

**Pathway Activity Analysis (PAA) as a new class of mechanistic biomarker to predict drug responses in drug repositioning for cancer patients**

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**ANNEX 1. Signalling Pathways**  
**Functional Annotation**

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# Signalling Pathways Functional Annotation

**TABLE 1. Functional annotation of the final effectors of the MAPK Signalling Pathway.**

Condition	Protein	Function	Key Word
JNK and p38	NFKB1	NF- $\kappa$ B acts through the transcription of anti-apoptotic proteins, leading to increased proliferation of cells and tumour growth (Escárcega, Fuentes-Alexandro, García-Carrasco, Gatica, & Zamora, 2007). Misregulated transcription in cancer (Escárcega et al., 2007).	Antiapoptosis  Cancer Transcriptional Misregulation Differentiation
		Regulates osteoclast formation, function, and survival and is essential for osteoclast precursors to differentiate into TRAP+ osteoclasts (Soysa & Alles, 2009)	
		Plays a central role in inflammation through its ability to induce transcription of proinflammatory genes (Tak & Firestein, 2001).	Inflammatory Response
Classical and JNK	MAPT	Tubulin assembly and microtubule stabilization in the nervous system (Cleveland, Hwo, & Kirschner, 1977).	Microtubule Stabilization
	STMN1	Microtubule destabilization and transition from microtubule growth to shortening (Cassimeris, 2002). Plays an inhibitory role in classically activated macrophages and its down-regulation is required for the phenotypic changes and activation of macrophages (Xu & Harrison, 2015)	Microtubule Destabilization  Immunity Regulation
		Merkel cell polyomavirus (MCPyV) drives Merkel Cell Cancer (MCC), and its highly metastatic nature is due to the increased expression and microtubule destabilization of stathmin (Whitehouse & Macdonald, 2015).	Viral Carcinogenesis
	PLA2G4A	Selectively hydrolyzes arachidonyl phospholipids in the sn-2 position releasing arachidonic acid. Together with its lysophospholipid activity, it is implicated in the initiation of the inflammatory response (The UniProt Consortium, 2017).	Inflammatory Response

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Condition	Protein	Function	Key Word
Classical and JNK	PLA2G4A	Requirement for eicosanoid synthesis and subsequent platelet activation (Kirkby et al., 2015)	Platelet Activation
	ATF4	In concert with DDIT3/CHOP, activates the transcription of TRIB3 and promotes ER stress-induced neuronal apoptosis by regulating the transcriptional induction of BBC3/PUMA (The UniProt Consortium, 2017).	Apoptotic Stress Response
		Role in multidrug resistance through glutathione-dependent redox system (Igarashi et al., 2007)	Cancer Drug Resistance
		Biomarker for Esophageal Squamous Cell Carcinoma (ESCC) prognosis, its dysregulation correlates with cell invasion and metastasis (Zhu et al., 2014)	Cancer Invasion
	FOS	Overexpressed in solid tumours, its inhibition reduced proliferation (Ye et al., 2010)	Proliferation
		Osteoblast (Grigoriadis et al., 1994) and adipocyte differentiation (Luther et al., 2014)	Differentiation
Increased expression in response to growth factors, leading to proliferation via the Activating Protein-1 (AP1) complex (Angel & Karin, 1991).		Proliferation	
MYC	Dependent and independently of TP53, through death receptor pathways at multiple junctions and amplifies apoptotic signalling at the mitochondria (Hoffman & Liebermann, 2008).	Apoptosis	
	Overexpression correlates with multiple myeloma (A. G. Szabo et al., 2016).	Cancer Transcriptional Misregulation	
	Induces positive cell cycle regulators required for initiating replication, binds replication origins, antagonizes cell cycle inhibitors p21 and p27 (Bretones, Delgado, & León, 2015).	Cell Cycle Progression	

(Continued)

Condition	Protein	Function	Key Word
Classical and JNK	MYC	Activates the transcription of growth-related genes (Dang, 1999).	Cell Growth
		Differentiation of epidermal stem cells (Gandarillas & Watt, 1997). It also controls the balance between Hematopoietic Stem Cell (HSC) renewal and differentiation (Wilson, 2004).	Differentiation
		HSCs are activated to self-renew and to differentiate at the interface between the niche and non-niche microenvironments (Murphy, Wilson, & Trumpp, 2005).	Stem Cell Self Renewal
Classical activates JNK and p38 inhibit	NFATC1	Participates in the cardiovascular system development (Horsley & Pavlath, 2002) and osteoclast formation (Teitelbaum, 2007).	Differentiation
		Transcription of cytokine genes and other genes involved in the immune response (Rao, Luo, & Hogan, 1997).	Immune Response
	NFATC3	Regulation of gene expression in T cells and thymocytes, specially cytokine IL-2 (The UniProt Consortium, 2017).	Immune Response
JNK and p38	JUN	DNAzymes targeting c-Jun act as inhibitors of angiogenesis (Folkman, 2004). Activated c-Jun is predominantly expressed at the invasive front in breast cancer and is associated with proliferation and angiogenesis (Vleugel, Greijer, Bos, Wall, & Diest, 2006).	Angiogenesis
		Targets the tumour suppressor TP53, which has an increased expression during cell division and in response to growth factors (Shaulian & Karin, 2001).	Proliferation
		G1 progression through repression of tumour suppressor genes and induction of CCND1 transcription (Shaulian & Karin, 2001).	Cell Cycle Progression
		Expression is altered early during lung and liver carcinogenesis (E. Szabo, Riffe, Steinberg, Birrer, & Linnoila, 1996).	Cancer Transcriptional Misregulation
		NFAT/Fos/Jun is a critical osteoclastogenic complex, and deletion of any of the three arrests osteoclast formation (Teitelbaum, 2007).	Differentiation

(Continued)

Condition	Protein	Function	Key Word
JNK and p38	JUND	Protects cells from TP53 dependent apoptosis (Ameyar, Wisniewska, & Weitzman, 2003).	Antiapoptosis
		Negative regulator of cell growth by maintaining the cells in a quiescent state (“The mammalian Jun proteins,” 2001).	Quiescence
	ATF2	In response to stress, ATF-2, a member of the ATF/cAMP response element-binding protein family, is phosphorylated by p38/Jun NH2-terminal protein kinase and activates the transcription of apoptosis-related genes (Makino, Sano, Shinagawa, Millar, & Ishii, 2006)	Apoptotic Stress Response
		The phosphorylated form (mediated by ATM) plays a role in the DNA damage response and is involved in the ionizing radiation (IR)-induced S phase checkpoint control and in the recruitment of the MRN complex into the IR-induced foci (IRIF) (The UniProt Consortium, 2017).	DNA Damage Response
		HBZ activates transcription of ATF2 pro-survival genes (Mesri, Feitelson, & Munger, 2014).	Viral Carcinogenesis
	ELK1	One of the mechanisms by which BRCA1a/1b proteins function as growth/tumour suppressors is through inhibition of the expression of Elk-1 target genes like FOS (Chai et al., 2001).	Growth Repressor
		Transcription factor that binds to purine-rich DNA sequences. Forms a ternary complex with SRF and the ETS and SRF motifs of the serum response element (SRE) on the promoter region of immediate early genes such as FOS and IER2 (The UniProt Consortium, 2017).	Transcription
	TTP53	(See TP53 Signalling Pathway)	Apoptosis Cell Cycle Arrest
	ELK4	Forms a ternary complex with the serum response factor (SRF). Interaction with SIRT7 leads to recruitment its stabilization at promoters, followed by deacetylation of histone H3 at Lys-18 and subsequent transcription repression (The UniProt Consortium, 2017).	Transcription Regulation

(Continued)

Condition	Protein	Function	Key Word
JNK and p38	DDIT3	Inducible inhibitor of adipocytic differentiation in response to metabolic stress (Batchvarova, Wang, & Ron, 1995).	Differentiation Inhibition
	DDIT3	Intrinsic pathway. Response to toxic and metabolic insults that perturb function of the endoplasmic reticulum (ER stress) (Zinszner et al., 1998).	Apoptotic Stress Response
		Nuclear DDIT3 causes cell cycle arrest at the G1/S (Jauhainen et al., 2012).	Cell Cycle Arrest
		Cytoplasmic DDIT3 inhibits cell migration (Jauhainen et al., 2012).	Cell Migration
		Enhances differentiation in erythroid cells (Cui, Coutts, Stahl, & Sytkowski, 2000).	Erythropoiesis
		Induction of CASP4/CASP11 which induces the activation of CASP1 and both of these increase the activation of pro-IL1B to mature IL1B (The UniProt Consortium, 2017).	Immune Response
	MAX	Transcription regulator. Forms a sequence-specific DNA-binding protein complex with MYC or MAD which recognizes the core sequence 5-CAC[GA]TG-3. The MYC-MAX complex is a transcriptional activator, whereas the MAD:MAX complex is a repressor (The UniProt Consortium, 2017).	Transcription Regulation
	(Kanehisa, Sato, Kawashima, Furumichi, & Tanabe, 2016)	Differentiation Proliferation	
MEF2C		Heart development, skeletal muscle differentiation, dendrite morphogenesis, control of vascular integrity, T-cell development, neuronal differentiation and survival (Potthoff & Olson, 2007).	Differentiation
		Required for B-cell survival and proliferation in response to BCR stimulation (Wilker et al., 2008).	Immune Response
HSPB1		Inhibits apoptotic and necrotic pathways under stress (Takayama, Reed, & Homma, 2003).	Antiapoptotic Stress Response

(Continued)

Condition	Protein	Function	Key Word
JNK and p38	ATF4	(See Classical Route)	Apoptotic Stress Response
			Cancer Drug Resistance
			Cancer Invasion
	ATF4	(See Classical Route)	Proliferation
	NLK	Kinase that regulates a number of transcription factors (The UniProt Consortium, 2017).	Transcription Regulation
MAPK7 pathway	NR4A1	Via migration to the mitochondrial outer membrane, converts anti-apoptotic BCL2 into a pro-apoptotic protein (Pawlak, Strzadala, & Kalas, 2015).	Apoptosis

**TABLE 2. Functional annotation of the final effectors of the TP53 Signalling Pathway.**

Condition	Protein	Function	Key Word
Stress Signalling	CCND1	Forms a complex with and functions as regulatory subunit of CDK4 and CDK6, whose activity is required for cell cycle G1/S transition (Hydbring, Malumbres, & Sicinski, 2016).	Cell Cycle Progression
	CCNE1	Essential master regulator of the G1/S transition which also cooperates with Cdc6 to allow prereplication complexes to form during the G0/S transition (Hwang & Clurman, 2005).	Cell Cycle Progression
	CCNB1	G2/M transition (Hydbring et al., 2016).	Cell Cycle Progression
	CASP3	Activated by the extrinsic and intrinsic pathways, cleaves and activates caspases 6, 7 and 9, and it is processed itself is by caspases 8, 9 and 10 (Salvesen, 2002).	Apoptosis

(Continued)



<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
Stress Signalling	IGF1	Regulates BCL2 family proteins, inhibitors of caspases and Signalling of death-inducing receptors inhibiting apoptosis in many cell types and in the presence of different apoptogenic stimuli (Kooijman, 2006).	Antiapoptosis
		Involved both in prenatal and postnatal development, enhances proliferation (Kemp, 2009).	Development
		Important growth hormone, endocrine when secreted by the liver or paracrine in cartilagenous cells important in protein anabolism (Laron, 2001).	Cell Growth
		Local repair mechanisms: promotion of cell recruitment to the injured muscle and the subsequent resolution of the inflammatory response (Mourkioti & Rosenthal, 2005).	Inflammatory Response
		Enhances proliferation and survival of mesenchymal stem cells before differentiation to neural progenitor-like cells (Huat et al., 2014).	Proliferation
SERPINB5	SERPINB5	The tumour suppressor activity of SERPINB5 may depend in large part on its ability to inhibit angiogenesis (Zhang, Volpert, Shi, & Bouck, 2000).	Antiangiogenesis
		Blocks the growth, invasion, and metastatic properties of mammary tumours (Streuli, 2002).	Cancer Invasion Inhibition
SESN1	SESN1	Antioxidant defense in response to oxidative stress (The UniProt Consortium, 2017).	Antioxidant
IGFBP3	IGFBP3	Induces apoptosis and mediates the effects of TGFb1 on programmed cell death through TP53 and IGF mechanisms (Rajah, 1997).	Apoptosis
		Inhibits proliferation of neural progenitor cells (Kalluri & Dempsey, 2011).	Antiproliferation
		Modulates the early stages of keratinocyte differentiation (Edmondson et al., 2005).	Differentiation

(Continued)

Condition	Protein	Function	Key Word
Stress Signalling	IGFBP3	Prolongs IGF1 and IGF2 half-life in circulation and regulates the available amount for interaction with their receptors (Cerri, Gonzales, Ballard, & Cohen, 1999).	Growth Inhibition
	STEAP3	Enhances susceptibility to apoptosis cooperating with Nix (Passer et al., 2003).	Apoptosis
		Augments MYT1 activity, a negative regulator of G2/M transition (Passer et al., 2003).	Cell Cycle Inhibition
		Transferrin uptake in erythroid cells (Sendamarai, Ohgami, Fleming, & Lawrence, 2008).	Ion Transporter
TP73	In response to DNA damage (Allocati, Di Ilio, & De Laurenzi, 2012).	Apoptosis	

**TABLE 3. Functional annotation of the final effectors of the Wnt Signalling Pathway.**

Condition	Protein	Function	Key Word
Canonical	MYC	(See MAPK Signalling Pathway)	Apoptosis Cancer Transcriptional Misregulation Cell Cycle Progression Cell Growth Differentiation Stem Cell Renewal
	JUN	(See MAPK Signalling Pathway)	Angiogenesis Proliferation Cell Cycle Progression Cancer Transcriptional Misregulation

*(Continued)*

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
Canonical	JUN	(See MAPK Signalling Pathway)	Differentiation
	FOSL1	High Fra-1 expression is associated with a more malignant cell phenotype (Belguise, Kersual, Galtier, & Chalbos, 2004).	Cancer Invasion Cancer Proliferation
		Negatively regulates LPS-induced responses in macrophages and inhibits fracture-induced ossification through suppression of inflammation-induced chondrogenesis (Morishita et al., 2009).	Antiinflammatory
		Dimerizes with Jun family proteins forming the transcription factor AP-1 (Shaulian & Karin, 2002).	Proliferation
	CCND1	(See TP53 Signalling pathway)	Cell Cycle Progression
	PPARD	Pronounced anti-inflammatory effects (Kilgore & Billin, 2008).	Antiinflammatory
		Redirects fatty acids from adipose tissue to skeletal muscle and increases its oxidative capacity, genetic variations determine change in aerobic physical fitness and insulin resistance (Stefan et al., 2007).	Lipid Metabolism
	MMP7	Breakdown of extracellular matrix in development, reproduction and tissue remodeling. Degrades casein, gelatins of types I, III, IV, and V, and fibronectin. Activates procollagenase. (The UniProt Consortium, 2017).	Extracellular Matrix Degradation
	ROCK2	Acts as a negative regulator of VEGF-induced angiogenic endothelial cell activation (The UniProt Consortium, 2017).	Antiangiogenesis
		Involved in regulation of smooth muscle contraction, actin cytoskeleton organization, focal adhesion formation, neurite retraction and motility via phosphorylation of ADD1, BRCA2, CNN1, EZR, DPYSL2, EP300, MSN, MYL9/MLC2, NPM1, RDX, PPP1R12A and VIM. The UniProt Consortium, 2017).	Cell Motility Regulation Cell Polarity

(Continued)

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
Canonical	ROCK2	Plays an important role in the timely initiation of centrosome duplication (The UniProt Consortium, 2017).	Centrosome Amplification
Wnt/Ca <sup>2+</sup>	NFATC1	(See MAPK Signalling Pathway)	Differentiation
	CAMK2A	Plasticity at glutamatergic synapses, hippocampal long-term potentiation (LTP) and spatial learning (The UniProt Consortium, 2017).	Immune Response Learning
	PRKCA	Required for full endothelial cell migration, adhesion to vitronectin (VTN) and VEGFA-dependent regulation of kinase activation and vascular tube formation. Involved in the stabilization of VEGFA mRNA level and mediates VEGFA-induced cell proliferation (The UniProt Consortium, 2017).	Angiogenesis
		Phosphorylates BCL2, required for its antiapoptotic activity (Ruvolo, Deng, Carr, & May, 1998).	Antiapoptosis
		Translocates from focal contacts to lamellipodia and participates in the modulation of desmosomal adhesion. Plays a role in cell motility by phosphorylating CSPG4, which induces association of CSPG4 with extensive lamellipodia at the cell periphery and cell polarity of the cell accompanied by increases in cell motility (The UniProt Consortium, 2017).	Cell Motility
		Calcium-induced platelet aggregation, mediates signals from the CD36/GP4 receptor for granule release, and activates the integrin heterodimer ITGA2B-ITGB3 through the RAP1GAP pathway for adhesion (The UniProt Consortium, 2017).	Platelet Aggregation
		Activates Raf1, Rap1 and Ras in the classical MAPK pathway, which leads to activation of STMN1, cPLA2, ATF4 and FOS. (Via FOS)	Angiogenesis Differentiation

