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Front. Genet., 07 May 2019 | <https://doi.org/10.3389/fgene.2019.00420> (<https://doi.org/10.3389/fgene.2019.00420>)

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Triple-negative breast cancer (TNBC), which is largely synonymous with the basal-like molecular subtype, is the 5th leading cause of cancer deaths for women in the United States. The overall prognosis for TNBC patients remains poor given that few treatment options exist; including targeted therapies (not FDA approved), and multi-agent chemotherapy as standard-of-care treatment. TNBC like other complex diseases is governed by the perturbations of the complex interaction networks thereby elucidating the underlying molecular mechanisms of this disease in the context of network principles, which have the potential to identify targets for drug development. Here, we present an integrated “omics” approach based on the use of transcriptome and interactome data to identify dynamic/active protein-protein interaction networks (PPINs) in TNBC patients. We have identified three highly connected modules, EED, DHX9, and AURKA, which are extremely activated in TNBC tumors compared to both normal tissues and other breast cancer subtypes. Based on the functional analyses, we propose that these modules are potential drivers of proliferation and, as such, should be considered candidate molecular targets for drug development or drug repositioning in TNBC. Consistent with this argument, we repurposed steroids, anti-inflammatory agents, anti-infective agents, cardiovascular agents for patients with basal-like breast cancer. Finally, we have performed essential metabolite analysis on personalized genome-scale metabolic models and found that metabolites such as sphingosine-1-phosphate and cholesterol-sulfate have utmost importance in TNBC tumor growth.

## Introduction

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**Data Collection**Materials and  
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Throughout the study, we integrated multi-omics data including genomics, transcriptomics, and proteomics using network analysis (Table 1). TCGA data were obtained from <https://gdac.broadinstitute.org/> (<https://gdac.broadinstitute.org/>), METABRIC and CPTAC data were collected from Supplementary Files of these studies. At transcriptomic level, gene expressions were obtained from two major initiatives presenting RNA-Seq data from the TCGA study and microarray data from the METABRIC study. Normalized gene expression values from 179 basal and 852 non-basal like breast cancer samples ( $n = 1031$ ) from TCGA, and 331 basal and 1665 non-basal samples from the METABRIC project ( $n = 1992$ ) were used in integrative analysis. At the protein level, two different sources were used, (i) expression data of 160 basal and 777 non-basal like samples ( $n = 937$ ) in TCGA, using Reverse Phase Protein Array (RPPA)- based analysis of 226 proteins, and (ii) expression data of 19 basal and 61 non-basal like samples ( $n = 77$ ) from CPTAC which performed comprehensive mass-spectrometry methods including around 10,000 proteins (Mertins et al., 2016).

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RNA sequencing data from TCGA ( $n = 1031$ ) were used as a discovery set whereas, microarray data from METABRIC and proteomic data from TCGA and/or CPTAC were used as independent validation data sets in the study (Table 1).

**Differential Interactome**

To obtain a differential view of human interactome between two different phenotypes, and to identify PPIs that are up- or down-regulated in each phenotype relative to the other one, we used the gene expression profiles of interacting protein pairs and recruited the differential interactome analysis as previously described (Ayyildiz et al., 2017). For this purpose, normalized gene expression profiles from TCGA (179 basal-like and 852 non-basal like samples) were categorized into three levels: high (1), moderate (0), and low (-1) expression levels according to comparison of each gene expression with the average expression within each sample. The probability distributions for any possible co-expression profile of gene pairs (encoding proteins interacting with each other) were estimated, and the uncertainty of determining whether or not a PPI is encountered in a phenotype was estimated through an entropy formulation. In order to define possible PPIs, we used the high confidence human PPIs (Karagoz et al., 2016), comprising 147,923 interactions among 13,213 proteins. Karagoz and coworkers assembled and integrated physical PPIs of Homo sapiens from six publicly available databases including BioGRID (Chatr-Aryamontri et al., 2015), DIP (Salwinski, 2004), IntAct (Orchard et al., 2014), HIPPIE (Schaefer et al., 2012), HomoMINT (Persico et al., 2005), and HPRD (Prasad et al., 2009). Then, PPIs analyzed the differential view of human interactome between the basal and non-basal subtypes of breast cancer;  $P < 0.05$  was considered statistically significant for these analyses.

**Differentially Expressed Genes and Proteins**

Both differentially expressed genes (DEGs) between 179 basal and 852 non-basal samples in TCGA cohort, and differentially expressed proteins (DEPs) between 19 basal and 61 non-basal samples in CPTAC cohort were identified by using the Significance Analysis of Microarrays (SAM) method implemented in R software (Tusher et al., 2001; Hu et al., 2016; Gámez-Pozo et al., 2017). False Discovery Rate (FDR), adjusted  $p$ -value was set at  $p < 0.05$ , and fold changes  $> 1$  between basal-like and non-basal samples were considered as up-regulated DEGs and proteins in basal tumors.

**Module Extraction From Basal Specific Networks**

Basal subtype specific PPI networks were constructed by using the differential interactome from basal-like tumors. The interactions associated with proteins corresponding to DEGs that are up-regulated in basal-like tumors were identified and used to construct up-regulated PPI networks specific to basal-like breast cancer. The networks were visualized by using Cytoscape software (version 3.4.0) (Lopes et al., 2011). The topological analysis of the networks was performed via CytoNCA plugin of Cytoscape (version 2.1) (Tang et al., 2015). Two different

topological metrics, degree, which is defined by the number of adjacent nodes of a node in the network, and

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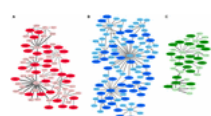
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study, we employed differential interactome algorithm utilizing the entropy concept using a comprehensive gene expression data and human PPI network to reveal the heterogeneity among the breast cancer subtypes (i.e., basal-like vs. non-basal-like). To do so, we categorized the expression of each gene and for each patient using 179 basal-like and 852 non-basal-like samples from TCGA into three classes as -1, 0, 1. These classes were then integrated with a high-confident PPI network (Karagoz et al., 2016) and the frequency of PPIs estimated for both basal-like and non-basal-like tumors. Using a 95% confidence interval ( $p < 0.05$ ), significant values  $< 0.2$  and  $> 0.8$  as well as corresponding  $H < 0.7$  were calculated for each class. As a result, 3,002 interactions among 1,652 proteins were considered significant across the entire dataset. These analyses identified 2,291 interactions among 1,391 proteins as being significantly activated in basal-like tumors whereas 712 interactions among 612 proteins were identified as significant in non-basal-like samples; 351 proteins were common across both subgroups of tumors (Supplementary Table S1).

Since low entropy presents low uncertainty, low redundancy and deterministic signaling resulting with homogeneity in the population, we next focused on the basal-like subtype to identify low entropy interactions ( $H < 0.1$ ). These analyses identified the EED protein network which is defined by 82 interactions within the group of 98 proteins. Importantly, the lowest entropy profile of the EED centroid network only identified an interaction with one protein (CTCF) in non-basal-like tumors. We further identified a sub-set of proteins, excluding 351 common signatures evident in both basal-like and non-basal-like tumors to identify a basal-like subtype specific network (Supplementary Table S2). All differential interactome networks and basal-like subtype specific networks were delimited regarding up-regulated genes in the basal-like tumors through 2-class SAM analysis (Tusher et al., 2001; Supplementary Table S3). Through the integration of SAM analysis and the above detailed differential interactome framework, we identified three significant modules: EED centroid module, covering relatively low entropy PPIs (Figure 1A); the DHX9 centroid module, covering mixed of low and high entropy PPIs (Figure 1B); and the AURKA centroid module, covering relatively high entropy PPIs (Figure 1C).

FIGURE 1



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**Figure 1.** Basal like breast cancer specific highly connected protein-protein interaction modules. **(A)** EED module, **(B)** DHX9 module, **(C)** AURKA module. Darker nodes indicate the statistically significant positive correlations between mRNA and protein pairs. Thicker edges indicate lowest entropy levels between interacting pairs.

Further analyses of the EED, DHX9, and AURKA modules determined that genes included in EED-module play roles in cyclins and cell cycle regulation ( $p = 6.1e-19$ ), cell cycle: G1/S checkpoint regulation ( $p = 3.5e-18$ ), regulation of cellular mechanics by calpain protease ( $p = 1.6e-11$ ), aryl hydrocarbon receptor signaling ( $p = 4.3e-11$ ), apoptosis signaling ( $p = 7.0e-10$ ), TWEAK signaling ( $p = 1.8e-09$ ), and GADD45 signaling ( $p = 4.3e-9$ ). In contrast, the genes in DHX9-module contribute to mTOR signaling ( $p = 4.1e-06$ ), regulation of eIF4 and p70S6K signaling ( $p = 7.9e-06$ ), EIF2 signaling ( $p = 7.2e-05$ ), Inflammasome pathway ( $p = 1.4e-04$ ), assembly of RNA Polymerase I Complex ( $p = 1.1e-03$ ), DNA double strand break repair ( $p = 1.8e-03$ ) and cell cycle ( $p = 3.5e-03$ ) while the genes associated with the AURKA-module are involved in DNA damaged-induced 14-3-3A signaling ( $p = 1.8e-10$ ), mitotic roles of Polo like kinase ( $p = 2.1e-09$ ), role of CHK proteins in cell cycle checkpoint control ( $p = 6.0e-08$ ), ATM signaling ( $p = 9.3e-07$ ) and mismatch repair ( $p = 3.1e-06$ ), role of BRCA1 in DNA damage response ( $p = 1.3e-05$ ), and cell cycle ( $p = 9.8e-05$ ). These data suggest that each module represent a unique aspect of basal-like breast cancer signaling. Some of these pathways such as TWEAK signaling, apoptosis signaling, mTOR signaling, ATM signaling showed that the chemotherapy targeted pathways are also activated in basal-like tumors in which chemotherapy is the front-line treatment option, nowadays (Supplementary Figure S1).

## Proteomic Analysis of Basal Specific Modules

We next reconstructed PPI networks using transcriptome data and validated our findings at proteomic level by leveraging orthogonal genomic and proteomic data from the TCGA and CPTAC projects. Transcriptome data from 937 sample was compared to RPPA analysis of the same samples to assess the relationship between each network

We used the 226 proteins and phosphoproteins from TCGA and CPTAC datasets (<https://www.frontiersin.org/legal/privacy-policy>) and a set of 77 of

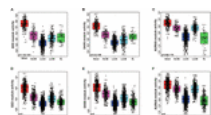
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these samples was used to examine the relationship between each module and 10,062 proteins and phosphoproteins using mass spectrometry-derived proteomic data from the CPTAC project. First, we used CPTAC proteome data to compare each gene to its corresponding protein across all basal-like tumors and assessed correlation for those pairs. Overall, 52.6–64.5% of the mRNA-protein pairs showed statistically significant positive Spearman correlations ( $P < 0.05$ ) when changes in mRNA abundance were compared to changes in relative protein abundance. These proteins in basal-like samples are shown in darker colors in **Figures 1A–C**. Then, we identified DEPs between basal-like and non-basal-like samples by using both RPPA and CPTAC data. Although RPPA data has limited number of proteins, we identified several up-regulated proteins including CCNE1, RAF1, SRC, CDK1, EGFR, MYC, MYH9, PCNA associated with the EED-module. Similarly, NDGR1 and CCNB1 were associated with the DHX9 and AURKA modules, respectively. We also analyzed DEPs between basal-like and non-basal-like tumors by using CPTAC data which is more comprehensive than RPPA data and it covered 69.4–56.4% of the module genes and 29.4–36.4% of these proteins were identified as being up-regulated in basal-like tumors (**Supplementary Table S3**).

## Modules as Basal Specific Signatures

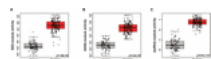
In order to quantitatively assess the activity of each modular in each patient sample, we next generated a gene expression signature on the basis of median expression of each gene in the module. This strategy was used to calculate a module score for each sample in the TCGA (discovery set) and METABRIC (validation set) datasets. We then quantitatively evaluated the differences in the module activities across breast cancer subtypes by an ANOVA test. These analyses demonstrated that EED ( $P = 1.13\text{e-}244$ ), DHX9 ( $P = 2.4\text{e-}236$ ), and AURKA ( $P = 2.05\text{e-}175$ ) activity was highest in basal-like tumors in the TCGA cohort (**Figures 2A–C**); these findings were validated by analysis of module activity in the METABRIC cohort (**Figures 2D–F**). Finally, we determined that the EED ( $P = 1.06\text{e-}96$ ), DHX9 ( $P = 2.44\text{e-}85$ ), and AURKA modules ( $P = 6.61\text{e-}127$ ) were expressed at significantly higher levels in basal-like tumors compared to adjacent normal tissue (**Figures 3A–C**).

FIGURE 2



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**Figure 2.** The pattern of basal like breast cancer specific modules activity across breast cancer subtypes. **(A–C)** EED, DHX9, and AURKA modules are highly activated in basal like tumors by using TCGA cohort-discovery set. **(D–F)** EED, DHX9, and AURKA modules are highly activated in basal like tumors by using METABRIC cohort-validation set.

FIGURE 3



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**Figure 3.** The activity levels of basal like breast cancer specific modules in normal and basal like tumors. **(A)** EED module, **(B)** DHX9 module, **(C)** AURKA module.

