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**New targeted therapies for breast cancer: A focus on tumor microenvironmental signals and chemoresistant breast cancers**

Kamdje AHN *et al.* New targeted therapies for breast cancer

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# Abstract

Breast cancer is the most frequent female malignancy worldwide. Current strategies in breast cancer therapy, including classical chemotherapy, hormone therapy, and targeted therapies, are usually associated with chemoresistance and serious adverse effects. Advances in our understanding of changes affecting the interactome in advanced and chemoresistant breast tumors have provided novel therapeutic targets, including, cyclin dependent kinases, mammalian target of rapamycin, Notch, Wnt, and Shh. Inhibitors of these molecules recently entered clinical trials in mono- and combination therapy in metastatic and chemo-resistant breast cancers. Anticancer epigenetic drugs, mainly histone deacetylase inhibitors and DNA methyltransferase inhibitors, also entered clinical trials. Because of the complexity and heterogeneity of breast cancer, the future in therapy lies in the application of individualized tailored regimens. Emerging therapeutic targets and the implications for personalized-based therapy development in breast cancer are herein discussed.

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**Key words:** Breast cancer; Microenvironment; Signaling molecule; Targeted therapy; Chemoresistance

**Core tip:** Emerging therapeutic targets may overcome chemoresistance in breast cancer.

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# **INTRODUCTION**

The incidence of breast cancer, the most common cancer in women and the second cause of cancer death in women worldwide[1,2], is currently growing[3,4]. Cancers are diseases characterized by aberrant microenvironment and intrinsic signaling causing a continuous proliferation of affected cells (“cancer cells”). Clinical features and prognosis of cancers vary tremendously according to the tissue and organs they originate from and affect. Breast cancer may start in milk ducts, and can be invasive (invasive ductal carcinoma, IDC) or not (ductal carcinoma in situ, DCIS). IDC would represent up to 80% of cases[5,6]. Breast cancer may also start in the lobules, with invasive features (invasive lobular carcinoma, ILC) or not (lobular carcinoma in situ, LCIS). In metastatic breast cancer malignant cells originating from breast primary tumors invade other tissues and organs of the body, resulting in a systemic disease. As disease early detection is associated with better prognosis, screening campaigns involving healthy female subjects are performed worldwide. Notably, mammography, which requires the use of low-dose X-rays to capture images inside the breast, is the current goal standard screening for detection of breast cancer asymptomatic cases[7,8]. However, although the technique requires X-rays, the benefits of the earlier detection of breast cancer outweigh the risk of radiation exposure, which can be associated with the development of breast cancer in previously healthy women is present[9,10]. New approaches for early detection have been proposed, and may also contribute to reducing breast cancer mortality (for review see[11,12]).

Three major therapeutic approaches are used today to treat or control breast cancer: surgical removal of primary tumors, irradiation of cancer cells to stop their growth, and anticancer drugs, which kill cancer cells or inhibit their proliferation. Notably, oncoplastic surgery, a technique combining classical lumpectomy (or partial mastectomy) and plastic surgery techniques have revolutionized breast-conserving surgery for removal of lumps and malignant masses. However, surgery or radiotherapy still requires chemotherapy to eradicate remaining malignant cells and impede relapses. Anticancer drugs are based on three therapeutic approaches: (1) the classical chemotherapy, where cancer cell proliferation is stopped by the indiscriminate targeting of rapid cell divisions in the body; (2) hormone therapy, devised to stop cancer cell growth by targeting the receptors and downstream signaling molecules of hormones pivotal for the proliferation of these cells; and (3) and the emerging and promising targeted therapy, where signaling pathways deregulated in primary breast tumors are specifically targeted. Breast cancer treatment is still challenging, as drugs in use are expensive, have serious undesired effects[13-15], and drug resistance is common, particularly in metastatic cases[16,17], underlying the need for new targeted therapies. Interestingly, recent advances in the understanding of breast cancer biology have highlighted the tumor microenvironment as a major player in breast carcinogenesis and have provided new avenues for targeted therapy.

The present review summarizes and discusses the current understanding of changes affecting breast microenvironment during breast tumorigenesis, with a particular emphasis on signaling pathways currently targeted for therapy and emerging therapeutic targets. Personalized-based targeting implementation is also discussed.

# TUMOR MICROENVIRONMENT IS PIVOTAL FROM BREAST CANCER INITIATION TO METASTASIS

Numerous stromal cell types are found in the extracellular matrix (ECM) of the breast stroma, including endothelial cells, fibroblasts, adipocytes, and resident immune cells[18]. In addition to these cell types, cancer-affected microenvironment contains malignant cells termed as cancer-associated fibroblasts (CAFs), which are the most numerous cell type, and infiltrating macrophages termed as tumor-associated macrophages (TAMs).

## *Cancer-associated fibroblasts*

CAFs were reported to play key roles in malignant cell proliferation and tumor maintenance[19,19]. An *in vivo* study involving xenograft of MDA-MB-231 breast cells in SCID mice revealed that CAFs induce p53-dependent antimitogenic responses in normal stromal fibroblast[20], at least partly through Notch-dependent mechanisms[21]. In another study, CAFs expressed VEGF in presence of hypoxia inducible factor 1 alpha/G-protein estrogen receptor (HIF-1α/GPER) signaling, suggesting a role for these cells in hypoxia-dependent tumor angiogenesis[22]. Under the same conditions, CAFs were shown to express Notch molecules[23], which promotes cancer cell survival, proliferation[24,24], as well as angiogenesis[26]. In addition, Luga and colleagues showed that CAFs release exosomes, which stimulate invasiveness and malignant cell metastasis via a Wnt11-dependent mechanism[27]. On the same hand, CAFs induced phenotypical changes in adipocytes resulting in the generation of fibroblast-like cells (adipocyte-derived fibroblasts, ADF), which in turn increased migratory abilities of metastatic cells by releasing high levels of collagen I and fibronectin[28]. Notably, CAF-induced ADF phenotype generation was mediated by reactivation of the oncogenic Wnt/β-catenin pathway in the latter cells in response to Wnt3a produced by the cancer cells, suggesting CAFs and ADFs as potential therapeutic targets in metastatic breast cancer. Furthermore, CAFs may promote breast cancer initiation and progression to metastasis via tumor-α9β1 integrin signaling[29] and fibroblast growth factor (FGF) signaling[30], as well as malignancy orchestration and tumor stroma reprogramming through activation of heat shock factor 1 (HSF1)[31], a transcriptional regulator.

Interestingly, Capparelli and colleagues have hypothesized that senescent fibroblasts may promote tumor growth through an autophagy-dependent mechanism[32,33] termed as “autophagy-senescence transition” (AST). In order to test such hypothesis, these authors introduced autophagy genes such as *bnip3*, *ctsb*, or *ATG16L1* in immortalized human fibroblasts that resulted in the induction of a constitutive autophagic phenotype (characterized by mitophagy, aerobic glycolysis, L-lactate and ketone body production) with senescence features associated with increased β-galactosidase activity, increased level of cyclin dependent kinase inhibitor (CDKI) p21, and cellular hypertrophy. Interestingly, “autophagic-senescent” fibroblasts were able to induce tumor growth and metastasis independently of angiogenesis, with stronger effects (up to 11-fold) in autophagic fibroblasts producing large amounts of ketone bodies. These observations were confirmed *in vivo*, as the lysosomal enzyme and biomarker of senescence, β-galactosidase, was also found in human breast cancer stroma. A recent *in vivo* study revealed the ability of CAF autophagy and senescence to promote tumor growth and metastasis increasing the rate of glycolysis and enhancing the generation of mitochondrial fuels including bodies[33] in a compartment-specific fashion, thus supporting the role of CAFs to metabolically regulate tumorigenesis. In this study, the injection of the antidiabetic molecule along with peroxisome proliferator-activated receptor gamma (PPARγ), known to stimulate glycolysis and pro-autophagy, into stromal cells enhanced the growth of co-injected breast cancer cells by 60%, whereas PPARγ injection in cancer cells reduced the growth of breast cancer cells by 40%[34].

## *Tumor-associated macrophages*

TAMs infiltration into neoplastic tissues is an important negative prognostic factor[35,36], and a hallmark of triple negative breast cancer[37], a chemoresistant subtype of breast cancer[38,39]. Overall, emerging evidence suggests that TAMs are major player in anticancer drug resistance in breast cancer. For instance, Yamashina and colleague recently reported that cancer stem-like cells originating from chemoresistant tumor promote macrophage colony-stimulating factor (M-CSF) production via an interferon regulatory factor 5 (IRF5) -dependent mechanism[40], and transform recruited CD14(+) monocytes in tumorigenic M2-macrophages (immunoregulatory), probably through CXCR3 downregulation[41]. Interestingly, the differentiation inducer dimethyl sulfoxide (DMSO) exerted antitumor effects in a mouse breast cancer model (4T1) possibly by inducing M1-phenotype in TAMs[42].

Furthermore, TAMs may promote carcinogenesis and metastasis via Wnt signaling, which mediates the angiogenic switch and metastatic processes in breast cancer[43,44]. Notably, TAMs release high levels of the Wnt family ligand Wnt7b[45], and cancer stem-like cells may trigger the metastatic effect of TAMs through enhancement of the β-catenin pathway via vitamin D receptor suppression by tumor necrosis factor alpha (TNFα)[46]. In addition, *in vivo* and *in vitro* studies supported a pivotal role for Wnt 5a signaling in TAMs-induced metastasis[47,48], and a strong correlation was found between Wnt5a expression in malignant cells and the number of CD163(+) M2-macrophages[49]. In a relatively recent study investigating the potential of the phosphodiesterase type 5 (PDE5) inhibitor (vasodilator) drug dipyridamole in xenograft mice, anticancer effects were mediated at least partly by decreasing β-catenin cytosolic levels[50]. Altogether, these findings implicated TAMs as a key links between chemoresistance and tumorigenic activities of cancer stem-like cells, and thus, positioning TAMS as potential therapeutic targets for breast cancer. Figure 1 shows the main signaling pathways currently in use for targeted breast cancer therapy, as well as some possible new targets.

# NOTCH SIGNALING

## *Notch family of molecules*

The Notch family of membrane bound receptors and ligands regulate several cell processes including cell invasion, survival and apoptosis, via the Notch signaling pathway. The pathway comprises four receptors (Notch1 through Notch4) and five Notch ligands (Delta-like 1, 3, and 4, and Jagged1 and 2). Notch ligands include an extracellular domain containing multiple epidermal growth factor (EGF)-like repeats and an extracellular DSL where ligand binding occurs, and an intracellular domain with a PDZ-binding motif at C-terminal domain[51,52]. Notch receptors are also made of an extracellular and an intracellular domain covalently linked. Notch receptor extracellular domain (NECD) also contains EGF-like repeats (26-29 depending on the Notch receptor), whereas Notch intracellular domain (NICD) presents with LIN12/Notch-related (LNR) repeats preventing ligand-independent signaling, cysteine residues, and a C-terminal transactivation domain containing a PEST sequence with proteolytic activity.

Notch ligands are expressed on the plasma membrane of one cell and interact with Notch receptors on the plasma membrane of a neighboring cell, initiating the cleavage of the receptor by proteases (ADAM [a disintegrin and metalloprotease] and γ-secretase) that culminates in the release of the Notch intracellular domain (NICD)[53]. Released NICD translocate to the nucleus and forms a transcriptional activator complex with CBF-1 (C-promoter binding factor 1)/Suppressor of Hairless and Lag-1 (CSL) transcription factor. Together with cofactors like mastermind-like (MAML) protein, NICD-CSL complex induces the transcription of cell fate key target genes such as *vegfr3* and, *notch1* that regulate angiogenesis and apoptosis, *p21* that regulates the cell cycle, as well as transcription factor genes such as the basic helix-loop-helix and hairy/enhancer of split/-related (*hes* and *hey*) [54,55] (Figure 1).

## *Notch signaling as a therapeutic target*

As already mentioned (section 2), Notch signaling is used by CAFs to promote cancer cell survival and proliferation. Early reports revealed that upregulation of Notch signaling suffices to transform normal breast epithelial cells in malignant cells *in vitro*, and that high levels of NICD are present in breast primary tumors[56-59]. Notch carcinogenic effects are mediated via the silencing pro-apoptotic signaling pathways and growth-inhibitory molecules like TGF-β[58]. Notch-induced TGF-β silencing also promotes bone metastasis[60,61]. In addition, Notch signaling, which is required for physiological angiogenesis, may also be a key player in neoangiogenesis[62]. A Notch 3 addiction of the lymphovascular embolus was reported in a xenograft model of inflammatory breast carcinoma (IBC), a subtype of breast cancer whose hallmark is lymphovascular invasion[63].

*In vitro* studies in estrogen receptor (ER)-negative breast cancer cells (MDA-MB-231) performed by Lee and colleagues revealed that Notch signaling up-regulates the transcription of the apoptosis inhibitor survivin[64]. In another study, these authors showed that Notch-1-survivin functional gene signature is common in basal breast cancer[65]. In addition, crosstalk between Notch and signaling pathways involved in cell growth were reported as well, including the estrogen receptor[66], human epidermal growth factor receptor 2 (HER2)[67], and the metabolic signaling pathways phosphatidylinositol 3-kinase (PI3K)/Akt (protein kinase B) /mammalian target of rapamycin (mTOR)[68,69] and MAP kinase/ERK[70,71]. Interestingly combined targeting of Notch and EGFR signaling suppressed chemoresistance in a basal-like breast cancer *in vivo* model[72], suggesting that co-targeting of Notch and associated pathways may represent a new avenue for overcoming chemoresistance (Figure 1).

Tumor initiating cells of tumors overexpressing HER2/neu also express high levels of Notch molecules, whose signaling is known to enhance HER2 expression[73]. Chemoresistance to HER2+ breast cancers to trastuzumab, a monoclonal antibody against HER2, is associated with the overexpression of Notch-1 and its ligand Jagged-1[74,75]. Similarly, cancer stem-like cells also achieve resistance against chemotherapy and radiotherapy via Notch signaling[76], and targeting of this signaling pathway reduces the stem-like population[77]. The γ-secretase inhibitor MRK-003 induced long-term recurrence-free survival in a transgenic mouse model of HER2+ breast cancer[78]. Similarly, co-targeting of Notch and HER2 signaling pathways prevented breast tumor recurrence in orthotopic breast tumor xenograft using trastuzumab-resistant BT474 cells[79].

Platelet-derived growth factor-D (PDGF-D), another marker of breast cancer poor prognosis, may increase breast tumor aggressiveness by activating Notch and NF-κB signaling pathways[80]. Furthermore, Notch-1 and Notch-4, established bio-markers of the chemoresistant breast cancer subtype[81], were reported as novel transcriptional targets in triple negative breast cancer[82,83]. Jagged1/Notch4 signaling was shown to induce epithelial-to-mesenchymal transition (EMT)[84]. Notch signaling was also reported as a mechanism of resistance to PI3K inhibitors[85] and hormone therapy[86].

## *Clinical evaluation of Notch signaling targeting*

Notch signaling inhibitors have a promising clinical efficacy as they abrogate HER2-Notch axis of chemoresistance. Notch silencing by ɣ-secretase inhibitors (GSIs) inhibited the proliferation of breast cancer cells partly by causing cell cycle arrest and apoptosis[76], and by sensitizing chemoresistant breast cancer cells to the BH3 mimetic ABT-737[87]. Notably, GSIs induce toxicity to breast cancer both *in vitro* and *in vivo* models, however mechanisms of such cytotoxicity are complex and may involve proteasome inhibition and downregulation of Bax and Bcl-2[88,89].

Following encouraging pre-clinical studies[83,90,91], the oral gamma secretase inhibitor R04929097 recently entered phase-I trial in patients with advanced solid tumors. Early reports of combination therapies with the kinase inhibitor temsirolimus[92], the antimetabolites of the pyrimidine analog family gemcitabine (PHL-078/CTEP 8575)[93] or cediranib (PJC-004/NCI 8503) revealed that the combinations were safe and promising in breast, tracheal, and pancreas cancer patients. However, anemia, diarrhea, fatigue, hypertension, neutropenia, and nausea were observed, among other side effects. GSI reported side effects seem to be mediated primarily through proteasome inhibition[88,94]. Thus, CSL inhibition, which was reported to mediate a more effective inhibition of Notch-dependent carcinogenic processes than GSIs[95], may represent a less toxic approach for Notch signaling targeting.

Another GSI, PF-03084014, also presented promising results in breast xenograft models[96], with gastrointestinal toxicity easily abrogated by glucocorticoids[97]. Other promising pre-clinical observations included a synergistic effect with the antimitotic drug docetaxel in breast cancer[98], colorectal cancer[99], and metastatic pancreatic cancer[100] models. Antiangiogenic effects where also reported in combinations with the tyrosine kinase inhibitor sunitinib in solid tumors[101], whereas in chronic lymphocytic leukemia (CLL) cells combinations with the nucleoside metabolic inhibitor fludarabine inhibited angiogenesis as well as migration and invasion of Notch 1-mutated cancer cells[102,103]. PF-03084014 therefore appears as an appealing GSI for both solid and blood cancers and may be a good targeted-therapy drug in breast cancer.

# CYCLIN DEPENDENT KINASES

## *CDKs, cyclins and CDK inhibitors*

Cyclins, CDK inhibitors (CDKIs, *e.g.,* p16INK4, p15INK4B, p18INK4C. p21WAF1/CIP1[104,105]) and CDKs are the three key classes of regulatory molecules that determine cell cycle progression through the G0-G1-S-G2 and M phases[106,107]. Numerous CDKs are found in eukaryotic cells, of which some are pivotal cell cycle regulators, such as CDK1/2/4/6 (**Figure 2**). CDKs (catalytic subunits, heterodimeric serine/threonine kinase class) associate with cyclins (regulatory subunits) to form an active catalytic complex favoring G1/S cell-cycle progression in mitosis. For instance, CDK1/A2 or CDK1/B1 complexes trigger mitosis in mammalian cells by phosphorylating downstream cell cycle regulatory proteins[108]. Other CDKs are involved in the regulation of cellular transcription, such as CDK7-11[107,109]. A recent proteomic analysis of the CDK family in human cells has identified a CDK5 complex as a key regulator of non-neural cell growth and migration factor[110].