(Continued)

Condition	Protein	Function	Key Word
Wnt/Ca2+	PRKCA	(Via ATF4 and FOS)	Proliferation
		(Via ATF4)	Apoptotic Stress Response Cancer Drug Resistance Cancer Invasion
		(Via STMN1)	Microtubule Destabilization
	PRKCA	(Via STMN1)	Viral Carcinogenesis
		(Via cPLA2)	Immunity Regulation Immune Response Phagocytosis Platelet Activation
		Promotes cell growth by phosphorylating and activating RAF1 (The UniProt Consortium, 2017).	Cell Growth

**TABLE 4. Functional annotation of the final effectors of the TGF- $\beta$  Signalling Pathway.**

Condition	Protein	Function	Key Word
BMP	ID1	Can inhibit the DNA binding and transcriptional activation ability of basic HLH proteins with which it interacts. Regulates: cellular growth, senescence, differentiation, apoptosis, angiogenesis, and neoplastic transformation. Inhibits skeletal muscle and cardiac myocyte differentiation. Leads to osteoblast differentiation, neurogenesis, neurogenesis, ventral mesoderm specification (The UniProt Consortium, 2017).	Transcription Regulation
TGF $\beta$	CDKN2B	Interacts strongly with CDK4 and CDK6 preventing their action, thus causing a cell cycle arrest at the G1 phase (Hydbring et al., 2016).	Cell Cycle Arrest

*(Continued)*

Condition	Protein	Function	Key Word
TGFβ	ROCK1	Acts as a negative regulator of VEGF-induced angiogenic endothelial cell activation, reducing cell interactions and mediates angiogenic processes (Bryan et al., 2010).	Angiogenesis
		Suppressor of inflammatory cell migration by regulating PTEN phosphorylation and stability (Vemula, Shi, Hanneman, Wei, & Kapur, 2010).	Antiinflammatory
		Rho-kinases are modulators of processes involving cytoskeletal rearrangement: regulation of smooth muscle contraction, cell adhesion and motility via phosphorylation of DAPK3, GFAP, LIMK1, LIMK2, MYL9/MYL2, PFN1 and PPP1R12A, promotes src-dependent blebbing (The UniProt Consortium, 2017).	Cytoskeletal Organization
Activin	SMAD2	(Kanehisa, Sato, Kawashima, Furumichi, & Tanabe, 2016)	Gonadal Growth
	SMAD3		Embryo Differentiation
	SMAD4		Placenta Formation
Nodal	PITX2	Transcriptional regulator involved in basal and hormone-regulated activity of prolactin. Involved in the development of the eye, tooth and abdominal organs. During embryonic development, exerts a role in the expansion of muscle progenitors (The UniProt Consortium, 2017).	Morphogenesis

**TABLE 5. Functional annotation of the final effectors of the Focal Adhesion Pathway.**

Condition	Protein	Function	Key Word
ECM – Receptor Interaction	ZYX	Adhesion plaque protein. Binds α-actinin and the CRP protein. Important for targeting TES and ENA/VASP family members to focal adhesions and for the formation of actin-rich structures. (The UniProt Consortium, 2017).	Cytoskeleton Organization Scaffold

*(Continued)*

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
ECM – Receptor Interaction	ZYX	Abnormal regulation of the actin cytoskeleton leads to the invasive and metastatic phenotypes of malignant cancer cells (Olson & Sahai, 2009).	Cancer Invasion
		Molecules that link migratory signals to the actin cytoskeleton are upregulated in invasive and metastatic cancer cells leading to formation of invasive protrusions used by tumour cells, such as lamellipodia and invadopodia (Yamaguchi & Condeelis, 2007)	Cancer Invasion
	VASP	Ena/VASP proteins are actin-associated proteins involved in a range of processes dependent on cytoskeleton remodeling and cell polarity such as axon guidance, lamellipodial and filopodial dynamics, platelet activation and cell migration. VASP promotes actin filament elongation. It protects the barbed end of growing actin filaments against capping and increases the rate of actin polymerization in the presence of capping protein. VASP stimulates actin filament elongation by promoting the transfer of profilin-bound actin monomers onto the barbed end of growing actin filaments. Plays a role in actin-based mobility of <i>Listeria monocytogenes</i> in host cells. Regulates actin dynamics in platelets and plays an important role in regulating platelet aggregation (The UniProt Consortium, 2017).	Cytoskeletal Organization  Platelet Aggregation
		Abnormal regulation of the actin cytoskeleton leads to the invasive and metastatic phenotypes of malignant cancer cells (Olson & Sahai, 2009). Molecules that link migratory signals to the actin cytoskeleton are upregulated in invasive and metastatic cancer cells leading to formation of invasive protrusions used by tumour cells, such as lamellipodia and invadopodia (Yamaguchi & Condeelis, 2007).	Cancer Invasion

(Continued)

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
ECM – Receptor Interaction or Interaction of Cytokines and their Receptors	ACTA1	Involved in cell motility, structure, and integrity. It is found in two main states: G-actin is the globular monomeric form and F-actin forms helical polymers. Both G- and F-actin are intrinsically flexible structures.	Cytoskeleton Organization
ECM – Receptor Interaction or Interaction of Cytokines and their Receptors	ACTA1	Actin polymerization leads to formation of lamellipodia and filopodia (The UniProt Consortium, 2017).	Motility Scaffold
		Abnormal regulation of the actin cytoskeleton leads to invasive and metastatic phenotypes of malignant cancer cells (Olson & Sahai, 2009). Molecules that link migratory signals to the actin cytoskeleton are upregulated in invasive and metastatic cancer cells leading to formation of invasive protrusions used by tumour cells, such as lamellipodia and invadopodia (Yamaguchi & Condeelis, 2007).	Cancer Invasion
	FLNB	Connects cell membrane constituents to the actin cytoskeleton. May promote orthogonal branching of actin filaments and links actin filaments to membrane glycoproteins. Anchors various transmembrane proteins to the actin cytoskeleton. Interaction with FLNA may allow neuroblast migration from the ventricular zone into the cortical plate. Various interactions and localizations of isoforms affect myotube morphology and myogenesis (The UniProt Consortium, 2017).	Cellular Community Morphogenesis Cytoskeleton Organization Motility Scaffold
		Abnormal regulation of the actin cytoskeleton leads to the invasive and metastatic phenotypes of malignant cancer cells (Olson & Sahai, 2009). Molecules that link migratory signals to the actin cytoskeleton are upregulated in invasive and metastatic cancer cells leading to formation of invasive protrusions used by tumour cells, such as lamellipodia and invadopodia (Yamaguchi & Condeelis, 2007).	Cancer Invasion

(Continued)



<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
ECM – Receptor Interaction or Interaction of Cytokines and their Receptors	FLNB	Tumour-promoting effect by interacting with signalling molecules. At the nucleus, interacts with transcription factors suppressing tumour growth and inhibit metastasis. It correlates patient prognosis, depending on its localization and cancer type (Savoy & Ghosh, 2013).	Tumour Suppressor
	PAK4	Prevents caspase-8 binding to death domain receptors (Gnesutta, Qu, & Minden, 2001).	Antiapoptosis
		Roll in cell-cycle progression by phosphorylating RAN, if silenced induces a blockade at the G2/M transition (Bompard et al., 2010).	Cell Cycle Progression
		Stimulates cell survival by phosphorylating the BCL2 antagonist of cell death BAD (The UniProt Consortium, 2017).	Cell Survival
	CCND1	Phosphorylates and inactivates the protein phosphatase SSH1 and LIMK1, leading to increased inhibitory phosphorylation of the actin binding/depolymerizing factor cofilin. Decreased cofilin activity may lead to stabilization of actin filaments. Also phosphorylates ARHGEF2 and activates the downstream target RHOA that plays a role in the regulation of assembly of focal adhesions and actin stress fibres (The UniProt Consortium, 2017).	Cytoskeleton Regulation
		(See TP53 Signalling Pathway)	Cell Cycle Progression
BIRC2	Inhibits apoptosis by binding to TRAF1 and TRAF2 and targets caspases for inactivation acting as a E3 ubiquitin-protein ligase (Darding et al., 2011).	Antiapoptosis	
	Protects from spontaneous formation of the ripoptosome, a large multi-protein complex that has the capability to kill cancer cells, by ubiquitinating RIPK1 and CASP8 (Tenev et al., 2011).	Cancer Survival	

(Continued)

Condition	Protein	Function	Key Word
ECM – Receptor Interaction or Interaction of Cytokines and their Receptors	BIRC2	Acts as an important regulator of innate immune signalling via regulation of Toll-like receptors (TLRs), Nodlike receptors (NLRs) and RIG-I like receptors (RLRs), collectively referred to as pattern recognition receptors (PRRs) (Sharma, Kaufmann, & Biswas, 2017).	Inflammatory Response
	BCL2	This gene encodes an integral outer mitochondrial membrane protein that blocks the apoptotic death of some cells, such as lymphocytes (The UniProt Consortium, 2017).	Antiapoptosis

**TABLE 6. Functional annotation of the final effectors of the Adherens Junction Pathway.**

Condition	Protein	Function	Key Word
Nectin	PARD3	Adapter protein involved in asymmetrical cell division and cell polarity processes, also has a central role in the formation of epithelial tight junctions (The UniProt Consortium, 2017).	Cell Polarity Scaffold
	WASL	Regulates actin polymerization by stimulating the actin-nucleating activity of the Arp2/3 complex. It is also involved in mitosis and cytokinesis. (The UniProt Consortium, 2017).	Cytoskeleton Organization
	WAS	Interacts with the Arp2/3 complex to induce actin polymerization (The UniProt Consortium, 2017). Mediates actin filament reorganization and the formation of actin pedestals upon infection by pathogenic bacteria (The UniProt Consortium, 2017).	Cytoskeleton Organization Immune Response
	IQGAP1	It interacts with components of the cytoskeleton and adhesion molecules and other molecules to regulate cell morphology and motility (The UniProt Consortium, 2017).  Contributes to the transformed cancer cell phenotype by regulating signalling pathways involved in cell proliferation and transformation,	Cytoskeleton Organization  Cancer Invasion

*(Continued)*

Condition	Protein	Function	Key Word
Nectin	IQGAP1	weakening of cell – cell adhesion contacts and stimulation of cell motility and invasion (Johnson, Sharma, & Henderson, 2009).	Cancer Invasion
	BAIAP2	Associated with formation of stress fibres and cytokinesis. Involved in lamellipodia and filopodia formation in motile cells acting synergistically with ENAH. Pays a role in neurite growth (The UniProt Consortium, 2017).	Cytoskeleton Organization
		Plays a role in the reorganization of the actin cytoskeleton in response to bacterial infection. Participates in actin bundling when associated with EPS8, promoting filopodial protrusions (The UniProt Consortium, 2017).	Immune Response
WASF2	Associated with formation of stress fibres and cytokinesis. Involved in lamellipodia and filopodia formation in motile cells acting synergistically with ENAH. Pays a role in neurite growth (The UniProt Consortium, 2017).	Cytoskeleton Organization	
		Plays a role in the reorganization of the actin cytoskeleton in response to bacterial infection. Participates in actin bundling when associated with EPS8, promoting filopodial protrusions (The UniProt Consortium, 2017).	Immune Response
Nectin and Cadherin	ACTA1	(See Focal Adhesion Pathway)	Cytoskeleton Organization  Motility  Scaffold  Cancer Invasion
Cadherin	CTNNB1	Mutations are commonly found in various cancer such as colorectal and ovarian cancer, pilomatrixoma or medulloblastoma (Forbes et al., 2010). These mutations lead to impossible degradation of the protein and its translocation to the nucleus in the absence of external stimulus, where it continuously drives transcription of its target genes (Stamos & Weis, 2013).	Cancer Development

(Continued)

Condition	Protein	Function	Key Word
Cadherin	CTNNB1	It anchors the actin cytoskeleton and may be responsible for transmitting the contact inhibition signal that causes cells to stop dividing once the epithelial sheet is complete (The UniProt Consortium, 2017).	Cell Proliferation Inhibition
		Part of the complex of proteins that constitute adherens junctions (AJs), necessary for the creation and maintenance of epithelial cell layers by regulating cell growth and adhesion between cells	Scaffold
	LEF1	Hair cell differentiation and follicle morphogenesis (The UniProt Consortium, 2017).	Cell Differentiation
	SNAI2	Critical role for SNAI2 in the pathogenesis of mesenchymal tumours and contributes to cancer progression (Pérez-Mancera et al., 2005). Forced expression of SNAI2 in collaboration with Sox9 in breast cancer cells can efficiently induce entrance into the Tumour Initiating Cell (TIC) state (Ye et al., 2015).	Cancer Development
		Involved in epithelial-mesenchymal transitions and has antiapoptotic activity. Transcriptional repressor, represses BRCA2 expression in breast cells and ITGA3 in keratinocytes. Involved in the regulation of ITGB1 and ITGB4 expression and cell adhesion and proliferation in epidermal keratinocytes. Represses E-Cadherin transcription (The UniProt Consortium, 2017).	EMT Transcription Regulation

**TABLE 7. Functional annotation of the final effectors of the Tight Junction Pathway.**

Condition	Protein	Function	Key Word
CRB3	MPP4	Localized to the outer limiting membrane in the retina, functions in photoreceptor polarity and the organization of specialized intercellular junctions (The UniProt Consortium, 2017).	Polarity Scaffold (Continued)

Condition	Protein	Function	Key Word
CRB3	CDC42	RAC1 and CDC42 are active in their GTP-bound state. When active, they bind to a variety of effector proteins to regulate epithelial cell polarity. Furthermore, RAC1 is responsible for growth-factor induced formation of membrane ruffles and promotes cell migration and invasion in glioma cells (Ensign et al., 2013).	Cancer Invasion Cell Polarity Proliferation
	RAC1	RAC1 and CDC42 are active in their GTP-bound state. When active, they bind to a variety of effector proteins to regulate epithelial cell polarity. Furthermore, RAC1 is responsible for growth-factor induced formation of membrane ruffles and promotes cell migration and invasion in glioma cells (Ensign et al., 2013).	Cancer Invasion Cell Polarity Proliferation
	DLG1	Multi-domain scaffolding protein, recruits channels, receptors and Signalling molecules to discrete plasma membrane domains in polarized cells (The UniProt Consortium, 2017).	Cell Polarity Scaffold
	SCRIB	Scaffold protein involved in different aspects of cell Cell Polarity processes, regulating epithelial and neuronal morphogenesis, such as the establishment of apico-basal cell polarity (The UniProt Consortium, 2017).	Cell Polarity
Claudin with Claudin	MPP4	(See CRB3 above)	Polarity Scaffold
	CDC42	(See CRB3 above)	Cancer Invasion Cell Polarity Proliferation (Continued)

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
Claudin with Claudin	DLG1	(See CRB3 above)	Cell Polarity Scaffold
	SCRIB	(See CRB3 above)	Cell Polarity
	RAC1	(See CRB3 above)	Cancer Invasion Cell Polarity Proliferation
	DLG2	Regulates surface expression of NMDA receptors, is part of the postsynaptic protein scaffold of excitatory synapses (The UniProt Consortium, 2017).	Cell Polarity Scaffold
	DLG3	Clustering of NMDA receptors at excitatory synapses, regulates surface expression of NMDA receptors, is part of the postsynaptic protein scaffold of excitatory synapses (The UniProt Consortium, 2017).	Cell Polarity Scaffold
	CLDN2	Major integral membrane proteins localized exclusively at tight junctions. Its increased expression leads to less paracellular permeability between cells (The UniProt Consortium, 2017).	Decreased Permeability Scaffold
	WAS	(See Adherens Junction Pathway)	Cytoskeleton Organization Immune Response
	ACTN1	Actin is a ubiquitous globular protein that is one of the most highly-conserved proteins known. It is found in two main states: G-actin is the globular monomeric form, whereas F-actin forms helical polymers. Both G- and F-actin are intrinsically flexible structures (The UniProt Consortium, 2017).	Cytoskeleton Organization

(Continued)

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
Claudin with Claudin	Arp2/3	Arp2/3-mediated actin polymerization both at the Golgi apparatus and along tubular membrane and actin branching (The UniProt Consortium, 2017).	Cytoskeleton Organization
	MYL2	Very important for cardiac muscle contraction via tight junction assembly, it increases myosin lever arm stiffness and myosin head diffusion (The UniProt Consortium, 2017).	Scaffold
	VASP	(See Focal Adhesion Pathway)	Cytoskeleton Organization Cancer Invasion Platelet Aggregation
Occludin with Occludin	RAC1	(See CRB3 above)	Cancer Invasion Cell Polarity Proliferation
	DLG2	(See Claudins above)	Cell Polarity Scaffold
	DLG3		Cell Polarity Scaffold
Occludin with Occludin	CLDN2	(See Claudins above)	Decreased Permeability Scaffold
	WAS	(See Adherens Junction Pathway)	Cytoskeleton Organization Immune Response
	ACTN1	(See Claudins above)	Cytoskeleton Organization
			<i>(Continued)</i>

