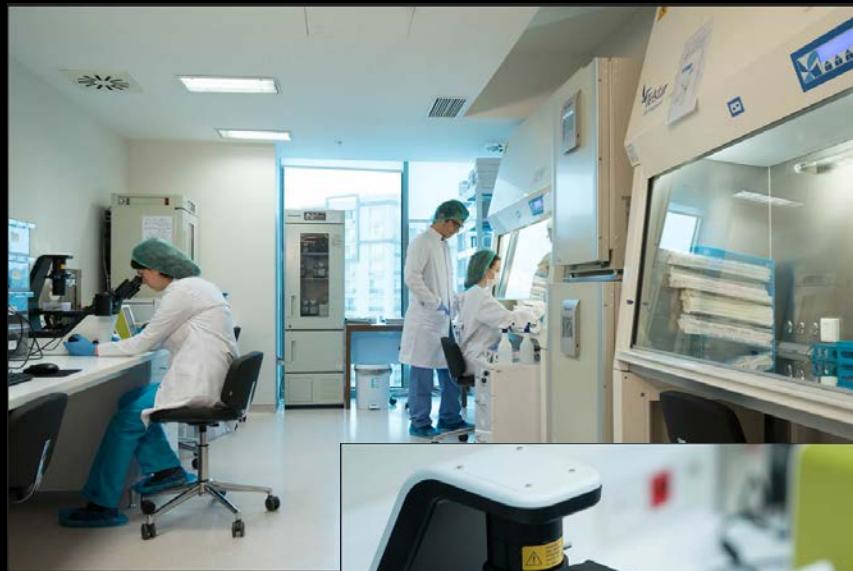


Kanser Araştırma Özelinde Akademisyenin Sağlık Teknolojilerindeki Rolü

- Prof. Dr. Engin Ulukaya (MD, PhD)
- İstinye Üniversitesi Tıp Fakültesi
- Moleküler Kanser Araştırma Merkez (İSÜMKAM) Md.
- Moleküler Kanser Araştırma Derneği Başkanı
- EACR Council Member
- EORTC PathoBiology Full Member
- COST ACTIONS MC Member





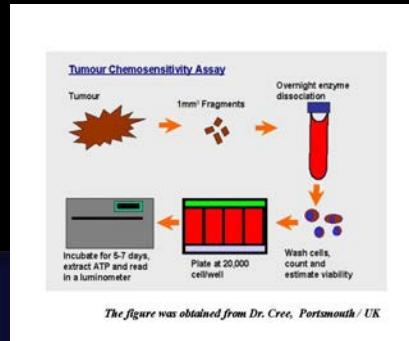
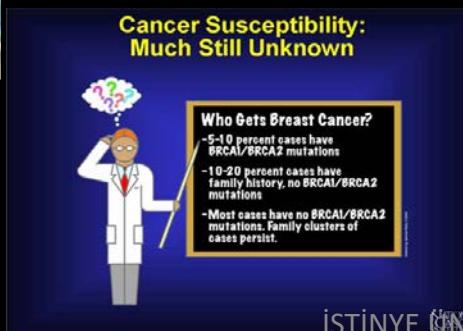
İSTİNYE ÜNİVERSİTESİ

A. PERSONALIZED ONCOLOGY STUDIES

Liquid biopsy: Deciding on the targeted therapies on the basis of mutations/deletions etc in cancer patients

Tumor Chemosensitivity Assay (3D Cultures): The selection of anticancer drugs that are specific for cancer patients

M30/M65 assay: Prediction of efficacy of chemotherapy 48 h after its appl.



Each patient's
cancer is as
unique as
the human
fingerprint

B. ANTI-CANCER DRUG DEVELOPMENT STUDIES

In vitro AND In vivo preclinical studies (Cell culture, animal studies)

Many publications (>100) in respected peer-reviewed journals

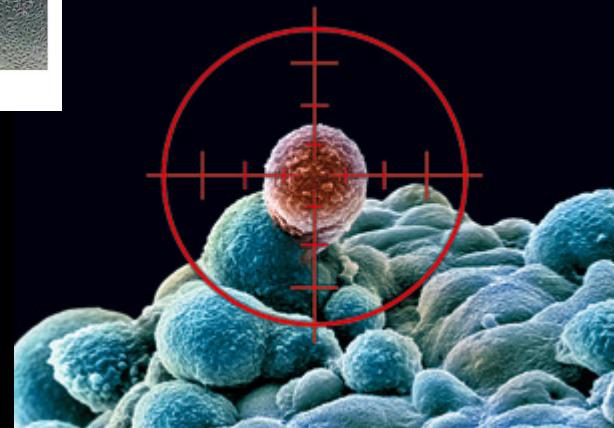
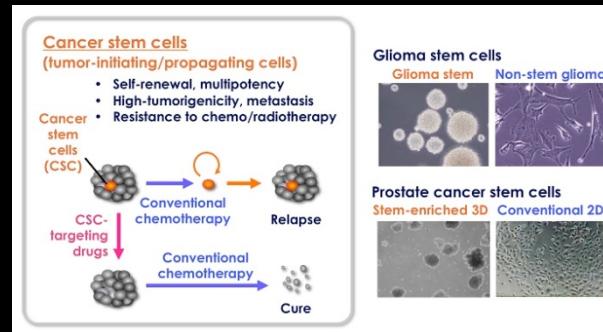
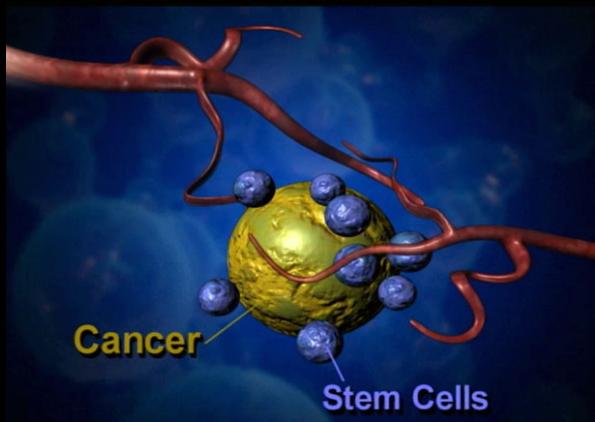
Many ongoing collaborations with national and international groups dealing with anticancer drug development



C. CANCER STEM CELL STUDIES

Cancer stem cell is responsible for the recurrence of the disease.

Survival pathways of these cells are new targets for drug development.



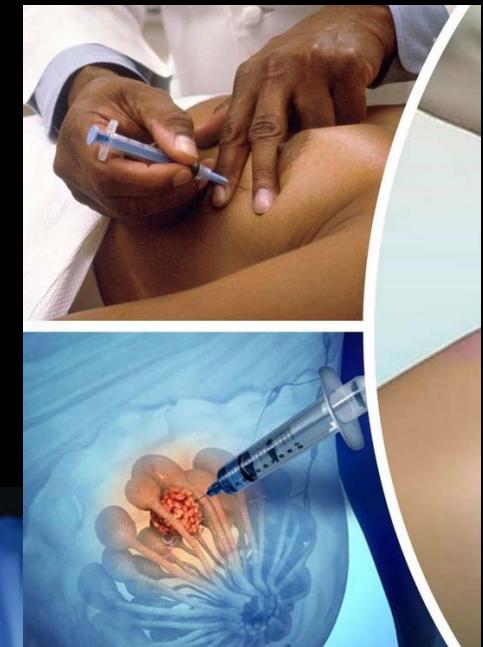
D. DEVICE DEVELOPMENT FOR IN-OPERATION CANCER CELL VISUALIZATION

For breast cancer

Nano compounds (quantum dots) with an antibody

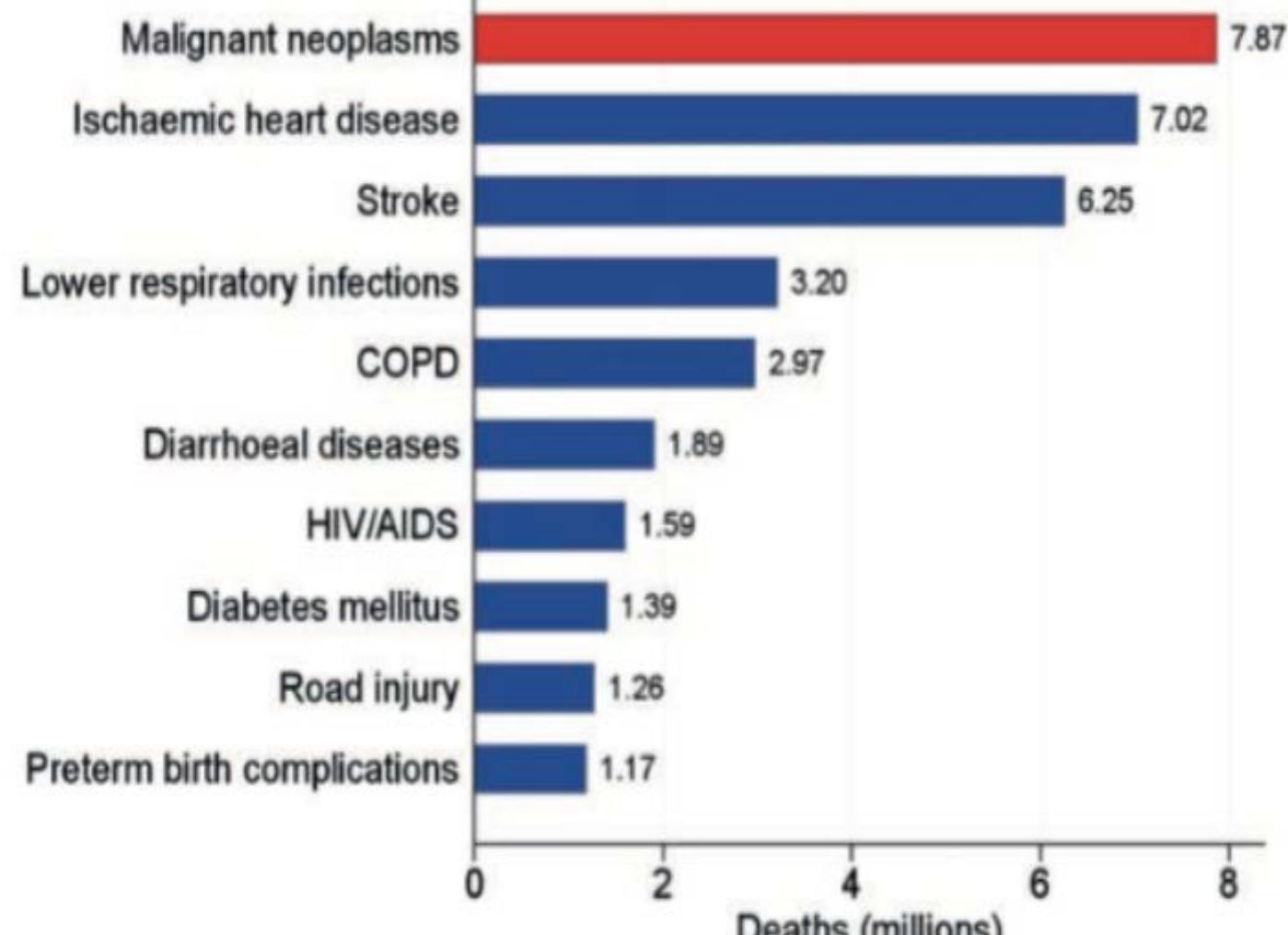
Infrared technology

Visualisation of tumor cells/margins to help surgeons.



NATIONAL AND INTERNATIONAL COLLABORATORS

- 1. Koc University, Istanbul**
- 2. Uludag University, Bursa**
- 3. Ankara Üniversitesi**
- 4. İstanbul University, İstanbul**
- 5. Anadolu University, Eskişehir**
- 6. Dicle University, Diyarbakır**
- 7. Dumlupınar University, Kütahya**
- 8. National Cancer Research Center, Milano/ITALY**
- 9. MD Anderson Cancer Research Center, Texas, USA**
- 10. York Cancer Research Unit, York, UK**
- 11. Sapienza University, Milano, ITALY**
- 12. University of Zagreb, Zagrep, CROATIA**
- 13. Utrecht University, Amsterdam, THE NEDERLANDS**
- 14. Thesally University, Larissa, GREECE**



World Cancer Report, 2014



2050 yılında
bakteriler
nedeniyle ölüm
kanserden
ölümlerin
önüne geçecek!