## *CDK involvement in breast cancer*

Early and emerging evidence suggests that cyclin D1 promotes breast tumorigenesis[111,112]. CDK1 activity was recently reported as a powerful predictor of taxane chemosensitivity, indicating a role for CDK1 in breast tumorigenesis[111]. Notably, taxanes are the drug class most used for breast cancer pre-operative chemotherapy; they induce apoptosis in malignant cells by stopping their replication[113,114]. Moreover, studies investigating genes that are synthetically lethal in Myc-dependent cancer identified numerous CDKs as Myc synthetic-lethal genes[115,117]. Interestingly, in one of such studies CDK1, but not CDK2 or CDK4/6 was selectively lethal to Myc-dependent breast cancer cells[117]. This observation indicates that targeting CDK1 may induce apoptosis in Myc-dependent cancers, where Myc drives cancer cell growth and cycle progression[118]. Increases in activities and levels of other CDK complexes were also reported in breast cancer primary tumors and experimental models, including CDK4/6 and cyclin E/CDK2 complexes[119-121]. The occurrence of cyclin E/CDK2 proteolytic cleavage products associates with poor clinical outcome in breast cancer patients and increases tumorigenicity in experimental models at least partly by promoting stem-like properties of tumor cells[120]. Transcriptional regulator CDK8 targeting was also recently reported to inhibit both the proliferation and the migration of breast cancer cells 122. In addition, BRCA2 gene, whose aberrant activating mutations associate with familial breast cancer[123,124], was reported to induce genomic stability in malignant cells through a CDK-dependent mechanism[125].

A link between the cell cycle and steroid hormone metabolism involving CDK4/6 was recently uncovered in breast cancer primary tumor cells[126]. In this study, malignant cells appeared to control the activity of steroid metabolic enzymes, *i.e.,* the expression of steroid hormone receptors (including ER), by alteration of CDK4/6-levels (overexpression of CDK4 and decrease of its homolog CDK6). Such mechanism may play a pivotal role in the carcinogenesis and chemoresistance of steroid hormone-dependent cancers. In another recent study the newly synthesized compound KU004 that had a potent anticancer effect by targeting HER2 induced a decrease in CDK4 expression[127]. On the same hand, CDK 4/6 inhibitors sensitized *PIK3CA* mutant breast cancer to PI3K inhibitors in a xenograft study[128]  (Figure 2), further suggesting a role for CDK4/6 imbalance in breast tumorigenesis.

## *CDK inhibitors*

CDK4/6 inhibitors are more efficient and less toxic antineoplastic agents than molecules targeting other CDKs[129]. The selective cyclin D kinase 4/6 inhibitor palbocyclib (PD-0332991) is currently entering phase III trial for ER+ breast cancer patients, following encouraging results in progression free survival in phase II trials[130]. Using the bioluminescence imaging technology, an early study in xenograft models displaying metastatic progression revealed powerful antimetastatic effects, comparable to avastin, and docetaxel effects[131]. In addition, palbocyclib, preferentially inhibited the proliferation of luminal ER+ breast cancer cell lines *in vitro*[132], suppressed malignant cell proliferation in approximately 85% of cases irrespective of ER+/- or HER2+/- statuses[133]. Furthermore, palbocyclib induced growth arrest in hormone-resistant MCF-7 breast cancer cells by a mechanism consistent with cellular senescence[134]. This observation is not surprising considering the functional link between tumor microenvironment carcinogenic activity, ageing, and autophagy discussed above (section 2.1), and indicate that the drug may also affect metabolic processes in CAFs and stem-like tumor cells[33,34].

Chemoresistance to CDK4/6 inhibitors has been reported[133,135]. Analyses of primary tumor cells of cases resistant to CDK4/6 inhibitors showed that these cells lack the tumor suppressor retinoblastoma protein (RB)[133], which is necessary for CDK4/6 control of the cell cycle restriction point[135]. Interestingly, RB-deficient chemoresistant breast cancers, such as RB-deficient triple negative breast cancers, are more sensitive to the metabolic inhibitor of the folate analog family methotrexate and to the anthracycline topoisomerase inhibitor doxorubicin compared to RB+ cell lines[136], indicating that combination therapy may improve CDK4/6 inhibitor response in resistant cases. However, a report by Roberts and colleagues cautioned against the use of these agents in combination with DNA-damaging drugs (*e.g.*, doxorubicin, carboplatin), considering the potential genotoxic side effects[129]. The dangers that may result from such combination also emerged in other pre-clinical studies[137,138].

The CDKI dinaciclib (MK-7965), which selectively binds to the ATP site of CDKs and acts as a protein-protein inhibitor of bromodomains[139,140], also displayed encouraging anticancer properties in pre-clinical studies in human cancer models[141,142]. The drug recently entered phase III in leukemia[139] and phase II trial in solid cancers. The drug is well tolerated in monotherapy, but revealed an antitumor activity whose efficacy was not superior to the nucleoside metabolic inhibitor capecitabine in a phase II trial in advanced breast cancer patients[143]. Comparable observations were reported in non-small cell lung cancer (NSCLC) where the drug was compared with the protein kinase inhibitor erlotinib[144]. Similar combination therapy studies in progress for breast cancer[143,144] may provide alternative strategies for breast cancer therapy.

# OTHER EMERGING THERAPEUTIC TARGETS

## *Wnt signaling*

A number of reports have suggested that Wnt signaling pathway, which is normally involved in embryonic induction and cell fate[145,146], is aberrantly activated in blood cancers[147-149] and solid cancers, such as head and neck, lung, gastrointestinal, and breast cancer[27,150-155]. Wnt5a and Wnt11 are major players in macrophage-induced malignant invasion in metastatic breast cancer[27,151], and several breast tumors constitutively release-inducible Wnt ligands[156]. In addition, the naturally occurring pentacyclic triterpenoid ursolic acid, which is known to exert antitumor activity in various solid cancers including breast cancer, may act through inhibition of canonical (Wnt/β-catenin) signaling[150]. Similarly, the natural plant polyphenol rottlerin was reported to inhibit Wnt/β-catenin signaling in cancer cells by promoting the degradation of Wnt co-receptor LRP6 (low density lipoprotein receptor-related protein 6)[157]. Such inhibition resulted in cell death in various cancer cell lines, including MDA-MB-231 and T-47D breast cancer cells. Salinomycin, another novel LRP6 inhibitor, induced comparable effects in breast and prostate cancer cell lines, by inhibiting both Wnt/β-catenin and PI3K/Akt/mTOR signaling[158].

The development of specific Wnt inhibitors is in progress. Recently, a specific inhibitor of Porcupine (PORCN, an O-acyltransferase required for the secretion of Wnt ligands[159]) termed as LGK974 was developed. LGK974 displayed potent anticancer properties in *in vitro* and *in vivo* models of breast cancer and pancreatic adenocarcinoma mediated by reduction of the transcriptional expression of Wnt target genes[147,160]. However, another recent report revealed that Wnt signaling molecules are differentially expressed in breast cancer clinical subtypes and in cancer stem-like cells, indicating that the development of more specific Wnt-targeted therapies in breast cancer may be necessary[161]. Wnt signaling was also reported a major role in malignant cell acquired resistance to classical chemotherapy, including resistance to tamoxifen[162], and in chemoresistant cells from triple negative breast cancer patients[163], suggesting the potential of Wnt inhibitor combination therapies.

## *Shh signaling*

Early studies have suggested that Sonic Hedgehog (Shh) overexpression, mediated by both NF-κB up-regulation and *shh* promoter hypomethylation in breast cancer[164], is a critical event in the development of various solid cancers[165-167]. For instance, Shh signaling was reported to promote the survival of cancer epithelial cells, but not their normal counterparts[168]. Targeting of Shh transcription activator Gli1 enhanced apoptosis and attenuated migration in inflammatory breast cancer cells[169]. In addition, Shh non-classical activation was reported as a multidrug resistance enhancer, including resistance to Smo inhibitors[170], suggesting that targeting these pathways specifically may abrogate the associated chemoresistance.

Smo inhibitor anticancer drug cyclopamine, which inhibits Shh signaling by antagonizing its downstream target Smo, is metabolically stable and is currently investigated for the treatment of various cancers[171-173]. The chemotherapy drug paclitaxel used in combination with cyclopamine was shown to antagonize chemoresistant breast cancer cells both *in vivo* and *in vitro*[174], suggesting Shh signaling as a candidate for targeted therapy in chemoresistant cancer cells. Similarly, cyclopamine also sensitized chemoresistant tumor cells to taxane drugs in ovarian cancer[175], another hormone–related cancer. Not surprisingly, Shh targeting was reported as a therapeutic option in endocrine-resistant breast cancer due to its ability to sensitize PI3K/AKT signaling-induced tamoxifen chemoresistant malignant cells[176].

Notably, ER-ɑ physiologically regulates non-canonical Shh signaling in the mammary gland, and is essential for mammary gland morphogenesis at puberty[177,178]. However, Gli1 expression also enhances migration and invasion of malignant cells in ERα-negative and triple negative breast cancers, where it represents a predictor of poor prognosis[179]. These observations indicate that Shh signaling involvement in breast cancer cells is complex and therefore targeting Shh in chemoresistant cancer therapy can also compromise its normal physiological function.

# FUTURE DIRECTIONS: PERSONALIZED-BASED THERAPY AND EPIGENETIC TARGETS

## *Personalized-based therapy*

The major challenges in breast cancer treatment include resistance to chemotherapy, hormone therapy and even targeted therapy (Table 1), which underline the need for developing novel targeted therapies. Although the main molecular events driving cancer involve the activation of proto-oncogenes or the inactivation of tumor suppressors, deregulation of various signaling intermediates and metabolic factors have been well documented[72,77,82,83,149,161]. The events triggering cancer development affect proto-oncogenes such as Notch, Wnt, and Shh, which are the developmental genes driving embryonic induction and organogenesis during fetal life. These genes, whose expression is normally transcriptionally reduced or silenced in most adult tissues (except stem-like cells) by regulator molecules, are aberrantly overexpressed in cancer cells, conferring them stem-like properties[72,77,82,83,149,161].

Concomitantly, neoplastic tissue growth is fuelled by the upregulation and overexpression of receptors such as HER2, ER and, IGF-1R[70,71,180], the upregulation and/or activation of signaling molecules associated with cell proliferation[111,112], cell migration[181,182], oxidative stress, hypoxia and neoangiogenesis[22,26], all which are characteristic of tumor microenvironment. Thus, the complete characterization of all these tumor promoting events will pave the way for the development more efficient and less toxic anticancer drugs. Computational causal network models aimed at improving the current understanding of signaling molecule interactions in breast cancer, which will allow the determination of specific subsets of patients susceptible to a given therapeutic approach, are currently in development[156,183]. Although the complexity of such networks makes this effort challenging, nonetheless, the development of such tool would allow implementation of a highly efficient personalized-based therapy in breast cancer.

## *Epigenetic changes drive tumorigenesis*

Epigenetics describes heritable alterations in gene expression patterns that do not alter the primary DNA sequence, but play critical roles in normal differentiation and development. Epigenetic alterations include modifications such as DNA methylation, histone modifications and nucleosome remodeling. The plasticity and reversibility of epigenetic events enable a better control of the dynamism of cellular processes. However, deregulation of the normal epigenetic patterns can lead to aberrant expression of cell growth regulatory genes that can culminate in cancer. Epigenetic factors affect gene expression both pre- and post-transcriptionally and probably account for the high inter-individual variability in clinical course and treatment outcome of both blood and solid cancers[184,185]. There is ample evidence linking the etiology of breast to abnormal genetic and epigenetic events[180,186,187]. Cancer-specific DNA methylation changes and well as dysregulation of histone modification have been characterized as contributors to breast cancer development. Progress in our understanding of epigenetics mechanisms in breast cancer have led to the identification of novel therapeutic targets. Recent therapeutic strategies involving the use of epigenetic agents alone or in combination with chemotherapy and/or endocrine therapy are showing promising results in breast cancer patients including chemoresistant cases[186,188].

The technological breakthrough of “omics era” has allowed the development of high-throughput sequencing technology allowing both global and comprehensive investigations of the interactome, the epigenome, and the transcriptome (*i.e.*, active signaling pathways, cascades of pre- and post-translational changes affecting specific genes, and changes in gene expression)[189-191] at individual level. Epigenetic alterations in cancer constitute appealing therapeutic targets due to their pivotal roles in disease initiation, progression, and chemoresistance, and to their reversibility. For instance, chemoresistance to the ER antagonist fulvestrant is mediated by epigenetic modulation (more specifically hSWI/SNF-mediated chromatin remodeling) of G protein-coupled ER (GPER) and CDK6 expression[192], suggesting that adjuvant therapy targeting SWI/SNF activity may induce apoptosis in resistant cancer cells. SWI/SNF tumor-dependency has also been reported in other solid cancers and in leukemias[193,194].

## *Epigenetic targets in breast cancer: histone deacetylation and DNA hypermethylation*

Studies have shown that the transcriptional expression of various signaling molecules associated with breast cancer and other cancers may result from selective epigenetic silencing of regulator genes mediated by histone deacetylation and gene promoter (DNA) hypermethylation[195-197], among other potential epigenetic mechanisms[186,198]. For instance, the reduction in ER expression observed in various chemoresistant breast tumors may be mediated by epigenetic silencing (*e.g.*, *erβ1* silencing)[199]; and some histone deacetylases (HDACs) such as HDAC3/8 were reported to play pivotal regulatory roles in the proliferation of normal and MDA-MB-231 cells[200].

Data from numerous pre-clinical *in vivo* and *in vitro* studies support the potential of DNA methylation status targeting in breast cancer. Both the HDACI trichostatin A and the DNA methyltransferase (DNMT) inhibitor (DNMTI) deoxycytidine (5-aza-2'-deoxycytidine) induced apoptosis in various breast cancer cell lines[201-205]. The HDACI Romidepsin (FK-288) eliminated both primary and metastatic tumors in combination with Paclitaxel in the Mary-X pre-clinical model of inflammatory breast cancer[206]. The green tea-derived anticancer molecule epigallocatechin-3-gallate (EGCG) suppressed invasiveness in MDA-MB-231 and MCF-7 breast cancer cells by silencing matrix metalloproteinase 2 (MMP2) and MMP-9 and inducing TIMP-3 through increased activities of the enhancer of zeste homolog 2 (EZH2) and HDACs[207]. Suberoylanilide hydroxamic acid, another naturally occurring HDACI, restored radiosensitivity and suppressed breast cancer lung metastasis *in vitro* and *in vivo*[208].

The HDAC inhibitor (HDACI) Vorinostat sensitized mesenchymal-like triple-negative breast cancer cell lines to hormone therapy by reactivating ERα[209] and PI3K/Akt/mTOR signaling sensitivity[210], corroborating the role of epigenetic alterations in chemoresistance development in breast tumors. Furthermore, the HDACI abexinostat induced cancer-like stem cells differentiation in 16 breast cancer cell lines[211]. Because of these interesting observations, the HDACIs belinostat, panobinostat, and vorinostat, previously used only in blood cancers, have entered phase I and II clinical trials in solid tumors, such as lung, prostate, gastrointestinal, ovarian and breast cancer, where they are showing encouraging results (for review see[212]). Various DNMTI are also showing encouraging responses in metastatic and chemoresistant breast cancers in monotherapy and in combination therapies in phase I and II trials[213-217].

# CONCLUDING REMARKS

Targeted therapies are associated with reduced adverse effects and better outcome. Tumor microenvironment cells such as cancer-associated fibroblasts and tumor-associated macrophages undergo aberrant genetic and epigenetic changes that trigger the overexpression of signaling molecules promoting neoplasia and neoplastic tissue survival. Many therapeutic targets have emerged. They include Notch, CDKs, mTOR, Wnt, and Shh, whose inhibitors are showing promising results in ongoing clinical trials, both in monotherapy and in combination therapy. Similarly, epigenetic drugs are also showing encouraging results in breast cancer, particularly in advanced and chemoresistant cases. New technological advances will enable the identification of precise alterations affecting the interactome, transcriptome, and the epigenome, leading to the design of more specific tailored therapies. Such therapeutic approach may also be beneficial in the treatment of chemoresistant breast cancers.

