Big Data-Driven Drug Discovery

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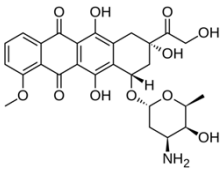
Doxorubicin (adriamycin)

In the **1950s**, an Italian research company, Farmitalia Research Laboratory, began an effort to isolate anticancer compounds from soil-based microbes. A soil sample was isolated from the area surrounding the 13th-centry castle, Castel del Monte, which is near to Apulia. A new strain of *Streptomyces peucetius*, which produced a red pigment was isolated, and an antibiotics was produced from this bacterium that was found to have good activity against murine tumors. At the about the same time a group of French researchers discovered the same compound, the two teams decided to name the compound as daunorubicin. Clinical trials began in the 1960s, and the drug saw success in treating acute leukemia and lymphoma.
However, by 1967, it was recognized that daunorubicin could produce fatal cardiac toxicity.



Researchers in Farmitalia soon discovered that changes in biological activity could be made by minor changes in the structure of the compound. A strain of *Streptomyces* was mutated using *N*-nitroso-*N*-methyl urethane, and this new strain produced a different, red-colored antibiotic. They named this new compound **Adriamycin**, after the **Adratic Sea** , and the name was later changed to doxorubicin to conform to the established naming convention. Doxorubicin showed better activity than daunorubicin against mouse tumors, and especially solid tumors. It also showed a higher therapeutic index, yet the cardiotoxicity remained.

Adriamycin-Induced DNA Damage Mediated by Mammalian DNA Topoisomerase II

Abstract. *Adriamycin (doxorubicin), a potent antitumor drug in clinical use, interacts with nucleic acids and cell membranes, but the molecular basis for its antitumor activity is unknown. Similar to a number of intercalative antitumor drugs and nonintercalative epipodophyllotoxins (VP-16 and VM-26), adriamycin has been shown to induce single- and double-strand breaks in DNA. These strand breaks are unusual because a covalently bound protein appears to be associated with each broken phosphodiester bond. In studies in vitro, mammalian DNA topoisomerase II mediates DNA damage by adriamycin and other related antitumor drugs.*

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gyrase-DNA complex (*11, 12, 19*). Many potent antitumor drugs affect the breakage-reunion reaction of mammalian DNA topoisomerase II by stabilizing the cleavable complex. Whether this unusual DNA damage is related to drug-induced cytotoxicity, sister chromatid exchange, or chromosomal aberration is still not clear. Our studies suggest a possible role of topoisomerase II in the action of these antitumor drugs.

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Nonintercalative Antitumor Drugs Interfere with the Breakage-Reunion Reaction of Mammalian DNA Topoisomerase II*

(Received for publication, April 16, 1984)

Grace L. Chen, Liu Yang, Thomas C. Rowe‡, Brian D. Halligan, Kathleen M. Tewey, and Leroy F. Liu

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J. Mol. Biol. (1971) **55**, 523–533

Interaction between DNA and an *Escherichia coli* Protein ω

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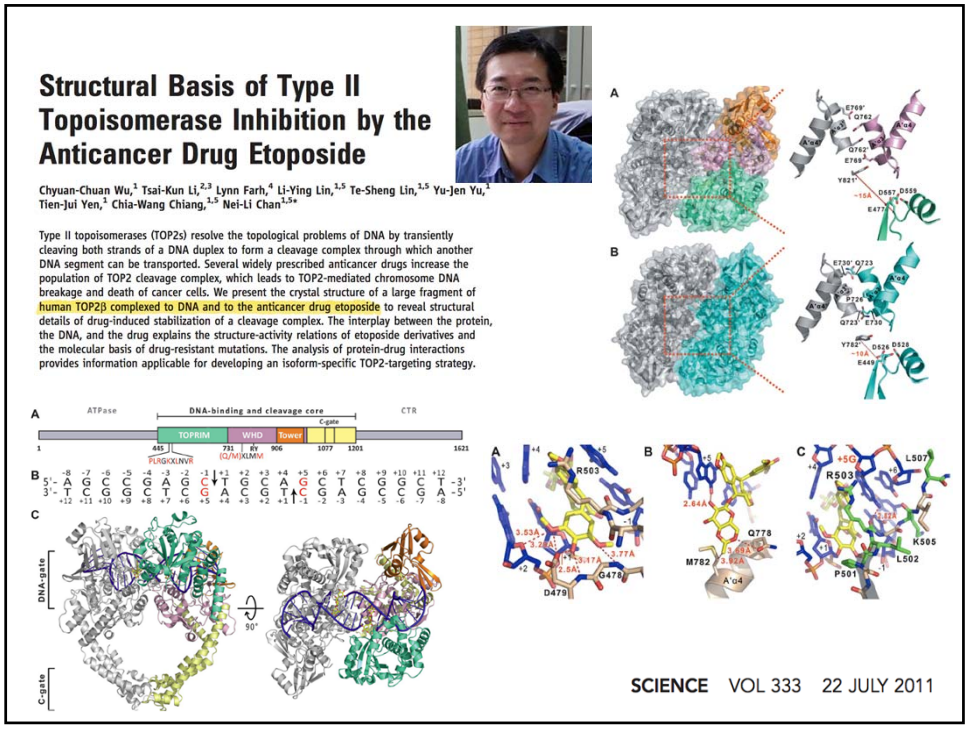
(*Received 20 July 1970, and in revised form 2 November 1970*)

In a previous communication on the degree of superhelicity of a number of closed cyclic DNA's from *Escherichia coli*, it was noted that there was a macromolecular species in an *E. coli* extract, which could convert a highly twisted superhelical DNA to a less twisted, covalently closed form (Wang, 1969*b*). This species has now been purified at least 1000-fold. All evidence indicates that it is a protein, and is designated ω. Some of its novel properties are described in this communication.

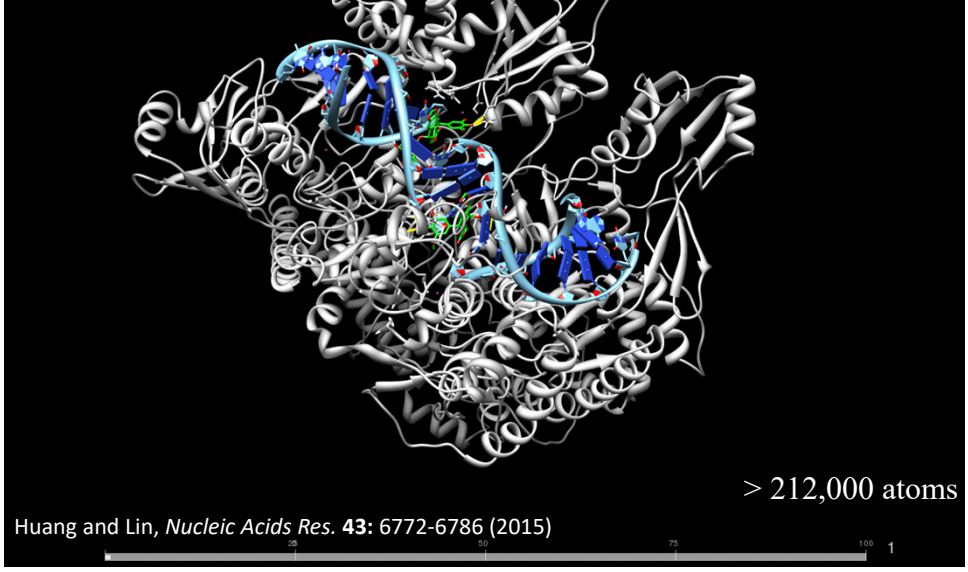


Structural Basis of Type II Topoisomerase Inhibition by the Anticancer Drug Etoposide

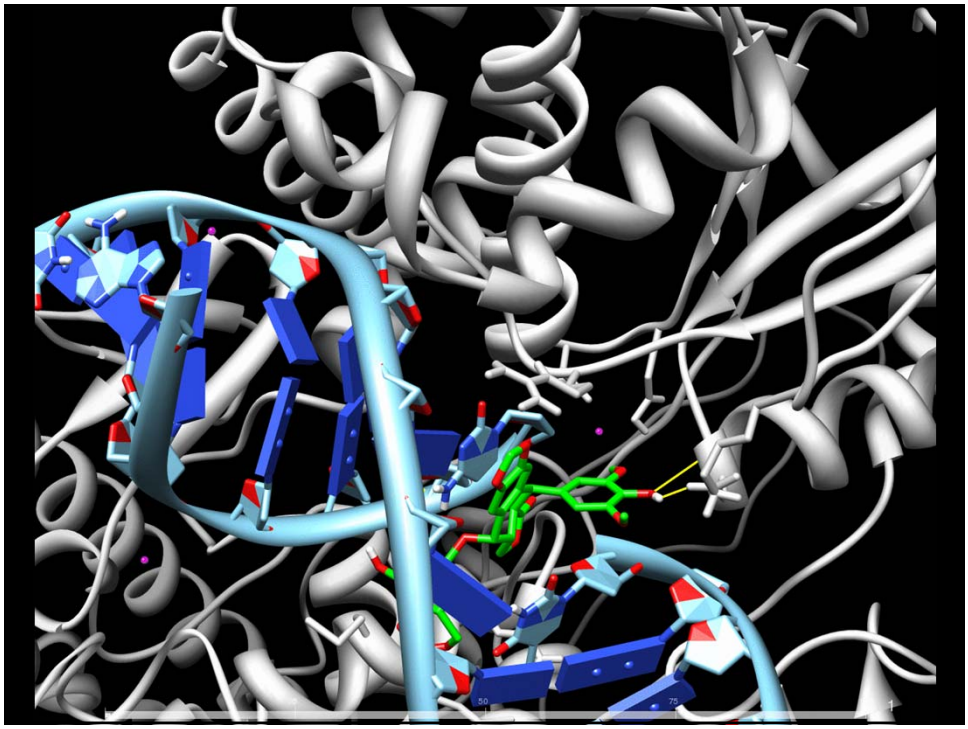
Chyuan-Chuan Wu,[1] Tsai-Kun Li,[2,3] Lynn Farh,[4] Li-Ying Lin,[1,5] Te-Sheng Lin,[1,5] Yu-Jen Yu,[1] Tien-Jui Yen,[1] Chia-Wang Chiang,[1,5] Nei-Li Chan[1,5]*

Type II topoisomerases (TOP2s) resolve the topological problems of DNA by transiently cleaving both strands of a DNA duplex to form a cleavage complex through which another DNA segment can be transported. Several widely prescribed anticancer drugs increase the population of TOP2 cleavage complex, which leads to TOP2-mediated chromosome DNA breakage and death of cancer cells. We present the crystal structure of a large fragment of human TOP2β complexed to DNA and to the anticancer drug etoposide to reveal structural details of drug-induced stabilization of a cleavage complex. The interplay between the protein, the DNA, and the drug explains the structure-activity relations of etoposide derivatives and the molecular basis of drug-resistant mutations. The analysis of protein-drug interactions provides information applicable for developing an isoform-specific TOP2-targeting strategy.

SCIENCE VOL 333 22 JULY 2011



Huang and Lin, *Nucleic Acids Res.* **43:** 6772-6786 (2015)



BRIEF COMMUNICATIONS

Identification of the molecular basis of doxorubicin-induced cardiotoxicity

Sui Zhang[1], Xiaobing Liu[2,3], Tasneem Bawa-Khalfe[1], Long-Sheng Lu[2], Yi Lisa Lyu[4], Leroy F Liu[4] & Edward TH Yeh[1,2]

To investigate the role of Top2β in doxorubicin-induced cardiac toxicity, we established a mouse model with cardiomyocyte-specific deletion of *Top2b* (α-MHC-MerCreMer-*Top2b*$^{flox/flox}$ mice). We crossed mice carrying a *loxP*-flanked *Top2b* allele (*Top2b*$^{flox/flox}$)[10] with mice carrying a myosin heavy chain promoter and a fusion protein containing Cre and mutated estrogen receptor (α-MHC-MerCreMer)[11]. The resulting α-MHC-MerCreMer-*Top2b*$^{flox/flox}$ mice were viable, fertile and normal in size, and did not display any

The implications of our findings are twofold. First, drugs that specifically target the Top2α isozyme, but not Top2β, should be less cardiotoxic and, hence, more useful clinically. This conclusion is based on the assumption that Top2β does not contribute significantly to doxorubicin's tumoricidal activity. Second, patients with higher expression of Top2β in cardiomyocytes may be more susceptible to doxorubicin-induced cardiotoxicity. These predictions can be tested in animals and humans.