## Functionality of Basal Specific Modules

We examined the functional roles of these modules by exploring the correlations with a series of previously published gene expression signatures which are capable of measuring oncogene or tumor suppressor pathway activity, aspects of the tumor microenvironment and other tumor characteristics. We identified pathway activities, which were positively (or negatively) correlated with module activities using a Spearman rank correlation to assess the relationship between pathway activity and the EED, DHX9, or AURKA module activity scores. As expected, our data recapitulated known characteristics of basal-like tumors including low hormone receptor signaling and high expression of proliferation pathway activity and demonstrated the relationship between these characteristics and the expression of each module (i.e., EED, DHX9, and AURKA). Moreover, these modules were associated with multiple indicators of proliferation including, RB\_LOSS, RB\_LOH, and MYB highly correlated

with these module activities as well as RAS, PIK3CA,  $\beta$ -catenin, MYC and HER1\_Cluster 1, HER1\_Cluster 2, and HER1\_Cluster 3 signatures (Figure 4A). Consistent results were obtained using the METABRIC data (Figure 4B). Importantly, we also confirmed the ability of the transcriptomic module signatures to assess the functional roles of EED, DHX9, and AURKA modules by exploring relationships between the module signature scores and protein expression. Analysis of RPPA data from basal-like samples confirmed that these tumors with high module scores have significantly higher levels of CHK1, CHK2, CDK1, Cyclin B1, Cyclin E1, FOXM1, and PCNA protein expression consistent with their role in cell cycle regulation and proliferation (Figure 4C).

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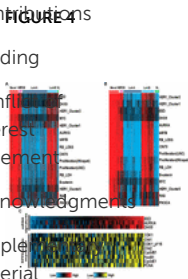
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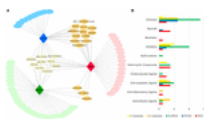
**Figure 4.** The functional analysis of basal like breast cancer specific modules (A) The activity of oncogenic pathways correlated with module activities in TCGA cohort-discovery set. (B) The activity of oncogenic pathways correlated with module activities in METABRIC cohort-validation set. (C) High module activities characterized by high expression of cell cycle proteins.

### Drug Repositioning Based on Basal Subtype Specific Modules

As discussed above, the EED, DHX9, and AURKA modules were converted to gene expression signatures on the basis of up-regulated genes specific to each module; as would be expected down-regulated genes (Fold Change < 0.2) were common for all modules. We asked the question of whether each module/signature identified potential therapeutic opportunities. To do so, we queried each gene signatures separately against the LINCS database L1000CDS2 (Duan et al., 2016) in order to identify concordant and discordant patterns of gene expression between each module and gene expression profiles associates with drug-induced and/or disease expression. Drugs that resulted in a gene expression profile that was negatively correlated with each module were identified and selected as potential candidate compounds that had the potential to reverse the activity of each module network that was associated with basal-like tumors (Supplementary Figure S2). Since we have demonstrated specificity of the modules to basal-like tumors, we may also propose that our candidate drugs are specifically targeting basal-like tumors.

After removing the duplicated drugs from query results, we found that EED and AURKA modules were associated with 41 candidate compounds while DHX9 was associated with 31 candidate small molecules. Networks comprising drug candidates and modules were found to have 114 interaction between three modules and 80 drugs (Figure 5A). The 80 identified drugs were categorized as molecular inhibitors (23%), anti-neoplastic agents (15%), heterocyclic compounds (10%), anti-infective agents (6%), or steroids (6%). Moreover, a number of the drugs specific to each module (as well as some common candidates) were also identified in each drug category (Figure 5B). There are at least 19 approved, 24 investigational, and 6 experimental drugs listed in DrugBank (version 5.1.1), however there are perturbagens used in L1000 platform without detailed information (Supplementary Table S4).

FIGURE 5



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**Figure 5.** Drug repositioning for basal like breast cancer specific modules (A) Module-drug networks (B) Drug categories of module specific drugs and common drugs among modules.

TABLE 2

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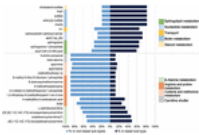
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**Table 2.** Various drug candidates that already associated with breast cancer via different sources.

Nine of the drugs including selumetinib, trametinib, and several other investigational drugs were common to each of the three modules. Consistent with our results, selumetinib as MEK inhibitor was reported to suppresses cell proliferation, migration, and trigger apoptosis, following G1 arrest in TNBC cells (Zhou et al., 2016). Furthermore, the MEK inhibitor, trametinib is also a therapy of significant interest for the treatment of TNBC since TNBC cell lines have been shown to be especially sensitive to this drug (Jing et al., 2012; Davis et al., 2014). Finally, we noted some overlap between drugs associated with each module. For instance, the three common drugs (i.e., wortmannin, mestanolone, NVP-TAE684) are associated with both the EED and AURKA modules while 12 drugs (i.e., radicicol, lapatinib, alvocidib, zileuton, geldanamycin, exemestane) are consistent between the EED and DHX9 module (Supplementary Table S4). Intriguingly, 10 of our candidate drugs were previously associated with the breast cancer based on at least one of the sources including CTD, KEGG Drug, Clinical Trials, and scientific literature (Table 2).

### Essential Metabolites and Anti-metabolites as Drug Candidates

GEMs reconstructed for different cancer tissues have been used for characterization of metabolic modifications; disease stratification and determination of drug targets using essential genes or metabolites (Folger et al., 2011; Agren et al., 2012; Bidkhori et al., 2018). To address this question, we first identified a panel of 917 personalized GEMs derived from breast cancer patients (Uhlen et al., 2017). We then categorized each GEMs based on clinical information to create subtype-specific patient metabolic models. These models were then used to identify subtype-specific metabolites essential for tumor growth. After categorization of BCS, percentage of abundance for each essential metabolite was calculated. Significant alteration between the abundance of basal-like and non-basal BCS were determined based on FDR adjusted P-value threshold ( $P\text{-adj} < 0.05$ ) (Supplementary Table S5). These analyses identified 27 essential metabolites (Supplementary Table S6); 11 were significantly enriched in basal-like tumors while the remaining 16 were enriched in non-basal-like samples. Further analyses determined that the essential metabolites that are expressed at higher levels in basal-like tumors were associated with steroid metabolism, biotin metabolism, nucleotide metabolism, sphingolipid metabolism and transport. Conversely, the identified metabolites down-regulated in basal-like samples were involved in beta-alanine metabolism, arginine and proline metabolism, cysteine and methionine metabolism, and carnitine shuttle (Figure 6).

FIGURE 6



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**Figure 6.** Significant essential metabolite differences between non-basal and basal like breast cancer specific personalized metabolic models and their associated pathways.

### Discussion

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The dynamics of cells are regulated by PPIs and properties of networks such as entropy provide information about the current state of the network. Given that cancer cells are reported to have an increase in network entropy, several previous studies have integrated gene expression data with PPI network information to compute the energetic state of cancer cells by calculating entropy (West et al., 2012; Teschendorff et al., 2015; Rietman et al., 2016). Likewise, a number of studies have used a network-based entropy approach to identify disease specific PPIs as biomarker candidates, proliferative and prognostic markers in lung and breast cancer, as well as to demonstrate the association between network entropy and tumor initiation, progression, and anticancer drug responses (Varadan and Anastassiou, 2006; Xiong et al., 2010; Banerji et al., 2013; Lecca and Re, 2015; Cheng et al., 2016; Ayyildiz et al., 2017).

The current study employed a novel multi-omics-based approach to integrate genomic, proteomic and metabolomic tumor data. Our analyses of mRNA expression data identified three highly connected modules which are centered on the activation of the EED, DHX9, and AURKA signaling networks. These data demonstrated that each module is highly activated in basal-like tumors compared to non-basal-like tumors as well as adjacent normal tissues. Importantly, by analyzing proteome data, our results confirmed the correlation between the expression of genes and proteins that comprise each identified module. By analyzing the association between module expression and oncogenic signaling using a panel of more than 250 gene expression signatures, we were able to assess the functional relationship of these modules with known oncogenic and signaling features. Our results demonstrated the correlation between EED, DHX9, and AURKA module activity and proliferative oncogenic pathways including RAS, PI3K, and Rb/E2F signaling in basal-like tumors. Consistent with these results, CHK1, CHK2, CDK1, Cyclin B1, Cyclin E1, and PCNA protein expression levels were identified higher in tumors with high module scores. Through integrated analyses, we identified candidate drugs to target three modules by drug repositioning. Utilizing multiple omics data including genome, transcriptome, and interactome, we repurposed 519 agents for breast cancer by incorporating data from the LINCS project (Duan et al., 2016) into our analyses. In another drug repositioning study, five of the identified repurposed candidate agents showed superior therapeutic indices compared to doxorubicin in *in vitro* assays in basal sub-type cell line (SUM149) in addition to luminal cell line (MCF7) (Chen et al., 2016). Moreover, Lee et al. (2016) developed an integrative approach for drug repositioning using the expression signature, chemical structure, target signatures and LINCS data. They applied this strategy to identify candidate anti-cancer drugs for breast cancer (Lee et al., 2016). Although there are previous computational drug-repositioning efforts that utilized LINCS as mentioned, the methodologies are focused on breast cancer regardless of disease heterogeneity and subtype information.

In addition, our analyses identified subtype-specific metabolites, including several specific to basal-like tumors, which may provide opportunity to design anti-metabolite drugs for breast cancer. Results in essential metabolite analysis emphasized sphingolipids and steroid metabolism for basal-like breast cancer. Sphingolipid levels in breast cancer tissue are generally higher than normal breast tissue and bioactive sphingolipids, such as sphingosine-1-phosphate (S1P) has many cellular functions like cell proliferation, migration, survival, immune cell trafficking, and angiogenesis which are related to cancer progression and metastasis (Nagahashi et al., 2016). However, sphingosine and S1P were recently highlighted as important for signaling mechanisms in metastatic TNBC and its targeted therapy (Maiti et al., 2017). A recent lipidomics profiling of TNBC tumors also supported sphingolipids as potential prognostic markers and associated enzymes as candidate therapeutic targets (Purwaha et al., 2018) in parallel to our results.

TNBC was associated with expression pattern of 2-pore domain potassium (K2p) channels which enable background leak of potassium (K<sup>+</sup>). Differential expression on K2p-channels may be suggested as a novel molecular marker related to potassium levels in basal like BCS (Dookeran et al., 2017). In another study, expression of calcium-activated potassium (SK4) channels were also associated with TNBC and cellular functions such as proliferation, migration, apoptosis, and EMT processes (Zhang et al., 2016).

Breast cancer is known as one of the malignancies in which steroid hormones drive cellular proliferation (Capper et al., 2017). As steroid metabolism associated metabolite, cholesterol sulfate, is quantitatively the most important known sterol sulfate in human plasma and may play a role in cell adhesion, differentiation and signal transduction (Strott and Higashi, 2003). Given that current standard-of-care therapy for TNBC is largely limited to multi-agent cytotoxic chemotherapy, the potential of incorporating identified repurposed drugs and/or targeting identified modules and/or metabolites represents a potential therapeutic opportunity for a subset of patients with limited treatment options.

Given these data, we would propose that the strategy outlined here can be used to repurposed drugs in order to identify novel candidate compounds or drugs to be utilized in not only monotherapy but also in combination therapy for the treatment of TNBC. Consistent with this argument, a number of the candidate drugs identified by our analyses have been incorporated in ongoing clinical trials. For instance, TNBC patients who received pre-operative sequential epirubicin and cyclophosphamide followed by docetaxel were found to have a significant increase in pathological complete response (PCR) (Warm et al., 2010). Although a great number of pre-clinical trials will be necessary to support the *in silico* modeling detailed in the current study prior to initiation of clinical trials, a large number of identified candidates have significant *in vitro* and *in vivo* support to indicate that these represent potential therapeutic opportunities. For instance, drugs inhibiting cyclin-dependent kinases (CDKs), including the CDK9 inhibitor alvociclib have been reported to be effective against TNBC (Ocana and Pandiella, 2015). Erlotinib also showed anti-tumor effect on TNBC in a xenograft model (Ueno and Zhang, 2011). Likewise, targeting the MET and EGFR receptors, which regulate RAS/ERK and PI3K/AKT signaling, resulted in improved treatment compared to monotherapy (Linklater et al., 2016).

The current study has defined a novel approach to identify breast cancer subtype-specific network modules via a network entropy-based approach. This strategy can be used for both the identification of potentially novel signaling networks but also to identify subtype-specific therapeutic opportunities through drug repositioning. Importantly, we demonstrate that this approach can be used to link signaling networks with and subtype-specific essential metabolites which represents additional therapeutic opportunities. As such, the current studies have the potential enhancing the impact of existing therapeutics or multi-agent therapeutic strategies by identifying novel drug/target networks in the context of breast cancer and in breast cancer subtypes. On a broader scale, this strategy is largely applicable to all cancer and disease type/subtypes where multi-platform genomic, proteomic, and metabolomic data exists and thus represents a potential strategy to define novel signaling networks unique to each disease and identify disease/subtype-specific therapeutic strategies.

