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

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. noticed inconsistency in viability estimates and IC-50s between CCLE and CGP results. The same observations were made about the NCI60 screen by Baggerly KA et al. and Reinhold WC et al. In addition, the examination of the previous studies and other large-scale studies, especially their experimental protocols validate Haibe-Kains 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:

II. Experimental in vitro cell culture conditions
1. Cell densities
A quick survey of the cell densities used in these studies shows three figures. First, a fixed cell seeding number going from 250 to 500 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, 300-3600, and 1,000-15,000. Third, cell density expressed as cellular confluence degree: 70% and 80%. 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 100 μl, 20 μl and 5 μl. 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, 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. For the large scale studies the drug exposure time is variable: 48h for JFCR screen and NCI60/DTP screen, 72h for CGP, 72-84h for CCLE, and 72h-168h until cell reach 80% confluent. 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/DTP screen is between 17.4h (colon HCT-116) and 79.4h (lung HOP-92) cancer cell lines, 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.

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. For the large scale studies the drug exposure time is variable: 48h for JFCR screen and NCI60/DTP screen, 72h for CGP, 72-84h for CCLE, and 72h-168h until cell reach 80% confluent. 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/DTP screen is between 17.4h (colon HCT-116) and 79.4h (lung HOP-92) cancer cell lines, 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.
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.\(^2\) In the cancer research field, it was Osawa et al\(^3\) who showed that anticancer drug cytotoxicity is \( (C \times T) \) dependent, \( C \) being the concentration and \( T \) the time. Then Adams et al\(^4\) 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”\(^5\) 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\(^5\) combined cytotoxicity with the Hill model and established a modified Hill model, \( IC^n \times T = k \), in which \( IC^n \) 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 \( IC_{50} = (k/T)^{1/n} \).\(^2\) 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\(^5\) 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 allostatic 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-monotonon/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,\(^3\) Baggerly KA et al,\(^3\) Reinhold WC et al,\(^7\) Levasseur LM et al,\(^5\) 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?\(^5\)\(^,\)\(^3\)