Table. Top-Selling Cancer Drugs

Drug	Sales 1st to 3rd Quartile 2017 (\$ billion)	Sales 1st to 3rd Quartile 2016 (\$ billion)	Change (%)
Lenalidomide	5.999	5.166	16.1
Rituximab	5.760	5.620	2.5
Trastuzumab	5.363	5.252	2.1
Bevacizumab	5.121	5.241	-2.3
Filgrastim	3.864	4.151	-6.9
Nivolumab	3.587	2.464	45.6
Ibrutinib	3.236	2.226	45.4
Pembrolizumab	2.512	0.919	173.3
Palbociclib	2.410	1.492	61.5
Bortezomib	1.780	1.876	-5.1



- Target identification
- Receptor binding
- Drug targeting
- Proof of mechanism
- Efficacy
- Safety
- PK/PD
- ADME
- Drug transporters
- Dose ranging
- Drug delivery
- Phase 0 microdosing
- Phase I safety, PK
- Phase II - III efficacy
- Human PK
- Dose selection
- Bioavailability



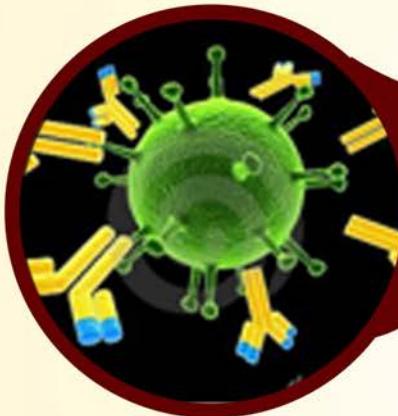
The Future of Cancer Treatment



Cancer Immunotherapy

The Next Generation of Cancer Treatment

Monoclonal Antibodies



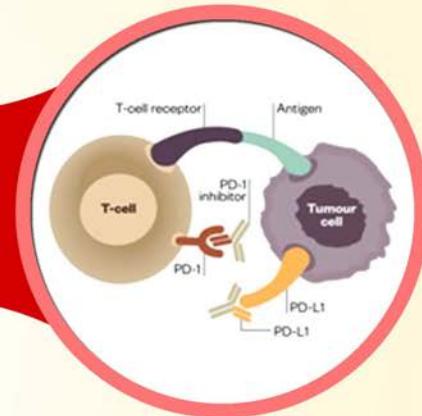
Antibodies can be produced that target and destroy cancer cells

Cancer Vaccines



Vaccines can be given to:
Prevent cancer, i.e. HPV, HBV
Treat cancer, i.e. Provenge for prostate cancer

Nonspecific Immunotherapies



Cytokines - Stimulate the immune system

Checkpoint inhibitors – Release the brakes on the immune system, i.e. PD-1/PD-L1

Immunomodulating drugs – Boost the immune system, i.e. Thalidomide



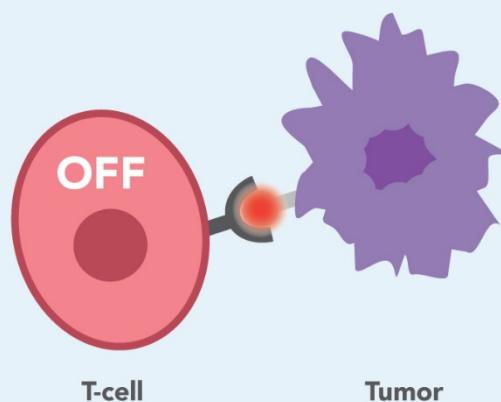
All Treatment Begins With a Diagnosis Made by Pathologists



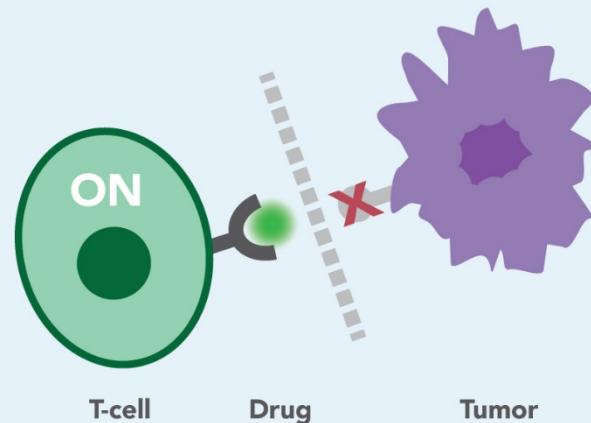
For more information visit
www.pathreport.org

How Does Immunotherapy Work?

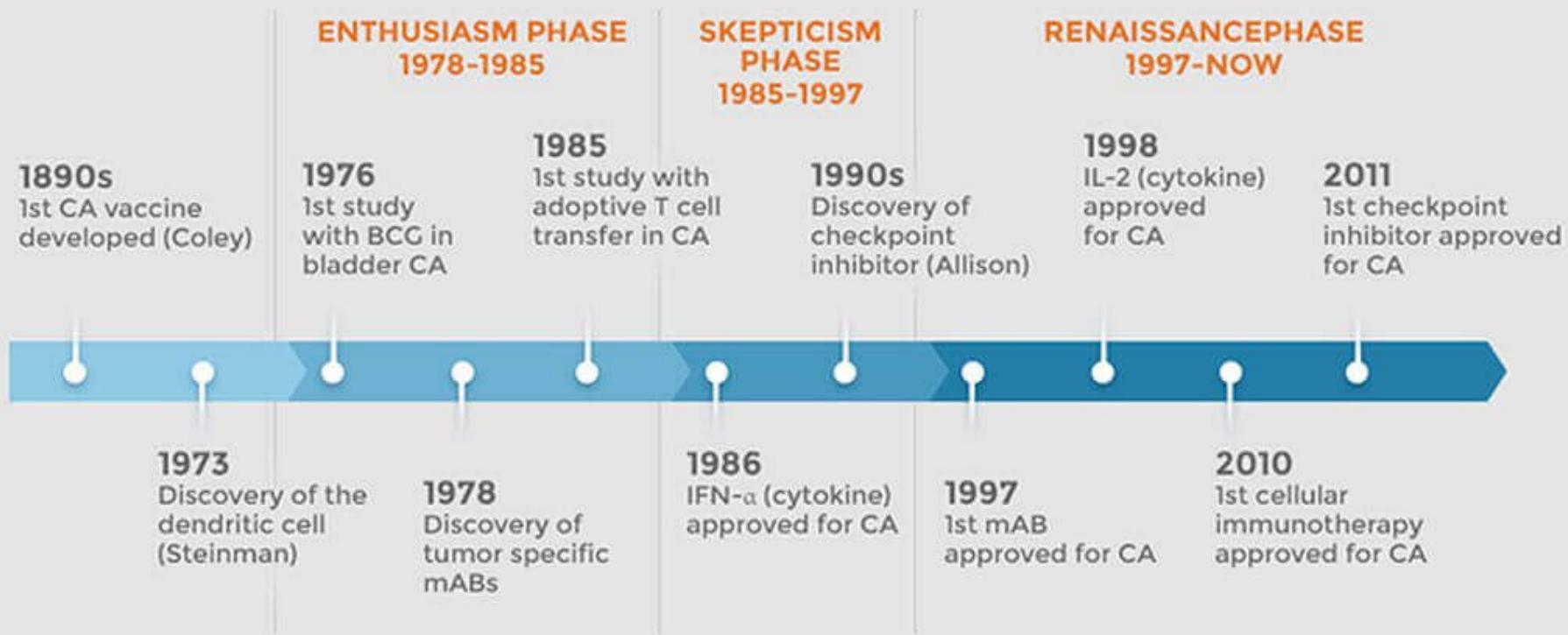
Tumor cells bind to T-cells
to deactivate them



Immunotherapy drugs can block
tumor cells from deactivating T-cells



COLUMBIA UNIVERSITY
MEDICAL CENTER



The Value and Cost of Immunotherapy Cancer Treatments

The problem of cost

We're talking about treatments that cost over \$100,000 per year
Combine drugs and it's over \$200,000 per year.

Who will benefit and who won't,
it will make a big difference in cost for overall healthcare costs.



Harvoni

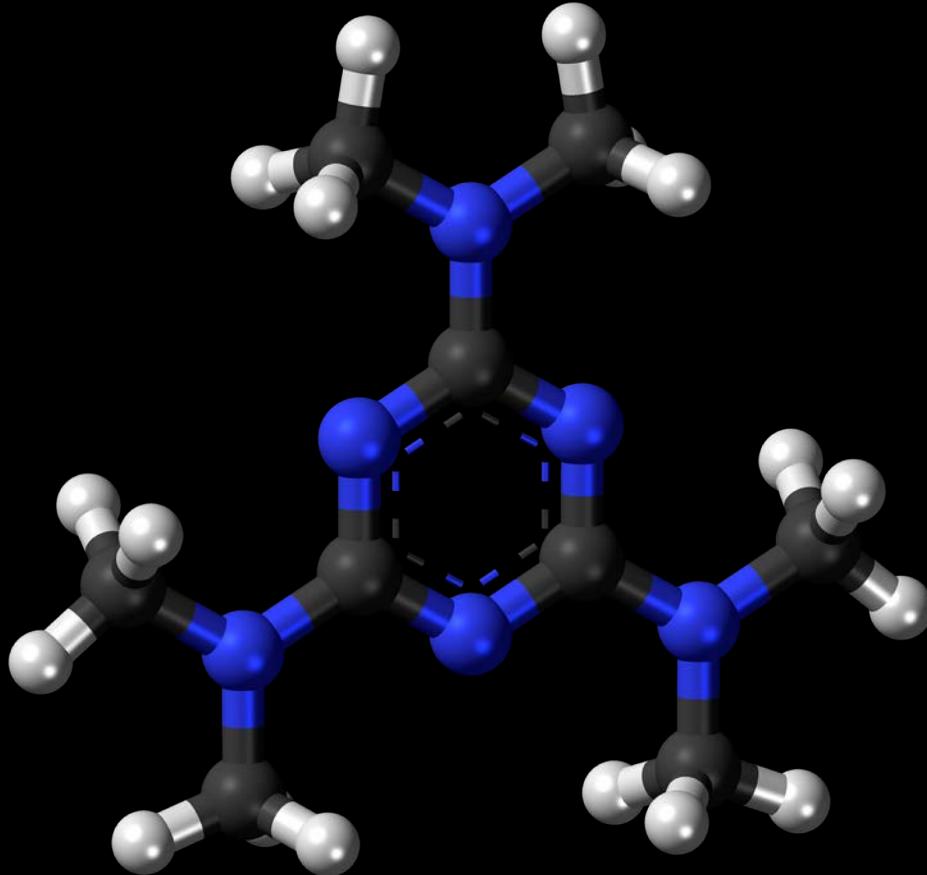
Harvoni's total treatment **cost** is \$94,500 for a 12-week regimen.



\$1125 per pill



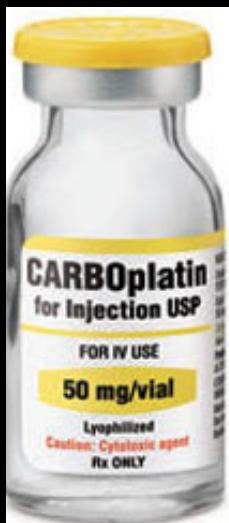
Bu bileşikleri kendimiz yapacağız!.
Yok başka çaremiz



Cisplatin



Carboplatin



Oxaliplatin



A Novel Promising Anti-Cancer Compound Against Cancer: A Palladium (II)-Saccharinate Complex of Terpyridine

Engin ULUKAYA (MD, PhD)

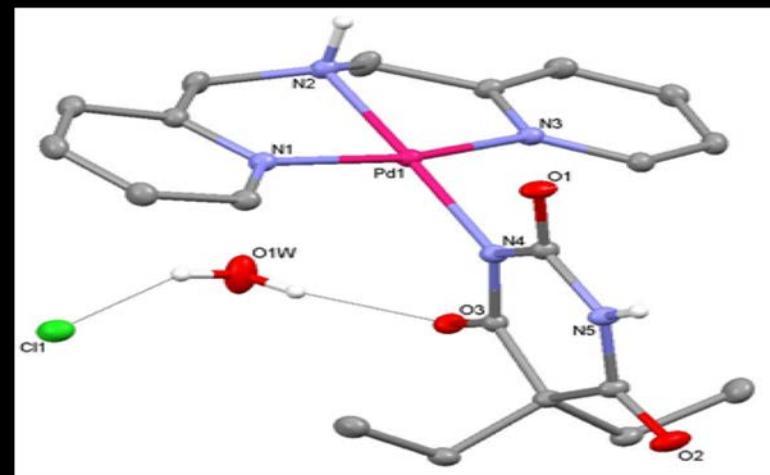
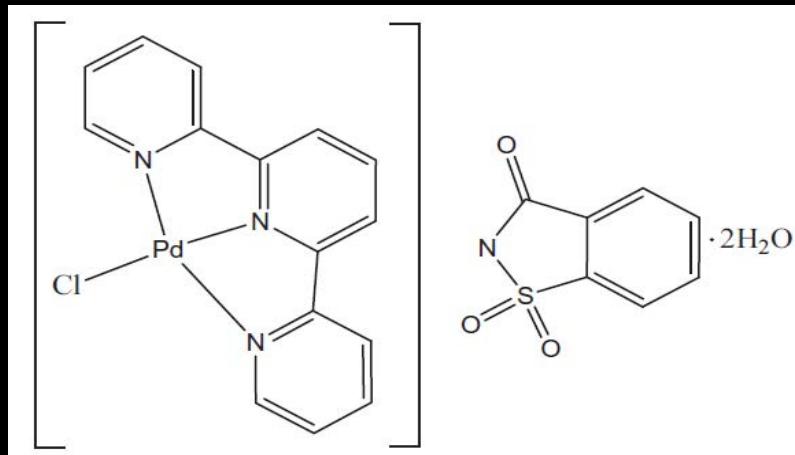
Medical School of Uludağ University

