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Evaluation of the Efficacy of Cancer Drugs by Using the Second Largest Eigenvalue of Metabolic Cancer Pathways

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Abstract

Cancer is a system with thousands of genes and proteins with the complex interactions between them. By examining the cancer drug activity on only part of this system, we do not know in which direction the whole system will evolve, and whether therapy will be useful or not. This is one of the main reasons why cancer therapies still do not meet our expectations. In order to find more effective anticancer therapies, it is important to consider the impact of drugs on the entire cancer system.

The second largest eigenvalue plays a key role in complex systems optimization. The algorithms minimizing the second largest eigenvalue of graphs have been already used to speed up processes in computer networks and differential cryptanalysis. Based on the aforementioned, it could be assumed that maximizing the second highest eigenvalue could slow down the processes in metabolic networks that describe processes in cancer. To verify our hypothesis, we have built the in silico model of cancer Vini and run it on a supercomputer. Vini transformed the metabolic pathways of cancer from Kyoto Encyclopedia of Genes and Genomes into the binding energy matrices representing binding energies between the genes and proteins on one side and drugs being investigated on another side. Some matrix elements also represent interactions between proteins and genes. Then, it calculated the second largest eigenvalues of these matrices.

In the end, we compared the calculated results against the existing *in vitro* and *in vivo* experimental results. The calculated efficacy of cancer drugs was confirmed in 79.31% of *in vivo* experimental cases, and in 92.30% of *in vitro* experimental cases.

These results show that the second largest eigenvalue plays an important role in metabolic cancer networks and that the Vini model can be an effective aid in finding more effective cancer therapies.

Keywords: Eigenvalue of graph; Complex systems optimization; Metabolic cancer networks; Supercomputer; Binding energy matrices

Introduction

Despite the major improvements in the effectiveness of cancer therapy over the last decades, cancer remains one of the leading causes of mortality in the world. Cancer was responsible for 8.8 million deaths worldwide in 2012 [1] and according to World Health Organization cancer fact sheets, with approximately 14 million new cases every year, the second leading cause of death globally. In addition, an increase in the number of new cases from 14.1 million in 2012 to 21.6 million in 2030 is expected. According to the US National Cancer Institute, a 5-year survival rates for patients with metastatic stage IV colon cancer, rectal cancer, kidney and pancreatic cancer, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC) and hepatocellular carcinoma are 11, 12, 8, 1, 2, 1 and 3 percent respectively, giving an average 5-year survival rate of 5.42 percent. This means that out of 1,000 patients diagnosed with one of these types of cancer in stage IV, and after the period of 5 years, about five of them will still be alive. Even if we take into account that some of these patients will die from some other diseases not directly related to cancer, the five-year average survival rate is weak and unsatisfactory. However, with the emergence of supercomputers, we can analyze in more depth the natural laws of life on Earth, including the metabolic processes regarding cancer. We can analyze data obtained from high-throughput genomic and proteomic tools, solve systems with millions of linear equations, and analyze graphs that represent thousands of genes and proteins. The better we

understand life, the more chances we have of finding more effective cancer therapies. Efficient processing of huge amount of data condensed in human genome, with the goal to find the optimal cancer therapy, lies at the heart of our in silico model of cancer Vini. The Vini model was developed as a parallel application for supercomputers. The need for supercomputing power lies in the complexity of cancer disease, where thousands of molecules are organized in multi-molecular complexes and interact with one another. In addition, these complexes interact with one another, leading to exponentially increased complexity [2].

There are several approaches that help us understand the complexity of cancer and the processes from one genetically mutated cell to the last metastatic cancer phase. The chaos theory, which is the theory of highly non-linear dynamical systems, is trying to find

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the laws to model this complexity [3], either by setting systems of nonlinear equations describing cancer behavior or by investigating cancer mechanisms by means of strange attractors [4]. In contrary to the chaos theory, omics approaches gather huge amounts of data generated by changes of all genes and proteins, trying to find functional entities within the complex cancer organization [5]. System biology is different from the omics approach and from the chaos theory. It tries to disclose the molecular structures of individual genes and proteins, and then integrate them into larger information structures [6]. These larger information structures are organized into databases focusing on cancer-related genes such as COSMIC [7], or focusing on cancer drugs such as Cancer Cell Line Encyclopedia [8]. They are analyzed using methods based on known pathways such as PathScan [9] and Netbox [10], or using networks describing metabolic pathways such as those from Kyoto Encyclopedia of Genes and Genomes (KEGG) database [11], and MetaCyc [12], which contain proteins, chemical compounds, and relationships between these entities.

The Vini model approaches cancer in the spirit of system biology, and is oriented towards analysis of metabolic pathways. It was tested with the data from KEGG database, which, along with Reactome [13], is considered the most reliable source of experimentally confirmed metabolic reactions. Systematic analysis [14] revealed 15161 compounds in KEGG, 14621 of them with structure, and with the mean associated pathway per compound of 0.67. Since Vini is an in silico model of cancer [15], it only analyzes cancer pathways, in this case KEGG cancer pathways. They contain more than 600 compounds of which about 400 have a structure. KEGG cancer pathways are network diagrams describing the metabolism of 17 specific cancer types: gastric cancer, colorectal cancer, pancreatic cancer, hepatocellular carcinoma, endometrial cancer, breast cancer, prostate cancer, thyroid cancer, bladder cancer, acute and chronic myeloid leukemia, melanoma, basal cell carcinoma, small cell lung cancer, non-small cell lung cancer, renal cell carcinoma, and glioma. There is additional cancer pathway providing the general overview of cancer metabolism, and besides some of the main hallmarks of cancers [16] like genomic instability,

proliferation, insensitivity to anti-growth signals, evading apoptosis sustained angiogenesis and tissue invasion and metastasis, it describes additional cancer mechanisms like mitochondrion, immortality, resistance to chemotherapy, block of differentiation, microtubule, fumarate to S-malate conversion, and genomic damage. Typical KEGG cancer pathway elements are rectangles representing genes, circles representing chemical compounds and glycans, and lines representing reactions and interactions. Specific boxes may exist providing additional information (Figure 1).

Besides homo *sapiens* cancer pathways, KEGG cancer pathways are available for more than fifty other species, e.g., *Canis familiaris, Felix domesticus, Mus musculus, Gorilla gorilla* etc.

There are various ways of how in silico models of cancer complement *in vitro* and *in vivo* experiments, thus helping us to find better and more effective cancer therapies and to set better diagnosis. These models analyze cancer processes either at higher scale, like tumor extracellular matrix [17], or at the molecular level [18]. The cancer analysis can be performed with statistically based graphing models developed on genomic [19], transcriptional [20] and trajectory levels [21], statistically derived network models [22] trying to detect the basic distribution of probability from data samples and metabolic models that use ordinary [23] or partial differential equations [24]. A comprehensive overview of the various statistical and mathematical methods used in various *in silico* models of cancer can be found [25].

Although *in silico* models of cancer are already valuable tools for the detection of new drugs [26] and the establishment of more precise cancer diagnoses [27], they are still not accurate enough to be implemented in clinical practice. Increasing the in silico model accuracy is one of the most important goals, and this can be accomplished by using larger and more complete datasets, by personalized approach to each cancer patient, and by using well developed mathematical algorithms which solve large optimization problems. Optimal solution means more precise diagnosis and more effective therapy.