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
Occludin with Occludin	Arp2/3	(See Claudins above)	Cytoskeleton Organization
	MYL2	(See Claudins above)	Scaffold
	VASP	(See Claudins above)	Cytoskeleton Organization
			Scaffold
	PCNA	Involved in the control of eukaryotic DNA replication by increasing the polymerases processibility during elongation of the leading strand (The UniProt Consortium, 2017).	Proliferation
	CCND1	(See TP53 Signalling Pathway)	Cell Cycle Progression
	ERBB2	Regulates outgrowth and stabilization of peripheral microtubules. Implicated in transcriptional activation of CDKN1A; the function involves STAT3 and SRC. Involved in the transcription of rRNA genes by RNA Pol I and enhances protein synthesis and cell growth (The UniProt Consortium, 2017).	Growth Cytoskeleton Organization
	Runx1	Runx1 is the alpha subunit of CBF, which is involved in the development of normal hematopoiesis (Hart & Foroni, 2002).	Hematopoiesis
JAM/JAM	RAC1	(See CRB3 above)	Cancer Invasion Cell Polarity Proliferation
	DLG3	(See Claudins above)	Cell Polarity Scaffold
	DLG2	(See Claudins above)	Cell Polarity (Continued)



<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
JAM/JAM	DLG2	(See Claudins above)	Scaffold
	CLDN2	(See Claudins above)	Decreased Permeability Scaffold
	Integrin	Integrins are receptors for collagen and support cell migration through collagen rich extracellular matrix. They mediate dynamic interactions between the extracellular matrix and the actin cytoskeleton during cell motility (Huttenlocher & Horwitz, 2011).	Cell Migration
	MYL2	(See Claudins above)	Decreased Permeability Scaffold
Bves/Bves	CLDN2	(See Claudins above)	Decreased Permeability Scaffold
MarvelD3/MarvelD3	CD1	Mediate the presentation of primarily lipid and glycolipid antigens of self or microbial origin to T cells (Barral & Brenner, 2007).	Cell Survival Immune Response
CFTR	PCNA/CCND1	(See Occludins above)	Proliferation
	ERBB2	(See Occludins above)	Growth Cytoskeleton Organization
	Runx1	(See Occludins above)	Hematopoiesis
	PRKCE	Assembly of the Tight Junction, PCK epsilon triggers the anchorage of the actin cytoskeleton to the plasma membrane via moesin (Newton & Messing, 2010).	Scaffold
aPKC/PAR6	MYL2	(See Claudins Above)	Scaffold

(Continued)

Condition	Protein	Function	Key Word
JAM4/JAM4	RAB8A	Regulators of intracellular membrane trafficking, from the formation of transport vesicles to their fusion with membranes (The UniProt Consortium, 2017).	AJ Assembly Vesicular Transport
JAM4/JAM4	RAB13	Regulates transport to the plasma membrane of transmembrane proteins, thereby, it regulates the assembly and the activity of tight junction. Key regulator of intracellular membrane trafficking, from the formation of transport vesicles to their fusion with membranes. Plays also a role in angiogenesis through regulation of endothelial cells chemotaxis (The UniProt Consortium, 2017).	Angiogenesis Tight Junction Assembly Vesicular Transport
Tricellulin/Tricellulin	WAS	(See Adherens Junction Pathway)	Cytoskeleton Organization Immune Response
	ACTN1	(See Claudins above)	Cytoskeleton Organization
	Arp2/3		Cytoskeleton Organization

**TABLE 8. Functional annotation of the final effectors of the mTOR Signalling Pathway.**

Condition	Protein	Function	Key Word
mTORC1	CLIP1	Promotes microtubule growth and microtubule bundling. Links cytoplasmic vesicles to microtubules and thereby plays an important role in intracellular vesicle trafficking (The UniProt Consortium, 2017).	Microtubule Organization
	GRB10	Key regulator of adiposity, thermogenesis, and energy expenditure (Liu et al., 2014).	Lipolysis

*(Continued)*

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
mTORC1	LPIN1	Catalyzes the penultimate step in triglyceride synthesis. Expression of this gene is required for adipocyte differentiation (The UniProt Consortium, 2017).	Differentiation Lipid Biosynthesis
	ULK1	Involved in autophagy in response to starvation. Acts upstream of phosphatidylinositol 3-kinase PIK3C3 to regulate the formation of autophagophores, the precursors of autophagosomes. Part of regulatory feedback loops in autophagy: downstream effector and a negative regulator of mTORC1 (The UniProt Consortium, 2017).	Autophagy
	EIF4E	component of the eukaryotic translation initiation factor 4F complex in translation initiation by recruiting ribosomes to the 5'-cap structure (The UniProt Consortium, 2017).	Protein Synthesis
	EIF4B	Required for the binding of mRNA to ribosomes. binds near the 5-terminal cap of mRNA in presence of EIF-4F and ATP. Promotes the ATPase activity and the ATP-dependent RNA unwinding activity of both EIF4-A and EIF4-F (The UniProt Consortium, 2017).	Protein Synthesis
	RPS6KB1	Cytoplasmic ribosomal protein that is a component of the 40S subunit (The UniProt Consortium, 2017).	Protein Synthesis
mTORC2	RHOA	Role in the regulation of assembly of focal adhesions and actin stress fibres (Sit & Manser, 2011).	Cytoskeleton Organization
	PKC	(See Wnt Signalling Pathway)	Angiogenesis Apoptosis Apoptotic Stress Response

(Continued)

Condition	Protein	Function	Key Word
mTORC2	PKC	(See Wnt Signalling Pathway)	Cancer Drug Resistance Cancer Invasion Cancer Proliferation Cytoskeleton Organization Cytoskeleton Regulation Differentiation Immunity Regulation Immune Response Phagocytosis Platelet Activation Proliferation Viral Carcinogenesis
	SGK1	SGKs are related to Akt (also called PKB), a serine/threonine kinase that plays a crucial role in promoting cell survival. Like Akt, SGKs are activated by the phosphoinositide-3 kinase (PI3K) and translocate to the nucleus upon growth factor stimulation. SGK1, like Akt, promotes cell survival and that it does so in part by phosphorylating and inactivating FKHL1 (Brunet et al., 2001).	Cell Survival

**TABLE 9. Functional annotation of the final effectors of the AMPK Signalling Pathway.**

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
AMPK	PFKFB1	Catalyses the synthesis and degradation of fructose 2,6-bisphosphate, phosphorylated by AMPK leads to increased glycolysis (The UniProt Consortium, 2017).	Glycolysis
	G6PC	Hydrolyzes glucose-6-phosphate to glucose in the endoplasmic reticulum. Forms with the glucose-6-phosphate transporter complex responsible for glucose production through glycogenolysis and gluconeogenesis. Hence, it is the key enzyme in homeostatic regulation of blood glucose level (The UniProt Consortium, 2017).	Gluconeogenesis
	PCK2	Catalyzes the conversion of oxaloacetate (OAA) to phosphoenolpyruvate (PEP), the rate-limiting step in the metabolic pathway that produces glucose from lactate and other precursors derived from the citric acid cycle (The UniProt Consortium, 2017).	Gluconeogenesis
	PPARGC1A	Transcriptional coactivator, can regulate key mitochondrial genes that contribute to the program of adaptive thermogenesis. Plays an essential role in metabolic reprogramming in response to dietary availability through coordination of the expression of a wide array of genes involved in glucose and fatty acid metabolism (The UniProt Consortium, 2017).	Gluconeogenesis
	CCND1	(See TP53 Signalling Pathway)	Cell Cycle Progression
	CCNA	Essential for the control of the cell cycle at the G1/S (start) and the G2/M (mitosis) transitions (The UniProt Consortium, 2017).	Cell Cycle Progression
	EEF2	Essential factor for protein synthesis, it promotes the GTP-dependent translocation of the nascent protein chain from the A-site to the P-site of the ribosome (The UniProt Consortium, 2017).	Protein Synthesis

*(Continued)*

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
AMPK	SIRT1	Sirt1's deacetylation of Peroxisome proliferator-activated receptor Gamma Coactivator-1 $\alpha$ (PGC-1 $\alpha$ ) has been extensively implicated in metabolic control and mitochondrial biogenesis (Tang, 2016).	Mitochondrial Biogenesis
	SLC2A4	Insulin-regulated facilitative glucose transporter, within minutes of insulin stimulation, the protein moves to the cell surface and begins to transport glucose across the cell membrane (The UniProt Consortium, 2017).	Glucose Transporter
	GYS	Catalyzes the addition of glucose monomers to the growing glycogen molecule through the formation of alpha-1,4-glycoside linkages	Glycogen Synthesis
	LIPE	In adipose tissue and heart, it primarily hydrolyzes stored triglycerides to free fatty acids, while in steroidogenic tissues, it converts cholesteryl esters to free cholesterol for steroid hormone production (The UniProt Consortium, 2017).	Lipolysis
	HMGCR	Catalyzes the conversion of 3-hydroxy-3-methyl-glutaryl-CoA to mevalonic acid, the rate limiting step in cholesterol biosynthesis (The UniProt Consortium, 2017).	Cholesterol Synthesis
	FAS	Catalyzes the conversion of acetyl-CoA and malonyl-CoA to the 16-carbon fatty acid palmitate (The UniProt Consortium, 2017). FASN overexpression and hyperactivity is commonly associated with malignant cells (Menendez & Lupu, 2007).	Lipid Biosynthesis Cancer Transcriptional Misregulation
	ACACA	Catalyzes the rate-limiting reaction in the biogenesis of long-chain fatty acids (The UniProt Consortium, 2017).	Lipid Biosynthesis
	SCD	Enzyme involved in fatty acid biosynthesis, primarily the synthesis of oleic acid (The UniProt Consortium, 2017).	Lipid Biosynthesis

(Continued)

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
AMPK	CFTR	Transporter, secretes chloride outside of the cell (The UniProt Consortium, 2017).	Chloride Secretion
	ACACB	Thought to control fatty acid oxidation by means of the ability of malonyl-CoA to inhibit carnitine-palmitoyl-CoA transferase I, the rate-limiting step in fatty acid uptake and oxidation by mitochondria (The UniProt Consortium, 2017).	Fatty Acid Oxidation
	MLYCD	Catalyses the breakdown of malonyl-CoA to acetyl-CoA and carbon dioxide. Malonyl-CoA is an intermediate in fatty acid biosynthesis, also inhibits the transport of fatty acyl CoAs into mitochondria. Consequently, the encoded protein acts to increase the rate of fatty acid oxidation (The UniProt Consortium, 2017).	Fatty Acid Oxidation
	CPT1A	Regulates the beta-oxidation and transport of long-chain fatty acids into mitochondria (The UniProt Consortium, 2017).	Fatty Acid Oxidation Regulation
	RPS6KB1	(See mTOR Signalling Pathway)	Protein Synthesis
	EIF4E	(See mTOR Signalling Pathway)	Protein Synthesis
	PPARG	Nuclear receptor that binds peroxisome proliferators such as fatty acids. Binds to DNA specific PPAR response elements (PPRE) and modulates the transcription of its target genes, such as acyl-CoA oxidase. It therefore controls the peroxisomal beta-oxidation pathway of fatty acids. Key regulator of adipocyte differentiation and glucose homeostasis (The UniProt Consortium, 2017).	Differentiation
	ULK1	(See mTOR Signalling Pathway)	Autophagy

**TABLE 10. Functional annotation of the final effectors of the PI3K-AKT Signalling Pathway.**

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
Hypoxia/AMP/LKB1	EIF4E	(See mTOR Signalling Pathway)	Protein Synthesis
	EIF4B	(See mTOR Signalling Pathway)	Protein Synthesis
	RPS6KB1	(See mTOR Signalling Pathway)	Protein Synthesis
GF	MAPK1	Translocates to the nucleus of the stimulated cells, where it phosphorylates nuclear target, mediating diverse biological functions such as cell growth, adhesion, survival and differentiation. Plays also a role in initiation and regulation of meiosis, mitosis, and post-mitotic functions in differentiated cells (Sato et al., 2011). Endothelial angiogenic response via frequency-sensitive MAPK/ERK pathway activation (Sheikh et al., 2013).	Angiogenesis DNA Repair Proliferation
PIP3	PKC	(See Wnt Signalling Pathway)	Angiogenesis Apoptosis Apoptotic Stress Response Cancer Drug Resistance Cancer Invasion Cancer Proliferation Cytoskeleton Organization Cytoskeleton Regulation Differentiation
PIP3	PKC	(See Wnt Signalling Pathway)	Immunity Regulation Immune Response Phagocytosis (Continued)





Condition	Protein	Function	Key Word
PIP3	BRCA1	Probable predisposing mutations have been detected in five of eight kindreds presumed to segregate BRCA1 susceptibility alleles (Miki et al., 1994).	Cancer Development
	GYS	(See AMPK Signalling Pathway)	Glycogen Synthesis
	PCK2	(See AMPK Signalling Pathway)	Gluconeogenesis
	G6Pase	(See AMPK Signalling Pathway)	Gluconeogenesis
	MYC	(See MAPK Signalling Pathway)	Cell Cycle Progression Cell Growth Differentiation Stem Cell Self Renewal
	CCND1	(See Wnt Signalling Pathway)	Cell Cycle Progression
	CDKN1B	Regulator of cell cycle progression. Involved in G1 arrest. Potent inhibitor of cyclin E- and CCNA-CDK2 complexes. Forms a complex with cyclin type D-CDK4 complexes and is involved in the assembly, stability, and modulation of CCND1-CDK4 complex activation. Controls the cell cycle progression at G1. The degradation of this protein is required for the cellular transition from quiescence to the proliferative state (The UniProt Consortium, 2017).	Cell Cycle Arrest
	RBL2	Key regulator of entry into cell division. Directly involved in heterochromatin formation by maintaining overall chromatin structure. In particular, that of constitutive heterochromatin by stabilizing histone methylation (The UniProt Consortium, 2017).	Cell Cycle Progression
	FASLG	Induction of apoptosis triggered by binding to FAS (The UniProt Consortium, 2017).	Apoptosis <i>(Continued)</i>

Condition	Protein	Function	Key Word
PIP3	FASLG	<p>The Fas/FASLG system plays a significant role in tumorigenesis. Research has shown that its impairment in cancer cells may lead to apoptosis resistance and contribute to tumor progression (Villa-Morales &amp; Fernández-Piqueras, 2012).</p> <p>Essential for immune system regulation, including activation-induced cell death (AICD) of T cells and cytotoxic T lymphocyte induced cell death (The UniProt Consortium, 2017).</p>	<p>Cancer Development</p> <p>Immune Response</p>
	BCL2L11	<p>It has been shown to interact with other members of the BCL2 protein family and to act as an apoptotic activator. The expression of this gene can be induced by nerve growth factor (NGF), as well as by the forkhead transcription factor FKHR-L1, which suggests a role of this gene in neuronal and lymphocyte apoptosis. Transgenic studies of the mouse counterpart suggested that this gene functions as an essential initiator of apoptosis in thymocyte-negative selection (The UniProt Consortium, 2017).</p>	Apoptosis
	BCL2L1	<p>Potent inhibitor of cell death. Inhibits activation of caspases. Appears to regulate cell death by blocking the voltage-dependent anion channel (VDAC) by binding to it and preventing the release of the caspase activator, CYC1, from the mitochondrial membrane (The UniProt Consortium, 2017).</p>	Antiapoptosis
	BCL2	(See Focal Adhesion Pathway)	Antiapoptosis

(Continued)

Condition	Protein	Function	Key Word
	CASP9	This protein can undergo autoproteolytic processing and activation by the apoptosome; this step is thought to be one of the earliest in the caspase activation cascade (The UniProt Consortium, 2017).	Apoptosis
	MCL1	Antiapoptotic, regulates apoptosis versus cell survival, and maintenance of viability. Mediates its effects by interacting with other regulators of apoptosis (The UniProt Consortium, 2017).	Antiapoptosis
	MYB	Essential role in hematopoiesis regulation (The UniProt Consortium, 2017).	Hematopoiesis
		Aberrantly expressed or rearranged in leukemias and lymphomas, an oncogene (Ramsay & Gonda, 2008).	Cancer Development
	TP53	Induces growth arrest or apoptosis depending on the physiological circumstances and cell type. Involved in cell cycle regulation as a trans-activator that negatively regulates cell division. Apoptosis induction seems to be mediated either by stimulation of BAX and FAS antigen expression, or by repression of BCL2 expression. With PPIF is involved in activating oxidative stress-induced necrosis. Induces transcription of long intergenic non-coding RNA p21, which participates in TTP53-dependent transcriptional repression leading to apoptosis and seems to have to effect on cell-cycle regulation. Implicated in Notch signalling cross-over. Prevents CDK7 kinase activity when associated to CAK complex in response to DNA damage, thus stopping cell cycle progression (The UniProt Consortium, 2017).	Apoptosis