Dept. Of Clinical Biochemistry, BURSA, TURKEY



İSTİNDE ÜNİVERSİTESİ

Pd (II) complexes





Contents lists available at ScienceDirect

Inorganica Chimica Acta

journal homepage: www.elsevier.com/locate/ica



Platinum(II) and palladium(II) saccharinato complexes with 2,2':6,2"-terpyridine: Synthesis, characterization, crystal structures, photoluminescence and thermal studies

Emel Guney^a, Veysel T. Yilmaz^{a,*}, Abdurrahman Sengul^b, Orhan Buyukgungor^c

^aDepartment of Chemistry, Faculty of Arts and Sciences, Uludag University, 16059 Bursa, Turkey

^bDepartment of Chemistry, Faculty of Arts and Sciences, Karabulut University, 67100 Zonguldak, Turkey

^cDepartment of Physics, Faculty of Arts and Sciences, Ondokuz Mayıs University, 55139 Samsun, Turkey

OPEN ACCESS Freely available online



Differential Cytotoxic Activity of a Novel Palladium-Based Compound on Prostate Cell Lines, Primary Prostate Epithelial Cells and Prostate Stem Cells

Engin Ulukaya^{1,2*}, Fiona M. Frame^{2,3}, Buse Cevatemre³, Davide Pellaconi², Hannah Walker², Vincent M. Mann⁴, Matthew S. Simms⁵, Michael J. Stower⁶, Veysel T. Yilmaz⁷, Norman J. Maitland²

¹Department of Medical Biochemistry, Medical School, Uludag University, Bursa, Turkey, ²Department of Biology, YCR Cancer Research Unit, University of York, Heslington, York, North Yorkshire, United Kingdom, ³Department of Biology, Faculty of Arts and Sciences, Uludag University, Bursa, Turkey, ⁴Hull York Medical School, University of Hull, Hull, United Kingdom, ⁵Department of Urology, Castle Hill Hospital (Hull and East Yorkshire Hospitals NHS Trust), Cottingham, United Kingdom, ⁶York District Hospital, York, United Kingdom, ⁷Department of Chemistry, Faculty of Arts and Sciences, Uludag University, Bursa, Turkey

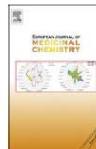
European Journal of Medicinal Chemistry 46 (2011) 4957–4963



Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: <http://www.elsevier.com/locate/ejmec>



Original article

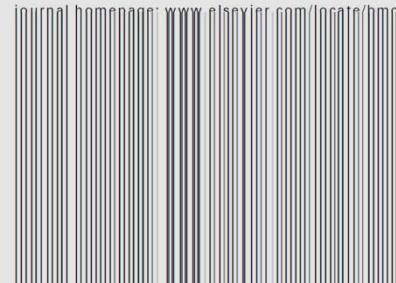
Anti-cancer activity of a novel palladium(II) complex on human breast cancer cells *in vitro* and *in vivo*

Engin Ulukaya^{a,*}, Ferda Ari^b, Konstantinos Dimas^c, Elif Ilkay Ikitimur^d, Emel Guney^e, Veysel T. Yilmaz^e



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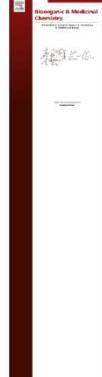
Bioorganic & Medicinal Chemistry



Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc



Addition of niclosamide to palladium(II) saccharinate complex of terpyridine results in enhanced cytotoxic activity inducing apoptosis on cancer stem cells of breast cancer

Didem Karakas^{a,†}, Buse Cevatemre^{a,†}, Nazlihan Aztopal^a, Ferda Ari^a, Veysel Turan Yilmaz^b, Engin Ulukaya^{c,*}



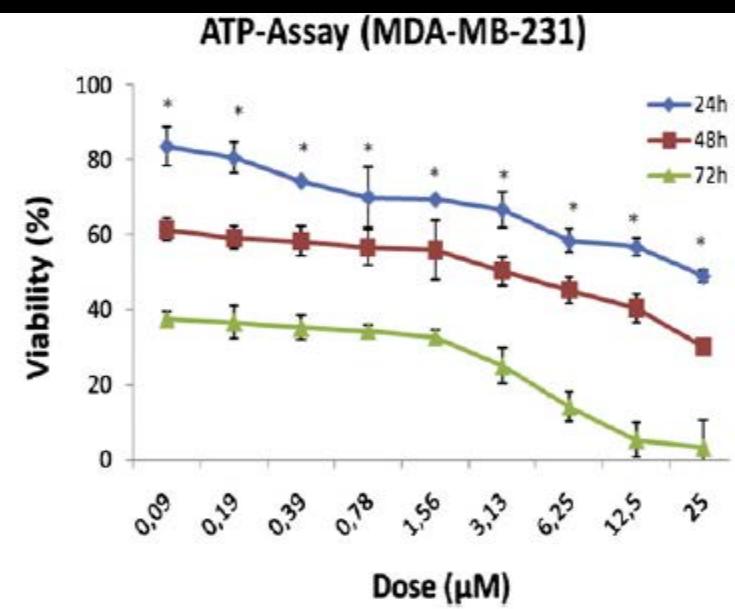
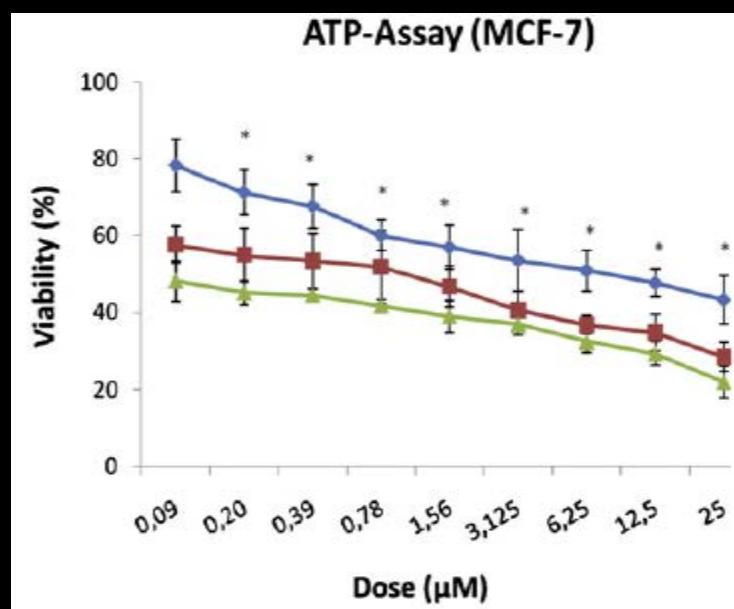
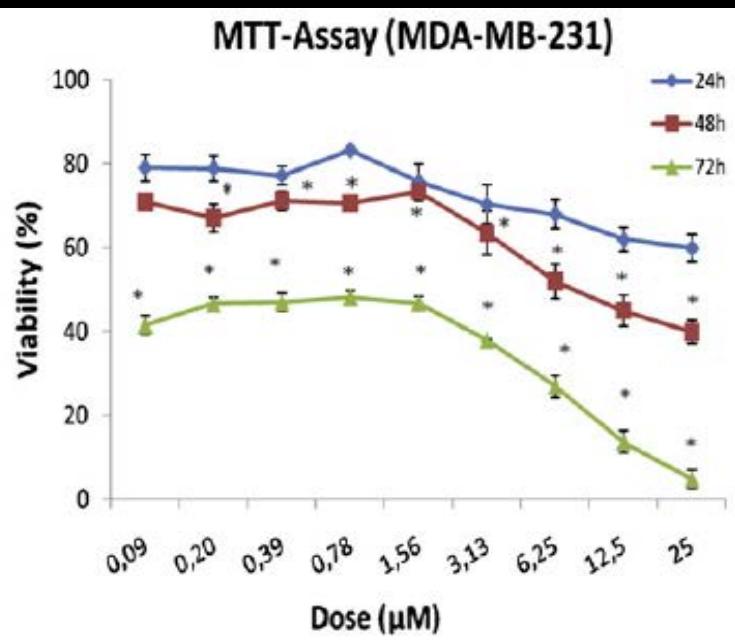
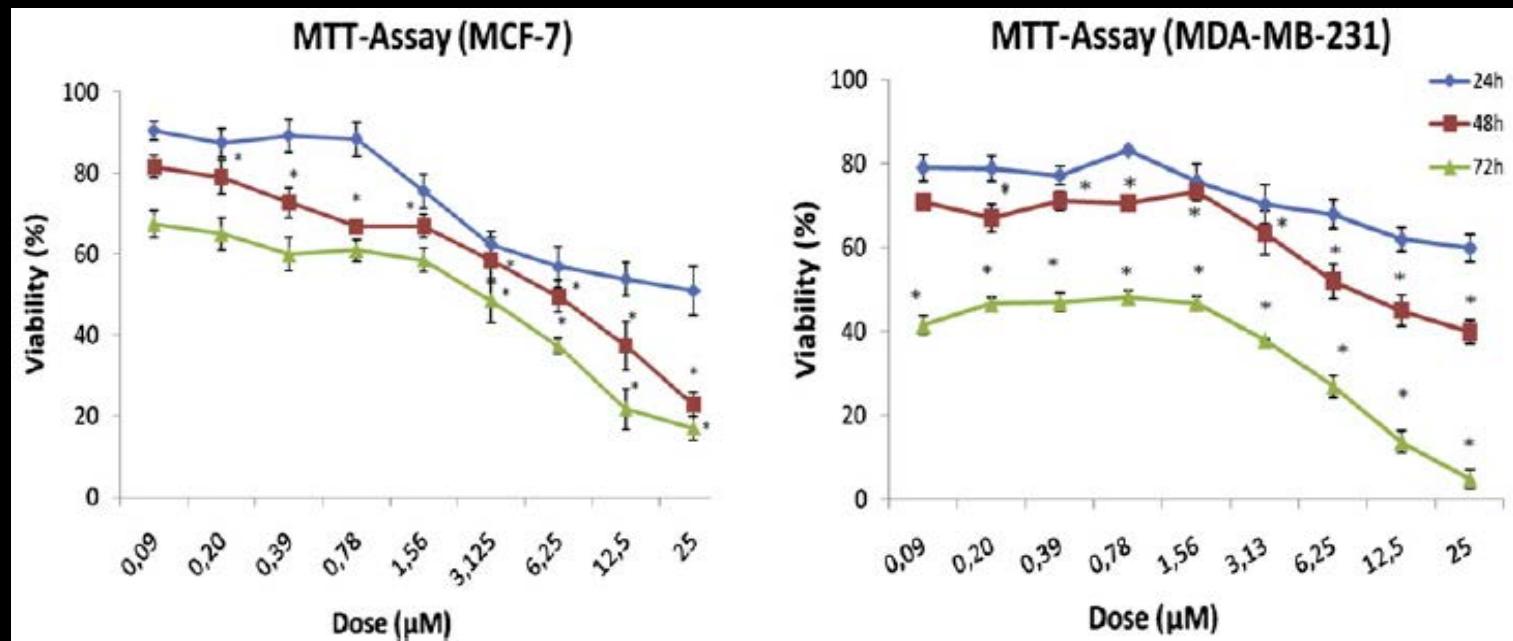
Journal of
proteome
research