Some actions in this direction have already been made. Non-convex
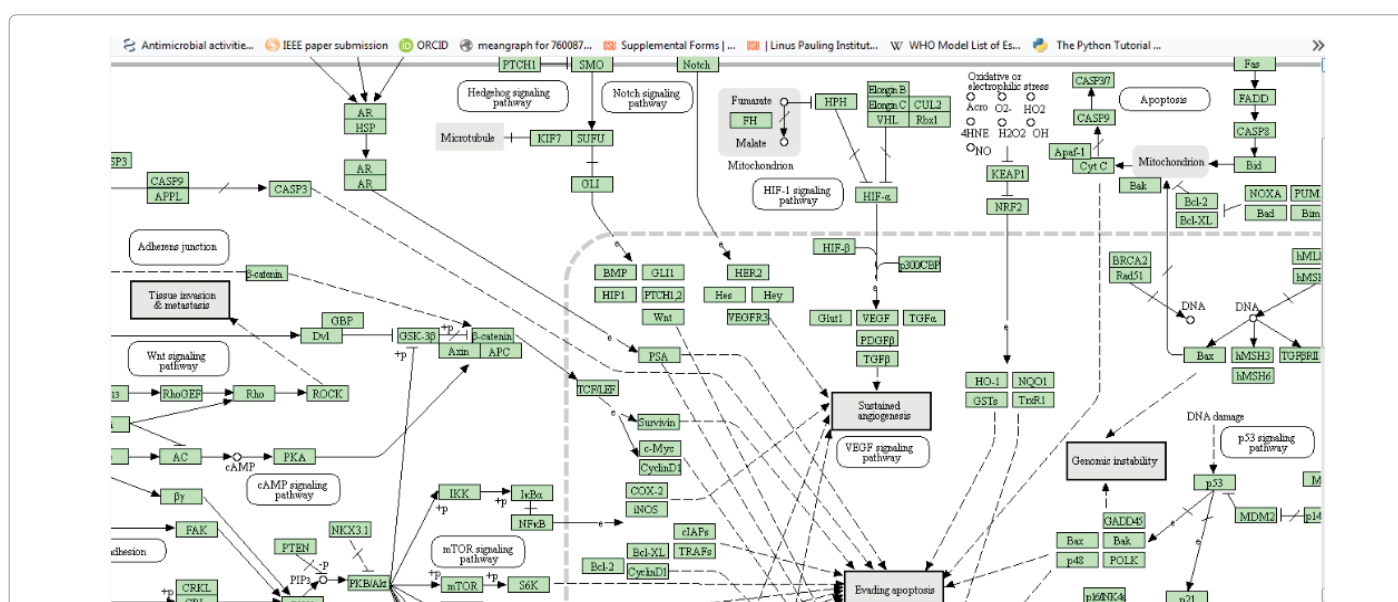

Figure 1: An example of KEGG metabolic pathway of cancer (hsa05200). Green rectangles hold gene and protein names, lines between nodes represent interactions, while gray rectangles annotate main cancer mechanisms.

and convex optimization [28] were applied in liver cancer radiotherapy with a significant improvement in tumor reduction [29]. Semidefinite programming [30] has helped to classify patients with breast cancer on those with benign and malignant tumors with a high accuracy of 95.5 percent [31]. Correlation of the eigenvalues of networks representing normal and carcinogenic breast tissue at the proteomic level was investigated [32].

Enabling more effective cancer therapies by using eigenvalue optimization [33] is the main goal of this study and lies at the heart of the *in silico* model of cancer Vini. It is to be expected that by increasing the second largest eigenvalue (in further text abbreviated SLEM) of the network describing the metabolic pathway of cancer the carcinogenesis process will slow down and perhaps even completely stop, which will be discussed in the next section. Since the algorithm for maximizing the SLEM of a certain network which describes the metabolic pathway of cancer is unknown, Vini uses supercomputing power and seeks for the solution with the highest SLEM value in the space of all available solutions. This space is defined as a set of matrices whose elements represent the binding energies between the genes and proteins defined by the metabolic pathway of cancer and drugs whose efficacy is being investigated.

The Model

Network diagrams are graphical presentations of networks. Network theory is a part of graph theory, and the network can be viewed as a graph in which nodes have attributes [34]. In that sense, KEGG network diagrams are graphs with nodes representing the names of genes, proteins, and compounds. Besides, KEGG networks describe the various types of relationships between genes, proteins, and compounds. Therefore they can be also viewed as weighted and directed graphs, that is, graphs that have some values associated with directed edges. In computer science and other applications, these values are usually real numbers, but may also be complex numbers, lists, structures, and so on. We may here recall that in the graph theory, a loop is defined as an edge that connects the node to itself. This allows us to define fully weighted graphs, with values assigned both to nodes and edges.

Definition 1

Fully weighted graphs are graphs with weighted edges and weighted loops. Edges and loops in fully weighted graphs may have directions. This allows us to define fully weighted and directed graphs.

Definition 2

Fully weighted and directed graphs are graphs with weighted and directed edges and weighted and directed loops.

In case of metabolic networks, fully weighted and directed graphs allow allocating molecular structures of genes, proteins and compounds to graph nodes, and relationships to graph edges. Matrices representing such graphs can be constructed, and algebraic operations performed on these matrices. For example, consider the fully weighted and directed graph, each node with one loop. Weights are molecular structures pdb(r1), pdb(r2), pdb(r3) and pdb(r4), associated to loops on nodes 1, 2, 3 and 4, as shown the next (Figure 2).

Adjacency matrices are used for the algebraic representation of graphs. The adjacency matrix A for this graph is:

$$A = \begin{bmatrix} pdb(r1) & 0 & 0. & 0 \\ 0 & pdb(r2) & 0 & 0 \\ 0 & 0 & pdb(r3) & 0 \\ 0 & 0 & 0 & pdb(r4) \end{bmatrix} \quad (1)$$

By multiplying the matrix A with the structure $pdb(l)$, original matrix is transformed to the matrix $A^{.}$:

$$A^{.} = pdb(l)A = \begin{bmatrix} pdb(l)pdb(r1) & 0 & 0. & 0 \\ 0 & pdb(l)pdb(r2) & 0 & 0 \\ 0 & 0 & pdb(l)pdb(r3) & 0 \\ 0 & 0 & 0 & pdb(l)pdb(r4) \end{bmatrix} \quad (2)$$

Let's define operator $V(A')$ acting on the main-diagonal elements of A':

$$V(A') = \begin{bmatrix} V(pdb(l)pdb(r1) & 0 & 0. & 0 \\ 0 & V(pdb(l)pdb(r2) & 0 & 0 \\ 0 & 0 & V(pdb(l)pdb(r3) & 0 \\ 0 & 0 & 0 & V(pdb(l)pdb(r4) \end{bmatrix} \quad (3)$$

As the next, let's node 1 connects to nodes 2 and 3 via added edges with weights rel (12) and rel(13). In addition, let's nodes 2 and 3 connect to node 4 via edges with weights rel(24) and rel(34) (Figure 3).