# REFERENCES

1 **Azim HA**, Ibrahim AS. Breast cancer in Egypt, China and Chinese: statistics and beyond. *J Thorac Dis* 2014; **6**: 864-866 [PMID: 25093081 DOI: 10.3978/j.issn.2072-1439.2014.06.38]

2 **Youlden DR**, Cramb SM, Yip CH, Baade PD. Incidence and mortality of female breast cancer in the Asia-Pacific region. *Cancer Biol Med* 2014; **11**: 101-115 [PMID: 25009752 DOI: 10.7497/j.issn.2095-3941.2014.02.005]

3 **Villarreal-Garza C**, Aguila C, Magallanes-Hoyos MC, Mohar A, Bargalló E, Meneses A, Cazap E, Gomez H, López-Carrillo L, Chávarri-Guerra Y, Murillo R, Barrios C. Breast cancer in young women in Latin America: an unmet, growing burden. *Oncologist* 2013; **18**: 1298-1306 [PMID: 24277771 DOI: 10.1634/theoncologist.2013-0321]

4 **de Azambuja E**, Ameye L, Paesmans M, Zielinski CC, Piccart-Gebhart M, Preusser M. The landscape of medical oncology in Europe by 2020. *Ann Oncol* 2014; **25**: 525-528 [PMID: 24425791 DOI: 10.1093/annonc/mdt559]

5 [**Zengel B**](http://www.ncbi.nlm.nih.gov/pubmed?term=Zengel%20B%5BAuthor%5D&cauthor=true&cauthor_uid=23925582)**,**[Yararbas U](http://www.ncbi.nlm.nih.gov/pubmed?term=Yararbas%20U%5BAuthor%5D&cauthor=true&cauthor_uid=23925582), [Duran A](http://www.ncbi.nlm.nih.gov/pubmed?term=Duran%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23925582), [Uslu A](http://www.ncbi.nlm.nih.gov/pubmed?term=Uslu%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23925582), [Elıyatkın N](http://www.ncbi.nlm.nih.gov/pubmed?term=El%C4%B1yatk%C4%B1n%20N%5BAuthor%5D&cauthor=true&cauthor_uid=23925582), [Demırkıran MA](http://www.ncbi.nlm.nih.gov/pubmed?term=Dem%C4%B1rk%C4%B1ran%20MA%5BAuthor%5D&cauthor=true&cauthor_uid=23925582), [Cengiz F](http://www.ncbi.nlm.nih.gov/pubmed?term=Cengiz%20F%5BAuthor%5D&cauthor=true&cauthor_uid=23925582), [Simşek C](http://www.ncbi.nlm.nih.gov/pubmed?term=Sim%C5%9Fek%20C%5BAuthor%5D&cauthor=true&cauthor_uid=23925582), [Postacı H](http://www.ncbi.nlm.nih.gov/pubmed?term=Postac%C4%B1%20H%5BAuthor%5D&cauthor=true&cauthor_uid=23925582), [Vardar E](http://www.ncbi.nlm.nih.gov/pubmed?term=Vardar%20E%5BAuthor%5D&cauthor=true&cauthor_uid=23925582), [Durusoy R](http://www.ncbi.nlm.nih.gov/pubmed?term=Durusoy%20R%5BAuthor%5D&cauthor=true&cauthor_uid=23925582). Comparison of the clinicopathological features of invasive ductal, invasive lobular, and mixed (invasive ductal + invasive lobular) carcinoma of the breast. *Breast Cancer* 2013: Epub ahead of print [PMID: 23925582 DOI: 10.1007/s12282-013-0489-8]

6 [**Arps DP**](http://www.ncbi.nlm.nih.gov/pubmed?term=Arps%20DP%5BAuthor%5D&cauthor=true&cauthor_uid=24980090)**,** [Jorns JM](http://www.ncbi.nlm.nih.gov/pubmed?term=Jorns%20JM%5BAuthor%5D&cauthor=true&cauthor_uid=24980090), [Zhao L](http://www.ncbi.nlm.nih.gov/pubmed?term=Zhao%20L%5BAuthor%5D&cauthor=true&cauthor_uid=24980090), [Bensenhaver J](http://www.ncbi.nlm.nih.gov/pubmed?term=Bensenhaver%20J%5BAuthor%5D&cauthor=true&cauthor_uid=24980090), [Kleer CG](http://www.ncbi.nlm.nih.gov/pubmed?term=Kleer%20CG%5BAuthor%5D&cauthor=true&cauthor_uid=24980090), [Pang JC](http://www.ncbi.nlm.nih.gov/pubmed?term=Pang%20JC%5BAuthor%5D&cauthor=true&cauthor_uid=24980090). Re-Excision Rates of Invasive Ductal Carcinoma with Lobular Features Compared with Invasive Ductal Carcinomas and Invasive Lobular Carcinomas of the Breast. *Ann Surg Oncol* 2014: Epub ahead of print [PMID: 24980090 DOI: 10.1245/s10434-014-3871-7]

7 **Al-Foheidi M**, Al-Mansour MM, Ibrahim EM. Breast cancer screening: review of benefits and harms, and recommendations for developing and low-income countries. *Med Oncol* 2013; **30**: 471 [PMID: 23420062 DOI: 10.1007/s12032-013-0471-5]

8 [**Onega T**](http://www.ncbi.nlm.nih.gov/pubmed?term=Onega%20T%5BAuthor%5D&cauthor=true&cauthor_uid=24682769)**,**[Weaver D](http://www.ncbi.nlm.nih.gov/pubmed?term=Weaver%20D%5BAuthor%5D&cauthor=true&cauthor_uid=24682769), [Geller B](http://www.ncbi.nlm.nih.gov/pubmed?term=Geller%20B%5BAuthor%5D&cauthor=true&cauthor_uid=24682769), [Oster N](http://www.ncbi.nlm.nih.gov/pubmed?term=Oster%20N%5BAuthor%5D&cauthor=true&cauthor_uid=24682769), [Tosteson AN](http://www.ncbi.nlm.nih.gov/pubmed?term=Tosteson%20AN%5BAuthor%5D&cauthor=true&cauthor_uid=24682769), [Carney PA](http://www.ncbi.nlm.nih.gov/pubmed?term=Carney%20PA%5BAuthor%5D&cauthor=true&cauthor_uid=24682769), [Nelson H](http://www.ncbi.nlm.nih.gov/pubmed?term=Nelson%20H%5BAuthor%5D&cauthor=true&cauthor_uid=24682769), [Allison KH](http://www.ncbi.nlm.nih.gov/pubmed?term=Allison%20KH%5BAuthor%5D&cauthor=true&cauthor_uid=24682769), [O'Malley FP](http://www.ncbi.nlm.nih.gov/pubmed?term=O'Malley%20FP%5BAuthor%5D&cauthor=true&cauthor_uid=24682769), [Schnitt SJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Schnitt%20SJ%5BAuthor%5D&cauthor=true&cauthor_uid=24682769), [Elmore JG](http://www.ncbi.nlm.nih.gov/pubmed?term=Elmore%20JG%5BAuthor%5D&cauthor=true&cauthor_uid=24682769). Digitized Whole Slides for Breast Pathology Interpretation: Current Practices and Perceptions. *J Digit Imaging* 2014: Epub ahead of print [PMID: 24682769]

9 **Suzuki A**, Ishida T, Ohuchi N. Controversies in breast cancer screening for women aged 40-49 years. *Jpn J Clin Oncol* 2014; **44**: 613-618 [PMID: 24821976 DOI: 10.1093/jjco/hyu054]

10 **Paci E**, Broeders M, Hofvind S, Puliti D, Duffy SW. European breast cancer service screening outcomes: a first balance sheet of the benefits and harms. *Cancer Epidemiol Biomarkers Prev* 2014; **23**: 1159-1163 [PMID: 24991022 DOI: 10.1158/1055-9965.EPI-13-0320

11 **Plescia M**, White MC. The National Prevention Strategy and breast cancer screening: scientific evidence for public health action. *Am J Public Health* 2013; **103**: 1545-1548 [PMID: 23865665 DOI: 10.2105/AJPH.2013.301305

12 **Nishikawa RM**, Gur D. CADe for Early Detection of Breast Cancer-Current Status and Why We Need to Continue to Explore New Approaches. *Acad Radiol* 2014; **21**: 1320-1321 [PMID: 25086951 DOI: 10.1016/j.acra.2014.05.018]

13 **Stockler MR**, Harvey VJ, Francis PA, Byrne MJ, Ackland SP, Fitzharris B, Van Hazel G, Wilcken NR, Grimison PS, Nowak AK, Gainford MC, Fong A, Paksec L, Sourjina T, Zannino D, Gebski V, Simes RJ, Forbes JF, Coates AS. Capecitabine versus classical cyclophosphamide, methotrexate, and fluorouracil as first-line chemotherapy for advanced breast cancer. *J Clin Oncol* 2011; **29**: 4498-4504 [PMID: 22025143 DOI: 10.1200/JCO.2010.33.9101]

14[**Dadla A**](http://www.ncbi.nlm.nih.gov/pubmed?term=Dadla%20A%5BAuthor%5D&cauthor=true&cauthor_uid=24993705)**,** [Tannenbaum S](http://www.ncbi.nlm.nih.gov/pubmed?term=Tannenbaum%20S%5BAuthor%5D&cauthor=true&cauthor_uid=24993705), [Yates B](http://www.ncbi.nlm.nih.gov/pubmed?term=Yates%20B%5BAuthor%5D&cauthor=true&cauthor_uid=24993705), [Holle L](http://www.ncbi.nlm.nih.gov/pubmed?term=Holle%20L%5BAuthor%5D&cauthor=true&cauthor_uid=24993705). Delayed hypersensitivity reaction related to the use of pegfilgrastim. *J Oncol Pharm Pract* 2014: Epub ahead of print [PMID: 24993705 DOI: 1078155214542493]

15 **Karczmarek-Borowska B**, Drzymała M, Golon K. [Hepatotoxicity of acetaminophen in a patient treated with capecitabine due to breast cancer]. *Pol Merkur Lekarski* 2014; **36**: 348-351 [PMID: 24964515]

16 **Hurvitz S**, Guerin A, Brammer M, Guardino E, Zhou ZY, Latremouille Viau D, Wu EQ, Lalla D. Investigation of adverse-event-related costs for patients with metastatic breast cancer in a real-world setting. *Oncologist* 2014; **19**: 901-908 [PMID: 25085897]

17 **Hansen RN**, Ramsey SD, Lalla D, Masaquel A, Kamath T, Brammer M, Hurvitz SA, Sullivan SD. Identification and cost of adverse events in metastatic breast cancer in taxane and capecitabine based regimens. *Springerplus* 2014; **3**: 259 [PMID: 24926422 DOI: 10.1186/2193-1801-3-259]

18 **Mao Y**, Keller ET, Garfield DH, Shen K, Wang J. Stromal cells in tumor microenvironment and breast cancer. *Cancer Metastasis Rev* 2013; **32**: 303-315 [PMID: 23114846 DOI: 10.1007/s10555-012-9415-3]

19 **Vivacqua A**, Romeo E, De Marco P, De Francesco EM, Abonante S, Maggiolini M. GPER mediates the Egr-1 expression induced by 17β-estradiol and 4-hydroxitamoxifen in breast and endometrial cancer cells. *Breast Cancer Res Treat* 2012; **133**: 1025-1035 [PMID: 22147081 DOI: 10.1007/s10549-011-1901-8]

20 **Farmaki E**, Chatzistamou I, Bourlis P, Santoukou E, Trimis G, Papavassiliou AG, Kiaris H. Selection of p53-Deficient Stromal Cells in the Tumor Microenvironment. *Genes Cancer* 2012; **3**: 592-598 [PMID: 23486847 DOI: 10.1177/1947601912474002]

21 **Tao L**, Roberts AL, Dunphy KA, Bigelow C, Yan H, Jerry DJ. Repression of mammary stem/progenitor cells by p53 is mediated by Notch and separable from apoptotic activity. *Stem Cells* 2011; **29**: 119-127 [PMID: 21280161 DOI: 10.1002/stem.552]

22 **De Francesco EM**, Lappano R, Santolla MF, Marsico S, Caruso A, Maggiolini M. HIF-1α/GPER signaling mediates the expression of VEGF induced by hypoxia in breast cancer associated fibroblasts (CAFs). *Breast Cancer Res* 2013; **15**: R64 [PMID: 23947803 DOI: 10.1186/bcr3458]

23 **Pupo M**, Pisano A, Abonante S, Maggiolini M, Musti AM. GPER activates Notch signaling in breast cancer cells and cancer-associated fibroblasts (CAFs). *Int J Biochem Cell Biol* 2014; **46**: 56-67 [PMID: 24275097 DOI: 10.1016/j.biocel.2013.11.011]

24 **Nwabo Kamdje AH**, Mosna F, Bifari F, Lisi V, Bassi G, Malpeli G, Ricciardi M, Perbellini O, Scupoli MT, Pizzolo G, Krampera M. Notch-3 and Notch-4 signaling rescue from apoptosis human B-ALL cells in contact with human bone marrow-derived mesenchymal stromal cells. *Blood* 2011; **118**: 380-389 [PMID: 21602525 DOI: 10.1182/blood-2010-12-326694]

25 **Nwabo Kamdje AH**, Bassi G, Pacelli L, Malpeli G, Amati E, Nichele I, Pizzolo G, Krampera M. Role of stromal cell-mediated Notch signaling in CLL resistance to chemotherapy. *Blood Cancer J* 2012; **2**: e73 [PMID: 22829975 DOI: 10.1038/bcj.2012.17]

26 **Guo S**, Gonzalez-Perez RR. Notch, IL-1 and leptin crosstalk outcome (NILCO) is critical for leptin-induced proliferation, migration and VEGF/VEGFR-2 expression in breast cancer. *PLoS One* 2011; **6**: e21467 [PMID: 21731759]

27 **Luga V**, Wrana JL. Tumor-stroma interaction: Revealing fibroblast-secreted exosomes as potent regulators of Wnt-planar cell polarity signaling in cancer metastasis. *Cancer Res* 2013; **73**: 6843-6847 [PMID: 24265274 DOI: 10.1158/0008-5472.CAN-13-1791]

28 **Bochet L**, Lehuédé C, Dauvillier S, Wang YY, Dirat B, Laurent V, Dray C, Guiet R, Maridonneau-Parini I, Le Gonidec S, Couderc B, Escourrou G, Valet P, Muller C. Adipocyte-derived fibroblasts promote tumor progression and contribute to the desmoplastic reaction in breast cancer. *Cancer Res* 2013; **73**: 5657-5668 [PMID: 23903958 DOI: 10.1158/0008-5472.CAN-13-0530]

29 [**Ota D**](http://www.ncbi.nlm.nih.gov/pubmed?term=Ota%20D%5BAuthor%5D&cauthor=true&cauthor_uid=25099519)**,** [Kanayama M](http://www.ncbi.nlm.nih.gov/pubmed?term=Kanayama%20M%5BAuthor%5D&cauthor=true&cauthor_uid=25099519), [Matsui Y](http://www.ncbi.nlm.nih.gov/pubmed?term=Matsui%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=25099519), [Ito K](http://www.ncbi.nlm.nih.gov/pubmed?term=Ito%20K%5BAuthor%5D&cauthor=true&cauthor_uid=25099519), [Maeda N](http://www.ncbi.nlm.nih.gov/pubmed?term=Maeda%20N%5BAuthor%5D&cauthor=true&cauthor_uid=25099519), [Kutomi G](http://www.ncbi.nlm.nih.gov/pubmed?term=Kutomi%20G%5BAuthor%5D&cauthor=true&cauthor_uid=25099519), [Hirata K](http://www.ncbi.nlm.nih.gov/pubmed?term=Hirata%20K%5BAuthor%5D&cauthor=true&cauthor_uid=25099519), [Torigoe T](http://www.ncbi.nlm.nih.gov/pubmed?term=Torigoe%20T%5BAuthor%5D&cauthor=true&cauthor_uid=25099519), [Sato N](http://www.ncbi.nlm.nih.gov/pubmed?term=Sato%20N%5BAuthor%5D&cauthor=true&cauthor_uid=25099519), [Takaoka A](http://www.ncbi.nlm.nih.gov/pubmed?term=Takaoka%20A%5BAuthor%5D&cauthor=true&cauthor_uid=25099519), [Chambers AF](http://www.ncbi.nlm.nih.gov/pubmed?term=Chambers%20AF%5BAuthor%5D&cauthor=true&cauthor_uid=25099519), [Morimoto J](http://www.ncbi.nlm.nih.gov/pubmed?term=Morimoto%20J%5BAuthor%5D&cauthor=true&cauthor_uid=25099519), [Uede T](http://www.ncbi.nlm.nih.gov/pubmed?term=Uede%20T%5BAuthor%5D&cauthor=true&cauthor_uid=25099519). Tumor-α9β1 integrin-mediated signaling induces breast cancer growth and lymphatic metastasis via the recruitment of cancer-associated fibroblasts. *J Mol Med* (Berl) 2014: Epub ahead of print [PMID: 25099519 DOI: 10.1007/s00109-014-1183-9]

30 **Ishikawa M**, Inoue T, Shirai T, Takamatsu K, Kunihiro S, Ishii H, Nishikata T. Simultaneous expression of cancer stem cell-like properties and cancer-associated fibroblast-like properties in a primary culture of breast cancer cells. *Cancers* (Basel) 2014; **6**: 1570-1578 [PMID: 25089665 DOI: 10.3390/cancers6031570]

31 **Scherz-Shouval R**, Santagata S, Mendillo ML, Sholl LM, Ben-Aharon I, Beck AH, Dias-Santagata D, Koeva M, Stemmer SM, Whitesell L, Lindquist S. The Reprogramming of Tumor Stroma by HSF1 Is a Potent Enabler of Malignancy. *Cell* 2014; **158**: 564-578 [PMID: 25083868 DOI: 10.1016/j.cell.2014.05.045]

32 **Capparelli C**, Guido C, Whitaker-Menezes D, Bonuccelli G, Balliet R, Pestell TG, Goldberg AF, Pestell RG, Howell A, Sneddon S, Birbe R, Tsirigos A, Martinez-Outschoorn U, Sotgia F, Lisanti MP. Autophagy and senescence in cancer-associated fibroblasts metabolically supports tumor growth and metastasis via glycolysis and ketone production. *Cell Cycle* 2012; **11**: 2285-2302 [PMID: 22684298 DOI: 10.4161/cc.20718]

33 **Capparelli C**, Chiavarina B, Whitaker-Menezes D, Pestell TG, Pestell RG, Hulit J, Andò S, Howell A, Martinez-Outschoorn UE, Sotgia F, Lisanti MP. CDK inhibitors (p16/p19/p21) induce senescence and autophagy in cancer-associated fibroblasts, "fueling" tumor growth via paracrine interactions, without an increase in neo-angiogenesis. *Cell Cycle* 2012; **11**: 3599-3610 [PMID: 22935696 DOI: 10.4161/cc.21884]