The Structure of DNA-Bound Human Topoisomerase II Alpha: Conformational Mechanisms for Coordinating Inter-Subunit Interactions with DNA Cleavage

J. Mol. Biol. (2012) **424**, 109–124

Timothy J. Wendorff[1], Bryan H. Schmidt[2], Pauline Heslop[3], Caroline A. Austin[3] and James M. Berger[1,2]

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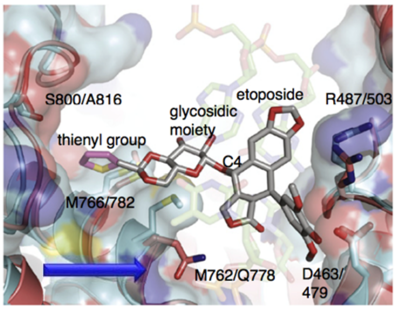
http://dx.doi.org/10.1016/j.jmb.2012.07.014
Edited by S. Kowalczykowski

Residues of TOP2-α/TOP2-β

Potential target residues for designing new inhibitors that are specific to Topoisomerase II-α.



FEATURE

Getting the right drug into the right patient

Pharmacogenomics will help explain why drugs work better in some patients than in others. These tools should be used as early in the drug development process as possible.

Andrew Marshall

Pharmaceutical medicine today is geared around taking statistical information about the general population and applying it to the individual: Physicians make empirical decisions about types of treatment and drug dosage during the initial consultation with a patient; only after the individual returns following the first course of treatment is the prescription "personalized," and only then by varying the dosage.

"Everything is back to front," says Gualberto Ruano, CEO of Genaissance Pharmaceuticals (New Haven, CT), a startup company that aims to set up exploratory programs with pharmaceutical companies for isotyping patients' genes in trials. "Drug safety and efficacy profiles are geared toward the average person, when they should be geared to the individual." He believes that the "one-size-fits-all" approach ignores the fact that humans show incredible genetic diversity. By demonstrating the molecular basis of variations in patients' responses to drugs, Ruano and many others contend that pharmacogenomics can address many of the deficiencies that pervade pharmaceutical development.

"Pharmacogenomics is a logical progression could represent a way of both improving health care and reducing overheads. There is a cost to unnecessary drugs, ineffective drugs, and drugs with side effects. Underdosing, overdosing, or missed doses currently cost the US more than $100 billion a year in increased hospital admissions, lost productivity, and premature death[1].

It seems that it is in everybody's interests—patients, small companies, large companies, and payers—to take differences between human beings seriously.

Underdosing, overdosing, or missed doses costs the US more than $100 billion a year

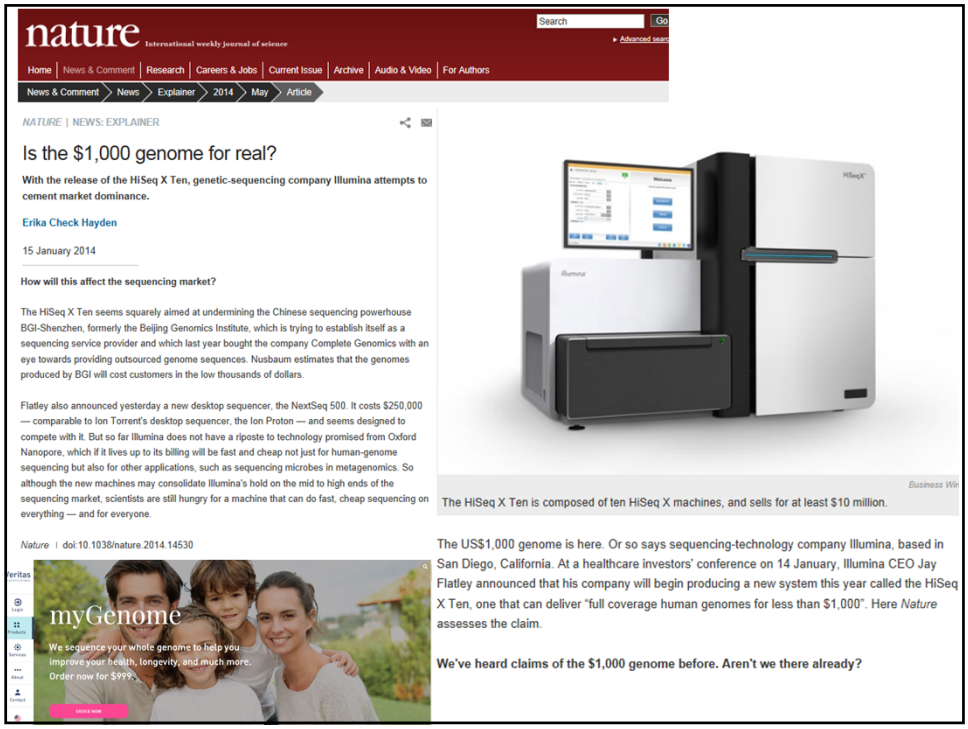
Differentiating Alzheimer's

Perhaps the best current illustration of the power of pharmacogenomics is in Alzheimer's disease. What physicians are looking for here is benefit from tacrine. And roughly the same fraction suffer debilitating side effects such as liver toxicity, nausea, and vomiting. No surprise, then, that many either stop taking tacrine or don't take it at the prescribed dosage. To make tacrine work, doctors need a way of distinguishing at the outset which patients will respond to the drug. Recent studies show that pharmacogenomics can do just that.

Judes Poirer and colleagues[2,3] at McGill University (Montreal, Canada) looked at the relationships between Alzheimer's patients' genotypes and their drug response. They subdivided 440 patients[3] according to their type of apolipoprotein E *(APOE)* gene, a known predisposing factor in Alzheimer's disease. It appears that *APOE* is also a good predictor of response to tacrine. Individuals who were homogeneous for the *APOE* ε4 allele (ε4/ε4) responded much more poorly to tacrine than patients with other *APOE* genotypes.

The same kind of genetic dissection can, of course, make the clinical phases of drug development more pertinent, as was shown in another Alzheimer's study, reported in February this year by researchers at INSERM[4] (Lille,

Precision Medicine Initiative



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NATURE | NEWS: EXPLAINER

Is the $1,000 genome for real?

With the release of the HiSeq X Ten, genetic-sequencing company Illumina attempts to cement market dominance.

Erika Check Hayden

15 January 2014

How will this affect the sequencing market?

The HiSeq X Ten seems squarely aimed at undermining the Chinese sequencing powerhouse BGI-Shenzhen, formerly the Beijing Genomics Institute, which is trying to establish itself as a sequencing service provider and which last year bought the company Complete Genomics with an eye towards providing outsourced genome sequences. Nusbaum estimates that the genomes produced by BGI will cost customers in the low thousands of dollars.

Flatley also announced yesterday a new desktop sequencer, the NextSeq 500. It costs $250,000 — comparable to Ion Torrent's desktop sequencer, the Ion Proton — and seems designed to compete with it. But so far Illumina does not have a riposte to technology promised from Oxford Nanopore, which if it lives up to its billing will be fast and cheap not just for human-genome sequencing but also for other applications, such as sequencing microbes in metagenomics. So although the new machines may consolidate Illumina's hold on the mid to high ends of the sequencing market, scientists are still hungry for a machine that can do fast, cheap sequencing on everything — and for everyone.

Nature | doi:10.1038/nature.2014.14530

The HiSeq X Ten is composed of ten HiSeq X machines, and sells for at least $10 million.

The US$1,000 genome is here. Or so says sequencing-technology company Illumina, based in San Diego, California. At a healthcare investors' conference on 14 January, Illumina CEO Jay Flatley announced that his company will begin producing a new system this year called the HiSeq X Ten, one that can deliver "full coverage human genomes for less than $1,000". Here *Nature* assesses the claim.

We've heard claims of the $1,000 genome before. Aren't we there already?

Clustering genes by their correlation

1. Construct a matrix of similarity measures between all pairs of genes.
2. Recursively cluster the genes into a tree-like hierarchy.
   a) Find the pair of clusters with the highest correlation and combine the pair into a single cluster.
   b) Update the correlation matrix using the average values of the newly combined cluster.
   c) Repeat step (a) and (b) N-1 times until all genes have been clustered.
3. Determine the boundaries between individual genes.

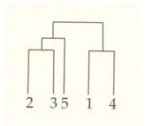
$$c_{ij} = \frac{1}{N}\sum_{t=1}^{N}\left(\frac{E_i(t)-\overline{E_i}}{\sigma_i}\right)\left(\frac{E_j(t)-\overline{E_j}}{\sigma_j}\right)$$

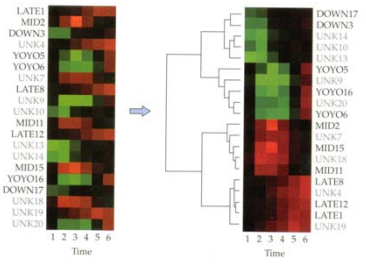
$$\overline{E_i} = \frac{1}{N}\sum_{t=1}^{N}E_i(t), \quad \overline{E_j} = \frac{1}{N}\sum_{t=1}^{N}E_j(t)$$

$$\sigma_i = \sqrt{\frac{1}{N}\sum_{t=1}^{N}\left(E_i(t)-\overline{E_i}\right)}, \quad \sigma_j = \sqrt{\frac{1}{N}\sum_{t=1}^{N}\left(E_j(t)-\overline{E_j}\right)}$$

	2	3	4	5
1	0.3	0.2	0.8	0.1
2		0.9	0.1	0.8
3			0.2	0.7
4				0.1

	23	4	5
1	0.25	0.8	0.1
23		0.15	0.75
4			0.1

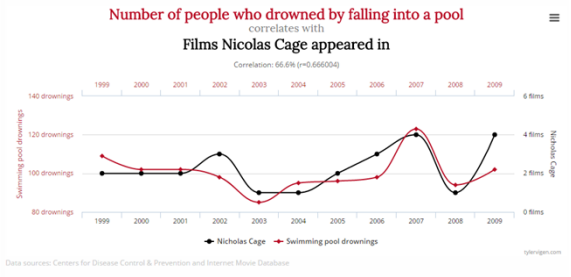


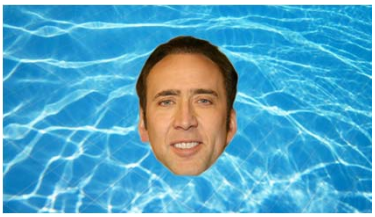


Eisen et al., *Proc. Natl. Acad. Sci. USA*. **95:** 14863-14868 (1998)

Correlation does not imply causation

That is, unless we do have Nicholas Cage to blame for all those people drowning in swimming pools.