Then, the adjacency matrix A'' of this graph will be:

$$A'' = \begin{bmatrix} V(pdb(l)pdb(rl)) & rel(12) & rel(13) & 0 \\ 0 & V(pdb(l)pdb(r2)) & 0 & rel(24) \\ 0 & 0 & V(pdb(l)pdb(r3)) & rel(34) \\ 0 & 0 & 0 & V(pdb(l)pdb(r4)) \end{bmatrix} \quad (4)$$

As the next, assume that nodes are genes in a certain KEGG cancer pathway, and edges are interactions between them. $pdb(r1)$ to $pdb(r4)$ are molecular structure files of these genes in pdb format from Protein Data Bank [35]. $pdb(l)$ is molecular structure file of cancer drug in pdb format. $rel(12)$, $rel(13)$, $rel(2,4)$ and $rel(3,4)$ are interactions between genes. Operator V is a program for molecular docking computing the binding energies $e1, e2, e3, e4$ between genes and chemical compound. Then, matrix A'' transforms into a new matrix. We call this matrix binding energy matrix, abbreviated BE. For this simple example, the BE matrix will be:

$$B = \begin{bmatrix} e1 & 1 & 1 & 0 \\ 0 & e2 & 0 & 1 \\ 0 & 0 & e3 & 1 \\ 0 & 0 & 0 & e4 \end{bmatrix} \quad (5)$$
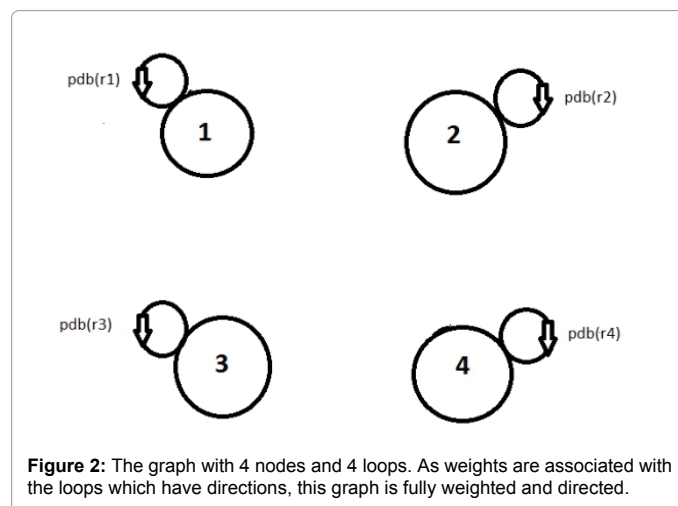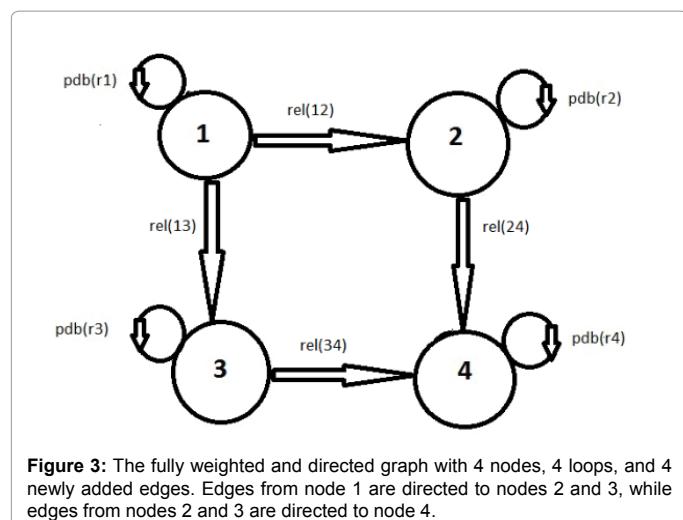

Figure 2: The graph with 4 nodes and 4 loops. As weights are associated with the loops which have directions, this graph is fully weighted and directed.

Figure 3: The fully weighted and directed graph with 4 nodes, 4 loops, and 4 newly added edges. Edges from node 1 are directed to nodes 2 and 3, while edges from nodes 2 and 3 are directed to node 4.

BE matrices are of the much bigger size than the matrix in this example. Their size depends on cancer type and is in the range from several thousand to several tens of thousands of elements, with dozens of interactions between them. Consequently, screening for the most efficient drug candidates against the cancer is computationally expensive. It consists of two stages. In the first stage, Vini downloaded KEGG cancer pathway structure from Genome Net, a Japanese network of database and computational services for genome research and related research areas in biomedical sciences. The structure is then parsed for genes, proteins, compounds and relation entries. Then, the adjacency matrix is created according to the procedure already explained through (1)-(5). *V* operator is Auto dock Vina program for molecular docking [36], which calculates $e1, e2, \ldots, en$ binding energy levels between genes and drugs. For each drug, one *BE* matrix is created, and the process is repeated until all available drugs are screened. In the second stage, second largest eigenvalues of these matrices are computed.

Our thesis is that the drug with the highest second largest eigenvalue has the highest anticancer activity. There are several reasons for such thinking. In 1973, Fiedler [37] and Donath and Hoffmann [38] pointed to the possibility of using eigenvalues for graph partitioning. According to Tomic [39], the SLEM was reported as the measure of the execution speed of parallel processing systems. Boyd et al. [40] developed the algorithm for minimizing the SLEM in stochastic networks. With some modifications, this algorithm was successfully implemented for the optimization of High Performance Linpack benchmark [41] on supercomputer [42]. Consequently, since a lower SLEM value ensures the faster run in computer networks, it is expected that the cancer drugs with higher SLEM values will more effectively slow down carcinogenesis in cancer networks.

Vini is written in Linux shell scripting language and Python, and uses Auto dock Vina for computing molecular binding energies. As the calculation of binding energies and the creation of binding energy matrices is computationally intensive, Vini is targeted to run on the supercomputer. It is an open source code and is available from the authors of this research on the request. However, the usage of metabolic cancer pathways generally requires the proper licensing from the providers of these pathways.

Results

KEGG cancer pathways are network diagrams with various entities representing genes, proteins, RNAs, chemical compounds, glycans and chemical reactions. Based on additional information on chemical compounds whose anti-cancer effectiveness needs to be estimated. Vini transforms cancer pathways into binding energy matrices and after that calculates SLEM values of these matrices. Binding energy matrices describe the interaction of cancer with chemical compounds, such as with approved cancer drugs, anticancer herbal substances, vitamins, dietary supplements, opioids, anti-inflammatory and other drugs sometimes accompanying the cancer therapy. We assumed that the SLEM values of these matrices are related to the rate of development of the cancer processes defined by these metabolic pathways, with the higher SLEM value expressing the slower rate and vice versa. In order to check our assumption, we let Vini to process 17 KEGG cancer pathways against the number of chemical compounds, to create binding energy matrices, and finally to calculate their SLEM values. The calculation was performed on 600 Intel core processors and lasted for about 160 hours.

During this time Vini created 3417 binding energy matrices representing interactions between 17 metabolic cancer pathways and 201 chemical compounds, among them 132 cancer drugs, 15 *vitamins* (A, C, D2, D3, E, K1, K2, B1, B2, B3, B5, B6, B9, B12, aminobensoic_acid), 11 Anticancer herbal compounds (artemisinin, beta-glucan, beta-lapachone, lapachol, curcumin, cannabidiol, tetrahydrocannabinol, epigallocatechin-gallate, genistein, hirsutine, resveratrol), 8 supplements (chondroitin-sulfate, D-methionine, decarenone, glucosamine, glutathione, hyaluronic acid, omega-3-fatty-acid, soy-lecithin), 7 Antibiotic compounds (amoxicillin, clavulanate, norfloxacin, ciprofloxacin, enrofloxacin, sulfamethoxazole, trimethoprim), 4 NSAID drugs *(meloxicam, carprofen, firocoxib, aspirin),* two opioids (morphine, oxycodone), 2 drugs for inflammatory bowel disease (sulfasalazine, mesalazine) and 3 other drugs (diazepam, edetic acid, ranitidine). As an example, the following two tables list the SLEM values of 60 cancer drugs and 69 other chemical compounds computed against the KEGG prostate cancer pathway (Tables 1 and 2).

