleukin–13 signaling TNFR2 non–canonical NF–kB pathway TNFs bind their physiological receptors NF–kappaB noncanonical NF–kB signaling TNF receptor superfamily (TNFSF) members mediating non–canonical NF–kB pathway Interferon Signaling <ul style="list-style-type: none"> Antiviral mechanism by IFN–stimulated genes PKR–mediated signaling Interferon gamma signaling Interferon alpha/beta signaling <ul style="list-style-type: none"> Regulation of IFNA/IFNB signaling Growth hormone receptor signaling <p>Innate Immune System</p> <ul style="list-style-type: none"> Toll–like Receptor Cascades <ul style="list-style-type: none"> Toll Like Receptor 3 (TLR3) Cascade <ul style="list-style-type: none"> TICAM1, RIF-mediated IKK complex recruitment TAK1–dependent IKK and NF–kappa–B activation TICAM1–dependent activation of IRF3/IRF7 TICAM1, TRAF6–dependent induction of TAK1 complex DDX58/IFIH1–mediated induction of interferon–alpha/beta TRAF3–dependent IRF activation pathway Negative regulators of DDX58/IFIH1 signaling Cytosolic sensors of pathogen–associated DNA Fcgamma receptor (FCGR) dependent phagocytosis Regulation of actin dynamics for phagocytic cup formation Role of phospholipids in phagocytosis DAP12 interactions DAP12 signaling Fc epsilon receptor (FCER1) signaling <ul style="list-style-type: none"> FCER1 mediated MAPK activation FCER1 mediated Ca+2 mobilization FCER1 mediated NF–kB activation C–type lectin receptors (CLRs) <ul style="list-style-type: none"> CLEC7A (Dectin–1) signaling Dectin–1 mediated noncanonical NF–kB signaling Neutrophil degranulation <ul style="list-style-type: none"> Alpha–protein kinase 1 signaling pathway <p>Metabolism</p> <ul style="list-style-type: none"> Biological oxidations <ul style="list-style-type: none"> Phase I – Functionalization of compounds Metabolism of amino acids and derivatives <ul style="list-style-type: none"> Selenoamino acid metabolism Selenocysteine synthesis Metabolism of polyamines <ul style="list-style-type: none"> Regulation of ornithine decarboxylase (ODC) Metabolism of carbohydrates <ul style="list-style-type: none"> Glycogen metabolism Glycogen synthesis Metabolism of lipids <ul style="list-style-type: none"> Phospholipid metabolism PI Metabolism <ul style="list-style-type: none"> Synthesis of PIPs at the plasma membrane Metabolism of nucleotides <ul style="list-style-type: none"> Nucleotide salvage Metabolism of vitamins and cofactors <ul style="list-style-type: none"> Metabolism of water–soluble vitamins and cofactors Cobalamin (Cbl, vitamin B12) transport and metabolism Metabolism of cofactors <ul style="list-style-type: none"> The citric acid (TCA) cycle and respiratory electron transport Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat Formation of ATP by chemiosmotic coupling Respiratory electron transport Complex I biogenesis <p>Metabolism of RNA</p> <ul style="list-style-type: none"> Mitochondrial RNA degradation <ul style="list-style-type: none"> FASTK family proteins regulate processing and stability of mitochondrial RNAs Nonsense Mediated Decay (NMD) independent of the Exon Junction Complex (EJC) <ul style="list-style-type: none"> Nonsense Mediated Decay (NMD) enhanced by the Exon Junction Complex (EJC) Regulation of mRNA stability by proteins that bind AU–rich elements <ul style="list-style-type: none"> AUF1 (hnRNP D0) binds and destabilizes mRNA <p>rRNA processing in the mitochondrion</p> <ul style="list-style-type: none"> rRNA processing in the nucleus and cytosol rRNA modification in the nucleus and cytosol Major pathway of rRNA processing in the nucleolus and cytosol <p>tRNA processing in the mitochondrion</p> <ul style="list-style-type: none"> tRNA processing in the mitochondrion <p>Metabolism of proteins</p> <ul style="list-style-type: none"> Mitochondrial protein degradation <ul style="list-style-type: none"> Sumoylation SUMO E3 ligases SUMOylate target proteins