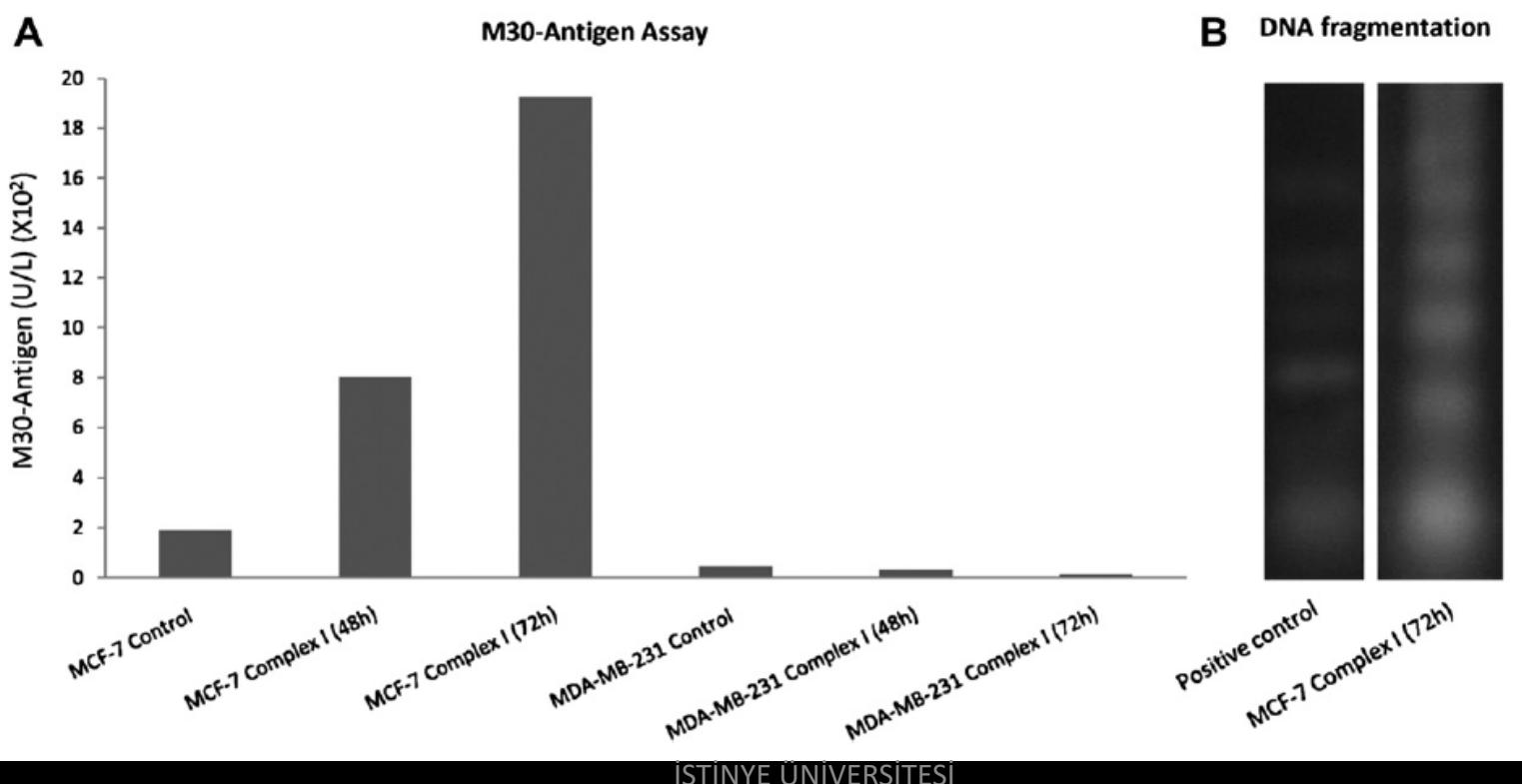
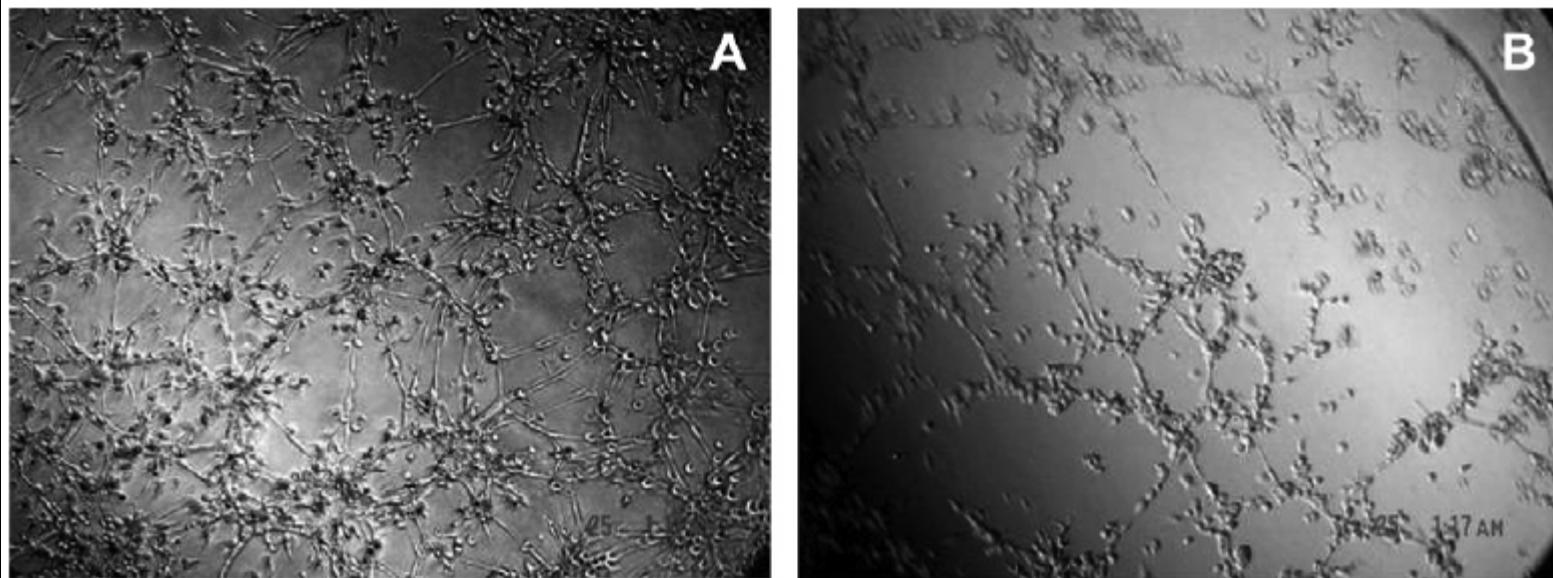
Article

pubs.acs.org/jpr

Biochemical and Proteomic Analysis of a Potential Anticancer Agent: Palladium(II) Saccharinate Complex of Terpyridine Acting through Double Strand Break Formation

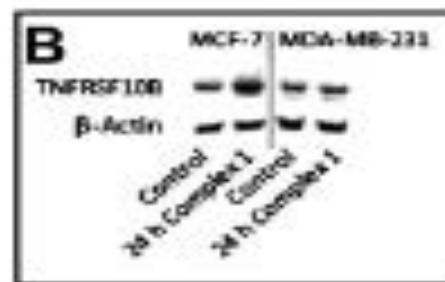
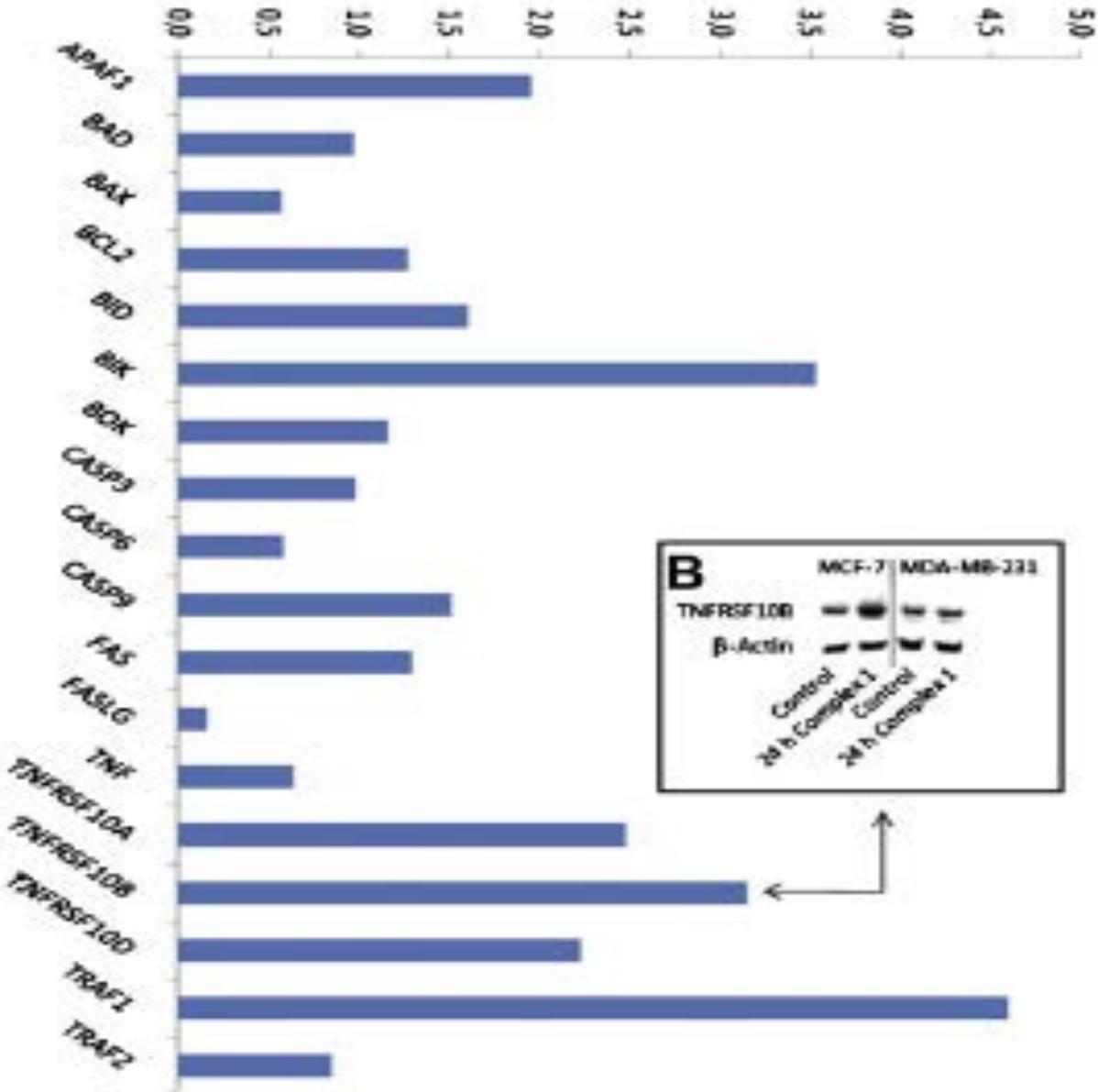
Zelal Adiguzel,^{†,‡} Ahmet Tarik Baykal,^{†,‡} Omer Kacar,[†] Veysel T. Yilmaz,[§] Engin Ulukaya,^{||} and Ceyda Acilan^{*†,‡}

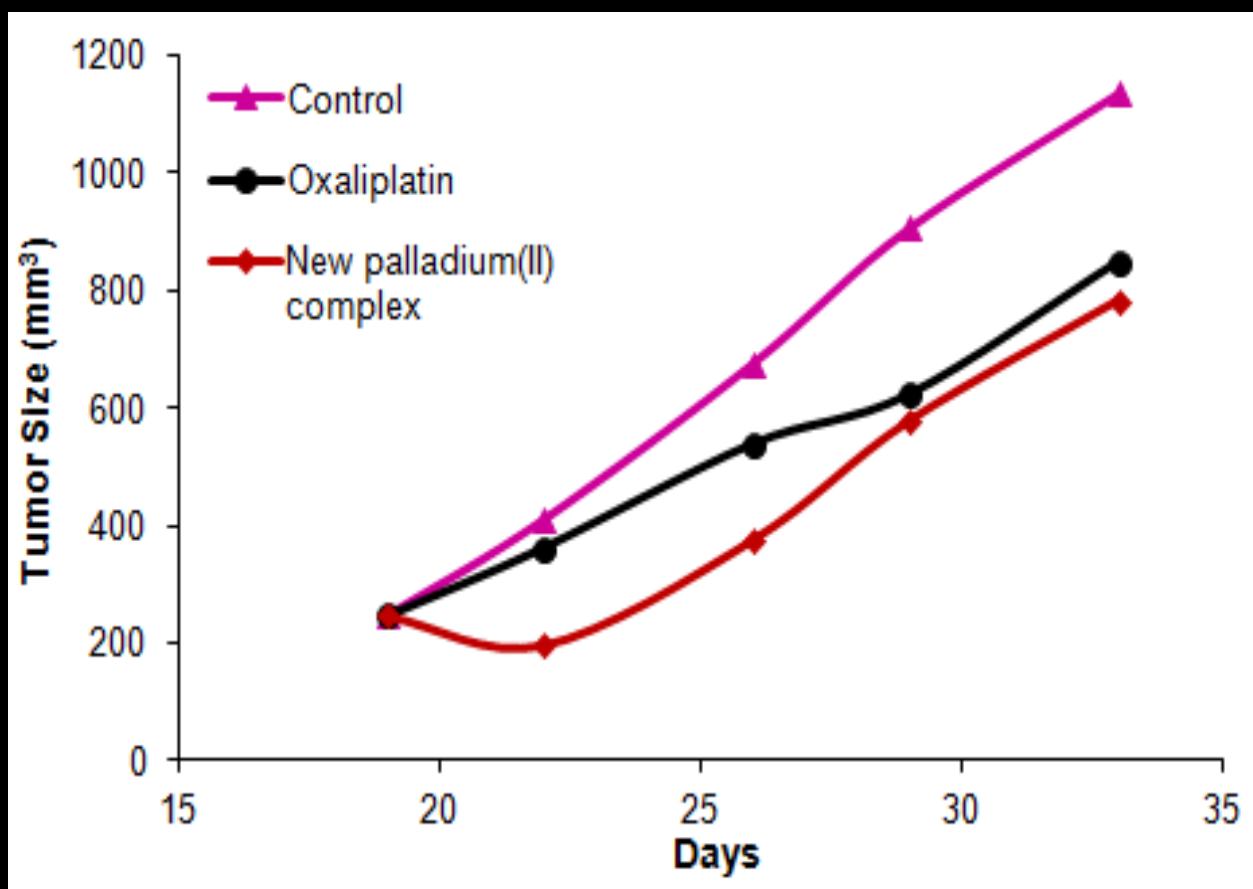




A

Fold change relative to control







Tumor tissue size after the application of the agents.