Besides, Table S1 in the supplementary information lists the SLEM values for all KEGG cancer pathways and chemical compounds investigated.

Evaluation of the model was performed by comparing the SLEM values with the cancer drugs efficiency results obtained from the existing *in vivo* and *in vitro* experiments. The results of the evaluation against *in vivo* experimental results are given in Table 3.

The fields in the table for cancer drugs with no *in vivo* reference are labeled in yellow. The numbers in the table fields are references [43-99] of the relevant studies. The probability that Vini will correctly predict the efficiency of a cancer drug against a specific type of cancer is defined as the ratio of the number of green fields to the sum of green and violet fields and is 0.793. The abbreviations: PTX- *paclitaxel*, DTX - docetaxel, VNB- vinorelbine tartrate, TRP- triptorelin pamoate, EVE-everolimus, EBU- eribulin mesylate, IDA- idarubicin hydrochloride, MDT- midostaurin, TES- temsirolimus, RCC- renal cell carcinoma, HCC-hepatocellular carcinoma, BCC- basal cell carcinoma, CML-chronic myeloid leukemia, AML- acute myeloid leukemia, SCLC-small cell lung cancer, non-small cell lung cancer. The short description of each study, together with the results and conclusion from the study, is in Table S2 of supplementary information.

The accuracy of the Vini model in predicting *in vitro* efficacy of cancer drugs was estimated by comparing the SLEM values with data from the NCI-60 database. This database contains data about

Cancer drug	SLEM	Cancer drug	SLEM	Cancer drug	SLEM
docetaxel	12.8	Epirubicin hydrochloride	10.3	Estradiolvalerate	9.7
triptorelin pamoate	12.7	Degarelix	10.2	Etoposide phosphate	9.7
paclitaxel	12.5	Sonidegib phosphate	10.2	Testosterone enanthate	9.7
vinorelbine tartrate	12.1	Bosutinib hydrate	10.2	Sorafenib tosylate	9.7
everolimus	12	Daunorubicin hydrochloride	10.2	Crizotinib	9.6
eribulin mesylate	11.6	Idarubicin hydrochloride	10.2	Lapatinib ditosylate	9.6
midostaurin	11.3	Exemestane	10.1	Palbociclib	9.6
vincristine sulfate	11.2	Cabazitaxel acetonate	10.1	Ibrutinib	9.6
Irinotecan hydrochloride	11.2	prednisolone	10.1	Sorafenib	9.6
temsirolimus	11.1	Valrubicin	10	Pazopanib hydrochloride	9.6
Megestrol acetate	11	Imatinib mesylate	10	Regorafenib hydrate	9.5
Abiraterone acetate	10.8	Enasidenib mesylate	10	Topotecan hydrochloride	9.5
Ixabepilone	10.8	Trametinib dimethyl_sulfoxide	10	Sorafenib tosylate	9.4
Cabozantinib s_malate	10.6	Abemaciclib	9.9	Axitinib	9.4
Nilotinib hydrochloride hydrate	10.6	Alectinib hydrochloride	9.9	Bicalutamide	9.4
Olaparib	10.6	Ponatinib hydrochloride	9.8	Tamibarotene	9.4
Dabrafenib mesylate	10.5	Ceritinib	9.8	Enzalutamide	9.3
Neratinib maleate	10.4	Goserelin acetate	9.8	Cobimetinib fumarate	9.3
Goserelin acetate	10.3	Bexarotene	9.8	Dasatinib	9.3
Doxorubicin hydrochloride	10.3	Etoposide	9.8	Brigatinib	9.3

Table 1: 60 anticancer drugs with the highest SLEM values against the KEGG prostate cancer pathway.

Vitamin	SLEM	Anticancer herbal compounds	SLEM	Nutraceuticals	SLEM
A	7.5	artemisinin	9.1	chondroitin sulfate	8.7
C	5.9	beta glucan	8.4	D_methionine	4.3
B1	6.5	beta lapachone	8.7	decarenone	8.2
B2	9,10	cannabidiol	9.2	glucosamine	5.9
B6	5.6	tetrahydrocannabinol	9	glutathione	7
B9	8.5	curcumin	7.6	hyaluronic acid	10
B12	11.8	epigallocatechin-gallate	10.6	omega_3_fatty_acid	6.9
D2	9.4	genistein	8.4	soy lecithin	6.5
D3	9.5	hirsutine	8.2		
E	8.5	lapachol	8.4		
K1	8.3	resveratrol	7.7		
K2	9.4				
aminobensoic acid	5.6				

Table 2: The SLEM values for vitamins, anticancer herbal compounds, and supplements. These eigenvalues were calculated against the KEGG metabolic pathway representing the prostate cancer.

in vitro anti-cancer efficacy for more than 100,000 compounds and 50,000 natural products extracts against 60 types of tumor cells, which represent nine types of cancer tissues [100]. In the NCI-60 database, the efficacy of a cancer drug is defined as the logarithm of a drug concentration which by 50% inhibits cancer cell division. The drug with the highest SLEM value for the specific KEGG cancer pathways was validated in the NCI-60 database considering its efficacy against the corresponding tumor cell type. If that drug is not found in the NCI-60 database, the search is repeated for the drug with the next highest SLEM value and so on, until the five drugs with the highest SLEM values were found. Similarly, the drug with the lowest SLEM value for the specific KEGG cancer pathway is searched in the NCI-60 database against the same type of cancer modeled with that specific pathway. If this drug is not found in the NCI-60 database, the search is repeated for the drug with the next lowest SLEM value and so on, until the five drugs with the lowest SLEM values were found. The search is repeated for 9 KEGG cancer pathways for which NCI-60 has data on the efficacy of cancer drugs against corresponding cancer cells, including cells of colon cancer, renal cell carcinoma, glioma, prostate cancer, melanoma, chronic myeloid leukemia, acute myeloid leukemia, non-small cell lung cancer and breast cancer. For example, *in vitro* activity of five cancer drugs with the highest SLEM values and five cancer drugs with the highest SLEM values against the KEGG prostate cancer pathway is shown in Table 4.

Besides, Table S3 in the supplementary information lists the drugs with the highest and the lowest SLEM values and their logarithmic ($-\log_4$) concentrations that inhibit cell division by 50% for all 9 cancer tissues in NCI-60 database.

The probability that Vini will accurately identify the drugs according to their *in vitro* activity depends on the cancer type and is shown in Table 5.

Conclusions

In silico model of cancer Vini was developed on the hypothesis that there is a correlation between the anti-cancer activity of chemical compounds and SLEM values of binding energy matrices. Thereby, binding energy matrices represent binding energies between the genes and proteins on one side and drugs being investigated on another side.