**TABLE 11. Functional annotation of the final effectors of the PPAR Signalling Pathway.**

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
PPAR $\alpha$ /RXR	HMGCS2	Catalyzes the first reaction of ketogenesis, a metabolic pathway that provides lipid-derived energy for various organs during times of carbohydrate deprivation, such as fasting (The UniProt Consortium, 2017).	Ketogenesis
	APOA1	Components of the high density lipoprotein (HDL) and very low density lipoproteins (VLDL) in plasma, promotes cholesterol efflux from tissues to the liver for excretion into plasma (The UniProt Consortium, 2017).	Lipid Transport
	APOA2		Lipid Transport
	APOC3		Lipid Transport
	APOA5		Lipid Transport
PLTP	Lipid Transport		
PPAR $\alpha$ /RXR or PPAR $\gamma$ /RXR	ME1	Generates NADPH for fatty acid biosynthesis (The UniProt Consortium, 2017).	Lipid Biosynthesis
	SCD	Stearyl-CoA desaturase that utilizes O(2) and electrons from reduced cytochrome b5 to introduce the first double bond into saturated fatty acyl-CoA substrates (The UniProt Consortium, 2017).	Lipid Biosynthesis
	FADS2	Catalyzes biosynthesis of highly unsaturated fatty acids from precursor essential polyunsaturated fatty acids (The UniProt Consortium, 2017).	Lipid Biosynthesis
	CYP7A1	Catalyzes the first reaction in the cholesterol catabolic pathway in the liver, which converts cholesterol to bile acids. which is the primary mechanism for the removal of cholesterol from the body (The UniProt Consortium, 2017).	Cholesterol Catabolism
	CYP8B1	Catalyzes many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. Determines the relative amounts of cholic acid and chenodeoxycholic acid, both secreted in the bile and affect the solubility of cholesterol (The UniProt Consortium, 2017).	Cholesterol Metabolism

*(Continued)*

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
PPAR $\alpha$ /RXR or PPAR $\gamma$ /RXR	CYP27A1	Catalyzes a rate-limiting step in cholesterol catabolism and bile acid biosynthesis (The UniProt Consortium, 2017).	Cholesterol Catabolism
	NR1H3	The NR1 family members are key regulators of macrophage function, controlling transcriptional programs involved in lipid homeostasis and inflammation. It forms a heterodimer with retinoid X receptor (RXR), and regulates expression of target genes containing retinoid response elements. Plays an important role in the regulation of cholesterol homeostasis (The UniProt Consortium, 2017).	Cholesterol Metabolism Immune Response
PPAR $\alpha$ /RXR or PPAR $\gamma$ /RXR or PPAR $\beta\delta$ /RXR	ACBP	Binds medium- and long-chain acyl-CoA esters with very high affinity and may function as an intracellular carrier of acyl-CoA esters (The UniProt Consortium, 2017).	Fatty Acid Transport
	FABP1	Plays a role in lipoprotein-mediated cholesterol uptake in hepatocytes. Binds cholesterol and free fatty acids and their coenzyme A derivatives, bilirubin, and some other small molecules in the cytoplasm. May be involved in intracellular lipid transport (The UniProt Consortium, 2017).	Fatty Acid Transport
	FABP1/4	Lipid transport protein in adipocytes. Binds both long chain fatty acids and retinoic acid. Delivers them to their cognate receptors in the nucleus (The UniProt Consortium, 2017).	Fatty Acid Transport
	FABP3	Intracellular transport of long-chain fatty acids and their acyl-CoA esters (The UniProt Consortium, 2017).	Fatty Acid Transport
	CD36	Glycoprotein on platelet surfaces, serves as a receptor for thrombospondin in platelets and various cell lines, binds to collagen, thrombospondin, anionic phospholipids, oxidized LDL and long chain fatty acids and functions in the transport and/or as a regulator of fatty acid transport (The UniProt Consortium, 2017).	Fatty Acid Transport

(Continued)

Condition	Protein	Function	Key Word
PPAR $\alpha$ /RXR or PPAR $\gamma$ /RXR or PPAR $\beta\delta$ /RXR	LPL	LPL functions as a homodimer, and has the dual functions of triglyceride hydrolase and ligand/bridging factor for receptor-mediated lipoprotein uptake (The UniProt Consortium, 2017).	Fatty Acid Transport
	ACSL1	Activation of long-chain fatty acids for both synthesis of cellular lipids, and degradation via beta-oxidation (The UniProt Consortium, 2017).	Lipid Metabolism
	OLR1	Receptor that mediates the recognition, internalization and degradation of oxidatively modified low density lipoprotein (oxLDL) by vascular endothelial cells. Its association with oxLDL induces the activation of NF-kappa-B through an increased production of intracellular reactive oxygen and a variety of pro-atherogenic cellular responses including a reduction of nitric oxide (NO) release, monocyte adhesion and apoptosis (The UniProt Consortium, 2017).	Apoptosis Fatty Acid Transport
		Receptor for the HSP70 protein involved in antigen cross-presentation to naive T-cells in dendritic cells, thereby participating in cell-mediated antigen cross-presentation. Involved in inflammatory process, by acting as a leukocyte-adhesion molecule at the vascular interface in endotoxin-induced inflammation. Also, acts as a receptor for advanced glycation end (AGE) products, activated platelets, monocytes, apoptotic cells and both Gram-negative and Gram-positive bacteria (The UniProt Consortium, 2017).	Immune Response
	EHHADH	Bifunctional enzyme and is one of the four enzymes of the peroxisomal beta-oxidation pathway (The UniProt Consortium, 2017).	Fatty Acid Oxidation
	ACAA1	Enzyme operative in the beta-oxidation system of the peroxisomes (The UniProt Consortium, 2017).	Fatty Acid Oxidation (Continued)

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
PPAR $\alpha$ /RXR or PPAR $\gamma$ /RXR or PPAR $\beta\delta$ /RXR	SCP2  ACOX1	Peroxisome-associated thiolase that is involved in the oxidation of branched chain fatty acids  First enzyme of the fatty acid beta-oxidation pathway (The UniProt Consortium, 2017).	Fatty Acid Oxidation  Fatty Acid Oxidation
	CPT1A	Rate-controlling enzyme of the long-chain fatty acid beta-oxidation pathway in muscle mitochondria, required for the net transport of long-chain fatty acyl-CoAs from the cytoplasm into the mitochondria (The UniProt Consortium, 2017).	Fatty Acid Oxidation
	CPT2	Oxidizes long-chain fatty acids in the mitochondria (The UniProt Consortium, 2017).	Fatty Acid Oxidation
	ACADL	Mitochondrial flavoenzyme involved in fatty acid and branched chain amino-acid metabolism. Catalyzes the initial step of mitochondrial beta-oxidation of straight-chain fatty acid (The UniProt Consortium, 2017).	Fatty Acid Oxidation
	ACADM	Acyl-CoA dehydrogenase specific for acyl chain lengths of 4 to 16 that catalyzes the initial step of fatty acid beta-oxidation (The UniProt Consortium, 2017).	Fatty Acid Oxidation
	ANGPTL4	Hypoxia-induced expression in endothelial cells. May act as a regulator of angiogenesis and modulate tumorigenesis. Can prevent metastasis by inhibiting vascular growth and tumor cell invasion. In response to hypoxia, the unprocessed form of the protein accumulates in the subendothelial extracellular matrix, which limits the formation of actin stress fibers and focal contacts in the adhering endothelial cells and inhibits their adhesion. It also decreases motility of endothelial cells and inhibits the sprouting and tube formation (Galaup et al., 2006).	Antiproliferation Cancer Invasion Inhibition

(Continued)



Condition	Protein	Function	Key Word
PPAR $\alpha$ /RXR or PPAR $\gamma$ /RXR Or PPAR $\beta\delta$ /RXR	ANGPTL4	Serum hormone that regulates glucose homeostasis, lipid metabolism, and insulin sensitivity (The UniProt Consortium, 2017).	Glucose Metabolism
	FABP4	Lipid transport protein in adipocytes. Delivers long-chain fatty acids and retinoic acid to their cognate receptors in the nucleus (The UniProt Consortium, 2017). (Kanehisa et al., 2016)	Lipid Metabolism Adipocyte Differentiation Lipid Transport
	SORBS1	CBL-associated protein which functions in the signalling and stimulation of insulin. Required for insulin-stimulated glucose transport (The UniProt Consortium, 2017). (Kanehisa et al., 2016)	Glucose Transport Adipocyte Differentiation
	PLIN2	Involved in development and maintenance of adipose tissue (The UniProt Consortium, 2017).	Adipocyte Differentiation
	ADIPOQ	Antagonizes TNF-alpha by negatively regulating its expression in various tissues such as liver and macrophages, and also by counteracting its effects. Inhibits endothelial NF-kappa-B signalling through a cAMP-dependent pathway (The UniProt Consortium, 2017). Control of fat metabolism and insulin sensitivity, with direct anti-diabetic, anti-atherogenic and anti-inflammatory activities. In the liver and the skeletal muscle, enhances glucose utilization and fatty-acid combustion (The UniProt Consortium, 2017). (Kanehisa et al., 2016)	Antiinflammatory Glucose Metabolism Lipid Metabolism Adipocyte Differentiation (Continued)

Condition	Protein	Function	Key Word
PPAR $\alpha$ /RXR or PPAR $\gamma$ /RXR Or PPAR $\beta\delta$ /RXR	MMP1	Secreted protease, breaks down the interstitial collagens, including types I, II, and III. Overexpression has a role in initiating tumorigenesis by degrading the stroma, facilitating metastasis (Poola et al., 2005).  (Kanehisa et al., 2016)	Cancer Invasion  Cancer Transcriptional Misregulation  Adipocyte Differentiation
	UCP1	Separates oxidative phosphorylation from ATP synthesis with energy dissipated as heat, also referred to as the mitochondrial proton leak. Is responsible for thermogenic respiration, a specialized capacity of brown adipose tissue and beige fat that participates to non-shivering adaptive thermogenesis to temperature and diet variations and more generally to the regulation of energy balance (The UniProt Consortium, 2017).	Adaptive Thermogenesis
	ILK	Important in the epithelial to mesenchymal transition, and over-expression of this gene is implicated in tumor growth and metastasis (The UniProt Consortium, 2017).  Mediator of inside-out integrin signalling. Focal adhesion protein part of the complex ILK-PINCH. This complex is considered to be one of the convergence points of integrin- and growth factor-signalling pathway (The UniProt Consortium, 2017).	Cancer Invasion  Cell Survival
	PDK1	Important role in cellular responses to hypoxia and is important for cell proliferation under hypoxia. Protects cells against apoptosis in response to hypoxia and oxidative stress (The UniProt Consortium, 2017).	Antiapoptosis

(Continued)

Condition	Protein	Function	Key Word
	UBC	If polyubiquitin chains are attached in the 6 <sup>th</sup> Lys, involved in DNA repair. Lys-11-linked, involved in endoplasmic reticulum-associated degradation and in cell-cycle regulation. Lys-29-linked is involved in lysosomal degradation. Lys-33-linked is involved in kinase modification. Lys-48-linked is involved in protein degradation via the proteasome. Lys-63-linked is involved in endocytosis, DNA-damage responses as well as in signalling processes leading to activation of the transcription factor NF-kappa-B. Linear polymer chains formed via attachment by the initiator Met lead to cell signalling (The UniProt Consortium, 2017).	Ubiquitination
PPAR $\gamma$ /RXR	PCK2	(See AMPK Pathway)	Gluconeogenesis
	GK	Key enzyme in the regulation of glycerol uptake and metabolism (The UniProt Consortium, 2017).	Glycerol Metabolism
	AQP7	The encoded protein localizes to the plasma membrane and allows movement of water, glycerol and urea across cell membranes. This gene is highly expressed in the adipose tissue where the encoded protein facilitates efflux of glycerol. In the proximal straight tubules of kidney, the encoded protein is localized to the apical membrane and prevents excretion of glycerol into urine (The UniProt Consortium, 2017).	Glycerol Transport Urea Transport Water Transport

**TABLE 12. Functional annotation of the final effectors of the VEGF Signalling Pathway.**

Condition	Protein	Function	Key Word
VEGFR2	MAPK1	(See PIK3-AKT Signalling Pathway)	Angiogenesis DNA Repair Proliferation (Continued)

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
VEGFR2	cPLA2	(See MAPK Signalling Pathway)	Immune Response Phagocytosis Platelet Activation
	MT-CO2	PTGS2 is responsible for production of inflammatory prostaglandins. Up-regulation of PTGS2 is also associated with increased cell adhesion, phenotypic changes, resistance to apoptosis and tumour angiogenesis (The UniProt Consortium, 2017).	Antiapoptosis Cancer Angiogenesis Cell Adhesion Inflammatory Response
	PTK2	Essential role in regulating cell migration, adhesion, spreading, reorganization of the actin cytoskeleton, formation and disassembly of focal adhesions and cell protrusions (The UniProt Consortium, 2017).	Cell Migration
	PXN	Cytoskeletal protein involved in actin-membrane attachment at sites of cell adhesion to the extracellular matrix (focal adhesion) (The UniProt Consortium, 2017).	Cell Migration
	HSPB1	(See MAPK Signalling Pathway)	Antiapoptotic Stress Response
	RAC1	(See Tight Junction Pathway)	Cancer Invasion Cell Polarity Proliferation
	NOS3	(See PIK3-AKT Signalling Pathway)	Angiogenesis Platelet Activation Proliferation Arrest
	CASP9	(See PIK3-AKT Signalling Pathway)	Apoptosis
	BAD	Positively regulates cell apoptosis by forming heterodimers with BCL2L1 and BCL2, and reversing their death repressor activity (The UniProt Consortium, 2017).	Apoptosis

**TABLE 13. Functional annotation of the final effectors of the Jak-STAT Signalling Pathway.**

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
STAT/STAT	BCL2	(See Focal Adhesion Pathway)	Antiapoptosis
	MCL1	(See PIK3-AKT Signalling Pathway)	Antiapoptosis
	BCL2L1	(See PIK3-AKT Signalling Pathway)	Antiapoptosis
	PIM1	Contributes to cell proliferation and survival, and thus provides a selective advantage in tumorigenesis (The UniProt Consortium, 2017).  Overexpressed in hematopoietic malignancies and in prostate cancer (Brasó-Maristany et al., 2016).	Antiapoptosis  Cancer Transcriptional Misregulation
	MYC	(See MAPK Signalling Pathway)	Apoptosis  Cancer Transcriptional Misregulation  Cell Cycle Progression  Cell Growth  Differentiation  Stem Cell Self Renewal
	CCND1	(See TP53 Signalling Pathway)	Cell Cycle Progression
	CDKN1A	Regulator of cell cycle progression at G1 (The UniProt Consortium, 2017).	Cell Cycle Arrest
	AOX1	Oxidase with broad substrate specificity, oxidizing aromatic azaheterocycles as well as aldehydes. reduces hydrogen peroxide and, under certain conditions, can catalyze the formation of superoxide (The UniProt Consortium, 2017).	Lipid Metabolism
	GFAP	One of the major intermediate filament proteins of mature astrocytes. It is used as a marker to distinguish astrocytes from other glial cells during development (The UniProt Consortium, 2017).	Differentiation

**TABLE 14. Functional annotation of the final effectors of the cAMP Signalling Pathway.**

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
cAMP	PLD1	Yields Phosphatidic Acid, precursor for the biosynthesis of many other lipids, influencing the membrane (The UniProt Consortium, 2017).	Cytoskeleton Organization
	PLCE1	Catalyzes the hydrolysis of phosphatidylinositol-4,5-bisphosphate to generate two second messengers: inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG), which are involved in calcium handling (The UniProt Consortium, 2017).	Calcium Handling
	PAK1	Phosphorylates BAD and protects cells against apoptosis (The UniProt Consortium, 2017). Plays a role in RUFY3-mediated facilitating gastric cancer cells migration and invasion (Wang et al., 2015). Involved in the reorganization of the actin cytoskeleton, actin stress fibers and of focal adhesion complexes. Phosphorylates the tubulin chaperone TBCB and thereby plays a role in the regulation of microtubule biogenesis and organization of the tubulin cytoskeleton. Part of a ternary complex that contains PAK1, DVL1 and MUSK that is important for MUSK-dependent regulation of AChR clustering during the formation of the neuromuscular junction (NMJ) (The UniProt Consortium, 2017). Plays a role in the regulation of insulin secretion in response to elevated glucose levels (The UniProt Consortium, 2017).	Antiapoptosis Cancer Invasion Cytoskeleton Organization Insulin Secretion
	RHOA	(See mTOR Signalling Pathway)	Cytoskeleton Organization
	AFDN	Belongs to the E-cadherin-catenin system, which plays a role in the organization of homotypic, interneuronal and heterotypic cell-cell adherens junctions (AJs). Nectin- and actin-filament-binding protein that connects nectin to the actin cytoskeleton (The UniProt Consortium, 2017).	Cytoskeleton Organization