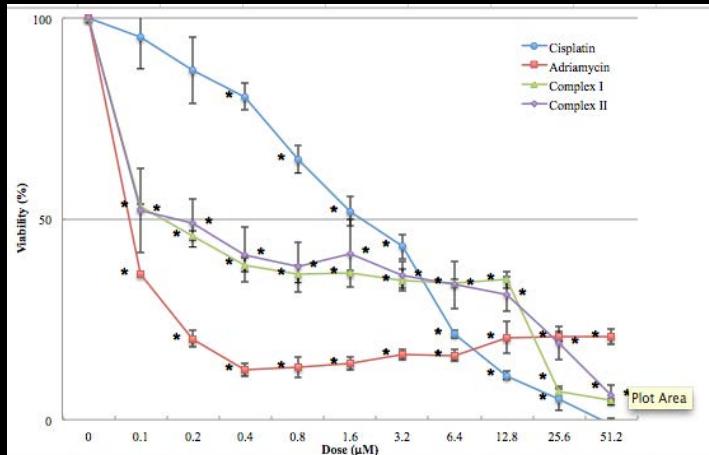
	Tumor size (mm ³)	%T/C ^a	DRD ^a	Weight (g) ^c
Control	14 690.9 ± 9054.6			27.52
Complex	4780.4 ± 2562.9 ^b	32.3	1	29.10
Cisplatin	9343.9 ± 3298.0	67.1	2	26.35
Paclitaxel	5498.7 ± 2593.1 ^b	39.0	1	26.88

^a T: Treated, C: Untreated, DRD: Drug Related Deaths.

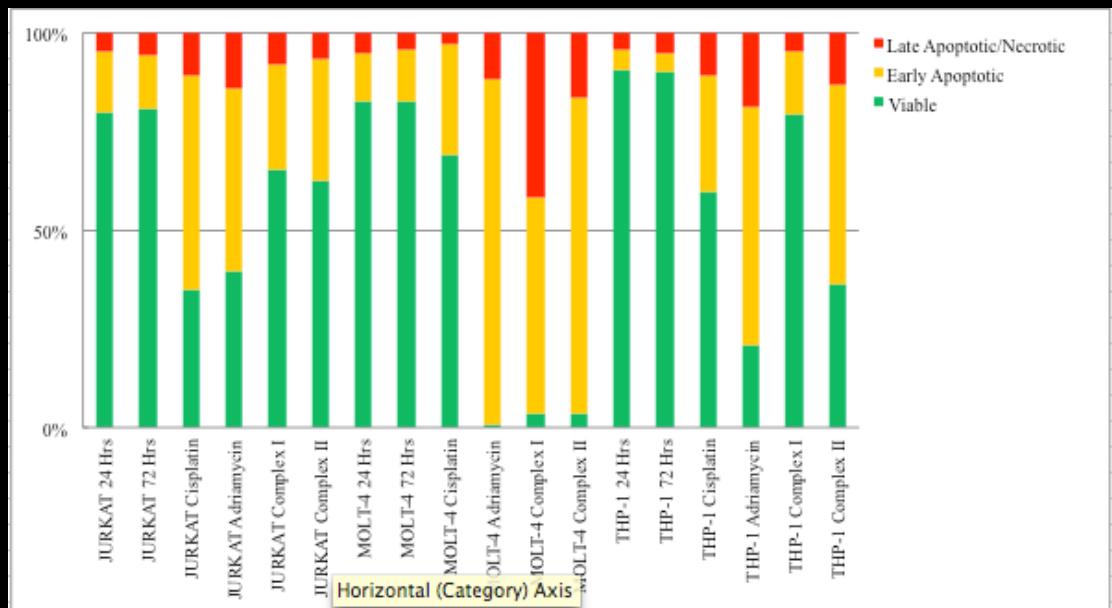
^b Statistically significant differences in comparison with the untreated control group ($p < 0.05$).

^c The mean weights of animals at the end of the experiment (on day 14th).

Ulukaya, Eur J Med Chem, 2011

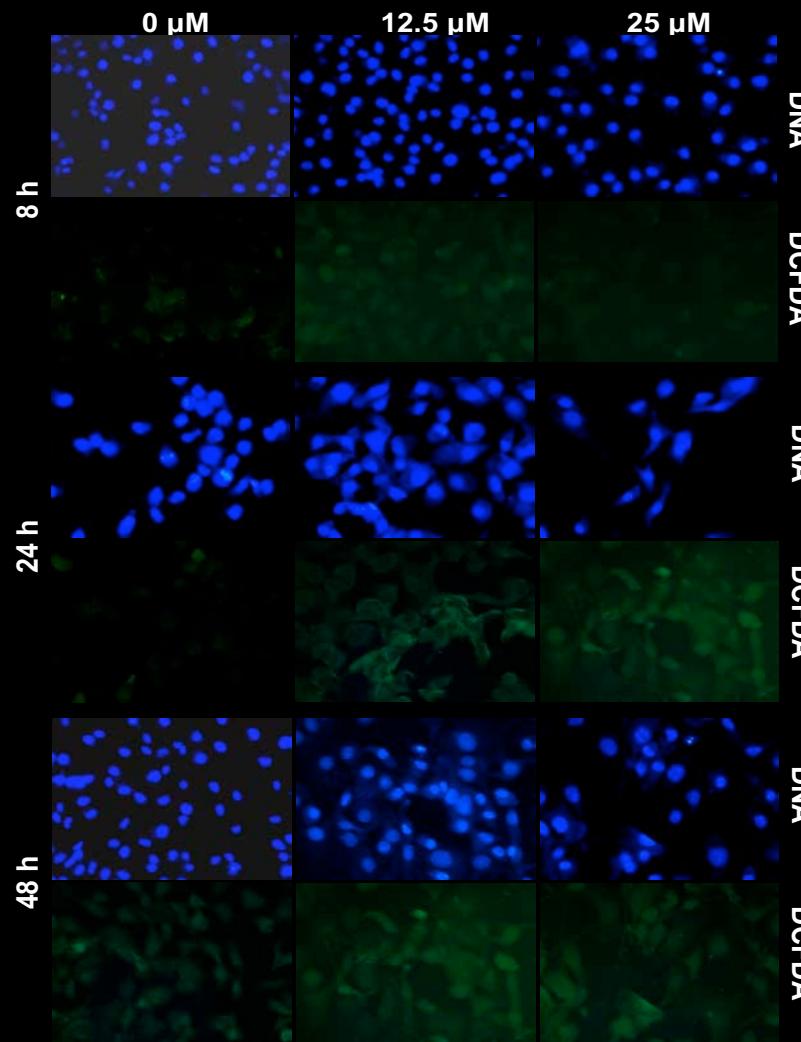


Cell line	Treatment	$\text{IC}_{50} (\mu\text{M})$
Jurkat	Cisplatin	1.94
	Adriamycin	0.08
	Compleks I	0.14
	Compleks II	0.18
MOLT-4	Cisplatin	1.38
	Adriamycin	0.1
	Compleks I	12.22
	Compleks II	11.45
THP-1	Cisplatin	0.94
	Adriamycin	0.05
	Complex I	0.06
	Complex II	0.24

