Check for updates

REVIEW

The IC-50-time evolution is a new model to improve drug responses consistency of large scale studies [version 1; peer review: awaiting peer review]

ABDELKRIM ALILECHE

Biology, Boise State University, Boise, ID, 83725, USA

V1 First published: 07 Mar 2022, 11:284
<https://doi.org/10.12688/f1000research.108673.1>
Latest published: 07 Mar 2022, 11:284
<https://doi.org/10.12688/f1000research.108673.1>

Open Peer Review

Approval Status AWAITING PEER REVIEW

Any reports and responses or comments on the article can be found at the end of the article.

Abstract

Abstract: Large-scale studies combining hundreds of cancer cell lines and many cancer drugs, with their promises and challenges, represent a new development in the *in vitro* screening of cancer drugs. However, drugs sensitivity results of the same cancer cell lines exposed to the same cancer drugs generated different IC50s by these studies as noticed by Haibe-Kains B *et al* (1). These inconsistencies are due to many factors: the experimental conditions and the use of the Four Parameter Logistic (4PL) regression model to analyze drugs sensitivity results. A new model based on the Levasseur LM *et al* model, the Gompertzian growth model of *in vitro* monolayer culture, and the IC-50 time course evolution is more appropriate to improve the accuracy of these large scale studies.

Keywords

CANCER, DRUGS, IC-50, GOMPERTZ, TIME POINT EVOLUTION, MONOLAYER

Corresponding author: ABDELKRIM ALILECHE (abdelkrimalileche@boisestate.edu)

Author roles: ALILECHE A: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2022 ALILECHE A. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: ALILECHE A. The IC-50-time evolution is a new model to improve drug responses consistency of large scale studies [version 1; peer review: awaiting peer review] F1000Research 2022, 11:284
<https://doi.org/10.12688/f1000research.108673.1>

First published: 07 Mar 2022, 11:284 <https://doi.org/10.12688/f1000research.108673.1>

List of abbreviations

μM: micro Molar
 2D: Two Dimension
 3D: Three Dimension
 CCLE: Cancer Cell Line Encyclopedia
 CGP: Cancer Genome Project
 DT: Doubling time
 DTP: Developmental Therapeutics Program
 DNA: Deoxyribonucleic acid
 h: hour
 IC-50: Inhibition Concentration 50
 miRNA: micro Ribonucleic acid
 mRNA: messenger Ribonucleic acid
 NCI60: National Cancer Institute 60
 USA: United States of America

I. Introduction

In a recent study Haibe-Kaines B *et al*¹ noticed inconsistency in viability estimates and IC-50s between CCLE² and CGP³ results. The same observations were made about the NCI60 screen by Baggerly KA *et al*⁴ and Reinhold WC *et al*.⁵ In addition, the examination of the previous studies²⁻⁴ and other large-scale studies,⁶⁻¹² especially their experimental protocols validate Haibe-Kaines B *et al* concerns and predicts coming ones. The whole high throughput screening idea of exposing large panels of cancer cell lines to anticancer drugs and the viability results (symbolized by the classical IC-50s), when combined with the availability of many data bases (DNA, mRNA, proteomics, miRNA etc.) can identify novel biomarkers suitable for diagnosis and treatment. This endeavor has many challenges to overcome to be successful. This type of studies is only possible *in vitro*. In order to investigate the reasons of inconsistency let's examine the specifics: parameters of *in vitro* cell culture, drug exposure timing, the IC-50 as an essential factor of drugs potency and usefulness.

II. Experimental *in vitro* cell culture conditions

1. Cell densities

A quick survey of the cell densities used in these studies^{2,3,6-12} shows three figures. First, a fixed cell seeding number going from 250² to 500¹¹ cells per well. Second, a range variation between low and high cell densities depending on cell lines doubling time: 5000-40,000 for the NCI60/DTP screen,¹² 300-3600,⁷ and 1,000-15,000.⁹ Third, cell density expressed as cellular confluence degree: 70%³ and 80%.⁸ In addition, the microplates 'size used in these studies have between 96, 384 and 1536 wells with a reaction volume (which contain cells, media, serum and drugs) respectively 100μl, 20μl and 5μl. The combination of these experimental conditions cannot guarantee for one cancer cell line to grow and respond to the same drug the same way in different studies. The growth inhibitory effects of anticancer drugs depend on cell density used as shown in multiple studies,^{13,136-142} this being a main cause of inconsistency in viability results between the mentioned large-scale studies.

2. Duration of cell exposure to drugs

It has been known since the early days of cancer chemotherapy that cytotoxicity of anticancer drugs depends on drugs concentration and exposure time.^{14,15} For the large scale studies the drug exposure time is variable: 48h for JFCR screen⁶ and NCI60/DT screen,¹² 72h for CGP,³ 72-84h for CCLE,² and 72h-168h until cell reach 80% confluent.⁸ For the four-other large-scale studies the exposure is 72h but cell densities are not the same. If the cell doubling time is included, which just for the NCI60/DT screen is between 17.4h (colon HCT-116) and 79.4h (lung HOP-92) cancer cell lines,¹⁶ some cell lines have some growth while others didn't grow at all in the drug exposure time allowed. The same cell line used in the previous studies cannot exhibit the same viability and the IC-50 for every drug. Up to this point the basic parameters of *in vitro* cancer cell culture (cell density whether expressed as cell seeding number or degree of confluence, cell doubling time and drug exposure time) are not harmonized at all between the different large-scale studies.¹⁷

III. The limitations of the Hill model

1. Time factor

The viability results in the large-scale studies are processed with the four-parameter logistic (4PL) regression derived from the Hill function,^{18,19} so are determined the IC-50s and Hill coefficient. The 4PL is practical in fitting the dose-response curves and deliver the IC-50 that characterized every drug and determine its future as an anticancer drug. However, the Hill model from its inception in 1910, does not include the factor time in anticancer drugs cytotoxicity. It was Fritz Haber¹⁴³ and others,¹⁴⁴⁻¹⁴⁸ being out of cancer research field, to link a toxicant concentration and exposure time of an organism to evaluate the resulting toxicity. The Haber's law is expressed as $C \times t = k$ ¹⁴³ where C is the lethal

concentration of the toxicant; t , the exposure time and k , a constant. The Haber's law did generate many variants as reviewed by Connell *et al.*¹⁴⁵ In the cancer research field, it was Osawa *et al.*²⁰ who showed that anticancer drug cytotoxicity is $(C \times T)$ dependent, C being the concentration and T the time. Then Adams *et al.*²¹ extended it to $C^n \times T = k$, where n is the concentration coefficient and k is the drug exposure constant. All this body of research brings the concept of "dose-time response curves",¹⁴⁸ totally different from the concept "dose response curves" mentioned by a lot of cancer research papers and especially the large-scale studies.^{2,3,6-12} Levasseur LM *et al.*¹⁵ combined cytotoxicity with the Hill model and established a modified Hill model, $IC_x^n \times T = k$, in which IC_x is the amount of inhibition, the equivalent of the IC-50. This is a new "paradigm to facilitate the quantitative assessment of the growth-inhibitory effect of anticancer agents as a function of concentration and exposure time".¹⁵ In addition, the Levasseur LM *et al.* model linked drug exposure time to the IC-50 by this equation $IC50 = (k/T)^{1/n}$.²² This shows clearly that in the large-scale studies^{2,3,6-12} there is no connection between the IC50 and the exposure time to drugs, thus the inconsistency noticed by Haibe-Kains B *et al.*¹ and Reinhold *et al.*⁵ In these large-scale studies, there is a kind of tacit assumption the IC-50 is constant over the time exposure of cancer cells to cancer drugs. I will prove in this review such statement is incorrect.

2. Inflection point

The S shaped dose response curve fitted with the Hill model has only one inflection point and therefore a unique IC-50 taken at one-time point. Prinz *et al.*²³ inspecting the NCI60/DT results analyzed with the Hill model, noticed that some results do not fit in it because of the complexity of their dose-response curves. Levasseur LM *et al.*¹⁵ noticed that the "double or triple Hill roller coaster concentration-effect curve" can be explained by the coexistence of two populations of cells with different sensitivities (IC-50a and IC-50b) to drugs, by the target's multiplicity for the same drug,²² and the allosteric nature of the drug-target interaction.²³ DiVeroli *et al.*²⁴ point to the multiphasic dose-response curves also referred to as hormesis. Hormesis is a non-monotonic/biphasic dose response, with specific dose response patterns coming in many shapes^{25,26}: U, inverted U, J and bell shapes.^{152,153} This has been reported with 138 cancer cell lines treated by over 120 drugs.^{27,28} As a solution to this problem Di Veroli *et al.* developed an algorithm referred to as Dr Fit.

3. Cellular heterogeneity

It is another hurdle to the Hill model used to determine drugs IC-50s and can explain the inconsistency between the IC50s noticed by Haibe-Kains B *et al.*¹ Baggerly KA *et al.*⁴ Reinhold WC *et al.*⁵ Levasseur LM *et al.*¹⁵ DiVeroli *et al.*²⁴ Calabrese *et al.*²⁸ and Rashkov *et al.*²⁹ The issue is how to explain the heterogeneity of cancer cell lines used *in vitro* and considered homogenous cell lines and checked thoroughly as such?^{2,3}

IV. The Gompertzian growth of cancer cells *in vitro*

1. The Gompertzian model

Since the Norton *et al.* 1976 landmark paper³⁰ tumor growth has two phases, an initial avascular exponential phase followed by the retardation or decremented exponential phase due to feedback inhibition. It fits well with the Gompertzian model.³¹ The growth type of cancer cells cultured *in vitro* as a monolayer or spheroids was not addressed by Haibe-Kains *et al.*¹ and also by all the commentaries³²⁻³⁸ related to Haibe-Kains *et al.* concerns. It should be considered one of the hallmarks of cancer whether in *in vitro* or *in vivo* clinical studies³⁹ since it will have a huge impact in the selection of future cancer drugs. According to results obtained by three research groups, Drasdo *et al.*⁴⁰ Demicheli *et al.*^{41,42} and Poplawski *et al.*⁴³ cancer cells cultured *in vitro*, as monolayers or spheroids, or *in vivo* (injected into mice to induce tumors) have the same Gompertzian growth type. For *in vitro* spheroids and tumors induced in mice there is always a central necrotic zone (due the difficulty of internal cancer cells to have access to oxygen and other nutrients) surrounded by a growing outer layer of cancer cells. Cancer cell growth in two dimensional (2D) monolayers have similar situation in spite of equal accessibility of all cell in 2D to oxygen and nutrients. In both cases, 2D and 3D, the growth is limited to the outer layer as shown by Bru *et al.*⁴⁴ In monolayers, internal cancer cells, squeezed by other surrounding cells, survive by two mechanisms: size reduction divisions⁴⁵ and quiescence.⁴⁶ Therefore *in vitro* monolayers of cancer cells although derived from the same cell line are heterogeneous in their behavior and respond differently to anticancer drugs. The Gompertzian growth type of *in vitro* cancer cells monolayers are well explained by the "two compartment of cell population growth".^{47,48} This cellular heterogeneity had been already mentioned previously by Levasseur LM *et al.*¹⁵ and Rashkov *et al.*²⁹

2. One time point IC-50

The Gompertzian growth of cancer cells *in vitro* had been neglected by the all the large-scale studies and that has serious consequences on the sampling of IC50s at only one time point from 48h to 156h.^{2,3,6-12} The dual effect of doubling times diversity and the Gompertzian growth type of these cells applied to large number of cancer cells (60 for the NCI-60 to a thousand and even more), is the main reason of inconsistency of the IC-50s between the different large-scale studies. The same cell line won't have the same growth level since the sampling of the IC-50 at different times points in these different large-scale studies.

3. Dose dense chemotherapy

The Gompertzian growth type of human tumors has led to the introduction of the *dose dense* chemotherapy protocols.^{49,50} Tumor growth is faster for small size tumors than for large size ones. Cancer cells cultured *in vitro* exhibit the same phenomenon, in the beginning the growth is exponential and after it slows down. Therefore, the IC-50 should be evaluated at different time points especially at an early time point.

4. *In vitro* self-seeding

Human tumors are characterized by metastasis due to self-seeding.⁵¹ There is no metastasis *in vitro*, but a similar phenomenon is operating since cancer cells are heterogeneous in their growth (a growing population and a quiescent population) and their response to drugs. Once some cancer cells are killed the quiescent cells start growing because there is more space and nutrient available.

5. 2D vs 3D debate

In vitro 2D monolayers of cancer cells does not reproduce the complexity of *in vivo* mice or human 3D tumors. The stromal reaction, vascular networks, the immune system are missing *in vitro*.^{52,53} In addition, the failure to reproduce *in vivo* the *in vitro* results obtained with 2D cultures, the 3D cultures became the solution to bridge the gap in this 2D vs 3D debate. However, the Gompertzian growth of cancer cells cultured in 2D or 3D formats, in both cases there is a heterogeneous population of cancer cells, thus in both cases cellular dynamics are similar. Unfortunately, many studies using 3D cell culture systems *in vitro*, time exposure of cancer cells to drugs is variable: 24h,⁵⁴ 48h,⁵⁵ 72h⁵⁶ and 168h.^{57,58} This fact limits the capacity of the 3D spheroids model to improve the accuracy of the 2D monolayers *in vitro* screening of cancer drugs.

V. The IC-50 time course evolution model

After analysis of the multiple sources of inconsistencies of IC-50s between large scale studies, I would like to propose the following model.