## Author Contributions

BT and KK designed the study, performed the all other analyses, and wrote the manuscript. GB performed essential metabolite analysis. MG, RS, AM, MU, and KA supervised the work and contributed to the manuscript during the progress of the work. All authors reviewed and approved the final manuscript.

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## Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary Material

The Supplementary Material for this article can be found online at:

<https://www.frontiersin.org/articles/10.3389/fgene.2019.00420/full#supplementary-material>  
(<https://www.frontiersin.org/articles/10.3389/fgene.2019.00420/full#supplementary-material>)

**FIGURE S1** | Functional enrichment results of the genes involved in each basal-like module using Ingenuity Pathway Analysis (IPA).

Abstract

**FIGURE S2** | The gene signatures of three modules separately on L1000CDS2 for elucidating the differences and similarities between drug-induced expression profiles and disease expression. Drugs were ranked for each module and we elected drugs that showed negatively correlated action mechanisms with the module gene signatures to reverse disease gene expression.

Results

**TABLE S1** | Non-basal and basal-like subtype specific PPI elucidation via differential interactome.

Discussion

**TABLE S2** | Three modules for only in basal-like subtype specific networks.

Author

**TABLE S3** | Statistical values of differential expressed genes and proteins.

Contributions

**TABLE S4** | Information of repurposed module specific and common drug signatures.

Funding

**TABLE S5** | Essential metabolite and personalized model matrix and breast cancer categorization of personalized GEMs.

Conflict of Interest

**TABLE S6** | Significant essential metabolites between non-basal and basal-like breast cancer.

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Supplementary

Material

## Footnotes

Footnotes

References [www.qiagen.com/ingenuity](http://www.qiagen.com/ingenuity) (<http://www.qiagen.com/ingenuity>)

## References

Agren, R., Bordel, S., Mardinoglu, A., Pornputtapong, N., Nookaew, I., and Nielsen, J. (2012). Reconstruction of genome-scale active metabolic networks for 69 human cell types and 16 cancer types using INIT. *PLoS Comput. Biol.* 8:e1002518. doi: 10.1371/journal.pcbi.1002518

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22615553>) | **CrossRef Full Text** (<https://doi.org/10.1371/journal.pcbi.1002518>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Reconstruction+of+genome-scale+active+metabolic+networks+for+69+human+cell+types+and+16+cancer+types+using+INIT%2E&journal=PLoS+Comput%2E+Biol%2E&author=Agren+R.&author=Bordel+S.&author=Mardinoglu+A.&author=Pornputtapong+N.&author=Nookaew+I.&author=and+Nielsen+J.&publication\\_year=2012](http://scholar.google.com/scholar_lookup?&title=Reconstruction+of+genome-scale+active+metabolic+networks+for+69+human+cell+types+and+16+cancer+types+using+INIT%2E&journal=PLoS+Comput%2E+Biol%2E&author=Agren+R.&author=Bordel+S.&author=Mardinoglu+A.&author=Pornputtapong+N.&author=Nookaew+I.&author=and+Nielsen+J.&publication_year=2012))

Ayyildiz, D., Gov, E., Sinha, R., and Arga, K. Y. (2017). Ovarian cancer differential interactome and network entropy analysis reveal new candidate biomarkers. *Omi. A J. Integr. Biol.* 21, 285–294. doi: 10.1089/omi.2017.0010

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28375712>) | **CrossRef Full Text** (<https://doi.org/10.1089/omi.2017.0010>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Ovarian+cancer+differential+interactome+and+network+entropy+analysis+reveal+new+candidate+biomarkers%2E&journal=Omi%2E+A+J%2E+Integr%2E+Biol%2E&author=Ayyildiz+D.&author=Gov+E.&author=Sinha+R.&author=and+Arga+K.+Y.&publication\\_year=2017&volume=21&pages=285-294](http://scholar.google.com/scholar_lookup?&title=Ovarian+cancer+differential+interactome+and+network+entropy+analysis+reveal+new+candidate+biomarkers%2E&journal=Omi%2E+A+J%2E+Integr%2E+Biol%2E&author=Ayyildiz+D.&author=Gov+E.&author=Sinha+R.&author=and+Arga+K.+Y.&publication_year=2017&volume=21&pages=285-294))

Banerji, C. R. S., Miranda-Saavedra, D., Severini, S., Widschwendter, M., Enver, T., Zhou, J. X., et al. (2013). Cellular network entropy as the energy potential in Waddington's differentiation landscape. *Sci. Rep.* 3:3039. doi: 10.1038/srep03039

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24154593>) | **CrossRef Full Text** (<https://doi.org/10.1038/srep03039>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Cellular+network+entropy+as+the+energy+potential+in+Waddington%27s+differentiation+landscape%2E&journal=Sci%2E++Rep%2E&author=Banerji+C.+R.+S.&author=Miranda-Saavedra+D.&author=Severini+S.&author=Widschwendter+M.&author=Enver+T.&author=Zhou+J.+X.&publication\\_year=2013](http://scholar.google.com/scholar_lookup?&title=Cellular+network+entropy+as+the+energy+potential+in+Waddington%27s+differentiation+landscape%2E&journal=Sci%2E++Rep%2E&author=Banerji+C.+R.+S.&author=Miranda-Saavedra+D.&author=Severini+S.&author=Widschwendter+M.&author=Enver+T.&author=Zhou+J.+X.&publication_year=2013))

Bidkhor, G., Benfeitas, R., Elmas, E., Kararoudi, M. N., Arif, M., Uhlen, M., et al. (2018). Metabolic network-based identification and prioritization of anticancer targets based on expression data in hepatocellular carcinoma. *Front. Physiol.* 9:916. doi: 10.3389/fphys.2018.00916

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=30065658>) | **CrossRef Full Text** (<https://doi.org/10.3389/fphys.2018.00916>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Metabolic+network-based+identification+and+prioritization+of+anticancer+targets+based+on+expression+data+in+hepatocellular+carcinoma%2E&journal=Front%2E++Physiol%2E&author=Bidkhor+G.&author=Benfeitas+R.&author=Elmas+E.&author=Kararoudi+M.+N.&author=Arif+M.&author=Uhlen+M.&publication\\_year=2018](http://scholar.google.com/scholar_lookup?&title=Metabolic+network-based+identification+and+prioritization+of+anticancer+targets+based+on+expression+data+in+hepatocellular+carcinoma%2E&journal=Front%2E++Physiol%2E&author=Bidkhor+G.&author=Benfeitas+R.&author=Elmas+E.&author=Kararoudi+M.+N.&author=Arif+M.&author=Uhlen+M.&publication_year=2018))

Campillos, M., Kuhn, M., Gavin, A. C., Jensen, L. J., and Bork, P. (2008). Drug target identification using side-effect similarity. *Science* 321, 263–266. doi: 10.1126/science.1158140

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=18621671>) | **CrossRef Full Text** (<https://doi.org/10.1126/science.1158140>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Drug+target+identification+using+side-effect+similarity%2E&journal=Science&author=Campillos+M.&author=Kuhn+M.&author=Gavin+A.+C.&author=Jensen+L.+J.&author=and+Bork+P.&publication\\_year=2008&volume=321&pages=263-266](http://scholar.google.com/scholar_lookup?&title=Drug+target+identification+using+side-effect+similarity%2E&journal=Science&author=Campillos+M.&author=Kuhn+M.&author=Gavin+A.+C.&author=Jensen+L.+J.&author=and+Bork+P.&publication_year=2008&volume=321&pages=263-266))

Capper, C. P., Rae, J. M., and Auchus, R. J. (2017). The metabolism, analysis, and targeting of steroid hormones in breast and prostate cancer. *Horm Cancer* 7, 149–164. doi: 10.1007/s12672-016-0259-0

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26969590>) | **CrossRef Full Text** (<https://doi.org/10.1007/s12672-016-0259-0>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=The+metabolism%2C+analysis%2C+and+targeting+of+steroid+hormones+in+breast+and+prostate+cancer%2E&journal=Horm+Cancer&author=Capper+C.+P.&author=Rae+J.+M.&author=and+Auchus+R.+J.&publication\\_year=2017&volume=7&pages=149-164](http://scholar.google.com/scholar_lookup?&title=The+metabolism%2C+analysis%2C+and+targeting+of+steroid+hormones+in+breast+and+prostate+cancer%2E&journal=Horm+Cancer&author=Capper+C.+P.&author=Rae+J.+M.&author=and+Auchus+R.+J.&publication_year=2017&volume=7&pages=149-164))

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CLOSE



Catania, C., De Pas, T. M., Pelosi, G., Manzotti, M., Adamoli, L., Nolè, F., et al. (2006). Erlotinib-induced breast cancer regression. *Ann. Pharmacother.* 40, 2043–2047. doi: 10.1345/aph.1H252

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17062833>) | **CrossRef Full Text** (<https://doi.org/10.1345/aph.1H252>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Erlotinib-induced+breast+cancer+regression%2E&journal=Ann%2E+Pharmacother%2E&author=Catania+C.&author=De+Pas+T.+M.&author=Pelosi+G.&author=Manzotti+M.&author=Adamoli+L.&author=Nolè+F.&publication\\_year=2006&volume=40&pages=2043-2047](http://scholar.google.com/scholar_lookup?&title=Erlotinib-induced+breast+cancer+regression%2E&journal=Ann%2E+Pharmacother%2E&author=Catania+C.&author=De+Pas+T.+M.&author=Pelosi+G.&author=Manzotti+M.&author=Adamoli+L.&author=Nolè+F.&publication_year=2006&volume=40&pages=2043-2047))

**Materials and Methods**  
Chatr-Aryamontri, A., Breitkreutz, B. J., Oughtred, R., Boucher, L., Heinicke, S., Chen, D., et al. (2015). The BioGRID interaction database: 2015 update. *Nucleic Acids Res.* 43, D470–D478. doi: 10.1093/nar/gku1204

**Results**  
**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=25428363>) | **CrossRef Full Text** (<https://doi.org/10.1093/nar/gku1204>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=The+BioGRID+interaction+database%3A+2015+update%2E&journal=Nucleic+Acids+Res%2E&author=Chatr-Aryamontri+A.&author=Breitkreutz+B.+J.&author=Oughtred+R.&author=Boucher+L.&author=Heinicke+S.&author=Chen+D.&publication\\_year=2015&volume=43&pages=D470-D478](http://scholar.google.com/scholar_lookup?&title=The+BioGRID+interaction+database%3A+2015+update%2E&journal=Nucleic+Acids+Res%2E&author=Chatr-Aryamontri+A.&author=Breitkreutz+B.+J.&author=Oughtred+R.&author=Boucher+L.&author=Heinicke+S.&author=Chen+D.&publication_year=2015&volume=43&pages=D470-D478))

**Funding**  
Chen, H.-R., Sherr, D. H., Hu, Z., DeLisi, C., Jin, G., Fu, C., et al. (2016). A network based approach to drug repositioning identifies plausible candidates for breast cancer and prostate cancer. *J. Natl. Compr. Canc. Netw.* 8, 1–21. doi: 10.1186/s12920-016-0212-7

**Conflict of Interest**  
**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27475327>) | **CrossRef Full Text** (<https://doi.org/10.1186/s12920-016-0212-7>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=A+network+based+approach+to+drug+repositioning+identifies+plausible+candidates+for+breast+cancer+and+prostate+cancer%2E&journal=J%2E+Natl%2E+Compr%2E+Canc%2E+Netw%2E&author=Chen+H.-R.&author=Sherr+D.+H.&author=Hu+Z.&author=DeLisi+C.&author=Jin+G.&author=Fu+C.&publication\\_year=2016&volume=8&pages=1-21](http://scholar.google.com/scholar_lookup?&title=A+network+based+approach+to+drug+repositioning+identifies+plausible+candidates+for+breast+cancer+and+prostate+cancer%2E&journal=J%2E+Natl%2E+Compr%2E+Canc%2E+Netw%2E&author=Chen+H.-R.&author=Sherr+D.+H.&author=Hu+Z.&author=DeLisi+C.&author=Jin+G.&author=Fu+C.&publication_year=2016&volume=8&pages=1-21))

**Supplementary Material**  
Cheng, F., Liu, C., Shen, B., and Zhao, Z. (2016). Investigating cellular network heterogeneity and modularity in cancer: a network entropy and unbalanced motif approach. *BMC Syst. Biol.* 10:65. doi: 10.1186/s12918-016-0309-9

**Supplementary Material**  
**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27585651>) | **CrossRef Full Text** (<https://doi.org/10.1186/s12918-016-0309-9>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Investigating+cellular+network+heterogeneity+and+modularity+in+cancer%3A+a+network+entropy+and+unbalanced+motif+approach%2E&journal=BMC+Syst%2E+Biol%2E&author=Cheng+F.&author=Liu+C.&author=Shen+B.&author=and+Zhao+Z.&publication\\_year=2016](http://scholar.google.com/scholar_lookup?&title=Investigating+cellular+network+heterogeneity+and+modularity+in+cancer%3A+a+network+entropy+and+unbalanced+motif+approach%2E&journal=BMC+Syst%2E+Biol%2E&author=Cheng+F.&author=Liu+C.&author=Shen+B.&author=and+Zhao+Z.&publication_year=2016))