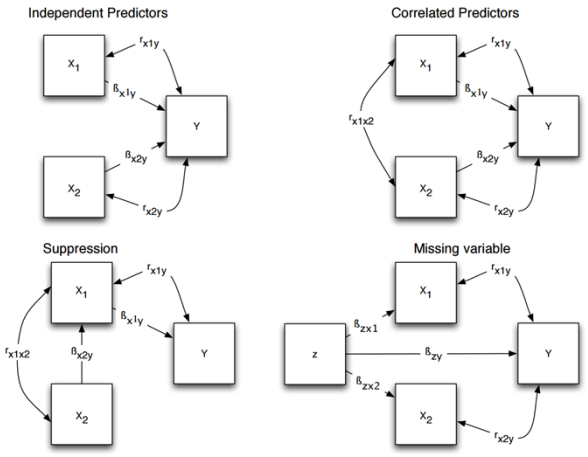




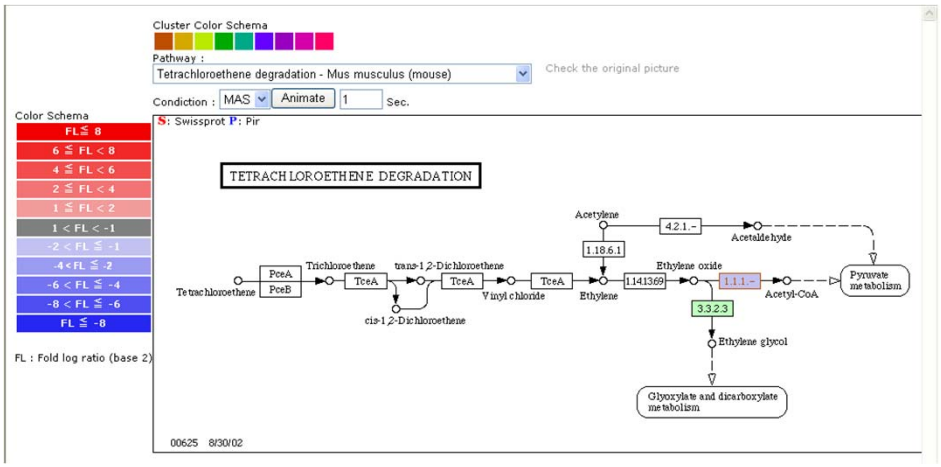
http://www.tylervigen.com/spurious-correlations

http://www.tylervigen.com/view_correlation?id=359

However, it does not mean that correlation *cannot* imply causation

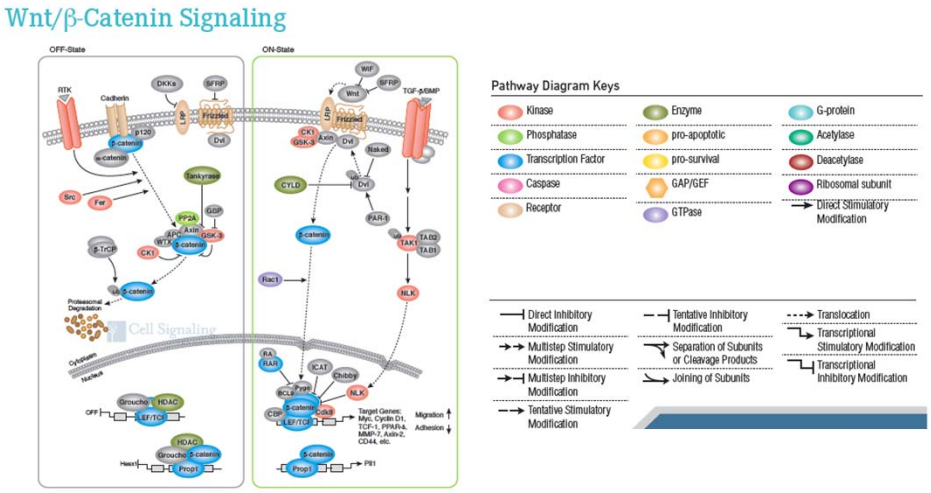


http://rationalwiki.org/w/images/0/01/Variable_interactions.png



Signaling Pathways

Cell Signaling Technology (http://www.cellsignal.com/common/content/content.jsp?id=science-pathways)

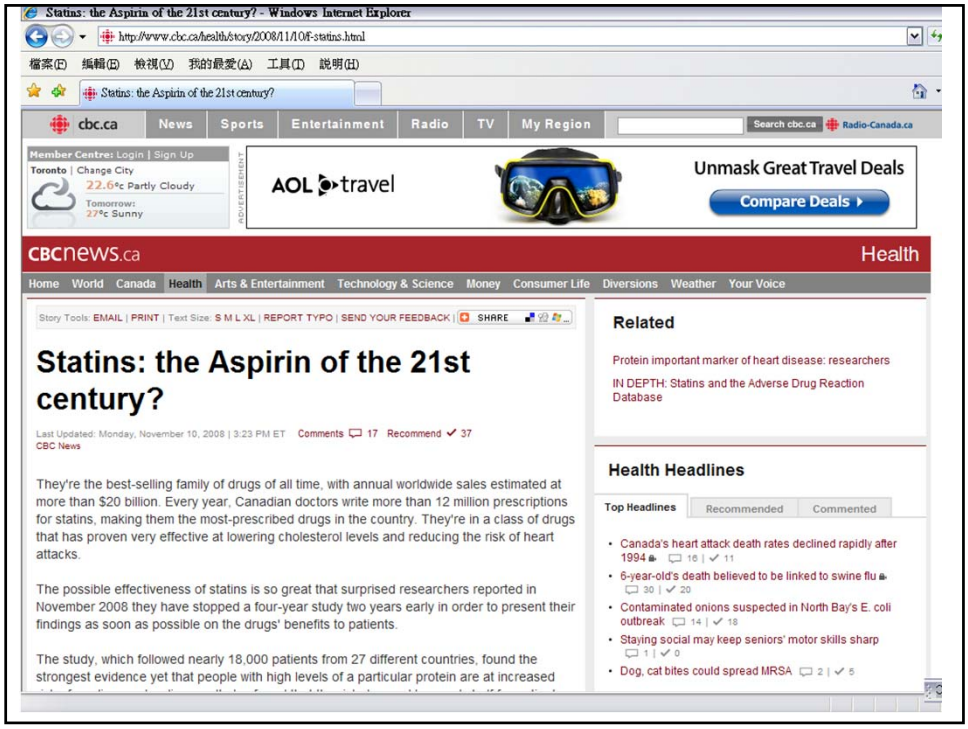


"Do-no-harm" drugs for cancer prevention

- Aspirin and other non-steroid anti-inflammatory drugs.
- Statins and other anti-hypercholesterolemia medications.
- Metform (anti-diabetic agent)
- Bisphosphonates (anti-osteoporosis drugs)

A low-adverse-effect profile is the key.

Gronic and Rennert, *Nature Rev. Clin. Oncol.* **10:** 625-642 (2013)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Statins: the Aspirin of the 21st century?
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CBC News
They're the best-selling family of drugs of all time, with annual worldwide sales estimated at more than $20 billion. Every year, Canadian doctors write more than 12 million prescriptions for statins, making them the most-prescribed drugs in the country. They're in a class of drugs that has proven very effective at lowering cholesterol levels and reducing the risk of heart attacks.
The possible effectiveness of statins is so great that surprised researchers reported in November 2008 they have stopped a four-year study two years early in order to present their findings as soon as possible on the drugs' benefits to patients.
The study, which followed nearly 18,000 patients from 27 different countries, found the strongest evidence yet that people with high levels of a particular protein are at increased
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偽藥風波止不住 食藥署：全面下架冠脂妥
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偽藥案如滾雪球，食藥署日前確定MV503是假藥後，今天再次確認另一批號MK479的冠脂妥，也是偽藥，食藥署署長吳秀梅今天表示，因無法判定到底市面上流通還有多少偽藥，因此將全面下架回收所有冠脂妥，並進行換貨，確保民眾不再吃到偽藥。
Up to 70% OFF
冠脂妥偽藥事件擴大 另一批號MK479也中鏢！
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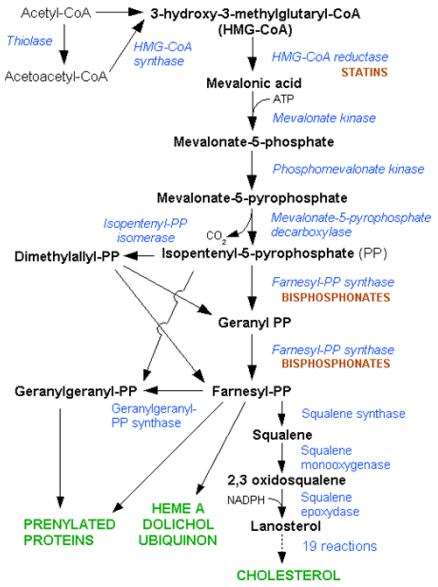
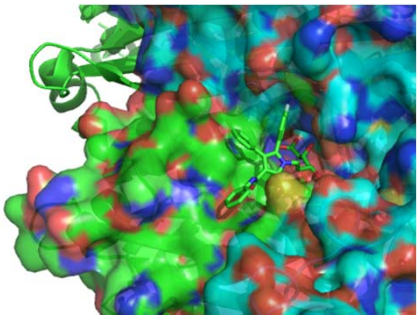
Mechanism of Statins





Atorvastatin bound to HMG-CoA reductase: PDB entry 1hwk

Discovery of Statins

- Young Investigator Award in agricultural chemistry (Japan), 1966
- Heinrich Wieland Prize for the discovery of the HMG-CoA reductase inhibitors (West Germany), 1987
- Toray Science and Technology Prize (Japan), 1988
- Warren Alpert Foundation Prize (Harvard Medical School, U.S.A), 2000
- Massry Prize from the Keck School of Medicine, University of Southern California in 2006
- Albert Lasker Award for Clinical Medical Research, 2008

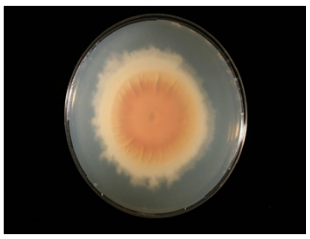
Akira Endo (遠藤 章, *Endō Akira*, born 14 November 1933) is a Japanese biochemist whose research into the relationship between fungi and cholesterol biosynthesis led to the development of statin drugs, which are some of the best-selling pharmaceuticals in history.

Endo studied 6,000 compounds, of which three extrolites from a *Penicillium* mold showed an effect. One of them, **mevastatin**, was the first member of the statin class of drugs. Soon after, lovastatin, the first commercial statin, was found in the *Aspergillus* mold. Although mevastatin never became an approved drug, the mevastatin derivative pravastatin did.

Discovery of lovastatin

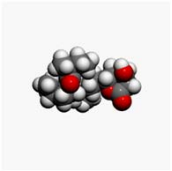
P. Roy Vagelos (born October 8, 1929 in Westfield, New Jersey), was president and chief executive officer (1985) and chairman (1986) of the multinational pharmaceutical company Merck.

Mevastatin was never marketed, because of its adverse effects of tumors, muscle deterioration, and sometimes death in laboratory dogs. P. Roy Vagelos, chief scientist and later CEO of Merck & Co, was interested, and made several trips to Japan starting in 1975. By 1978, Merck had isolated lovastatin (mevinolin, MK803) from the fungus *Aspergillus terreus*, first marketed in 1987 as Mevacor



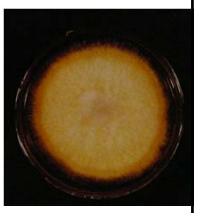
Aspergillus terreus

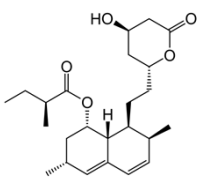
土麴黴, 髮菌科麴菌屬下的一個種

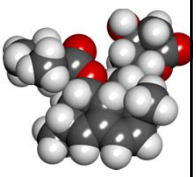


Red Yeast Rice (紅麴米、紅曲米)

- Red yeast rice is a bright reddish purple fermented rice, which acquire its color from being cultivated with the mold *Monascus purpureus*.
- In addition to its culinary use, red yeast rice is also used in traditional Chinese herbology and traditional Chinese medicine.
- Its use has been documented as far back as the Tang Dynasty in 800 AD. It is taken internally to invigorate the body, aid in digestion, and revitalize the blood. A more complete description is in the traditional Chinese pharmacopeia, Ben Cao Gang Mu, from the Ming Dynasty (1378-1644).
- In the late 1970s, researchers in the United States and Japan were isolating lovastatin from *Aspergillus* and monacolins from *Monascus*, respectively. Chemical analysis showed that lovastatin and monacolin K are identical.







The Risk of Cancer in Users of Statins

Matthijs R. Graaf, Annette B. Beiderbeck, Antoine C.G. Egberts, Dick J. Richel, and Henk-Jan Guchelaar

A B S T R A C T

Purpose
Several preclinical studies suggested a role for 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) in the treatment of cancer. The objective of this study was to compare the risk of incident cancer between users of statins and users of other cardiovascular medication.