1. The evaluation of drugs IC50 at multiple time points

As above mentioned the large-scale studies the IC-50s were evaluated at only one time point between 48h and 168h.^{2,3,6-12} The drugs IC-50s were supposed to be constant over time regardless of the chosen time point. This is not always true.

2. At least three times points are necessary

Early time points (2-3h, 24h) are necessary for drugs high doses supposed to kill all cells. This will show how much time is necessary for high doses need to kill all cells, and that depend on cancer cell line (it depends on the doubling time and the genetic makeup). Some drugs have a toxic effect in just 2-3 hours.⁵⁴ Late time points are necessary for medium and low doses. In addition, drugs 'killing mechanisms, whether cell cycle dependent like paclitaxel or independent like carboplatin, whether by apoptosis or necrosis, the influence of all these factors cannot be explored by one time point drugs IC50s.

3. New experimental protocol

Current experimental protocols in the large-scale studies and a lot of small-scale studies use one cell set and expose cancer cells to increasing drug doses for a unique period of time going from 48h to 168h, and after determine the IC-50. The new protocol recommends multiple sets, every set specific for a drug exposure time: from 2-3h, 24h, 48h, 72h and even further if the doubling time is long. For every time point, there is an IC-50, thus an IC-50-time course because drugs IC-50s are variable over time. The inconsistency of the drugs IC-50s noticed by Haibe-Kains *et al*¹ is due to the difference in cell drugs exposure times.^{2,3}

4. The IC50 time evolution model

It reflects the cellular phenomenology which is Gompertzian for *in vitro* monolayers and spheroids. The current large-scale studies using *in vitro* monolayers are completely disconnected from the reality of cellular dynamic evolution. The same problem exists with the *in vitro* spheroids. Thus, the 2D vs 3D debate aimed at replacing *in vitro* monolayers with spheroids should include the new model exposed here for a better accuracy of drugs IC-50s measurement over time.

VI. The IC-50 time course has five different shapes

As presented in Tables 1–6 and Figure 1, a data base collated from www.pubmed.gov and google search, some eighty publications in which 109 cell lines treated with 124 drugs and their IC-50 were evaluated at different time points shows for the first time the IC-50 variation over time. This new model is more appropriate to explore the interaction complexities of cancer drugs and their cellular targets, complexities ignored by the one-time point IC-50 practiced nowadays according

Table 1. IC-50 Time Evolution IC-50 Type 1.

Case	Type	IC-50 24h	IC-50 48h	IC-50 72h	Cell line	Drug	Ref
1	1	8µM	1.8µM	1.2µM	MCF-7	Arsenic trioxide	72
2	1	17µM	7µM	4.8µM	MDA-MB-231	Arsenic trioxide	72
3	1	28.1µM	0.0986µM	0.0043µM	A-375	SLN Docetaxel	71
4	1	51.1µM	0.231µM	0.004µM	A-375	Taxotere	71
5	1	0.769µM	0.125µM	0.0856µM	C-26	SLN Docetaxel	71
6	1	2.083µM	0.456µM	0.0846µM	C-26	Taxotere	71
7	1	13.45µg/ml	13.00µg/ml	12.50µg/ml	MCF-7	TAM	70
8	1	13.18µg/ml	12.50µg/ml	11.78µg/ml	MCF-7	TAM-SLN	70
9	1	17.21µg/ml	16.87µg/ml	15.97µg/ml	MDA-MB-231	TAM	70
10	1	16.93µg/ml	16.00µg/ml	15.80µg/ml	MDA-MB-231	TAM-SLN	70
11	1	96µM	90µM	65µM	HepG2	Mycotoxin AOH	69
12	1	8.1µM	5.3µM	5.2µM	HepG2	Mycotoxin 15-ADON	69
13	1	15.01µg/ml	6.19µg/ml	0.94µg/ml	BEL7402	CNP	68
14	1	182.8µM	55.4µM	17.2µM	U-266	Justicidin B	59
15	1	86.2µM	68.4µM	27.4µM	U-266	Etoposide	59
16	1	>160µM	19.9µM	5µM	DOHH-2	Justicidin B	59
17	1	>160µM	100.7µM	9.5µM	DOHH-2	Etoposide	59
18	1	25.3µM	10.3µM	8µM	REH	Justicidin B	59
19	1	0.027µM	0.014µM	0.015µM	REH	Etoposide	59
20	1	88.8µM	19µM	16.2µM	HH	Justicidin B	59
21	1	104.7µM	48.6µM	14.7µM	HH	Etoposide	59
22	1	46µM	18.1µM	6.1µM	HUT78	Justicidin B	59
23	1	9.3µM	4.3µM	4.2µM	HUT78	Etoposide	59
24	1	14.1µM	2.4µM	1.5µM	OPM-2	Justicidin B	59
25	1	24.1µM	4µM	1.3µM	OPM-2	Etoposide	59
26	1	19.3µM	0.41µM	0.17µM	RPMI-8226	Justicidin B	59
27	1	106.6µM	91.1µM	14.9µM	RPMI-8226	Etoposide	59

Table 1. Continued

Case	Type	IC-50 24h	IC-50 48h	IC-50 72h	Cell line	Drug	Ref
28	1	9.20µM	8.30µM	4.63µM	HepG2	Goniothalamine	62
29	1	79.10µM	63.75µM	35.01µM	Chang	Goniothalamine	62
30	1	>3mg/ml	2.6mg/ml	0.5mg/ml	HeLa	Hyd. F Eth. Extract	61
31	1	2.20mg/ml	1.72mg/ml	0.3mg/ml	HeLa	Hyd. F Ph. Extract	61
32	1	2.35mg/ml	2.04mg/ml	0.9mg/ml	HeLa	Sinapinic acid	61
33	1	2.63mM	2.22mM	1.2mM	HeLa	Sodium butyrate	61
34	1	2.97mg/ml	2.2mg/ml	1.6mg/ml	HT-29	Sinapinic acid	61
35	1	>3mM	2.2mM	2.1mM	HCT-116	Sinapinic acid	61
36	1	>3mM	2.2mM	2.0mM	HCT-116	Sodium butyrate	61
37	1	>3mM	2.36mM	1.5mM	JURKAT	Sodium butyrate	61
38	1	>3mM	>3mM	0.28mM	JURKAT	Sinapinic acid	61
39	1	6.1µM	4.5µM	1.6µM	A549	Capillin	60
40	1	2.8µM	0.8µM	0.6µM	Hep-2	Capillin	60
41	1	1.5µM	1.3µM	0.9µM	A431	Hypocretinamide 1	63
42	1	1.5µM	1.3µM	1.1µM	Hep-2	Hypocretinamide 1	63
43	1	2.8µM	2.6µM	1.2µM	SK28	Hypocretinamide 1	63
44	1	3.2µM	2.4µM	1.8µM	SK37	Hypocretinamide 1	63
45	1	0.9µM	0.9µM	0.8µM	A431	Helenalin	63
46	1	0.9µM	0.9µM	0.8µM	Hep-2	Helenalin	63
47	1	1.3µM	0.9µM	0.5µM	SK28	Helenalin	63
48	1	1.3µM	1.2µM	0.7µM	SK37	Helenalin	63
49	1	1.4µM	1.2µM	1.2µM	SW872	Helenalin	63
50	1	463.3µM	280.8µM	149.3µM	UACC-903	JS-21 (3a)	64
51	1	150.8µM	126.5µM	118.5µM	UACC-903	JS-23 (3c)	64
52	1	193.5µM	145.7µM	108.2µM	UACC-903	JS-25 (4)	64
53	1	614.3µM	266.8µM	112.7µM	UACC-903	JS-20 (3)	64
54	1	0.51µg/ml	0.31µg/ml	0.27µg/ml	MCF-7	DOX-Sol	66

Table 1. Continued

Case	Type	IC-50 24h	IC-50 48h	IC-50 72h	Cell line	Drug	Ref
55	1	0.61 µg/ml	0.51 µg/ml	0.37 µg/ml	MCF-7/Adr	DOX-GNMs	66
56	1	>40 µM	7 µM	1.25 µM	Ishikawa	Perifosine	74
57	1	>40 µM	25 µM	6 µM	Ishikawa	Perifosine	74
58	1	15.01 µg/ml	6.19 µg/ml	0.94 µg/ml	BEL7402	Chitosan NP	75
59	1	0.51 mM/l	0.33 mM/l	0.25 mM/l	COLO829	Lomefloxacin	76
60	1	2.5 ng/ml	2 ng/ml	1.5 ng/ml	HL-2	Bortezomib	77
61	1	38 µM	10 µM	10 µM	HeLa	Apigenin	87
62	1	89 µM	72 µM	68 µM	SiHa	Apigenin	87
63	1	19 µM	9.2 µM	4.1 µM	EC109	Jesridonin	88
64	1	61.0 µM	38.2 µM	38.9 µM	EC109	Oridonin	88
65	1	41.7 µM	14.4 µM	4 µM	EC9706	Jesridonin	88
66	1	37.5 µM	28.0 µM	23.9 µM	EC9706	Oridonin	88
67	1	>100 µM	11.4 µM	2.0 µM	KYSE450	Jesridonin	88
68	1	30.5 µM	28.2 µM	17.1 µM	KYSE450	Oridonin	88
69	1	>100 µM	61.4 µM	16.2 µM	KYSE750	Jesridonin	88
70	1	35.3 µM	23.4 µM	14.3 µM	KYSE750	Oridonin	88
71	1	45.8 µM	21.4 µM	9.4 µM	TE-1	Jesridonin	88
72	1	25.2 µM	18.0 µM	8.4 µM	TE-1	Oridonin	88
73	1	86.6 µM	49.8 µM	28.2 µM	GES-1	Jesridonin	88
74	1	>100 µM	35.4 µM	25.2 µM	HL7702	Jesridonin	88
75	1	5 µg/ml	0.6 µg/ml	0.06 µg/ml	Primary Hepatocytes	AFB1	89
76	1	18 µg/ml	9 µg/ml	4 µg/ml	HCT15	Zerumbone	90
77	1	25 µg/ml	16 µg/ml	8 µg/ml	HCT15	Cisplatin	90
78	1	1954 µg/ml	1700 µg/ml	1540 µg/ml	MCF-7	MCRE	91
79	1	86.34 mM	17.83 mM	8.64 mM	A549	Doxorubicin	92
80	1	93.86 mM	43.28 mM	37.12 mM	H1299	Doxorubicin	92
81	1	7.45 µM	5.13 µM	3.98 µM	JURKAT	PJ-34	93

Table 1. Continued

Case	Type	IC-50 24h	IC-50 48h	IC-50 72h	Cell line	Drug	Ref
82	1	20.301µM	9.785µM	7.008µM	HL60	PJ-34	93
83	1	131mM	89mM	38mM	JURKAT	Doxorubicin	93
84	1	83mM	23mM	10mM	HL60	Doxorubicin	93
85	1	31.25µM	5.1µM	3µM	A549	Cisplatin	94
86	1	24.75µM	15µM	13.5µM	A549	Silver Nitrate	94
87	1	20µM	13µM	8µM	MDA-MB-231	EPC-3	95
88	1	10.58µg/ml	8.81µg/ml	6.59µg/ml	A549	TQ	96
89	1	19.39µg/ml	17.51µg/ml	15.62µg/ml	A549	TQG	96
90	1	15.63µg/ml	14.97µg/ml	12.40µg/ml	A549	TQ-Fe ₃ O ₄	96
91	1	27.31µg/ml	18.68µg/ml	11.88µg/ml	A549	TQG-Fe ₃ O ₄	96
92	1	16.10µg/ml	12.71µg/ml	7.04µg/ml	A549	TQ-Fe ₃ O ₄ (MF)	96
93	1	23.45µg/ml	10.78µg/ml	9.579µg/ml	A549	TQ-G-Fe ₃ O ₄ (MF)	96
94	1	13.8µM	6.888µM	4.362µM	A2780	Salinomycin	97
95	1	12.7µM	9.869µM	5.022µM	SK-OV-3	Salinomycin	97
96	1	56.6µM	51.14µM	32.86µM	HT-29	Apatinib	98
97	1	48.76µM	44.11µM	29.25µM	HCT116	Apatinib	98
98	1	0.59µM	0.36µM	<0.03125µM	NB1 Amp	Crizotinib	99
99	1	2.21µM	0.77µM	<0.5µM	NB3 R1275Q	Crizotinib	99
100	1	1.6µM	1.34µM	1.1µM	SH-SY5Y F1174L	Crizotinib	99
101	1	2.19µM	0.71µM	0.64µM	IMR32 WT	Crizotinib	99
102	1	0.31µM	0.035µM	0.03µM	NB1 Amp	Entrectinib	99
103	1	4.34µM	3.32µM	2.42µM	SH-SY5Y F1174L	Entrectinib	99
104	1	3.68µM	3.29µM	3.06µM	IMR32 WT	Entrectinib	99
105	1	5.13µM	3.51µM	2.13µM	MCF-7	Mitoxantrone	103
106	1	2.58µM	1.64µM	1.25µM	MCF-7	Mitoxantrone SLN	103
107	1	92.64µM	67.34µM	52.48µM	MCF-7	Paclitaxel	103
108	1	98.70µM	62.31µM	46.70µM	MCF-7	Paclitaxel SLN	103