KEGG cancer pathway	PTX	DTX	VNB	TRP	EVE	EBU	IDA	MDT	TES
Colorectal cancer	43	44	45		46				
RCC	47	47	48		49	50			
HCC	52				51		53		
Endometrial cancer		55		54	57	56			
Glioma	59	58	61		60				
Prostate cancer	63	62	65	64	66				
Thyroid cancer	69	68			67				
BCC	70								
Melanoma	71	72	75		73	74			
Bladder cancer		76	77			78			
CML			79						
AML		80		81	82				
SCLC	84	83	87	85	86				
NSCLC	88	89	91		90				
Breast cancer	95	93			92				94
Gastric cancer	98	97			96		99		
Legend:			active			inactive		no reference	
		numbers: trial references							

Table 3: The list of cancer drugs with the five largest SLEM values for the specific KEGG cancer pathways. The only exception to this "rule five" is in case of melanoma, where eribulin on the 5th and vinorelbine on the 6th place has the same SLEM value. If the efficiency of a drug is confirmed by the existing in vivo testing, the appropriate field of the table is labeled green. Otherwise it is labeled purple. The fields in the table for cancer drugs with no in vivo reference are labeled in yellow. The numbers in the table fields are references [43-99] of the relevant studies. The probability that Vini will correctly predict the efficiency of a cancer drug against a specific type of cancer is defined as the ratio of the number of green fields to the sum of green and violet fields and is 0.793. The abbreviations: PTX-paclitaxel, DTX-docetaxel, VNB-vinorelbine tartrate, TRP-triptorelin pamoate, EVE-everolimus, EBU-eribulin mesylate, IDA-idarubicin hydrochloride, MDT-midostaurin, TES-temsirolimus, RCC-renal cell carcinoma, HCC-hepatocellular carcinoma, BCC-basal cell carcinoma, CML-chronic myeloid leukemia, AML-acute myeloid leukemia, SCLC-small cell lung cancer, non-small cell lung cancer. The short description of each study, together with the results and conclusion from the study, is in the S2 table of supplementary information.

Prostate cancer	SLEM	PC-3	DU-145
docetaxel	12.8	-8	-8
paclitaxel	12.5	-8.032	-7.667
triptorelin pamoate	12.2	NA	NA
vinorelbine tartrate	12.1	-8	-8
everolimus	12	-8	-7.02
thioguanine	5.4	-5.475	-6.269
fluorouracil	5.3	-4.352	-5.547
dacarbazine	5.3	-4.016	-4.143
thiotepa	4.7	NA	NA
Mechlorethamine hydrochloride	4.2	-5.182	-5.783

Table 4: The NCI-60 logarithmic ($-log_4$) concentration values of some cancer drugs required for 50% inhibition of PC-3 and DU-145 prostate cancer cell division. Listed are the five drugs with the highest SLEM values and the five drugs with the lowest SLEM values. All five cancer drugs with the highest SLEM values belong to a group of drugs that express the high inhibition of cancer cells PC-3 and DU-145, while all five drugs with the lowest SLEM values express the low inhibition of cancer cells PC-3 and DU-145. There is no case that the value of the concentration of any drug in the group of those with the highest SLEM values is greater than or equal to the concentration of any drug from the group with the lowest SLEM values, and vice versa. It follows that Vini 100% accurately identifies cancer drugs with the highest and lowest in vitro activity against PC-3 and DU-145 prostate cancer cells.

To confirm this, we used Vini to create 3417 matrices that describe the interactions of 132 cancer drugs and 69 other chemical compounds with 17 KEGG cancer pathways and to calculate their SLEM values.

Calculated SLEM values were compared with the logarithmic concentration values of cancer drugs in NCI-60 database that inhibit the cancer cells division by 50%, and with the results of relevant *in vivo* experiments. The correlation of the SLEM values with the data from the NCI-60 base was found in 92.30% of cases, while the correlation with the data from *in vivo* experiments was found in 79.31% of cases.

The difference in predicting *in vivo* and *in vitro* drug efficacy is inherent to the model. *Vini* acts at the genomic and proteomic level defined by the metabolic pathways of cancer. Therefore, it does not take into the account effects of tumor stroma [101], extracellular matrix [102], pharmacokinetics [103], and toxicity [104] of cancer drugs.

Other well-developed computer models like Swiss ADME [105]

can be used to bridge this gap. Besides, as Vini calculates the binding energies between a certain drug and only one domain of each gene in metabolic pathways, there is a certain loss of information. In addition, Auto dock Vina performs well molecular docking calculations of drugs with molar masses of up to several hundred Daltons but is not suitable for the drugs with higher molar masses. Therefore, further improvement in the accuracy and the functionality of Vini can be obtained by letting Vini compute the binding energies of drugs across several domains of genes, and by integrating additional molecular docking tools able to work with large molecule drugs [106]. Besides KEGG, other metabolic pathway databases like Reactome [107] can be used. Thus there is a chance to further increase the functionality of Vini and accuracy of drug efficacy prediction by combining two or more metabolic pathways.

Vini already points out that some drugs not approved for certain types of cancer are effective but *in vivo* and *in vitro* experiments

Colorectal cancer	RCC	Glioma	Prostate cancer	Melanoma	CML	ACL	NSCLC	Breast cancer
0.78	0.84	0.96	1	0.91	0.96	0.95	0.94	0.96

Table 5: Lists the probabilities of the correct differentiation of in vitro activity of the drugs against various NCI-60 cell lines. The mean probability for nine NCI-60 cell lines is 0.92. These results confirm the high accuracy of Vini in differentiating between the drugs with strong and weak in vitro activity against specific cancer types. Table S4 in the supporting information lists the drugs with the highest and the lowest SLEM values and their corresponding inhibitory values for all 9 cancer tissues in NCI-60 database. The abbreviations: RCC - renal cell carcinoma, CML - chronic myeloid leukemia, ACL - acute myeloid leukemia, NSCLC - non-small cell lung cancer.

are missing to confirm this. A good example for this is triptorelin pamoate, approved only for the therapy of prostate cancer. However, Vini declares it as effective in colorectal cancer, melanoma, and acute myeloid leukemia. There are also other chemical compounds calculated by Vini as effective against various cancer types, like several herbal compounds and high molecular weight hyaluronic acid [108]. Additionally, these substances have relatively low toxicity, and there is a chance they may work in synergy with the approved cancer drugs. That reinforces our opinion that Vini is an effective aid in the process of screening new drug candidates for cancer therapy.

Likewise, it's presumable that the results are applicable also in veterinary oncology, which is to be more profoundly investigated in the future.

One of the major problems in cancer therapy is frequent appearance of chemoresistence in case of chemotherapy with only one drug. That is why our future research will focus on the evaluation of the effectiveness of combinations of two or more drugs. Another problem is the resistance of some types of cancer to radiotherapy. Therefore, in our future research, a special emphasis will be put on extending the functionality of the *Vini* model in this direction.

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References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, et al. (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International Journal of Cancer 136: 359-386.

2. Dimitrakopoulos CM, Beerenwinkel N (2017) Computational approaches for the identification of cancer genes and pathways. Wiley Interdiscip Rev Syst Biol Med 9: 1364-1382.

3. Dalgleish A (1999) The relevance of non-linear mathematics (chaos theory) to the treatment of cancer, the role of the immune response and the potential for vaccines, QJM: An International Journal of Medicine 92: 347-359.

4. Deb D (2016) Understanding the Unpredictability of Cancer using Chaos Theory and Modern Art Techniques. Leonardo 49: 66-67.