SUMOylation of intracellular receptors Asparagine N–linked glycosylation <ul style="list-style-type: none"> N–glycan trimming in the ER and Calnexin/Calreticulin cycle Calnexin/calreticulin cycle Deubiquitination <ul style="list-style-type: none"> UCH proteinases Ub–specific processing proteases Ovarian tumor domain proteases Metalloprotease DUBs Protein ubiquitination <ul style="list-style-type: none"> Synthesis of active ubiquitin: roles of E1 and E2 enzymes E3 ubiquitin ligases ubiquitinate target proteins Protein methylation Neddylation Carboxyterminal post–translational modifications of tubulin <p>Protein folding</p> <ul style="list-style-type: none"> Post–chaperonin tubulin folding pathway Chaperon–mediated protein folding <ul style="list-style-type: none"> Cooperation of Prefoldin and TriC/CCT in actin and tubulin folding Prefoldin mediated transfer of substrate to CCT/TriC Formation of tubulin folding intermediates by CCT/TriC <p>Translation</p> <ul style="list-style-type: none"> Eukaryotic Translation Elongation <ul style="list-style-type: none"> Peptide chain elongation SRP–dependent cotranslational protein targeting to membrane Eukaryotic Translation Initiation <ul style="list-style-type: none"> L13a–mediated translational silencing of Ceruloplasmin expression Cap–dependent Translation Initiation <ul style="list-style-type: none"> Activation of the mRNA upon binding of the cap–binding complex and eIFs, and sub Formation of a pool of free 40S subunits Formation of the ternary complex, and subsequently, the 43S complex Ribosomal scanning and start codon recognition GTP hydrolysis and joining of the 60S ribosomal subunit Eukaryotic Translation Termination <p>Neuronal System</p> <ul style="list-style-type: none"> Transmission across Chemical Synapses <ul style="list-style-type: none"> Neurotransmitter receptors and postsynaptic signal transmission Activation of kainate receptors upon glutamate binding Organelle biogenesis and maintenance Cilium Assembly <ul style="list-style-type: none"> Anchoring of the basal body to the plasma membrane Intraflagellar transport Mitochondrial biogenesis Cristae formation <p>Programmed Cell Death</p> <ul style="list-style-type: none"> Apoptosis <ul style="list-style-type: none"> Regulation of Apoptosis Regulation of activated PAK–2p34 by proteasome mediated degradation Regulated Necrosis <ul style="list-style-type: none"> RIK1–mediated regulated necrosis Regulation of necroptotic cell death <p>Protein localization</p> <ul style="list-style-type: none"> Peroxisomal protein import <p>Signal Transduction</p> <ul style="list-style-type: none"> Death Receptor Signaling <ul style="list-style-type: none"> p75 NTR receptor–mediated signalling p75NTR signals via NF–kB p75NTR recruits signalling complexes NF–kB is activated and signals survival Cell death signalling via NRAGE, NRIF and NADE NRAGE signals death through JNK NRIF signals cell death from the nucleus TNF signaling <ul style="list-style-type: none"> Regulation of TNFR1 signaling Intracellular signaling by second messengers <ul style="list-style-type: none"> PIP3 activates AKT signaling PI3EN Regulation <ul style="list-style-type: none"> Regulation of PI3EN stability and activity MAPK family signaling cascades <ul style="list-style-type: none"> RAF/MAP kinase cascade Regulation of RAS by GAPs MAPK6/MAPK4 signaling Signaling by GPCR <ul style="list-style-type: none"> GPCR downstream signalling G alpha (q) signalling events G alpha (12/13) signalling events G alpha (s) signalling events <ul style="list-style-type: none"> GP1R1 signaling G alpha (i) signalling events GPCR ligand binding Class A/1 (Rhodopsin–like receptors) Class B/2 (Secretin family receptors) Signaling by Hedgehog <ul style="list-style-type: none"> Hedgehog ligand biogenesis Hedgehog ‘off’ state <ul style="list-style-type: none"> Degradation of GLI1 by the proteasome Degradation