*(Continued)*

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
cAMP	BDNF	Binding of this protein to its cognate receptor promotes neuronal survival in the adult brain (The UniProt Consortium, 2017).	Cell Survival
	FOS	(See MAKP Signalling Pathway)	Differentiation
	JUN	(See MAKP Signalling Pathway)	Proliferation Angiogenesis Proliferation Cell Cycle Progression Cancer Transcriptional Misregulation Differentiation Angiogenesis
	GLI1	The encoded transcription factor is activated by the sonic hedgehog signal transduction cascade and regulates stem cell proliferation	Stem Cell Proliferation Regulation
	PTCH1	The encoded protein is the receptor for sonic hedgehog, a secreted molecule implicated in the formation of embryonic structures (The UniProt Consortium, 2017).  Inactivation of this protein is probably a necessary, if not sufficient step for tumorigenesis. Mutations of this gene have been associated with basal cell nevus syndrome, esophageal squamous cell carcinoma, trichoepitheliomas, transitional cell carcinomas of the bladder (The UniProt Consortium, 2017).	Embryonic Structures Formation  Tumour Suppressor
	HIP1	Membrane-associated protein that functions in clathrin-mediated endocytosis and protein trafficking within the cell. The encoded protein binds to the huntingtin protein in the brain (The UniProt Consortium, 2017).	Endocytosis Protein Trafficking

(Continued)

Condition	Protein	Function	Key Word
cAMP	AMH	This complex binds to the anti-Mullerian hormone receptor type 2 and causes the regression of Mullerian ducts in the male embryo that would otherwise differentiate into the uterus and fallopian tubes. This protein also plays a role in Leydig cell differentiation and function and follicular development in adult females (The UniProt Consortium, 2017).	Development
		Able to inhibit the growth of tumours derived from tissues of Muellerian duct origin (The UniProt Consortium, 2017).	Tumour Suppressor
	ACOX1	(See PPAR Signalling Pathway)	Fatty Acid Oxidation
	F2R	Coagulation factor II receptor is a 7-transmembrane receptor involved in the regulation of thrombotic response (The UniProt Consortium, 2017).	Thrombotic Response Regulation
	BAD	(See VEGF Signalling Pathway)	Apoptosis
	LIPE	(See AMPK Signalling Pathway)	Lipolysis
	MYL2	(See tight Junction Pathway)	Scaffold
	TNNI3	Inhibitory subunit of troponin, the thin filament regulatory complex which confers calcium-sensitivity to striated muscle actomyosin ATPase activity, blocking actin-myosin interactions and thereby mediating striated muscle relaxation (The UniProt Consortium, 2017).	Cardiac Myocyte Relaxation
	PLN	Major substrate for the cAMP-dependent protein kinase in cardiac muscle. The encoded protein is an inhibitor of cardiac muscle sarcoplasmic reticulum Ca(2+)-ATPase in the unphosphorylated state, but inhibition is relieved upon phosphorylation of the protein. The subsequent activation of the Ca(2+) pump leads to enhanced muscle relaxation rates, thereby contributing to the inotropic response elicited in heart by beta-agonists. The encoded protein is a key regulator of cardiac diastolic function (The UniProt Consortium, 2017).	Cardiac Diastolic Function

(Continued)



<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
cAMP	RYR2	Calcium channel that mediates the release of Ca <sup>2+</sup> from the sarcoplasmic reticulum into the cytoplasm and thereby plays a key role in triggering cardiac muscle contraction (The UniProt Consortium, 2017).	Cardiac Myocyte Contraction
	GRIN3A	Glutamate-regulated ion channels, and function in physiological and pathological processes in the central nervous system, such as long term potentiation (Lüscher & Malenka, 2012).	Long Term Potentiation
	CACNG8	Ionotropic glutamate receptor. L-glutamate acts as an excitatory neurotransmitter at many synapses in the central nervous system. Binding of the excitatory neurotransmitter L-glutamate induces a conformation change, leading to the opening of the cation channel, and thereby converts the chemical signal to an electrical impulse (The UniProt Consortium, 2017).	Excitatory Synapses
	CFTR	Involved in the excretion of chloride ions (Kanehisa et al., 2016).	Chloride Excretion
	FXYP1	Ion transporter, uses ATP to contribute to the uptake of 2K <sup>+</sup> coupled with the secretion of 3Na <sup>+</sup> (Kanehisa et al., 2016).	Ion Transporter
	SLC9A1	Na <sup>+</sup> /H <sup>+</sup> antiporter, is a plasma membrane transporter expressed in the kidney and intestine. Plays a central role in regulating pH homeostasis (The UniProt Consortium, 2017).	Ion Transporter
	ORAI1	Calcium channel, primary way for calcium influx into T-cells. Defects in this gene are a cause of immune dysfunction with T-cell inactivation due to calcium entry defect type (The UniProt Consortium, 2017).	Ion Transporter
	ATP2B1	Catalyses ATP coupled with the transport of calcium out of the cell (The UniProt Consortium, 2017).	Ion Transporter
	CACNA1C	Calcium channel, mediates the influx of calcium ions into the cell upon membrane polarization (Kanehisa et al., 2016).	Ion Transporter

(Continued)

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
	HCN2	HCN (hyperpolarization-activated, cyclic nucleotide-gated) channels are members of the cyclic nucleotide-regulated channel family along with cyclic nucleotide-gated (CNG) channels. They are cationic channels that open under hyperpolarization (The UniProt Consortium, 2017).	Ion Transporter
	HCN4	HCN (hyperpolarization-activated, cyclic nucleotide-gated) channels are members of the cyclic nucleotide-regulated channel family along with cyclic nucleotide-gated (CNG) channels. They are cationic channels that open under hyperpolarization (The UniProt Consortium, 2017).	Ion Transporter

**TABLE 15. Functional annotation of the final effectors of the Hedgehog Signalling Pathway.**

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
With Hh	GLI1	(See c-AMP Signalling Pathway)	Stem Cell Proliferation Regulation
	PTCH1	(See c-AMP Signalling Pathway)	Embryonic Structures Formation Tumour Suppressor
	HHIP	Interacts with all three HH family members, SHH, IHH and DHH. Modulates hedgehog signalling in several cell types including brain and lung through direct interaction with members of the hedgehog family (The UniProt Consortium, 2017).	Transcription Regulation
	CCND1	(See TP53 Signalling Pathway)	Cell Cycle Progression
	BCL2	Integral outer mitochondrial membrane protein that blocks the apoptotic death of some cells such as lymphocytes (The UniProt Consortium, 2017).	Antiapoptosis

**TABLE 16. Functional annotation of the final effectors of the Cell Cycle.**

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
DNA damage checkpoint	TP53	(See TP53 Signalling Pathway)	Apoptosis Cell Cycle Arrest
Cyclin D and CDK4/6	E2F4	Inhibit DNA transcription of S-phase proteins (Dimova & Dyson, 2005).	Cell Cycle Arrest
	E2F5		
	E2F2	DNA transcription of S-phase proteins and Cyclin E (Dimova & Dyson, 2005).	Cell Cycle Progression
	E2F3		
CCNA and CDK2	E2F1		
	CDC6	DNA synthesis, during S phase levels of CDK increase which phosphorylate Cdc6 and Cdt1, they lose their affinity for the complex and the DNA, so that the helicase stops being inhibited, leading to the double helix to be available for initiation of replication (The UniProt Consortium, 2017).	Cell Cycle Progression DNA Biosynthesis
	ORC	DNA synthesis, during S phase levels of CDK increase which phosphorylate Cdc6 and Cdt1, they lose their affinity for the complex and the DNA, so that the helicase stops being inhibited, leading to the double helix to be available for initiation of replication (The UniProt Consortium, 2017).	Cell Cycle Progression DNA Biosynthesis

**TABLE 17. Functional annotation of the final effectors of Apoptosis.**

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
Extrinsic	GZMB	Disruption of alpha - tubulin leads to disruption of microtubule function, disruption of Mcl-1 leads to BCL2L11-mediated mitochondrial apoptotic events, cleavage of Lamin leads to loss of integrity of the nuclear membrane, cleavage of PARP leads to low synthesis of poly-ADP-ribose, and of ICAD/CAD to DNA fragmentation (The UniProt Consortium, 2017).	Apoptosis

*(Continued)*

Condition	Protein	Function	Key Word
Extrinsic	GZMB	Granizyme B is secreted by natural killer (NK) cells and cytotoxic T lymphocytes (CTLs) and proteolytically processed to generate the active protease, which induces target cell apoptosis. This protein processes cytokines and degrades extracellular matrix proteins, and these roles are implicated in chronic inflammation and wound healing (The UniProt Consortium, 2017).	Inflammation
	CASP3	Disruption of Lamin leads to loss of integrity of the nuclear membrane, of PARP leads to low synthesis of poly-ADP-ribose (The UniProt Consortium, 2017).	Apoptosis
	JUN	Leads to transcription of pro-apoptotic genes (Fan & Chambers, 2001). (See Wnt Signalling Pathway)	Apoptosis Angiogenesis Proliferation Cell Cycle Progression Cancer Transcriptional Misregulation Differentiation Cell Polarity Cell Migration
	AP1	(See Wnt Signalling Pathway)	Angiogenesis Proliferation Cell Cycle Progression Cancer Transcriptional Misregulation Differentiation Cell Polarity Cell Migration
		Leads to transcription of pro-apoptotic genes (Fan & Chambers, 2001).	Apoptosis (Continued)

<b>Condition</b>	<b>Protein</b>	<b>Function</b>	<b>Key Word</b>
Extrinsic and Intrinsic	CASP6	Disruption of Actin and Fodrin leads to cell shrinkage and membrane blebbing (The UniProt Consortium, 2017).	Apoptosis
	CASP7	Cleavage of ICAD/CAD leads to DNA fragmentation (The UniProt Consortium, 2017).	Apoptosis
Intrinsic	BAK1	Undergoes conformational change that induces its oligomerization leading to increased permeability of the external mitochondrial membrane, leakage of intermembrane factors such as cytochrome-c (The UniProt Consortium, 2017).	Apoptosis
	BAX	After apoptotic Signalling is inserted in the external membrane of the mitochondria leading to increased permeability of the external mitochondrial membrane, leakage of intermembrane factors such as cytochrome-c (The UniProt Consortium, 2017).	Apoptosis
	BCL2L1	(See PI3K/AKT Signalling Pathway)	Antiapoptosis
	BCL2		
	ENDO G AIFM1	DNA fragmentation (The UniProt Consortium, 2017).	Apoptosis
NFKB1	NFKB1	(See MAPK Signalling Pathway)	Antiapoptosis Cancer Transcriptional Misregulation Differentiation Inflammatory Response
IL-3	BCL2	(See PI3K/AKT Signalling Pathway)	Antiapoptosis

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**Pathway Activity Analysis (PAA) as a new class of mechanistic biomarker to predict drug responses in drug repositioning for cancer patients**

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## **ANNEX 2. Drug Actions Annotation**

## Drug Actions Annotation

TABLE 1. Categorization of drugs into activating or inhibiting based on Drug Bank terms and bibliography.

DrugBank Term	Drug-Target Explanation	Action
Acetylation	Acetylsalicylic Acid - TP53 Not known pharmacological action (Wishart, 2006).	Remove
Activator	Triggers the target.	Activation
Adduct	Tigecycline Binds 30S ribosome, inhibiting translation (Wishart, 2006). To remove because it affects bacteria.	Remove
	Vinblastine Binds tubulin, inhibiting mitosis at metaphase (Wishart, 2006).	Inhibition
	Ethionamide Inhibits InhA, the enoyl reductase from Mycobacterium tuberculosis, by forming a covalent adduct with the NAD cofactor (Wishart, 2006). To remove because affects bacteria.	Remove
	Isoniazid Inhibits InhA, the enoyl reductase from Mycobacterium tuberculosis, by forming a covalent adduct with the NAD cofactor (Wishart, 2006). To remove because affects bacteria.	
	Gentamicin Irreversibly binds to specific 30S-subunit proteins and 16S rRNA (Wishart, 2006). To remove because affects bacteria.	
Agonist	Activates a receptor	Activation
Agonistinhibitor	Inhibits a receptor upon binding	Inhibition
Agonistmodulator	Aldesleukin Binds to the IL-2 receptor which leads to heterodimerization of the cytoplasmic domains of the IL-2R beta and gamma(c) chains, activation of the tyrosine kinase Jak3, and phosphorylation of tyrosine residues on the IL-2R beta chain. These events led to the creation of an activated receptor complex, to which various cytoplasmic signalling	Activation

(Continued)

<b>DrugBank Term</b>	<b>Drug-Target Explanation</b>	<b>Action</b>
Agonistmodulator	Molecules are recruited and become substrates for regulatory enzymes (especially tyrosine kinases) that are associated with the receptor. These events stimulate growth and differentiation of T cells (Wishart, 2006).	Activation
	Quinestrol 3-cyclopentyl ether of ethinyl estradiol (the active metabolite). After gastrointestinal absorption, it is stored in adipose tissue where it is slowly released and metabolized principally to the parent compound, ethinyl estradiol. Ethinyl estradiol is a synthetic derivative of the natural estrogen estradiol (Wishart, 2006).	
Agonistpartial agonist	Ergotamine Unknown pharmacological action on Alpha-2B adrenergic receptors (Wishart, 2006).	Remove
	Pseudoephedrine Unknown pharmacological action on Beta-1 adrenergic receptors (Wishart, 2006).	
	Ketamine Unknown pharmacological action on D(2) dopamine receptors (Wishart, 2006).	
	Cariprazine Agonist on Dopamine receptors (Wishart, 2006).	Activation
Allosteric Modulator	Carglumic Acid Synthetic structural analogue of N-acetylglutamate (NAG), an essential allosteric activator of the liver enzyme carbamoyl phosphate synthetase 1 (Wishart, 2006).	Activation
	Galantamine Not known pharmacological action (Wishart, 2006).	Remove
	Vardenafil Unknown pharmacological action (Wishart, 2006).	
	Trilostane In breast cancer, exerts estrogen-like actions through ER $\beta$ (Koonce, Walf, & Frye, 2009).	Activation
Allosteric Modulator	Halothane Unknown action (Wishart, 2006).	Remove (Continued)

<b>DrugBank Term</b>	<b>Drug-Target Explanation</b>	<b>Action</b>
Antagonist	Binds a receptor dampening a biological response	Inhibition
Antagonistagonist	Olanzapine Antagonism at D2 receptors (Wishart, 2006).	Inhibition
	Ergoloid mesylate Unknown pharmacological action at Dopamine receptors (Wishart, 2006). To remove.	Remove
	Tamoxifen Activates and inhibits (Goodsell, 2002). To remove.	
	Risperidone Unknown pharmacological action at lpha-2B adrenergic receptors (Wishart, 2006). To remove.	
	Clomifene Both estrogenic and anti-estrogenic properties (Wishart, 2006). To remove.	
	Ospemifene Ospemifene is a next generation SERM (selective estrogen receptor modulator) that selectively binds to estrogen receptors and either stimulates or blocks estrogen's activity in different tissue types. It has an agonistic effect on the endometrium (Wishart, 2006). To remove.	
Antagonistantibody	Antibody which agonizes its target.	Inhibition
Antagonistbinder	Antagonizes upon binding.	Inhibition
Antagonistblocker	Antagonizes by blocking the target.	Inhibition
Antagonistinhibitor	Antagonizes, inhibits the target.	Inhibition
AntagonistInhibitor	Antagonizes, inhibits the target.	Inhibition
Antagonistinhibitor, competitive	Competes with the target.	Inhibition
Antagonistinhibitory allosteric modulator	Induces a conformational change which diminishes the target's effect.	Inhibition
Antagonistmultitarget	Antagonist with many targets.	Inhibition
Antagonistother/unknown	Antagonizes.	Inhibition
Antagonistpartial agonist	Mivacurium No pharmacological actions on Muscarinic acetylcholine receptor M2 and M3 (Wishart, 2006). To remove.	Remove

(Continued)

<b>DrugBank Term</b>	<b>Drug-Target Explanation</b>	<b>Action</b>
Antagonistpartial agonist	Tegaserod Agonist of human 5-HT4 receptors (Wishart, 2006).	Activation
	Aripiprazole Antipsychotic activity is likely due to a combination of antagonism at D2 receptors in the mesolimbic pathway and 5HT2A receptors in the frontal cortex. Antagonism at D2 receptors relieves positive symptoms while antagonism at 5HT2A receptors relieves negative symptoms of schizophrenia (Wishart, 2006).	Inhibition
Antibody	Penbutolol Blocks the catecholamine activation of $\beta$ 1 adrenergic receptors (Wishart, 2006).	
	Etanercept Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind to two TNF molecules, thereby effectively removing them from circulation (Wishart, 2006).	Inhibition
	Adalimumab Binds to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors (Wishart, 2006).	
	Basiliximab Blocking the interleukin-2 receptor $\alpha$ -chain (Wishart, 2006).	
	Efalizumab Binds to CD11a, a subunit of leukocyte function antigen-1 (LFA-1), expressed on all leukocytes, as a result decreases cell surface expression of CD11a (Wishart, 2006).	
Antibody	Natalizumab Binds $\alpha$ 4b1 and $\alpha$ 4b7 integrins expressed on the all leukocytes except neutrophils, and inhibits thei adhesion of leukocytes to their counter-receptor(s) (Wishart, 2006).	
	Daclizumab IL-2 receptor antagonist (Wishart, 2006).	Inhibition
	Eculizumab Blocks C5 cleavage (Wishart, 2006).	