Table 1. Continued

Case	Type	IC-50 24h	IC-50 48h	IC-50 72h	Cell line	Drug	Ref
109	1	267.84µM	195.16µM	153.16µM	MCF-7	Methotrexate	103
110	1	154.76µM	98.48µM	93.80µM	MCF-7	Mehtotrexate SLN	103
111	1	88.89µM	13.20µM	9.553µM	A2780	Cisplatin	104
112	1	350.5µM	50.96µM	25.39µM	A2780/DDP	Cisplatin	104
113	1	105.1µM	51.73µM	16.13µM	SKOV3	Cisplatin	104
114	1	446.7µM	135.0µM	66.70µM	SKOV3/DDP	Cisplatin	104
115	1	10.66µM	2.51µM	2.08µM	HS578T	Cediranib	105
116	1	30.77µM	15.57µM	2.52µM	MDA-MB-231	Cediranib	105
117	1	38.69µM	26.54µM	18.85µM	T47D	Cediranib	105
118	1	15.27µM	8.13µM	3.69µM	MCF-7	Arsenic Disulfide	106
119	1	25.5µM	9.18µM	5.37µM	MDA-MB-231	Arsenic Disulfide	106
120	1	49.15µg/ml	47.18g/m	45.80g/ml	PC-3	Boswellic Acid	107
121	1	49.27g/ml	48.58g/ml	46.77g/ml	PC-3	Montelukast Sodium	107
122	1	16µM	11.5µM	9.75µM	HL-60	As2O3	108
123	1	12.27µM	7.57µM	0.45µM	HT-29	5-FU	109
124	1	14.56µM	11.20µM	1.324µM	CACO-2	5-FU	109
125	1	107µM	73µM	47µM	T47D	Silibinin	110
126	1	1.71mM	0.99mM	0.06mM	HeLa	Safranal	111
127	1	2.30mM	1.28mM	0.5mM	MCF-7	Safranal	111
128	1	2.12mM	1.18mM	0.29mM	L929	Safranal	111
129	1	0.093mM	0.063mM	0.039mM	HeLa	Safranal Loaded	111
130	1	0.39mM	0.24mM	0.13mM	MCF-7	Safranal Loaded	111
131	1	0.14mM	0.075mM	0.063mM	L929	Safranal Loaded	111
132	1	1207µM	720µM	298µM	U251	β-Asarone	116
133	1	1150µM	900µM	195µM	C6	β-Asarone	116
134	1	7.5µM	5.0µM	3.0µM	Jurkat	Beauvericin	117
135	1	0.74mM	0.17mM	0.10mM	COLO827	Ciprofloxacin	118

Table 1. Continued

Case	Type	IC-50 24h	IC-50 48h	IC-50 72h	Cell line	Drug	Ref
136	1	0.75µM/ml	0.57µM/ml	0.53µM/ml	U87MG	Ciprofloxacin	119
137	1	0.48µM/ml	0.22µM/ml	0.15µM/ml	U87MG	Moxifloxacin	119
138	1	0.83µM/ml	0.14µM/ml	0.03µM/ml	MDA-MB-231	Ciprofloxacin	120
139	1	22.5µM	19µM	17µM	T47D	Curcumin	121
140	1	10.5µM	9.5µM	9µM	T47D	PAMAM Curcumin	121
141	1	1.734mM	0.742mM	0.500mM	HCT-116	DHCA	123
142	1	2.595mM	1.188mM	0.704mM	HCT-15	DHCA	123
143	1	8.148mM	3.018mM	1.66mM	HeLa	DHCA	123
144	1	6.942mM	4.511mM	3.223mM	SiHa	DHCA	123
145	1	18µM	15µM	13µM	HL-60	EA-137	124
146	1	76.72nM/l	34.05nM/l	16.7nM/l	SW620	Bufalin	125
147	1	8.89µM	3.58µM	1.86µM	Hep-G2	OTA	126
148	1	55.79µM	39.88µM	29.48µM	Hep-G2	ZEa	126
149	1	34.25µM	10.08µM	7.36µM	Hep-G2	OTA+ZEa	126
150	1	35.64µM	4.99µM	4.05µM	Hep-G2	OTA+α-ZOL	126
151	1	27.67µM	11.05µM	3.42µM	Hep-G2	OTA+ZEa+α-ZOL	126
152	1	1954µg/ml	1700µg/ml	1560µg/ml	MCF-7	Mat. Chamomilla	127
153	1	0.42µM	0.25µM	0.04µM	RL	ABT-737	128
154	1	5.65µM	3.66µM	2.92µM	H9	ABT-737	128
155	1	12.72µM	14.19µM	9.54µM	JJN-3	ABT-737	128
156	1	0.28µM	0.12µM	0.10µM	SKI	ABT-737	128
157	1	76µg/ml	58µg/ml	39µg/ml	MCF-7	EADs	129
158	1	47µM	44µM	43µM	A549	Diosgenin	130
159	1	7.14µM	5.05µM	4.23µM	MCF-7	BBSKE	131
160	1	10.54µM	10.13µM	7.29µM	MCF-7	PM	131
161	1	4.14µM	3.99µM	3.43µM	MCF-7	FA+PM	131
162	1	7.84µM	6.88µM	6.30µM	MCF-7	FA+PM+free FA	131

Table 1. Continued

Case	Type	IC-50 24h	IC-50 48h	IC-50 72h	Cell line	Drug	Ref
163	1	40nM/I	27nM/I	17nM/I	DU-145	Triptolide	133
164	1	2.17ng/ml	1.31ng/ml	1.16ng/ml	A2780	Triptolide	135
165	1	92ng/ml	10.2ng/ml	7.34ng/ml	OVCAR-3	Triptolide	135
166	1	102ng/ml	85ng/ml	81ng/ml	HIO-180	Triptolide	135
167	1	142ng/ml	111ng/ml	99ng/ml	CCD-19Ln	Triptolide	135
168	1	584ng/ml	217ng/ml	207ng/ml	J774A.1	Triptolide	135
169	1	0.276mM	0.244mM	0.213mM	LnCap	Ciprofloxacin	154
170	1	168.8µg/ml	22.15µg/ml	8.04µg/ml	U14	Paclitaxel	155
171	1	15.0µg/ml	1.27µg/ml	0.62µg/ml	A549	Goniothalamin	157
172	1	14.43µg/ml	0.27µg/ml	0.24µg/ml	A549	Doxorubicin	157
173	1	26.93µg/ml	10.27µg/ml	1.64µg/ml	HT29	Goniothalamin	157
174	1	11.6µg/ml	8.57µg/ml	6.23µg/ml	HMSC	Goniothalamin	157
175	1	30.98µg/ml	23.63µg/ml	18.08µg/ml	HCT16	SGC	158
176	1	129.67µg/ml	116.30µg/ml	82.27µg/ml	HCT16	SGE	158
177	1	175.70µg/ml	105.8µg/ml	61.9µg/ml	SiHa	SGC	158
178	1	255.03µg/ml	113.03µg/ml	66.08µg/ml	SiHa	SGEA	158
179	1	460.4µg/ml	291.7µg/ml	149.7µg/ml	SiHa	SGW	158
180	1	185.66µg/ml	109.7µg/ml	66.7µg/ml	HeLa	SGC	158
181	1	260.46µg/ml	116.5µg/ml	68.48µg/ml	HeLa	SGEA	158
182	1	360.56µg/ml	275.9µg/ml	146.43µg/ml	HeLa	SGE	158
183	1	472.6µg/ml	291.26µg/ml	149.46µg/ml	HeLa	SGW	158
184	1	301.83µg/ml	267.23µg/ml	113.7µg/ml	MDA-MB-231	SGC	158
185	1	408.37µg/ml	351.43µg/ml	175.90µg/ml	MDA-MB-231	SGEA	158
Case	Type	IC-50 3h	IC-50 24h	IC-50 120h	Cell line	Drug	Ref
186	1	>32µM	0.29µM	0.0099µM	NCI-H23	Paclitaxel	65
187	1	>32µM	0.93µM	0.078µM	NCI-H460	Paclitaxel	65
188	1	>32µM	24µM	0.03µM	NCI-H322	Paclitaxel	65

Table 1. Continued

Case	Type	IC-50 3h	IC-50 24h	IC-50 120h	Cell line	Drug	Ref	
189	1	>32µM	14µM	0.0091µM	NCI-H522	Paclitaxel	65	
190	1	>32µM	27µM	7.5µM	NCI-H727	Paclitaxel	65	
Case	Type	IC-50 2h	IC-50 24h	IC-50 48h	Cell line	Drug	Ref	
191	1	26µM	9µM	8µM	LnCap	9S1R	54	
192	1	39µM	29µM	16µM	MDA-MB-231	9R	54	
193	1	18µM	12µM	10µM	MDA-MB-231	9S1R	54	
194	1	93µM	39µM	37µM	HUT-102	9R	54	
Case	Type	IC-50 48h	IC-50 72h	IC-50 120h	Cell line	Drug	Ref	
195	1	129.8µM	42.5µM	31.0µM	HCT-116 WT	Resveratrol	100	
196	1	84.1µM	7.0µM	0.6µM	HCT-116 WT	IRA-5	100	
197	1	88.7µM	20.2µM	9.2µM	A-431	Resveratrol	100	
198	1	133.4µM	39.5µM	15.4µM	A-431	IRA-5	100	
199	1	186.0µM	52.4µM	16.1µM	Caco-2	Resveratrol	100	
200	1	348.7µM	46.1µM	13.4µM	Caco-2	IRA-5	100	
201	1	741.3µM	149.1µM	33.8µM	HCA-7	Resveratrol	100	
202	1	288.6µM	206.7µM	51.6µM	HCA-7	IRA-5	100	
203	1	149.1µM	71.8µM	28.6µM	HCT-116 p53-/-	Resveratrol	100	
204	1	134.2µM	57.6µM	16.1µM	HCT-116 p53-/-	IRA-5	100	
205	1	263.8µM	161.2µM	29.6µM	LnCap	Resveratrol	100	
206	1	342.3µM	166.3µM	24.9µM	LnCap	IRA-5	100	
Case	Type	IC-50 24h	IC-50 48h	IC-50 72h	IC-50 96h	Cell line	Drug	Ref
207	1	86.29µM/ml	75.34µM/ml	72.42µM/ml	69.82µM/ml	U-251	Temozolomide	101
208	1	66.25µM	64.00µM	57.99µM	37.36µM	PC-3	Flutamide	113
209	1	40.4µM	30.8µM	12.7µM	7.9µM	22Rv1	Cisplatin	114
210	1	61.5µM	44.0µM	7.9µM	3.7µM	PNT1A	Cisplatin	114
211	1	0.048µM	0.036µM	0.030µM	0.029µM	A549	Digoxin	149
212	1	0.104µM	0.107µM	0.070µM	0.057µM	H3255	Digoxin	149

Table 1. Continued

Case	Type	IC-50 24h	IC-50 48h	IC-50 72h	IC-50 96h	Cell line	Drug	Ref
213	1	0.767mM	0.238mM	0.212mM	0.193mM	PC-3	Ciprofloxacin	154
214	1	3.937µM	0.290µM	0.250µM	0.173µM	PC-3	Doxorubicin	154
215	1	26.25nM	7.655nM	3.951nM	3.194nM	PC-3	Docetaxel	154
Case	Type	IC-50 24h	IC-50 48h	IC-50 72h	IC-50 120h	Cell line	Drug	Ref
216	1	8.40µg/ml	7.60µg/ml	7.40µg/ml	6.84µg/ml	MRC5	TTHL	67
217	1	1.36µg/ml	0.73µg/ml	0.63µg/ml	0.30µg/ml	MCF-7	TTHL	67
218	1	6.50µg/ml	6.10µg/ml	5.45µg/ml	0.88µg/ml	HepG2	TTHL	67
219	1	5.55µg/ml	5.20µg/ml	1.09µg/ml	0.39µg/ml	T24	TTHL	67
220	1	7.05µg/ml	5.87µg/ml	5.20µg/ml	4.50µg/ml	HCT116	TTHL	67
221	1	8.00µg/ml	7.00µg/ml	6.15µg/ml	5.30µg/ml	HT-29	TTHL	67
222	1	8.55µg/ml	7.90µg/ml	6.35µg/ml	5.00µg/ml	CACO-2	TTHL	67
Case	Type	IC-50 24h	IC-50 48h	IC-50 72h	IC-50 96h	Cell line	Drug	Ref
223	1	4.0µM	2.7µM	MCF-7	MDA-MB-231	Doxorubicin	Doxorubicin	102
224	1	4.0µM	1.4µM	MDA-MB-231	HT-29	Doxorubicin	Doxorubicin	102
225	1	77.5µM	72µM	HT-29	HUT78	Valdecocixib	Valdecocixib	115
226	1	15.1µM	4.8µM	HUT78	GRANT A519	BKM10	BKM10	122
227	1	12.4µM	3.9µM	GRANT A519	WSU-NHL	BKM10	BKM10	122
228	1	14.8µM	4.1µM	WSU-NHL	HUT78	BKM10	BKM10	122
229	1	41.6µM	21.1µM	HUT78	GRANT A519	BEZ235	BEZ235	122
230	1	45.1µM	25.3µM	GRANT A519	WSU-NHL	BEZ235	BEZ235	122
231	1	39.2µM	18.5µM	WSU-NHL	MVA4-11	Triptolide	Triptolide	132
232	1	92.4nM	16.1nM	MVA4-11	OCM-AML3	Triptolide	Triptolide	132
233	1	76.1nM	6.9nM	OCM-AML3	OCM-1	Triptolide	Triptolide	132
Case	Type	IC-50 48h	IC-50 72h	Cell line	Drug	Ref		
234	1	1147.91µg/ml	921.1µg/ml	MCF-7	Capecitabine	112		
235	1	56.14nM/L	15.57nM/L	OCM-1	Triptolide	134		

Table 2. IC-50 Time evolution IC-50 Type 2.