Ciriello, G., Gatz, M. L., Beck, A. H., Wilkerson, M. D., Rhie, S. K., Pastore, A., et al. (2015). Comprehensive molecular portraits of invasive lobular breast cancer. *Cell* 163, 506–519. doi: 10.1016/j.cell.2015.09.033

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26451490>) | **CrossRef Full Text** (<https://doi.org/10.1016/j.cell.2015.09.033>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Comprehensive+molecular+portraits+of+invasive+lobular+breast+cancer%2E&journal=Cell&author=Ciriello+G.&author=Gatz+M.+L.&author=Beck+A.+H.&author=Wilkerson+M.+D.&author=Rhie+S.+K.&author=Pastore+A.&publication\\_year=2015&volume=163&pages=506-519](http://scholar.google.com/scholar_lookup?&title=Comprehensive+molecular+portraits+of+invasive+lobular+breast+cancer%2E&journal=Cell&author=Ciriello+G.&author=Gatz+M.+L.&author=Beck+A.+H.&author=Wilkerson+M.+D.&author=Rhie+S.+K.&author=Pastore+A.&publication_year=2015&volume=163&pages=506-519))

Coombes, R. C., Perez, D., Gazet, J.-C., Ford, H. T., and Powles, T. J. (1983). Danazol treatment for advanced breast cancer. *Cancer Chemother. Pharmacol.* 10, 194–195. doi: 10.1007/BF00255761

**CrossRef Full Text** (<https://doi.org/10.1007/BF00255761>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Danazol+treatment+for+advanced+breast+cancer%2E&journal=Cancer+Chemother%2E+Pharmacol%2E&author=Coombes+R.+C.&author=Perez+D.&author=Gazet+J.-C.&author=Ford+H.+T.&author=and+Powles+T.+J.&publication\\_year=1983&volume=10&pages=194-195](http://scholar.google.com/scholar_lookup?&title=Danazol+treatment+for+advanced+breast+cancer%2E&journal=Cancer+Chemother%2E+Pharmacol%2E&author=Coombes+R.+C.&author=Perez+D.&author=Gazet+J.-C.&author=Ford+H.+T.&author=and+Powles+T.+J.&publication_year=1983&volume=10&pages=194-195))

Curtis, C., Shah, S. P., Chin, S. F., Turashvili, G., Rueda, O. M., Dunning, M. J., et al. (2012). The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. *Nature* 486, 346–352. doi: 10.1038/nature10983

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22522925>) | **CrossRef Full Text** (<https://doi.org/10.1038/nature10983>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=The+genomic+and+transcriptomic+architecture+of+2%2C000+breast+tumours+reveals+novel+subgroups%2E&journal=Nature&author=Curtis+C.&author=Shah+S.+P.&author=Chin+S.+F.&author=Turashvili+G.&author=Rueda+O.+M.&author=Dunning+M.+J.&publication\\_year=2012&volume=486&pages=346-352](http://scholar.google.com/scholar_lookup?&title=The+genomic+and+transcriptomic+architecture+of+2%2C000+breast+tumours+reveals+novel+subgroups%2E&journal=Nature&author=Curtis+C.&author=Shah+S.+P.&author=Chin+S.+F.&author=Turashvili+G.&author=Rueda+O.+M.&author=Dunning+M.+J.&publication_year=2012&volume=486&pages=346-352))

Davis, A. P., Grondin, C. J., Johnson, R. J., Sciaky, D., King, B. L., McMorran, R., et al. (2017). The comparative toxicogenomics database: update 2017. *Nucleic Acids Res.* 45, D972–D978. doi: 10.1093/nar/gkw838

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27651457>) | **CrossRef Full Text** (<https://doi.org/10.1093/nar/gkw838>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=The+comparative+toxicogenomics+database%3A+update+2017%2E&journal=Nucleic+Acids+Res%2E&author=Davis+A.+P.&author=Grondin+C.+J.&author=Johnson+R.+J.&author=Sciaky+D.&author=King+B.+L.&author=McMorran+R.&publication\\_year=2017&volume=45&pages=D972-D978](http://scholar.google.com/scholar_lookup?&title=The+comparative+toxicogenomics+database%3A+update+2017%2E&journal=Nucleic+Acids+Res%2E&author=Davis+A.+P.&author=Grondin+C.+J.&author=Johnson+R.+J.&author=Sciaky+D.&author=King+B.+L.&author=McMorran+R.&publication_year=2017&volume=45&pages=D972-D978))

Davis, S. L., Eckhardt, S. G., Tentler, J. J., and Diamond, J. R. (2014). Triple-negative breast cancer: bridging the gap from cancer genomics to predictive biomarkers. *Ther. Adv. Med. Oncol.* 6, 88–100. doi: 10.1177/1758834013519843

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24790649>) | **CrossRef Full Text** (<https://doi.org/10.1177/1758834013519843>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Triple-negative+breast+cancer%3A+bridging+the+gap+from+cancer+genomics+to+predictive+biomarkers%2E&journal=Ther%2E+Adv%2E+Med%2E+Oncol%2E&author=Davis+S.+L.&author=Eckhardt+S.+G.&author=Tentler+J.+J.&author=and+Diamond+J.+R.&publication\\_year=2014&volume=6&pages=88-100](http://scholar.google.com/scholar_lookup?&title=Triple-negative+breast+cancer%3A+bridging+the+gap+from+cancer+genomics+to+predictive+biomarkers%2E&journal=Ther%2E+Adv%2E+Med%2E+Oncol%2E&author=Davis+S.+L.&author=Eckhardt+S.+G.&author=Tentler+J.+J.&author=and+Diamond+J.+R.&publication_year=2014&volume=6&pages=88-100))

Dookeran, K. A., Zhang, W., Stayner, L., and Argos, M. (2017). Associations of two-pore domain potassium channels and triple negative breast cancer subtype in the cancer genome atlas: systematic evaluation of gene expression and methylation. *BMC Res. Notes* 10:475. doi: 10.1186/s13104-017-2777-2774

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28899398>) | **CrossRef Full Text** (<https://doi.org/10.1186/s13104-017-2777-2774>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Associations+of+two-pore+domain+potassium+channels+and+triple-negative+breast+cancer+subtype+in+the+cancer+genome+atlas%3A+systematic+evaluation+of+gene+expression+and+methylation%2E&journal=BMC+Res%2E+Notes&author=Dookeran+K.+A.&author=Zhang+W.&author=Stayner+L.&author=and+Argos+M.&publication\\_year=2017](http://scholar.google.com/scholar_lookup?&title=Associations+of+two-pore+domain+potassium+channels+and+triple-negative+breast+cancer+subtype+in+the+cancer+genome+atlas%3A+systematic+evaluation+of+gene+expression+and+methylation%2E&journal=BMC+Res%2E+Notes&author=Dookeran+K.+A.&author=Zhang+W.&author=Stayner+L.&author=and+Argos+M.&publication_year=2017))

Duan, Q., Reid, S. P., Clark, N. R., Wang, Z., Fernandez, N. F., Rouillard, A. D., et al. (2016). L1000CDS2: LINCS L1000 characteristic direction signatures search engine. *NPJ Syst. Biol. Appl.* 2:16015. doi: 10.1038/npjsba.2016.15



**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28413689>) | **CrossRef Full Text** (<https://doi.org/10.1038/npjbsa.2016.15>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=L1000CDS2%3A+LINCS+L1000+characteristic+direction+signatures+search+engine%2E&journal=NPJ+Syst%2E+Bio%2E+Appl%2E&author=Duan+Q.&author=Reid+S.+P.&author=Clark+N.+R.&author=Wang+Z.&author=Fernandez+N.+F.&author=Rouillard+A.+D.&publication\\_year=2016](http://scholar.google.com/scholar_lookup?&title=L1000CDS2%3A+LINCS+L1000+characteristic+direction+signatures+search+engine%2E&journal=NPJ+Syst%2E+Bio%2E+Appl%2E&author=Duan+Q.&author=Reid+S.+P.&author=Clark+N.+R.&author=Wang+Z.&author=Fernandez+N.+F.&author=Rouillard+A.+D.&publication_year=2016))

**Introduction**

Finn, R. S., Martin, M., Rugo, H. S., Jones, S., Im, S.-A., Gelmon, K., et al. (2016). Palbociclib and letrozole in advanced breast cancer. *N. Engl. J. Med.* 375, 1925–1936. doi: 10.1056/NEJMoai607303

**Materials and methods**

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27959613>) | **CrossRef Full Text** (<https://doi.org/10.1056/NEJMoai607303>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Palbociclib+and+letrozole+in+advanced+breast+cancer%2E&journal=N%2E+Engl%2E+J%2E+Med%2E&author=Finn+R.+S.&author=Martin+M.&author=Rugo+H.+S.&author=Jones+S.&author=Im+S.-A.&author=Gelmon+K.&publication\\_year=2016&volume=375&pages=1925-1936](http://scholar.google.com/scholar_lookup?&title=Palbociclib+and+letrozole+in+advanced+breast+cancer%2E&journal=N%2E+Engl%2E+J%2E+Med%2E&author=Finn+R.+S.&author=Martin+M.&author=Rugo+H.+S.&author=Jones+S.&author=Im+S.-A.&author=Gelmon+K.&publication_year=2016&volume=375&pages=1925-1936))

**Author**

Folger, O., Jerby, L., Frezza, C., Gottlieb, E., Rupp, E., and Shlomi, T. (2011). Predicting selective drug targets in cancer through metabolic networks. *Mol. Syst. Biol.* 7, 1–10. doi: 10.1038/msb.2011.35

**Funding**

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=21694718>) | **CrossRef Full Text** (<https://doi.org/10.1038/msb.2011.35>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Predicting+selective+drug+targets+in+cancer+through+metabolic+networks%2E&journal=Mol%2E+Syst%2E+Bio%2E&author=Folger+O.&author=Jerby+L.&author=Frezza+C.&author=Gottlieb+E.&author=Rupp+E.&author=and+Shlomi+T.&publication\\_year=2011&volume=7&pages=1-10](http://scholar.google.com/scholar_lookup?&title=Predicting+selective+drug+targets+in+cancer+through+metabolic+networks%2E&journal=Mol%2E+Syst%2E+Bio%2E&author=Folger+O.&author=Jerby+L.&author=Frezza+C.&author=Gottlieb+E.&author=Rupp+E.&author=and+Shlomi+T.&publication_year=2011&volume=7&pages=1-10))

**Acknowledgments**

Gómez-Pozo, A., Trilla-Fuertes, L., Berges-Soria, J., Selevsek, N., López-Vacas, R., Díaz-Almirón, M., et al. (2017). Functional proteomics outlines the complexity of breast cancer molecular subtypes. *Sci. Rep.* 7:10100. doi: 10.1038/s41598-017-10493-w

**Supplementary Material** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28855612>) | **CrossRef Full Text** (<https://doi.org/10.1038/s41598-017-10493-w>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Functional+proteomics+outlines+the+complexity+of+breast+cancer+molecular+subtypes%2E&journal=Sci%2E+Rep%2E&author=Gómez-Pozo+A.&author=Trilla-Fuertes+L.&author=Berges-Soria+J.&author=Selevsek+N.&author=López-Vacas+R.&author=Díaz-Almirón+M.&publication\\_year=2017](http://scholar.google.com/scholar_lookup?&title=Functional+proteomics+outlines+the+complexity+of+breast+cancer+molecular+subtypes%2E&journal=Sci%2E+Rep%2E&author=Gómez-Pozo+A.&author=Trilla-Fuertes+L.&author=Berges-Soria+J.&author=Selevsek+N.&author=López-Vacas+R.&author=Díaz-Almirón+M.&publication_year=2017))

Gatza, M. L., Silva, G. O., Parker, J. S., Fan, C., and Perou, C. M. (2014). An integrated genomics approach identifies drivers of proliferation in luminal-subtype human breast cancer. *Nat. Genet.* 46, 1051–1059. doi: 10.1038/ng.3073

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=25151356>) | **CrossRef Full Text** (<https://doi.org/10.1038/ng.3073>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=An+integrated+genomics+approach+identifies+drivers+of+proliferation+in+luminal-subtype+human+breast+cancer%2E&journal=Nat%2E+Genet%2E&author=Gatza+M.+L.&author=Silva+G.+O.&author=Parker+J.+S.&author=Fan+C.&author=and+Perou+C.+M.&publication\\_year=2014&volume=46&pages=1051-1059](http://scholar.google.com/scholar_lookup?&title=An+integrated+genomics+approach+identifies+drivers+of+proliferation+in+luminal-subtype+human+breast+cancer%2E&journal=Nat%2E+Genet%2E&author=Gatza+M.+L.&author=Silva+G.+O.&author=Parker+J.+S.&author=Fan+C.&author=and+Perou+C.+M.&publication_year=2014&volume=46&pages=1051-1059))

Giampaglia, M., Chiuri, V. E., Tinelli, A., De Laurentiis, M., Silvestris, N., and Lorusso, V. (2010). Lapatinib in breast cancer: clinical experiences and future perspectives. *Cancer Treat. Rev.* 36(Suppl. 3), S72–S79. doi: 10.1016/S0305-7372(10)70024-4