5. Zhang H, Liu T, Zhang Z, Payne SH, Zhang B, et al. (2016) Integrated proteogenomic characterization of human high-grade serous ovarian cancer. Cell 166: 755-765.

6. Koutsogiannouli E, Papavassiliou AG, Papanikolaou NA (2013) Complexity in cancer biology: is systems biology the answer? Cancer Med 2: 164-177.

7. Forbes SA, Tang G, Bindal N, Bamford S, Cole C, et al. (2010) COSMIC (the Catalogue of Somatic Mutations in Cancer): a resource to investigate acquired mutations in human cancer. Nucleic Acids Res. 38: 652-657.

8. Barretina J, Caponigro G, Stransky N, Venkatesan K, Margolin AA, et al. (2012) The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity. Nature 483: 603-607.

9. Wendl MC, Wallis JW, Lin L, Kandoth C, Mardis ER, et al. (2011) PathScan: a tool for discerning mutational significance in groups of putative cancer genes. Bioinformatics 27: 1595-1602.

10. Cerami E, Demir E, Schultz N, Taylor BS, Sander C (2010) Automated network analysis identifies core pathways in glioblastoma. PLoS ONE 5: e8918.

11. Kanehisa M, Furumichi M, Tanabe M, Sato Y, Morishima K (2017) KEGG: new perspectives on genomes, pathways, diseases and drugs. Nucleic Acids Res 45: 353-361.

12. Caspi R, Billington R, Fulcher CA, Keseler IM, Kothari A, et al. (2018) The MetaCyc database of metabolic pathways and enzymes. Nucleic Acids Res 46: 633-639.

13. Matthews L, Gopinath G, Gillespie M, Caudy M, Croft D, et al. (2009) Reactome knowledgebase of human biological pathways and processes. Nucleic Acids Res 37: 619-622.

14. Altman T, Travers M, Kothari A, Caspi R, Karp PD (2013) A systematic comparison of the MetaCyc and KEGG pathway databases. BMC Bioinformatics 14: 1-15.

15. Edelman LB, Eddy JA, Price ND (2010) In silico models of cancer. Wiley Interdiscip Rev Syst Biol Med 2: 438-459.

16. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144: 646-674.

17. Anderson ARA (2005) A hybrid mathematical model of solid tumour invasion: the importance of cell adhesion. Math Med Biol 22: 163-186.

18. Ono K, Muetze T, Kolishovski G, Shannon P, Demchak B (2015) CyREST: Turbocharging Cytoscape Access for External Tools via a RESTful API. F1000 Research 4: 1-13.

19. Nigro J, Misra A, Zhang L, Smirnov I, Colman H, et al. (2005) Integrated array-comparative genomic hybridization and expression array profiles identify clinically relevant molecular subtypes of glioblastoma. Cancer Res 65: 1678-1686.

20. Gerstung M, Baudis M, Moch H, Beerenwinkel N (2009) Quantifying cancer progression with conjunctive Bayesian networks. Bioinformatics 25: 2809-2815.

21. Zhang N, Wang H, Fang Y, Wang J, Zheng X, et al. (2015) Predicting anticancer drug responses using a dual-layer integrated cell line-drug network model. PLoS Computational Biology 11: e1004498.

22. Klinke DJ, Birtwistlec MJ (2015) In silico model-based inference: an emerging approach for inverse problems in engineering better medicines. Curr Opin Chem Eng. 10: 14-24.

23. Werner SL, Barken D, Hoffmann A (2015) Stimulus Specificity of Gene Expression Programs Determined by Temporal Control of IKK Activity. Science 309: 1857-1861.

24. Johnston MD, Edwards CM, Bodmer WF, Maini PK, Chapman SJ (2007) Mathematical modeling of cell population dynamics in the colonic crypt and in colorectal cancer. Proceedings of the National Academy of Sciences.104: 4008-4013.

25. Blair RH, Trichler DL, Gaille DP (2012) Mathematical and statistical modeling in cancer systems biology. Front Physiol 3: 1-8.

26. San Lucas FA, Fowler J, Chang K, Kopetz S, Vilar E, et al. (2014) Cancer in silico drug discovery: a systems biology tool for identifying candidate drugs to target specific molecular tumor subtypes. Mol Cancer Ther 13: 3230-3240.

27. Kahn CE, Roberts L, Wang K, Jenks D, Haddawy P (1995) Preliminary investigation of a Bayesian network for mammographic diagnosis of breast cancer. Proc Annu Symp Comput Appl Med Care. 208-212.

28. Yin Z (2007) A review of: "Interior Point Algorithms" Theory and Analysis. IIE Transactions 31: 275-276.

29. Gaddy MR, Yıldız S, Unkelbach J, Papp D (2018) Optimization of spatiotemporally fractionated radiotherapy treatments with bounds on the achievable benefit. Physics in Medicine and Biology 63: 015036.

30. Vandenberghe L, Boyd S (1996) Semidefinite programming. SIAM Review 38: 49-95.

31. Conforti D, Guido R (2010) Kernel based support vector machine via semidefinite programming: Application to medical diagnosis. Computers & Operations Research 37: 1389-1394.

32. Rai A, Menon AV, Jalan S (2014) Randomness and preserved patterns in cancer network. Scientific Reports 4: 1-7.

33. Lewis A (2003) The mathematics of eigenvalue optimization. Mathematical Programming 97: 155-176.

34. Estrada E (2013) Graph and network theory in Physics.

35. Parasuraman S (2012) Protein data bank. J Pharmacol Pharmacother 3: 351-352.

36. Trott O, Olson AJ (2010) AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading. Journal of Computational Chemistry 31: 455-461.

37. Fiedler M (1973) Algebraic connectivity of graphs. Czechoslovak Mathematical Journal 23: 298-305.

38. Donath WE, Hoffman AJ (1973) Lower bounds for the partitioning of graphs. IBM J Res Develop 17: 420-425.

39. Tomic D (2002) Spectral performance evaluation of parallel processing systems. Chaos Solitons Fractals. 13: 25-38.

40. Boyd S, Diakonis P, Xiao L (2004) Fastest Mixing Markov Chain on a Graph. SIAM Review 46: 667-689.

41. Dongarra J, Luszczek P, Petitet A (2003) The LINPACK Benchmark: past, present and future. Concurrency and Computation: Practice and Experience 15: 803-820.

42. Tomic D, Gjenero L, Imamagic E (2013) Semidefinite optimization of High Performance Linpack on heterogeneous cluster. Proceedings of the 36th International Convention MIPRO, pp: 157-162.

43. Abbas A, Nehme E, Fakih M (2011) Single-agent paclitaxel in advanced anal cancer after failure of cisplatin and 5-fluorouracil chemotherapy. Anticancer Research 31: 4637-4640.

44. Clark TB, Kemeny NE, Conti JA, Huang Y, Andre AM, et al. (1998) Phase II trial of docetaxel (Taxotere) for untreated advanced colorectal carcinoma. Cancer Investigation 16: 314-318.

45. Gebbia V, Maiello E, Testa A, Cannata G, Colucci G, et al. (1996) Single agent vinorelbine in the treatment of unresectable lung metastases from colorectal cancer. Oncol Rep 3: 563-565.

46. Ng K, Tabernero J, Hwang J, Bajetta E, Sharma S, et al. (2013) Phase II study of everolimus in patients with metastatic colorectal adenocarcinoma previously treated with bevacizumab-, fluoropyrimidine-, oxaliplatin-, and irinotecan-based regimens. Clinical Cancer Research 19: 3987-3995.