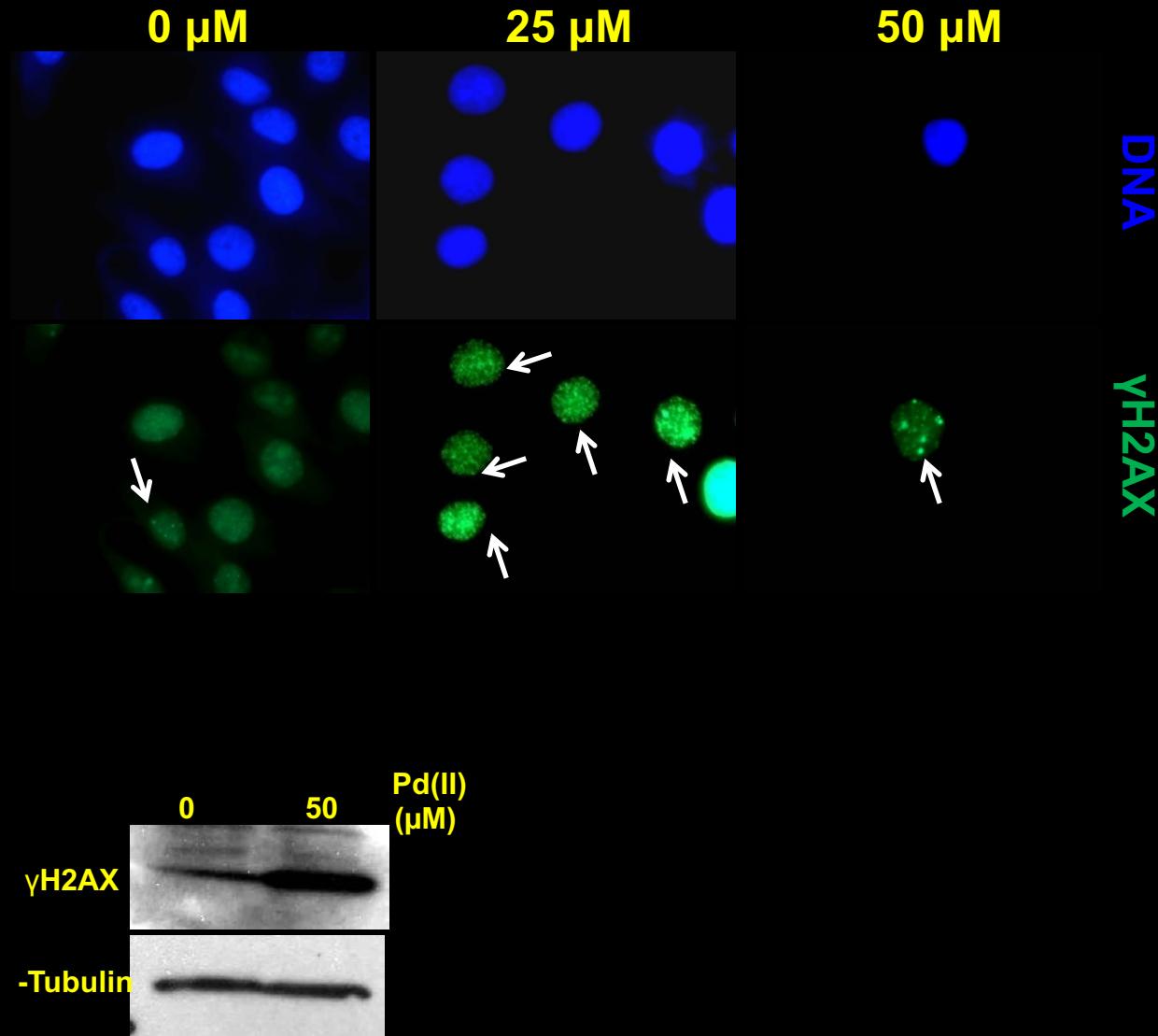


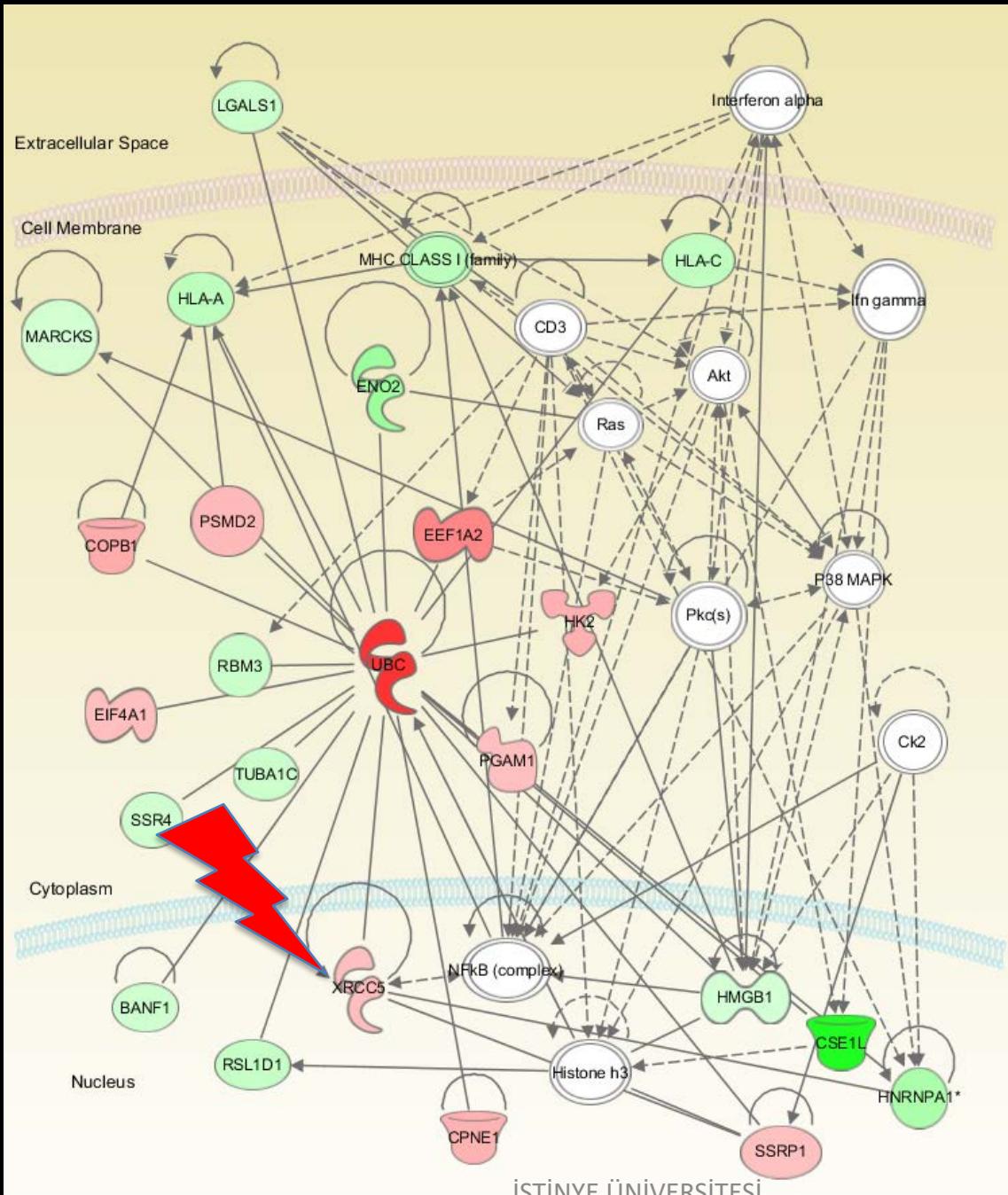


Detection of Total ROS *in Vivo*



Formation of double stranded DNA breaks *in vivo*





**Adiguzel,
Accepted by
J Proteom Res**

The
United
States
of
America



The Director of the United States
Patent and Trademark Office

Has received an application for a patent for
a new and useful invention. The title and
description of the invention are enclosed.
The requirements of law have been com-
piled with, and it has been determined that
a patent on the invention shall be granted
under the law.

Therefore, this

United States Patent

Grants to the person(s) having title to this
patent the right to exclude others from making,
using, offering for sale, or selling the
invention throughout the United States of
America or importing the invention into the
United States of America, and if the inven-
tion is a process, of the right to exclude others
from using, offering for sale or selling
throughout the United States of America, or
importing into the United States of
America, products made by that process,
for the term set forth in 35 U.S.C. 154(a)(2)
or (c)(1), subject to the payment of main-
tenance fees as provided by 35 U.S.C. 41(b).
See the Maintenance Fee Notice on the
inside of the cover.

Joseph Matof

Performing the Functions and Duties of the
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office



URKUNDE

CERTIFICATE

CERTIFICAT

Es wird hiermit bescheinigt,
dass für die in der Patentschrift
beschriebene Erfindung ein
europäisches Patent für die in der
Patentschrift bezeichneten Ver-
tragsstaaten erteilt worden ist.

It is hereby certified that a
European patent has been granted
in respect of the invention
described in the patent specifica-
tion for the Contracting States
designated in the specification.

Il est certifié qu'un brevet
européen a été délivré pour
l'invention décrite dans le
fascicule de brevet, pour les
Etats contractants désignés
dans le fascicule de brevet.

Europäisches Patent Nr.

European patent No.

Brevet européen n°

3140311

Patentinhaber

Proprietor of the patent

Titulaire du brevet

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Yilmaz, Vaysel Turan
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Bursa/TR

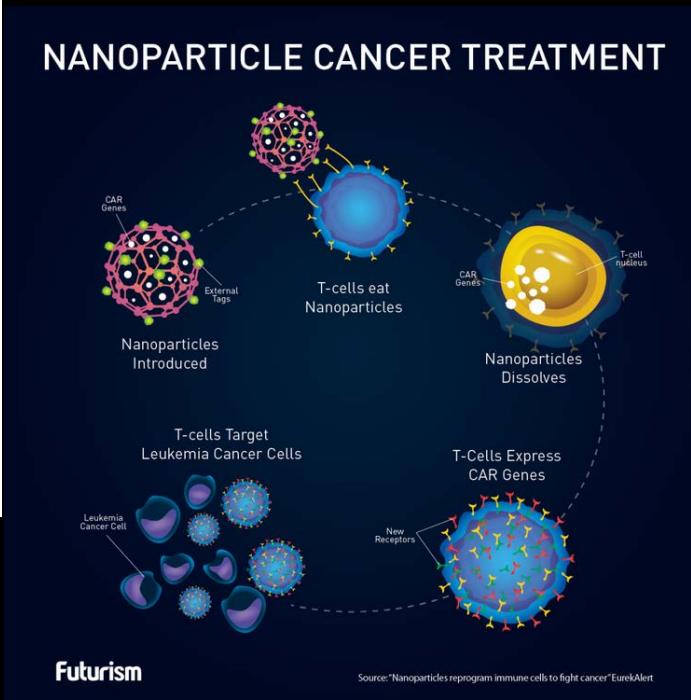
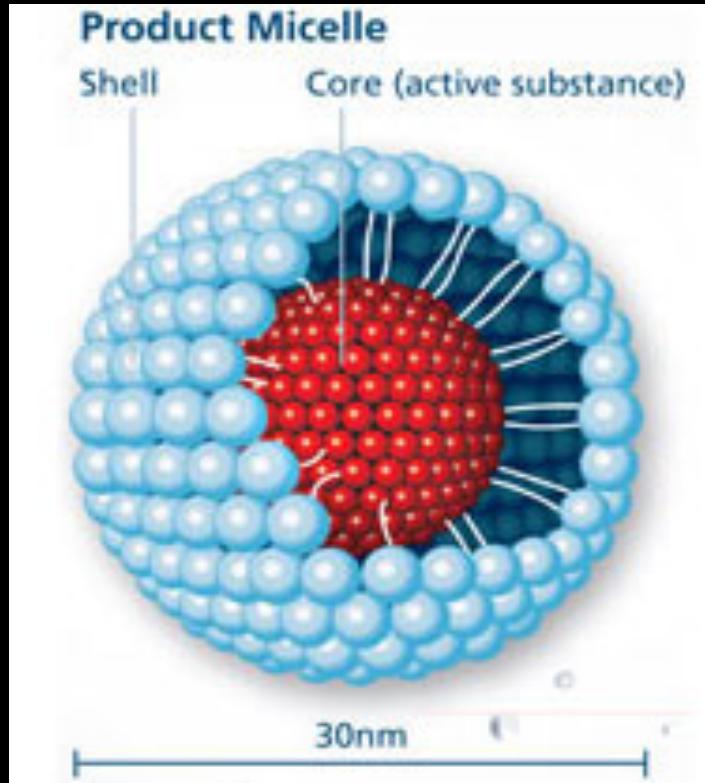
Dimas, Konstantinos
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Department of Pharmacology Faculty of Medicine
School of Health Sciences
Panepistimiou (Bipolis)
41500 Larissa/GR

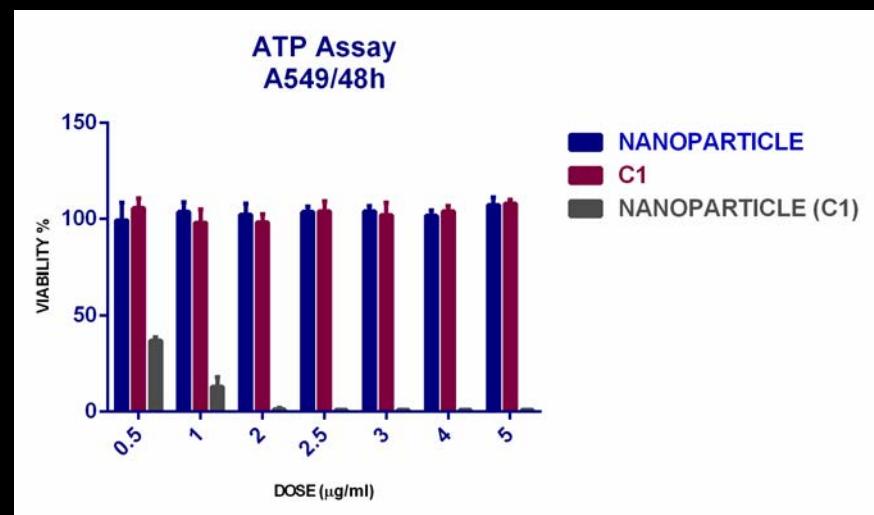
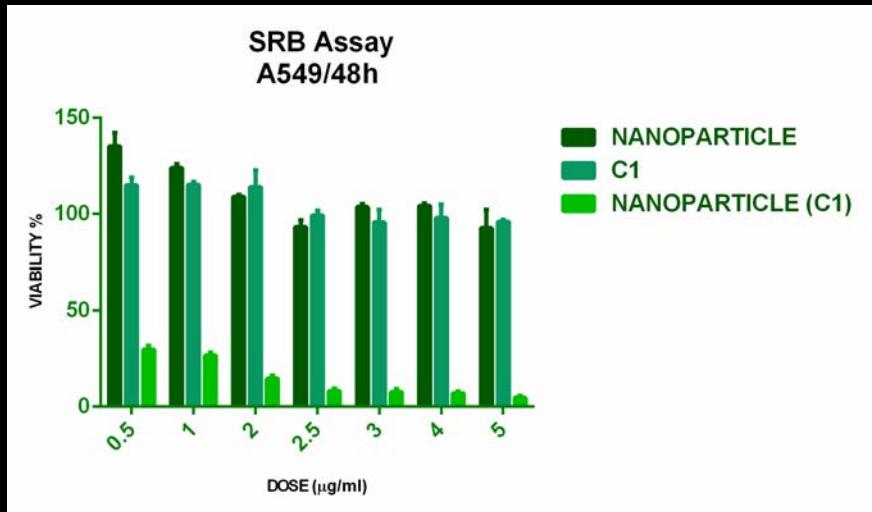
Benoît Battistelli
Präsident des Europäischen Patentamts
President of the European Patent Office
Président de l'Office européen des brevets