Case	Type	IC-50 24h	IC-50 48h	IC-50 72h	Cell line	Drug	Ref
236	2	0.6µM	0.9µM	1.0µM	ZR75-1	Hypocretenolide 1	63
237	2	0.7µM	0.8µM	1.1µM	ZR75-1	Helenalin	63
238	2	1.4µM	1.6µM	1.7µM	OVCAR3	Helenalin	63
239	2	0.184µM	0.919µM	1.652µM	AGS	Clofarabine	78
240	2	5.33µg/ml	5.34µg/ml	7.56µg/ml	K562	Para-nitro acetophenon	151
241	2	7.118µg/ml	8.62µg/ml	9.75µg/ml	PBMC	Para-nitro acetophenon	151
242	2	10µM	23µM	30µM	HL60	EA-136	124
243	2	16µM	20µM	90µM	HL60	EA-4	124
244	2	12.6µg/ml	82.8µg/ml	188.4µg/ml	N2a	3-FOC	156
245	2	9.25µg/ml	37.5µg/ml	83.6µg/ml	N2a	6-FOC	156
Case	Type	IC-50 2h	IC-50 24h	IC-50 48h	Cell line	Drug	Ref
246	2	38µM	43µM	43µM	HUT-102	951R	54
Case	Type	IC-50 48h	IC-50 72h	IC-50 72h	Cell line	Drug	Ref
247	2	59.22µg/ml		92.30µg/ml	BCSC	Dandelion Eth. Extr.	42
248	2	14.88µg/ml		69.40µg/ml	BCSC	Dandelion Met. Txtr.	42
Case	Type	IC-50 24h	IC-50 48h	IC-50 48h	Cell line	Drug	Ref
249	2	71µM		74µM	SW620	Valdecocib	115

Table 3. IC-50 Time evolution Type 3.

Case	Type	IC-50 24h	IC-50 48h	IC-50 72h	Cell line	Drug	Ref	
250	3	6.0µM	0.8µM	6.0µM	HT-29	Capillin	60	
251	3	3.4µM	0.8µM	1.4µM	MIA Pa Ca-2	Capillin	60	
252	3	3.1µM	2.2µM	2.8µM	SW872	Hypocretenolide 1	63	
253	3	0.8µM	0.7µM	1µM	MCF-7	Hypocretenolide 1	63	
254	3	2.03µg/ml	0.85µg/ml	0.86µg/ml	MCF-7/Adr	DOX-Sol	66	
255	3	6.2µM	3.6µM	5.2µM	HepG2	Mycotoxin 3-ADON	69	
256	3	2.65µM	2.24µM	3.27µM	NB3 R1275Q	Entrectinib	99	
257	3	50µg/ml	25µg/ml	40µg/ml	HCT-116	Bark CO AE	150	
258	3	65µg/ml	30µg/ml	45µg/ml	HCT-116	Bark CO ME	150	
259	3	>200µg/ml	112µg/ml	160µg/ml	HCT-116	Bark CO AqE	150	
260	3	11.56µg/ml	10.705µg/m	11.5µg/m	K562	Acetanilide	151	
261	3	13.93µg/m	13.16µg/m	13.53µg/m	PBMC	Acetanilide	151	
262	3	58µM	50µM	55µM	HL60	all-trans-RA	72	
263	3	362.3µM	234.4µM	270.5µM	A375M	JS-22(3b)	64	
264	3	0.8µM	0.5µM	0.7µM	MCF-7	Helenalin	63	
265	3	52.30µM	10.91µM	21.98µM	HepG2	α-ZOL	126	
266	3	55µM	21.12µM	29.77µM	HepG2	ZEA+Azol	126	
267	3	0.03µM	0.025µM	0.03µM	HBL-2	ABT-737	128	
268	3	68.9µg/ml	25µg/ml	95.6µg/ml	N2a	GOC	156	
Case	Type	IC-50 4h	IC-50 24h	IC-50 48h	Cell line	Drug	Ref	
269	3	1.55µM	0.31µM	1.68µM	A459	Osmium arene 1	73	
270	3	0.85µM	0.17µM	0.32µM	A459	Osmium arene 2	73	
271	3	33.95µM	3.64µM	35.73µM	A459	Osmuim arene 3	73	
272	3	1.92µM	1.78µM	1.79µM	A459	Cisplatin	73	
Case	Type	IC-50 2h	IC-50 24h	IC-50 48h	Cell line	Drug	Ref	
273	3	44µM	23µM	28µM	LnCap	9R	54	
Case	Type	IC-50 24h	IC-50 48h	IC-50 72h	IC-50 96h	Cell line	Drug	Ref
274	3	9.31µM	1.69µM	0.42µM	0.71µM	PC-3	Doxorubicin	113
275	3	10.53µM	1.11µM	0.57µM	0.68µM	PC-3	Epirubicin	113
276	3	127.08µM	15.31µM	18.35µM	18.77µM	PC-3	Cisplatin	113
Case	Type	IC-50 24h	IC-50 72h	IC-50 120h	Cell line	Drug	Ref	
277	3	48mM	6.6mM	120mM	SW13	Ouabain	41	
Case	Type	IC-50 3h	IC-50 48h	IC-50 72h	Cell line	Drug	Ref	
278	3	>32µM	22µM	31µM	NCI-H676	Paclitaxel	65	
279	3	0.31µM	0.0092µM	0.017µM	NCI-H1155	Paclitaxel	65	

Table 4. IC-50 Time Evolution Type 4.

Case	Type	IC-50 24h	IC-50 48h	IC-50 72h	Cell line	Drug	Ref
280	4	144.1µM	200µM	109.3µM	UACC-903	JS-22(3b)	64
281	4	219.0µM	605.4µM	100.9µM	A375M	JS-28(4c)	64
282	4	98.92µM	107.8µM	44.95µM	UACC-903	JS-26(4a)	64
283	4	180.8µM	191.9µM	58.1µM	UACC-903	JS-20(3)	64
284	4	0.67µg/ml	1.05µg/ml	0.69µg/ml	MCF-7	DOX-GNMs	66
285	4	73µM	77µM	74µM	T47D	Silibinin Loaded	110
286	4	6.1µg/ml	7.2µg/ml	4.8µg/ml	HeLa	Berberine	61
287	4	2.7µg/m	3.5µg/ml	1µg/ml	L1210	Berberine	61
288	4	1.9µM	2.1µM	1.8µM	OVCAR3	Hypocretenolide 1	63
Case	Type	IC-50 3h	IC-50 24h	IC-50 120h	Cell line	Drug	Ref
289	4	0.28µM	7.5µM	0.68µM	NCI-H1299	Paclitaxel	65
Case	Type	IC-50 12h	IC-50 24h	IC-50 48h	IC-50 72h	Cell line	Ref
290	4	18.3µM	74.9µM	10.6µM	1.0µM	PC-3	114
							Cisplatin

Table 5. IC-50 Time Evolution Type 5.

Case	Type	IC-50 24h	IC-50 48h	IC-50 72h	Cell line	Drug	Ref
291	5	5ng/ml	5ng/ml	5ng/ml	NCEB	Bortezomib	77

Table 6. Drugs do not have always the same IC-50 Time Evolution Type with different cancer cell lines.

Drug	Cell line	IC-50 TET	Ref
Cisplatin	HCT15	1	90
Cisplatin	A549	1	94
Cisplatin	A2780	1	104
Cisplatin	SKOV3	1	104
Cisplatin	22Rv1	1	114
Cisplatin	PNT1A	1	114
Cisplatin	PC-3	4	114
Cisplatin	PC-3	3	113
Hypocretenolide 1	A431	1	63
Hypocretenolide 1	Hep-2	1	63
Hypocretenolide 1	SK28	1	63
Hypocretenolide 1	SK37	1	63
Hypocretenolide 1	ZR75-1	2	63
Hypocretenolide 1	SW872	3	63
Hypocretenolide 1	MCF-7	3	63
Hypocretenolide 1	OVCAR3	4	63
Bortezomib	HLB-2	1	77
Bortezomib	NCEB	5	77
Resveratrol	HCT-116	1	100
Resveratrol	A431	1	100
Resveratrol	CaCO-2	1	100
Resveratrol	HCA-7	1	100
Resveratrol	HCT-116 553-/-	1	100
Resveratrol	LnCap	1	100
Cediranib	HS578T	1	105
Cediranib	MDA-MB-231	1	105
Cediranib	T47D	1	105
Etoposide	U-266	1	59
Etoposide	DOHH-2	1	59
Etoposide	REH	1	59
Etoposide	HH	1	59
Etoposide	HuT78	1	59
Etoposide	OPM-2	1	59
Etoposide	RPMI-8226	1	59
Safranal	HeLA	1	111
Safranal	MCF-7	1	111
Safranal	L929	1	111
Capillin	A549	1	60
Capillin	Hep-2	1	60
Capillin	HT-29	3	60
Capillin	MIA Pa Ca-2	3	60

Table 6. *Continued*

Drug	Cell line	IC-50 TET	Ref
Paclitaxel	MCF-7	1	103
Paclitaxel	NCI-H23	1	65
Paclitaxel	NCI-H460	1	65
Paclitaxel	NCI-H322	1	65
Paclitaxel	NCI-H522	1	65
Paclitaxel	NCI-H727	1	65
Paclitaxel	NCI-H676	3	65
Paclitaxel	NCI-H1155	3	65
Paclitaxel	NCI-H1299	4	65
Helnalin	A431	1	63
Helnalin	SK28	1	63
Helnalin	Hep-2	1	63
Helnalin	SK37	1	63
Helnalin	SW872	1	63
Helnalin	ZR75-1	2	63
Helnalin	OVCAR3	2	63
Helnalin	MCF-7	3	63
5-FU	HT-29	1	109
5-FU	CaCO-2	1	109
Sinapinic acid	HeLa	1	61
Sinapinic acid	HT-29	1	61
Sinapinic acid	HCT-116	1	61
Sinapinic acid	JURKAT	1	61
Berberine	HeLa	4	61
Berberine	L1210	4	61
Salinomycin	A2780	1	97
Salinomycin	SKOV3	1	97
Apatinib	HT-29	1	98
Apatinib	HCT-116	1	98

Table 7. Cancer cell lines and Drugs and their IC-50 TET.

Cell line	Drug	IC-50 TET	Ref
K562	Para-nitro acetophenon	2	55
K562	Acetanilide	3	55
MCF-7	Arsenic trioxide	1	72
MCF-7	TAM	1	70
MCF-7	Dox-Sol	1	66
MCF-7	MCRE	1	91
MCF-7	Mitoxantrone	1	103
MCF-7	Paclitaxel	1	103
MCF-7	Methotrexate	1	103
MCF-7	Arsenic disulfide	1	106
MCF-7	Safranal	1	111

Table 7. *Continued*

Cell line	Drug	IC-50 TET	Ref
MCF-7	Doxorubicin	1	102
MCF-7	Capecitabin	1	112
MCF-7	TTHL	1	67
MCF-7	Hypocretenolide 1	3	67
MCF-7	Helenalin	3	67
MCF-7	DOX-GNMs	4	66
UACC-903	JS-21(3a)	1	64
UACC-903	JS-23(3c)	1	64
UACC-903	JS-25(4)	1	64
UACC-903	JS-20(3)	4	64
UACC-903	JS-22(3b)	4	64
UACC-903	JS-26(4a)	4	64
A549	Capillin	1	60
A549	Doxorubicin	1	92
A549	Cisplatin	1	94
A549	Silver nitrate	1	94
A549	TQ	1	96
A549	TGG	1	96
A549	TQ-Fe ₃ O ₄	1	96
A549	TQG-Fe ₃ O ₄	1	96
A549	TQ-Fe ₃ O ₄ (MF)	1	96
A549	TQ-G-Fe ₃ O ₄ (MF)	1	96
HL-60	PJ-34	1	93
HL-60	Doxorubicin	1	93
HL-60	Arsenic trioxide	1	108
HL-60	EA-137	1	124
HL-60	EA-136	2	124
HL-60	EA-4	2	124
HL-60	all-trans-RA	3	72
HCT-116	Sinapinic acid	1	61
HCT-116	Sodium butyrate	1	61
HCT-116	Apatinib	1	98
HCT-116	DHCA	1	123
HCT-116	Resveratrol	1	100
HCT-116	IRA-5	1	100
HCT-116	TTHL	1	67
HCT-116	Bark CO AE	3	40
LnCap	9S1R	1	54
LnCap	Resveratrol	1	100
LnCap	IRA-5	1	100
LnCap	9R	3	54
HeLa	Sinapinic acid	1	61
HeLa	Sodium butyrate	1	61

Table 7. *Continued*

Cell line	Drug	IC-50 TET	Ref
HeLa	Apigenin	1	87
HeLa	Safranal	1	111
HeLa	DHCA	1	123
HeLa	Berberine	4	61
T47D	Cediranib	1	105
T47D	Curcumin	1	121
T47D	Silibinin	1	110
T47D	Silibilin Loaded.	4	110
A431	Hypocretenolide 1	1	63
A431	Helenalin	1	63
A-375	JS-20(3)	1	64
A-375	SLN Docetaxel	1	71
A-375	Taxotere	1	71
A-375	JS-22(3b)	3	64
A-375	JS-28(4c)	4	64
HT-29	Sinapinic acid	1	61
HT-29	Apatinib	1	98
HT-29	5-FU	1	109
HT-29	Valdecoxib	1	115
HT-29	TTHL	1	67
HT-29	Capillin	3	60
SW872	Helenalin	1	63
SW872	Hypocretenolide 1	3	63
HepG2	Mycotxin AOH	1	69
HepG2	Gpniiothalamine	1	62
HepG2	TTHL	1	67
HepG2	Mycotoxin 3-ADON	3	69
MDA-MB-231	Arsenic trioxide	1	72
MDA-MB-231	TAM	1	70
MDA-MB-231	EPC-3	1	95
MDA-MB-231	Cediranib	1	105
MDA-MB-231	Arsenic disulfide	1	106
MDA-MB-231	Ciprofloxacin	1	120
MDA-MB-231	9R	1	54
MDA-MB-231	9S1R	1	54
MDA-MB-231	Doxorubicin	1	102
PC-3	Boswellic acid	1	107
PC-3	Flutamide	1	113
PC-3	Doxorubicin	3	113
PC-3	Epirubicin	3	113
PC-3	Cisplatin	3	113
PC-3	Cisplatin	4	114
PC-3	Montelukast Sodium	1	107

Figure 1. Arbitrary values for IC-50 and Standard time points: 24h, 48 and 72h.

to the 4PL model. So instead of one single dot in the S shaped curve inspired by the Hill equation, the new model provides curves with five different shapes as shown in the theoretical arbitrary **Figure 1**. In total there are **291** cases of IC-50 variations over time: Type 1 (80.76%), Type 2 (4.81%), Type 3 (10.31%), Type 4 (3.78%) and Type 5 (0.34%).