(Continued)

<b>DrugBank Term</b>	<b>Drug-Target Explanation</b>	<b>Action</b>
Antibody	<p>Farletuzumab</p> <p>Against the FOLR1 which is overexpressed in ovarian cancer (Jelovac &amp; Armstrong, 2012).</p> <p>Tocilizumab</p> <p>Binds soluble and membrane-bound IL-6 receptors, inhibiting IL-6-mediated signalling (Wishart, 2006).</p> <p>Pertuzumab</p> <p>Binds to the HER2 receptor and inhibits the ability of HER2 to interact with other HER family members (Wishart, 2006).</p> <p>Denosumab</p> <p>Prevents RANKL from activating its receptor (Wishart, 2006).</p> <p>Golimumab</p> <p>Inhibits soluble and transmembrane human TNF<math>\alpha</math> (Wishart, 2006).</p> <p>Raxibacumab</p> <p>Inhibits the binding of PA to its cellular receptors (Wishart, 2006).</p> <p>Vedolizumab</p> <p>Inhibits the <math>\alpha 4\beta 7</math> integrin (Wishart, 2006).</p> <p>Nivolumab</p> <p>Binds programmed cell death 1 (PD-1) receptor, blocks interaction with its ligands PD-L1 and PD-L2 (Wishart, 2006).</p>	Inhibition
	<p>Gemtuzumab ozogamicin</p> <p>Against the CD33 antigen expressed by hematopoietic cells. Binding of the anti-CD33 antibody portion of Mylotarg with the CD33 antigen results in the formation of a complex that is internalized. Upon internalization, the calicheamicin derivative is released inside the lysosomes of the myeloid cell. The released calicheamicin derivative binds to DNA in the minor groove resulting in DNA double strand breaks and cell death (Wishart, 2006). Too broad a function.</p>	Remove
	<p>Trastuzumab</p> <p>Binds to the HER2 cells, leading to their antibody mediated killing (Wishart, 2006). Too broad a function.</p>	

(Continued)

DrugBank Term	Drug-Target Explanation	Action
Antibody	<p>Rituximab</p> <p>Binds to the CD20 antigen, which is predominantly expressed on mature B cells and on &gt;90% of B-cell non-Hodgkin's lymphomas. The antibody leads to selective killing of B-cells (Wishart, 2006). Too broad a function.</p>	Remove
	<p>Ibritumomab</p> <p>Targets CD20 on B-cells, radioactive yttrium to destroy the cell via production of beta particles (Wishart, 2006). Too broad a function.</p>	
	<p>Tositumomab</p> <p>CD20, binding appears to induce apoptosis, complement-dependent cytotoxicity and cell death through ionizing radiation (Wishart, 2006). Too broad a function.</p>	
	<p>Alemtuzumab</p> <p>CD52 on B and T, antibody-dependent lysis of leukemic cells (Wishart, 2006). Too broad a function.</p>	
	<p>Methyl aminolevulinate</p> <p>Topical application, porphyrins accumulate intracellularly in the treated skin lesions, upon light activation in the presence of oxygen, singlet oxygen is formed which causes damage to mitochondria, phototoxicity (Wishart, 2006). Too broad a function.</p>	
	<p>ado-trastuzumab emtansine</p> <p>Binds to the HER2 (or c-erbB2) proto-oncogene, an EGF receptor-like protein found on 20-30% of breast cancer cells, leads to antibody mediated killing of the positive cells (Wishart, 2006). Too broad a function.</p>	
	<p>Obinutuzumab</p> <p>Binds to type II CD20, higher induction of antibody-dependant cytotoxicity and direct cytotoxic effect (Wishart, 2006). Too broad a function.</p>	

(Continued)



<b>DrugBank Term</b>	<b>Drug-Target Explanation</b>	<b>Action</b>
Binder	Antihemophilic Factor ASGR2 Unknown pharmacological action (Wishart, 2006).	Remove
	Antihemophilic Factor VWF - Promotes adhesion and aggregation of platelets at wound sites, thereby inducing platelet plug formation. Antihemophilic Factor binds it (Wishart, 2006).	Activation
	Menotropins Bind the FSH Receptor, which results in ovulation in the absence of sufficient endogenous LH (Wishart, 2006).	
	Interferon gamma-1b Agonist of IFNGR1, leading to a complex of IFNGR1 and IFNGR2 and activation of the pathway (Wishart, 2006).	
	Palifermin Binds the KGF receptor and activates it (Wishart, 2006).	
	Somatropin recombinant Agonist of GH (Wishart, 2006).	
	Interferon alfacon-1 Interferon alfa receptors agonist (Wishart, 2006).	
	Insulin, porcine Activates the insulin receptor (Wishart, 2006).	
	Choriogonadotropin alfa FSHR agonist (Wishart, 2006).	
	Octreotide Octreotide exerts pharmacologic actions similar to the natural hormone, somatostatin (Wishart, 2006).	
	Interferon Alfa-2b, Recombinant Exerts actions like the natural Interferon alfa- 2b (Wishart, 2006).	
	Oxytocin Unknown pharmacological action on Oxytocin-neurophysin 1 (Wishart, 2006).	
	Thiamine Binds its transporter SLC19A (Wishart, 2006). To remove. NADH. Remove	

(Continued)

<b>DrugBank Term</b>	<b>Drug-Target Explanation</b>	<b>Action</b>
Binder	Folic Acid Binds its transporter (Wishart, 2006).	Activation
	Levonorgestrel Synthetic form of the naturally occurring female sex hormone, progesterone (Wishart, 2006).	
	Niacin Precursor of NAD and NADP (Wishart, 2006).	
	Guanabenz $\alpha$ -2 adrenergic agonist (Wishart, 2006).	
	Methoxamine Acting as a pure alpha-1 adrenergic receptor agonist (Wishart, 2006).	
	Potassium Chloride SLC12A1 transporter(Wishart, 2006).	
	Alglucosidase alfa Exogenous source of GAA (Wishart, 2006).	
	Teriparatide Substitute of endogenous PTH (Wishart, 2006).	
	Tesamorelin Stimulates production and release of the endogenous hormone (hGRF) (Wishart, 2006).	
	Cyclosporine CAMLG binds to cyclophilin, the complex then inhibits calcineurin (Wishart, 2006).	Inhibition
	PPIF Unknown pharmacological action (Wishart, 2006). To remove.	Remove
	Chlorpromazine Inhibits DRD4 (Wishart, 2006).	Inhibition
	HTR2A, ORM1, HTR6/7 and HRH4 Unknown pharmacological action (Wishart, 2006). To remove.	Remove
Binder	Loxapine Unknown pharmacological action (Wishart, 2006). To remove.	Remove
	Intravenous Immunoglobulin for C3/4A/4B/5 Inhibits the complement cascade (Wishart, 2006).	Inhibition

(Continued)

<b>DrugBank Term</b>	<b>Drug-Target Explanation</b>	<b>Action</b>	
Binder	Botulinum Toxin Type B Binds to and cleaves the synaptic VAMP, inhibits acetylcholine release at the neuromuscular junction (Wishart, 2006).	Inhibition	
	Citalopram Inhibits HRH1 ADRA1A CHRM1 with less affinity than to SLC6A4 (Wishart, 2006)		
	Trimipramine Unknown pharmacological actions (Wishart, 2006). To remove.	Remove	
	Metyrosine Inhibits tyrosine hydroxylase (Wishart, 2006).	Inhibition	
	Gliclazide ABCC8 blockade of the channels (Wishart, 2006).		
	Halothane Alters the flow of potassium in cells, functions as anesthetic (Wishart, 2006). Too broad.	Remove	
	Ciclopirox Acts via chelation of polyvalent metal cations, leading to inactivation of the enzymes which use them (Wishart, 2006).	Inhibition	
	Glatiramer Acetate Strong and promiscuous binding to MHC molecules, and consequent competition with various myelin antigens for their presentation to T cells (Wishart, 2006).		
	Canakinumab Neutralizes IL1B (Wishart, 2006).		
	Rilonacept Blocks IL-1 (Wishart, 2006).		
	Cabazitaxel Microtubule inhibitor (Wishart, 2006).		
	Aflibercept Anti-VEGF drug (Wishart, 2006).		
	Binder	Denileukin diftitox The diphtheria toxin associated with Ontak then selectively kills the IL-2 bearing cells (Wishart, 2006).	Remove
		Pegademase bovine Unknown pharmacological action (Wishart, 2006).	

(Continued)

<b>DrugBank Term</b>	<b>Drug-Target Explanation</b>	<b>Action</b>
Binder	Muromonab Binds to the T-cell CD3 epsilon chain. Kills CD-3 positive cells by inducing Fc mediated apoptosis, antibody mediated cytotoxicity and complement-dependent cytotoxicity (Wishart, 2006). Too broad an action.	Remove
	L-Phenylalanine Unknown pharmacological action (Wishart, 2006). To remove.	
	L-Tyrosine Unknown pharmacological action (Wishart, 2006). To remove.	
	L-Proline Unknown pharmacological action (Wishart, 2006). To remove.	
	Amphetamine Unknown pharmacological action on SLC6A4 and DR2 (Wishart, 2006).	
	Methysergide Unknown pharmacological action on HTR1B/F/W (Wishart, 2006).	
	Cabergoline Unknown pharmacological action on ADRA1A/1B/1D ADRB1/2 (Wishart, 2006).	
	Atomoxetine Unknown pharmacological action on SLC6A3	
	Amitriptyline Unknown pharmacological action on HRH4, HTR2C, HTR1D, OPRM1, HTR1B, ADRB1 (Wishart, 2006). To remove.	
	Terfenadine Unknown pharmacological action on CHRM1/2/4/5 (Wishart, 2006). To remove.	
	Norepinephrine Unknown pharmacological action on SLC18A1/2 (Wishart, 2006). To remove.	
	Mirtazapine Unknown pharmacological action on ADRA1A/2C, ADRB1/2/, DRD1/2, SLC6A2/3/4, HTR2B (Wishart, 2006). To remove.	

(Continued)

<b>DrugBank Term</b>	<b>Drug-Target Explanation</b>	<b>Action</b>
Binder	Spironolactone Unknown pharmacological action on SHBG (Wishart, 2006). To remove.	Remove
	Pethidine Unknown pharmacological action on CHRM1 (Wishart, 2006). To remove.	
	Prazosin Unknown pharmacological action on ADRA2A/B (Wishart, 2006). To remove.	
	Imipramine Unknown pharmacological action on DRD1/2 AND HTR6 (Wishart, 2006). To remove.	
	Oxycodone Unknown pharmacological action on ORM1 (Wishart, 2006). To remove.	
	Dextromethorphan Unknown pharmacological action on PGRMC1 (Wishart, 2006). To remove.	
	Nortriptyline Unknown pharmacological action on HTR6, PGRMC1 (Wishart, 2006). To remove.	
	Amoxapine Unknown pharmacological action on SLC6A3, HRH4, GABRA1	
	Cinnarizine Unknown pharmacological action on DRD1, CHRM1 (Wishart, 2006). To remove.	
	Insulin Unknown pharmacological action on CFT (Wishart, 2006). To remove.	
	Procaine Unknown pharmacological action on KCNMA1 (Wishart, 2006). To remove.	
	Tolazoline Unknown pharmacological action on ADRA2B/C (Wishart, 2006). To remove.	
	Cysteamine Unknown pharmacological action on SST (Wishart, 2006). To remove.	
	Maprotiline Unknown pharmacological action on HTR2A/C and DRD2 (Wishart, 2006). To remove.	

(Continued)

<b>DrugBank Term</b>	<b>Drug-Target Explanation</b>	<b>Action</b>
Binder	Oxymetazoline Unknown pharmacological action on ADRA2B (Wishart, 2006). To remove.	Remove
	Glycopyrrolate Unknown pharmacological action on CHRM2 (Wishart, 2006). To remove.	
	Dopamine Unknown pharmacological action on HTR1A and HTR7 (Wishart, 2006). To remove.	
	Guanfacine Unknown pharmacological action on ADRA2B (Wishart, 2006). To remove.	
	Ketoconazole Unknown pharmacological action on AR (Wishart, 2006). To remove.	
	Thalidomide Unknown pharmacological action on ORM1 (Wishart, 2006). To remove.	
	Memantine Unknown pharmacological action on GRIN1	
	Ibuprofen Unknown pharmacological action on FABP2 (Wishart, 2006). To remove.	
	Doxepin Unknown pharmacological action on HTR6 HRH4 (Wishart, 2006). To remove.	
	Desipramine Unknown pharmacological action on HTR1A/C DRD2 ADRA2A (Wishart, 2006). To remove.	
	Ketamine Unknown pharmacological action on OPRD1 OPRM1 CHRM1 (Wishart, 2006). To remove.	
	Bepidil Unknown pharmacological action on CALM1 (Wishart, 2006). To remove.	
	Docetaxel Unknown pharmacological action on NR1I2 (Wishart, 2006). To remove.	
	Aluminium Astringent (Wishart, 2006). To remove.	

(Continued)

<b>DrugBank Term</b>	<b>Drug-Target Explanation</b>	<b>Action</b>
Binder	Dehydroepiandrosterone Unknown pharmacological action on ESR1 (Wishart, 2006). To remove.	Remove
	Indirubin-3'-Monoxime Unknown pharmacological action on CDK1 (Wishart, 2006). To remove.	
	Olomoucine Unknown pharmacological action on CDK1 (Wishart, 2006). To remove.	
	SU9516 - Not found	
	Nicotinamide Unknown pharmacological action on PARP1 (Wishart, 2006). To remove.	
	Nesiritide Unknown pharmacological action on NPR1 (Wishart, 2006). To remove.	
	Mianserin Unknown pharmacological action on HRH4/6 HTR2B/1F DRD1/3 SLC6A3 (Wishart, 2006). To remove.	
	Tinzaparin Unknown pharmacological action on CXCL12 (Wishart, 2006). To remove.	
	Hyaluronic acid Unknown pharmacological action on VCAN C1QBP HAPLN1 HAPLN3 HAPLN4 HABP2 LAYN STAB2 TNFAIP6 IMPG2 HABP4 (Wishart, 2006). To remove.	
	Binding	
Pethidine Unknown pharmacological action on SLC6A4 (Wishart, 2006). To remove.		
Dimethyl fumarate Unknown pharmacological action on KEAP1 (Wishart, 2006). To remove.		
Acetylsalicylic acid Unknown pharmacological action on HSPA5 (Wishart, 2006). To remove.		
Inhibits the target's action upon binding.		
Blocker		Inhibition (Continued)

<b>DrugBank Term</b>	<b>Drug-Target Explanation</b>	<b>Action</b>
Chaperone	Aids in folding, may help stabilize the protein or may tag the protein for degradation. To remove.	Remove
Cleavage	Breakage of peptide bonds.	Inhibition
Cofactor	Necessary component to carry out the effect.	Activation
Desensitize the target	Diminishes the response.	Inhibition
Inducer	Transcriptional activator.	Activation
inhibitor	Decreases the target's activity.	Inhibition
Inhibitor	Decreases the target's activity.	Inhibition
Inhibitor, competitive	Competes with the substrate with the active site of an enzyme.	Inhibition
Inverse agonist	Opposite action of an agonist.	Inhibition
Intercalation	Insertion between planar structures.	Inhibition
Ligand	Binds its target to form an active complex.	Activation
Modulator	Toremifene compete with estrogen for binding sites in the cancer (Wishart, 2006). Rufinamide prolongs the inactive state of voltage gated sodium channels (Wishart, 2006).	Inhibition
	Antihemophilic Factor	Remove
	Unknown pharmacologic action on LRP1 MACFD2 (Wishart, 2006).	
Modulator	Loperamide	Remove
	Unknown pharmacologic action on POMC (Wishart, 2006).	
	Glyburide	
	Unknown pharmacologic action on ABCC8/9 KCNJ11 (Wishart, 2006).	
	Minocycline	
	Unknown pharmacologic action on ILB1 (Wishart, 2006). To remove.	
	Ibuprofen	
	Unknown pharmacologic action on BCL2 THBD (Wishart, 2006). To remove.	
	Carvedilol	
	Unknown pharmacologic action on HIF1A (Wishart, 2006). To remove.	
	Fingolimod	
	Binds with high affinity to sphingosine 1-phosphate receptors 1, 3, 4, and 5. The mechanism in multiple sclerosis may involve reduction of lymphocyte migration into the central nervous system (Wishart, 2006).	

