**Preliminary Analysis:** We have done a case study to run the pipeline for Aim1 with the RNA-seq data from cell lines MDA-MB-231 and MCF10A as well as ChIP-seq data, CNV data, methylation profiles, mutational profiles, and proteomic data from MDA-MB-231. All the source code for this preliminary analysis has already been deposited in Vera-Licona’s Github public repository <https://github.com/VeraLiconaResearchGroup/CancerReversion>.

**Preliminarystatic network of CL TNBC tumorigenesis for cell line MDA-MB-231**:The preliminary network we have built consists of 198 nodes, and 387 edges (fig1). The first layer of functionally enriched DEGs contains 75 genes. MATCH and IPA algorithms identified 8 expressed TFs, which were confirmed to be in open chromatin regions by CHIP-Seq data and methylation profile [59]. For the final network layer, 49 upstream MRs were identified and confirmed to have protein present. The network has several genes known to be associated with TNBC tumorigenesis, including ICAM1, ANXA1 [22343619], and TP53 [27611952]. It also captures genes that are known to be highly expressed in claudin low tumors: EGFR, SRC, STAT3, and members of the TGFβ pathway [25277734]. Genes associated with EMT and cell migration are also included in the network, such as STAT3 [28030809], SMAD2 [30012564], RHOA [[29535813](https://www.ncbi.nlm.nih.gov/pubmed/29535813)], WNT5A [30171384], and members of the Ras/MAPK pathway [24882719]. We identified 13 readout nodes. Heatmaps with hierarchical clustering show that network nodes separate between MCF10A and MDA-MB231 using normalized expression values from RNA-seq data (Fig3).

**Consideration of Mutational Data:** The preliminary network includes 2 mutated genes: TP53, and NF2. The TP53 R280K mutation is a known gain of function mutation in MDA-MB-231 [22822097]. A literature search provided insight to the pathways affected by this gain-of-function mutant p53. One such pathway is the mevalonate pathway, whose increased activity promotes tumor cell survival [27562463]. Mutant p53 also activates the TGFβ pathway by binding to and inhibiting p63, which typically inhibits the pathway, leading to increased cell migration [19345189, 21263025]. Furthermore, mutant p53 also interacts functionally and physically with the vitamin D receptor to increase transcription of vitamin D response elements, transforming vitamin D into an antiapoptotic agent [20227041]. The increased vitamin D and TGFβ pathway signaling by Mutp53 causes an increase of the non-canonical wnt5a pathway, leading to increased cell migration [21416313]. In the network, NF2 is a master regulator that inactivates ERK and JNK. The NF2 p.E231\* mutation is a truncating loss-of-function mutation, so we decided to remove it from the network. We also considered mutations in expressed genes that weren’t included in our network through ReKINect and KnimoeXplorer. We found one mutated kinase, BRAF, that over activates the MAPK growth pathway including MEK and ERK, so we added it to the network. We did not find any mutations creating atypical phosphorylation sites that altered pathways in our network. We also considered mutations in promoter regions of our functionally related genes that could alter TF binding affinity, but there were no mutations located in the 5’ UTR of these genes.

**Attractor Analysis with SFA.** Using SFA we estimated the attractors from the MCF10A and MDA-MB-231 initial states. The direction of activity change (DAC) of the readout nodes was calculated between the MDA-MB231 and MCF10A attractors. For each readout node, the DAC was compared to the corresponding readout’s log2 FC values from our RNA-seq data. The readout nodes’ DAC matched the RNA-seq data, giving evidence that SFA is yielding reliable results (Fig4).

**FC Control Analysis.** There were 6 FVS, each containing either 5, 6, or 7 nodes, of which none are mutated. The smallest FVS set was chosen for further analysis and combined with the network’s 29 source nodes, resulting in a FC set, *FC1*, of 34 nodes. FC1 contains CSNK2B and the oncogene MYC, which have been identified as potential targets in TNBC therapeutics [27527857, 30076412] as well as AKT, a member of the PI3K signaling pathway and known to be important in TNBC pathogenesis [23748695], and JUN, which is an important part of TNBC tumorigenesis and a marker of the cancer stem-like cell phenotype [27941886].

***In Silico* Screening on FC1 Set.** SFA was performed taking as input our MD-MBA-231 network nodes, the RNA-seq normalized expression values of the MDA-MB-231 and a set of perturbations (activations or inhibitions) on FC1. SFA ran until reaching an attractor. A perturbation pattern is deemed successful if, we observe a change in the direction of expression of as many readout nodes from those expression values in the MDA-MB-231 attractor. After 75 simulations, one perturbation pattern was found to successfully change 8 of the 13 readout nodes’ attractor activity. OCSANA [SOURCE] canalized the signal from our network source nodes to our readout nodes and identified 6 CIs each of size 6. We combined the highest scoring CI with our FVS set of size 5 to obtain an FC set of 9 due to overlap of RELA and MYC. When running SFA with this FC set, one perturbation pattern successfully changed 7 of the 13 readout nodes’ attractor activity after 20 simulations, the only difference between these 7 and the previously controlled 8 being CAV1.

The 8 controlled readout nodes cover various hallmarks of cancer. Several genes of note are CAV1, CDKN1A, and HMGA2, which are associated with EMT in TNBC cells [[22671595](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&amp;Cmd=ShowDetailView&amp;TermToSearch=22671595), 19440234, 16831886].