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=21129615>) | **CrossRef Full Text** ([https://doi.org/10.1016/S0305-7372\(10\)70024-4](https://doi.org/10.1016/S0305-7372(10)70024-4)) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Lapatinib+in+breast+cancer%3A+clinical+experiences+and+future+perspectives%2E&journal=Cancer+Treat%2E+Rev%2E&author=Giampaglia+M.&author=Chiuri+V.+E.&author=Tinelli+A.&author=De+Laurentiis+M.&author=Silvestris+N.&author=and+Lorusso+V.&publication\\_year=2010&pages=S72-S79](http://scholar.google.com/scholar_lookup?&title=Lapatinib+in+breast+cancer%3A+clinical+experiences+and+future+perspectives%2E&journal=Cancer+Treat%2E+Rev%2E&author=Giampaglia+M.&author=Chiuri+V.+E.&author=Tinelli+A.&author=De+Laurentiis+M.&author=Silvestris+N.&author=and+Lorusso+V.&publication_year=2010&pages=S72-S79))

Goss, P. E., Ingle, J. N., Pritchard, K. I., Ellis, M. J., Sledge, G. W., Budd, G. T., et al. (2013). Exemestane versus anastrozole in postmenopausal women with early breast cancer: NCIC CTG MA.27 - A randomized controlled phase III trial. *J. Clin. Oncol.* 31, 1398–1404. doi: 10.1200/JCO.2012.44.7805

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23358971>) | **CrossRef Full Text** (<https://doi.org/10.1200/JCO.2012.44.7805>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Exemestane+versus+anastrozole+in+postmenopausal+women+with+early+breast+cancer%3A+NCIC+CTG+MA%2E27+-+A+randomized+controlled+phase+III+trial%2E&journal=J%2E+Clin%2E+Oncol%2E&author=Goss+P.+E.&author=Ingle+J.+N.&author=Pritchard+K.+I.&author=Ellis+M.+J.&author=Sledge+G.+W.&author=Budd+G.+T.&publication\\_year=2013&volume=31&pages=1398-1404](http://scholar.google.com/scholar_lookup?&title=Exemestane+versus+anastrozole+in+postmenopausal+women+with+early+breast+cancer%3A+NCIC+CTG+MA%2E27+-+A+randomized+controlled+phase+III+trial%2E&journal=J%2E+Clin%2E+Oncol%2E&author=Goss+P.+E.&author=Ingle+J.+N.&author=Pritchard+K.+I.&author=Ellis+M.+J.&author=Sledge+G.+W.&author=Budd+G.+T.&publication_year=2013&volume=31&pages=1398-1404))

Gschwanter-Kaulich, D., Grunt, T. W., Muhr, D., Wagner, R., Kölbl, H., and Singer, C. F. (2016). HER specific TKIs exert their antineoplastic effects on breast cancer cell lines through the involvement of STAT5 and JNK. *PLoS One* 11:e0146311. doi: 10.1371/journal.pone.0146311

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26735495>) | **CrossRef Full Text** (<https://doi.org/10.1371/journal.pone.0146311>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=HER+specific+TKIs+exert+their+antineoplastic+effects+on+breast+cancer+cell+lines+through+the+involvement+of+STAT5+and+JNK%2E&journal=PLoS+One&author=Gschwanter-Kaulich+D.&author=Grunt+T.+W.&author=Muhr+D.&author=Wagner+R.&author=Kölbl+H.&author=and+Singer+C.+F.&publication\\_year=2016](http://scholar.google.com/scholar_lookup?&title=HER+specific+TKIs+exert+their+antineoplastic+effects+on+breast+cancer+cell+lines+through+the+involvement+of+STAT5+and+JNK%2E&journal=PLoS+One&author=Gschwanter-Kaulich+D.&author=Grunt+T.+W.&author=Muhr+D.&author=Wagner+R.&author=Kölbl+H.&author=and+Singer+C.+F.&publication_year=2016))

Hu, J., Ye, F., Cui, M., Lee, P., Wei, C., Hao, Y., et al. (2016). Protein profiling of bladder urothelial cell carcinoma. *PLoS One* 11:e0161922. doi: 10.1371/journal.pone.0161922

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27626805>) | **CrossRef Full Text** (<https://doi.org/10.1371/journal.pone.0161922>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Protein+profiling+of+bladder+urothelial+cell+carcinoma%2E&journal=PLoS+One&author=Hu+J.&author=Ye+F.&author=Cui+M.&author=Lee+P.&author=Wei+C.&author=Hao+Y.&publication\\_year=2016](http://scholar.google.com/scholar_lookup?&title=Protein+profiling+of+bladder+urothelial+cell+carcinoma%2E&journal=PLoS+One&author=Hu+J.&author=Ye+F.&author=Cui+M.&author=Lee+P.&author=Wei+C.&author=Hao+Y.&publication_year=2016))

Jing, J., Greshock, J., Holbrook, J. D., Gilmartin, A., Zhang, X., McNeil, E., et al. (2012). Comprehensive predictive biomarker analysis for MEK inhibitor GSK1120212. *Mol. Cancer Ther.* 11, 720–729. doi: 10.1158/1535-7163.MCT-11-0505

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22169769>) | **CrossRef Full Text** (<https://doi.org/10.1158/1535-7163.MCT-11-0505>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Comprehensive+predictive+biomarker+analysis+for+MEK+inhibitor+GSK1120212%2E&journal=Mol%2E+Cancer+Ther%2E&author=Jing+J.&author=Greshock+J.&author=Holbrook+J.+D.&author=Gilmartin+A.&author=Zhang+X.&author=McNeil+E.&publication\\_year=2012&volume=11&pages=720-729](http://scholar.google.com/scholar_lookup?&title=Comprehensive+predictive+biomarker+analysis+for+MEK+inhibitor+GSK1120212%2E&journal=Mol%2E+Cancer+Ther%2E&author=Jing+J.&author=Greshock+J.&author=Holbrook+J.+D.&author=Gilmartin+A.&author=Zhang+X.&author=McNeil+E.&publication_year=2012&volume=11&pages=720-729))

Kanehisa, M., Goto, S., Sato, Y., Furumichi, M., and Tanabe, M. (2012). KEGG for integration and interpretation of large-scale molecular data sets. *Nucleic Acids Res.* 40, 109–114. doi: 10.1093/nar/gkr988

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22080510>) | **CrossRef Full Text** (<https://doi.org/10.1093/nar/gkr988>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=KEGG+for+integration+and+interpretation+of+large-scale+molecular+data+sets%2E&journal=Nucleic+Acids+Res%2E&author=Kanehisa+M.&author=Goto+S.&author=Sato+Y.&author=Furumichi+M.&author=and+Tanabe+M.&publication\\_year=2012&volume=40&pages=109-114](http://scholar.google.com/scholar_lookup?&title=KEGG+for+integration+and+interpretation+of+large-scale+molecular+data+sets%2E&journal=Nucleic+Acids+Res%2E&author=Kanehisa+M.&author=Goto+S.&author=Sato+Y.&author=Furumichi+M.&author=and+Tanabe+M.&publication_year=2012&volume=40&pages=109-114))

Introduction  
Karagoz, K., Sevimoglu, T., and Arga, K. Y. (2016). Integration of multiple biological features yields high confidence human protein interactome. *J. Proteome Res.* 15, 403–414. doi: 10.1021/acs.jproteome.5b01020

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27196966>) | **CrossRef Full Text** (<https://doi.org/10.1016/j.jtbi.2016.05.020>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Integration+of+multiple+biological+features+yields+high+confidence+human+protein+interactome%2E&journal=J%2E+Theor%2E++Biomed+Sci%2E&author=Karagoz+K.&author=Sevimoglu+T.&author=and+Arga+K.+Y.&publication\\_year=2016&volume=403&pages=85-96](http://scholar.google.com/scholar_lookup?&title=Integration+of+multiple+biological+features+yields+high+confidence+human+protein+interactome%2E&journal=J%2E+Theor%2E++Biomed+Sci%2E&author=Karagoz+K.&author=Sevimoglu+T.&author=and+Arga+K.+Y.&publication_year=2016&volume=403&pages=85-96))

Karagoz, K., Sinha, R., and Arga, K. Y. (2015). Triple negative breast cancer: a multi-omics network discovery strategy for candidate targets and driving pathways. *OMICS* 19, 115–130. doi: 10.1089/omi.2014.0135

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=25611337>) | **CrossRef Full Text** (<https://doi.org/10.1089/omi.2014.0135>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Triple+negative+breast+cancer%3A+a+multi-omics+network+discovery+strategy+for+candidate+targets+and+driving+pathways%2E&journal=OMICS&author=Karagoz+K.&author=Sinha+R.&author=and+Arga+K.+Y.&publication\\_year=2015&volume=19&pages=115-130](http://scholar.google.com/scholar_lookup?&title=Triple+negative+breast+cancer%3A+a+multi-omics+network+discovery+strategy+for+candidate+targets+and+driving+pathways%2E&journal=OMICS&author=Karagoz+K.&author=Sinha+R.&author=and+Arga+K.+Y.&publication_year=2015&volume=19&pages=115-130))

Kibble, M., Saarinen, N., Tang, J., Wennerberg, K., Mäkelä, S., and Aittokallio, T. (2015). Network pharmacology applications to map the unexplored target space and therapeutic potential of natural products. *Nat. Prod. Rep.* 32, 1249–1266. doi: 10.1039/c5np00005j

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26030402>) | **CrossRef Full Text** (<https://doi.org/10.1039/c5np00005j>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Network+pharmacology+applications+to+map+the+unexplored+target+space+and+therapeutic+potential+of+natural+products%2E&journal=Nat%2E++Prod%2E+Rep%2E&author=Kibble+M.&author=Saarinen+N.&author=Tang+J.&author=Wennerberg+K.&author=Mäkelä+S.&author=and+Aittokallio+T.&publication\\_year=2015&volume=32&pages=1249-1266](http://scholar.google.com/scholar_lookup?&title=Network+pharmacology+applications+to+map+the+unexplored+target+space+and+therapeutic+potential+of+natural+products%2E&journal=Nat%2E++Prod%2E+Rep%2E&author=Kibble+M.&author=Saarinen+N.&author=Tang+J.&author=Wennerberg+K.&author=Mäkelä+S.&author=and+Aittokallio+T.&publication_year=2015&volume=32&pages=1249-1266))

Lecca, P., and Re, A. (2015). Detecting modules in biological networks by edge weight clustering and entropy significance. *Front. Genet.* 6:265. doi: 10.3389/fgene.2015.00265

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26379697>) | **CrossRef Full Text** (<https://doi.org/10.3389/fgene.2015.00265>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Detecting+modules+in+biological+networks+by+edge+weight+clustering+and+entropy+significance%2E&journal=Front%2E+Genet%2E&author=Lecca+P.&author=and+Re+A.&publication\\_year=2015](http://scholar.google.com/scholar_lookup?&title=Detecting+modules+in+biological+networks+by+edge+weight+clustering+and+entropy+significance%2E&journal=Front%2E+Genet%2E&author=Lecca+P.&author=and+Re+A.&publication_year=2015))

Lee, H., Kang, S., and Kim, W. (2016). Drug repositioning for cancer therapy based on large-scale drug-induced transcriptional signatures. *PLoS One* 11:e0150460. doi: 10.1371/journal.pone.0150460

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26954019>) | **CrossRef Full Text** (<https://doi.org/10.1371/journal.pone.0150460>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Drug+repositioning+for+cancer+therapy+based+on+large-scale+drug-induced+transcriptional+signatures%2E&journal=PLoS+One&author=Lee+H.&author=Kang+S.&author=and+Kim+W.&publication\\_year=2016](http://scholar.google.com/scholar_lookup?&title=Drug+repositioning+for+cancer+therapy+based+on+large-scale+drug-induced+transcriptional+signatures%2E&journal=PLoS+One&author=Lee+H.&author=Kang+S.&author=and+Kim+W.&publication_year=2016))

Li, C., Luo, L., Wei, S., and Wang, X. (2018). Identification of the potential crucial genes in invasive ductal carcinoma using bioinformatics analysis. *Oncotarget* 9, 6800–6813. doi: 10.18632/oncotarget.23239

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=29467930>) | **CrossRef Full Text** (<https://doi.org/10.18632/oncotarget.23239>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Identification+of+the+potential+crucial+genes+in+invasive+ductal+carcinoma+using+bioinformatics+analysis%2E&journal=Oncotarget&author=Li+C.&author=Luo+L.&author=Wei+S.&author=and+Wang+X.&publication\\_year=2018&volume=9&pages=6800-6813](http://scholar.google.com/scholar_lookup?&title=Identification+of+the+potential+crucial+genes+in+invasive+ductal+carcinoma+using+bioinformatics+analysis%2E&journal=Oncotarget&author=Li+C.&author=Luo+L.&author=Wei+S.&author=and+Wang+X.&publication_year=2018&volume=9&pages=6800-6813))

Li, J., Li, F., Wang, H., Wang, X., Jiang, Y., and Li, D. (2012). Wortmannin reduces metastasis and angiogenesis of human breast cancer cells via nuclear factor- $\kappa$ B-dependent matrix metalloproteinase-9 and interleukin-8 pathways. *J. Int. Med. Res.* 40, 867–876. doi: 10.1177/147323001204000305