(Continued)



<b>DrugBank Term</b>	<b>Drug-Target Explanation</b>	<b>Action</b>
Multitarget	Drotrecogin alfa Inhibits factor Va and VIIIa (Wishart, 2006).	Inhibition
	Dasatinib Unknown pharmacologic action for SRC, ABLS2, FYN, LCK, ABL1 (Wishart, 2006). To remove.	Inhibition
	Sunitinib Unknown pharmacological action on KDR, FLT3 (Wishart, 2006). To remove	Remove
	Ramelteon Melatonin receptor agonist (Wishart, 2006).	Activation
Negative Modulator	Allosteric negative modulator.	Inhibition
Neutralizer	Inhibits the target's effect.	Inhibition
Other	Lovastatin Unknown pharmacological action on HDAC2 (Wishart, 2006). To remove.	Remove
	Vancomycin Unknown pharmacological action on GFTA (Wishart, 2006). To remove.	
	Simvastatin Unknown pharmacological action on ITGB2 (Wishart, 2006). To remove.	Remove
	Oseltamivir Binds CES1, which converts it to active form (Wishart, 2006).	Activation
	Levonorgestrel The affinity for the ESR1 is very low (Wishart, 2006).	Remove
	Sirolimus binds to FKBP-12 activating its immunosuppressive actions (Wishart, 2006).	Activation
	Riboflavin Binding to ribE on Ecoli. To remove. (Wishart, 2006).	Remove
	Lorazepam Binds the transporter TSPO (Wishart, 2006). To remove.	
	Hydroxocobalamin Unknown pharmacological action on MTRR TCN1 AMN CUBN MMAB (Wishart, 2006). To remove.	
	Temazepam Binds the transporter protein TSPO (Wishart, 2006). To remove	

(Continued)

<b>DrugBank Term</b>	<b>Drug-Target Explanation</b>	<b>Action</b>
Other	Chloramphenicol Unknown pharmacological action on CD55 (Wishart, 2006). To remove.	Remove
	Quinine Unknown pharmacological action on GP9 (Wishart, 2006). To remove.	
	Aminocaproic Acid Unknown pharmacological action on LPA (Wishart, 2006). To remove.	
	Lactulose Binds ebgA , a sugar receptor on EColi (Wishart, 2006). To remove.	
	Diclofenac Unknown pharmacological action on KCNQ2/3 (Wishart, 2006). To remove.	
	Verapamil Unknown pharmacological action on SCN5A (Wishart, 2006). To remove.	
	Sufentanil Unknown pharmacological action on OPRK1 (Wishart, 2006). To remove.	
	Adefovir Dipivoxil Unknown pharmacological action on virus HBV (Wishart, 2006). To remove.	
	Pentamidine Unknown pharmacological action on TRDMT1 (Wishart, 2006). To remove.	
	Etodolac Unknown pharmacological action on RXRA (Wishart, 2006). To remove.	
	Triazolam Binds translocator protein TSPO (Wishart, 2006). To remove.	
	Meclofenamic acid Unknown pharmacological action on KCNQ2/3 (Wishart, 2006). To remove.	
	Zaleplon Binds transporter TSPO (Wishart, 2006). To remove.	
	Ezetimibe Unknown pharmacological action on ANPEP (Wishart, 2006). To remove.	

(Continued)

<b>DrugBank Term</b>	<b>Drug-Target Explanation</b>	<b>Action</b>
Other	<p>Ketoprofen Unknown pharmacological action on CXCR1 (Wishart, 2006). To remove.</p> <p>Felodipine Unknown pharmacological action on CALM1 TNNC2 TNNC1 (Wishart, 2006). To remove.</p> <p>Procainamide Unknown pharmacological action on DNMT1 (Wishart, 2006). To remove.</p> <p>Flucytosine Unknown pharmacological action on DNMT1 (Wishart, 2006). To remove.</p> <p>Diazoxide Unknown pharmacological action on ATP1A1 KCNMA1 (Wishart, 2006). To remove.</p> <p>Carvedilol Unknown pharmacological action on EGFA NPPB GJA1 (Wishart, 2006). To remove.</p> <p>Desipramine Unknown pharmacological action on ADRB1 (Wishart, 2006). To remove.</p> <p>Halothane Unknown pharmacological action on RHO (Wishart, 2006). To remove.</p> <p>Bepriidil Unknown pharmacological action on TNNC1 (Wishart, 2006). To remove.</p> <p>Chenodeoxycholic acid Binds NR1H4, suppresses hepatic synthesis of both cholesterol and cholic acid, gradually replacing the latter and its metabolite Chenodeoxycholic acid (Wishart, 2006). To remove.</p>	Remove
Other/unknown	Unknown.	Remove
Partial agonist	Partial activating effect on the target.	Activation
Partial antagonist	Partial inhibiting effect on the target.	Inhibition
Positive allosteric modulator	Binds to a site distinct from that of the orthosteric agonist binding site inducing the activation of the target.	Activation
Positive modulator	Binds to a site distinct from that of the orthosteric agonist binding site inducing the activation of the target.	Activation

(Continued)

<b>DrugBank Term</b>	<b>Drug-Target Explanation</b>	<b>Action</b>
Potentiator	Enhances sensitization.	Activation
Product of	Unknown.	Remove
Stimulator	Excites the functional activity.	Activation
Suppressor	Inhibits the target's effects.	Inhibition
Unknown	Unknown.	Remove

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**Pathway Activity Analysis (PAA) as a new class of mechanistic biomarker to predict drug responses in drug repositioning for cancer patients**

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**ANNEX 3. R Scripts**

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# Script 1. Functions

```
# FUNCTIONS TO BE SOURCED

# Read experimental data
read.expression.matrix <- function(file){
  data.matrix(read.table(file, header=T, sep="\t", stringsAsFactors=F, row.names=1,
comment.char=""))
}

read.experimental.design <- function(file){
  des <- read.table(file,header=F,stringsAsFactors=F,row.names=1)
  colnames(des)[1] <- c("Condition")
  return(des)
}

# Functional analysis function
prettyfuns.average <- function(results, pathigraphs, dbannot, entrez2hgnc){

  # Calculates a value per function by estimating the average of the values obtained in
  those pathways that lead to that function
  annofuns <- do.call("rbind", lapply(pathigraphs,function(pathigraph){
    new.pathigraph <- pathigraph
    new.pathigraph$graph <- induced.subgraph(new.pathigraph$graph,
V(new.pathigraph$graph)$name[!grepl("_func", V(new.pathigraph$graph)$name)])
    funs <- get.pathway.functions(new.pathigraph, dbannot, entrez2hgnc,
use.last.nodes=T)
    paths <- lapply(names(funs), function(path) rep(paste0(pathigraph$path.id, "__",
path), times=length(funs[[path]])))
    df <- data.frame(paths = unlist(paths), funs=unlist(funs), stringsAsFactors=F)
  )))

  annofuns <- annofuns[!is.na(annofuns$funs),]
  fun.names <- unique(annofuns$funs)
  fun.vals <- matrix(0, ncol=ncol(results$all$effector.path.vals), nrow =
length(fun.names), dimnames = list(fun.names, colnames(results$all$effector.path.vals)) )

  # By using the mean value, saturation of the signal is avoided
  for( fun in fun.names){
    print(fun)
    paths <- annofuns$paths[annofuns$funs==fun]
    minimat <- results$all$effector.path.vals[paths,,drop=F]
    fun.vals[fun,] <- apply(minimat, 2, mean)
  }
  print(dim(fun.vals))
  return(fun.vals)
}
```

## Script 2. Drugs into Data Frame

```
# Drug Data comes in a complex list that needs to be organized
# Drugs that do not meet the criteria are removed: have targets and actions
# Actions are categorized as "activation" or "inhibition"

drugs.into.data.frame <- function(data){
  # Selects drugs for which targets and actions are known
  # Returns data.frame

  drugs <- names(data)
  d <- data.frame(Drug = NA, Targets = NA, Actions = NA)

  for(i in 1:length(drugs)){
    targets <- names(data[[i]]$targets)
    if(is.character(targets)){
      drug <- drugs[i]
      for(j in 1:length(targets)){
        target_name <- data[[i]]$targets[[j]]$geneName
        drug_action <- data[[i]]$targets[[j]]$actions
        lista <- c(Drug = drug, Targets = target_name, Actions = drug_action)
        d <- rbind(d, lista)
      }
    }
  }

  # Remove NA and empty strings
  d <- d[complete.cases(d),]
  d <- d[!apply(d, 1, function(x) any(x == "")),]

  # See all possible actions drugs have to decide if they activate or not
  Actions <- sort(unique(d$Actions))

  # Manually curated activating and inhibition actions
  activatingActions <- c("acetylation", "activator", "agonist", "agonistmodulator",
    "agonistpartial agonist", "cofactor", "inducer", "ligand",
    "partial agonist", "positive allosteric modulator",
    "positive modulator", "potentiator", "stimulator" )

  inhibitingActions <- c("adduct", "agonistinhibitor", "antagonist",
    "antagonistantibody", "antagonistbinder", "antagonistblocker",
    "antagonistinhibitor", "antagonistInhibitor",
    "antagonistinhibitor, competitive",
    "antagonistinhibitory allosteric modulator",
    "antagonistmultitarget",
    "antagonistother/unknown", "antibody", "blocker", "cleavage",
    "desensitize the target", "inhibitor", "Inhibitor",
    "inhibitor, competitive", "inverse agonist", "intercalation",
    "negative modulator", "neutralizer", "partial antagonist",
    "suppressor")

  # Some actions need to be removed
  actionsToDelete <- c("acetylation", "other/unknown", "product of", "unknown", "binding",
    "chaperone")
  d <- subset(d, !d$Actions %in% actionsToDelete )

  # Replace actions on the data.frame to inhibiting or activating
```



```

activatingRows <- d$Actions %in% activatingActions
d$Actions[activatingRows] <- "activation"

inhibitingRows <- d$Actions %in% inhibitingActions
d$Actions[inhibitingRows] <- "inhibition"

# Special Cases that need to be removed
d <- d[!(d$Actions == "allosteric modulator" & d$Drug == "Vardenafil"),]
d <- d[!(d$Actions == "allosteric modulator" & d$Drug == "Halothane"),]
d <- d[!(d$Actions == "antagonistagonist" & d$Drug == "Risperidone"),]
d <- d[!(d$Actions == "antagonistagonist" & d$Drug == "Tamoxifen"),]
d <- d[!(d$Actions == "antagonistagonist" & d$Drug == "Clomifene"),]
d <- d[!(d$Actions == "antagonistagonist" & d$Drug == "Ospemifene"),]
d <- d[!(d$Actions == "antagonistpartial agonist" & d$Drug == "Mivacurium"),]
d <- d[!(d$Actions == "agonistpartial agonist" & d$Drug == "Ergotamine"),]
d <- d[!(d$Actions == "agonistpartial agonist" & d$Drug == "Pseudoephedrine"),]
d <- d[!(d$Actions == "agonistpartial agonist" & d$Drug == "Ketamine"),]
d <- d[!(d$Actions == "antibody" & d$Drug == "Trastuzumab"),]
d <- d[!(d$Actions == "antibody" & d$Drug == "Rituximab"),]
d <- d[!(d$Actions == "antibody" & d$Drug == "Ibritumomab"),]
d <- d[!(d$Actions == "antibody" & d$Drug == "Tositumomab"),]
d <- d[!(d$Actions == "antibody" & d$Drug == "Alemtuzumab"),]
d <- d[!(d$Actions == "antibody" & d$Drug == "Methyl aminolevulinate"),]
d <- d[!(d$Actions == "antibody" & d$Drug == "ado-trastuzumab emtansine"),]
d <- d[!(d$Actions == "antibody" & d$Drug == "Obinutuzumab"),]
d <- d[!(d$Actions == "adduct" & d$Drug == "Ethionamide"),]
d <- d[!(d$Actions == "adduct" & d$Drug == "Isoniazid"),]
d <- d[!(d$Actions == "adduct" & d$Drug == "Gentamicin"),]
d <- d[!(d$Actions == "adduct" & d$Drug == "Tigecycline"),]
d <- d[!(d$Targets == "DRD1" & d$Drug == "Aripiprazole"),]
d <- d[!(d$Targets == "DRD5" & d$Drug == "Aripiprazole"),]
d <- d[!(d$Targets == "DRD3" & d$Drug == "Aripiprazole"),]
d <- d[!(d$Targets == "DRD4" & d$Drug == "Aripiprazole"),]
d <- d[!(d$Targets == "ATP1A1" & d$Drug == "Aripiprazole"),]
d <- d[!(d$Targets == "ASGR2" & d$Drug == "Antihemophilic Factor"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Oxytocin"),]
d <- d[!(d$Drug == "NADH"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Niacin"),]
d <- d[!(d$Targets == "PPIF" & d$Drug == "Cyclosporine"),]
d <- d[!(d$Targets == "HTR2C" & d$Drug == "Chlorpromazine"),]
d <- d[!(d$Targets == "HTR2A" & d$Drug == "Chlorpromazine"),]
d <- d[!(d$Targets == "ORM1" & d$Drug == "Chlorpromazine"),]
d <- d[!(d$Targets == "HTR6" & d$Drug == "Chlorpromazine"),]
d <- d[!(d$Targets == "HTR7" & d$Drug == "Chlorpromazine"),]
d <- d[!(d$Targets == "HRH4" & d$Drug == "Chlorpromazine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Loxapine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Trimipramine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Thiamine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Folic Acid"),]
d <- d[!(d$Drug == "Metyrosine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Halothane"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Pegademase bovine"),]
d <- d[!(d$Drug == "L-Phenylalanine"),]
d <- d[!(d$Drug == "L-Tyrosine"),]
d <- d[!(d$Drug == "L-Proline"),]
d <- d[!(d$Targets == "SLC6A4" & d$Drug == "Amphetamine"),]
d <- d[!(d$Targets == "DRD2" & d$Drug == "Amphetamine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Methysergide"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Cabergoline"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Atomoxetine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Amitriptyline"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Terfenadine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Norepinephrine"),]

```

```

d <- d[!(d$Actions == "binder" & d$Drug == "Mirtazapine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Spironolactone"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Pethidine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Prazosin"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Imipramine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Oxycodone"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Dextromethorphan"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Nortriptyline"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Amoxapine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Cinnarizine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Inulin"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Procaine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Tolazoline"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Cysteamine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Maprotiline"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Oxymetazoline"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Glycopyrrolate"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Dopamine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Guanfacine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Ketoconazole"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Thalidomide"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Memantine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Ibuprofen"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Doxepin"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Desipramine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Ketamine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Bepiridil"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Docetaxel"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Aluminium"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Almitrine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Dehydroepiandrosterone"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Indirubin-3'-Monoxime"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Olomoucine"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Nicotinamide"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Brentuximab vedotin"),]
d <- d[!(d$Drug == "SU9516"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Nesiritide"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Mianserin"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Tinzaparin"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Hyaluronic acid"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Dimethyl fumarate"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Muromonab"),]
d <- d[!(d$Actions == "binder" & d$Drug == "Denileukin diftitox"),]
d <- d[!(d$Actions == "modulator" & d$Drug == "Antihemophilic Factor"),]
d <- d[!(d$Actions == "modulator" & d$Drug == "Loperamide"),]
d <- d[!(d$Actions == "modulator" & d$Drug == "Glyburide"),]
d <- d[!(d$Actions == "modulator" & d$Drug == "Minocycline"),]
d <- d[!(d$Actions == "modulator" & d$Drug == "Ibuprofen"),]
d <- d[!(d$Actions == "modulator" & d$Drug == "Carvedilol"),]
d <- d[!(d$Actions == "modulator" & d$Drug == "Fingolimod"),]
d <- d[!(d$Actions == "multitarget" & d$Drug == "Dasatinib"),]
d <- d[!(d$Actions == "multitarget" & d$Drug == "Sunitinib"),]
d <- d[!(d$Actions == "other" & d$Drug == "Lovastatin"),]
d <- d[!(d$Actions == "other" & d$Drug == "Vancomycin"),]
d <- d[!(d$Actions == "other" & d$Drug == "Simvastatin"),]
d <- d[!(d$Actions == "other" & d$Drug == "Levonorgestrel"),]
d <- d[!(d$Actions == "other" & d$Drug == "Sirolimus"),]
d <- d[!(d$Actions == "other" & d$Drug == "Riboflavin"),]
d <- d[!(d$Actions == "other" & d$Drug == "Lorazepam"),]
d <- d[!(d$Actions == "other" & d$Drug == "Hydroxocobalamin"),]
d <- d[!(d$Actions == "other" & d$Drug == "Temazepam"),]
d <- d[!(d$Actions == "other" & d$Drug == "Chloramphenicol"),]
d <- d[!(d$Actions == "other" & d$Drug == "Quinine"),]
d <- d[!(d$Actions == "other" & d$Drug == "Aminocaproic Acid"),]