1. Type 1

(Cases 1-235) is characterized by an IC-50 decrease over time (**Table 1** and **Figure 1a**). There are several choices of time points: [24h, 48h and 72h for Cases 1-185], [3h, 24h and 120h for Cases 186-190], [2h, 24h, and 48h for Cases 191-194], [48h, 72h, and 120h for Cases 195-206], [24h, 48h, 72h and 96h for Cases 207-215], [24h, 48h, 72h and 120h for Cases 216-222], [24h, and 48h for Cases 223-233], and [48h and 72h for Cases 234-235]. The IC-50 decrease is dramatic in many Cases (3, 4, 13, 14, 21, 24-27, 65, 67, 75, 79, 111, 112, 114, 116, 123, 151, 163, 165, 170, 171, 173, 197, 199, 200, 201, 201, 206 and 210). The IC-50 decrease over time depends on the cell lines and drugs. This shows that one IC-50

taken at one time point is misleading in its value and can explain the inconsistency noticed by Haibe-Kains et al.¹ Baggerly et al.⁴ and Reinhold et al.⁵ The increase of sensitivity of cancer cells to drugs, missing with the 4PL model based on one time point IC-50, is consistent with Haber's law of increase of drug toxicity with time.

2. Type 2

(Cases 236-249) is characterized by an IC-50 increase over time (Table 2 and Figure 1b). There are several choices of time points: [24h, 48h and 72h for Cases 236-245], [2h, 24h and 48h for Case 246], [48h and 72h for Cases 247-248], and [24h, 48h and 72h for Case 249]. This IC-50 increase can be dramatic as in Cases 243-245 and 248. This IC-50 increase over time is not predicted by the Haber's law and the 4PL model. It is only described by the multiple time points IC-50 introduced by this paper. It shows how cancer cells drug resistance is evidenced *in vitro* over a short period of time and shows the usefulness of the multiple IC-50-time points model.

3. Type 3

(Cases 250-279) is a V shaped curve characterized by two phases in the interaction between cancer cells and drugs, a decrease phase of the IC-50 followed by an increase of the IC-50 over time (Table 3 and Figure 1c). There are several choices of time points: [24h, 48h and 72h for Cases 250-268], [4h, 24h and 48h for Cases 269-272], [2h, 24h and 48h for Case 273], [24h, 48h and 72h for Cases 274-276], [24h, 72h and 120h for Case 277] and [3h, 48h and 72h for Cases 278-279]. Type 3 is not predicted by the Haber's law and the 4PL model. This type shows how complex the interaction between cancer cells and drugs can be. In this type we are *in vitro* out of reach of the immune system and whatever a living organism can do to stop the growth of cancer cells. There are two possible interpretations. The *first* is based on what have been said before, that not all cancer cells *in vitro* are growing according to the Gompertzian model. The IC-50 decrease phase is the killing of growing cells *in vitro*, and the IC-50 increase phase shows the resistance of non-growing quiescent cancer cells. After all the majority of cancer drugs are targeting growing cells. The *second* can be explained by the killing of the bulk of cancer cells in the first phase and the takeover by a resistant clone like cancer stem cells in the second phase. It is an *in vitro* self-seeding mechanism.⁵¹ Type 3 shows the advantage of the multiple IC-50 time points and its far-reaching capacity to explore the complex behavior of cancer cells. This is a clear demonstration that cancer cells monolayer is heterogeneous and respond differently to cancer drugs. In addition, the IC-50 taken in different time points between the large-scale studies will lead to dramatic inconsistency.

4. Type 4

Is an Arabic eight-digit Λ or the Greek lambda Λ letter shaped curve also characterized by two phases in the interaction between cancer cells and drugs⁶⁴⁻⁶⁶ (Table 4 and Figure 1d). There are several choices of time points: [24h, 48h and 72h for Cases 280-288], [3h, 24h and 120h for Case 289], [12h, 24h, 48h and 72h for Case 290]. This Type in addition of showing the heterogeneity of cancer *in vitro* (growing cells vs quiescent cells), demonstrates in IC-50 increasing phase cancer cells resistance, then suddenly in the IC-50 decreasing phase the resistance collapse. So, any IC-50 taken at the time point corresponding to the apex of the Λ is seriously misleading. This type of situation is not predicted by the Haber's law or the 4PL model.

5. Type 5

Is characterized by a constant IC50 over time (Table 4 and Figure 1e). I found only one case [24h, 48h and 72h for Case 291]. The proteasome inhibitor Bortezomib killing mechanism is not cell cycle dependent.

6. Is there a relationship between cancer drugs molecular targets and their IC-50 Time Evolution Type (TET)?

As Table 5 shows, it is difficult to find a clear pattern for cancer drugs TET. Etoposide which targets DNA Topoisomerase II kills seven cancer cell lines with IC-50 TET 1. Cisplatin kills six cell lines with TET 1 and kills PC-3 cell line with different TET in two different papers: TET3¹¹³ and TET4.¹¹⁴ Resveratrol's molecular target still unknown, it kills six cancer cell lines with TET1. Paclitaxel which targets microtubules kills cancer cells with TET1, 3 and 4. Bortezomib which targets the proteasome system kills cancer cells with TET 1 and 5. Further studies are necessary to explore this relationship, if there is any, between cancer drugs and their IC-50 TET.

7. Is there a relationship between cancer cell lines and cancer drugs IC-50 Time Evolution Type (TET)?

As shown in Table 6 it is hard to find a general pattern. Cancer cell line A549 exposed to 10 drugs respond with the same IC-50 TET1 as reported by different papers.^{60,92,94,96} Cancer cell line MDA-MB-231 exposed to 9 different drugs respond with the same TET1 as reported by 8 different papers.^{54,70,72,95,102,105,106 and 120} Cancer cell line MCF-7 has a mixed response to drugs but responds with IC-50 TET1 to 12 drugs as reported by 9 papers.^{54,70,72,95,102,105,106 and 120} Cancer cell line HCT-116 has a mixed response to drugs but responds with IC-50 TET1 to 7 drugs as reported by 5 papers.^{61,67,98,100 and 112} Cancer cell line HeLa has a mixed response to drugs but responds with IC-50 TET1 to 5 drugs as reported by 4 papers.^{61,87,111 and 123} Cancer cell line HT-29 has a mixed response to drugs but responds with IC-50

TET1 to 5 drugs as reported by 5 papers.^{61,67,98,109 and 115} As shown in Table 6 a variety of cancer cells (K-562, MCF-7, UACC-903, HL-60, HCT-116, LnCap, HeLa, T47D, A-375, HT-29, SW872 and PC-3) have a mixed response of IC-50 TET^{1,2,3,4 and 5} to many cancer drugs. The good thing is that the response of each cancer cell line is reported by several research groups in the world. That is proof of validity, the strength and the usefulness of the IC-50-time evolution model compared to the one time point IC-50, aka 4PL model based on the Hill equation.

VII. Conclusions

The *in vitro* testing of cancer drugs remains a necessary step in their evaluation. To solve the inconsistencies of the drugs IC-50s between large scale studies several attempts^{24,37,79–83} failed. It is my opinion that the *in vitro* assessment of drugs is still a necessary step before going to *in vivo* mice studies and human clinical trials. Considering the failure of many drugs at the end, and the billions of dollars to support that, it is necessary to strengthen the prediction power of *in vitro* studies by considering a better understanding of cancer cells behavior in microplates. It is tempting to use high capacity microplates in which the reaction volume can be as small as 5µl and the number of cells is in the hundreds, making any statistical analysis futile. The automation of the process imposing an arbitrary one time point IC-50 regardless of the diversity of hundreds cancer cells doubling times provides this technology euphoria but does not advance cancer research field nor it improves patient's life. The growth of cancer cells *in vitro* as it is *in vivo* is not a continuous growth. Jacques Monod used to say “*the dream of a bacteria is to become two bacteria*”. Cancer cells have another dream referred to as the “Gompertzian model”. This model applied *in vivo* has dramatically improved cancer treatment, the same model governs cancer cells growth in microplates whether in 2D or 3D formats. As I explained the meaning of different IC-50-time evolution Types 1-5, the effects of cancer drugs on cancer cells is time dependent. It was Fritz Haber who noticed that a low dose applied at long time has the same effect as a high dose applied at a short time. The Hill model short of the time factor is the main source of our problems with the *in vitro* screening of cancer drugs.⁸⁴ We need to go beyond the Hill model and embrace the IC-50-time course evolution already predicted by Levasseur LM *et al* modified Hill model,¹⁵ the Gompertzian growth type of *in vitro*,^{30,40–43} the heterogeneous nature of *in vitro* monolayers⁴⁷ and microspheres, and the hormesis phenomenon.^{25–29} This new model, still a work in progress, connects the IC50 time evolution to *in vitro* cellular monolayer dynamics: cancer cells exposed to killing drugs do not respond as individual cells but as group of cells governed by quorum sensing.^{85,86} In addition, the results gathered in 80 papers validate the new model I am presenting.

Declarations

Data availability: No data are associated with this article.

References

1. Halibe-Kains B, El-Hachem N, Birkbak NJ, *et al.*: **Inconsistency in large pharmacogenomics studies.** *Nature.* 2013; **504**: 389–393. [PubMed Abstract](#) | [Publisher Full Text](#)
2. Barretina J, Caponigro G, Stransky N, *et al.*: **The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity.** *Nature.* 2012; **483**: 603–607. [PubMed Abstract](#) | [Publisher Full Text](#)
3. Garnett MJ, Edelman EJ, Heidorn SJ, *et al.*: **Systematic identification of genomic markers of drug sensitivity in cancer cells.** *Nature.* 2012; **483**: 570–575. [PubMed Abstract](#) | [Publisher Full Text](#)
4. Baggerly KA, Coombes KR: **Deriving chemosensitivity from cell lines: forensic bioinformatics and reproducible research in high-throughput biology.** *Ann. Appl. Stat.* 2009; **3**: 1309–1334. [Publisher Full Text](#)
5. Reinhold WC, Varma S, Rajapakse VN, *et al.*: **Using drug response data to identify molecular effectors, and molecular “omic” data to identify candidate drugs in cancer.** *Hum. Genet.* 2015; **134**: 3–11. [PubMed Abstract](#) | [Publisher Full Text](#)
6. Yamori T, Matsunaga SS, Yamazaki K, *et al.*: **Potent Antitumor Activity of MS-247, a Novel DNA Minor Groove Binder, Evaluated by an *In Vitro* and *In Vivo* Human Cancer Cell Line Panel.** *Cancer Res.* 1999; **59**: 4042–4049. [PubMed Abstract](#)
7. Greshock J, Bachman KE, Degenhardt YY, *et al.*: **Molecular Target Class Is Predictive of *in vitro* Response Profile.** *Cancer Res.* 2010; **70**: 3677–3686. [PubMed Abstract](#) | [Publisher Full Text](#)
8. Hook KE, Garza SJ, Lira ME, *et al.*: **Integrated Genomic Approach to Identify Predictive Biomarkers of Response to the Aurora Kinase Inhibitor PF-03814735.** *Mol. Cancer Ther.* 2012; **11**: 710–719. [PubMed Abstract](#) | [Publisher Full Text](#)
9. Heiser LM, Sadanandam A, Kuo WL, *et al.*: **Subtype and pathway specific responses to anticancer compounds in breast cancer.** *PNAS.* 2012; **109**: 2724–2729. [PubMed Abstract](#) | [Publisher Full Text](#)
10. Yang W, Soares J, Greninger P, *et al.*: **Genomics of Drug Sensitivity in Cancer (GDSC): a resource for therapeutic biomarker discovery in cancer cells.** *Nucleic Acids Res.* 2013; **41**: D955–D961. [Publisher Full Text](#)
11. Seashore-Ludlow B, Rees MG, Cheah JH, *et al.*: **Harnessing Connectivity in a Large-Scale Small-Molecule Sensitivity Dataset.** *Cancer Discov.* 2015; **5**: 1210–1223. [Publisher Full Text](#)
12. Shoemaker RH: **Development of human tumor cell line panels for use in disease-oriented drug screening.** *Prog. Clin. Biol. Res.* 1988; **276**: 265–286. [PubMed Abstract](#)
13. Lieberman MM, Patterson GML, Moore RE: ***In vitro* bioassays for anticancer drug screening: effects of cell concentration and other assay parameters on growth inhibitory activity.** *Cancer Lett.* 2001; **173**: 21–29. [Publisher Full Text](#)
14. Rupniak HT, Whelan RDH, Hill BT: **Concentration and time-dependent inter-relationships for antitumour drug cytotoxicities against tumour cells *in vitro*.** *Int. J. Cancer.* 1983; **32**:

- 7–12.
Publisher Full Text
15. Levasseur LM, Slocum HK, Rustum YM, *et al.*: **Modeling of the time-dependency of *in vitro* drug cytotoxicity and resistance.** *Cancer Res.* 1998; **58**: 5749–5761.
PubMed Abstract
 16. **Reference Source**
 17. Fallahi-Sichani M, Honarnejad S, Heiser LM, *et al.*: **Metrics other than potency reveal systematic variation in responses to cancer drugs.** *Nature Chem. Biol.* 2013; **9**: 708–714.
PubMed Abstract | Publisher Full Text
 18. Hill AV: **The possible effects of the aggregation of the molecules of hemoglobin on its dissociation curves.** *J. Physiol.* 1910; **40**: 4–7.
 19. Goutelle S, Maurin M, Rougier F, *et al.*: **The Hill equation: a review of its capabilities in pharmacological modelling.** *Fundam. Clin. Pharmacol.* 2008; **22**: 633–648.
PubMed Abstract | Publisher Full Text
 20. Ozawa S, Sugiyama Y, Mitsuhashi J, *et al.*: **Kinetic analysis of cell killing effect induced by 1- β -D-arabinofuranosylcytosine and cisplatin in relation to cell cycle phase specificity in human colon cancer and Chinese hamster cells.** *Cancer Res.* 1998; **49**: 3823–3828.
 21. Adams DJ: **In Vitro Pharmacodynamic Assay for Cancer Drug Development: Application to Crisnatol, a New DNA Intercalator.** *Cancer Res.* 1989; **49**: 6615–6620.
PubMed Abstract
 22. Gardner SN: **A Mechanistic, Predictive Model of Dose-Response Curves for Cell Cycle Phase-specific and -nonspecific Drugs.** *Cancer Res.* 2000; **60**: 1417–1425.
PubMed Abstract
 23. Prinz H: **Hill coefficients, dose-response curves and allosteric mechanisms.** *J. Chem. Biol.* 2010; **3**: 37–44.
PubMed Abstract | Publisher Full Text
 24. DiVeroli GY, Fornari C, Goldlust I, *et al.*: **An automated fitting procedure and software for dose-response curves with multiphasic features.** *Sci. Rep.* 2015; **5**: 14701.
PubMed Abstract | Publisher Full Text
 25. Maynard KI: **Hormesis Pervasiveness and its Potential Implications for Pharmaceutical Research and Development.** *Dose Response.* 2011; **9**: 377–386.
PubMed Abstract | Publisher Full Text | Free Full Text
 26. Conolly RB, Lutz WK: **Nonmonotonic Dose-Response Relationships: Mechanistic Basis, Kinetic Modeling, and Implications for Risk Assessment.** *Toxicol. Sci.* 2004; **77**: 151–157.
PubMed Abstract | Publisher Full Text
 27. Edward J, Calabrese EJ: **Hormesis and medicine.** *Br. J. Clin. Pharmacol.* 2008; **66**: 594–617.
Publisher Full Text
 28. Calabrese EJ: **Cancer biology and hormesis: human tumor cell lines commonly display hormetic (biphasic) dose responses.** *Crit. Rev. Toxicol.* 2005; **35**: 463–582.
PubMed Abstract | Publisher Full Text
 29. Rashkov P, Barrett IP, Beardmore RE, *et al.*: **Kinase Inhibition Leads to Hormesis in a Dual Phosphorylation Dephosphorylation Cycle.** *PLoS Comput. Biol.* 2016; **12**: e1005216.
PubMed Abstract | Publisher Full Text
 30. Norton L, Simon R, Brereton HD, *et al.*: **Predicting the course of gompertzian growth.** *Nature.* 1976; **264**: 542–545.
PubMed Abstract | Publisher Full Text
 31. Gompertz B: **On the nature of the function expressive of the law of human mortality, and on the mode of determining the value of life contingencies.** *Phil. Trans. Roy. Soc.* 1825; **115**: 513–583.
Publisher Full Text
 32. Bouhaddou M, DiStefano MS, Riesel EA, *et al.*: **Drug response consistency in CCLE and CGP.** *Nature.* 2016; **540**: E9–E10.
PubMed Abstract | Publisher Full Text
 33. Mpindi JP, Yadav B, Östling P, *et al.*: **Consistency in drug response profiling.** *Nature.* 2016; **540**: E5–E6.
PubMed Abstract | Publisher Full Text
 34. Geeleher P, Gamazon ER, Seoighe C, *et al.*: **Consistency in large pharmacogenomics studies.** *Nature.* 2016; **540**: E1–E2.
PubMed Abstract | Publisher Full Text
 35. Weinstein JN, Lorenzi P: **Discrepancies in drug sensitivity.** *Nature.* 2013; **504**: 381–383.
Publisher Full Text
 36. Stransky N, Ghandi M, Kryukov GV, *et al.*: **Pharmacogenomic agreement between two cancer cell line data sets.** *Nature.* 2015; **528**: 84–87.
Publisher Full Text
 37. Safikhani Z, El-Hachem N, Quevedo R, *et al.*: **Assessment of pharmacogenomic agreement.** *F1000Res.* 2016; **5**: 825.
PubMed Abstract | Publisher Full Text
 38. Haverty PM, Lin E, Tan J, *et al.*: **Reproducible pharmacogenomics profiling of cancer cell line panels.** *Nature.* 2015; **533**: 333–337.
Publisher Full Text
 39. Hanahan D, Weinberg RA: **Hallmarks of Cancer: The Next Generation.** *Cell.* 2011; **144**: 646–674.
Publisher Full Text
 40. Drasdo D, Hohme S: **A single-cell-based model of tumor growth in vitro: monolayers and spheroids.** *Phys. Biol.* 2005; **2**: 133–147.
PubMed Abstract | Publisher Full Text
 41. Demicheli R, Foroni R, Ingrosso A, *et al.*: **An Exponential-Gompertzian Description of LoVo Cell Tumor Growth from in Vivo and in Vitro Data.** *Cancer Res.* 1989; **49**: 6543–6546.
PubMed Abstract
 42. Demicheli R, Pratesi G, Foroni R: **The Exponential-Gompertzian Tumor Growth Model: Data From Six Tumor Cell Lines in vitro And In Vivo. Estimate of The Transition Point From Exponential To Gompertzian Growth And Potential Clinical Implications.** *Tumori.* 1991; **77**: 189–195.
PubMed Abstract | Publisher Full Text
 43. Poplawski NJ, Shirinifard A, Agero U, *et al.*: **Front Instabilities and Invasiveness of Simulated 3D Avascular Tumors.** *PLoS One.* 2010; **5**: e10641.
PubMed Abstract | Publisher Full Text
 44. Bru A, Albertos S, Subiza JL, *et al.*: **The Universal Dynamics of Tumor Growth.** *Biophys. J.* 2003; **85**: 2948–2961.
PubMed Abstract | Publisher Full Text | Free Full Text
 45. Puliafito A, Hufnagel L, Neveu P, *et al.*: **Collective and single cell behavior in epithelial contact inhibition.** *PNAS.* 2012; **109**: 739–744.
PubMed Abstract | Publisher Full Text
 46. Castro MAA, Klamt F, Grieneisen VA, *et al.*: **Gompertzian growth pattern correlated with phenotypic organization of colon carcinoma, malignant glioma and non-small cell lung carcinoma cell lines.** *Cell Prolif.* 2003; **36**: 65–73.
PubMed Abstract | Publisher Full Text
 47. Gyllenberg M, Webb GF: **Quiescence as an explanation of Gompertzian tumor growth.** *Growth Dev. Aging.* 1989; **53**: 25–33.
 48. Kozusko F, Bajzer Z: **Combining Gompertzian growth and cell population dynamics.** *Math. Biosci.* 2003; **185**: 153–167.
PubMed Abstract | Publisher Full Text
 49. Comen E, Morris PG, Norton L: **Translating mathematical modeling of tumor growth patterns into novel therapeutic approaches for breast cancer.** *J. Mammary. Gland Biol. Neoplasia.* 2012; **17**: 241–249.
PubMed Abstract | Publisher Full Text
 50. Bayraktar S, Arun B: **Dose-dense chemotherapy for breast cancer.** *Breast J.* 2012; **18**: 261–266.
Publisher Full Text
 51. Kim MY, Oskarsson T, Acharyya S, *et al.*: **Tumor Self-Seeding by Circulating Cancer Cells.** *Cell.* 2009; **139**: 1315–1326.
PubMed Abstract | Publisher Full Text
 52. Xu X, Farach-Carson MC, Jia X: **Three-dimensional in vitro tumor models for cancer research and drug evaluation.** *Biotechnol. Adv.* 2014; **32**: 1256–1268.
PubMed Abstract | Publisher Full Text
 53. Adcock AF, Trivedi G, Edmondson R, *et al.*: **Three-Dimensional (3D) Cell Cultures in Cell-based Assays for in-vitro Evaluation of Anticancer Drugs.** *J. Anal. Bioanal. Tech.* 2005; **6**: 247.
 54. Alileche A, Goswami J, Bourland W, *et al.*: **Nullomer derived peptides (NulloPs): differential lethal effects on normal and cancer cell in vitro.** *Peptides.* 2012; **38**: 302–311.
PubMed Abstract | Publisher Full Text
 55. Theodoraki MA, Rezende CO Jr, Chantarasriwong O, *et al.*: **Spontaneously-forming spheroids as an in vitro cancer cell model for anticancer drug screening.** *Oncotarget.* 2015; **6**: 21255–21267.
PubMed Abstract | Publisher Full Text
 56. Hongisto V, Jernström S, Fey V, *et al.*: **High-Throughput 3D Screening Reveals Differences in Drug Sensitivities between Culture Models of JIMT1 Breast Cancer Cells.** *PLoS One.* 2013; **8**: e77232.
PubMed Abstract | Publisher Full Text
 57. Zanoni M, Piccinini F, Arienti C, *et al.*: **3D tumor spheroid models for in vitro therapeutic screening: a systematic approach to enhance the biological relevance of data obtained.** *Sci. Rep.* 2016; **6**: 19103.
PubMed Abstract | Publisher Full Text
 58. Ivanov DP, Parker TL, Walker DA, *et al.*: **Multiplexing Spheroid Volume, Resazurin and Acid Phosphatase Viability Assays for**