Methods
Data were used from the PHARMO database, containing drug dispensing records from community pharmacies and linked hospital discharge records for residents of eight Dutch cities. The study base included all patients with one or more prescriptions for cardiovascular drugs in the period between January 1, 1985 and December 31, 1998. Cases were identified as patients in the study base with a diagnosis of incident cancer and matched with four to six controls on sex, year of birth, geographic region, duration of follow-up, and index date. The analysis was adjusted for diabetes mellitus; prior hospitalizations; comorbidity; and use of diuretics, angiotensin-converting enzyme inhibitors, calcium-channel blockers, nonsteroidal anti-inflammatory drugs, sex hormones, and other lipid-lowering drug therapies.

Results
In the study base, 3,129 patients were identified and matched to 16,976 controls. Statin use was associated with a risk reduction of cancer of 20% (adjusted odds ratio [OR], 0.80; 95% CI, 0.66 to 0.96). Our data suggest that statins are protective when used longer than 4 years (adjusted OR, 0.64; 95% CI, 0.44 to 0.93) or when more than 1,350 defined daily doses are taken (adjusted OR, 0.60; 95% CI, 0.40 to 0.91).

Conclusion
This observational study suggests that statins may have a protective effect against cancer.

Graaf *et al.,* J. *Clin. Onco*. **22:** 2388-2394 (2004)

STATINS AND CANCER PREVENTION

Marie-France Demierre[*#], *Peter D. R. Higgins*[‡#], *Stephen B. Gruber*[§], *Ernest Hawk*[‖] *and Scott M. Lippman*[¶]

Abstract | Randomized controlled trials for preventing cardiovascular disease indicated that statins had provocative and unexpected benefits for reducing colorectal cancer and melanoma. These findings have led to the intensive study of statins in cancer prevention, including recent, large population-based studies showing statin-associated reductions in overall, colorectal and prostate cancer. Understanding the complex cellular effects (for example, on angiogenesis and inflammation) and the underlying molecular mechanisms of statins (for example, 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase-dependent processes that involve geranylgeranylation of Rho proteins, and HMG-CoA-independent processes that involve lymphocyte-function-associated antigen 1) will advance the development of molecularly targeted agents for preventing cancer. This understanding might also help the development of drugs for other ageing-related diseases with interrelated molecular pathways.

Demierre *et al., Nature Rev. Cancer* **5:** 930-942 (2005)

Statins use was associated with a 47 percent reduction in the risk of colorectal cancer

The NEW ENGLAND JOURNAL of MEDICINE

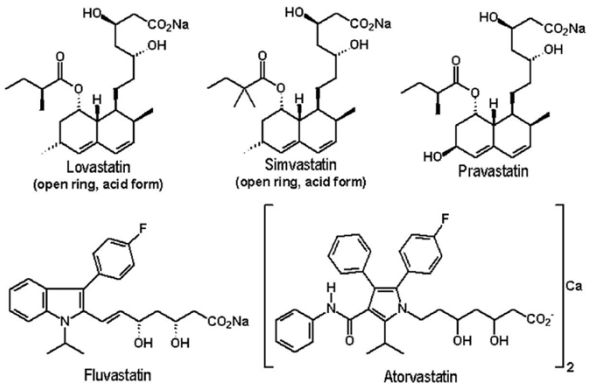
ORIGINAL ARTICLE

Statins and the Risk of Colorectal Cancer

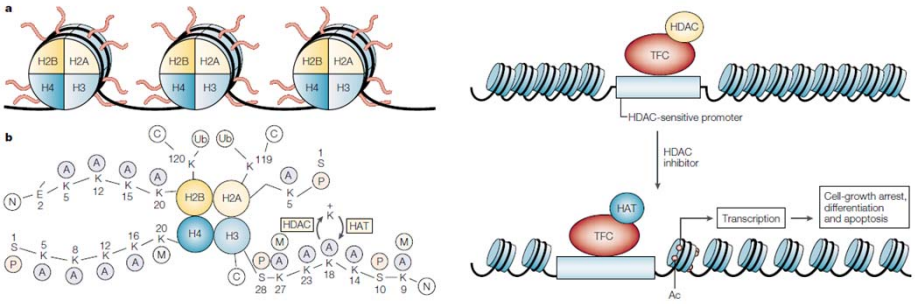
Jenny N. Poynter, M.P.H., Stephen B. Gruber, M.D., Ph.D., M.P.H., Peter D.R. Higgins, M.D., Ph.D., Ronit Almog, M.D., M.P.H., Joseph D. Bonner, M.S., Hedy S. Rennert, M.P.H., Marcelo Low, M.P.H., Joel K. Greenson, M.D., and Gad Rennert, M.D., Ph.D.

N. Engl. J. Med. 352: 2184-92, 2005 **29**

Can statins inhibit HDAC?



Histone Deacetylase and Cancer



It was proposed that there are specific sites in the promotor region of a subset of genes (e.g., SP1 sites) that recruit the transcription factor complex (TFC) with HDAC, and finally lead to cell-growth arrest.

Marks *et al., Nature Rev. Cancer* **1:** 194-202 (2001)

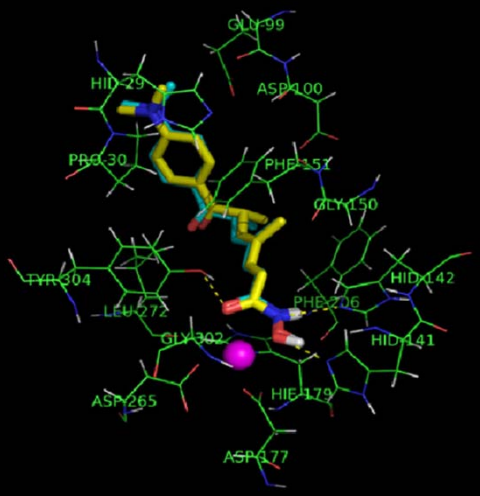
Validation of Docking Parameters

Structure: HDLP

Nature **401:** 188-193 (1999)

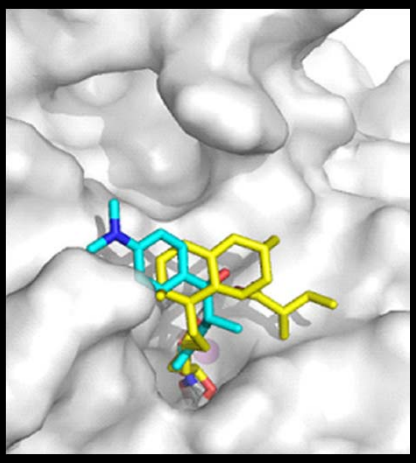
CPK: Experimental pose

Yellow: Docked pose



Lin *et al. Cancer Res.* **68:** 2375-2383 (2008)

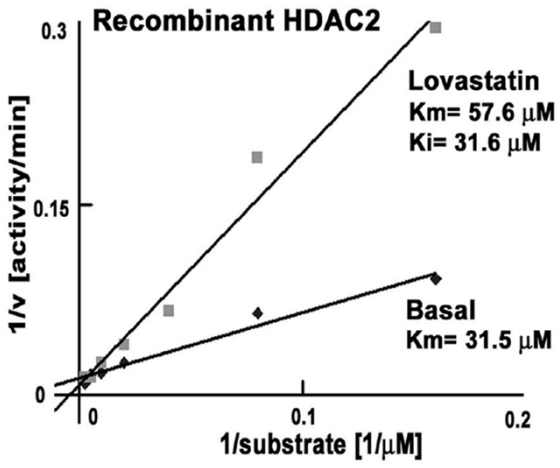
Lovastatin and TSA both can bind competitively at the catalytic site



Cyan: TSA
Yellow: Lovastatin

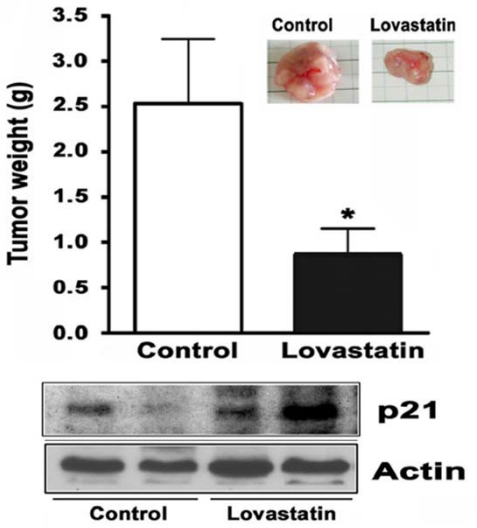
Lin *et al. Cancer Res.* **68:** 2375-2383 (2008)

Lineweaver-Burk plot of enzymatic assay confirms nearly competitive inhibition of lovastatin



Lin *et al. Cancer Res.* **68:** 2375-2383 (2008)

Lovastatin reduced the tumor size and weight after 45 days



Lin *et al. Cancer Res.* **68:** 2375-2383 (2008)

Why don't we increase statins' activity for HDAC inhibition?

Cocktail drugs may work, but there are other problems

Available online at www.sciencedirect.com
ScienceDirect
Biochemical and Biophysical Research Communications 365 (2008) 386–392
BBRC
www.elsevier.com/locate/ybbrc

Synergistic induction of apoptosis by HMG-CoA reductase inhibitor and histone deacetylases inhibitor in HeLa cells

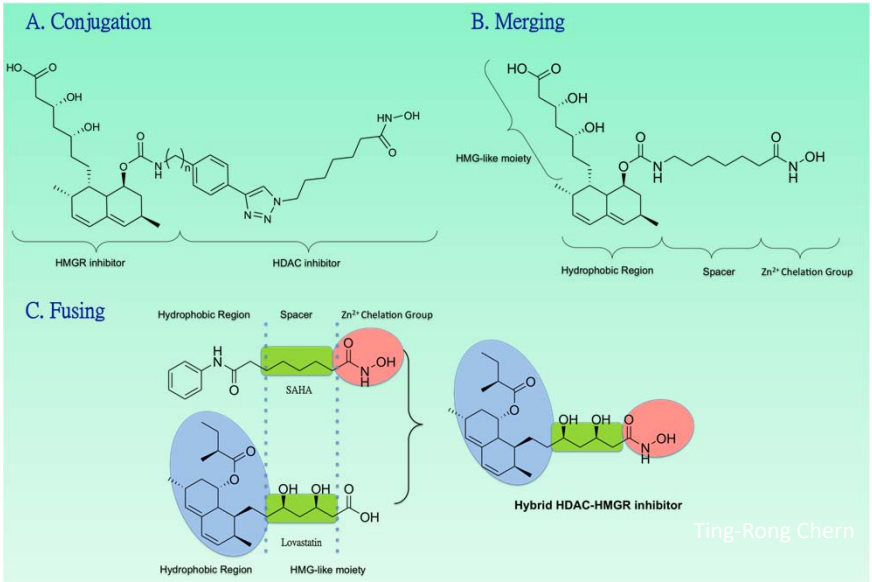
Yehua Gan [a,b,*], Jian Wang [b], Joseph Coselli [b], Xing Li Wang [b,*]

[a] Laboratory of Molecular Biology and Center for TMJ Disorders, Peking University School and Hospital of Stomatology, 22 Zhongguancun Nandajie, Beijing 100081, PR China
[b] Division of Cardiothoracic Surgery, Michael E. DeBakey Department of Surgery, Texas Heart Institute at St. Luke's Episcopal Hospital, MS NAB 2010, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA

Received 31 October 2007
Available online 19 November 2007

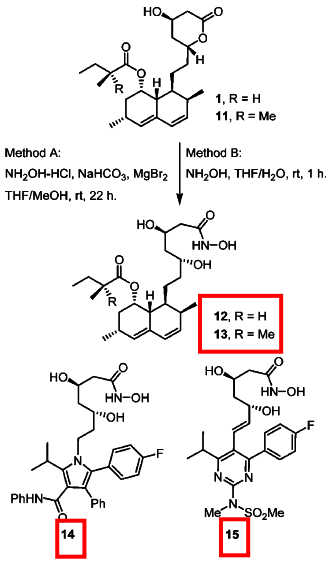
- Complex pharmacokinetics
- Unpredictable drug–drug interaction
- Formulation problems due to different solubilities of individual drugs.