34 **Avena P**, Anselmo W, Whitaker-Menezes D, Wang C, Pestell RG, Lamb RS, Hulit J, Casaburi I, Andò S, Martinez-Outschoorn UE, Lisanti MP, Sotgia F. Compartment-specific activation of PPARγ governs breast cancer tumor growth, via metabolic reprogramming and symbiosis. *Cell Cycle* 2013; **12**: 1360-1370 [PMID: 23574724 DOI: 10.4161/cc.24289]

35 **Tymoszuk P**, Evens H, Marzola V, Wachowicz K, Wasmer MH, Datta S, Müller-Holzner E, Fiegl H, Böck G, van Rooijen N, Theurl I, Doppler W. In situ proliferation contributes to accumulation of tumor-associated macrophages in spontaneous mammary tumors. *Eur J Immunol* 2014; **44**: 2247-2262 [PMID: 24796276 DOI: 10.1002/eji.201344304]

36 **Xuan QJ**, Wang JX, Nanding A, Wang ZP, Liu H, Lian X, Zhang QY. Tumor-associated macrophages are correlated with tamoxifen resistance in the postmenopausal breast cancer patients. *Pathol Oncol Res* 2014; **20**: 619-624 [PMID: 24414992 DOI: 10.1007/s12253-013-9740-z]

37 **Chaturvedi P**, Gilkes DM, Takano N, Semenza GL. Hypoxia-inducible factor-dependent signaling between triple-negative breast cancer cells and mesenchymal stem cells promotes macrophage recruitment. *Proc Natl Acad Sci U S A* 2014; **111**: E2120-E2129 [PMID: 24799675 DOI: 10.1073/pnas.1406655111]

38 **Liu H**, Wang Y, Li X, Zhang YJ, Li J, Zheng YQ, Liu M, Song X, Li XR. Expression and regulatory function of miRNA-182 in triple-negative breast cancer cells through its targeting of profilin 1. *Tumour Biol* 2013; **34**: 1713-1722 [PMID: 23430586 DOI: 10.1007/s13277-013-0708-0]

39 **Ouyang M**, Li Y, Ye S, Ma J, Lu L, Lv W, Chang G, Li X, Li Q, Wang S, Wang W. MicroRNA profiling implies new markers of chemoresistance of triple-negative breast cancer. *PLoS One* 2014; **9**: e96228 [PMID: 24788655 DOI: 10.1371/journal.pone.0096228]

40 **Yamashina T**, Baghdadi M, Yoneda A, Kinoshita I, Suzu S, Dosaka-Akita H, Jinushi M. Cancer stem-like cells derived from chemoresistant tumors have a unique capacity to prime tumorigenic myeloid cells. *Cancer Res* 2014; **74**: 2698-2709 [PMID: 24638980 DOI: 10.1158/0008-5472.CAN-13-2169]

41 **Oghumu S**, Varikuti S, Terrazas C, Kotov D, Nasser MW, Powell CA, Ganju RK, Satoskar AR. CXCR3 deficiency enhances tumor progression by promoting macrophage M2 polarization in a murine breast cancer model. *Immunology* 2014; **143**: 109-119 [PMID: 24679047 DOI: 10.1111/imm.12293]

42 **Deng R**, Wang SM, Yin T, Ye TH, Shen GB, Li L, Zhao JY, Sang YX, Duan XG, Wei YQ. Dimethyl Sulfoxide Suppresses Mouse 4T1 Breast Cancer Growth by Modulating Tumor-Associated Macrophage Differentiation. *J Breast Cancer* 2014; **17**: 25-32 [PMID: 24744794 DOI: 10.4048/jbc.2014.17.1.25]

43 **Milovanovic T**, Planutis K, Nguyen A, Marsh JL, Lin F, Hope C, Holcombe RF. Expression of Wnt genes and frizzled 1 and 2 receptors in normal breast epithelium and infiltrating breast carcinoma. *Int J Oncol* 2004; **25**: 1337-1342 [PMID: 15492823 DOI: 10.3892/ijo.25.5.1337]

44 **Benhaj K**, Akcali KC, Ozturk M. Redundant expression of canonical Wnt ligands in human breast cancer cell lines. *Oncol Rep* 2006; **15**: 701-707 [PMID: 16465433 DOI: 10.3892/or.15.3.701]

45 **Yeo EJ**, Cassetta L, Qian BZ, Lewkowich I, Li JF, Stefater JA, Smith AN, Wiechmann LS, Wang Y, Pollard JW, Lang RA. Myeloid WNT7b mediates the angiogenic switch and metastasis in breast cancer. *Cancer Res* 2014; **74**: 2962-2973 [PMID: 24638982 DOI: 10.1158/0008-5472.CAN-13-2421]

46 **Zhang Y**, Guo Q, Zhang Z, Bai N, Liu Z, Xiong M, Wei Y, Xiang R, Tan X. VDR Status Arbitrates the Prometastatic Effects of Tumor-Associated Macrophages. *Mol Cancer Res* 2014; **12**: 1181-1191 [PMID: 24821711 DOI: 10.1158/1541-7786.MCR-14-0036]

47 **Pukrop T**, Klemm F, Hagemann T, Gradl D, Schulz M, Siemes S, Trümper L, Binder C. Wnt 5a signaling is critical for macrophage-induced invasion of breast cancer cell lines. *Proc Natl Acad Sci U S A* 2006; **103**: 5454-5459 [PMID: 16569699 DOI: 10.1073/pnas.0509703103]

48 **Ojalvo LS**, Whittaker CA, Condeelis JS, Pollard JW. Gene expression analysis of macrophages that facilitate tumor invasion supports a role for Wnt-signaling in mediating their activity in primary mammary tumors. *J Immunol* 2010; **184**: 702-712 [PMID: 20018620]

49 **Bergenfelz C**, Medrek C, Ekström E, Jirström K, Janols H, Wullt M, Bredberg A, Leandersson K. Wnt5a induces a tolerogenic phenotype of macrophages in sepsis and breast cancer patients. *J Immunol* 2012; **188**: 5448-5458 [PMID: 22547701 DOI: 10.4049/jimmunol.1103378]

50 **Spano D**, Marshall JC, Marino N, De Martino D, Romano A, Scoppettuolo MN, Bello AM, Di Dato V, Navas L, De Vita G, Medaglia C, Steeg PS, Zollo M. Dipyridamole prevents triple-negative breast-cancer progression. *Clin Exp Metastasis* 2013; **30**: 47-68 [PMID: 22760522 DOI: 10.1007/s10585-012-9506-0]

51 **Lai EC**. Notch signaling: control of cell communication and cell fate. *Development* 2004; **131**: 965-973 [PMID: 14973298 DOI: 10.1242/dev.01074]

52 **Pintar A**, De Biasio A, Popovic M, Ivanova N, Pongor S. The intracellular region of Notch ligands: does the tail make the difference? *Biol Direct* 2007; **2**: 19 [PMID: 17623096 DOI: 10.1186/1745-6150-2-19]

53 **Zhang P**, Ostrander JH, Faivre EJ, Olsen A, Fitzsimmons D, Lange CA. Regulated association of protein kinase B/Akt with breast tumor kinase. *J Biol Chem* 2005; **280**: 1982-1991 [PMID: 15539407 DOI: 10.1074/jbc.M412038200]

54 **Wu L**, Sun T, Kobayashi K, Gao P, Griffin JD. Identification of a family of mastermind-like transcriptional coactivators for mammalian notch receptors. *Mol Cell Biol* 2002; **22**: 7688-7700 [PMID: 12370315 DOI: 10.1128/MCB.22.21.7688-7700.2002]

55 **Weng AP**, Millholland JM, Yashiro-Ohtani Y, Arcangeli ML, Lau A, Wai C, Del Bianco C, Rodriguez CG, Sai H, Tobias J, Li Y, Wolfe MS, Shachaf C, Felsher D, Blacklow SC, Pear WS, Aster JC. c-Myc is an important direct target of Notch1 in T-cell acute lymphoblastic leukemia/lymphoma. *Genes Dev* 2006; **20**: 2096-2109 [PMID: 16847353 DOI: 10.1101/gad.1450406]

56 **Sun Y**, Lowther W, Kato K, Bianco C, Kenney N, Strizzi L, Raafat D, Hirota M, Khan NI, Bargo S, Jones B, Salomon D, Callahan R. Notch4 intracellular domain binding to Smad3 and inhibition of the TGF-beta signaling. *Oncogene* 2005; **24**: 5365-5374 [PMID: 16007227 DOI: 10.1038/sj.onc.1208528]

57 **Stylianou S**, Clarke RB, Brennan K. Aberrant activation of notch signaling in human breast cancer. *Cancer Res* 2006; **66**: 1517-1525 [PMID: 16452208 DOI: 10.1158/0008-5472.CAN-05-3054]

58 **Liu Z**, Teng L, Bailey SK, Frost AR, Bland KI, LoBuglio AF, Ruppert JM, Lobo-Ruppert SM. Epithelial transformation by KLF4 requires Notch1 but not canonical Notch1 signaling. *Cancer Biol Ther* 2009; **8**: 1840-1851 [PMID: 19717984]

59 **Brabletz S**, Bajdak K, Meidhof S, Burk U, Niedermann G, Firat E, Wellner U, Dimmler A, Faller G, Schubert J, Brabletz T. The ZEB1/miR-200 feedback loop controls Notch signalling in cancer cells. *EMBO J* 2011; **30**: 770-782 [PMID: 21224848 DOI: 10.1038/emboj.2010.349]

60 **Sethi N**, Dai X, Winter CG, Kang Y. Tumor-derived JAGGED1 promotes osteolytic bone metastasis of breast cancer by engaging notch signaling in bone cells. *Cancer Cell* 2011; **19**: 192-205 [PMID: 21295524 DOI: 10.1016/j.ccr.2010.12.022]

61 **Xing F**, Okuda H, Watabe M, Kobayashi A, Pai SK, Liu W, Pandey PR, Fukuda K, Hirota S, Sugai T, Wakabayshi G, Koeda K, Kashiwaba M, Suzuki K, Chiba T, Endo M, Mo YY, Watabe K. Hypoxia-induced Jagged2 promotes breast cancer metastasis and self-renewal of cancer stem-like cells. *Oncogene* 2011; **30**: 4075-4086 [PMID: 21499308 DOI: 10.1038/onc.2011.122]

62 **Shi W**, Harris AL. Notch signaling in breast cancer and tumor angiogenesis: cross-talk and therapeutic potentials. *J Mammary Gland Biol Neoplasia* 2006; **11**: 41-52 [PMID: 16947085 DOI: 10.1007/s10911-006-9011-7]

63 **Xiao Y**, Ye Y, Zou X, Jones S, Yearsley K, Shetuni B, Tellez J, Barsky SH. The lymphovascular embolus of inflammatory breast cancer exhibits a Notch 3 addiction. *Oncogene* 2011; **30**: 287-300 [PMID: 20838375 DOI: 10.1038/onc.2010.405]

64 **Lee CW**, Raskett CM, Prudovsky I, Altieri DC. Molecular dependence of estrogen receptor-negative breast cancer on a notch-survivin signaling axis. *Cancer Res* 2008; **68**: 5273-5281 [PMID: 18593928 DOI: 10.1158/0008-5472.CAN-07-6673]

65 **Lee CW**, Simin K, Liu Q, Plescia J, Guha M, Khan A, Hsieh CC, Altieri DC. A functional Notch-survivin gene signature in basal breast cancer. *Breast Cancer Res* 2008; **10**: R97 [PMID: 19025652 DOI: 10.1186/bcr2200]

66 **Rizzo P**, Miao H, D'Souza G, Osipo C, Song LL, Yun J, Zhao H, Mascarenhas J, Wyatt D, Antico G, Hao L, Yao K, Rajan P, Hicks C, Siziopikou K, Selvaggi S, Bashir A, Bhandari D, Marchese A, Lendahl U, Qin JZ, Tonetti DA, Albain K, Nickoloff BJ, Miele L. Cross-talk between notch and the estrogen receptor in breast cancer suggests novel therapeutic approaches. *Cancer Res* 2008; **68**: 5226-5235 [PMID: 18593923 DOI: 10.1158/0008-5472.CAN-07-5744]

67 **Dai J**, Ma D, Zang S, Guo D, Qu X, Ye J, Ji C. Cross-talk between Notch and EGFR signaling in human breast cancer cells. *Cancer Invest* 2009; **27**: 533-540 [PMID: 19219656 DOI: 10.1080/07357900802563036]

68 **Mungamuri SK**, Yang X, Thor AD, Somasundaram K. Survival signaling by Notch1: mammalian target of rapamycin (mTOR)-dependent inhibition of p53. *Cancer Res* 2006; **66**: 4715-4724 [PMID: 16651424 DOI: 10.1158/0008-5472.CAN-05-3830]

69 **Efferson CL**, Winkelmann CT, Ware C, Sullivan T, Giampaoli S, Tammam J, Patel S, Mesiti G, Reilly JF, Gibson RE, Buser C, Yeatman T, Coppola D, Winter C, Clark EA, Draetta GF, Strack PR, Majumder PK. Downregulation of Notch pathway by a gamma-secretase inhibitor attenuates AKT/mammalian target of rapamycin signaling and glucose uptake in an ERBB2 transgenic breast cancer model. *Cancer Res* 2010; **70**: 2476-2484 [PMID: 20197467 DOI: 10.1158/0008-5472.CAN-09-3114]

70 **Sridhar SS**, Hedley D, Siu LL. Raf kinase as a target for anticancer therapeutics. *Mol Cancer Ther* 2005; **4**: 677-685 [PMID: 15827342 DOI: 10.1158/1535-7163.MCT-04-0297]

71 **Mittal S**, Subramanyam D, Dey D, Kumar RV, Rangarajan A. Cooperation of Notch and Ras/MAPK signaling pathways in human breast carcinogenesis. *Mol Cancer* 2009; **8**: 128 [PMID: 20030805 DOI: 10.1186/1476-4598-8-128]

72 **Dong Y**, Li A, Wang J, Weber JD, Michel LS. Synthetic lethality through combined Notch-epidermal growth factor receptor pathway inhibition in basal-like breast cancer. *Cancer Res* 2010; **70**: 5465-5474 [PMID: 20570903 DOI: 10.1158/0008-5472.CAN-10-0173]

73 **Magnifico A**, Albano L, Campaner S, Delia D, Castiglioni F, Gasparini P, Sozzi G, Fontanella E, Menard S, Tagliabue E. Tumor-initiating cells of HER2-positive carcinoma cell lines express the highest oncoprotein levels and are sensitive to trastuzumab. *Clin Cancer Res* 2009; **15**: 2010-2021 [PMID: 19276287 DOI: 10.1158/1078-0432.CCR-08-1327]

74 **Dickson BC**, Mulligan AM, Zhang H, Lockwood G, O'Malley FP, Egan SE, Reedijk M. High-level JAG1 mRNA and protein predict poor outcome in breast cancer. *Mod Pathol* 2007; **20**: 685-693 [PMID: 17507991 DOI: 10.1038/modpathol.3800785]

75 **Osipo C**, Patel P, Rizzo P, Clementz AG, Hao L, Golde TE, Miele L. ErbB-2 inhibition activates Notch-1 and sensitizes breast cancer cells to a gamma-secretase inhibitor. *Oncogene* 2008; **27**: 5019-5032 [PMID: 18469855 DOI: 10.1038/onc.2008.149]

76 **Zang S**, Ji Ch, Qu X, Dong X, Ma D, Ye J, Ma R, Dai J, Guo D. A study on Notch signaling in human breast cancer. *Neoplasma* 2007; **54**: 304-310 [PMID: 17822320 DOI: 10.1186/1471-2407-13-307]

77 **Grudzien P**, Lo S, Albain KS, Robinson P, Rajan P, Strack PR, Golde TE, Miele L, Foreman KE. Inhibition of Notch signaling reduces the stem-like population of breast cancer cells and prevents mammosphere formation. *Anticancer Res* 2010; **30**: 3853-3867 [PMID: 21036696]

78 **Kondratyev M**, Kreso A, Hallett RM, Girgis-Gabardo A, Barcelon ME, Ilieva D, Ware C, Majumder PK, Hassell JA. Gamma-secretase inhibitors target tumor-initiating cells in a mouse model of ERBB2 breast cancer. *Oncogene* 2012; **31**: 93-103 [PMID: 21666715 DOI: 10.1038/onc.2011.212]

79 **Pandya K**, Meeke K, Clementz AG, Rogowski A, Roberts J, Miele L, Albain KS, Osipo C. Targeting both Notch and ErbB-2 signalling pathways is required for prevention of ErbB-2-positive breast tumour recurrence. *Br J Cancer* 2011; **105**: 796-806 [PMID: 21847123 DOI: 10.1038/bjc.2011.321]

80 **Ahmad A**, Wang Z, Kong D, Ali R, Ali S, Banerjee S, Sarkar FH. Platelet-derived growth factor-D contributes to aggressiveness of breast cancer cells by up-regulating Notch and NF-κB signaling pathways. *Breast Cancer Res Treat* 2011; **126**: 15-25 [PMID: 20379844 DOI: 10.1007/s10549-010-0883-2]

81 **Speiser J**, Foreman K, Drinka E, Godellas C, Perez C, Salhadar A, Erşahin Ç, Rajan P. Notch-1 and Notch-4 biomarker expression in triple-negative breast cancer. *Int J Surg Pathol* 2012; **20**: 139-145 [PMID: 22084425 DOI: 10.1177/1066896911427035]

82 **Clementz AG**, Rogowski A, Pandya K, Miele L, Osipo C. NOTCH-1 and NOTCH-4 are novel gene targets of PEA3 in breast cancer: novel therapeutic implications. *Breast Cancer Res* 2011; **13**: R63 [PMID: 21679465 DOI: 10.1186/bcr2900]