München, den
Münich,
Fait à Munich, le

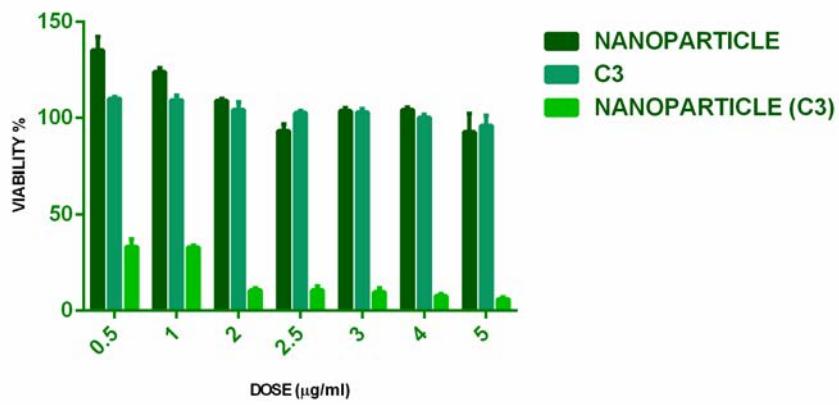
27.06.18

Loading of the Complex in a Nanoparticles

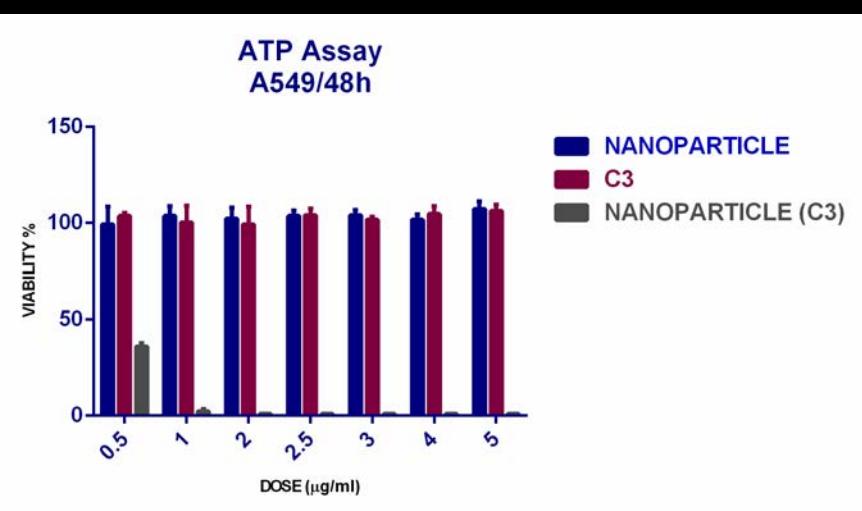


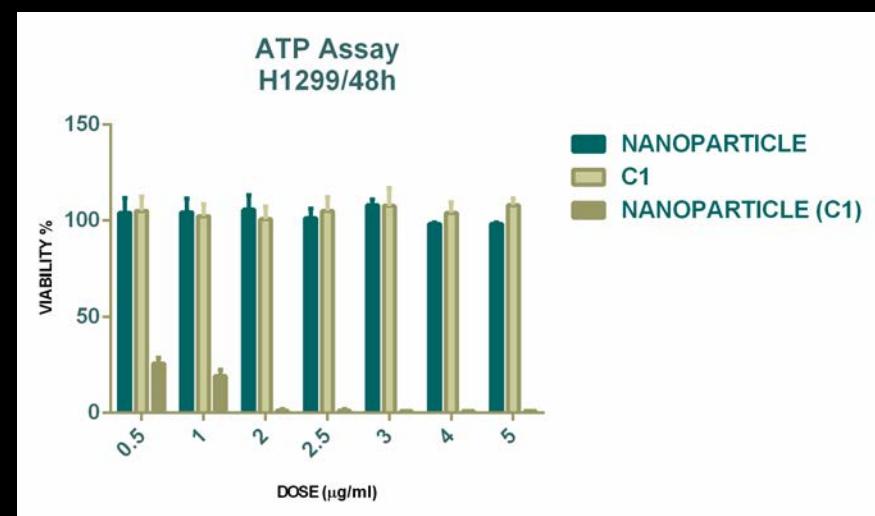
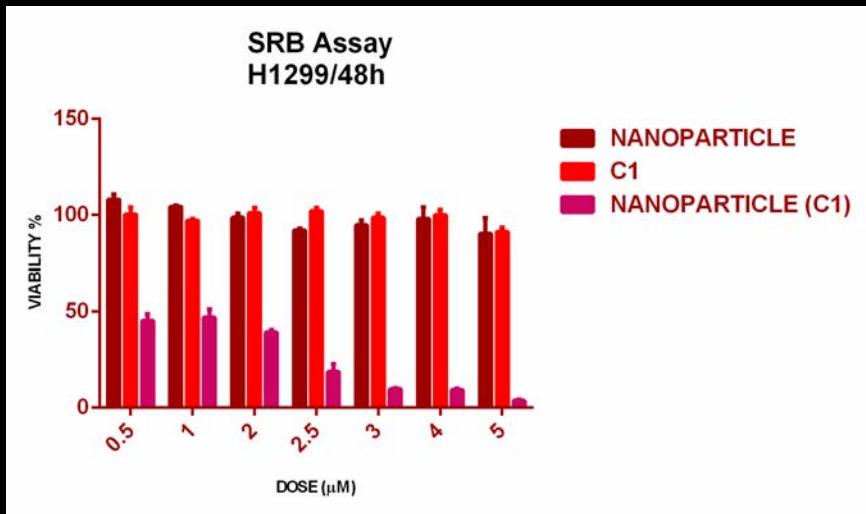


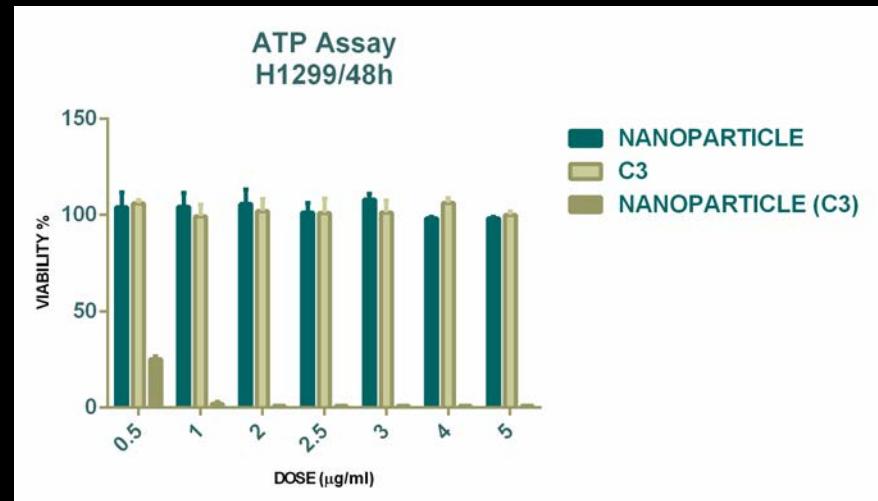
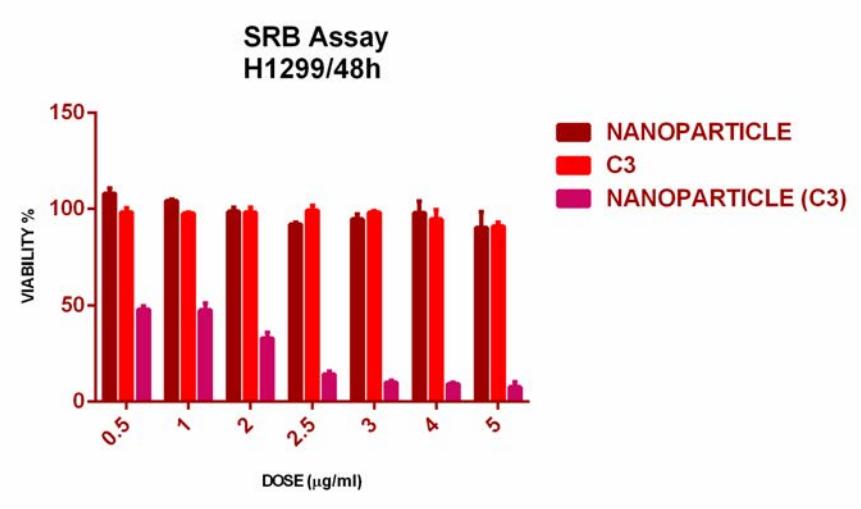
SRB Assay
A549/48h



ATP Assay
A549/48h





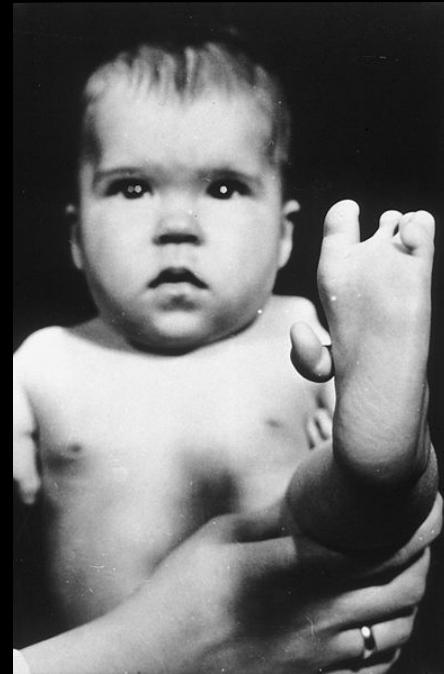
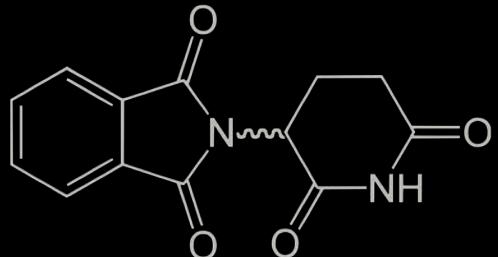


Mesaj....

- Çeşitli biyolojik uyumlu nanopartiküller dizayn etmeli ve sentezini başarmalıyız!

Ülkemizin Başarısı/Olası Başarı Alanına Dair İki Örnek

- Thalidomide !!!
- Mesothelioma*
- HCC
- MM

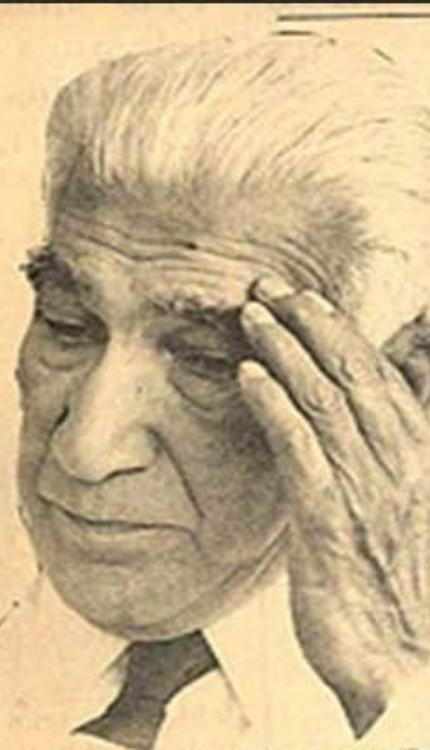


*Kao SCH, Lung Cancer, 2012



ORD. PROF. DR. SÜREYYA TAHSİN AYGÜN, KAN KANSERİNE YADA
ELENAN KOÇUK HASTASI UĞUR VE ANNESİ İLE

6
iyileşmenin mümkün olmayan
hastalıklar arasında yer alan
 lösemi (kan kanseri) ve diğer kanser hastalıkları, kronik nefrit gibi hastalıkların tedavisiini artık mümkün hale getiren Ord.
 Prof. Dr. Sureyya Tahsin Aygün, sadecə
 ülkemizdeki hastaların tedavi etmekle kal-
 emıyor ve Avrupa ülkelerinden
 gelen hastaların sağlık için de
 çabaşlarında bulunuyor...



ORD. PROF. DR. SÜREYYA TAHSİN AY-

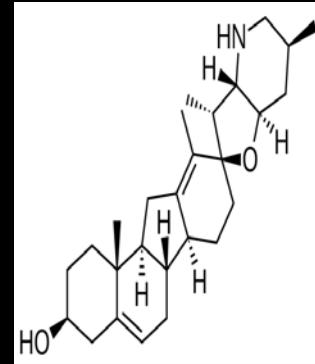
EĞEMAN ALINACAKTIR

«Her derdin devası var»
**“Hücre üretilerek her türlü
hastalık tedavi ediliyor,,**

ANNELİK

Promising Compounds

- Sonic hedgehog inhibitors : **CYCLOPAMINE**



- Poor solubility, stability, and moderate activity!
- IPI- 926, a derivative of cyclopamine