```

```

d <- d[!(d$Actions == "other" & d$Drug == "Lactulose"),]
d <- d[!(d$Actions == "other" & d$Drug == "Diclofenac"),]
d <- d[!(d$Actions == "other" & d$Drug == "Verapamil"),]
d <- d[!(d$Actions == "other" & d$Drug == "Sufentanil"),]
d <- d[!(d$Actions == "other" & d$Drug == "Adefovir"),]
d <- d[!(d$Actions == "other" & d$Drug == "Adefovir Dipivoxil"),]
d <- d[!(d$Actions == "other" & d$Drug == "Pentamidine"),]
d <- d[!(d$Actions == "other" & d$Drug == "Etodolac"),]
d <- d[!(d$Actions == "other" & d$Drug == "Triazolam"),]
d <- d[!(d$Actions == "other" & d$Drug == "Meclofenamic acid"),]
d <- d[!(d$Actions == "other" & d$Drug == "Zaleplon"),]
d <- d[!(d$Actions == "other" & d$Drug == "Ezetimibe"),]
d <- d[!(d$Actions == "other" & d$Drug == "Ketoprofen"),]
d <- d[!(d$Actions == "other" & d$Drug == "Felodipine"),]
d <- d[!(d$Actions == "other" & d$Drug == "Procainamide"),]
d <- d[!(d$Actions == "other" & d$Drug == "Flucytosine"),]
d <- d[!(d$Actions == "other" & d$Drug == "Diazoxide"),]
d <- d[!(d$Actions == "other" & d$Drug == "Carvedilol"),]
d <- d[!(d$Actions == "other" & d$Drug == "Desipramine"),]
d <- d[!(d$Actions == "other" & d$Drug == "Halothane"),]
d <- d[!(d$Actions == "other" & d$Drug == "Bepridil"),]
d <- d[!(d$Actions == "other" & d$Drug == "Chenodeoxycholic acid"),]
d <- d[!(d$Actions == "other" & d$Drug == "Iron Dextran"),]

# Special Cases that need to be modified
d <- within(d, Actions[ Drug == "Galantamine" & Actions == "allosteric modulator" ] <-
"inhibition")
d <- within(d, Actions[ Drug == "Trilostane" & Actions == "allosteric modulator" ] <-
"activation")
d <- within(d, Actions[ Drug == "Aldesleukin" & Actions == "agonistmodulator" ] <-
"activation")
d <- within(d, Actions[ Drug == "Carglumic Acid" & Actions == "allosteric modulator" ]
<- "activation")
d <- within(d, Actions[ Drug == "Quinestrol" & Actions == "agonistmodulator" ] <-
"activation")
d <- within(d, Actions[ Drug == "Olanzapine" & Actions == "antagonistagonist" ] <-
"inhibition")
d <- within(d, Actions[ Drug == "Ergoloid mesylate" & Actions == "antagonistagonist" ]
<- "activation")
d <- within(d, Actions[ Drug == "Tegaserod" & Actions == "antagonistpartial agonist" ]
<- "activation")
d <- within(d, Actions[ Drug == "Aripiprazole" & Targets == "DRD2" ] <- "inhibition")
d <- within(d, Actions[ Drug == "Aripiprazole" & Targets == "HTR1A" ] <- "inhibition")
d <- within(d, Actions[ Drug == "Penbutolol" & Actions == "antagonistpartial agonist" ]
<- "inhibition")
d <- within(d, Actions[ Drug == "Menotropins" ] <- "activation")
d <- within(d, Actions[ Drug == "Interferon gamma-1b" ] <- "activation")
d <- within(d, Actions[ Drug == "Palifermin" ] <- "activation")
d <- within(d, Actions[ Drug == "Somatropin recombinant" ] <- "activation")
d <- within(d, Actions[ Drug == "Interferon alfacon-1" ] <- "activation")
d <- within(d, Actions[ Drug == "Insulin, porcine" ] <- "activation")
d <- within(d, Actions[ Drug == "Choriogonadotropin alfa" ] <- "activation")
d <- within(d, Actions[ Drug == "Octreotide" ] <- "activation")
d <- within(d, Actions[ Drug == "Interferon Alfa-2b, Recombinant" ] <- "activation")
d <- within(d, Actions[ Drug == "Thiamine" & Actions == "binder" ] <- "activation")
d <- within(d, Actions[ Drug == "Antihemophilic Factor" & Targets == "VWF" ] <-
"activation")
d <- within(d, Actions[ Drug == "Folic Acid" & Actions == "binder" ] <- "activation")
d <- within(d, Actions[ Drug == "Levonorgestrel" & Actions == "binder" ] <-
"activation")
d <- within(d, Actions[ Drug == "Guanabenz" & Actions == "binder" ] <- "activation")
d <- within(d, Actions[ Drug == "Methoxamine" & Actions == "binder" ] <- "activation")
d <- within(d, Actions[ Drug == "Potassium Chloride" ] <- "activation")

```

```

d <- within(d, Actions[ Drug == "Alglucosidase alfa"] <- "activation")
d <- within(d, Actions[ Drug == "Teriparatide"] <- "activation")
d <- within(d, Actions[ Drug == "Tesamorelin"] <- "activation")
d <- within(d, Actions[ Drug == "Cyclosporine" & Actions == "binder"] <- "inhibition")
d <- within(d, Actions[ Drug == "Chlorpromazine" & Actions == "binder"] <-
"inhibition")
d <- within(d, Actions[ Drug == "Intravenous Immunoglobulin" & Actions == "binder"] <-
"inhibition")
d <- within(d, Actions[ Drug == "Botulinum Toxin Type B" ] <- "inhibition")
d <- within(d, Actions[ Drug == "Citalopram"] <- "inhibition")
d <- within(d, Actions[ Drug == "Gliclazide"] <- "inhibition")
d <- within(d, Actions[ Drug == "Ciclopirox"] <- "inhibition")
d <- within(d, Actions[ Drug == "Glatiramer Acetate"] <- "inhibition")
d <- within(d, Actions[ Drug == "Canakinumab"] <- "inhibition")
d <- within(d, Actions[ Drug == "Rilonacept"] <- "inhibition")
d <- within(d, Actions[ Drug == "Cabazitaxel"] <- "inhibition")
d <- within(d, Actions[ Drug == "Aflibercept"] <- "inhibition")
d <- within(d, Actions[ Drug == "Toremifene"] <- "inhibition")
d <- within(d, Actions[ Drug == "Rufinamide" & Actions == "modulator"] <- "inhibition")
d <- within(d, Actions[ Drug == "Drotrecogin alfa"] <- "inhibition")
d <- within(d, Actions[ Drug == "Ramelteon"] <- "activation")
d <- within(d, Actions[ Drug == "Oseltamivir" & Actions == "other"] <- "activation")
d <- within(d, Actions[ Drug == "Sirolimus" & Actions == "other"] <- "activation")
}

```

## Script 3. Functions for the Drug Analysis

```
# MODIFY EXP
drug.exp <- function(drug, expD = expT, effect = drugEffect){

  # Drug targets in xref
  affected_genes <- effect[which(effect$Drug == drug),]$ID

  # Drug effect on targets
  effect_on_genes <- effect[which(effect$Drug == drug),]$Actions

  # Copies the original exp for tumors and adds the drug name to the column name
  colnames(expD) <- paste(unique(drugEffect$DrugCode[drugEffect$Drug == drug]),
  colnames(expD), sep = "_")

  # Calculate new values for the affected genes
  iteration <- 1
  for(gen in affected_genes){

    action <- effect_on_genes[iteration]

    if(action == "inhibition"){expD[rownames(expD) %in% gen, ] <-
expD[rownames(expD) %in% gen, ]*0.001}
    else if(action == "activation"){expD[rownames(expD) %in% gen, ] <- 0.99}

    iteration <- iteration +1
  }

  # Returns a modified exp after applying a drug
  return(expD)
}

# MODIFY DES
drug.des <- function(drug, desD = desT, effect = drugEffect){

  d <- unique(effect$DrugCode[effect$Drug == drug])
  # Condition is drug name
  desD$Condition <- d

  # rows maintain name and add drug as a prefix
  rownames(desD) <- paste(unique(effect$DrugCode[effect$Drug == drug]), rownames(desD),
sep = "_")

  # Returns a modified des after applying a drug
  return(desD)
}
```

## Script 4. Code to Run the Program

```
# ORIGINAL CODE NEEDS TO BE SOURCED (GitHub HiPathia repository)
# igraph version 0.7.0.
library("igraph")
source("prettyways.R")
source("stats.R")
source("utils.R")
source("functions.r")

# Source developed code
source("drugs.into.data.frame.R")
source("functions.drug.analysis.R")
source("drug.statistics.R")
source("other.functions.R")

# OBTAIN DATA
# Load graphs and xref
load("files/meta_graph_info_hsa.RData")
for(pw in names(metainfo$pathigraphs)){
  metainfo$pathigraphs[[pw]]$graph
  for(eff in names(metainfo$pathigraphs[[pw]]$effector.subgraphs)){
    metainfo$pathigraphs[[pw]]$effector.subgraphs[[eff]]
  }
}

load("files/xref/hsa/xref.rdata")

# Load experimental data
des <- read.experimental.design("KIRC_des.txt")
exp <-
read.expression.matrix("exp_KIRC__hiseq_data_combat_WO_batch_corrected_by_gcc_and_plate.txt
")

# Load drug data
load("drugList.RData")
drugEffect <- drugs.into.data.frame(drugList)

# PREPARE EXPERIMENTAL DATA
exp <- translate.matrix(exp,xref)
exp <- normalize.data(exp, by.quantiles=F, by.gene=F, percentil=F)
exp <- add.missing.genes(exp, genes=metainfo$all.genes)

# PREPARE DRUG DATA
# Eliminate targets that are not in the experimental data
toRemove <- setdiff(unique(ID), rownames(exp))
drugEffect <- drugEffect[which( !drugEffect$ID %in% toRemove), ]

# Add column with targets translated to xref
drugEffect$ID <- unname(translate.ids(drugEffect$Targets, xref)$translation)

# Set unique code for each drug
drugEffect <- transform(drugEffect, DrugCode = match(Drug, unique(Drug)))
drugEffect$DrugCode <- sprintf('%i', drugEffect$DrugCode)

# EXTEND EXPERIMENTAL DATA WITH DRUG MODIFICATIONS TO PATIENTS
# File with the drugs to be tested
dat <- readLines("drugs_to_test.txt")
```

```

# Copy the original data for the tumor conditions to modify
expT <- exp[,which(des$Condition == "Tumor")[1]:nrow(des)]
desT <- des[des$Condition %in% c("Tumor"),1, drop = FALSE]

# Create a new modified matrix per drug and add it to the original data
for(d in dat){
  # For each drug given creates a new matrix modifying the original tumor data
  new_expD <- drug.exp(drug = d)

  # Append the new matrix to the full matrix
  exp <- cbind2(exp, new_expD)

  # Same for des
  new_desD <- drug.des(drug = d)
  des <- rbind2(des, new_desD)
}

# PATHWAY ANALYSIS
pathway_data <- prettyways(exp, metainfo$pathigraphs, verbose=T)

# FUNCTIONAL ANALYSIS
# Load the manual annotations file
entrez2hgnc <-
read.table("files/annotations/hsa/entrez_hgnc_hsa.annot",header=F,sep="\t",stringsAsFactors
=F)
annot <- load.annot.file("files/annotations/hsa/annot_manual_hsa.annot")
annot <- unique(annot)

# Pathways into Functions
functions <- prettyfuns.average(pathway_data, metainfo$pathigraphs, annot, entrez2hgnc)

```

## Script 5. Statistics and Output

```
# wilcox function
wilcox.function <- function(A, B, c){
  column <- data.frame(ncol = NA)
  colnames(column) <- c
  for(i in 1:nrow(A)){
    column <- rbind2(column, wilcox.test(A[i,], B[i,])$p.value)}
  column <- na.omit(column)
  rownames(column) <- rownames(A)
  return(column)
}

# Classification function
drug.type.per.function <- function(mD, mN, mT, df){
  # Per function it estimates the type of drug it is
  for(i in 1:nrow(df)){
    if(df$SignificantDN[i] == "N"){df$Classification[i] <- c("Optimum")}
    if(df$SignificantDN[i] == "Y"){
      if(mN[i,] < mT[i,]){
        if(mD[i,] < mN[i,]){df$Classification[i] <-c("Overdose")}
        else if(mN[i,] < mD[i,] & mD[i,] < mT[i,]){df$Classification[i] <-
c("Underdose")}}
        else if(mT[i,] < mD[i,]){df$Classification[i] <-c("Undesired")}}
      }
      if(mN[i,] > mT[i,]){
        if(mD[i,] > mN[i,]){df$Classification[i] <-c("Overdose")}
        else if(mN[i,] > mD[i,] & mD[i,] > mT[i,]){df$Classification[i] <-
c("Underdose")}}
        else if(mT[i,] > mD[i,]){df$Classification[i] <-c("Undesired")}}
      }
    }
  }
  return(df)
}

# TUMOR & NORMAL ANALYSIS
Tumor <- functions[,which(des$Condition == "Tumor")]
Normal <- functions[,which(des$Condition == "Normal")]

# Functions significantly different are set as Y
NT <- wilcox.function(Normal, Tumor, c = "pvalue_NT")
NT$SignificantNT[NT$pvalue <= 0.05]<- c("Y")
NT$SignificantNT[NT$pvalue > 0.05] <- c("N")

# DRUGS ANALYSIS
Conditions <- unique(des$Condition)
Conditions <- setdiff(Conditions, c("Tumor", "Normal"))

# All_Drugs_resume will contain pvalues for all drugs compared
All_Drugs_Resume <- NT

for(Condition in Conditions){
  dir.create(Condition)
  D <- functions[, which(des$Condition == Condition)]
}
```



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# 1. COMPARISONS
# Wilcoxt test Drug vs Tumor
DT <- wilcox.function(D, Tumor, c = "pvalue_DT")
DT$SignificantDT[DT$pvalue <= 0.05] <- c("Y")
DT$SignificantDT[DT$pvalue > 0.05] <- c("N")

# Wilcox test Drug vs Normal
DN <- wilcox.function(D, Normal, c = "pvalue_DN")
DN$SignificantDN[DN$pvalue <= 0.05] <- c("Y")
DN$SignificantDN[DN$pvalue > 0.05] <- c("N")

# Combine the information in aResume file of the drug for the folder
# Combine the Resume with the global Resume for all Drugs
Resume <- cbind2(NT, DT)
Resume <- cbind2(Resume, DN)
All_Drugs_Resume <- cbind2(All_Drugs_Resume,DT)
All_Drugs_Resume <- cbind2(All_Drugs_Resume, DN)

# Significant functions are those different between NT and DT
Significant <- Resumen[Resumen$pvalue_NT <= 0.05,]
Significant <- Significant[Significant$pvalue_DT <= 0.05,]

# 2. HOW IS THE DIFFERENCE WITH THE NORMAL?
# Get the average per function for those tumoral functions
# Original data reduced to significant for TN and DT comparisons
Tum <- Tumor[which(NT[,1] <= 0.05 & DT[,1] <= 0.05),]
Nor <- Normal[which(NT[,1] <= 0.05 & DT[,1] <= 0.05),]
D <- D[which(NT[,1] <= 0.05 & DT[,1] <= 0.05),]

# The means for N and T data and D per function:
meansN <- data.frame(unnname(rowMeans(Nor, na.rm = FALSE, dims = 1)))
rownames(meansN) <- rownames(Nor)
colnames(meansN) <- c("meansN")

meansT <- data.frame(unnname(rowMeans(Tum, na.rm = FALSE, dims = 1)))
rownames(meansN) <- rownames(Tum)
colnames(meansN) <- c("meansT")

meansD <- data.frame(unnname(rowMeans(D, na.rm = FALSE, dims = 1)))
rownames(meansD) <- rownames(D)
colnames(meansD) <- Condition

DrugTypeData <- DN[which(NT[,1] <= 0.05 & DT[,1] <= 0.05),]
DrugType <- drug.type.per.function(mD = meansD, mN = meansN, mT=meansT, df =
DrugTypeData)

# 3. WRITE THE OUTPUT
write.csv(Resume, 'Resume.csv', row.names=T)
write.csv(Significant, 'Significant.csv', row.names=T)
write.csv(DrugType, 'DrugType.csv', row.names=T)

setwd('Prettyways')

}

write.csv(Resume, 'All_Drugs_Resume.csv', row.names=T)

# Get Plot for Normal and Tumor
m <- cbind(Normal, Tumor)
m <- t(m)
m <- data.frame(m)
m$Condition <- des$Condition

```

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#### PLOTS

# Load Libraries
library(reshape)
library("plotly")

m <- melt(m, id.var = "Condition" )
X <- list(title = "")
Plot<- m, x = ~variable, y = ~value, color = ~Condition, colors = c("red", "blue"), type =
"box", opacity = 0.4) %>% layout(xaxis = ax)
```