Design Strategy



Chen, *et al. J. Med. Chem.* 56, 3646-3655 (2013) **38**

Synthesis of HDAC-HMGR Dual Action Compounds



Prof. Jim-Ming Fang
Department of Chemistry
National Taiwan University

Dr. Jih-Bin Chen
Department of Chemistry
National Taiwan University

Chen, *et al. J. Med. Chem.* 56, 3646-3655 (2013)

Inhibitory Activity (IC_{50}) against HMGR and HDACs

Professor Ching-Chow Chen

Tzu-Tang Wei

compd	IC_{50}[a] (nM)			
	HMGR	HDAC1	HDAC2	HDAC6
lovastatin	29.5 ± 3.5	11911 ± 681	25933 ± 651	16285 ± 1575
atorvastatin	12.9 ± 1.3	11619 ± 382	22547 ± 1618	14466 ± 567
SAHA	>10000	20.9 ± 7.1	100.9 ± 10.0	19.4 ± 6.0
6a	36.5 ± 5.3	159.0 ± 8.4	463.3 ± 28.0	127.4 ± 21.5
6b	53.8 ± 5.2	124.7 ± 6.3	881.8 ± 9.7	34.0 ± 4.3
10	54.1 ± 2.1	122.0 ± 12.7	657.7 ± 21.1	139.7 ± 5.7
12	16.8 ± 1.9	64.8 ± 5.4	468.3 ± 27.2	51.0 ± 6.1
13	13.1 ± 1.5	63.4 ± 4.5	414.2 ± 15.5	69.5 ± 4.1
14	12.3 ± 2.7	122.9 ± 9.5	467.2 ± 19.0	86.6 ± 6.0
15	43.7 ± 1.6	125.2 ± 7.1	600.1 ± 34.0	133.3 ± 5.5

[a]Data are shown as the mean ± SD of three experiments.

Chen, *et al. J. Med. Chem.* 56, 3646-3655 (2013)

Inhibition on the Growth of Cancer, but Not on Normal Cells

compd	IC_{50}[a] (μM) A549	MEF	HS68	SI[b] A549/MEF	A549/HS68
lovastatin	11.4 ± 6.3	35.0 ± 5.9	23.2 ± 3.5	3.1	2.0
simvastatin	16.3 ± 0.1	36.7 ± 4.4	26.4 ± 2.1	2.3	1.6
atorvastatin	8.7 ± 1.1	30.7 ± 3.2	22.7 ± 2.0	3.5	2.6
SAHA	4.5 ± 0.8	4.4 ± 1.4	4.6 ± 0.7	1.0	1.0
12	18.2 ± 3.4	>100	>100	>5.6	>5.6
13	20.0 ± 3.1	>100	>100	>5.0	>5.0
14	17.5 ± 4.7	>100	>100	>5.7	>5.7

[a]Cells were treated with the indicated doses of test compounds for 72 h, and the cell viability was measured by MTT assay. Data are shown as the mean ± SD of three experiments. A549 = human lung cancer cells, MEF = normal mouse fibroblast cells, and HS68 = normal human fibroblast cells. [b]The selectivity index is the ratio of IC_{50} on a cancer cell to IC_{50} on a normal cell.

Chen, *et al. J. Med. Chem.* 56, 3646-3655 (2013)

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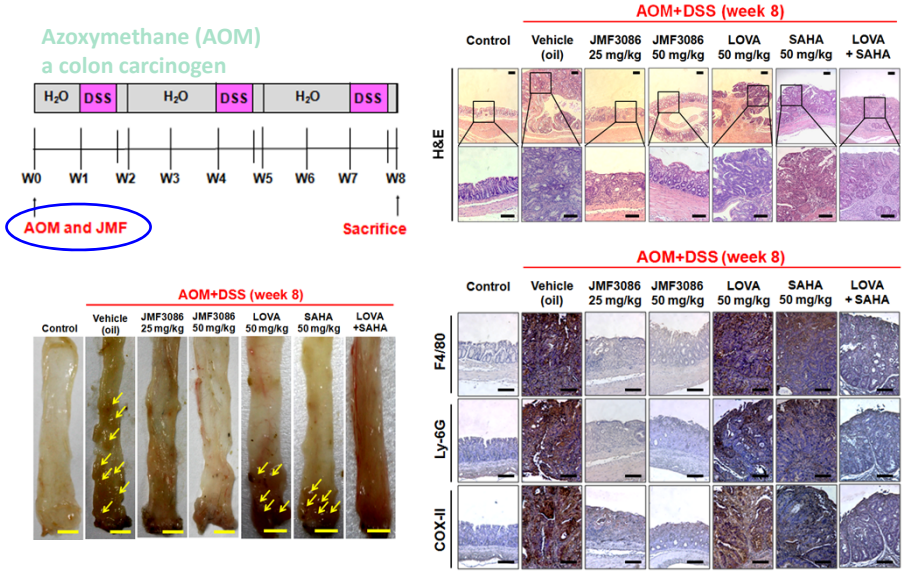
REVIEWS

Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders

Katrina J. Falkenberg[1] and Ricky W. Johnstone[1,2]

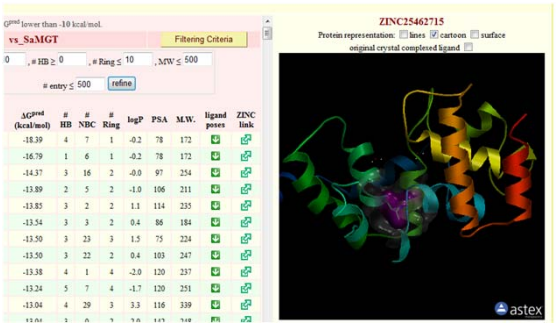
Abstract | Epigenetic aberrations, which are recognized as key drivers of several human diseases, are often caused by genetic defects that result in functional deregulation of epigenetic proteins, their altered expression and/or their atypical recruitment to certain gene promoters. Importantly, epigenetic changes are reversible, and epigenetic enzymes and regulatory proteins can be targeted using small molecules. This Review discusses the role of altered expression and/or function of one class of epigenetic regulators — histone deacetylases (HDACs) — and their role in cancer, neurological diseases and immune disorders. We highlight the development of small-molecule HDAC inhibitors and their use in the laboratory, in preclinical models and in the clinic.

JMF3086 prevents AOM/DSS-induced CRC



Wei, *et al. Clin. Cancer. Res.* 22, 4158-4169 (2016)

Virtual screen of large chemical library in search of new drug candidates

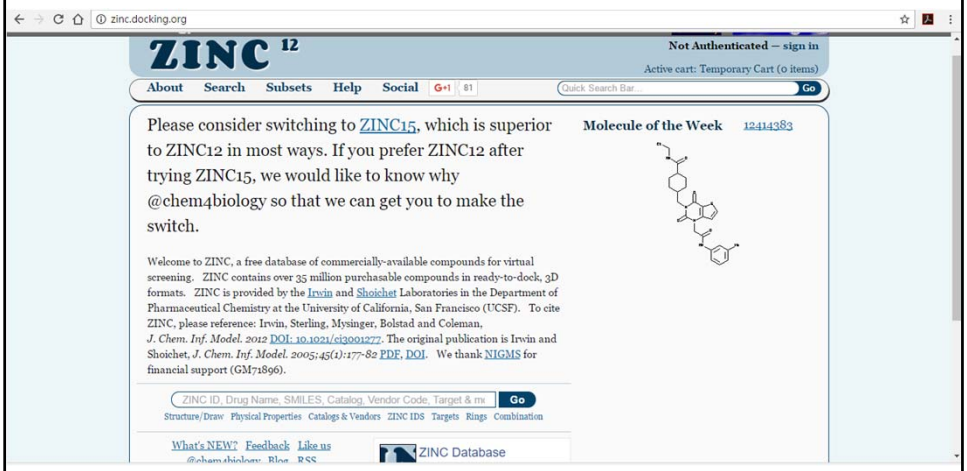


Virtual screening results in the search of new generation antibiotics. The hits are ranked according to the predicted binding affinity.

By using 1056 cores, we are able to screen the entire over 10,000,000 compound library within 1 or 2 weeks. It will take more than 1 year for a typical lab which owns less than 100 cores.

Such application is especially useful when time is a critical issue, e.g., finding effective compounds against H5N1, H7N9, SARS, and other infectious disease.

In general, for new drug targets of any disease without any known effective therapeutic agents, virtual screen is an effective approach to find out drug candidates.



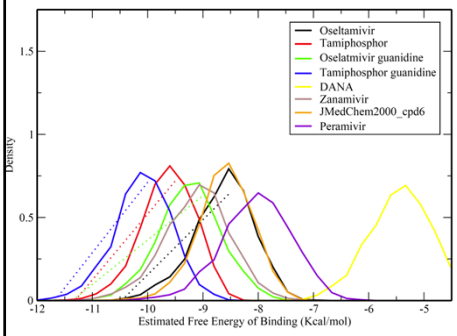
The Extended Relaxed Complex Scheme

- Multivalent drug design in a building-block fashion
- Computational analogue of "SAR by NMR"

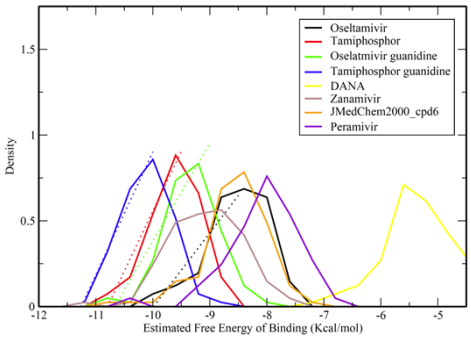
1. Accommodating receptor flexibility by molecular dynamics
2. Assigning compound molecular properties using rigorous quantum chemical approaches
3. Rapid docking using efficient global search algorithms.
4. Ranking compounds by *binding free energy spectra*, instead of single binding free energy.
5. Molecular dynamics simulations of complexes with top ranked compounds.
6. Automatic free energy calculation with the double decoupling method or with the adaptive umbrella sampling scheme.

Lin *et al. J. Am. Chem. Soc.*, **124**, 5632 (2002) , Lin *et al. Biopolymers*, **68**, 47 (2003)
Amaro *et al. J. Comput-Aid Mol. Des*, **22**, 639 (2008)
Lin, *Curr. Top. Med. Chem.* **11:** 171 (2011) , Lin, *Biopolymers*, **105**, 2 (2016)

Binding free energy spectra with affinity propagation clustering



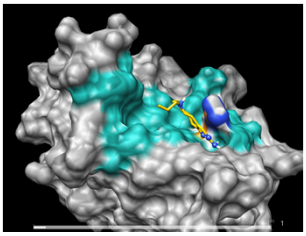
RCS binding spectra from 15-ns explicit solvent MD 3000 snapshots, no clustering



RCS binding spectra from AP-clustered 100 MD snapshots

Frey *et al. Science* **315**, 972,(2007)

ZINC0000XX41



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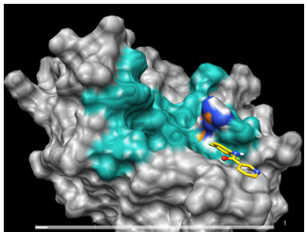
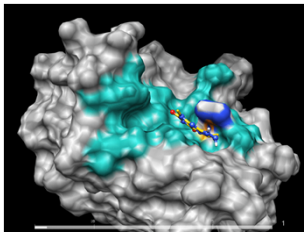


ZINC0003XX09



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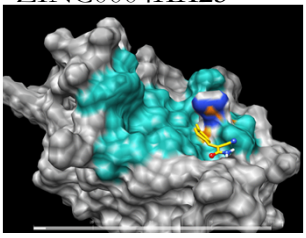
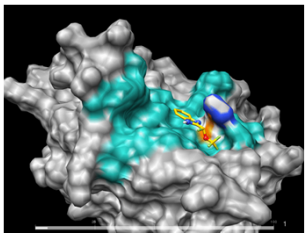


ZINC0004XX47



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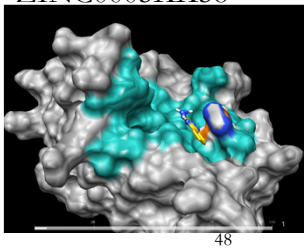