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22906259>) | **CrossRef Full Text** (<https://doi.org/10.1177/147323001204000305>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Wortmannin+reduces+metastasis+and+angiogenesis+of+human+breast+cancer+cells+via+nuclear+factor-kB-dependent+matrix+metalloproteinase-9+and+interleukin-8+pathways%2E&journal=J%2E+Int%2E+Med%2E+Res%2E&author=Li+J.&author=Li+F.&author=Wang+H.&author=Wang+X.&author=Jiang+Y.&author=and+Li+D.&publication\\_year=2012&volume=40&pages=867-876](http://scholar.google.com/scholar_lookup?&title=Wortmannin+reduces+metastasis+and+angiogenesis+of+human+breast+cancer+cells+via+nuclear+factor-kB-dependent+matrix+metalloproteinase-9+and+interleukin-8+pathways%2E&journal=J%2E+Int%2E+Med%2E+Res%2E&author=Li+J.&author=Li+F.&author=Wang+H.&author=Wang+X.&author=Jiang+Y.&author=and+Li+D.&publication_year=2012&volume=40&pages=867-876))

Linklater, E. S., Tovar, E. A., Essenburg, C. J., Turner, L., Madaj, Z., Winn, M. E., et al. (2016). Targeting MET and EGFR crosstalk signaling in triple-negative breast cancers. *Oncotarget* 7, 69903–69915. doi: 10.18632/oncotarget.12065

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27655711>) | **CrossRef Full Text** (<https://doi.org/10.18632/oncotarget.12065>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Targeting+MET+and+EGFR+crosstalk+signaling+in+triple-negative+breast+cancers%2E&journal=Oncotarget&author=Linklater+E.+S.&author=Tovar+E.+A.&author=Essenburg+C.+J.&author=Turner+L.&author=Madaj+Z.&author=Winn+M.+E.&publication\\_year=2016&volume=7&pages=69903-69915](http://scholar.google.com/scholar_lookup?&title=Targeting+MET+and+EGFR+crosstalk+signaling+in+triple-negative+breast+cancers%2E&journal=Oncotarget&author=Linklater+E.+S.&author=Tovar+E.+A.&author=Essenburg+C.+J.&author=Turner+L.&author=Madaj+Z.&author=Winn+M.+E.&publication_year=2016&volume=7&pages=69903-69915))

Liu, Y., Yin, X., Zhong, J., Guan, N., Luo, Z., Min, L., et al. (2017). Systematic identification and assessment of therapeutic targets for breast cancer based on genome-wide RNA interference transcriptomes. *Genes* 8:E86. doi: 10.3390/genes8030086

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28245581>) | **CrossRef Full Text** (<https://doi.org/10.3390/genes8030086>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Systematic+identification+and+assessment+of+therapeutic+targets+for+breast+cancer+based+on+genome-wide+RNA+interference+transcriptomes%2E&journal=Genes&author=Liu+Y.&author=Yin+X.&author=Zhong+J.&author=Guan+N.&author=Luo+Z.&author=Min+L.&publication\\_year=2017](http://scholar.google.com/scholar_lookup?&title=Systematic+identification+and+assessment+of+therapeutic+targets+for+breast+cancer+based+on+genome-wide+RNA+interference+transcriptomes%2E&journal=Genes&author=Liu+Y.&author=Yin+X.&author=Zhong+J.&author=Guan+N.&author=Luo+Z.&author=Min+L.&publication_year=2017))

Lopes, C. T., Franz, M., Kazi, F., Donaldson, S. L., Morris, Q., Bader, G. D., et al. (2011). Cytoscape web: an interactive web-based network browser. *Bioinformatics* 26, 2347–2348. doi: 10.1093/bioinformatics/btq430

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20656902>) | **CrossRef Full Text** (<https://doi.org/10.1093/bioinformatics/btq430>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Cytoscape+web%3A+an+interactive+web-based+network+browser%2E&journal=Bioinformatics&author=Lopes+C.T.&author=Franz+M.&author=Kazi+F.&author=Donaldson+S.L.&author=Morris+Q.&author=Bader+G.D.&author=et+al.&publication\\_year=2011&volume=26&pages=2347-2348](http://scholar.google.com/scholar_lookup?&title=Cytoscape+web%3A+an+interactive+web-based+network+browser%2E&journal=Bioinformatics&author=Lopes+C.T.&author=Franz+M.&author=Kazi+F.&author=Donaldson+S.L.&author=Morris+Q.&author=Bader+G.D.&author=et+al.&publication_year=2011&volume=26&pages=2347-2348))

based+network+browser%2E&journal=Bioinformatics&author=Lopes+C.+T.&author=Franz+M.&author=Kazi+F.&author=Donaldson+S.+L.&author=Mertins+P.&author=Bader+G.+D.&publication\_year=2011&volume=26&pages=2347-2348)

Maiti, A., Takabe, K., and Hait, N. C. (2017). Metastatic triple-negative breast cancer is dependent on SphKs/S1P signaling for growth and survival. *Cell. Signal.* 32, 85–92. doi: 10.1016/j.cellsig.2017.01.021

PubMed Abstract (http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28108260) | CrossRef Full Text (https://doi.org/10.1016/j.cellsig.2017.01.021) | Google Scholar (http://scholar.google.com/scholar\_lookup?&title=Metastatic+triple-negative+breast+cancer+is+dependent+on+SphKs%2FS1P+signaling+for+growth+and+survival%2E&journal=Cell%2E+Signal%2E&author=Maiti+A.&author=Takabe+K.&author=and+Hait+N.+C.&publication\_year=2017&volume=32&pages=85-92)

Mardinoglu, A., Boren, J., Smith, U., Uhlen, M., and Nielsen, J. (2018). Systems biology in hepatology: approaches and applications. *Nat. Rev. Gastroenterol. Hepatol.* 15, 365–377. doi: 10.1038/s41575-018-0007-8

PubMed Abstract (http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=29686404) | CrossRef Full Text (https://doi.org/10.1038/s41575-018-0007-8) | Google Scholar (http://scholar.google.com/scholar\_lookup?&title=Systems+biology+in+hepatology%3A+approaches+and+applications%2E&journal=Nat%2E++Rev%2E++Gastroenterol%2E+Hepatol%2E&author=Mardinoglu+A.&author=Boren+J.&author=Smith+U.&author=Uhlen+M.&author=and+Nielsen+J.&publication\_year=2018&volume=15&pages=365-377)

Mardinoglu, A., and Nielsen, J. (2015). New paradigms for metabolic modeling of human cells. *Curr. Opin. Biotechnol.* 34, 91–97. doi: 10.1016/j.copbio.2014.12.013

PubMed Abstract (http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=25559199) | CrossRef Full Text (https://doi.org/10.1016/j.copbio.2014.12.013) | Google Scholar (http://scholar.google.com/scholar\_lookup?&title=New+paradigms+for+metabolic+modeling+of+human+cells%2E&journal=Curr%2E++Opin%2E++Biotechnol%2E&author=Mardinoglu+A.&author=and+Nielsen+J.&publication\_year=2015&volume=34&pages=91-97)

Mertins, P., Mani, D. R., Ruggles, K. V., Gillette, M. A., Clauser, K. R., Wang, P., et al. (2016). Proteogenomics connects somatic mutations to signalling in breast cancer. *Nature* 534, 55–62. doi: 10.1038/nature18003

PubMed Abstract (http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27251275) | CrossRef Full Text (https://doi.org/10.1038/nature18003) | Google Scholar (http://scholar.google.com/scholar\_lookup?&title=Proteogenomics+connects+somatic+mutations+to+signalling+in+breast+cancer%2E&journal=Nature&author=Mertins+P.&author=Mani+D.+R.&author=Ruggles+K.+V.&author=Gillette+M.+A.&author=Clauser+K.+R.&author=Wang+P.&publication\_year=2016&volume=534&pages=55-62)

Murphy, C. G., and Dickler, M. N. (2015). The role of CDK4/6 inhibition in breast cancer. *Oncologist* 20, 483–490. doi: 10.1634/theoncologist.2014-0443

PubMed Abstract (http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=25876993) | CrossRef Full Text (https://doi.org/10.1634/theoncologist.2014-0443) | Google Scholar (http://scholar.google.com/scholar\_lookup?&title=The+role+of+CDK4%2F6+inhibition+in+breast+cancer%2E&journal=Oncologist&author=Murphy+C.+G.&author=and+Dickler+M.+N.&publication\_year=2015&volume=20&pages=483-490)

Nagahashi, M., Tsuchida, J., Moro, K., Hasegawa, M., Tatsuda, K., Woelfel, I. A., et al. (2016). High levels of sphingolipids in human breast cancer. *J. Surg. Res.* 204, 435–444. doi: 10.1016/j.jss.2016.05.022

PubMed Abstract (http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27565080) | CrossRef Full Text (https://doi.org/10.1016/j.jss.2016.05.022) | Google Scholar (http://scholar.google.com/scholar\_lookup?&title=High+levels+of+sphingolipids+in+human+breast+cancer%2E&journal=J%2E++Surg%2E+Res%2E&author=Nagahashi+M.&author=Tsuchida+J.&author=Moro+K.&author=Hasegawa+M.&author=Tatsuda+K.&author=Woelfel+I.+A.&publication\_year=2016&volume=204&pages=435-444)

Nuncia-Cantarero, M., Martinez-Canales, S., Andrés-Pretel, F., Santpere, G., Ocaña, A., and Galan-Moya, E. M. (2018). Functional transcriptomic annotation and protein–protein interaction network analysis identify NEK 2, BIRC5, and TOP2A as potential targets in obese patients with luminal a breast cancer. *Breast Cancer Res. Treat.* 168, 613–623. doi: 10.1007/s10549-017-4652-3

PubMed Abstract (http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=29330624) | CrossRef Full Text (https://doi.org/10.1007/s10549-017-4652-3) | Google Scholar (http://scholar.google.com/scholar\_lookup?&title=Functional+transcriptomic+annotation+and+protein-protein+interaction+network+analysis+identify+NEK+2&BIRC5%2C+and+TOP2A+as+potential+targets+in+obese+patients+with+luminal+a+breast+cancer%2E&journal=Breast+Cancer+Res%2E++Treat%2E&author=Nuncia-Cantarero+M.&author=Martinez-Canales+S.&author=Andrés-Pretel+F.&author=Santpere+G.&author=Ocaña+A.&author=and+Galan-Moya+E.+M.&publication\_year=2018&volume=168&pages=613-623)

Ocana, A., and Pandiella, A. (2015). Targeting oncogenic vulnerabilities in triple negative breast cancer: biological bases and ongoing clinical studies. *Oncotarget* 8, 22218–22234. doi: 10.18632/oncotarget.14731

PubMed Abstract (http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28108739) | CrossRef Full Text (https://doi.org/10.18632/oncotarget.14731) | Google Scholar (http://scholar.google.com/scholar\_lookup?&title=Targeting+oncogenic+vulnerabilities+in+triple+negative+breast+cancer%3A+biological+bases+and+ongoing+clinical+studies%2E&journal=Oncotarget&author=Ocana+A.&author=and+Pandiella+A.&publication\_year=2015&volume=8&pages=22218-22234)

Orchard, S., Ammari, M., Aranda, B., Breuza, L., Briganti, L., Broackes-Carter, F., et al. (2014). The MIntAct project - intAct as a common curation platform for 11 molecular interaction databases. *Nucleic Acids Res.* 42, D358–D363. doi: 10.1093/nar/gkt115

PubMed Abstract (http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24234451) | CrossRef Full Text (https://doi.org/10.1093/nar/gkt115) | Google Scholar (http://scholar.google.com/scholar\_lookup?&title=The+MIntAct+project+-+intAct+as+a+common+curation+platform+for+11+molecular+interaction+databases%2E&journal=Nucleic+Acids+Res%2E&author=Orchard+S.&author=Ammari+M.&author=Aranda+B.&author=Breuza+L.&author=Briganti+L.&author=Broackes-Carter+F.&publication\_year=2014&volume=42&pages=D358-D363)

Perou, C. M., Sørleie, T., Eisen, M. B., van de Rijn, M., Jeffrey, S. S., Rees, C., et al. (2000). Molecular portraits of human breast tumours. *Nature* 406, 747–752. doi: 10.1038/35021093

PubMed Abstract (http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=10963602) | CrossRef Full Text (https://doi.org/10.1038/35021093) | Google Scholar (http://scholar.google.com/scholar\_lookup?&title=Molecular+portraits+of+human+breast+tumours%2E&journal=Nature&author=Perou+C.+M.&author=Sørleie+T.&author=Eisen+M.+B.&author=van+de+Rijn+M.&author=Jeffrey+S.+S.&author=Rees+C.&publication\_year=2000&volume=406&pages=747-752)



Persico, M., Ceol, A., Gavrilu, C., Hoffman, R., Florio, A., and Cesareni, G. (2005). HomoMINT: An inferred human network based on orthology mapping of protein interactions discovered in model organisms. *BMC Bioinformatics*. 6(Suppl. 1):S21. doi: 10.1186/1471-2105-6-S1-S21