83 **Azzam DJ**, Zhao D, Sun J, Minn AJ, Ranganathan P, Drews-Elger K, Han X, Picon-Ruiz M, Gilbert CA, Wander SA, Capobianco AJ, El-Ashry D, Slingerland JM. Triple negative breast cancer initiating cell subsets differ in functional and molecular characteristics and in γ-secretase inhibitor drug responses. *EMBO Mol Med* 2013; **5**: 1502-1522 [PMID: 23982961 DOI: 10.1002/emmm.201302558]

84 **Leong KG**, Niessen K, Kulic I, Raouf A, Eaves C, Pollet I, Karsan A. Jagged1-mediated Notch activation induces epithelial-to-mesenchymal transition through Slug-induced repression of E-cadherin. *J Exp Med* 2007; **204**: 2935-2948 [PMID: 17984306]

85 **Muellner MK**, Uras IZ, Gapp BV, Kerzendorfer C, Smida M, Lechtermann H, Craig-Mueller N, Colinge J, Duernberger G, Nijman SM. A chemical-genetic screen reveals a mechanism of resistance to PI3K inhibitors in cancer. *Nat Chem Biol* 2011; **7**: 787-793 [PMID: 21946274 DOI: 10.1038/nchembio.695]

86 **Haughian JM**, Pinto MP, Harrell JC, Bliesner BS, Joensuu KM, Dye WW, Sartorius CA, Tan AC, Heikkilä P, Perou CM, Horwitz KB. Maintenance of hormone responsiveness in luminal breast cancers by suppression of Notch. *Proc Natl Acad Sci U S A* 2012; **109**: 2742-2747 [PMID: 21969591 DOI: 10.1073/pnas.1106509108]

87 **Séveno C**, Loussouarn D, Bréchet S, Campone M, Juin P, Barillé-Nion S. γ-Secretase inhibition promotes cell death, Noxa upregulation, and sensitization to BH3 mimetic ABT-737 in human breast cancer cells. *Breast Cancer Res* 2012; **14**: R96 [PMID: 22703841]

88 **Han J**, Ma I, Hendzel MJ, Allalunis-Turner J. The cytotoxicity of gamma-secretase inhibitor I to breast cancer cells is mediated by proteasome inhibition, not by gamma-secretase inhibition. *Breast Cancer Res* 2009; **11**: R57 [PMID: 19660128 DOI: 10.1186/bcr2347]

89 **Rasul S**, Balasubramanian R, Filipović A, Slade MJ, Yagüe E, Coombes RC. Inhibition of gamma-secretase induces G2/M arrest and triggers apoptosis in breast cancer cells. *Br J Cancer* 2009; **100**: 1879-1888 [PMID: 19513078 DOI: 10.1038/sj.bjc.6605034]

90 **Luistro L**, He W, Smith M, Packman K, Vilenchik M, Carvajal D, Roberts J, Cai J, Berkofsky-Fessler W, Hilton H, Linn M, Flohr A, Jakob-Røtne R, Jacobsen H, Glenn K, Heimbrook D, Boylan JF. Preclinical profile of a potent gamma-secretase inhibitor targeting notch signaling with in vivo efficacy and pharmacodynamic properties. *Cancer Res* 2009; **69**: 7672-7680 [PMID: 19773430 DOI: 10.1158/0008-5472.CAN-09-1843]

91 **Debeb BG**, Cohen EN, Boley K, Freiter EM, Li L, Robertson FM, Reuben JM, Cristofanilli M, Buchholz TA, Woodward WA. Pre-clinical studies of Notch signaling inhibitor RO4929097 in inflammatory breast cancer cells. *Breast Cancer Res Treat* 2012; **134**: 495-510 [PMID: 22547109 DOI: 10.1007/s10549-012-2075-8]

92 **Diaz-Padilla I**, Hirte H, Oza AM, Clarke BA, Cohen B, Reedjik M, Zhang T, Kamel-Reid S, Ivy SP, Hotte SJ, Razak AA, Chen EX, Brana I, Wizemann M, Wang L, Siu LL, Bedard PL. A phase Ib combination study of RO4929097, a gamma-secretase inhibitor, and temsirolimus in patients with advanced solid tumors. *Invest New Drugs* 2013; **31**: 1182-1191 [PMID: 23860641 DOI: 10.1007/s10637-013-0001-5]

93 **Richter S**, Bedard PL, Chen EX, Clarke BA, Tran B, Hotte SJ, Stathis A, Hirte HW, Razak AR, Reedijk M, Chen Z, Cohen B, Zhang WJ, Wang L, Ivy SP, Moore MJ, Oza AM, Siu LL, McWhirter E. A phase I study of the oral gamma secretase inhibitor R04929097 in combination with gemcitabine in patients with advanced solid tumors (PHL-078/CTEP 8575). *Invest New Drugs* 2014; **32**: 243-249 [PMID: 23645447 DOI: 10.1007/s10637-013-9965-4]

94 **Han J**, Shen Q. Targeting γ-secretase in breast cancer. *Breast Cancer* (Dove Med Press) 2012; **4**: 83-90 [PMID: 24367196 DOI: 10.2147/BCTT.S26437]

95 **Yong T**, Sun A, Henry MD, Meyers S, Davis JN. Down regulation of CSL activity inhibits cell proliferation in prostate and breast cancer cells. *J Cell Biochem* 2011; **112**: 2340-2351 [PMID: 21520243 DOI: 10.1002/jcb.23157]

96 **Zhang CC**, Pavlicek A, Zhang Q, Lira ME, Painter CL, Yan Z, Zheng X, Lee NV, Ozeck M, Qiu M, Zong Q, Lappin PB, Wong A, Rejto PA, Smeal T, Christensen JG. Biomarker and pharmacologic evaluation of the γ-secretase inhibitor PF-03084014 in breast cancer models. *Clin Cancer Res* 2012; **18**: 5008-5019 [PMID: 22806875 DOI: 10.1158/1078-0432.CCR-12-1379]

97 **Wei P**, Walls M, Qiu M, Ding R, Denlinger RH, Wong A, Tsaparikos K, Jani JP, Hosea N, Sands M, Randolph S, Smeal T. Evaluation of selective gamma-secretase inhibitor PF-03084014 for its antitumor efficacy and gastrointestinal safety to guide optimal clinical trial design. *Mol Cancer Ther* 2010; **9**: 1618-1628 [PMID: 20530712 DOI: 10.1158/1535-7163.MCT-10-0034]

98 **Zhang CC**, Yan Z, Zong Q, Fang DD, Painter C, Zhang Q, Chen E, Lira ME, John-Baptiste A, Christensen JG. Synergistic effect of the γ-secretase inhibitor PF-03084014 and docetaxel in breast cancer models. *Stem Cells Transl Med* 2013; **2**: 233-242 [PMID: 23408105 DOI: 10.5966/sctm.2012-0096]

99 **Arcaroli JJ**, Quackenbush KS, Purkey A, Powell RW, Pitts TM, Bagby S, Tan AC, Cross B, McPhillips K, Song EK, Tai WM, Winn RA, Bikkavilli K, Vanscoyk M, Eckhardt SG, Messersmith WA. Tumours with elevated levels of the Notch and Wnt pathways exhibit efficacy to PF-03084014, a γ-secretase inhibitor, in a preclinical colorectal explant model. *Br J Cancer* 2013; **109**: 667-675 [PMID: 23868008 DOI: 10.1038/bjc.2013.361]

100 **Yabuuchi S**, Pai SG, Campbell NR, de Wilde RF, De Oliveira E, Korangath P, Streppel MM, Rasheed ZA, Hidalgo M, Maitra A, Rajeshkumar NV. Notch signaling pathway targeted therapy suppresses tumor progression and metastatic spread in pancreatic cancer. *Cancer Lett* 2013; **335**: 41-51 [PMID: 23402814 DOI: 10.1016/j.canlet.2013.01.054]

101 **Zhang CC**, Yan Z, Giddabasappa A, Lappin PB, Painter CL, Zhang Q, Li G, Goodman J, Simmons B, Pascual B, Lee J, Levkoff T, Nichols T, Xie Z. Comparison of dynamic contrast-enhanced MR, ultrasound and optical imaging modalities to evaluate the antiangiogenic effect of PF-03084014 and sunitinib. *Cancer Med* 2014; **3**: 462-471 [PMID: 24573979 DOI: 10.1002/cam4.215]

102[**López-Guerra M**](http://www.ncbi.nlm.nih.gov/pubmed?term=L%C3%B3pez-Guerra%20M%5BAuthor%5D&cauthor=true&cauthor_uid=24781018), [Xargay-Torrent S](http://www.ncbi.nlm.nih.gov/pubmed?term=Xargay-Torrent%20S%5BAuthor%5D&cauthor=true&cauthor_uid=24781018), [Rosich L](http://www.ncbi.nlm.nih.gov/pubmed?term=Rosich%20L%5BAuthor%5D&cauthor=true&cauthor_uid=24781018), [Montraveta A](http://www.ncbi.nlm.nih.gov/pubmed?term=Montraveta%20A%5BAuthor%5D&cauthor=true&cauthor_uid=24781018), [Roldán J](http://www.ncbi.nlm.nih.gov/pubmed?term=Rold%C3%A1n%20J%5BAuthor%5D&cauthor=true&cauthor_uid=24781018), [Matas-Céspedes A](http://www.ncbi.nlm.nih.gov/pubmed?term=Matas-C%C3%A9spedes%20A%5BAuthor%5D&cauthor=true&cauthor_uid=24781018), [Villamor N](http://www.ncbi.nlm.nih.gov/pubmed?term=Villamor%20N%5BAuthor%5D&cauthor=true&cauthor_uid=24781018), [Aymerich M](http://www.ncbi.nlm.nih.gov/pubmed?term=Aymerich%20M%5BAuthor%5D&cauthor=true&cauthor_uid=24781018), [López-Otín C](http://www.ncbi.nlm.nih.gov/pubmed?term=L%C3%B3pez-Ot%C3%ADn%20C%5BAuthor%5D&cauthor=true&cauthor_uid=24781018), [Pérez-Galán P](http://www.ncbi.nlm.nih.gov/pubmed?term=P%C3%A9rez-Gal%C3%A1n%20P%5BAuthor%5D&cauthor=true&cauthor_uid=24781018),[Roué G](http://www.ncbi.nlm.nih.gov/pubmed?term=Rou%C3%A9%20G%5BAuthor%5D&cauthor=true&cauthor_uid=24781018), [Campo E](http://www.ncbi.nlm.nih.gov/pubmed?term=Campo%20E%5BAuthor%5D&cauthor=true&cauthor_uid=24781018), [Colomer D](http://www.ncbi.nlm.nih.gov/pubmed?term=Colomer%20D%5BAuthor%5D&cauthor=true&cauthor_uid=24781018). The γ-secretase inhibitor PF-03084014 combined with fludarabine antagonizes migration, invasion and angiogenesis in NOTCH1-mutated CLL cells. *Leukemia* 2014: Epub ahead of print [PMID: 24781018 DOI: 10.1038/leu.2014.143]

103 **Carol H**, Maris JM, Kang MH, Reynolds CP, Kolb EA, Gorlick R, Keir ST, Wu J, Kurmasheva RT, Houghton PJ, Smith MA, Lock RB, Lyalin D. Initial testing (stage 1) of the notch inhibitor PF-03084014, by the pediatric preclinical testing program. *Pediatr Blood Cancer* 2014; **61**: 1493-1496 [PMID: 24664981 DOI: 10.1002/pbc.25026]

104 **Musgrove EA**, Lilischkis R, Cornish AL, Lee CS, Setlur V, Seshadri R, Sutherland RL. Expression of the cyclin-dependent kinase inhibitors p16INK4, p15INK4B and p21WAF1/CIP1 in human breast cancer. *Int J Cancer* 1995; **63**: 584-591 [PMID: 7591270]

105 **Zariwala M**, Liu E, Xiong Y. Mutational analysis of the p16 family cyclin-dependent kinase inhibitors p15INK4b and p18INK4c in tumor-derived cell lines and primary tumors. *Oncogene* 1996; **12**: 451-455 [PMID: 8570224]

106 **Nurse PM**. Nobel Lecture. Cyclin dependent kinases and cell cycle control. *Biosci Rep* 2002; **22**: 487-499 [PMID: 12635846]

107 **Malumbres M**. Cyclins and related kinases in cancer cells. *J BUON* 2007; **12** Suppl 1: S45-S52 [PMID: 17935277]

108 **Satyanarayana A**, Kaldis P. Mammalian cell-cycle regulation: several Cdks, numerous cyclins and diverse compensatory mechanisms. *Oncogene* 2009; **28**: 2925-2939 [PMID: 19561645 DOI: 10.1038/onc.2009.170]

109 **Kuwajima M**, Kumano G, Nishida H. Regulation of the number of cell division rounds by tissue-specific transcription factors and Cdk inhibitor during ascidian embryogenesis. *PLoS One* 2014; **9**: e90188 [PMID: 24608898 DOI: 10.1371/journal.pone.0090188]

110 [**Xu S**](http://www.ncbi.nlm.nih.gov/pubmed?term=Xu%20S%5BAuthor%5D&cauthor=true&cauthor_uid=25096995), [Li X](http://www.ncbi.nlm.nih.gov/pubmed?term=Li%20X%5BAuthor%5D&cauthor=true&cauthor_uid=25096995), [Gong Z](http://www.ncbi.nlm.nih.gov/pubmed?term=Gong%20Z%5BAuthor%5D&cauthor=true&cauthor_uid=25096995), [Wang W](http://www.ncbi.nlm.nih.gov/pubmed?term=Wang%20W%5BAuthor%5D&cauthor=true&cauthor_uid=25096995), [Li Y](http://www.ncbi.nlm.nih.gov/pubmed?term=Li%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=25096995), [Nair BC](http://www.ncbi.nlm.nih.gov/pubmed?term=Nair%20BC%5BAuthor%5D&cauthor=true&cauthor_uid=25096995), [Piao H](http://www.ncbi.nlm.nih.gov/pubmed?term=Piao%20H%5BAuthor%5D&cauthor=true&cauthor_uid=25096995), [Yang K](http://www.ncbi.nlm.nih.gov/pubmed?term=Yang%20K%5BAuthor%5D&cauthor=true&cauthor_uid=25096995), [Wu G](http://www.ncbi.nlm.nih.gov/pubmed?term=Wu%20G%5BAuthor%5D&cauthor=true&cauthor_uid=25096995), [Chen J](http://www.ncbi.nlm.nih.gov/pubmed?term=Chen%20J%5BAuthor%5D&cauthor=true&cauthor_uid=25096995). Proteomic Analysis of the Human CDK Family Reveals a Novel CDK5 Complex Involved in Cell Growth and Migration. *Mol Cell Proteomics* 2014: Epub ahead of print [PMID: 25096995 DOI: 10.1074/mcp.M113.036699]

111 **Torikoshi Y**, Gohda K, Davis ML, Symmans WF, Pusztai L, Kazansky A, Nakayama S, Yoshida T, Matsushima T, Hortobagyi GN, Ishihara H, Kim SJ, Noguchi S, Ueno NT. Novel functional assay for spindle-assembly checkpoint by cyclin-dependent kinase activity to predict taxane chemosensitivity in breast tumor patient. *J Cancer* 2013; **4**: 697-702 [PMID: 24312139]

112 **Casimiro MC**, Velasco-Velázquez M, Aguirre-Alvarado C, Pestell RG. Overview of cyclins D1 function in cancer and the CDK inhibitor landscape: past and present. *Expert Opin Investig Drugs* 2014; **23**: 295-304 [PMID: 24387133 DOI: 10.1517/13543784.2014.867017]

113 **Jinno H**, Matsuda S, Hayashida T, Takahashi M, Hirose S, Ikeda T, Kitagawa Y. Differential pathological response to preoperative chemotherapy across breast cancer intrinsic subtypes. *Chemotherapy* 2012; **58**: 364-370 [PMID: 23207824 DOI: 10.1159/000343663]

114 **Yamaguchi T**, Mukai H. Ki-67 index guided selection of preoperative chemotherapy for HER2-positive breast cancer: a randomized phase II trial. *Jpn J Clin Oncol* 2012; **42**: 1211-1214 [PMID: 23129778 DOI: 10.1093/jjco/hys161]

115 **Toyoshima M**, Howie HL, Imakura M, Walsh RM, Annis JE, Chang AN, Frazier J, Chau BN, Loboda A, Linsley PS, Cleary MA, Park JR, Grandori C. Functional genomics identifies therapeutic targets for MYC-driven cancer. *Proc Natl Acad Sci U S A* 2012; **109**: 9545-9550 [PMID: 22623531 DOI: 10.1073/pnas.1121119109]

116 **Kessler JD**, Kahle KT, Sun T, Meerbrey KL, Schlabach MR, Schmitt EM, Skinner SO, Xu Q, Li MZ, Hartman ZC, Rao M, Yu P, Dominguez-Vidana R, Liang AC, Solimini NL, Bernardi RJ, Yu B, Hsu T, Golding I, Luo J, Osborne CK, Creighton CJ, Hilsenbeck SG, Schiff R, Shaw CA, Elledge SJ, Westbrook TF. A SUMOylation-dependent transcriptional subprogram is required for Myc-driven tumorigenesis. *Science* 2012; **335**: 348-353 [PMID: 22157079 DOI: 10.1126/science.1212728]

117 **Kang J**, Sergio CM, Sutherland RL, Musgrove EA. Targeting cyclin-dependent kinase 1 (CDK1) but not CDK4/6 or CDK2 is selectively lethal to MYC-dependent human breast cancer cells. *BMC Cancer* 2014; **14**: 32 [PMID: 24444383 DOI: 10.1186/1471-2407-14-32]

118 **Cunningham JT**, Pourdehnad M, Stumpf CR, Ruggero D. Investigating Myc-dependent translational regulation in normal and cancer cells. *Methods Mol Biol* 2013; **1012**: 201-212 [PMID: 24006066 DOI: 10.1007/978-1-62703-429-6\_13]