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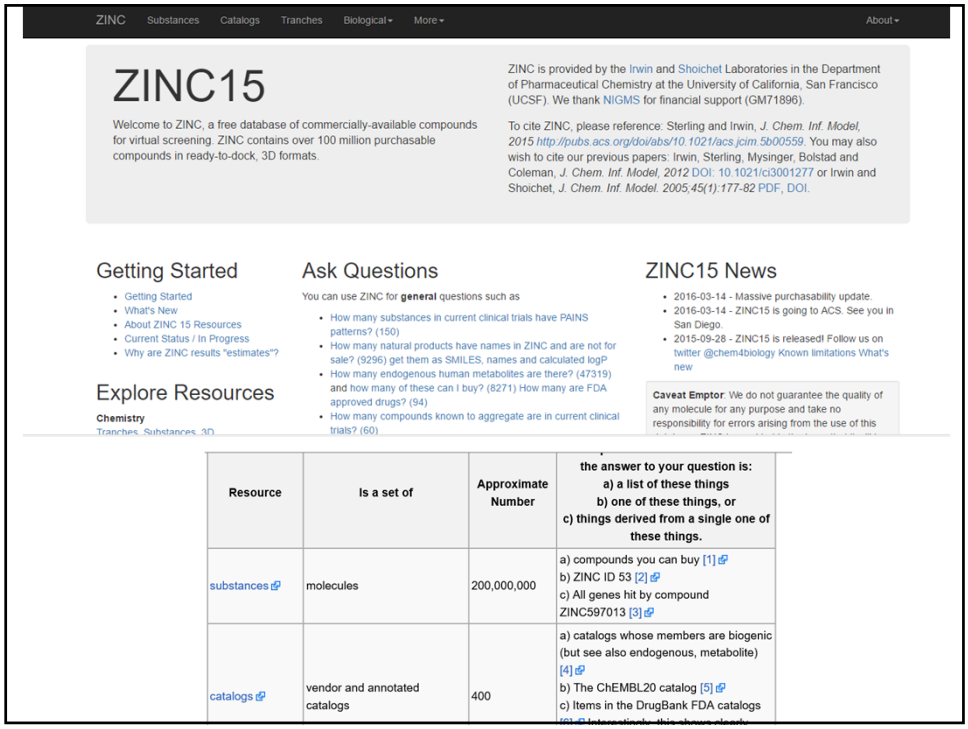

ZINC Substances Catalogs Tranches Biological More About

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Welcome to ZINC, a free database of commercially-available compounds for virtual screening. ZINC contains over 100 million purchasable compounds in ready-to-dock, 3D formats.

ZINC is provided by the Irwin and Shoichet Laboratories in the Department of Pharmaceutical Chemistry at the University of California, San Francisco (UCSF). We thank NIGMS for financial support (GM71896).

To cite ZINC, please reference: Sterling and Irwin, *J. Chem. Inf. Model, 2015* http://pubs.acs.org/doi/abs/10.1021/acs.jcim.5b00559. You may also wish to cite our previous papers: Irwin, Sterling, Mysinger, Bolstad and Coleman, *J. Chem. Inf. Model, 2012* DOI: 10.1021/ci3001277 or Irwin and Shoichet, *J. Chem. Inf. Model. 2005;45(1):177-82* PDF, DOI.

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- Getting Started
- What's New
- About ZINC 15 Resources
- Current Status / In Progress
- Why are ZINC results "estimates"?

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Chemistry
Tranches, Substances, 3D

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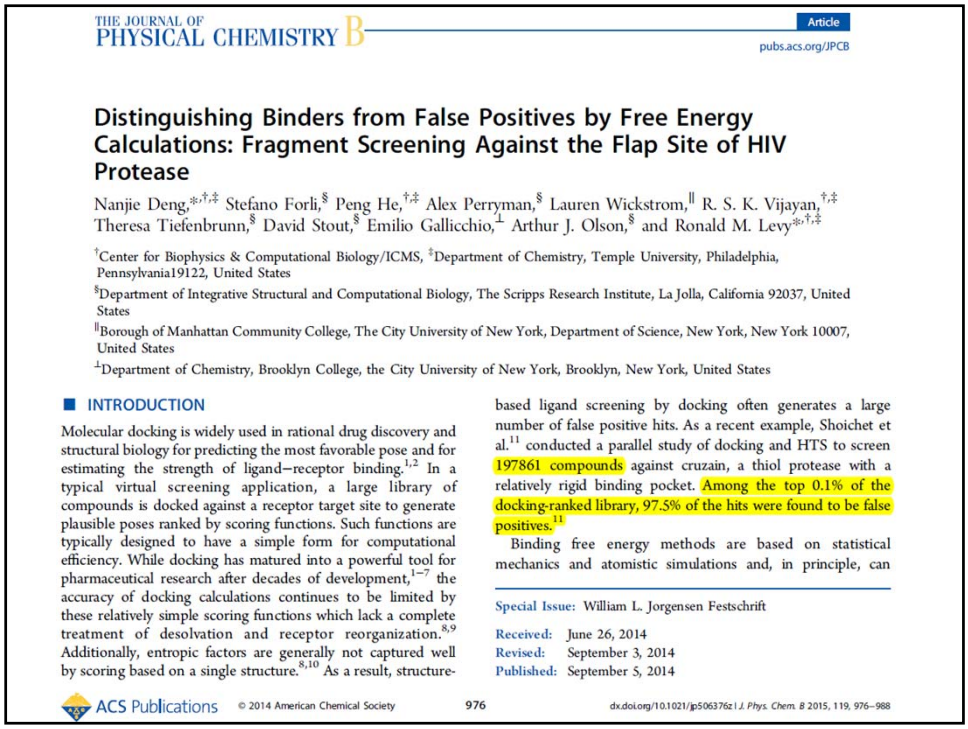
- How many natural products have names in ZINC and are not for sale? (9296) get them as SMILES, names and calculated logP
- How many endogenous human metabolites are there? (47319) and how many of these can I buy? (8271) How many are FDA approved drugs? (94)
- How many compounds known to aggregate are in current clinical trials? (60)

ZINC15 News

- 2016-03-14 - Massive purchasability update.
- 2016-03-14 - ZINC15 is going to ACS. See you in San Diego.
- 2015-09-28 - ZINC15 is released! Follow us on twitter @chem4biology Known limitations What's new

Caveat Emptor: We do not guarantee the quality of any molecule for any purpose and take no responsibility for errors arising from the use of this

Resource	Is a set of	Approximate Number	the answer to your question is: a) a list of these things b) one of these things, or c) things derived from a single one of these things.
substances	molecules	200,000,000	a) compounds you can buy [1] b) ZINC ID 53 [2] c) All genes hit by compound ZINC597013 [3]
catalogs	vendor and annotated catalogs	400	a) catalogs whose members are biogenic (but see also endogenous, metabolite) [4] b) The ChEMBL20 catalog [5] c) Items in the DrugBank FDA catalogs



THE JOURNAL OF PHYSICAL CHEMISTRY B

Article

pubs.acs.org/JPCB

Distinguishing Binders from False Positives by Free Energy Calculations: Fragment Screening Against the Flap Site of HIV Protease

Nanjie Deng,*[,†,‡] Stefano Forli,[§] Peng He,[†,‡] Alex Perryman,[§] Lauren Wickstrom,[∥] R. S. K. Vijayan,[†,‡] Theresa Tiefenbrunn,[§] David Stout,[§] Emilio Gallicchio,[⊥] Arthur J. Olson,[§] and Ronald M. Levy*[,†,‡]

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[⊥]Department of Chemistry, Brooklyn College, the City University of New York, Brooklyn, New York, United States

INTRODUCTION

Molecular docking is widely used in rational drug discovery and structural biology for predicting the most favorable pose and for estimating the strength of ligand−receptor binding.[1,2] In a typical virtual screening application, a large library of compounds is docked against a receptor target site to generate plausible poses ranked by scoring functions. Such functions are typically designed to have a simple form for computational efficiency. While docking has matured into a powerful tool for pharmaceutical research after decades of development,[1−7] the accuracy of docking calculations continues to be limited by these relatively simple scoring functions which lack a complete treatment of desolvation and receptor reorganization.[8,9] Additionally, entropic factors are generally not captured well by scoring based on a single structure.[8,10] As a result, structure-based ligand screening by docking often generates a large number of false positive hits. As a recent example, Shoichet et al.[11] conducted a parallel study of docking and HTS to screen 197861 compounds against cruzain, a thiol protease with a relatively rigid binding pocket. Among the top 0.1% of the docking-ranked library, 97.5% of the hits were found to be false positives.[11]

Binding free energy methods are based on statistical mechanics and atomistic simulations and, in principle, can

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Published: September 5, 2014

dx.doi.org/10.1021/jp506376z | J. Phys. Chem. B 2015, 119, 976−988

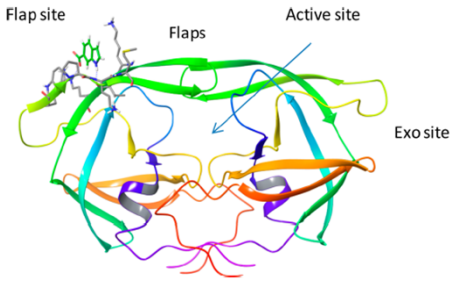


Figure 1. Crystal structure of HIV PR (pdb id: 3kfr) with its flap site occupied by the ligand 1F1 shown in green stick. The active site ligand is removed from the figure for clarity.

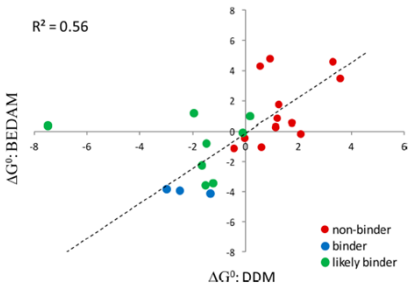
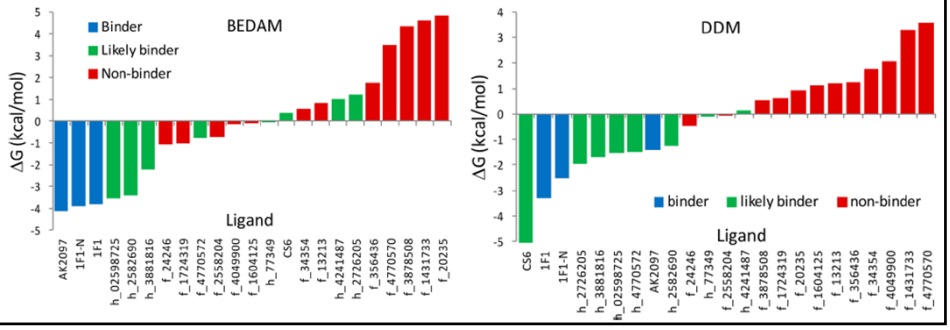


Figure 3. Correspondence between the binding free energies computed using BEDAM and DDM. Unit in kcal/mol. The ligand CS6 is excluded from the linear regression.