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=15960834>) | **CrossRef Full Text** (<https://doi.org/10.1186/1471-2105-6-S1-S21>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=HomoMINT%3A+An+inferred+human+network+based+on+orthology+mapping+of+protein+interactions+discovered+in+model+organisms%2E&journal=BMC+Bioinformatics%2E&author=Persico+M.&author=Ceol+A.&author=Gavrilu+C.&author=Hoffman+R.&author=Florio+A.&author=and+Cesareni+G.&publication\\_year=2005](http://scholar.google.com/scholar_lookup?&title=HomoMINT%3A+An+inferred+human+network+based+on+orthology+mapping+of+protein+interactions+discovered+in+model+organisms%2E&journal=BMC+Bioinformatics%2E&author=Persico+M.&author=Ceol+A.&author=Gavrilu+C.&author=Hoffman+R.&author=Florio+A.&author=and+Cesareni+G.&publication_year=2005))

Prasad, T. S. K., Kandasamy, K., and Pandey, A. (2009). Human protein reference database and human proteinpedia as discovery tools for systems biology. *Methods Mol. Biol.* 577, 67–79. doi: 10.1007/978-1-60761-232-2\_6

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=19718509>) | **CrossRef Full Text** ([https://doi.org/10.1007/978-1-60761-232-2\\_6](https://doi.org/10.1007/978-1-60761-232-2_6)) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Human+protein+reference+database+and+human+proteinpedia+as+discovery+tools+for+systems+biology%2E&journal=Methods+Mol+Biol%2E&author=Prasad+T.+S.+K.&author=Kandasamy+K.&author=and+Pandey+A.&publication\\_year=2009&volume=577&pages=67-79](http://scholar.google.com/scholar_lookup?&title=Human+protein+reference+database+and+human+proteinpedia+as+discovery+tools+for+systems+biology%2E&journal=Methods+Mol+Biol%2E&author=Prasad+T.+S.+K.&author=Kandasamy+K.&author=and+Pandey+A.&publication_year=2009&volume=577&pages=67-79))

Purwaha, P., Gu, F., Piyaathna, D. W. B., Rajendiran, T., Ravindran, A., Omilian, A. R., et al. (2018). Unbiased lipidomic profiling of triple-negative breast cancer tissues reveals the association of sphingomyelin levels with patient disease-free survival. *Metabolites* 8, 1–14. doi: 10.3390/metabo8030041

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=30011843>) | **CrossRef Full Text** (<https://doi.org/10.3390/metabo8030041>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Unbiased+lipidomic+profiling+of+triple-negative+breast+cancer+tissues+reveals+the+association+of+sphingomyelin+levels+with+patient+disease-free+survival%2E&journal=Metabolites&author=Purwaha+P.&author=Gu+F.&author=Piyaathna+D.+W.+B.&author=Rajendiran+T.&author=Ravindran+A.&author=Omilian+A.+R.&publication\\_year=2018&volume=8&pages=1-14](http://scholar.google.com/scholar_lookup?&title=Unbiased+lipidomic+profiling+of+triple-negative+breast+cancer+tissues+reveals+the+association+of+sphingomyelin+levels+with+patient+disease-free+survival%2E&journal=Metabolites&author=Purwaha+P.&author=Gu+F.&author=Piyaathna+D.+W.+B.&author=Rajendiran+T.&author=Ravindran+A.&author=Omilian+A.+R.&publication_year=2018&volume=8&pages=1-14))

Rietman, E. A., Platig, J., Tuszyński, J. A., and Lakka Klement, G. (2016). Thermodynamic measures of cancer: gibbs free energy and entropy of protein interactions. *J. Biol. Phys.* 42, 339–350. doi: 10.1007/s10867-016-9410-y

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27012959>) | **CrossRef Full Text** (<https://doi.org/10.1007/s10867-016-9410-y>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Thermodynamic+measures+of+cancer%3A+gibbs+free+energy+and+entropy+of+protein-protein+interactions%2E&journal=J%2E+and+Biol%2E+Phys%2E&author=Rietman+E.+A.&author=Platig+J.&author=Tuszyński+J.+A.&author=and+Lakka+Klement+G.&publication\\_year=2016&volume=42&pages=339-350](http://scholar.google.com/scholar_lookup?&title=Thermodynamic+measures+of+cancer%3A+gibbs+free+energy+and+entropy+of+protein-protein+interactions%2E&journal=J%2E+and+Biol%2E+Phys%2E&author=Rietman+E.+A.&author=Platig+J.&author=Tuszyński+J.+A.&author=and+Lakka+Klement+G.&publication_year=2016&volume=42&pages=339-350))

Salwinski, L. (2004). The database of interacting proteins: 2004 update. *Nucleic Acids Res.* 31, 248–250. doi: 10.1093/nar/gkho86

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=14681454>) | **CrossRef Full Text** (<https://doi.org/10.1093/nar/gkho86>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=The+database+of+interacting+proteins%3A+2004+update%2E&journal=Nucleic+Acids+Res%2E&author=Salwinski+L.&publication\\_year=2004&volume=31&pages=248-250](http://scholar.google.com/scholar_lookup?&title=The+database+of+interacting+proteins%3A+2004+update%2E&journal=Nucleic+Acids+Res%2E&author=Salwinski+L.&publication_year=2004&volume=31&pages=248-250))

Schaefer, M. H., Fontaine, J. F., Vinayagam, A., Porras, P., Wanker, E. E., and Andrade-Navarro, M. A. (2012). Hippie: integrating protein interaction networks with experiment based quality scores. *PLoS One* 7:e31826. doi: 10.1371/journal.pone.0031826

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22348130>) | **CrossRef Full Text** (<https://doi.org/10.1371/journal.pone.0031826>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Hippie%3A+integrating+protein+interaction+networks+with+experiment+based+quality+scores%2E&journal=PLoS+One&author=Schaefer+M.+H.&author=Fontaine+J.+F.&author=Vinayagam+A.&author=Porras+P.&author=Wanker+E.+E.&author=and+Andrade-Navarro+M.+A.&publication\\_year=2012](http://scholar.google.com/scholar_lookup?&title=Hippie%3A+integrating+protein+interaction+networks+with+experiment+based+quality+scores%2E&journal=PLoS+One&author=Schaefer+M.+H.&author=Fontaine+J.+F.&author=Vinayagam+A.&author=Porras+P.&author=Wanker+E.+E.&author=and+Andrade-Navarro+M.+A.&publication_year=2012))

Siegel, R. L., Miller, K. D., and Jemal, A. (2019). Cancer statistics, 2019. *CA. Cancer J. Clin.* 69, 7–34. doi: 10.3322/caac.21551

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=30620402>) | **CrossRef Full Text** (<https://doi.org/10.3322/caac.21551>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Cancer+statistics%2C+2019%2E&journal=CA%2E+Cancer+J%2E+Clin%2E&author=Siegel+R.+L.&author=Miller+K.+D.&author=and+Jemal+A.&publication\\_year=2019&volume=69&pages=7-34](http://scholar.google.com/scholar_lookup?&title=Cancer+statistics%2C+2019%2E&journal=CA%2E+Cancer+J%2E+Clin%2E&author=Siegel+R.+L.&author=Miller+K.+D.&author=and+Jemal+A.&publication_year=2019&volume=69&pages=7-34))

Solzak, J. P., Atale, R. V., Hancock, B. A., Sinn, A. L., Pollok, K. E., Jones, D. R., et al. (2017). Dual PI3K and Wnt pathway inhibition is a synergistic combination against triple negative breast cancer. *NPJ Breast Cancer* 3:17. doi: 10.1038/s41523-017-0016-8

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28649657>) | **CrossRef Full Text** (<https://doi.org/10.1038/s41523-017-0016-8>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Dual+PI3K+and+Wnt+pathway+inhibition+is+a+synergistic+combination+against+triple+negative+breast+cancer%2E&journal=NPJ+Breast+Cancer&author=Solzak+J.+P.&author=Atale+R.+V.&author=Hancock+B.+A.&author=Sinn+A.+L.&author=Pollok+K.+E.&author=Jones+D.+R.&publication\\_year=2017](http://scholar.google.com/scholar_lookup?&title=Dual+PI3K+and+Wnt+pathway+inhibition+is+a+synergistic+combination+against+triple+negative+breast+cancer%2E&journal=NPJ+Breast+Cancer&author=Solzak+J.+P.&author=Atale+R.+V.&author=Hancock+B.+A.&author=Sinn+A.+L.&author=Pollok+K.+E.&author=Jones+D.+R.&publication_year=2017))

Strott, C. A., and Higashi, Y. (2003). Cholesterol sulfate in human physiology. *J. Lipid Res.* 44, 1268–1278. doi: 10.1194/jlr.R300005-JLR200

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12730293>) | **CrossRef Full Text** (<https://doi.org/10.1194/jlr.R300005-JLR200>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Cholesterol+sulfate+in+human+physiology%2E&journal=J%2E+Lipid+Res%2E&author=Strott+C.+A.&author=and+Higashi+Y.&publication\\_year=2003&volume=44&pages=1268-1278](http://scholar.google.com/scholar_lookup?&title=Cholesterol+sulfate+in+human+physiology%2E&journal=J%2E+Lipid+Res%2E&author=Strott+C.+A.&author=and+Higashi+Y.&publication_year=2003&volume=44&pages=1268-1278))

Tang, Y., Li, M., Wang, J., Pan, Y., and Wu, F. X. (2015). CytoNCA: A cytoscape plugin for centrality analysis and evaluation of protein interaction networks. *BioSystems* 127, 67–72. doi: 10.1016/j.biosystems.2014.11.005

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=25451770>) | **CrossRef Full Text** (<https://doi.org/10.1016/j.biosystems.2014.11.005>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=CytoNCA%3A+A+cytoscape+plugin+for+centrality+analysis+and+evaluation+of+protein+interaction+networks%2E&journal=BioSystems&author=Tang+Y.&author=Li+M.&author=Wang+J.&author=Pan+Y.&author=and+Wu+F.+X.&publication\\_year=2015&volume=127&pages=67-72](http://scholar.google.com/scholar_lookup?&title=CytoNCA%3A+A+cytoscape+plugin+for+centrality+analysis+and+evaluation+of+protein+interaction+networks%2E&journal=BioSystems&author=Tang+Y.&author=Li+M.&author=Wang+J.&author=Pan+Y.&author=and+Wu+F.+X.&publication_year=2015&volume=127&pages=67-72))

Teschendorff, A. E., Banerji, C. R. S., Severini, S., Kuehn, R., and Sollich, P. (2015). Increased signaling entropy in cancer requires the scale-free property of protein interaction networks. *Sci. Rep.* 5:9646. doi: 10.1038/srep09646

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=25919796>) | **CrossRef Full Text** (<https://doi.org/10.1038/srep09646>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Increased+signaling+entropy+in+cancer+requires+the+scale-free+property+of+protein+interaction+networks%2E&journal=Sci.+Rep.%2E&author=Teschendorff+A.+E.&author=Banerji+C.+R.+S.&author=Severini+S.&author=Kuehn+R.&author=and+Sollich+P.&publication\\_year=2015&volume=5&pages=9646-9652](http://scholar.google.com/scholar_lookup?&title=Increased+signaling+entropy+in+cancer+requires+the+scale-free+property+of+protein+interaction+networks%2E&journal=Sci.+Rep.%2E&author=Teschendorff+A.+E.&author=Banerji+C.+R.+S.&author=Severini+S.&author=Kuehn+R.&author=and+Sollich+P.&publication_year=2015&volume=5&pages=9646-9652))

free+property+of+protein+interaction+networks%2E&journal=Sci%2E+Rep%2E&author=Teschendorff+A.+E.&author=Banerji+C.+R.+S.&author=Severini+S.&author=Kuehn+R.&author=and+Sollich+P.&publication\_year=2015)

Turanli, B., Grötl, M., Boren, J., Nielsen, J., Uhlen, M., Arga, K. Y., et al. (2018). Drug repositioning for effective prostate cancer treatment. *Front. Physiol.* 9:500. doi: 10.3389/fphys.2018.00500

**CrossRef Full Text** (<https://doi.org/10.3389/fphys.2018.00500>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Drug+repositioning+for+effective+prostate+cancer+treatment%2E&journal=Front%2E++Physiol%2E&author=Turanli+B.&author=Grötl+M.&author=Boren+J.&author=Nielsen+J.&author=Uhlen+M.&author=Arga+K.+Y.&publication\\_year=2018](http://scholar.google.com/scholar_lookup?&title=Drug+repositioning+for+effective+prostate+cancer+treatment%2E&journal=Front%2E++Physiol%2E&author=Turanli+B.&author=Grötl+M.&author=Boren+J.&author=Nielsen+J.&author=Uhlen+M.&author=Arga+K.+Y.&publication_year=2018))

Turanli, B., Gulfidan, G., and Arga, K. Y. (2017). Transcriptomic-guided drug repositioning supported by a new bioinformatics search tool: geneXpharma. *Omi. A J. Integr. Biol.* 21, 584–591. doi: 10.1089/omi.2017.0127