IV. The Gompertzian growth of cancer cells in vitro

1. The Gompertzian model

Since the Norton et al 1976 landmark paper 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.\(^3\) The growth type of cancer cells cultured in vitro as a monolayer or spheroids was not addressed by Haibe-Kains et al\(^5\) and also by all the commentaries related to Haibe-Kains et al concerns. It should be considered one of the hallmarks of cancer whether in vitro or in vivo clinical studies 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,\(^15\) 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 divisions and quiescence.\(^40\) 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, \(^55\) 72h, \(^56\) 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/m | 12.50μg/m | 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  |
| Case | Type | IC-50 24h  | IC-50 48h  | IC-50 72h  | Cell line | Drug               | Ref |
|------|------|-----------|-----------|-----------|-----------|--------------------|-----|
| 28   | 1    | 9.20μM    | 8.30μM    | 4.63μM    | HepG2     | Goniothalamin      | 62  |
| 29   | 1    | 79.10μM   | 63.75μM   | 35.01μM   | Chang     | Goniothalamin      | 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     | Sodium butyrate    | 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      | >3mM      | 0.28mM    | JURKAT    | Sodium butyrate    | 61  |
| 38   | 1    | >3mM      | >3mM      | 1.6mM     | 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      | Hypocretenolide 1  | 63  |
| 42   | 1    | 1.5μM     | 1.3μM     | 1.1μM     | Hep-2     | Hypocretenolide 1  | 63  |
| 43   | 1    | 2.8μM     | 2.6μM     | 1.2μM     | SK28      | Hypocretenolide 1  | 63  |
| 44   | 1    | 3.2μM     | 2.4μM     | 1.8μM     | SK37      | Hypocretenolide 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  |
| 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 | HBL-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  |
| 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    | 131nM    | 89nM    | 38nM    | JURKAT    | Doxorubicin | 93  |
| 84   | 1    | 83nM     | 23nM    | 10nM    | HL60      | Doxorubicin | 93  |
| 85   | 1    | 31.25μM  | 5.1μM   | 3μM     | AS49      | Cisplatin | 94  |
| 86   | 1    | 24.75μM  | 15μM    | 13.5μM  | AS49      | 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 | AS49 | TQ | 96 |
| 89   | 1    | 19.39μg/ml | 17.51μg/ml | 15.62μg/ml | AS49 | TQG | 96 |
| 90   | 1    | 15.63μg/ml | 14.97μg/ml | 12.40μg/ml | AS49 | TQ-Fe_{3}O_{4} | 96 |
| 91   | 1    | 27.31μg/ml | 18.68μg/ml | 11.88μg/ml | AS49 | TQG-Fe_{3}O_{4} | 96 |
| 92   | 1    | 16.10μg/ml | 12.71μg/ml | 7.04μg/ml | AS49 | TQ-Fe_{3}O_{4} (MF) | 96 |
| 93   | 1    | 23.45μg/ml | 10.78μg/ml | 9.57μg/ml | AS49 | 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 |
| 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 SLN | Methotrexate SLN | 103 |
| 111  | 1    | 88.89μM   | 13.20μM   | 9.553μM   | A2780/DDP | Cisplatin | 104 |
| 112  | 1    | 350.5μM   | 50.96μM   | 25.39μM   | A2780/DDP | Cisplatin | 104 |
| 113  | 1    | 105.1μM   | 51.73μM   | 16.13μM   | SKOV3/DDP | Cisplatin | 104 |
| 114  | 1    | 446.7μM   | 135.0μM   | 66.70μM   | SKOV3/DDP | Cisplatin | 104 |
| 115  | 1    | 10.66μM   | 2.51μM    | 2.08μM    | SKOV3/DDP | Cisplatin | 104 |
| 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    | 10.66μM   | 2.51μM    | 2.08μM    | MDA-MB-231 | Arsenic Disulfide | 106 |
| 120  | 1    | 49.15μg/ml| 47.18g/ml | 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    | 0.74μM    | 0.17μM    | 0.10μM    | COLO827   | Ciprofloxacin | 118 |
| 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 |
| Case | Type | IC-50 2h | IC-50 4h | IC-50 12h | Cell line | Drug     | Ref   |
|------|------|---------|---------|---------|-----------|----------|-------|
| 163  | 1    | 40nM/l  | 27nM/l  | 17nM/l  | 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 | HM5C      | 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    | SGC      | 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      | SGC      | 158   |
| 179  | 1    | 460.4μg/ml | 291.7μg/ml | 149.7μg/ml | SiHa      | SGE      | 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      | SGE      | 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 2h** | **IC-50 4h** | **IC-50 12h** | **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    |
| 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    | Temozolamide | 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    | Z2Rv1   | 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 |
| 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    | 3.93μM    | 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 | Cell line | Drug | Ref |
|------|------|-----------|-----------|-----------|------|-----|
| 223  | 1    | 4.0μM     | 2.7μM     | MCF-7     | Doxorubicin | 102 |
| 224  | 1    | 4.0μM     | 1.4μM     | MDA-MB-231 | Doxorubicin | 102 |
| 225  | 1    | 77.5μM    | 72μM      | HT-29     | Valdecoxib | 115 |
| 226  | 1    | 15.1μM    | 4.8μM     | HUT78     | BKM10 | 122 |
| 227  | 1    | 12.4μM    | 3.9μM     | GRANT A519 | BKM10 | 122 |
| 228  | 1    | 14.8μM    | 4.1μM     | WSU-NHL   | BKM10 | 122 |
| 229  | 1    | 41.6μM    | 21.1μM    | HUT78     | BEZ235 | 122 |
| 230  | 1    | 45.1μM    | 25.3μM    | GRANT A519 | BEZ235 | 122 |
| 231  | 1    | 39.2μM    | 18.5μM    | WSU-NHL   | BEZ235 | 122 |
| 232  | 1    | 92.4μM    | 16.1μM    | MVA4-11   | Triptolide | 132 |
| 233  | 1    | 76.1nM    | 6.9nM     | OCM-AML3  | Triptolide | 132 |

| Case | Type | IC-50 48h | IC-50 72h | Cell line | Drug | Ref |
|------|------|-----------|-----------|-----------|------|-----|
| 234  | 1    | 1147.91μg/ml | 921.1μg/ml | MCF-7     | Capedistabine | 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 | 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 |
|------|------|----------|-----------|-----------|-----------|------|-----|
| 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 | Cell line | Drug | Ref |
|------|------|-----------|-----------|-----------|------|-----|
| 249  | 2    | 71μM      | 74μM      | SW620     | Valdecoxib | 115 |
### Table 3. IC-50 Time evolution Type 3.