- High-Throughput Screening of Tumour Spheroids and Stem Cell Neurospheres.** *PLoS One.* 2014; **9**: e103817.
[PubMed Abstract](#) | [Publisher Full Text](#)
59. Ilieva Y, Zhelezova I, Atanasova T, et al.: **Cytotoxic effect of the biotechnologically-derived justicidin B on human lymphoma cells.** *Biotechnol. Lett.* 2014; **36**: 2177–2183.
[PubMed Abstract](#) | [Publisher Full Text](#)
 60. Whelan LC, Ryan MF: **Effects of the polyacetylene capillin on human tumour cell lines.** *Anticancer Res.* 2004; **24**: 2281–2286.
[PubMed Abstract](#)
 61. Senawong T, Misuna S, Khaopa S, et al.: **Histone deacetylase (HDAC) inhibitory and antiproliferative activities of phenolic-rich extracts derived from the rhizome.** *BMC Complement. Altern. Med.* 2013; **13**: 232–242.
[PubMed Abstract](#) | [Publisher Full Text](#)
 62. Al-Qubaisi M, Rozita R, Yeap SK, et al.: **Selective cytotoxicity of goniothalamin against hepatoblastoma HepG2 cells.** *Molecules.* 2011; **16**: 2944–2959.
[PubMed Abstract](#) | [Publisher Full Text](#)
 63. Zidorn C, Stuppner H, Tiefenthaler M, et al.: **Cytotoxic activities of Hypocretenolides from *Leontodon hispidus*.** *J. Nat. Prod.* 1999; **62**: 984–987.
[PubMed Abstract](#) | [Publisher Full Text](#)
 64. Soman SS, Soni JN, Inamdar GS, et al.: **Synthesis and anticancer activity of 4-hydroxy naphtho coumarin derivatives and naphtho coumestans.** *Der Pharma Chemica.* 2013; **5**: 201–207.
 65. Georgiadis MS, Russell EK, Gazdar AF, et al.: **Paclitaxel Cytotoxicity against human lung cancer cell lines increases with prolonged exposure durations.** *Clin. Cancer Res.* 1997; **3**: 449–454.
[PubMed Abstract](#)
 66. Zhang W, Sun J, Fang W, et al.: **Nanomicelles based on X- shaped four-armed pegylated distearyl glycerol as long circulating system for doxorubicin delivery.** *Eur. J. Pharm. Sci.* 2015; **66**: 96–106.
[PubMed Abstract](#) | [Publisher Full Text](#)
 67. Macagnan VC, Moura DJ, Facundo VA, et al.: **The natural triterpene 3 β , 6 β , 16 β -trihydroxy-lup-20(29)-ene obtained from the flowers of *Combretum leprosum* induces apoptosis in MCF-7 breast cancer cells.** *BMC Complement. Altern. Med.* 2014; **14**: 280–291.
[Publisher Full Text](#)
 68. Qi L, Xu Z, Chen M: **In vitro and in vivo suppression of hepatocellular carcinoma growth by chitosan nanoparticles.** *Eur. J. Cancer.* 2007; **43**: 184–193.
[PubMed Abstract](#) | [Publisher Full Text](#)
 69. Juan-Garcia A, Juan C, Konig S, et al.: **Cytotoxic effects and degradation products of three mycotoxins: Alternariol, 3-acetyl-deoxynivalenol and 15-acetyl-deoxynivalenol in liver hepatocellular carcinoma cells.** *Toxicol. Lett.* 2015; **235**: 8–16.
[PubMed Abstract](#) | [Publisher Full Text](#)
 70. Abbasalipourkabar R, Salehzadeh A, Abdullah R: **In vitro investigations on the toxicity by tamoxifen and tamoxifen-loaded solid lipid nanoparticles on two breast cancer cell types.** *Avicenna J. Medical Biochem.* 2013; **1**: 36–40.
[Publisher Full Text](#)
 71. Mosallaei N, Jaafari MR, Hanafi-Bojd MY, et al.: **Docetaxel-loaded solid lipid nanoparticles: preparation, characterization, in vitro, and in vivo evaluations.** *J. Pharmacol. Sci.* 2013; **102**: 1994–2004.
[PubMed Abstract](#) | [Publisher Full Text](#)
 72. Chow SKY, Chan JYW, Fung KP: **Suppression of cell proliferation and regulation of estrogen receptor α signaling pathway by arsenic trioxide on human breast cancer MCF-7 cells.** *J. Endocrinol.* 2004; **182**: 325–337.
[PubMed Abstract](#) | [Publisher Full Text](#)
 73. Van Rijt SH, Romero-Canelon I, Fu Y, et al.: **Potent organometallic osmium compounds induce mitochondria-mediated apoptosis and S-phase cell cycle arrest in A549 non-small cell lung cancer cells.** *Metallomics.* 2014; **6**: 1014–1022.
[PubMed Abstract](#) | [Publisher Full Text](#)
 74. Enge JB, Honig A, Schönhals T, et al.: **Perifosine inhibits growth of human experimental endometrial cancers by blockade of AKT phosphorylation.** *Eur. J. Obstet. Gynecol. Reprod. Biol.* 2008; **141**: 64–69.
[PubMed Abstract](#) | [Publisher Full Text](#)
 75. Qi L, Xu Z, Chen M: **In vitro and in vivo suppression of hepatocellular carcinoma growth by chitosan nanoparticles.** *Eur. J. Cancer.* 2006; **43**: 184–193.
[PubMed Abstract](#) | [Publisher Full Text](#)
 76. Beberok A, Wrzesniok D, Szałachta M, et al.: **Lomefloxacin Induces Oxidative Stress and Apoptosis in COLO829 Melanoma Cells.** *Int. J. Mol. Sci.* 2017; **18**: 2194.
[PubMed Abstract](#) | [Publisher Full Text](#)
 77. Uziel O, Cohen O, Beery E, et al.: **The effect of Bortezomib and Rapamycin on Telomerase Activity in Mantle Cell Lymphoma.** *Transl. Oncol.* 2014; **7**: 741–751.
[PubMed Abstract](#) | [Publisher Full Text](#)
 78. Izadi M, Charoudeh HN, Rashidi M, et al.: **Antiproliferative effects of clofarabine on AGS gastric adenocarcinoma cell line.** *Silvae Genetica.* 2015; **57**: 1–10.
 79. Costello JC, Heiser LM, Georgii E, et al.: **NCI DREAM Community, A community effort to assess and improve drug sensitivity prediction algorithms.** *Nature Biotech.* 2014; **32**: 1202–1212.
[PubMed Abstract](#) | [Publisher Full Text](#)
 80. Menden MP, Iorio F, Garnett MJ, et al.: **Machine Learning Prediction of Cancer Cell Sensitivity to Drugs Based on Genomic and Chemical Properties.** *PLoS One.* 2013; **8**: e61318.
[PubMed Abstract](#) | [Publisher Full Text](#)
 81. Hatzis C, Bedard P, Birkbak NJ, et al.: **Enhancing Reproducibility in Cancer Drug Screening: How Do We Move Forward?.** *Cancer Res.* 2014; **74**: 4016–4023.
[PubMed Abstract](#) | [Publisher Full Text](#)
 82. Vis DJ, Bombardelli L, Lightfoot H, et al.: **Multilevel models improve precision and speed of IC50 estimates.** *Pharmacogenomics.* 2016; **17**: 691–700.
[PubMed Abstract](#) | [Publisher Full Text](#)
 83. Stransky N, Garraway LA, Daniel A, et al.: **Pharmacogenomic agreement between two cancer cell line data sets.** *Nature.* 2015; **528**: 84–87.
[Publisher Full Text](#)
 84. Wong CC, Cheng KW, Rigas B: **Preclinical predictors of anticancer drug efficacy: critical assessment with emphasis on whether nanomolar potency should be required of candidate agents.** *J. Pharmacol. Exp. Ther.* 2012; **341**: 572–578.
[PubMed Abstract](#) | [Publisher Full Text](#)
 85. Patel SJ, Dao S, Darie CC, et al.: **Defective quorum sensing of acute lymphoblastic leukemia cells: evidence of collective behavior of leukemic populations as semi-autonomous aberrant ecosystems.** *Am. J. Cancer Res.* 2016; **6**: 1177–1230.
[PubMed Abstract](#)
 86. Agur Z, Kogan Y, Levi L, et al.: **Disruption of a Quorum Sensing mechanism triggers tumorigenesis: a simple discrete model corroborated by experiments in mammary cancer stem cells.** *Biol. Direct.* 2010; **5**: 20.
[PubMed Abstract](#) | [Publisher Full Text](#)
 87. Souza RP, Bonfim-Mendonça PdS, Gímenes F, et al.: **Oxidative Stress Triggered by Apigenin Induces Apoptosis in a Comprehensive Panel of Human Cervical Cancer-Derived Cell Lines.** *Oxidative Med. Cell. Longev.* 2017; **2017**: 1–18. Article ID 1512745.
[PubMed Abstract](#) | [Publisher Full Text](#)
 88. Wang C, Jiang L, Wang S, et al.: **The Antitumor Activity of the Novel Compound Jesridonin on Human Esophageal Carcinoma Cells.** *PLoS One.* 2015; **10**: e0130284.
[PubMed Abstract](#) | [Publisher Full Text](#)
 89. Centoducati G, Santacroce MP, Lestingi AL, et al.: **Characterization of the cellular damage induced by Aflatoxin B1 in sea bream (*Sparus aurata* Linnaeus, 1758) hepatocytes.** *Ital. J. Anim. Sci.* 2009; **8**(Suppl. 2): 848–850.
[Publisher Full Text](#)
 90. Thiyan R, Narasu ML: **Zerumbone Inhibits Proliferation And Induces Apoptosis, Cell Cycle Arrest In Human Colon Cancer Cell Line HCT15.** *International Journal of Research in Applied, Natural and Social Sciences.* 2017; **5**: 49–54.
 91. Kamali AM, Nikseresht M, Delaviz H, et al.: **In Vitro Cytotoxic Activity of Matricaria Chamomilla Root Extract in Human Breast Cancer Cell Line MCF-7.** *Life Sci. J.* 2014; **10**: 403–406.
 92. Punia R, Raina K, Agarwal R, et al.: **Acacetin enhances the therapeutic efficacy of doxorubicin in non-small-cell lung carcinoma cells.** *PLoS One.* 2017; **12**: e0182870.
[PubMed Abstract](#) | [Publisher Full Text](#)
 93. Stepnik M, Spryszynska S, Gorzkiewicz A, et al.: **Cytotoxicity of anticancer drugs and PJ-34 (poly (ADP-ribose) polymerase-1 (PARP-1) inhibitor) on HL-60 and Jurkat cells.** *Adv. Clin. Exp. Med.* 2017; **26**: 379–385.
[PubMed Abstract](#) | [Publisher Full Text](#)
 94. Kaplan A, Ciftci GA, Kutlu HM: **The apoptotic and genomic studies on A549 cell line induced by silver nitrate.** *Tumor Biol.* 2017; **39**: 101042831769503–101042831769512.
[Publisher Full Text](#)
 95. Stoyanova T, Uzunova V, Popova D, et al.: **Effect of Erufosine on MDA-MB 231 Breast Cancer Cells.** *J. Oncol Res Forecast.* 2018; **1**: 1005.
 96. İnce I, Müftüleri ZB, Medine EI, et al.: **Synthesis of Radioiodinated Thymoquinone Glucuronide Conjugated Magnetic Nanoparticle (¹²⁵I-TQG-Fe3O4) and its Cytotoxicity and in vitro Affinity 2018.** *Acta Pharm. Sci.* 2018; **56**: 7–26.

