IN SILICO PREDICTION OF ANTITUMOR CYTOTOXICITY OF PHRMACOLOGICALLY ACTIVE SUBSTANCES FOR HUMAN BREAST CANCER AND NORMAL CELL LINES

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Introduction

Modeling of pathologic processes for the analysis of causes and development of disease on the molecular genetic level contributes to better understanding of neoplastic disease pathogenesis and opens new perspectives for early disease detection[1,2]. Therefore, the systems biology approaches are required to study complex diseases at the proteins' and genes' level and the interactions between them[3]. These approaches allow the obtained genomic, transcriptomic, proteomic and metabolomic data to be integrated for the analysis of complex disorders occurring in the neoplastic disease development[4]. Currently, bio- and chemoinformatics methods, and mathematical modeling are widely used for the detection of pathogenic mechanisms of cancer and quest for potential drug-targets and their ligands. Regulatory network analysis based on signaling pathways and cell cycle regulation data combines in single system the genomics and proteomics data. The use of differential gene expression tumor data results in obtaining information on new therapeutic targets and treatment choices for individual patient[5].

Approach

The present work was focused on the development of approach for *in silico* prediction of cytotoxic effect of chemical compounds in normal and breast cancer cell lines based on the prediction of their cytotoxicity and action on human proteins, dichotomic modeling of regulatory networks and gene expression. General scheme of selection of possible antitumor compounds is shown schematically in Figure 1.

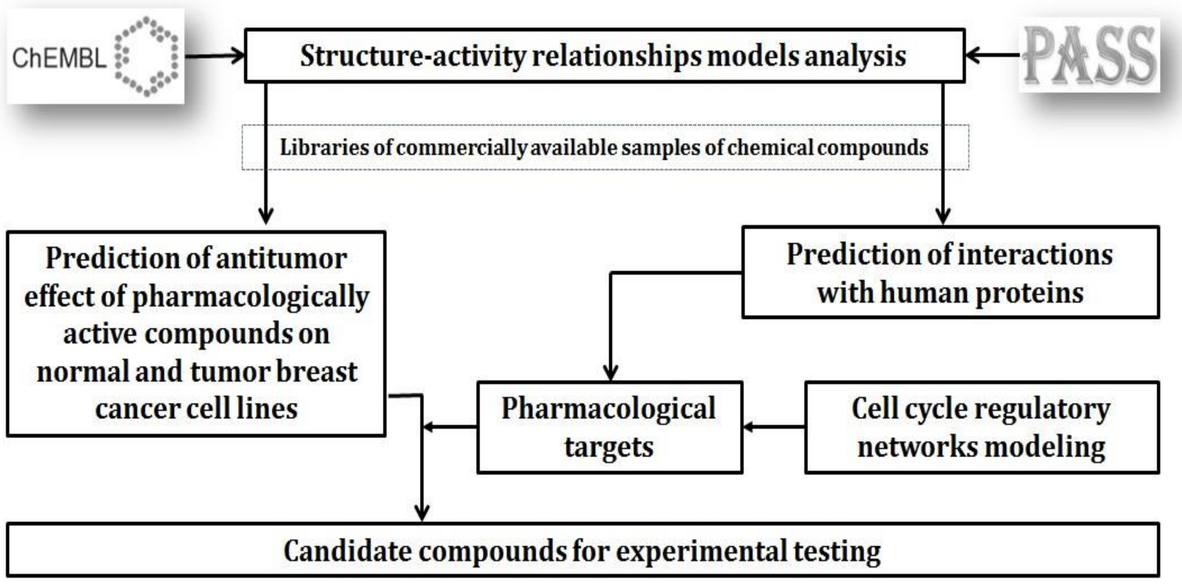


Figure 1. Scheme of selection of possible antitumor compounds.

We have created the cell cycle regulatory networks models including 2141 regulatory interactions between 1265 breast cancer genes/proteins and hypo-and hyperexpressed genes for 4 breast cancer cell lines (BT-20, MCF7, SK-BR-3, T47D) and 2 normal cell lines (HaCaT, WI-38). In the breast cancer cell cycle regulation modeling, several known and new pharmacological targets were found that further should be validated experimentally.