47. Hartmann JT, Bokemeyer C (1999) Chemotherapy for renal cell carcinoma. Anticancer Research 19: 1541-1543.

48. Sinha S, Cao Y, Dutta S, Wang E, Mukhopadhyay D (2010) VEGF neutralizing antibody increases the therapeutic efficacy of vinorelbine for renal cell carcinoma. Journal of Cellular and Molecular Medicine 14: 647-658.

49. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, et al. (2010) RECORD-1 Study Group. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. Cancer 116: 4256-4265.

50. Quinn DI, Ruel N, Twardowski P, Groshen SG, Dorff TB, et al. (2015) Eribulin in advanced urothelial cancer (AUC) patients (pts): A California Cancer Consortium trial-NCI/CTEP 7435. Journal of Clinical Oncology 33: 4504-4504.

51. Zhu AX, Kudo M, Assenat E, Cattan S, Kang YK, et al. (2014) Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. JAMA 312: 57-67.

52. Strumberg D, Erhard J, Harstrick A, Klaassen U, Müller C, et al. (1998) Phase I study of a weekly 1 h infusion of paclitaxel in patients with unresectable hepatocellular carcinoma. European Journal of Cancer 34: 1290-1292.

53. Boulin M, Hillon P, Cercueil JP, Bonnetain F, Dabakuyo S, et al. (2014) Idarubicin-loaded beads for chemoembolisation of hepatocellular carcinoma: results of the IDASPHERE phase I trial. Alimentary Pharmacology and Therapeutics 39: 1301-1313.

54. Lhomme C, Vennin P, Callet N, Lesimple T, Achard JL, et al. (1999) A. multicenter phase II study with triptorelin (sustained-release LHRH agonist) in advanced or recurrent endometrial carcinoma: a French anticancer federation study. Gynecologic Oncology 75: 187-193.

55. Hamed RH, Abdelkhalek SE (2012) Clinical outcome of docetaxel in advanced or metastatic endometrial cancer. Hematology/Oncology and Stem Cell Therapy 5: 146-151.

56. Goel S, Mita AC, Mita M, Rowinsky EK, Chu QS, et al. (2009) A phase I study of eribulin mesylate (E7389), a mechanistically novel inhibitor of microtubule dynamics, in patients with advanced solid malignancies. Clinical Cancer Research 15: 4207-4212.

57. Ray-Coquard I, Favier L, Weber B, Roemer-Becuwe C, Bougnoux P, et al. (2013) Everolimus as second- or third-line treatment of advanced endometrial cancer: ENDORAD, a phase II trial of GINECO. British Journal of Cancer 108: 1771-1777.

58. Sanson M, Napolitano M, Yaya R, Keime-Guibert F, Broët P, et al. (2000) Second Line Chemotherapy with Docetaxel in Patients with Recurrent Malignant Glioma: A Phase II Study. Journal of Neuro-Oncology 50: 245-249.

59. Prados MD, Schold SC, Spence AM, Berger MS, McAllister LD, et al. (1996) Phase II study of paclitaxel in patients with recurrent malignant glioma. Journal of Clinical Oncology 14: 2316-2321.

60. Wahl M, Chang SM, Phillips JJ, Molinaro AM, Costello JF, et al. (2017) Probing the phosphatidylinositol 3-kinase/mammalian target of rapamycin pathway in gliomas: A phase 2 study of everolimus for recurrent adult low-grade gliomas. Cancer 123: 4631-4639.

61. Cappellano AM, Petrilli AS, da Silva NS, Silva FA, Paiva PM, et al. (2015) Single agent vinorelbine in pediatric patients with progressive optic pathway glioma. Journal of Neuro-Oncology 121: 405-412.

62. South A, Burdett S, Clarke N, Gilson C, James N, et al. (2015) Upfront docetaxel for men with prostate cancer, Stampede clinical trial. MRC CTU at UCL Briefing Paper 14: 1-3.

63. Chiappino I, Destefanis P, Addeo A, Galetto A, Cucchiarale G, et al. (2007) Activity of weekly paclitaxel in advanced hormone-refractory prostate cancer. Journal of Clinical Oncology 30: 234-238.

64. Kao CC, Chang YH, Wu T, Sun GH, Yu DS, et al. (2012) Open, multi-center, phase IV study to assess the efficacy and tolerability of triptorelin in Taiwanese patients with advanced prostate cancer. Journal of the Chinese Medical Association 75: 255-261.

65. Oudard S, Caty A, Humblet Y, Beauduin M, Suc E, et al. (2001) Phase II study of vinorelbine in patients with androgen-independent prostate cancer. Ann Oncol 12: 847-852.

66. Templeton AJ, Dutoit V, Cathomas R, Rothermundt C, Bärtschi D, et al. (2013) Phase 2 trial of single-agent everolimus in chemotherapy-naive patients with castration-resistant prostate cancer (SAKK 08/08). European Urology 64: 150-158.

67. Schneider TC, de Wit D, Links TP, van Erp NP, van der Hoeven JJ, et al. (2017) Everolimus in Patients with Advanced Follicular-Derived Thyroid Cancer: Results of a Phase II Clinical Trial. The Journal of Clinical Endocrinology & Metabolism 102: 698-707.

68. Kawada K, Kitagawa K, Kamei S, Inada M, Mitsuma A, et al. (2010) The feasibility study of docetaxel in patients with anaplastic thyroid cancer. Japanese Journal of Clinical Oncology 40: 596-599.

69. Onoda N, Sugino K, Higashiyama T, Kammori M, Toda K, et al. (2016) The Safety and Efficacy of Weekly Paclitaxel Administration for Anaplastic Thyroid Cancer Patients: A Nationwide Prospective Study. Thyroid 26: 1293-1299.

70. Barcelo R, Viteri A, Muñoz A, Gil-Negrete A, Rubio I, et al. (2006) Paclitaxel for

progressive basal cell carcinoma. JAAD 54: 550-552.

71. Hersch EM, Del Vecchio M, Brown MP, Kefford R, Loquai C, et al. (2015) A randomized, controlled phase III trial of nab-Paclitaxel versus dacarbazine in chemotherapy-naïve patients with metastatic melanoma. Annals of Oncology 26: 2267-2274.

72. Einzig AI, Schuchter LM, Recio A, Coatsworth S, Rodriquez R, et al. (1996) Phase II trial of docetaxel (Taxotere) in patients with metastatic melanoma previously untreated with cytotoxic chemotherapy. Medical Oncology 13: 111-117.

73. Si L, Xu X, Kong Y, Flaherty KT, Chi Z, et al. (2012) Major Response to Everolimus in Melanoma with Acquired Imatinib Resistance. Journal of Clinical Oncology 30: 37-40.

74. Towle MJ, Salvato KA, Budrow J, Wels BF, Kuznetsov G, et al. (2001) In vitro and in vivo anticancer activities of synthetic macrocyclic ketone analogues of halichondrin B. Cancer Research 61: 1013-1021.

75. Whitehead RP, Moon J, McCachren SS, Hersh EM, Samlowski WE, et al. (2004) A Phase II Trial of Vinorelbine Tartrate in Patients with Disseminated Malignant Melanoma and One Prior Systemic Therapy. Cancer 100: 1699-1704.