97. Li R, Dong T, Hu C, *et al.*: **Salinomycin repressed the epithelial mesenchymal transition of epithelial ovarian cancer cells via downregulating Wnt/ β -catenin pathway.** *Onco. Targets. Ther.* 2017; **10**: 1317–1325.
[PubMed Abstract](#) | [Publisher Full Text](#)
98. Chenga X, Fenga H, Wua H, *et al.*: **Targeting autophagy enhances apatinib-induced apoptosis via endoplasmic reticulum stress for human colorectal cancer.** *Cancer Lett.* 2018; **431**: 105–114.
[PubMed Abstract](#) | [Publisher Full Text](#)
99. Aveic S, Pantile M, Seydel A, *et al.*: **Combating autophagy is a strategy to increase cytotoxic effects of novel ALK inhibitor entrectinib in neuroblastoma cells.** *Oncotarget.* 2016; **7**: 5646–5663.
[PubMed Abstract](#) | [Publisher Full Text](#)
100. Wang S, Willenberg I, Krohn M, *et al.*: **Growth-Inhibiting Activity of Resveratrol Imine Analogs on Tumor Cells In Vitro.** *PLoS One.* 2017; **12**: e0170502.
[PubMed Abstract](#) | [Publisher Full Text](#)
101. Shen W, Hu JA, Zheng JS: **Mechanism of temozolomide-induced antitumour effects on glioma cells.** *J. Int. Med. Res.* 2014; **42**: 164–172.
[PubMed Abstract](#) | [Publisher Full Text](#)
102. Chan K W Y, Jiang L, Cheng M, *et al.*: **CEST-MRI detects metabolite levels altered by breast cancer cell aggressiveness and chemotherapy response.** *NMR Biomed.* 2016; **29**: 806–816.
[PubMed Abstract](#) | [Publisher Full Text](#)
103. Zhuang YG, Xu B, Huang F, *et al.*: **Solid lipid nanoparticles of anticancer drugs against MCF-7 cell line and a murine breast cancer model.** *Pharmazie.* 2012; **67**: 925–929.
[PubMed Abstract](#)
104. Sun LM, Liu YC, Li W, *et al.*: **Nivolumab effectively inhibit platinum-resistant ovarian cancer cells via induction of cell apoptosis and inhibition of ADAM17 expression.** *Eur. Rev. Med. Pharmacol. Sci.* 2017; **21**: 1198–1205.
[PubMed Abstract](#)
105. Bordinhao ALR, Evangelista AF, Oliveira RJS, *et al.*: **MicroRNA profiling in human breast cancer cell lines exposed to the anti-neoplastic drug cediranib.** *Oncol. Rep.* 2016; **36**: 3197–3206.
[PubMed Abstract](#) | [Publisher Full Text](#)
106. Zhao Y, Yuan B, Onda K, *et al.*: **Anticancer efficacies of arsenic disulfide through apoptosis induction, cell cycle arrest, and pro-survival signal inhibition in human breast cancer cells.** *Am. J. Cancer Res.* 2018; **8**: 366–386.
[PubMed Abstract](#)
107. Gandhi T, Gandhi K, Monapara K: **Evaluation of Anticancer Activity of Boswellic Acid and Montelukast Sodium against Human Prostate Cancer Cell Line PC-3.** *Iran. J. Pharm. Sci.* 2016; **12**: 15–32.
108. Rostami S, Abroun S, Alimoghaddam K, *et al.*: **Evaluation of effect As2O3 on cell growth, cell cycle and apoptosis in human leukemia cell line HL-60.** *Intern. J. Hematol. Oncol. Stem Cell Res.* 2012; **6**: 30–35.
109. Di Paolo A, Orlandi P, Di Desidero T, *et al.*: **Simultaneous, But Not Consecutive, Combination With Folinic Salts Potentiates 5-Fluorouracil Antitumor Activity in vitro and In Vivo.** *Oncol. Res.* 2017; **25**: 1129–1140.
[PubMed Abstract](#) | [Publisher Full Text](#)
110. Ebrahimnezhad Z, Zarghami N, Keyhani M, *et al.*: **Inhibition of hTERT Gene Expression by Silibinin-Loaded PLGA-PEG-Fe3O4 in T47D Breast Cancer Cell Line.** *Bioimpacts.* 2013; **3**: 67–74.
[PubMed Abstract](#) | [Publisher Full Text](#)
111. Malaekheh-Nikouei B, Mousavi SH, Shahsavand S, *et al.*: **Assessment of Cytotoxic Properties of Safranal and Nanoliposomal Safranal in Various Cancer Cell Lines.** *Phytother. Res.* 2013; **27**: 1868–1873.
[PubMed Abstract](#) | [Publisher Full Text](#)
112. Akbari R, Javar HA: **Efficacy of Capecitabine and 5-Fluorouracil (5-FU) on the human breast cancer cell line (MCF7)-effect of concentration.** *American J. of Res. Communication.* 2013; **1**: 75–91.
113. Mamede AC, Abrantes AM, Pedrosa L, *et al.*: **Beyond the Limits of Oxygen: Effects of Hypoxia in a Hormone-Independent Prostate Cancer Cell Line.** *ISRN Oncology.* 2013; **2013**: 1–8.
[Publisher Full Text](#)
114. Gumulec J, Balvan J, Sztalmachova M, *et al.*: **Cisplatin-resistant prostate cancer model: Differences in antioxidant system, apoptosis and cell cycle.** *Int. J. Oncol.* 2014; **44**: 923–933.
[PubMed Abstract](#) | [Publisher Full Text](#)
115. Inan Genc AI, Gok S, Banerjee S, *et al.*: **Valdecobix Recovers the Lipid Composition, Order and Dynamics in Colon Cancer Cell Lines Independent of COX-2 Expression: An ATR-FTIR Spectroscopy Study.** *Appl. Spectrosc.* 2017; **71**: 105–117.
[PubMed Abstract](#) | [Publisher Full Text](#)
116. Wang N, Hana Y, Luoa L, *et al.*: **β -asarone induces cell apoptosis, inhibits cell proliferation and decreases migration and invasion of glioma cells.** *Biomed. Pharmacother.* 2018; **106**: 655–664.
[PubMed Abstract](#) | [Publisher Full Text](#)
117. Manyes L, Escrivá L, Ruiz MJ, *et al.*: **Beauvericin and enniatin B effects on a human lymphoblastoid Jurkat T-cell model.** *Food Chem. Toxicol.* 2018; **115**: 127–135.
[PubMed Abstract](#) | [Publisher Full Text](#)
118. Rok J, Delijewski M, Rzepka Z, *et al.*: **Ciprofloxacin-mediated induction of S-phase cell cycle arrest and apoptosis in COLO829 melanoma cells.** *Pharmacol. Rep.* 2018; **70**: 6–13.
[Publisher Full Text](#)
119. Beberok A, Rzepka Z, Respondek M, *et al.*: **GSH depletion, mitochondrial membrane breakdown, caspase-3/7 activation and DNA fragmentation in U87MG glioblastoma cells: New insight into the mechanism of cytotoxicity induced by fluoroquinolones.** *Eur. J. Pharmacol.* 2018; **835**: 94–107.
[PubMed Abstract](#) | [Publisher Full Text](#)
120. Beberok A, Wrześniok D, Rok J, *et al.*: **Ciprofloxacin triggers the apoptosis of human triple-negative breast cancer MDA-MB-231 cells via the p53/Bax/Bcl-2 signaling pathway.** *Int. J. Oncol.* 2018; **52**: 1727–1737.
[PubMed Abstract](#) | [Publisher Full Text](#)
121. Mollazade M, Nejati-Koshki K, Akbarzadeh A, *et al.*: **PAMAM Dendrimers Augment Inhibitory Effects of Curcumin on Cancer Cell Proliferation: Possible Inhibition of Telomerase.** *Asian Pac. J. Cancer Prev.* 2013; **14**: 6925–6928.
[PubMed Abstract](#) | [Publisher Full Text](#)
122. Civaliero M, Cosenza M, Pozzi S, *et al.*: **Activity of BKM120 and BEZ235 against Lymphoma Cells.** *Biomed. Res. Int.* 2015; Vol. 2015: 1–12. Article ID 870918.
[PubMed Abstract](#) | [Publisher Full Text](#)
123. Anantharaju PG, Reddy DB, Padukudru MA, *et al.*: **Induction of colon and cervical cancer cell death by cinnamic acid derivatives is mediated through the inhibition of Histone Deacetylases (HDAC).** *PLoS One.* 2017; **12**: e0186208.
[PubMed Abstract](#) | [Publisher Full Text](#)
124. Arsenoua ES, Papadimitriou EP, Kliafab E, *et al.*: **Effects of retinoic acid steroidal analogs on human leukemic HL60 cell proliferation in vitro and on angiogenesis in vivo.** *Anti-Cancer Drugs.* 2005; **16**: 151–158.
[PubMed Abstract](#) | [Publisher Full Text](#)
125. Zhu Z, Li E, Liu Y, *et al.*: **Inhibition of Jak-STAT3 pathway enhances bufalin-induced apoptosis in colon cancer SW620 cells 2012.** *World J. Surg. Oncol.* 2012; **10**: 228.
[PubMed Abstract](#) | [Publisher Full Text](#)
126. Wanga HW, Wang JQ, Zheng BQ, *et al.*: **Cytotoxicity induced by ochratoxin A, zearalenone, and a-zearalenol: Effects of individual and combined treatment.** *Food Chem. Toxicol.* 2014; **71**: 217–224.
[PubMed Abstract](#) | [Publisher Full Text](#)
127. Kamali AM, Nikseresht M, Delaviz H, *et al.*: **In Vitro Cytotoxic Activity of Matricaria Chamomilla Root Extract in Human Breast Cancer Cell Line MCF-7.** *Life Sci. J.* 2014; **10**: 403–406.
128. Paoluzzi L, Gonen M, Bhagat G, *et al.*: **The BH3-only mimetic ABT-737 synergizes the antineoplastic activity of proteasome inhibitors in lymphoid malignancies.** *Blood.* 2008; **112**: 2906–2916.
[PubMed Abstract](#) | [Publisher Full Text](#)
129. Tor YS, Yazan LS, Foo JB, *et al.*: **Induction of apoptosis through oxidative stress-related pathways in MCF-7, human breast cancer cells, by ethyl acetate extract of Dillenia suffruticosa.** *BMC Compl. and Alter. Medicine.* 2014; **14**: 55.
[PubMed Abstract](#) | [Publisher Full Text](#)
130. Mohammad RY, Somayye G, Gholamreza H, *et al.*: **Diosgenin Inhibits hTERT Gene Expression in the A549 Lung Cancer Cell Line.** *Asian Pac. J. Cancer Prev.* 2013; **14**: 6945–6948.
[PubMed Abstract](#) | [Publisher Full Text](#)
131. Liua M, Fua J, Li J, *et al.*: **Preparation of tri-block copolymer micelles loading novel organoselenium anticancer drug BBSKE and study of tissue distribution of copolymer micelles by imaging in vivo method.** *Int. J. Pharm.* 2010; **391**: 292–304.
[PubMed Abstract](#) | [Publisher Full Text](#)
132. Carter BZ, Mak DH, Shi Y, *et al.*: **MRx102, a triptolide derivative, has potent antileukemic activity in vitro and in murine model of AML.** *Leukemia.* 2012; **26**: 443–450.
[PubMed Abstract](#) | [Publisher Full Text](#)
133. Guo Q, Nan XX, Yang JR, *et al.*: **Triptolide inhibits the multidrug resistance in prostate cancer cells via the downregulation of MDR1 expression.** *Neoplasia.* 2013; **60**: 598–604.
[Publisher Full Text](#)
134. Chao LI, Xiao-xi L, Hai-yan FU, *et al.*: **Mechanism of apoptosis of triptolide induced human choroidal melanoma cell line OCM-1.** *Med. J. Chin. PLA.* 2015; **40**: 117–120.

135. Wu J, Li QQ, Zhou H, *et al.*: **Selective tumor cell killing by triptolide in p53 wild-type and p53 mutant ovarian carcinomas.** *Med. Oncol.* 2014; **31**: 14.
[PubMed Abstract](#) | [Publisher Full Text](#)
136. Bruno Chauffert B, Dimanche-Boitrel MT, Garrido C, *et al.*: **New insights into the kinetic resistance to anticancer agents.** *Cytotechnology.* 1998; **27**: 225–235.
[PubMed Abstract](#) | [Publisher Full Text](#)
137. Dimanche-Boitrel MT, Garrido C, Chauffert B: **Kinetic resistance to anticancer agents.** *Cytotechnology.* 1993; **12**: 347–356.
[Publisher Full Text](#)
138. Garrido C, Chauffert B, Pinard D, *et al.*: **Circumvention of confluence-dependent resistance in a human multi-drug-resistant colon-cancer cell line.** *Int. J. Cancer.* 1995; **61**: 873–879.
[PubMed Abstract](#) | [Publisher Full Text](#)
139. Fang Y, Sullivan R, Graham CH: **Confluence-dependent resistance to doxorubicin in human MDA-MB-231 breast carcinoma cells requires hypoxia-inducible factor-1 activity.** *Exp. Cell Res.* 2007; **313**: 867–877.
[PubMed Abstract](#) | [Publisher Full Text](#)
140. Jensen R, Glazer PM: **Cell-interdependent cisplatin killing by Ku/ DNA-dependent protein kinase signaling transduced through gap junctions.** *Proc. Natl. Acad. Sci. U. S. A.* 2004; **101**: 6134–6139.
[PubMed Abstract](#) | [Publisher Full Text](#)
141. Dimanche-Boitrel MT, Pelletier H, Genne P, *et al.*: **Confluence-dependent resistance in human colon cancer cells: role of reduced drug accumulation and low intrinsic chemosensitivity of resting cells.** *Int. J. Cancer.* 1992; **50**: 677–682.
[PubMed Abstract](#) | [Publisher Full Text](#)
142. Fan D, Beltran P, Wang Y, *et al.*: **Cell density-dependent regulation of mdr-1 gene expression in murine colon cancer cells.** *Int. J. Oncol.* 1996; **9**: 865–878.
[PubMed Abstract](#) | [Publisher Full Text](#)
143. Haber F: *On the history of gas warfar. Five Lectures from the years 1920-1923.* Berlin: Springer; 1924; 75–92.
144. Bliss CI: **The relation between exposure time, concentration and toxicity in experiments on insecticide.** *Ann. Entomol. Soc. Am.* 1940; **33**: 721–766.
[Publisher Full Text](#)
145. Connella DW, Yub QJ, Vermab V: **Influence of exposure time on toxicity-An overview.** *Toxicology.* 2016; **355-356**: 49–53.
[Publisher Full Text](#)
146. Rozman KK, Doull J: **Dose and time as variables of toxicity.** *Toxicology.* 2000; **144**: 169–178.
[Publisher Full Text](#)
147. Baas J, Jager T, Kooijman B: **Understanding toxicity as processes in time.** *Sci. Total Environ.* 2010; **408**: 3735–3739.
[Publisher Full Text](#)
148. Focke WW, Van der Westhuizen I, Musee N, *et al.*: **Kinetic interpretation of log-logistic dose-time response curves.** *Sci. Rep.* 2017; **7**: 2234.
[PubMed Abstract](#) | [Publisher Full Text](#)
149. Huang L, Garrett Injac S, Cui K, *et al.*: **Systems biology-based drug repositioning identifies digoxin as a potential therapy for groups 3 and 4 medulloblastoma.** *Sci. Transl. Med.* 2018; **10**.
[PubMed Abstract](#) | [Publisher Full Text](#)
150. Basri DF, Zainu Alamin ZA, Chan KM: **Assessment of cytotoxicity and genotoxicity of stem bark extracts from Canarium odontophyllum Miq. (dabai) against HCT 116 human colorectal cancer cell line.** *BMC Complement. Altern. Med.* 2016; **16**: 36.
[PubMed Abstract](#) | [Publisher Full Text](#)
151. Farshchi AA, Valikhani A, Nezhad RHB, *et al.*: **Anti-cancer Effect of Acetanilide and Para-nitroacetophenone in K562 Cells.** *Int. J. App. Sci. Physic. Edu.* 2017; **1**: 15–24.
152. Laird AK: **Dynamics of tumor growth.** *Br. J. Cancer.* 1964; **18**: 490–502.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
153. Wang ZJ, Liu SS, Qua R: **JS Fit: a method for the fitting and prediction of J and S-shaped concentration-response curves.** *RSC Adv.* 2018; **8**: 6572–6580.
[Publisher Full Text](#)
154. Pinto AC, Moreira JN, Simoes S: **Ciprofloxacin sensitizes hormone-refractory prostate cancer cell lines to doxorubicin and docetaxel treatment on a schedule-dependent manner.** *Cancer Chemother. Pharmacol.* 2009; **64**: 445–454.
[PubMed Abstract](#) | [Publisher Full Text](#)
155. Xuesong G, Shaoqiang L, Xiaoyu W: **The Effect of Paclitaxel on the Viability of U14 Cells.** *Int. J. Gynaecol. Obstet.* 2020; **8**: 51–54.
[Publisher Full Text](#)
156. Sargolzaeia J, Sadeghianb H, Golahmadic S, *et al.*: **Cytotoxic Effects of Hydroxy Coumarin Derivatives on Mouse Neuroblastoma N2a Cell Line.** *Iran. J. Pharm. Sci.* 2020; **16**: 95–106.
157. Abu Bakar SA, Ali AM, Ahmad NH: **Differential Antiproliferative Activity of Goniothalamin Against Selected Human Cancer Cell Lines.** *Mal J. Med Health Sci.* 2019; **15**(Suppl. 9): 66–73.
158. Jose A, Kannan E, Madhunapantula SRV: **Anti-proliferative potential of phytochemical fractions isolated from Simarouba glauca DC leaf.** *Heliyon.* 2020; **6**: e03836.
[Publisher Full Text](#)

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research