119 **Said TK**, Medina D. Cell cyclins and cyclin-dependent kinase activities in mouse mammary tumor development. *Carcinogenesis* 1995; **16**: 823-830 [PMID: 7728962 DOI: 10.1093/carcin/16.4.823]

120 **Duong MT**, Akli S, Macalou S, Biernacka A, Debeb BG, Yi M, Hunt KK, Keyomarsi K. Hbo1 is a cyclin E/CDK2 substrate that enriches breast cancer stem-like cells. *Cancer Res* 2013; **73**: 5556-5568 [PMID: 23955388 DOI: 10.1158/0008-5472.CAN-13-0013]

121 **Rath SL**, Senapati S. Why are the truncated cyclin Es more effective CDK2 activators than the full-length isoforms? *Biochemistry* 2014; **53**: 4612-4624 [PMID: 24947816 DOI: 10.1021/bi5004052]

122 **Li XY**, Luo QF, Wei CK, Li DF, Fang L. siRNA-mediated silencing of CDK8 inhibits proliferation and growth in breast cancer cells. *Int J Clin Exp Pathol* 2014; **7**: 92-100 [PMID: 24427329]

123 **Pisanò M**, Mezzolla V, Galante MM, Alemanno G, Manca C, Lorusso V, Malvasi A, Tinelli A. A new mutation of BRCA2 gene in an Italian healthy woman with familial breast cancer history. *Fam Cancer* 2011; **10**: 65-71 [PMID: 20878484 DOI: 10.1007/s10689-010-9389-7]

124 **Pruss D**, Morris B, Hughes E, Eggington JM, Esterling L, Robinson BS, van Kan A, Fernandes PH, Roa BB, Gutin A, Wenstrup RJ, Bowles KR. Development and validation of a new algorithm for the reclassification of genetic variants identified in the BRCA1 and BRCA2 genes. *Breast Cancer Res Treat* 2014; **147**: 119-132 [PMID: 25085752 DOI: 10.1007/s10549-014-3065-9]

125 **Yata K**, Bleuyard JY, Nakato R, Ralf C, Katou Y, Schwab RA, Niedzwiedz W, Shirahige K, Esashi F. BRCA2 coordinates the activities of cell-cycle kinases to promote genome stability. *Cell Rep* 2014; **7**: 1547-1559 [PMID: 24835992 DOI: 10.1016/j.celrep.2014.04.023]

126 **Jia Y**, Domenico J, Swasey C, Wang M, Gelfand EW, Lucas JJ. Modulated expression of genes encoding estrogen metabolizing enzymes by G1-phase cyclin-dependent kinases 6 and 4 in human breast cancer cells. *PLoS One* 2014; **9**: e97448 [PMID: 24848372 DOI: 10.1371/journal.pone.0097448]

127 **Fu J**, Tian C, Xing M, Wang X, Guo H, Sun L, Sun L, Jiang Z, Zhang L. KU004 induces G1 cell cycle arrest in human breast cancer SKBR-3 cells by modulating PI3K/Akt pathway. *Biomed Pharmacother* 2014; **68**: 625-630 [PMID: 24996960 DOI: 10.1016/j.biopha.2014.05.006]

128 **Vora SR**, Juric D, Kim N, Mino-Kenudson M, Huynh T, Costa C, Lockerman EL, Pollack SF, Liu M, Li X, Lehar J, Wiesmann M, Wartmann M, Chen Y, Cao ZA, Pinzon-Ortiz M, Kim S, Schlegel R, Huang A, Engelman JA. CDK 4/6 inhibitors sensitize PIK3CA mutant breast cancer to PI3K inhibitors. *Cancer Cell* 2014; **26**: 136-149 [PMID: 25002028 DOI: 10.1016/j.ccr.2014.05.02]

129 **Roberts PJ**, Bisi JE, Strum JC, Combest AJ, Darr DB, Usary JE, Zamboni WC, Wong KK, Perou CM, Sharpless NE. Multiple roles of cyclin-dependent kinase 4/6 inhibitors in cancer therapy. *J Natl Cancer Inst* 2012; **104**: 476-487 [PMID: 22302033 DOI: 10.1093/jnci/djs002]

130 **Akin S**, Babacan T, Sarici F, Altundag K. A novel targeted therapy in breast cancer: cyclin dependent kinase inhibitors. *J BUON* 2014; **19**: 42-46 [PMID: 24659641]

131 **Zhang C**, Yan Z, Arango ME, Painter CL, Anderes K. Advancing bioluminescence imaging technology for the evaluation of anticancer agents in the MDA-MB-435-HAL-Luc mammary fat pad and subrenal capsule tumor models. *Clin Cancer Res* 2009; **15**: 238-246 [PMID: 19118051]

132 **Finn RS**, Dering J, Conklin D, Kalous O, Cohen DJ, Desai AJ, Ginther C, Atefi M, Chen I, Fowst C, Los G, Slamon DJ. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. *Breast Cancer Res* 2009; **11**: R77 [PMID: 19874578 DOI: 10.1158/1078-0432.CCR-08-0897]

133 **Dean JL**, McClendon AK, Hickey TE, Butler LM, Tilley WD, Witkiewicz AK, Knudsen ES. Therapeutic response to CDK4/6 inhibition in breast cancer defined by ex vivo analyses of human tumors. *Cell Cycle* 2012; **11**: 2756-2761 [PMID: 22767154 DOI: 10.4161/cc.21195]

134 **Lange CA**, Yee D. Killing the second messenger: targeting loss of cell cycle control in endocrine-resistant breast cancer. *Endocr Relat Cancer* 2011; **18**: C19-C24 [PMID: 21613412 DOI: 10.1530/ERC-11-0112]

135 **Rocca A**, Farolfi A, Bravaccini S, Schirone A, Amadori D. Palbociclib (PD 0332991): targeting the cell cycle machinery in breast cancer. *Expert Opin Pharmacother* 2014; **15**: 407-420 [PMID: 24369047 DOI: 10.1517/14656566.2014.870555]

136 **Robinson TJ**, Liu JC, Vizeacoumar F, Sun T, Maclean N, Egan SE, Schimmer AD, Datti A, Zacksenhaus E. RB1 status in triple negative breast cancer cells dictates response to radiation treatment and selective therapeutic drugs. *PLoS One* 2013; **8**: e78641 [PMID: 24265703 DOI: 10.1371/journal.pone.0078641]

137 **McClendon AK**, Dean JL, Rivadeneira DB, Yu JE, Reed CA, Gao E, Farber JL, Force T, Koch WJ, Knudsen ES. CDK4/6 inhibition antagonizes the cytotoxic response to anthracycline therapy. *Cell Cycle* 2012; **11**: 2747-2755 [PMID: 22751436 DOI: 10.4161/cc.21127]

138 **DiRocco DP**, Bisi J, Roberts P, Strum J, Wong KK, Sharpless N, Humphreys BD. CDK4/6 inhibition induces epithelial cell cycle arrest and ameliorates acute kidney injury. *Am J Physiol Renal Physiol* 2014; **306**: F379-F388 [PMID: 24338822 DOI: 10.1152/ajprenal.00475.2013]

139 **Martin MP**, Olesen SH, Georg GI, Schönbrunn E. Cyclin-dependent kinase inhibitor dinaciclib interacts with the acetyl-lysine recognition site of bromodomains. *ACS Chem Biol* 2013; **8**: 2360-2365 [PMID: 24007471 DOI: 10.1021/cb4003283]

140 **Nguyen TK**, Grant S. Dinaciclib (SCH727965) inhibits the unfolded protein response through a CDK1- and 5-dependent mechanism. *Mol Cancer Ther* 2014; **13**: 662-674 [PMID: 24362465 DOI: 10.1158/1535-7163.MCT-13-0714]

141 **Paruch K**, Dwyer MP, Alvarez C, Brown C, Chan TY, Doll RJ, Keertikar K, Knutson C, McKittrick B, Rivera J, Rossman R, Tucker G, Fischmann T, Hruza A, Madison V, Nomeir AA, Wang Y, Kirschmeier P, Lees E, Parry D, Sgambellone N, Seghezzi W, Schultz L, Shanahan F, Wiswell D, Xu X, Zhou Q, James RA, Paradkar VM, Park H, Rokosz LR, Stauffer TM, Guzi TJ. Discovery of Dinaciclib (SCH 727965): A Potent and Selective Inhibitor of Cyclin-Dependent Kinases. *ACS Med Chem Lett* 2010; **1**: 204-208 [PMID: 24900195 DOI: 10.1021/ml100051d]

142 **Parry D**, Guzi T, Shanahan F, Davis N, Prabhavalkar D, Wiswell D, Seghezzi W, Paruch K, Dwyer MP, Doll R, Nomeir A, Windsor W, Fischmann T, Wang Y, Oft M, Chen T, Kirschmeier P, Lees EM. Dinaciclib (SCH 727965), a novel and potent cyclin-dependent kinase inhibitor. *Mol Cancer Ther* 2010; **9**: 2344-2353 [PMID: 20663931 DOI: 10.1158/1535-7163.MCT-10-0324]

143 **Mita MM**, Joy AA, Mita A, Sankhala K, Jou YM, Zhang D, Statkevich P, Zhu Y, Yao SL, Small K, Bannerji R, Shapiro CL. Randomized phase II trial of the cyclin-dependent kinase inhibitor dinaciclib (MK-7965) versus capecitabine in patients with advanced breast cancer. *Clin Breast Cancer* 2014; **14**: 169-176 [PMID: 24393852 DOI: 10.1016/j.clbc.2013.10.016]

144 **Stephenson JJ**, Nemunaitis J, Joy AA, Martin JC, Jou YM, Zhang D, Statkevich P, Yao SL, Zhu Y, Zhou H, Small K, Bannerji R, Edelman MJ. Randomized phase 2 study of the cyclin-dependent kinase inhibitor dinaciclib (MK-7965) versus erlotinib in patients with non-small cell lung cancer. *Lung Cancer* 2014; **83**: 219-223 [PMID: 24388167 DOI: 10.1016/j.lungcan.2013.11.020]

145 **Logan CY**, Nusse R. The Wnt signaling pathway in development and disease. *Annu Rev Cell Dev Biol* 2004; **20**: 781-810 [PMID: 15473860]

146 **Asai N**, Ohkawara B, Ito M, Masuda A, Ishiguro N, Ohno K. LRP4 induces extracellular matrix productions and facilitates chondrocyte differentiation. *Biochem Biophys Res Commun* 2014; **451**: 302-307 [PMID: 25091481 DOI: 10.1016/j.bbrc.2014.07.125]

147 **Liu J**, Pan S, Hsieh MH, Ng N, Sun F, Wang T, Kasibhatla S, Schuller AG, Li AG, Cheng D, Li J, Tompkins C, Pferdekamper A, Steffy A, Cheng J, Kowal C, Phung V, Guo G, Wang Y, Graham MP, Flynn S, Brenner JC, Li C, Villarroel MC, Schultz PG, Wu X, McNamara P, Sellers WR, Petruzzelli L, Boral AL, Seidel HM, McLaughlin ME, Che J, Carey TE, Vanasse G, Harris JL. Targeting Wnt-driven cancer through the inhibition of Porcupine by LGK974. *Proc Natl Acad Sci U S A* 2013; **110**: 20224-20229 [PMID: 24277854 DOI: 10.1073/pnas.1314239110]

148 **Lento W**, Congdon K, Voermans C, Kritzik M, Reya T. Wnt signaling in normal and malignant hematopoiesis. *Cold Spring Harb Perspect Biol* 2013; **5**: [PMID: 23378582 DOI: 10.1101/cshperspect.a008011]

149 **Seke Etet PF**, Vecchio L, Bogne Kamga P, Nchiwan Nukenine E, Krampera M, Nwabo Kamdje AH. Normal hematopoiesis and hematologic malignancies: role of canonical Wnt signaling pathway and stromal microenvironment. *Biochim Biophys Acta* 2013; **1835**: 1-10 [PMID: 22982245 DOI: 10.1016/j.bbcan.2012.08.002]

150 **Park JH**, Kwon HY, Sohn EJ, Kim KA, Kim B, Jeong SJ, Song JH, Koo JS, Kim SH. Inhibition of Wnt/β-catenin signaling mediates ursolic acid-induced apoptosis in PC-3 prostate cancer cells. *Pharmacol Rep* 2013; **65**: 1366-1374 [PMID: 24399733]

151 **Menck K**, Klemm F, Gross JC, Pukrop T, Wenzel D, Binder C. Induction and transport of Wnt 5a during macrophage-induced malignant invasion is mediated by two types of extracellular vesicles. *Oncotarget* 2013; **4**: 2057-2066 [PMID: 24185202]

152 **Tumova L**, Pombinho AR, Vojtechova M, Stancikova J, Gradl D, Krausova M, Sloncova E, Horazna M, Kriz V, Machonova O, Jindrich J, Zdrahal Z, Bartunek P, Korinek V. Monensin inhibits canonical Wnt signaling in human colorectal cancer cells and suppresses tumor growth in multiple intestinal neoplasia mice. *Mol Cancer Ther* 2014; **13**: 812-822 [PMID: 24552772 DOI: 10.1158/1535-7163.MCT-13-0625]

153 [**Kim JT**](http://www.ncbi.nlm.nih.gov/pubmed?term=Kim%20JT%5BAuthor%5D&cauthor=true&cauthor_uid=25098665), [Liu C](http://www.ncbi.nlm.nih.gov/pubmed?term=Liu%20C%5BAuthor%5D&cauthor=true&cauthor_uid=25098665), [Zaytseva YY](http://www.ncbi.nlm.nih.gov/pubmed?term=Zaytseva%20YY%5BAuthor%5D&cauthor=true&cauthor_uid=25098665), [Weiss HL](http://www.ncbi.nlm.nih.gov/pubmed?term=Weiss%20HL%5BAuthor%5D&cauthor=true&cauthor_uid=25098665), [Townsend CM Jr](http://www.ncbi.nlm.nih.gov/pubmed?term=Townsend%20CM%20Jr%5BAuthor%5D&cauthor=true&cauthor_uid=25098665), [Evers BM](http://www.ncbi.nlm.nih.gov/pubmed?term=Evers%20BM%5BAuthor%5D&cauthor=true&cauthor_uid=25098665). Neurotensin, a novel target of Wnt/β-catenin pathway, promotes growth of neuroendocrine tumor cells. *Int J Cancer* 2014: Epub ahead of print [PMID: 25098665 DOI: 10.1002/ijc.29123]

154 **Yu DH**, Zhang X, Wang H, Zhang L, Chen H, Hu M, Dong Z, Zhu G, Qian Z, Fan J, Su X, Xu Y, Zheng L, Dong H, Yin X, Ji Q, Ji J. The essential role of TNIK gene amplification in gastric cancer growth. *Oncogenesis* 2014; **2**: e89 [PMID: 24566388 DOI: 10.1038/oncsis.2014.2]

155 **Many AM**, Brown AM. Both canonical and non-canonical Wnt signaling independently promote stem cell growth in mammospheres. *PLoS One* 2014; **9**: e101800 [PMID: 25019931 DOI: 10.1371/journal.pone.0101800]

156 **Klinke DJ**. Induction of Wnt-inducible signaling protein-1 correlates with invasive breast cancer oncogenesis and reduced type 1 cell-mediated cytotoxic immunity: a retrospective study. *PLoS Comput Biol* 2014; **10**: e1003409 [PMID: 24426833 DOI: 10.1371/journal.pcbi.1003409]

157 **Lu W**, Li Y. Salinomycin Suppresses LRP6 Expression and Inhibits Both Wnt/β-catenin and mTORC1 Signaling in Breast and Prostate Cancer Cells. *J Cell Biochem* 2014; **115**: 1799-1807 [PMID: 24905570 DOI: 10.1002/jcb.24850]

158 **Lu W**, Lin C, Li Y. Rottlerin induces Wnt co-receptor LRP6 degradation and suppresses both Wnt/β-catenin and mTORC1 signaling in prostate and breast cancer cells. *Cell Signal* 2014; **26**: 1303-1309 [PMID: 24607787 DOI: 10.1016/j.cellsig.2014.02.018]

159 **Proffitt KD**, Madan B, Ke Z, Pendharkar V, Ding L, Lee MA, Hannoush RN, Virshup DM. Pharmacological inhibition of the Wnt acyltransferase PORCN prevents growth of WNT-driven mammary cancer. *Cancer Res* 2013; **73**: 502-507 [PMID: 23188502 DOI: 10.1158/0008-5472.CAN-12-2258]

160 **Jiang X**, Hao HX, Growney JD, Woolfenden S, Bottiglio C, Ng N, Lu B, Hsieh MH, Bagdasarian L, Meyer R, Smith TR, Avello M, Charlat O, Xie Y, Porter JA, Pan S, Liu J, McLaughlin ME, Cong F. Inactivating mutations of RNF43 confer Wnt dependency in pancreatic ductal adenocarcinoma. *Proc Natl Acad Sci U S A* 2013; **110**: 12649-12654 [PMID: 23847203 DOI: 10.1073/pnas.1307218110]

161 **Lamb R**, Ablett MP, Spence K, Landberg G, Sims AH, Clarke RB. Wnt pathway activity in breast cancer sub-types and stem-like cells. *PLoS One* 2013; **8**: e67811 [PMID: 23861811 DOI: 10.1371/journal.pone.0067811]

162 **Loh YN**, Hedditch EL, Baker LA, Jary E, Ward RL, Ford CE. The Wnt signalling pathway is upregulated in an in vitro model of acquired tamoxifen resistant breast cancer. *BMC Cancer* 2013; **13**: 174 [PMID: 23547709 DOI: 10.1186/1471-2407-13-174]