of GLI2 by the proteasome GLI3 is processed to GLI3R by the proteasome Hedgehog ‘on’ state Signaling by NOTCH <ul style="list-style-type: none"> Signaling by NOTCH1 <ul style="list-style-type: none"> Activated NOTCH1 Transmits Signal to the Nucleus Signaling by NOTCH2 <ul style="list-style-type: none"> NOTCH2 Activation and Transmission of Signal to the Nucleus Signaling by NOTCH3 <ul style="list-style-type: none"> NOTCH3 Activation and Transmission of Signal to the Nucleus NOTCH3 Intracellular Domain Regulates Transcription Signaling by NOTCH4 <ul style="list-style-type: none"> Negative regulation of NOTCH4 signaling Signaling by Non–Receptor Tyrosine Kinases <ul style="list-style-type: none"> Signaling by PTK <ul style="list-style-type: none"> PTK6 Regulates RHO GTPases, RAS GTPase and MAP kinases ESR–mediated signaling <ul style="list-style-type: none"> Extra–nuclear estrogen signaling Estrogen–dependent nuclear events downstream of ESR–membrane signaling Signaling by Receptor Tyrosine Kinases <ul style="list-style-type: none"> Signaling by ERBB2 <ul style="list-style-type: none"> Downregulation of ERBB2 signaling Signaling by SCF–KIT <ul style="list-style-type: none"> Regulation of KIT signaling Signaling by EGFR <ul style="list-style-type: none"> EGFR downregulation Signaling by FGFR <ul style="list-style-type: none"> Negative regulation of FGFR1 signaling Signaling by FGFR2 <ul style="list-style-type: none"> Negative regulation of FGFR2 signaling Signaling by FGFR3 <ul style="list-style-type: none"> Negative regulation of FGFR3 signaling Signaling by FGFR4 <ul style="list-style-type: none"> Negative regulation of FGFR4 signaling Signaling by VEGF <ul style="list-style-type: none"> VEGFA–VEGFR2 pathway VEGFR2 mediated vascular permeability Signaling by MET <ul style="list-style-type: none"> Negative regulation of MET activity Signaling by Rho GTPases, Miro GTPases and RHOBTB3 <ul style="list-style-type: none"> Signaling by Rho GTPases <ul style="list-style-type: none"> RHO GTPase cycle CDC42 GTPase cycle RAC1 GTPase cycle RHOH GTPase cycle RHOBTB3 GTPase cycle Signaling by TGF-beta family members <ul style="list-style-type: none"> Signaling by TGF–beta Receptor Complex <ul style="list-style-type: none"> Transcriptional activity of SMAD2/SMAD3:SMAD4 heterotrimer Downregulation of SMAD2/3:SMAD4 transcriptional activity SMAD2/SMAD3:SMAD4 heterotrimer regulates transcription Signaling by WNT <ul style="list-style-type: none"> Degradation of beta–catenin by the destruction complex TCF dependent signalling in response to WNT Deactivation of the beta–catenin/TCF transactivating complex Deactivation of the beta–catenin transactivating complex Degradation of AXIN Degradation of DVL Beta–catenin independent Wnt signaling Ca2+ pathway PCP/CE pathway <ul style="list-style-type: none"> Asymmetric localization of PCP proteins Transport of small molecules <ul style="list-style-type: none"> ABC–family proteins mediated transport Iron uptake and transport Plasma lipoprotein assembly, remodeling, and clearance VLDLR internalisation and degradation SLC–mediated transmembrane transport Transport of bile salts and organic acids, metal ions and admire compounds <p>Vesicle-mediated transport</p> <ul style="list-style-type: none"> Membrane Trafficking <ul style="list-style-type: none"> Gap junction trafficking and regulation ER to Golgi Anterograde Transport COP1–mediated anterograde transport trans–Golgi Network Vesicle Budding Golgi Associated Vesicle Biogenesis Intra–Golgi and retrograde Golgi–to–ER traffic Golgi–to–ER retrograde transport COP1–dependent Golgi–to–ER retrograde traffic COP1–independent Golgi–to–ER retrograde traffic Clathrin–mediated endocytosis Cargo recognition for clathrin–mediated endocytosis Rab regulation of trafficking Endosomal Sorting Complex Required For Transport (ESCRT)
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