| Case | Type | IC-50 2h | 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     | Hypocretonolide 1 | 63   |
| 253  | 3    | 0.8µM    | 0.7µM     | 1µM       | MCF-7     | Hypocretonolide 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| 10.70µg/ml| 11.5µg/ml | 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 | IC-50 72h | 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      | Osmium 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    | 48µM     | 6.6µM     | 120µM     | 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  |

### Table 5. IC-50 Time Evolution Type 5.

| 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 | Palcitaxel | 65  |

| Case | Type | IC-50 12h | IC-50 24h | IC-50 48h | IC-50 72h | Cell line | Drug | Ref | Drug |
|------|------|-----------|-----------|-----------|-----------|-----------|------|-----|------|
| 290  | 4    | 18.3μM   | 74.9μM    | 10.6μM    | 1.0μM     | PC-3      | Cisplatin | 114  |      |      |
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         | HBL-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  |
| Helminalin | A431      | 1         | 63  |
| Helminalin | SK28      | 1         | 63  |
| Helminalin | Hep-2     | 1         | 63  |
| Helminalin | SK37      | 1         | 63  |
| Helminalin | SW872     | 1         | 63  |
| Helminalin | ZR75-1    | 2         | 63  |
| Helminalin | OVCAR3    | 2         | 63  |
| Helminalin | MCF-7     | 3         | 63  |
| 5-FU       | HT-29     | 1         | 109 |
| 5-FU       | CaCO-2    | 1         | 109 |
| Sinapinic  | HeLa      | 1         | 61  |
| Sinapinic  | HT-29     | 1         | 61  |
| Sinapinic  | HCT-116   | 1         | 61  |
| Sinapinic  | 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 |
| 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  |
| 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-Fe₃O₄           | 1         | 96  |
| A549      | TQG-Fe₃O₆          | 1         | 96  |
| A549      | TQ-Fe₃O₆ (MF)      | 1         | 96  |
| A549      | TQ-G-Fe₃O₆ (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     | S-FU               | 1         | 109 |
| HT-29     | Valdecoxib         | 1         | 115 |
| HT-29     | TTHL               | 1         | 67  |
| HT-29     | Capillin           | 3         | 60  |
| SW872     | Helenalin          | 1         | 63  |
| SW872     | Hypocretenol ide 1 | 3         | 63  |
| HepG2     | Mycotoxin AOH      | 1         | 69  |
| HepG2     | Gpnothalamin       | 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 |
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

Figure 1. Arbitrary values for IC-50 and Standard time points: 24h, 48 and 72h.
taken at one time point is misleading in its value and can explain the inconsistency noticed by Haibe-Kains et al., Baggerly et al9 and Reinhold et al. 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 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. 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 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 drugs (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: TET2113 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.
TET1 to 5 drugs as reported by 5 papers. 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 TET1,2,3,4 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 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 I-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. 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, the Gompertzian growth type of in vitro, the heterogeneous nature of in vitro monolayers and microspheres, and the hormesis phenomenon. 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. 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. Haibe-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-0384735. Mol. Cancer Ther. 2012; 11: 710–719. PubMed Abstract | Publisher Full Text
9. Heiser LM, Sadanandam A, Kuo W, 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 biosassays 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. Rupnik HT, Whelan ROH, Hill BT: Concentration and time-dependent inter-relationships for antitumour drug cytotoxocities against tumour cells in vitro. Int. J. Cancer. 1983; 32:
High-Throughput Screening of Tumour Spheroids and Stem Cell Neurospheres, PLoS One. 2014; 9(10):e103049. PubMed Abstract | PubMed Full Text