163 **Yin S**, Xu L, Bonfil RD, Banerjee S, Sarkar FH, Sethi S, Reddy KB. Tumor-initiating cells and FZD8 play a major role in drug resistance in triple-negative breast cancer. *Mol Cancer Ther* 2013; **12**: 491-498 [PMID: 23445611 DOI: 10.1158/1535-7163.MCT-12-1090]

164 **Cui W**, Wang LH, Wen YY, Song M, Li BL, Chen XL, Xu M, An SX, Zhao J, Lu YY, Mi XY, Wang EH. Expression and regulation mechanisms of Sonic Hedgehog in breast cancer. *Cancer Sci* 2010; **101**: 927-933 [PMID: 20180807 DOI: 10.1111/j.1349-7006.2010.01495.x]

165 **Kasperczyk H**, Baumann B, Debatin KM, Fulda S. Characterization of sonic hedgehog as a novel NF-kappaB target gene that promotes NF-kappaB-mediated apoptosis resistance and tumor growth in vivo. *FASEB J* 2009; **23**: 21-33 [PMID: 18772349 DOI: 10.1096/fj.08-111096]

166 **Wang TP**, Hsu SH, Feng HC, Huang RF. Folate deprivation enhances invasiveness of human colon cancer cells mediated by activation of sonic hedgehog signaling through promoter hypomethylation and cross action with transcription nuclear factor-kappa B pathway. *Carcinogenesis* 2012; **33**: 1158-1168 [PMID: 22461522 DOI: 10.1093/carcin/bgs138]

167 **Singh AP**, Arora S, Bhardwaj A, Srivastava SK, Kadakia MP, Wang B, Grizzle WE, Owen LB, Singh S. CXCL12/CXCR4 protein signaling axis induces sonic hedgehog expression in pancreatic cancer cells via extracellular regulated kinase- and Akt kinase-mediated activation of nuclear factor κB: implications for bidirectional tumor-stromal interactions. *J Biol Chem* 2012; **287**: 39115-39124 [PMID: 22995914 DOI: 10.1074/jbc.M112.409581]

168 **Mukherjee S**, Frolova N, Sadlonova A, Novak Z, Steg A, Page GP, Welch DR, Lobo-Ruppert SM, Ruppert JM, Johnson MR, Frost AR. Hedgehog signaling and response to cyclopamine differ in epithelial and stromal cells in benign breast and breast cancer. *Cancer Biol Ther* 2006; **5**: 674-683 [PMID: 16855373]

169 **Thomas ZI**, Gibson W, Sexton JZ, Aird KM, Ingram SM, Aldrich A, Lyerly HK, Devi GR, Williams KP. Targeting GLI1 expression in human inflammatory breast cancer cells enhances apoptosis and attenuates migration. *Br J Cancer* 2011; **104**: 1575-1586 [PMID: 21505458 DOI: 10.1038/bjc.2011.133]

170 **Das S**, Samant RS, Shevde LA. Nonclassical activation of Hedgehog signaling enhances multidrug resistance and makes cancer cells refractory to Smoothened-targeting Hedgehog inhibition. *J Biol Chem* 2013; **288**: 11824-11833 [PMID: 23508962 DOI: 10.1074/jbc.M112.432302]

171 [**Bai R**](http://www.ncbi.nlm.nih.gov/pubmed?term=Bai%20R%5BAuthor%5D&cauthor=true&cauthor_uid=24765141)**,** [Zhao H](http://www.ncbi.nlm.nih.gov/pubmed?term=Zhao%20H%5BAuthor%5D&cauthor=true&cauthor_uid=24765141), [Zhang X](http://www.ncbi.nlm.nih.gov/pubmed?term=Zhang%20X%5BAuthor%5D&cauthor=true&cauthor_uid=24765141), [DU S](http://www.ncbi.nlm.nih.gov/pubmed?term=DU%20S%5BAuthor%5D&cauthor=true&cauthor_uid=24765141). Characterization of sonic hedgehog inhibition in gastric carcinoma cells. *Oncol Lett* 2014; **7**: 1381-1384 [PMID: 24765141]

172 [**Heiden KB**](http://www.ncbi.nlm.nih.gov/pubmed?term=Heiden%20KB%5BAuthor%5D&cauthor=true&cauthor_uid=25078145), [Williamson AJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Williamson%20AJ%5BAuthor%5D&cauthor=true&cauthor_uid=25078145), [Doscas ME](http://www.ncbi.nlm.nih.gov/pubmed?term=Doscas%20ME%5BAuthor%5D&cauthor=true&cauthor_uid=25078145), [Ye J](http://www.ncbi.nlm.nih.gov/pubmed?term=Ye%20J%5BAuthor%5D&cauthor=true&cauthor_uid=25078145), [Wang Y](http://www.ncbi.nlm.nih.gov/pubmed?term=Wang%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=25078145), [Liu D](http://www.ncbi.nlm.nih.gov/pubmed?term=Liu%20D%5BAuthor%5D&cauthor=true&cauthor_uid=25078145), [Xing M](http://www.ncbi.nlm.nih.gov/pubmed?term=Xing%20M%5BAuthor%5D&cauthor=true&cauthor_uid=25078145), [Prinz RA](http://www.ncbi.nlm.nih.gov/pubmed?term=Prinz%20RA%5BAuthor%5D&cauthor=true&cauthor_uid=25078145), [Xu X](http://www.ncbi.nlm.nih.gov/pubmed?term=Xu%20X%5BAuthor%5D&cauthor=true&cauthor_uid=25078145). The sonic hedgehog signaling pathway maintains the cancer stem cell self-renewal of anaplastic thyroid cancer by inducing Snail expression. *J Clin Endocrinol Metab* 2014: Epub ahead of print [PMID: 25078145]

173 **Balbous A**, Renoux B, Cortes U, Milin S, Guilloteau K, Legigan T, Rivet P, Boissonnade O, Martin S, Tripiana C, Wager M, Bensadoun RJ, Papot S, Karayan-Tapon L. Selective Release of a Cyclopamine Glucuronide Prodrug toward Stem-like Cancer Cell Inhibition in Glioblastoma. *Mol Cancer Ther* 2014; **13**: 2159-2169 [PMID: 25053823]

174 **Chai F**, Zhou J, Chen C, Xie S, Chen X, Su P, Shi J. The Hedgehog inhibitor cyclopamine antagonizes chemoresistance of breast cancer cells. *Onco Targets Ther* 2013; **6**: 1643-1647 [PMID: 24250231 DOI: 10.2147/OTT.S51914]

175 **Steg AD**, Katre AA, Bevis KS, Ziebarth A, Dobbin ZC, Shah MM, Alvarez RD, Landen CN. Smoothened antagonists reverse taxane resistance in ovarian cancer. *Mol Cancer Ther* 2012; **11**: 1587-1597 [PMID: 22553355 DOI: 10.1158/1535-7163.MCT-11-105]

176 **Ramaswamy B**, Lu Y, Teng KY, Nuovo G, Li X, Shapiro CL, Majumder S. Hedgehog signaling is a novel therapeutic target in tamoxifen-resistant breast cancer aberrantly activated by PI3K/AKT pathway. *Cancer Res* 2012; **72**: 5048-5059 [PMID: 22875023 DOI: 10.1158/0008-5472.CAN-12-1248]

177 **Moraes RC**, Zhang X, Harrington N, Fung JY, Wu MF, Hilsenbeck SG, Allred DC, Lewis MT. Constitutive activation of smoothened (SMO) in mammary glands of transgenic mice leads to increased proliferation, altered differentiation and ductal dysplasia. *Development* 2007; **134**: 1231-1242 [PMID: 17287253 DOI: dx.doi.org/10.1242/dev.02797]

178 **Okolowsky N**, Furth PA, Hamel PA. Oestrogen receptor-alpha regulates non-canonical Hedgehog-signalling in the mammary gland. *Dev Biol* 2014; **391**: 219-229 [PMID: 24769368 DOI: 10.1016/j.ydbio.2014.04.007]

179 **Kwon YJ**, Hurst DR, Steg AD, Yuan K, Vaidya KS, Welch DR, Frost AR. Gli1 enhances migration and invasion via up-regulation of MMP-11 and promotes metastasis in ERα negative breast cancer cell lines. *Clin Exp Metastasis* 2011; **28**: 437-449 [PMID: 21442356 DOI: 10.1007/s10585-011-9382-z]

180 **Djiogue S**, Nwabo Kamdje AH, Vecchio L, Kipanyula MJ, Farahna M, Aldebasi Y, Seke Etet PF. Insulin resistance and cancer: the role of insulin and IGFs. *Endocr Relat Cancer* 2013; **20**: R1-R17 [PMID: 23207292 DOI: 10.1530/ERC-12-0324]

181 **Zhou L**, Guo X, Jing BA, Zhao L. CD44 is involved in CXCL-12 induced acute myeloid leukemia HL-60 cell polarity. *Biocell* 2010; **34**: 91-94 [PMID: 20925198 DOI: NOT]

182 **Razis E**, Kalogeras KT, Kotoula V, Eleftheraki AG, Nikitas N, Kronenwett R, Timotheadou E, Christodoulou C, Pectasides D, Gogas H, Wirtz RM, Makatsoris T, Bafaloukos D, Aravantinos G, Televantou D, Pavlidis N, Fountzilas G. Improved outcome of high-risk early HER2 positive breast cancer with high CXCL13-CXCR5 messenger RNA expression. *Clin Breast Cancer* 2012; **12**: 183-193 [PMID: 22607768 DOI: 10.1016/j.clbc.2012.03.006]

183[**Jaeger S**](http://www.ncbi.nlm.nih.gov/pubmed?term=Jaeger%20S%5BAuthor%5D&cauthor=true&cauthor_uid=24518063)**,** [Min J](http://www.ncbi.nlm.nih.gov/pubmed?term=Min%20J%5BAuthor%5D&cauthor=true&cauthor_uid=24518063), [Nigsch F](http://www.ncbi.nlm.nih.gov/pubmed?term=Nigsch%20F%5BAuthor%5D&cauthor=true&cauthor_uid=24518063), [Camargo M](http://www.ncbi.nlm.nih.gov/pubmed?term=Camargo%20M%5BAuthor%5D&cauthor=true&cauthor_uid=24518063), [Hutz J](http://www.ncbi.nlm.nih.gov/pubmed?term=Hutz%20J%5BAuthor%5D&cauthor=true&cauthor_uid=24518063), [Cornett A](http://www.ncbi.nlm.nih.gov/pubmed?term=Cornett%20A%5BAuthor%5D&cauthor=true&cauthor_uid=24518063), [Cleaver S](http://www.ncbi.nlm.nih.gov/pubmed?term=Cleaver%20S%5BAuthor%5D&cauthor=true&cauthor_uid=24518063), [Buckler A](http://www.ncbi.nlm.nih.gov/pubmed?term=Buckler%20A%5BAuthor%5D&cauthor=true&cauthor_uid=24518063), [Jenkins JL](http://www.ncbi.nlm.nih.gov/pubmed?term=Jenkins%20JL%5BAuthor%5D&cauthor=true&cauthor_uid=24518063). Causal Network Models for Predicting Compound Targets and Driving Pathways in Cancer. *J Biomol Screen* 2014; **19**: 791-802 [PMID: 24518063 DOI: 10.1177/1087057114522690]

184 **Konkel MK**, Batzer MA. A mobile threat to genome stability: The impact of non-LTR retrotransposons upon the human genome. *Semin Cancer Biol* 2010; **20**: 211-221 [PMID: 20307669 DOI: 10.1016/j.semcancer.2010.03.001]

185 **Kipanyula MJ**, Seke Etet PF, Vecchio L, Farahna M, Nukenine EN, Nwabo Kamdje AH. Signaling pathways bridging microbial-triggered inflammation and cancer. *Cell Signal* 2013; **25**: 403-416 [PMID: 23123499 DOI: 10.1016/j.cellsig.2012.10.014]

186 **Vecchio L**, Seke Etet PF, Kipanyula MJ, Krampera M, Nwabo Kamdje AH. Importance of epigenetic changes in cancer etiology, pathogenesis, clinical profiling, and treatment: what can be learned from hematologic malignancies? *Biochim Biophys Acta* 2013; **1836**: 90-104 [PMID: 23603458 DOI: 10.1016/j.bbcan.2013.04.001]

187 **Flanagan JM**, Wilhelm-Benartzi CS, Metcalf M, Kaye SB, Brown R. Association of somatic DNA methylation variability with progression-free survival and toxicity in ovarian cancer patients. *Ann Oncol* 2013; **24**: 2813-2818 [PMID: 24114859 DOI: 10.1093/annonc/mdt370]

188 **Muntané J**, De la Rosa AJ, Docobo F, García-Carbonero R, Padillo FJ. Targeting tyrosine kinase receptors in hepatocellular carcinoma. *Curr Cancer Drug Targets* 2013; **13**: 300-312 [PMID: 23016985 DOI: 10.2174/15680096113139990075]

189 **Huang SS**, Clarke DC, Gosline SJ, Labadorf A, Chouinard CR, Gordon W, Lauffenburger DA, Fraenkel E. Linking proteomic and transcriptional data through the interactome and epigenome reveals a map of oncogene-induced signaling. *PLoS Comput Biol* 2013; **9**: e1002887 [PMID: 23408876 DOI: 10.1371/journal.pcbi.1002887]

190 **Zazzu V**, Regierer B, Kühn A, Sudbrak R, Lehrach H. IT Future of Medicine: from molecular analysis to clinical diagnosis and improved treatment. *N Biotechnol* 2013; **30**: 362-365 [PMID: 23165094 DOI: 10.1016/j.nbt.2012.11.002]

191 **Daniels M**, Goh F, Wright CM, Sriram KB, Relan V, Clarke BE, Duhig EE, Bowman RV, Yang IA, Fong KM. Whole genome sequencing for lung cancer. *J Thorac Dis* 2012; **4**: 155-163 [PMID: 22833821 DOI: 10.3978/j.issn.2072-1439.2012.02.01]

192 **Giessrigl B**, Schmidt WM, Kalipciyan M, Jeitler M, Bilban M, Gollinger M, Krieger S, Jäger W, Mader RM, Krupitza G. Fulvestrant induces resistance by modulating GPER and CDK6 expression: implication of methyltransferases, deacetylases and the hSWI/SNF chromatin remodelling complex. *Br J Cancer* 2013; **109**: 2751-2762 [PMID: 24169358 DOI: 10.1038/bjc.2013.583]

193 **Hohmann AF**, Vakoc CR. A rationale to target the SWI/SNF complex for cancer therapy. *Trends Genet* 2014; **30**: 356-363 [PMID: 24932742 DOI: 10.1016/j.tig.2014.05.001]

194 [**Kimura A**](http://www.ncbi.nlm.nih.gov/pubmed?term=Kimura%20A%5BAuthor%5D&cauthor=true&cauthor_uid=25083560)**,**[Arakawa N](http://www.ncbi.nlm.nih.gov/pubmed?term=Arakawa%20N%5BAuthor%5D&cauthor=true&cauthor_uid=25083560), [Hirano H](http://www.ncbi.nlm.nih.gov/pubmed?term=Hirano%20H%5BAuthor%5D&cauthor=true&cauthor_uid=25083560). Mass Spectrometric Analysis of the Phosphorylation Levels of the SWI/SNF Chromatin Remodeling/Tumor Suppressor Proteins ARID1A and Brg1 in Ovarian Clear Cell Adenocarcinoma Cell Lines. *J Proteome Res* 2014: Epub ahead of print [PMID: 25083560 DOI: 10.1021/pr500470h]

195 **Brglez V**, Pucer A, Pungerčar J, Lambeau G, Petan T. Secreted phospholipases A₂are differentially expressed and epigenetically silenced in human breast cancer cells. *Biochem Biophys Res Commun* 2014; **445**: 230-235 [PMID: 24508801 DOI: 10.1016/j.bbrc.2014.01.182]

196 **Al-Rayyan N**, Litchfield LM, Ivanova MM, Radde BN, Cheng A, Elbedewy A, Klinge CM. 5-Aza-2-deoxycytidine and trichostatin A increase COUP-TFII expression in antiestrogen-resistant breast cancer cell lines. *Cancer Lett* 2014; **347**: 139-150 [PMID: 24513177 DOI: 10.1016/j.canlet.2014.02.001]

197 **Wilson-Edell KA**, Yevtushenko MA, Rothschild DE, Rogers AN, Benz CC. mTORC1/C2 and pan-HDAC inhibitors synergistically impair breast cancer growth by convergent AKT and polysome inhibiting mechanisms. *Breast Cancer Res Treat* 2014; **144**: 287-298 [PMID: 24562770 DOI: 10.1007/s10549-014-2877-y]

198 **Nickel A**, Stadler SC. Role of epigenetic mechanisms in epithelial-to-mesenchymal transition of breast cancer cells. *Transl Res* 2014: Epub ahead of print [PMID: 24768944 DOI: 10.1016/j.trsl.2014.04.001]

199 **Al-Nakhle H**, Smith L, Bell SM, Burns PA, Cummings M, Hanby AM, Lane S, Parker MD, Hughes TA, Speirs V. Regulation of estrogen receptor β1 expression in breast cancer by epigenetic modification of the 5' regulatory region. *Int J Oncol* 2013; **43**: 2039-2045 [PMID: 24068253 DOI: 10.3892/ijo.2013.2112]

200 **Mohapatra DK**, Reddy DS, Ramaiah MJ, Ghosh S, Pothula V, Lunavath S, Thomas S, Valli SN, Bhadra MP, Yadav JS. Rugulactone derivatives act as inhibitors of NF-κB activation and modulates the transcription of NF-κB dependent genes in MDA-MB-231cells. *Bioorg Med Chem Lett* 2014; **24**: 1389-1396 [PMID: 24508135 DOI: 10.1016/j.bmcl.2014.01.030]