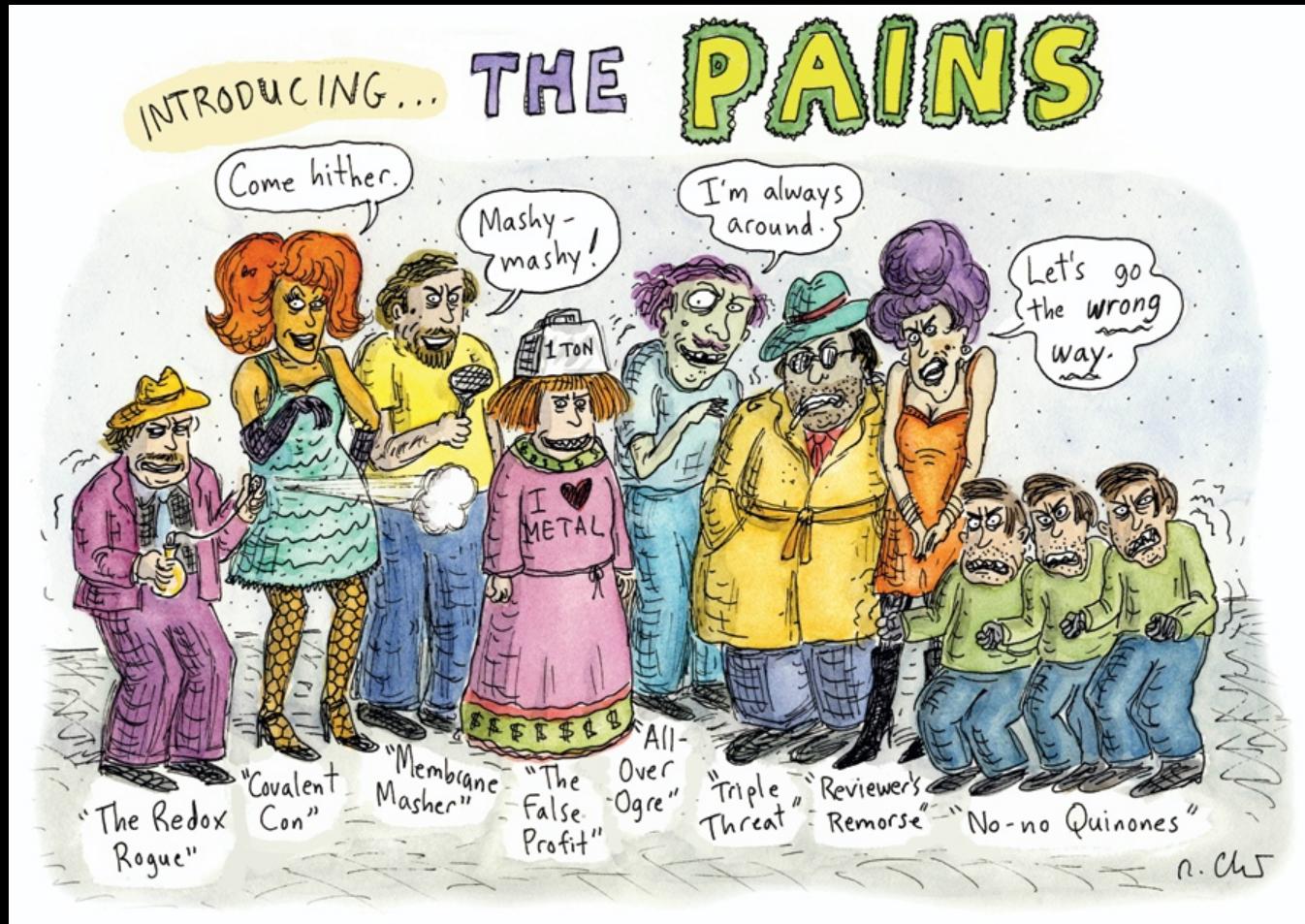
- Stemline therapeutics: SL-401. Anti IL-3 receptor. + toksin.
- Boston Biomedical Inc.: BBI608. Stemness Inhibitor. Faz I OK.
- Genentech: Siklopamin. Hedgehog inhibisyonu
- Geron: GRN163L. Telomeraz inhibisyonu.
- OncoMed + GSK: OMP-595R, OMP-21M18. Notch inhibisyonu



TÜRKİYE'NİN BİTKİ ÖRTÜSÜ

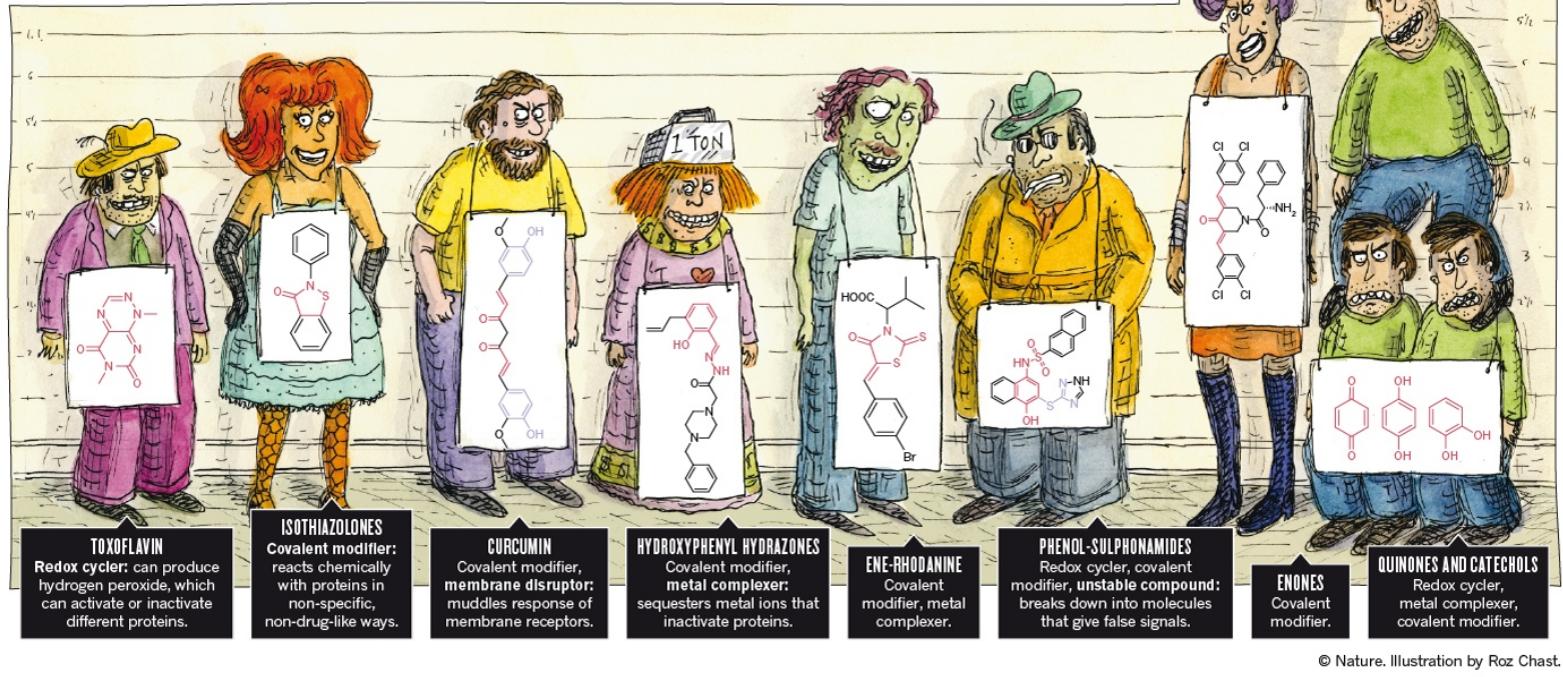
İSTANBUL ÜNİVERSİTESİ

Ülkemizde Dikkat Edilecekler Örnekler



WORST OFFENDERS

Par-assay interference compounds (PAINS) fall into hundreds of chemical classes, but some groups occur much more frequently than others. Among the most insidious are the eight shown here (reactive portions shown in red and purple). These and related compounds should set off alarm bells if they show up as 'hits' in drug screens.

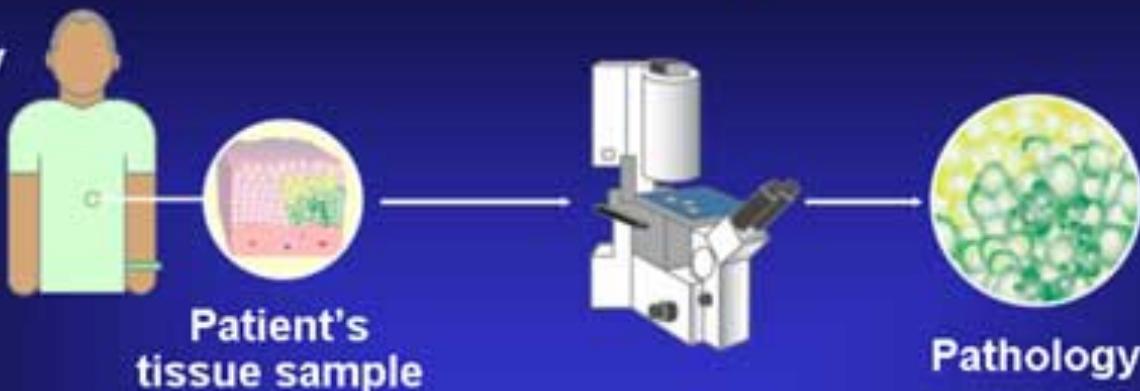


© Nature. Illustration by Roz Chast.

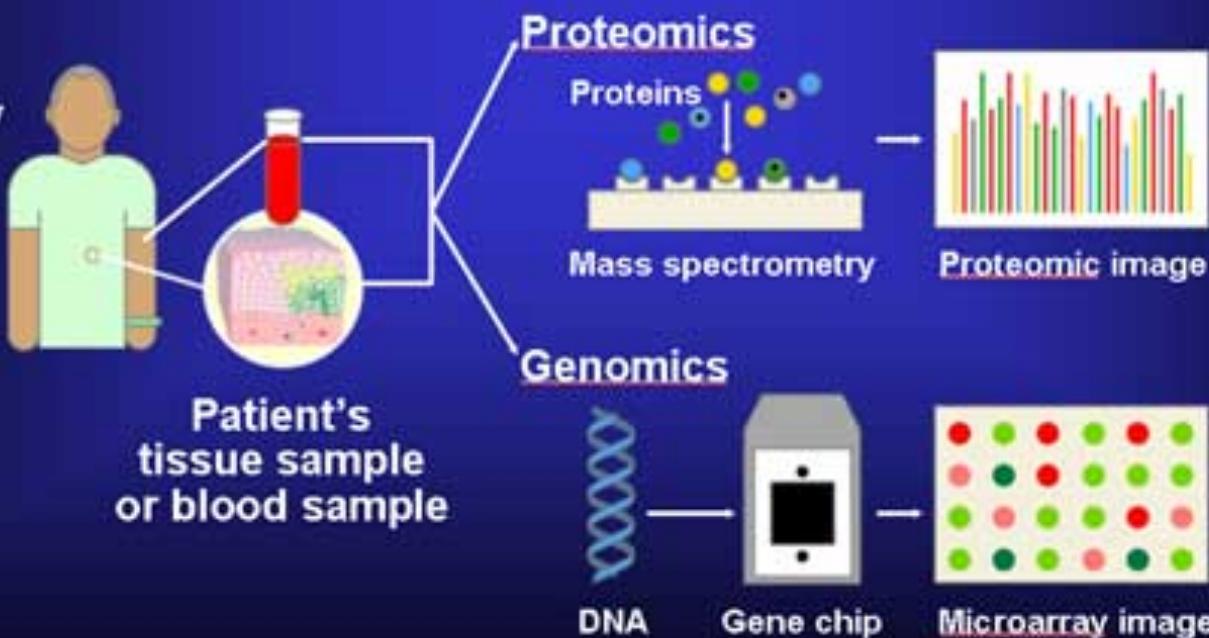
Kanserde Başka Bir Girişimcilik Alanı ve Olası Eksiklik...

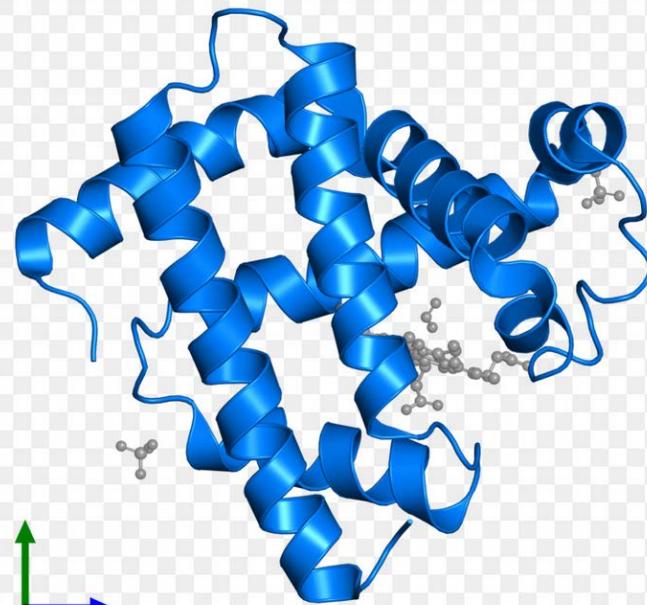
Molecular Diagnostics

Old Way



New Way





İSTİNYE ÜNİVERSİTESİ

Ev Ödevi 😊

Bir an evvel milli kanser ilaç/ ilaçlarımıızı
(+immünoterapötik aşımızı) yapmak zorundayız.

Endemik bitkilerimiz ülke bilim politikalarına dahil
edilerek olabilecek en üst düzeyde ele alınmalıdır.

Moleküller (özellikle proteomik) çağrı yakalamalıyız.
Tanı, прогноз vs kitlerimizi yapmalıyız.

Büyük veri (big data) ve yapay zekayı hızla
mükredatlara yerleştirmeliyiz.



Hayatta En Hakiki Mürşit İlimdir

Eğer bir gün benim sözlerim bilimle ters düşerse
bilimi seçin

Mustafa Kemal Atatürk