59. Iliade V, Zhelezeva I, Atanasova T, et al.: Cytoxic effect of the biotechnologically-derived justicidin B on human lymphoma cells. Biochim. Biophys. Acta. 2012; 1822:2177-2183. PubMed Abstract | PubMed Full Text

60. Whelan LC, Ryan MF: Effects of the polyclayene pillon in human tumour cell lines. Anticancer Res. 2004; 24: 2281-2286. PubMed Abstract

61. Senawong T, Misuna S, Khaopa S, et al.: Histone deacetaylase (HDAC) inhibitory and antiproliferative activities of phenolic-rich extracts derived from the rhume. BMC Complement. Altern. Med. 2013; 13: 232-242. PubMed Abstract | PubMed Full Text

62. Al-Qubaisi M, Rozita R, Yeap SK, et al.: Selective cytotoxicity of goniolithinam against hepatoblastoma HepG2 cells. Molecules. 2011; 16: 2944-2959. PubMed Abstract | PubMed Full Text

63. Zidorn C, Stuppner H, Tiefenthaler M, et al.: Synthesis and anticancer activity of 4-hydroxy naphto coumarine derivatives and naphto cuestomates. Der Pharma Chemica. 2013; 5: 201-207.

64. Georgiadi MS, Russell EK, Gazdar AF, et al.: Paclitaxel Cytotoxicity against human lung cancer cell lines increases with prolonged exposure duration. Clin. Cancer Res. 1997; 3: 449-454. PubMed Abstract

65. Zhang W, Sun J, Fang W, et al.: Nanomicles based on X-shaped four-armed pegylated distearylglycerol as long circulating system for doxorubicin delivery. Eur. J. Pharm. Sci. 2015; 66: 96-106. PubMed Abstract | PubMed Full Text

Macagnan VC, Moura DJ, Facundo VA, et al.: The natural triterpene 3β, 6β, 16dihydroxy-lup-20(29)-ene obtained from the flowers of the Combretum leprosum induces apoptosis in MCF-7 breast cancer cells. BMC Complement. Altern. Med. 2014; 14: 280-291. PubMed Abstract | PubMed Full Text

66. 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 | PubMed Full Text

67. Juan-Garcia A, Juan C, Konig S, et al.: Cytoxic 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 | PubMed Full Text

68. Abbasipourkabir R, Salehzadeh A, Abdullah R: In vitro investigations on the toxicity of tamoxifen and tamoxifen-loaded solid lipid nanoparticles on two breast cancer cell types. Anticancer Med. Biochem. 2013; 37: 36-40. PubMed Abstract | PubMed Full Text

69. Mosallane J, Jaffari MR, Hanafi-Bojd MY, et al.: Docetaxel-loaded solid lipid nanoparticles: preparation, characterization, in vitro, and in vivo evaluations. J. Pharm. Sci. 2013; 102: 1994-2004. PubMed Abstract | PubMed Full Text

70. 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 | PubMed Full Text

71. Van-Rijt SH, Romero-Canelon I, Lu 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 | PubMed Full Text

72. Enge JB, Honig A, Schirnhofer 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 | PubMed Full Text

73. 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 | PubMed Full Text

74. Beberok A, Wrzesniok D, Salachta M, et al.: Lomefloxacin Induces Oxidative Stress and Apoptosis in COLO205 Mammary Cells. Int. J. Mol. Sci. 2017; 18: 2194. PubMed Abstract | PubMed Full Text

75. Uziel O, Cohen O, Beer Y, et al.: The effect of Bortezomib and Rapamycin on Telomerase Activity in Mantle Cell Lymphoma. Transl. Oncol. 2014; 7: 741-751. PubMed Abstract | PubMed Full Text

76. Iliade V, Zhelezeva I, Atanasova T, et al.: Cytoxic effect of the biotechnologically-derived justicidin B on human lymphoma cells. Biochim. Biophys. Acta. 2012; 1822:2177-2183. PubMed Abstract | PubMed Full Text

77. Whelan LC, Ryan MF: Effects of the polyclayene pillon in human tumour cell lines. Anticancer Res. 2004; 24: 2281-2286. PubMed Abstract

78. Abbasalipourkabir R, Salehzadeh A, Abdullah R: Synthesis and anticancer activity of 4-hydroxy naphto coumarine derivatives and naphto cuestomates. Der Pharma Chemica. 2013; 5: 201-207.