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=29049014>) | **CrossRef Full Text** (<https://doi.org/10.1089/omi.2017.0127>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Transcriptomic-guided+drug+repositioning+supported+by+a+new+bioinformatics+search+tool%3A+geneXpharma%2E&journal=Omi%2E+A+J%2E+Integr%2E+Biol%2E&author=Turanli+B.&author=Gulfidan+G.&author=and+Arga+K.+Y.&publication\\_year=2017&volume=21&pages=584-591](http://scholar.google.com/scholar_lookup?&title=Transcriptomic-guided+drug+repositioning+supported+by+a+new+bioinformatics+search+tool%3A+geneXpharma%2E&journal=Omi%2E+A+J%2E+Integr%2E+Biol%2E&author=Turanli+B.&author=Gulfidan+G.&author=and+Arga+K.+Y.&publication_year=2017&volume=21&pages=584-591))

Tusher, V. G., Tibshirani, R., and Chu, G. (2001). Significance analysis of microarrays applied to the ionizing radiation response. *Proc. Natl. Acad. Sci. U.S.A.* 98, 10869–10874. doi: 10.1073/pnas.091062498

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11309499>) | **CrossRef Full Text** (<https://doi.org/10.1073/pnas.091062498>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Significance+analysis+of+microarrays+applied+to+the+ionizing+radiation+response%2E&journal=Proc%2E+Nat%2E+Acad%2E+Sci%2E+U.S.A.%2E&author=Tusher+V.+G.&author=Tibshirani+R.&author=and+Chu+G.&publication\\_year=2001&volume=98&pages=10869-10874](http://scholar.google.com/scholar_lookup?&title=Significance+analysis+of+microarrays+applied+to+the+ionizing+radiation+response%2E&journal=Proc%2E+Nat%2E+Acad%2E+Sci%2E+U.S.A.%2E&author=Tusher+V.+G.&author=Tibshirani+R.&author=and+Chu+G.&publication_year=2001&volume=98&pages=10869-10874))

Ueno, N. T., and Zhang, D. (2011). Targeting EGFR in triple negative breast cancer. *J. Cancer* 2, 324–328. doi: 10.7150/jca.2.324

**CrossRef Full Text** (<https://doi.org/10.7150/jca.2.324>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Targeting+EGFR+in+triple+negative+breast+cancer%2E&journal=J%2E+Cancer&author=Ueno+N.+T.&author=and+Zhang+D.&publication\\_year=2011&volume=2&pages=324-328](http://scholar.google.com/scholar_lookup?&title=Targeting+EGFR+in+triple+negative+breast+cancer%2E&journal=J%2E+Cancer&author=Ueno+N.+T.&author=and+Zhang+D.&publication_year=2011&volume=2&pages=324-328))

Uhlen, M., Zhang, C., Lee, S., Sjöstedt, E., Fagerberg, L., Bidkhor, G., et al. (2017). A pathology atlas of the human cancer transcriptome. *Science* 80:357. doi: 10.1126/science.aan2507

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28818916>) | **CrossRef Full Text** (<https://doi.org/10.1126/science.aan2507>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=A+pathology+atlas+of+the+human+cancer+transcriptome%2E&journal=Science&author=Uhlen+M.&author=Zhang+C.&author=Lee+S.&author=Sjöstedt+E.&author=Fagerberg+L.&author=Bidkhor+G.&publication\\_year=2017](http://scholar.google.com/scholar_lookup?&title=A+pathology+atlas+of+the+human+cancer+transcriptome%2E&journal=Science&author=Uhlen+M.&author=Zhang+C.&author=Lee+S.&author=Sjöstedt+E.&author=Fagerberg+L.&author=Bidkhor+G.&publication_year=2017))

Varadan, V., and Anastassiou, D. (2006). Inference of disease-related molecular logic from systems-based microarray analysis. *PLoS Comput. Biol.* 2:e68. doi: 10.1371/journal.pcbi.0020068

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16789819>) | **CrossRef Full Text** (<https://doi.org/10.1371/journal.pcbi.0020068>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Inference+of+disease-related+molecular+logic+from+systems-based+microarray+analysis%2E&journal=PLoS+Comput%2E+Biol%2E&author=Varadan+V.&author=and+Anastassiou+D.&publication\\_year=2006](http://scholar.google.com/scholar_lookup?&title=Inference+of+disease-related+molecular+logic+from+systems-based+microarray+analysis%2E&journal=PLoS+Comput%2E+Biol%2E&author=Varadan+V.&author=and+Anastassiou+D.&publication_year=2006))

Vitali, F., Cohen, L. D., Demartini, A., Amato, A., Eterno, V., Zambelli, A., et al. (2016). A network-based data integration approach to support drug repurposing and multi-Target therapies in triple negative breast cancer. *PLoS One* 11:e0162407. doi: 10.1371/journal.pone.0162407

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28076436>) | **CrossRef Full Text** (<https://doi.org/10.1371/journal.pone.0162407>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=A+network-based+data+integration+approach+to+support+drug+repurposing+and+multi-Target+therapies+in+triple+negative+breast+cancer%2E&journal=PLoS+One&author=Vitali+F.&author=Cohen+L.+D.&author=Demartini+A.&author=Amato+A.&author=Eterno+V.&author=Zambelli+A.&publication\\_year=2016](http://scholar.google.com/scholar_lookup?&title=A+network-based+data+integration+approach+to+support+drug+repurposing+and+multi-Target+therapies+in+triple+negative+breast+cancer%2E&journal=PLoS+One&author=Vitali+F.&author=Cohen+L.+D.&author=Demartini+A.&author=Amato+A.&author=Eterno+V.&author=Zambelli+A.&publication_year=2016))

Warm, M., Kates, R., Große-Onnebrink, E. M., Stoff-Khalili, M., Hoopmann, M., Mallmann, P., et al. (2010). Impact of tumor biology, particularly triple-negative status, on response to pre-operative sequential, dose-dense epirubicin, cyclophosphamide followed by docetaxel in breast cancer. *Anticancer Res.* 30, 4251–4259.

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=21036749>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Impact+of+tumor+biology%2C+particularly+triple-negative+status%2C+on+response+to+pre-operative+sequential%2C+dose-dense+epirubicin%2C+cyclophosphamide+followed+by+docetaxel+in+breast+cancer%2E&journal=Anticancer+Res%2E&author=Warm+M.&author=Kates+R.&author=Große-Onnebrink+E.+M.&author=Stoff-Khalili+M.&author=Hoopmann+M.&author=Mallmann+P.&publication\\_year=2010&volume=30&pages=4251-4259](http://scholar.google.com/scholar_lookup?&title=Impact+of+tumor+biology%2C+particularly+triple-negative+status%2C+on+response+to+pre-operative+sequential%2C+dose-dense+epirubicin%2C+cyclophosphamide+followed+by+docetaxel+in+breast+cancer%2E&journal=Anticancer+Res%2E&author=Warm+M.&author=Kates+R.&author=Große-Onnebrink+E.+M.&author=Stoff-Khalili+M.&author=Hoopmann+M.&author=Mallmann+P.&publication_year=2010&volume=30&pages=4251-4259))

Weigman, V. J., Chao, H.-H., Shabalín, A. A., He, X., Parker, J. S., Nordgard, S. H., et al. (2012). Basal-like Breast cancer DNA copy number losses identify genes involved in genomic instability, response to therapy, and patient survival. *Breast Cancer Res. Treat.* 133, 865–880. doi: 10.1007/s10549-011-1846-y

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22048815>) | **CrossRef Full Text** (<https://doi.org/10.1007/s10549-011-1846-y>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Basal-like+Breast+cancer+DNA+copy+number+losses+identify+genes+involved+in+genomic+instability%2C+response+to+therapy%2C+and+patient+survival%2E&journal=Breast+Cancer+Res%2E+Treat%2E&author=Weigman+V.+J.&author=Chao+H.-H.&author=Shabalín+A.+A.&author=He+X.&author=Parker+J.+S.&author=Nordgard+S.+H.&publication\\_year=2012&volume=133&pages=865-880](http://scholar.google.com/scholar_lookup?&title=Basal-like+Breast+cancer+DNA+copy+number+losses+identify+genes+involved+in+genomic+instability%2C+response+to+therapy%2C+and+patient+survival%2E&journal=Breast+Cancer+Res%2E+Treat%2E&author=Weigman+V.+J.&author=Chao+H.-H.&author=Shabalín+A.+A.&author=He+X.&author=Parker+J.+S.&author=Nordgard+S.+H.&publication_year=2012&volume=133&pages=865-880))

West, J., Bianconi, G., Severini, S., and Teschendorff, A. E. (2012). Differential network entropy reveals cancer system hallmarks. *Sci. Rep.* 2:802. doi: 10.1038/srep00802

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23150773>) | **CrossRef Full Text** (<https://doi.org/10.1038/srep00802>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Differential+network+entropy+reveals+cancer+system+hallmarks%2E&journal=Sci%2E+Rep%2E&author=West+J.&author=Bianconi+G.&author=Severini+S.&author=and+Teschendorff+A.+E.&publication\\_year=2012](http://scholar.google.com/scholar_lookup?&title=Differential+network+entropy+reveals+cancer+system+hallmarks%2E&journal=Sci%2E+Rep%2E&author=West+J.&author=Bianconi+G.&author=Severini+S.&author=and+Teschendorff+A.+E.&publication_year=2012))

Xiong, J., Liu, J., Rayner, S., Li, Y., and Chen, S. (2010). Protein-protein interaction reveals synergistic discrimination of cancer phenotype. *Cancer Inform.* 9,61–66.

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Zhang, P., Yang, X., Yin, Q., Yi, J., Shen, W., Zhao, L., et al. (2016). Inhibition of SK4 potassium channels suppresses cell proliferation, migration and the epithelial-mesenchymal transition in triple-negative breast cancer cells. *PLoS One* 11:e0154471. doi: 10.1371/journal.pone.0154471

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27124117>) | **CrossRef Full Text** (<https://doi.org/10.1371/journal.pone.0154471>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Inhibition+of+SK4+potassium+channels+suppresses+cell+proliferation%2C+migration+and+the+epithelial-mesenchymal+transition+in+triple-negative+breast+cancer+cells%2E&journal=PLoS+One&author=Zhang+P.&author=Yang+X.&author=Yin+Q.&author=Yi+J.&author=Shen+W.&author=Zhao+L.&publication\\_year=2016](http://scholar.google.com/scholar_lookup?&title=Inhibition+of+SK4+potassium+channels+suppresses+cell+proliferation%2C+migration+and+the+epithelial-mesenchymal+transition+in+triple-negative+breast+cancer+cells%2E&journal=PLoS+One&author=Zhang+P.&author=Yang+X.&author=Yin+Q.&author=Yi+J.&author=Shen+W.&author=Zhao+L.&publication_year=2016))

Zhang, Y. G., Du, Q., Fang, W. G., Jin, M. L., and Tian, X. X. (2008). Tyrphostin AG1478 supresses proliferation and invasion of human breast cancer cells. *Int. J. Oncol.* 33, 595–602. doi: 10.3892/ijo\_00000045

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=18695891>) | **CrossRef Full Text** ([https://doi.org/10.3892/ijo\\_00000045](https://doi.org/10.3892/ijo_00000045)) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Tyrphostin+AG1478+supresses+proliferation+and+invasion+of+human+breast+cancer+cells%2E&journal=Int%2E+J%2E+Oncol%2E&author=Zhang+Y.+G.&author=D+Q.&author=Fang+W.+G.&author=Jin+M.+L.&author=and+Tian+X.+X.&publication\\_year=2008&volume=33&pages=595-602](http://scholar.google.com/scholar_lookup?&title=Tyrphostin+AG1478+supresses+proliferation+and+invasion+of+human+breast+cancer+cells%2E&journal=Int%2E+J%2E+Oncol%2E&author=Zhang+Y.+G.&author=D+Q.&author=Fang+W.+G.&author=Jin+M.+L.&author=and+Tian+X.+X.&publication_year=2008&volume=33&pages=595-602))

Zhou, Y., Lin, S., Tseng, K. F., Han, K., Wang, Y., Gan, Z. H., et al. (2016). Selumetinib suppresses cell proliferation, migration and trigger apoptosis, G1 arrest in triple-negative breast cancer cells. *BMC Cancer* 16:818. doi: 10.1186/s12885-016-2773-4

**PubMed Abstract** (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27769200>) | **CrossRef Full Text** (<https://doi.org/10.1186/s12885-016-2773-4>) | **Google Scholar** ([http://scholar.google.com/scholar\\_lookup?&title=Selumetinib+suppresses+cell+proliferation%2C+migration+and+trigger+apoptosis%2C+G1+arrest+in+triple-negative+breast+cancer+cells%2E&journal=BMC+Cancer&author=Zhou+Y.&author=Lin+S.&author=Tseng+K.+F.&author=Han+K.&author=Wang+Y.&author=Gan+Z.+H.&publication\\_year=2016](http://scholar.google.com/scholar_lookup?&title=Selumetinib+suppresses+cell+proliferation%2C+migration+and+trigger+apoptosis%2C+G1+arrest+in+triple-negative+breast+cancer+cells%2E&journal=BMC+Cancer&author=Zhou+Y.&author=Lin+S.&author=Tseng+K.+F.&author=Han+K.&author=Wang+Y.&author=Gan+Z.+H.&publication_year=2016))

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