76. Wit R, Kruit WH, Stoter G, de Boer M, Kerger J, et al. (1998) Docetaxel (Taxotere): An active agent in metastatic urothelial cancer, results of a phase II study in non-chemotherapy-pretreated patients. British Journal of Cancer 78: 1342-1345.

77. June RR, Dougherty DW, Reese CT, Harpster LE, Hoffman SL, et al. (2012) Significant activity of single agent vinorelbine against small-cell cancer of the bladder as second line chemotherapy: a case series and review of the literature. Urologic Oncology 30: 192-195.

78. Quinn DI, Aparicio A, Tsao-Wei DD, Groshen SG, Dorff TB, et al. (2010) California Cancer Consortium. Phase II study of eribulin (E7389) in patients (pts) with advanced urothelial cancer (UC) Final report: A California Cancer Consortium-led NCI/CTEP-sponsored trial. Journal of Clinical Oncology 28: 4539-4539.

79. Uckun FM, Morar S, Qazi S (2006) Vinorelbine-based salvage chemotherapy for therapy-refractory aggressive leukaemias. Br J Haematol 135: 500-508.

80. Franklin JL, Seibel NL, Krailo M, Fu C, Adamson PC, et al. (2008) Children's Oncology Group, Phase 2 study of docetaxel in the treatment of childhood refractory acute leukemias: a Children's Oncology Group report. Pediatric Blood Cancer 50: 533-536.

81. Tsavaris N, Kopterides P, Kosmas C, Siakantaris M, Patsouris E, et al. (2006) Spontaneous remission of acute myeloid leukemia associated with GnRH agonist treatment. Leukemia and Lymphoma 47: 557-560.

82. Tan P, Tiong IS, Fleming S, Pomilio G, Cummings N, et al. (2016) The mTOR inhibitor everolimus in combination with azacitidine in patients with relapsed/refractory acute myeloid leukemia: a phase Ib/II study. Oncotarget 8: 52269-52280.

83. Smyth JF, Smith IE, Sessa C, Schoffski P, Wanders J, et al. (1994) Activity of docetaxel (Taxotere) in small cell lung cancer. The Early Clinical Trials Group of the EORTC. Eur J Cancer 30: 1058-1060.

84. Yamamoto N, Tsurutani J, Yoshimura N, Asai G, Moriyama A, et al. (2006) Phase II study of weekly paclitaxel for relapsed and refractory small cell lung cancer. Anticancer Research 26: 777-781.

85. Harlos C, Musto G, Lambert P, Ahmed R, Pitz MW (2015) Androgen pathway manipulation and survival in patients with lung cancer. Hormones and Cancer 6: 120-127.

86. Tarhini A, Kotsakis A, Gooding W, Shuai Y, Petro D, et al. (2010) Phase II study of everolimus (RAD001) in previously treated small cell lung cancer. Clinical Cancer Research 16: 5900-5907.

87. Jassem J, Karnicka-Młodkowska H, van Pottelsberghe C, van Glabbeke M, Noseda MA, et al. (1993) Phase II study of vinorelbine (Navelbine) in previously treated small cell lung cancer patients. EORTC Lung Cancer Cooperative Group. Eur J Cancer 29: 1720-1722.

88. Ranson M, Davidson N, Nicolson M, Falk S, Carmichael J, et al. (2000) Randomized trial of paclitaxel plus supportive care versus supportive care for patients with advanced non-small cell lung cancer. J Natl Cancer Inst 92: 1074-1080.

89. Roszkowski K, Pluzanska A, Krzakowski M, Smith AP, Saigi E, et al. (2000) A multicenter, randomized, phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapy-naive patients with metastatic or non-resectable localized non-small cell lung cancer (NSCLC). Lung Cancer 27: 145-157.

90. Owonikoko TK, Ramalingam SS, Miller DL, Force SD, Sica GL, et al. (2015) A Translational, Pharmacodynamic, and Pharmacokinetic Phase IB Clinical Study of Everolimus in Resectable Non-Small Cell Lung Cancer. Clin Cancer Res 21: 1859-1868.

91. The Elderly Lung Cancer Vinorelbine Italian Study Group (ELVIS) (1999) Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 91: 66-72.

92. Baselga J, Campone M, Piccart M, Burris HA, Rugo HS, et al. (2012) Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 366: 520-529.

93. Valero V (1997) Docetaxel as single-agent therapy in metastatic breast cancer: clinical efficacy. Semin Oncol 24: 1311-1318.

94. Fleming GF, Ma CX, Huo D, Sattar H, Tretiakova M, et al. (2012) Phase II trial of temsirolimus in patients with metastatic breast cancer. Breast Cancer Res Treat 136: 355-363.

95. ClinicalTrials.gov (2006) Phase II Trial Comparing ABI-007 (Abraxane®, Nab®-Paclitaxel) to Taxotere in First Line Therapy of Patients with Stage IV Breast Cancer.

96. Ohtsu A, Ajani JA, Bai YX, Bang YJ, Chung HC, et al. (2013) Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. J Clin Oncol 31: 3935-43.

97. Koizumi W, Kim YH, Fujii M, Kim HK, Imamura H, et al. (2014) JACCRO and KCSG Study Group. Addition of docetaxel to S-1 without platinum prolongs survival of patients with advanced gastric cancer: a randomized study (START). J Cancer Res Clin Oncol 140: 319-328.

98. Sasaki Y, Nishina T, Yasui H, Goto M, Muro K, et al. (2014) Phase II trial of nanoparticle albumin-bound paclitaxel as second-line chemotherapy for unresectable or recurrent gastric cancer. Cancer Science 105: 812-817.

99. MacCormick R, Hirsch G, Gupta S, Shannon P, Rotstein L (1991) A phase II study of idarubicin in the treatment of measurable gastric cancer. Cancer 67: 2988-2989.

100. Holbeck SL, Collins JM, Doroshow JH (2010) Analysis of FDA-Approved Anti-Cancer Agents in the NCI60 Panel of Human Tumor Cell Lines. Molecular Cancer Therapeutics 9: 1451-1460.

101. Bremnes RM, Dønnem T, Al-Saad S, Al-Shibli K, Andersen S, et al. (2011) The role of tumor stroma in cancer progression and prognosis: emphasis on carcinoma-associated fibroblasts and non-small cell lung cancer. J Thorac Oncol 6: 209-217.

102. Pickup MW, Mouw JK, Weaver VM (2014) The extracellular matrix modulates the hallmarks of cancer. EMBO Rep 15: 1243-1253.

103. Crombag MR, Joerger M, Thürlimann B, Schellens JH, Beijnen JH, et al. (2016) Pharmacokinetics of Selected Anticancer Drugs in Elderly Cancer Patients: Focus on Breast Cancer. Cancers (Basel) 8: 1-22.

104. Remesh A (2017) Toxicities of anticancer drugs and its management. International Journal of Basic & Clinical Pharmacology 1: 2-12.

105. Daina A, Michielin O, Zoete V (2017) SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports 7: 42717.

106. Pagadala NS, Syed K, Tuszynski J (2017) Software for molecular docking: a review. Biophys Rev 9: 91-102.

107. Matthews L, Gopinath G, Gillespie M, Caudy M, Croft D, et al. (2009) Reactome knowledgebase of human biological pathways and processes. Nucleic Acids Res 37: 619-622.

108. Fisher GJ (2015) Cancer resistance, high molecular weight hyaluronic acid, and longevity. J Cell Commun Signal 9: 91-92.