Assessment with a small and diverse external set

Performance of the robust AutoDock4 scoring functions and 17 scoring functions assessed in Cheng *et al*. on the 195 set of PDBbind v2007

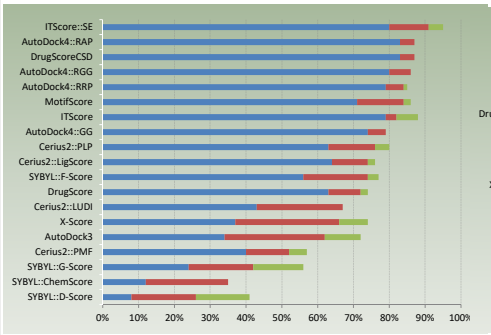
(Cheng, T.J. *et al*., *J. Chem. Inf. Model.*2009, 49, 1079-1093)

scoring function	N_{train}	N_{test}	R_p	R_s	SD
AutoDock4^{RGG}	147	195	0.654	0.696	1.81
AutoDock4^{RAP}	147	195	0.643	0.665	1.83
AutoDock4^{RRP}	147	194	0.615	0.634	1.88
original AutoDock4^{GG}	187	195	0.615	0.669	1.88
X-Score::HMScore			0.649	0.701	1.82
DrugScore^{CSD}			0.589	0.649	1.93
SYBYL::ChemScore			0.622	0.668	1.87
DS::PLP1			0.529	0.569	2.03
GOLD::ASP			0.518	0.558	2.04
SYBYL::G-Score			0.522	0.579	2.03
DS::LUDI3			0.477	0.478	2.10
DS::LigScore2			0.479	0.505	2.10
GlideScore-XP			0.555	0.556	2.01
DS::PMF			0.471	0.482	2.11
GOLD::ChemScore			0.528	0.553	2.05
by NHA			0.431	0.517	2.15
SYBYL::D-Score			0.388	0.443	2.20
DS::Jain			0.339	0.362	2.26
GOLD::GoldScore			0.329	0.386	2.26
SYBYL::PMF-Score			0.235	0.235	2.31
SYBYL::F-Score			0.238	0.208	2.31

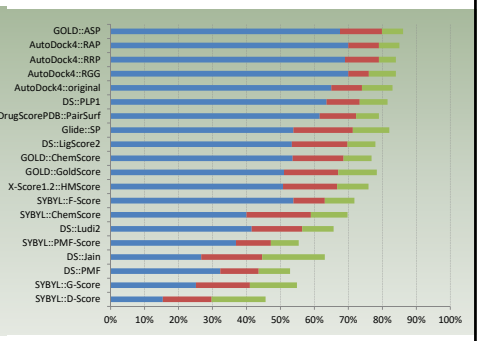
52

Wang *et al*., *J. Chem. Inf. Model.* **51:** 2528-2537 (2011)

Assessment of binding pose prediction with external decoys



Comparison of the success rates of AutoDock4 scoring functions and other scoring functions on the decoys set of 100 complexes (Wang, R.X. et al., *J. Med. Chem.* 2003, 46, 2287-2303)



Comparison of the success rates of AutoDock4 scoring functions and other scoring functions on the decoys set of 195 complexes. (Cheng, T.J. *et al.*, *J. Chem. Inf. Model.* 2009, 49, 1079-1093)

blue: < 1 Å
red: < 2 Å
green: < 3 Å

53

Wang *et al.*, *J. Chem. Inf. Model.* **51:** 2528-2537 (2011)

Biophysical Journal Volume 72 March 1997 1047–1069

The Statistical-Thermodynamic Basis for Computation of Binding Affinities: A Critical Review

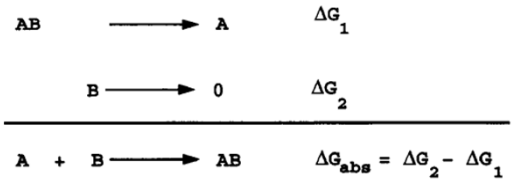
Michael K. Gilson,* James A. Given,* Bruce L. Bush,# and J. Andrew McCammon§
*Center for Advanced Research in Biotechnology, National Institute of Standards and Technology, Rockville, Maryland 20850-3479; #Department of Molecular Design and Diversity, Merck Research Laboratories, Rahway, New Jersey 07065; and §Departments of Chemistry and Biochemistry, and Pharmacology, University of California at San Diego, La Jolla, California 92093-0365 USA

ABSTRACT Although the statistical thermodynamics of noncovalent binding has been considered in a number of theoretical papers, few methods of computing binding affinities are derived explicitly from this underlying theory. This has contributed to uncertainty and controversy in certain areas. This article therefore reviews and extends the connections of some important computational methods with the underlying statistical thermodynamics. A derivation of the standard free energy of binding forms the basis of this review. This derivation should be useful in formulating novel computational methods for predicting binding affinities. It also permits several important points to be established. For example, it is found that the double-annihilation method of computing binding energy does not yield the standard free energy of binding, but can be modified to yield this quantity. The derivation also makes it possible to define clearly the changes in translational, rotational, configurational, and solvent entropy upon binding. It is argued that molecular mass has a negligible effect upon the standard free energy of binding for biomolecular systems, and that the cratic entropy defined by Gurney is not a useful concept. In addition, the use of continuum models of the solvent in binding calculations is reviewed, and a formalism is presented for incorporating a limited number of solvent molecules explicitly.

The Double-Decoupling Method

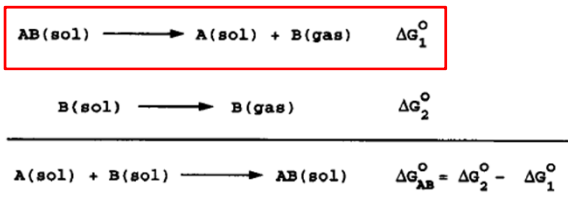
Double annihilation method

J. Chem. Phys. **89:** 3742-3746 (1988)



Double decoupling method

Biophys. J. **72:** 1047-1069 (1997)



Free energy for transferring the ligand from the receptor to the gas phase

$$\Delta G_1^{\circ} = -RT \ln\left(\frac{8\pi^2}{C^{\circ}} \frac{\sigma_{AB}}{\sigma_A \sigma_B} \frac{Z_{N,A} Z_{0,B}}{Z_{N,AB}}\right) + P^{\circ}(\bar{V}_A - \bar{V}_{AB})$$

σ: the symmetry number of the molecule

C°: the standard concentration

$$Z_{0,B} = \int e^{-\beta U(\mathbf{r}_B)} d\mathbf{r}_B$$

$$Z_{N,A} = \int\int e^{-\beta U(\mathbf{r}_A, \mathbf{r}_S)} d\mathbf{r}_A d\mathbf{r}_S$$

S: solvent

$$Z_{N,0} = \int e^{-\beta U(\mathbf{r}_S)} d\mathbf{r}_S$$

Computing the transfer free energy of the ligand from the receptor to the gas phase

$$\Delta G_1^{\circ} = \int \left\langle \frac{\partial U(\lambda, r_A, r_B, \zeta_B, r_S)}{\partial \lambda} \right\rangle_{\lambda, I(\zeta)=1} d\lambda$$

$$-RT \ln\left(\frac{\sigma_{AB}}{\sigma_A \sigma_B}\right)$$

The ligand is always constrained to occupy a region in the binding site.

$$+RT \ln\left(C^{\circ} V_I\right) + RT \ln\left(\xi_I / 8\pi^2\right)$$

$$+P^{\circ}\left(\bar{V}_A - \bar{V}_{AB}\right)$$

V_I: accessible positional volume of the ligand in the bound state

ξ_I: accessible orientational volume of the ligand in the bound state

These two terms correct the thermodynamic integration for the standard state.

Thermodynamic Integration

$$\Delta A = \int_0^1 \frac{\partial A(\lambda)}{\partial \lambda} d\lambda$$

$$A(\lambda) = -k_B T \ln Q(\lambda)$$

$$\Delta A = -k_B T \int_0^1 \left[\frac{\partial \ln Q(\lambda)}{\partial \lambda}\right] d\lambda = \int_0^1 \frac{-k_B T}{Q(\lambda)} \frac{\partial Q(\lambda)}{\partial \lambda} d\lambda$$

$$Q_{NVT}(\lambda) = \frac{1}{N!}\frac{1}{h^{3N}} \iint d\mathbf{p}^N d\mathbf{r}^N e^{-\beta \mathcal{H}(\mathbf{p}^N, \mathbf{r}^N, \lambda)}$$

$$\frac{\partial Q_{NVT}(\lambda)}{\partial \lambda} = \frac{1}{N!}\frac{1}{h^{3N}} \iint d\mathbf{p}^N d\mathbf{r}^N \frac{\partial e^{-\beta \mathcal{H}(\mathbf{p}^N, \mathbf{r}^N, \lambda)}}{\partial \lambda}$$

$$\frac{\partial Q_{NVT}(\lambda)}{\partial \lambda} = \frac{-1}{N!}\frac{1}{h^{3N}}\frac{1}{k_B T} \iint d\mathbf{p}^N d\mathbf{r}^N \frac{\partial \mathcal{H}(\mathbf{p}^N, \mathbf{r}^N, \lambda)}{\partial \lambda} e^{-\beta \mathcal{H}(\mathbf{p}^N, \mathbf{r}^N, \lambda)}$$

$$\frac{\partial A(\lambda)}{\partial \lambda} = \frac{1}{N!}\frac{1}{h^{3N}}\frac{1}{Q(\lambda)} \iint d\mathbf{p}^N d\mathbf{r}^N \frac{\partial \mathcal{H}(\mathbf{p}^N, \mathbf{r}^N, \lambda)}{\partial \lambda} e^{-\beta \mathcal{H}(\mathbf{p}^N, \mathbf{r}^N)}$$

$$= \iint d\mathbf{p}^N d\mathbf{r}^N \frac{\partial \mathcal{H}(\mathbf{p}^N, \mathbf{r}^N, \lambda)}{\partial \lambda} \frac{e^{-\beta \mathcal{H}(\mathbf{p}^N, \mathbf{r}^N, \lambda)}}{Q(\lambda)}$$

$$= \left\langle \frac{\partial \mathcal{H}(\mathbf{p}^N, \mathbf{r}^N, \lambda)}{\partial \lambda} \right\rangle_{NVT, \lambda}$$

$$\Delta A = \int_0^1 \left\langle \frac{\partial \mathcal{H}(\mathbf{p}^N, \mathbf{r}^N, \lambda)}{\partial \lambda} \right\rangle_{NVT, \lambda} d\lambda$$

$$= \int_0^1 \left\langle \frac{\partial \mathcal{V}(\mathbf{r}^N, \lambda)}{\partial \lambda} \right\rangle_{NVT, \lambda} d\lambda$$

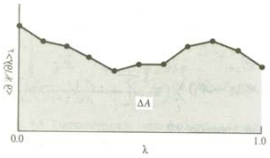


Fig. 9.4 Calculation of free energy differences by thermodynamic integration.

$$\Delta A = \int_0^1 \left\langle \frac{\partial \mathcal{V}(\mathbf{r}^N, \lambda)}{\partial \lambda} \right\rangle_{NVT, \lambda} d\lambda$$

$$\cong \sum_{i=1}^{n} w_i \left\langle \frac{\partial \mathcal{V}(\mathbf{r}^N, \lambda)}{\partial \lambda} \right\rangle_{NVT, \lambda_i}$$

$$\mathcal{V}(\lambda) = (1-\lambda)^k \mathcal{V}(X) + [1-(1-\lambda)^k]\mathcal{V}(Y$$

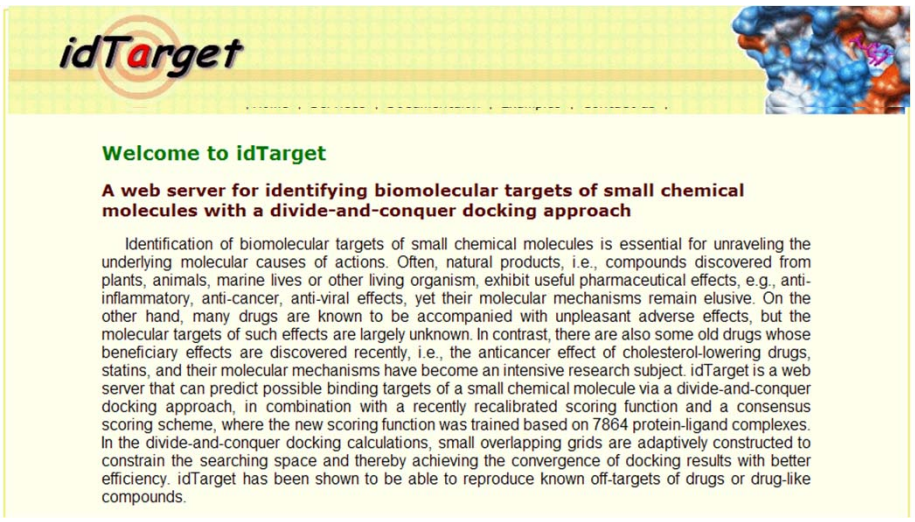
Abcissas and weights for Gaussian integration

n	λ_i^a	λ_i^b	w_i
1	0.50000		1.00000
2	0.21132	0.78867	0.50000
3	0.11270	0.88729	0.27777
	0.50000		0.44444
5	0.04691	0.95308	0.11846
	0.23076	0.76923	0.23931
	0.50000		0.28444
7	0.02544	0.97455	0.06474
	0.12923	0.87076	0.13985
	0.29707	0.70292	0.19091
	0.50000		0.20897
9	0.01592	0.98408	0.04064
	0.08198	0.91802	0.09032
	0.19331	0.80669	0.13031
	0.33787	0.66213	0.15617
	0.50000		0.16512
12	0.00922	0.99078	0.02359
	0.04794	0.95206	0.05347
	0.11505	0.88495	0.08004
	0.20634	0.79366	0.10158
	0.31608	0.68392	0.11675
	0.43738	0.56262	0.12457