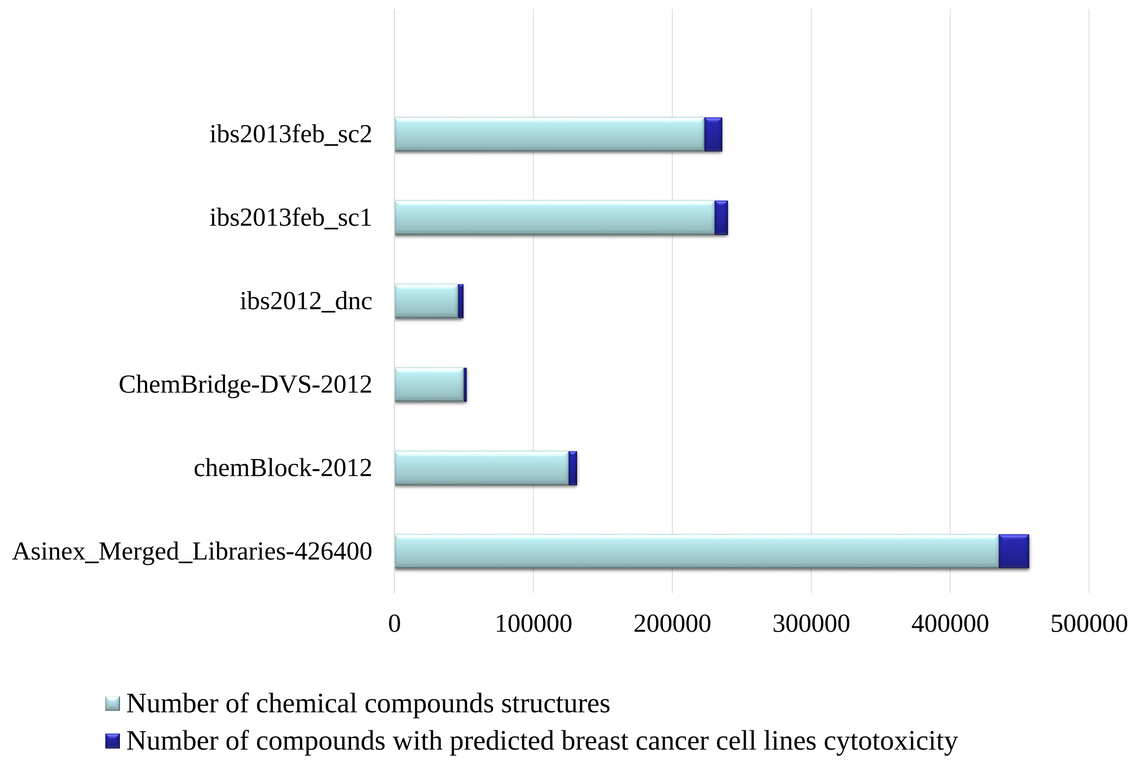
Desirable event	BT-20 (234 UP)	MCF-7 (504 UP)	SK-BR-3 (283 UP)	T47D (260 UP)
Cell cycle inhibition: Cyclin D:CDK4 Cyclin D:CDK6	CDK4, CDK6, CYCD1, CYCLIN D1			
Cell cycle inhibition: Cyclin A:CDK2 Cyclin E:CDK2	AKT-1, CDK2, CYCE, CYCLIN E, PLK1			
Cell cycle inhibition: Cyclin B1:CDK1	CDC25B, CDK1, PLK1			
Apoptosis stimulation: Cytochrome C	BCL-2			
Apoptosis stimulation: Caspase 3		C-IAP2, CIAP-2		
	CRKL, HPK1			
		MEK1		
		MKK3		
	MKK4, MKK6, P38ALPHA, PI3K, TAK1			

Results of targets selection by blocking the cell cycle or induce apoptosis in breast cancer cells obtained by using NetFlowEx[5].

The computer program PASS[6,7] (Prediction of Activity Spectra for Substances) was used to construct the structure-activity relationships models. The appropriate training sets were created based on the information from ChEMBLdb 16 database (www.ebi.ac.uk/chembldb/) about cytotoxicity and interactions of chemicals with 661 proteins involved in human cell cycle regulation. The average prediction accuracy calculated by a leave-one-out cross-validation procedure was approximately 96% for cytotoxicity prediction for 24 breast cancer cell lines and 31 normal cell lines and 97% for protein-ligand interactions.

Results

Libraries of commercially available samples of chemical compounds (Asinex, ChemBlock, ChemBridge, InterBioScreen) containing more than million structures, were used for *in silico* screening of promising antitumor ligands.



During the screening, we have selected few dozens promising compounds for which the interactions with identified targets, the cytotoxicity for breast cancer cell lines, and the absence of cytotoxicity for 31 normal human cell lines were predicted. Several selected compounds were experimentally tested for cytotoxicity to some breast cancer cell lines.

Libraries of commercially available samples of chemical compounds	**Target**								
	PI3K	**CDK1**	**CDK2**	**CDK6**	**AKT-1**	**P38ALPHA**	**HPK1**	**MKK3**	**MKK6**
Asinex_Merged_Libraries			2	3	14		2	23	5
chemBlock-2012	1			2				20	5
ChemBridge-DVS-2012								3	
ibs2012_dnc									
ibs2013feb_sc1	2		1	1				7	5
ibs2013feb_sc2	1	1	1	3		1			4

Results of possible antitumor compounds selection.

Conclusions

Thus, the developed approach allows revealing compounds possessing antitumor activity for breast cancer cell lines and action on proteins responsible for the cell cycle arrest and apoptosis.

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