79. Georgiadi MS, Russell EK, Gazdar AF, et al.: Paclitaxel Cytotoxicity against human lung cancer cell lines increases with prolonged exposure duration. Clin. Cancer Res. 1997; 3: 449-454. PubMed Abstract

80. Zhang W, Sun J, Fang W, et al.: Nanomicles based on X-shaped four-armed pegylated distearylglycerol as long circulating system for doxorubicin delivery. Eur. J. Pharm. Sci. 2015; 66: 96-106. PubMed Abstract | PubMed Full Text

81. Macagnan VC, Moura DJ, Facundo VA, et al.: The natural triterpene 3β, 6β, 16dihydroxy-lup-20(29)-ene obtained from the flowers of the Combretum leprosum induces apoptosis in MCF-7 breast cancer cells. BMC Complement. Altern. Med. 2014; 14: 280-291. PubMed Abstract | PubMed Full Text

82. 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 | PubMed Full Text

83. Juan-Garcia A, Juan C, Konig S, et al.: Cytoxic 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 | PubMed Full Text

84. Abbasipourkabir R, Salehzadeh A, Abdullah R: In vitro investigations on the toxicity of tamoxifen and tamoxifen-loaded solid lipid nanoparticles on two breast cancer cell types. Anticancer Med. Biochem. 2013; 37: 36-40. PubMed Abstract | PubMed Full Text

85. Mosallane J, Jaffari MR, Hanafi-Bojd MY, et al.: Docetaxel-loaded solid lipid nanoparticles: preparation, characterization, in vitro, and in vivo evaluations. J. Pharm. Sci. 2013; 102: 1994-2004. PubMed Abstract | PubMed Full Text

86. 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 | PubMed Full Text

87. Van-Rijt SH, Romero-Canelon I, Lu 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 | PubMed Full Text

88. Enge JB, Honig A, Schirnhofer 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 | PubMed Full Text

89. 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 | PubMed Full Text

90. Beberok A, Wrzesniok D, Salachta M, et al.: Lomefloxacin Induces Oxidative Stress and Apoptosis in COLO205 Mammary Cells. Int. J. Mol. Sci. 2017; 18: 2194. PubMed Abstract | PubMed Full Text

91. Uziel O, Cohen O, Beer Y, et al.: The effect of Bortezomib and Rapamycin on Telomerase Activity in Mantle Cell Lymphoma. Transl. Oncol. 2014; 7: 741-751. PubMed Abstract | PubMed Full Text
97. Li R, Dong J, Yu 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. Cheng X, Feng H, Wua H, et al.: Targeting autophagy enhances apanitib-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: 5646-5653. PubMed Abstract | Publisher Full Text

100. Wang S, Willenberg L, Krohn M, et al.: Growth-Inhibiting Activity of Resveratrol Imatinib Analogs on Tumor Cells. In Vivo. Pone.Org. 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 KWY, Jiang L, Cheng M, et al.: OATP1B3 is involved in the uptake of entrectinib in neuroblastoma cells. Cancer Lett. 2018; 431: 105–114. 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. Pharmac. 2017; 67: 925-929. PubMed Abstract

104. Sun LM, Liu YC, Liu W, et al.: Nivolumab effectively inhibit platinum-resistant ovarian cancer cells via induction of cell apoptosis and inhibition of ADAM17 expression. J. Oncol. 2018; 8: 366-386. PubMed Abstract

105. Borkhaoi AR, Evangelista AF, Oliveira RJ, et al.: MicroRNA profiling in human breast cancer cells 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, Monopara 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. PubMed Abstract | Publisher Full Text

108. Rostami S, Abruun S, Almoghadam K, et al.: Evaluation of effect Ac203 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. PubMed Abstract | Publisher Full Text