201 **Liao XH**, Li YQ, Wang N, Zheng L, Xing WJ, Zhao DW, Yan TB, Wang Y, Liu LY, Sun XG, Hu P, Zhou H, Zhang TC. Re-expression and epigenetic modification of maspin induced apoptosis in MCF-7 cells mediated by myocardin. *Cell Signal* 2014; **26**: 1335-1346 [PMID: 24607789 DOI: 10.1016/j.cellsig.2014.03.001]

202 **Sun S**, Han Y, Liu J, Fang Y, Tian Y, Zhou J, Ma D, Wu P. Trichostatin A targets the mitochondrial respiratory chain, increasing mitochondrial reactive oxygen species production to trigger apoptosis in human breast cancer cells. *PLoS One* 2014; **9**: e91610 [PMID: 24626188 DOI: 10.1371/journal.pone.0091610]

203 **Cody JJ**, Markert JM, Hurst DR. Histone deacetylase inhibitors improve the replication of oncolytic herpes simplex virus in breast cancer cells. *PLoS One* 2014; **9**: e92919 [PMID: 24651853 DOI: 10.1371/journal.pone.0092919]

204 **Pellon-Maison M**, Montanaro MA, Lacunza E, Garcia-Fabiani MB, Soler-Gerino MC, Cattaneo ER, Quiroga IY, Abba MC, Coleman RA, Gonzalez-Baro MR. Glycerol-3-phosphate acyltranferase-2 behaves as a cancer testis gene and promotes growth and tumorigenicity of the breast cancer MDA-MB-231 cell line. *PLoS One* 2014; **9**: e100896 [PMID: 24967918 DOI: 10.1371/journal.pone.0100896]

205 **Katz TA**, Vasilatos SN, Harrington E, Oesterreich S, Davidson NE, Huang Y. Inhibition of histone demethylase, LSD2 (KDM1B), attenuates DNA methylation and increases sensitivity to DNMT inhibitor-induced apoptosis in breast cancer cells. *Breast Cancer Res Treat* 2014; **146**: 99-108 [PMID: 24924415 DOI: 10.1007/s10549-014-3012-9]

206 **Robertson FM**, Chu K, Boley KM, Ye Z, Liu H, Wright MC, Moraes R, Zhang X, Green TL, Barsky SH, Heise C, Cristofanilli M. The class I HDAC inhibitor Romidepsin targets inflammatory breast cancer tumor emboli and synergizes with paclitaxel to inhibit metastasis. *J Exp Ther Oncol* 2013; **10**: 219-233 [PMID: 24416998]

207 [**Deb G**](http://www.ncbi.nlm.nih.gov/pubmed?term=Deb%20G%5BAuthor%5D&cauthor=true&cauthor_uid=24481780)**,** [Thakur VS](http://www.ncbi.nlm.nih.gov/pubmed?term=Thakur%20VS%5BAuthor%5D&cauthor=true&cauthor_uid=24481780), [Limaye AM](http://www.ncbi.nlm.nih.gov/pubmed?term=Limaye%20AM%5BAuthor%5D&cauthor=true&cauthor_uid=24481780), [Gupta S](http://www.ncbi.nlm.nih.gov/pubmed?term=Gupta%20S%5BAuthor%5D&cauthor=true&cauthor_uid=24481780). Epigenetic induction of tissue inhibitor of matrix metalloproteinase-3 by green tea polyphenols in breast cancer cells. *Mol Carcinog* 2014: Epub ahead of print [PMID: 24481780 DOI: 10.1002/mc.22121]

208 **Chiu HW**, Yeh YL, Wang YC, Huang WJ, Chen YA, Chiou YS, Ho SY, Lin P, Wang YJ. Suberoylanilide hydroxamic acid, an inhibitor of histone deacetylase, enhances radiosensitivity and suppresses lung metastasis in breast cancer in vitro and in vivo. *PLoS One* 2013; **8**: e76340 [PMID: 24130769 DOI: 10.1371/journal.pone.0076340]

209 **Stark K**, Burger A, Wu J, Shelton P, Polin L, Li J. Reactivation of estrogen receptor α by vorinostat sensitizes mesenchymal-like triple-negative breast cancer to aminoflavone, a ligand of the aryl hydrocarbon receptor. *PLoS One* 2013; **8**: e74525 [PMID: 24058584 DOI: 10.1371/journal.pone.0074525]

210 **Tuval-Kochen L**, Paglin S, Keshet G, Lerenthal Y, Nakar C, Golani T, Toren A, Yahalom J, Pfeffer R, Lawrence Y. Eukaryotic initiation factor 2α--a downstream effector of mammalian target of rapamycin--modulates DNA repair and cancer response to treatment. *PLoS One* 2013; **8**: e77260 [PMID: 24204783 DOI: 10.1371/journal.pone.0077260]

211 **Salvador MA**, Wicinski J, Cabaud O, Toiron Y, Finetti P, Josselin E, Lelièvre H, Kraus-Berthier L, Depil S, Bertucci F, Collette Y, Birnbaum D, Charafe-Jauffret E, Ginestier C. The histone deacetylase inhibitor abexinostat induces cancer stem cells differentiation in breast cancer with low Xist expression. *Clin Cancer Res* 2013; **19**: 6520-6531 [PMID: 24141629 DOI: 10.1158/1078-0432.CCR-13-0877]

212 **Grassadonia A**, Cioffi P, Simiele F, Iezzi L, Zilli M, Natoli C. Role of Hydroxamate-Based Histone Deacetylase Inhibitors (Hb-HDACIs) in the Treatment of Solid Malignancies. *Cancers* (Basel) 2013; **5**: 919-942 [PMID: 24202327 DOI: 10.3390/cancers5030919]

213 **Martin M**, Bonneterre J, Geyer CE, Ito Y, Ro J, Lang I, Kim SB, Germa C, Vermette J, Wang K, Wang K, Awada A. A phase two randomised trial of neratinib monotherapy versus lapatinib plus capecitabine combination therapy in patients with HER2+ advanced breast cancer. *Eur J Cancer* 2013; **49**: 3763-3772 [PMID: 23953056 DOI: 10.1016/j.ejca.2013.07.142]

214 **Curigliano G**, Pivot X, Cortés J, Elias A, Cesari R, Khosravan R, Collier M, Huang X, Cataruozolo PE, Kern KA, Goldhirsch A. Randomized phase II study of sunitinib versus standard of care for patients with previously treated advanced triple-negative breast cancer. *Breast* 2013; **22**: 650-656 [PMID: 23958375 DOI: 10.1016/j.breast.2013.07.037]

215 **Earl HM**, Vallier AL, Hiller L, Fenwick N, Young J, Iddawela M, Abraham J, Hughes-Davies L, Gounaris I, McAdam K, Houston S, Hickish T, Skene A, Chan S, Dean S, Ritchie D, Laing R, Harries M, Gallagher C, Wishart G, Dunn J, Provenzano E, Caldas C. Effects of the addition of gemcitabine, and paclitaxel-first sequencing, in neoadjuvant sequential epirubicin, cyclophosphamide, and paclitaxel for women with high-risk early breast cancer (Neo-tAnGo): an open-label, 2×2 factorial randomised phase 3 trial. *Lancet Oncol* 2014; **15**: 201-212 [PMID: 24360787 DOI: 10.1016/S1470-2045]

216 **Wang J**, Song P, Schrieber S, Liu Q, Xu Q, Blumenthal G, Amiri Kordestani L, Cortazar P, Ibrahim A, Justice R, Wang Y, Tang S, Booth B, Mehrotra N, Rahman A. Exposure-response relationship of T-DM1: insight into dose optimization for patients with HER2-positive metastatic breast cancer. *Clin Pharmacol Ther* 2014; **95**: 558-564 [PMID: 24488143 DOI: 10.1038/clpt.2014.24]

217 **Kashiwaba M**, Inaba T, Komatsu H, Ishida K, Kawagishi R, Matsui Y, Uesugi N, Sugai T, Wakabayashi G. A phase I study of capecitabine combined with CPT-11 in metastatic breast cancer pretreated with anthracyclines and taxanes. *Oncology* 2014; **86**: 206-211 [PMID: 24820348 DOI: 10.1159/000358596]

218 **Reddy JA**, Allagadda VM, Leamon CP. Targeting therapeutic and imaging agents to folate receptor positive tumors. *Curr Pharm Biotechnol* 2005; **6**: 131-150 [PMID: 15853692 DOI: 10.2174/1389201053642376]

219 **Harrap KR**, Jackman AL, Newell DR, Taylor GA, Hughes LR, Calvert AH. Thymidylate synthase: a target for anticancer drug design. *Adv Enzyme Regul* 1989; **29**: 161-179 [PMID: 2633608 DOI: 10.1016/0065-2571]

220 **Kolarevic A**, Yancheva D, Kocic G, Smelcerovic A. Deoxyribonuclease inhibitors. *Eur J Med Chem* 2014: Epub ahead of print [PMID: 25042005 DOI: 10.1016/j.ejmech.2014.07.040]

221 **Benzaïd I**, Mönkkönen H, Bonnelye E, Mönkkönen J, Clézardin P. In vivo phosphoantigen levels in bisphosphonate-treated human breast tumors trigger Vγ9Vδ2 T-cell antitumor cytotoxicity through ICAM-1 engagement. *Clin Cancer Res* 2012; **18**: 6249-6259 [PMID: 23032740 DOI: 10.1158/1078-0432.CCR-12-0918]

222 **Kollmannsberger C**, Mross K, Jakob A, Kanz L, Bokemeyer C. Topotecan - A novel topoisomerase I inhibitor: pharmacology and clinical experience. *Oncology* 1999; **56**: 1-12 [PMID: 9885371 DOI: 10.1159/000011923]

223 **Kumar N**. Taxol-induced polymerization of purified tubulin. Mechanism of action. *J Biol Chem* 1981; **256**: 10435-10441 [PMID: 6116707]

224 **Nicolaou KC**, Winssinger N, Pastor J, Ninkovic S, Sarabia F, He Y, Vourloumis D, Yang Z, Li T, Giannakakou P, Hamel E. Synthesis of epothilones A and B in solid and solution phase. *Nature* 1997; **387**: 268-272 [PMID: 9153390 DOI: 10.1038/387268a0]

225 **Schuurman HJ**, Cottens S, Fuchs S, Joergensen J, Meerloo T, Sedrani R, Tanner M, Zenke G, Schuler W. SDZ RAD, a new rapamycin derivative: synergism with cyclosporine. *Transplantation* 1997; **64**: 32-35 [PMID: 9233697 DOI: 10.1097/00007890-199707150-00007]

226 **McNeil C**. Herceptin raises its sights beyond advanced breast cancer. *J Natl Cancer Inst* 1998; **90**: 882-883 [PMID: 9637135 DOI: 10.1093/jnci/90.12.882]

227 [**Sabatier R**](http://www.ncbi.nlm.nih.gov/pubmed?term=Sabatier%20R%5BAuthor%5D&cauthor=true&cauthor_uid=25091659), [Gonçalves A](http://www.ncbi.nlm.nih.gov/pubmed?term=Gon%C3%A7alves%20A%5BAuthor%5D&cauthor=true&cauthor_uid=25091659). Pertuzumab (Perjeta(®)) approval in HER2-positive metastatic breast cancers. *Bull Cancer* 2014; **101**: 765-771 [PMID: 25091659]

228 [**Corrigan PA**](http://www.ncbi.nlm.nih.gov/pubmed?term=Corrigan%20PA%5BAuthor%5D&cauthor=true&cauthor_uid=25082874), [Cicci TA](http://www.ncbi.nlm.nih.gov/pubmed?term=Cicci%20TA%5BAuthor%5D&cauthor=true&cauthor_uid=25082874), [Auten JJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Auten%20JJ%5BAuthor%5D&cauthor=true&cauthor_uid=25082874), [Lowe DK](http://www.ncbi.nlm.nih.gov/pubmed?term=Lowe%20DK%5BAuthor%5D&cauthor=true&cauthor_uid=25082874). Ado-trastuzumab Emtansine: A HER2-Positive Targeted Antibody-Drug Conjugate. *Ann Pharmacother* 2014: Epub ahead of print [PMID: 25082874 DOI: 10.1177/1060028014545354]

229 **Xia W**, Mullin RJ, Keith BR, Liu LH, Ma H, Rusnak DW, Owens G, Alligood KJ, Spector NL. Anti-tumor activity of GW572016: a dual tyrosine kinase inhibitor blocks EGF activation of EGFR/erbB2 and downstream Erk1/2 and AKT pathways. *Oncogene* 2002; **21**: 6255-6263 [PMID: 12214266 DOI: 10.1038/sj.onc.1205794]

230 **Kangas L**, Nieminen AL, Cantell K. Additive and synergistic effects of a novel antiestrogen, toremifene (Fc-1157a), and human interferons on estrogen responsive MCF-7 cells in vitro. *Med Biol* 1985; **63**: 187-190 [PMID: 2419713]

231 **Wakeling AE**, Dukes M, Bowler J. A potent specific pure antiestrogen with clinical potential. *Cancer Res* 1991; **51**: 3867-3873 [PMID: 1855205]

232 **Nicholson RI**, Walker KJ, Maynard PV. Anti-tumour potential of a new luteinizing hormone releasing hormone analogue, ICI 118630. *Eur J Cancer* 1980; **Suppl 1**: 295-299 [PMID: 6459236]

233 **Plourde PV**, Dyroff M, Dukes M. Arimidex: a potent and selective fourth-generation aromatase inhibitor. *Breast Cancer Res Treat* 1994; **30**: 103-111 [PMID: 7949201 DOI: 10.1007/BF00682745]

234 **Giudici D**, Ornati G, Briatico G, Buzzetti F, Lombardi P, di Salle E. 6-Methylenandrosta-1,4-diene-3,17-dione (FCE 24304): a new irreversible aromatase inhibitor. *J Steroid Biochem* 1988; **30**: 391-394 [PMID: 3386266 DOI: 10.1016/0022-4731]

235 **Ansfield FJ**, Davis HL, Ellerby RA, Ramirez G. A clinical trial of megestrol acetate in advanced breast cancer. *Cancer* 1974; **33**: 907-910 [PMID: 4819220 DOI: 10.1002/1097-0142]

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## Figure 1 Notch signaling in breast cancer. In Notch-driven breast cancers, tumor cells and neighboring cells express Notch ligand and receptors. In presence of ADAM/TACE and γ-secretase enzymatic complex, Notch ligand-receptor interactions result in the release of Notch intracellular domain (NICD), which translocate to cell nucleus and activate CSL transcription factor. Target genes include signaling molecules involve in cancer cell survival, proliferation, angiogenesis, growth, energy metabolism, and chemoresistance. Inhibitors of many of these signaling molecules have been developed and are in use in various cancers, including γ-secretase inhibitors, VEGF inhibitors, estrogen signaling inhibitors, and HER2 inhibitors.



## Figure 2 CDK4/6 signaling in breast cancer. A: Cyclin dependent kinases (CDK) 4/6 signaling is overexpressed in breast cancer. Such overexpression, which results from the silencing of CDK endogenous inhibitors, participate directly to cancer cell proliferation by triggering G1-S transition, and indirectly to chemoresistance via a PI3K/Akt/mTOR-dependent mechanism; B: CDK4/6 inhibitors sensitize chemoresistant cells to PI3K inhibitors and various other anticancer agents.

## Table 1 Current therapeutics for breast cancer

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug** | **Trade name** | **Class** | **Anticancer mechanism**  |
|  |  |  |  |
| **Classical chemotherapy** |  |  |
| Methotrexate  | Abitrexate®, Mexate®, Folex® | Antimetabolites, folate analogs | Folate receptor competitive antagonist[218] |
| 5-fluorouracil  | Adrucil®, Efudex®, Fluoroplex®, prodrug capecitabine/Xeloda® | Antimetabolite, pyrimidine analogs | Inhibition of the phosphatase and tensin homolog (PTEN) thymidylate synthase[219] |
| Gemcitabine hydrochloride | Gemzar® |
| Doxorubicin Hydrochloride | Adriamycin® | Anthracycline  | Deoxyribonuclease inhibitor[220] |
| Epirubicin Hydrochloride  | Ellence® |
| Pamidronate disodium | Aredia® | Nitrogen-containing bisphosphonate | Inhibition of farnesyl pyrophosphate synthase activity[221] |
| Cyclophosphamide | Clafen®, Cytoxan®, Neosar® | Nitrogen mustard alkylating agent | Inhibition of DNA replication by interacting with the alkyl group of DNA guanine base[222] |
| Paclitaxel | Abraxane ® Taxol® | Taxanes | Microtubule Inhibitors[223,224] |
| Docetaxel | Docecad®, Taxotere® |
| Ixabepilone | Ixempra® | Epothilone B analog.  |
|  |  |  |  |
| **Targeted therapy** |  |  |  |
| Everolimus | Afinitor® | **mTOR inhibitor** | Silencing of PI3K/Akt/mTOR signaling[225] |
| Trastuzumab | Herceptin® | HER2 inhibitor | Anti-HER2 monoclonal antibodies[226,226] |
| Pertuzumab | Perjeta® |
| Ado-Trastuzumab Emtansine | Kadcyla® | Antibody-drug conjugate | HER2 inhibitor and cytotoxic agent[228] |
| Lapatinib ditosylate | Tykerb® | Dual tyrosine kinase inhibitor  | EGFR/HER2 inhibitor[229] |
|  |  |  |  |
| **Hormone therapy** |  |  |  |
| Toremifene | Fareston® | Selective ER modulator (SERM) | Silence ER signaling[230,231] |
| Fulvestrant | Faslodex® | ER antagonists  |
| Tamoxifen citrate | Nolvadex® |
| Anastrozole | Arimidex® | Aromatase inhibitors | Inhibit estrogen synthesis[232-234] |
| Exemestane | Aromasin ® |
| Letrozole | Femara® |
| Goserelin acetate | Zoladex® | GnRH agonist |
| Megestrol acetate | Megace® | Progesterone derivative | progestational and antigonadotropic effects[235] |