109. Di Paola A, Orlando P, Di Desidero T, et al.: Simultaneous, But Not Consecutive, Combination With Folic Salts Potentiates S-Fluorouracil Antitumor Activity in vitro and In Vivo. Oncol. Res. 2017; 25: 1129–1140. PubMed Abstract | Publisher Full Text

110. Ebrahimnejad Z, Zarghami N, Keyhani M, et al.: Inhibition of hTERT Gene Expression by Silibinin-Loaded PLGA-PEG-Fe3O4 in Neoplastic drug cediranib. Pharmacol. Sci. 2017; 7: 6945–6950. PubMed Abstract | Publisher Full Text

111. Beberok A, Rzepka Z, Respondek M, et al.: Oxalic acid decreases the size of ovarian cysts in rats: An in vivo study. J. Int. Med. Res. 2013; 41: 1868–1873. PubMed Abstract | Publisher Full Text

112. Arsenoussa ES, Papadimitriou EP, Klaafas 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

113. 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. 10: 228. PubMed Abstract | Publisher Full Text

114. Wang HW, Wang Q, Zhao BQ, et al.: Cytoxicity induced by ochratoxin A, zearealenon, and a-zearalenol: Effects of individual and combined treatment. Food Chem. Toxicol. 2014; 75: 217–224. PubMed Abstract | Publisher Full Text

115. Kamali AM, Nikesresht M, Delaviz H, et al.: In Vitro Cytoxic Activity of Matriaria Chamomilla Root Extract in Human Breast Cancer Cell Line MCF-7. Life Sci. 2014; 10: 463–466. PubMed Abstract | Publisher Full Text

116. Luu M, Fu 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

117. Hata YS, Yaman LS, Foo JB, et al.: Induction of apoptosis through oxidative stress-related pathways in MCF-7, human breast cancer cells, by etchyl acetate extract of Dillenia suffrutcosa. BMC Comp. and Alter. Medicine. 2014; 14: 55. PubMed Abstract | Publisher Full Text

118. Mohammad RY, Somayye G, Bhatagat G, et al.: The BH3-only mimeticABT-737 synergizes the antineoplastic activity of proteasome inhibitors in lymphoid malignancies. Blood. 2008, 112: 2906–2916. PubMed Abstract | Publisher Full Text

119. Tan YS, Yaman LS, Foo JB, 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

120. 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. PubMed Abstract | Publisher Full Text

121. Cho AL, Xiao L, Hai-yun Fu, et al.: Mechanism of apoptosis of triptolide induced human choroidal melanoma cell line OCM-1. Med. J. Chin. PLA. 2015; 40: 117–120. PubMed Abstract | Publisher Full Text
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. Bruna-Chauvett 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, Chauvett B: Kinetic resistance to anticancer agents. Cytotechnology. 1993; 12: 347–356. Publisher Full Text

138. Garrido C, Chauvett B, Pinard D, et al.: Circumvention of confluence-dependent resistance in a human multi-drug-resistant colon-cancer cell line. Int. J. Oncol. 1995: 6: 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, Pelleiter 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, Belfran 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. Publisher Full Text

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. Connelly DW, Yub Qi, Vermab V: Influence of exposure time on toxicity-An overview. Toxicology. 2016; 355-356: 49–53. Publisher Full Text

146. Rozman KK, Doul 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: 3733–3739. 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. Farshchii AA, Valikhanli 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. PubMed Abstract | Publisher Full Text

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: J5 Fit: a method for the fitting and prediction of J and S-shaped concentration-response curves. RSC Adv. 2018; 8: 6572–6580. PubMed Abstract | 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. PubMed Full Text

156. Sargolzasht J, Sadeghian 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. PubMed Abstract | Publisher Full Text

157. Abu Bakar SA, Ali AM, Ahmad NH: Differential Antiproliferative Activity of Goniothalamin Against Selected Human Cancer Cell Lines. Mol J. Med Health Sci. 2019; 15(Suppl): 91–66.73. PubMed Abstract | Publisher Full Text

158. Jose A, Kannan E, Madhunapantula SRV: Anti-proliferative potential of phytochemical fractions isolated from Simarouba glauca DC leaf. Helyon. 2020; 6: e03836. PubMed 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