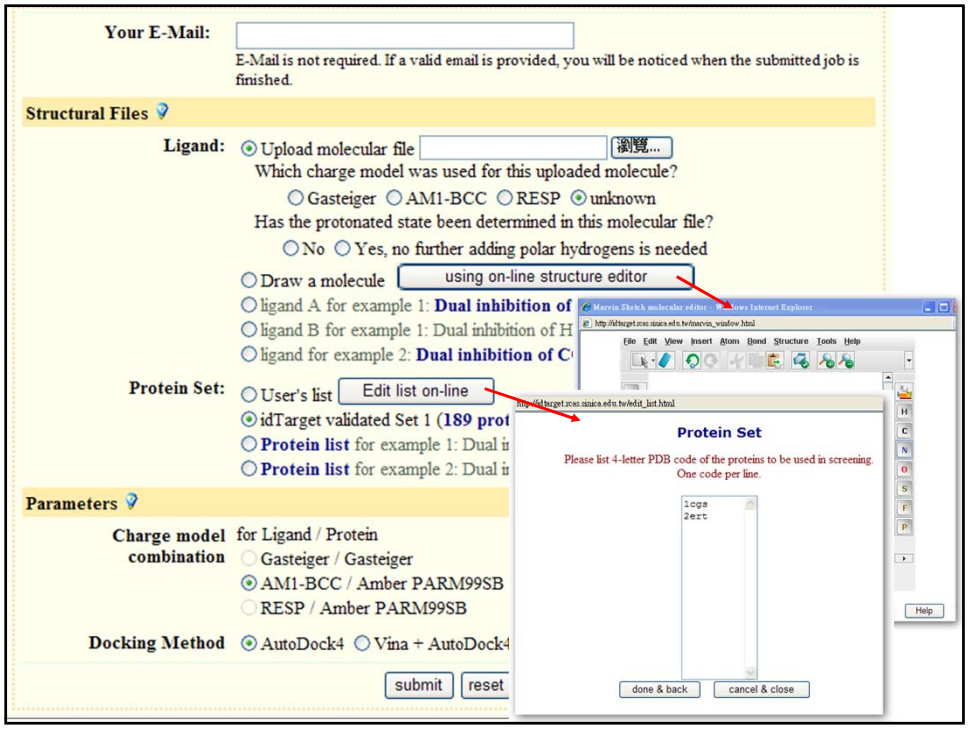
$$\lambda_1 = 0.04691, \lambda_2 = 0.23076, \lambda_3 = 0.5, \lambda_4 = 0.76923, \lambda_5 = 0.95308$$
$$w_1 = 0.11846, w_2 = 0.23931, w_3 = 0.28444, w_4 = w_2, w_5 = w_1$$

idTarget: Identification of Biomolecular Targets of Small Chemical Molecules

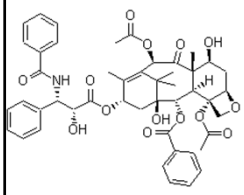
http://idtarget.rcas.sinica.edu.tw/

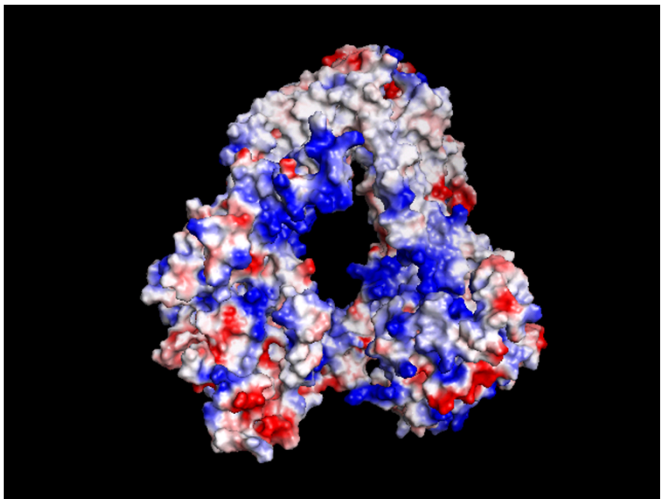


Wang *et al. Nucleic Acids Research* 40: W393-W399 (2012)

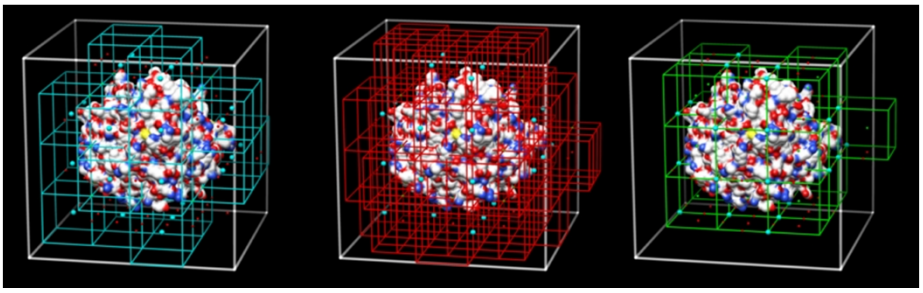


Some proteins could be very large : the case of P-glycoprotein with Paclitaxel (Taxol)



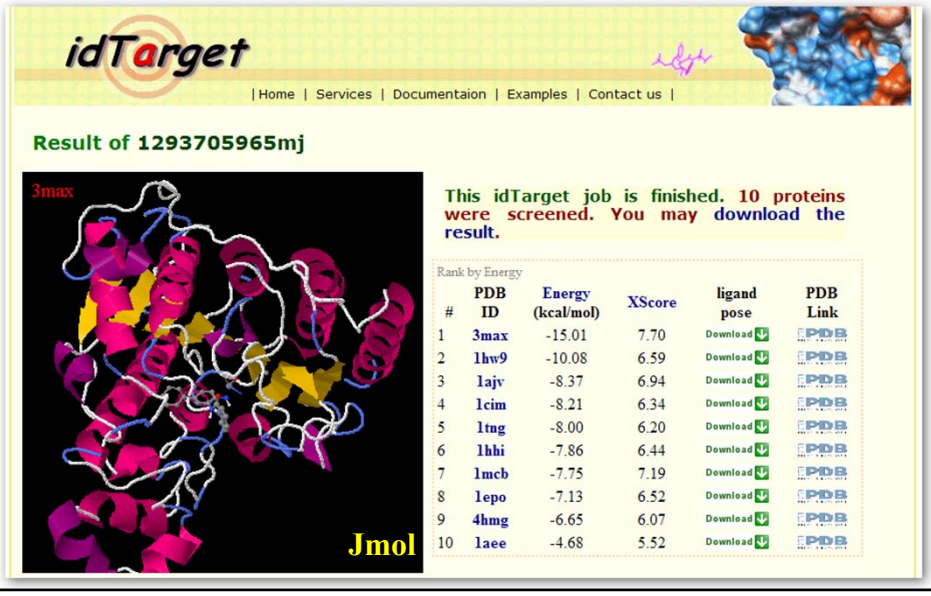


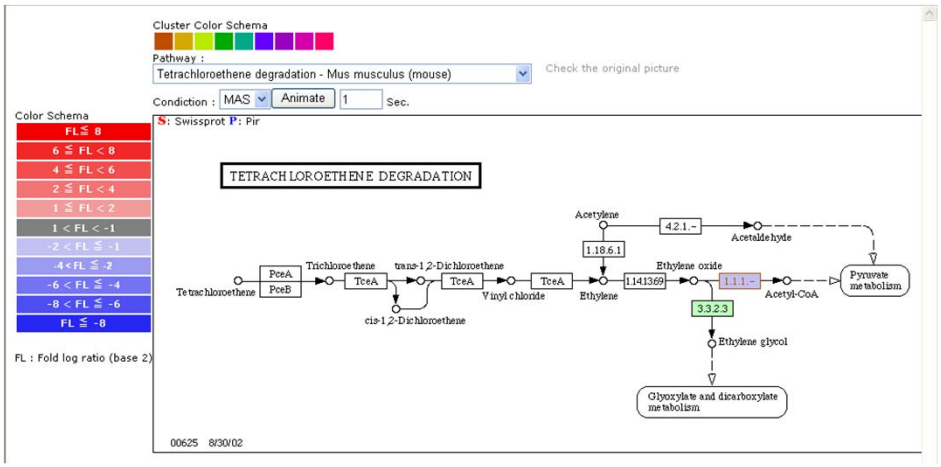
Divide-and-Conquer Docking

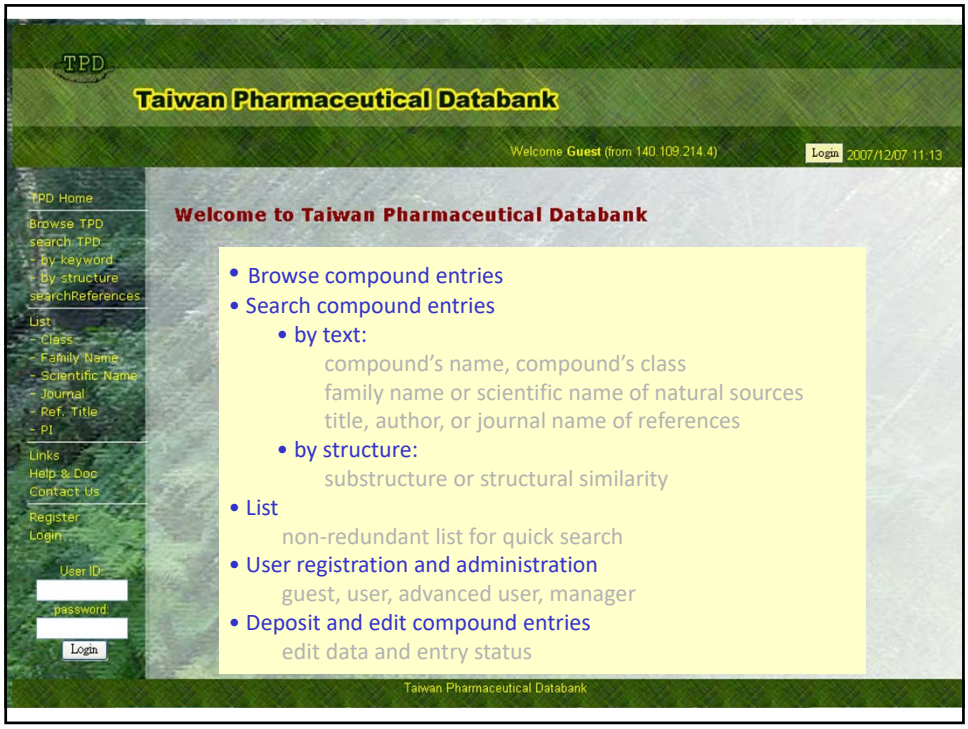


Firstly, a box with 10Å to each boundary of the receptor was drawn (white). This big box was subsequently divided into smaller boxes (cyan; the cyan dots are grid box centers) where the size box was dynamically determined according to the size of query ligand. The overlapped boxes (red and green dots are the grid box centers of overlapped boxes) should be taken into count. If a grid box is far away the receptor (no atom is within 1.42*length of the grid box to the center), it will be eliminated to reduce the computational cost. Finally, the boxes shown above are retained.

Example: Off-target screening for the inhibitor in 3MAX



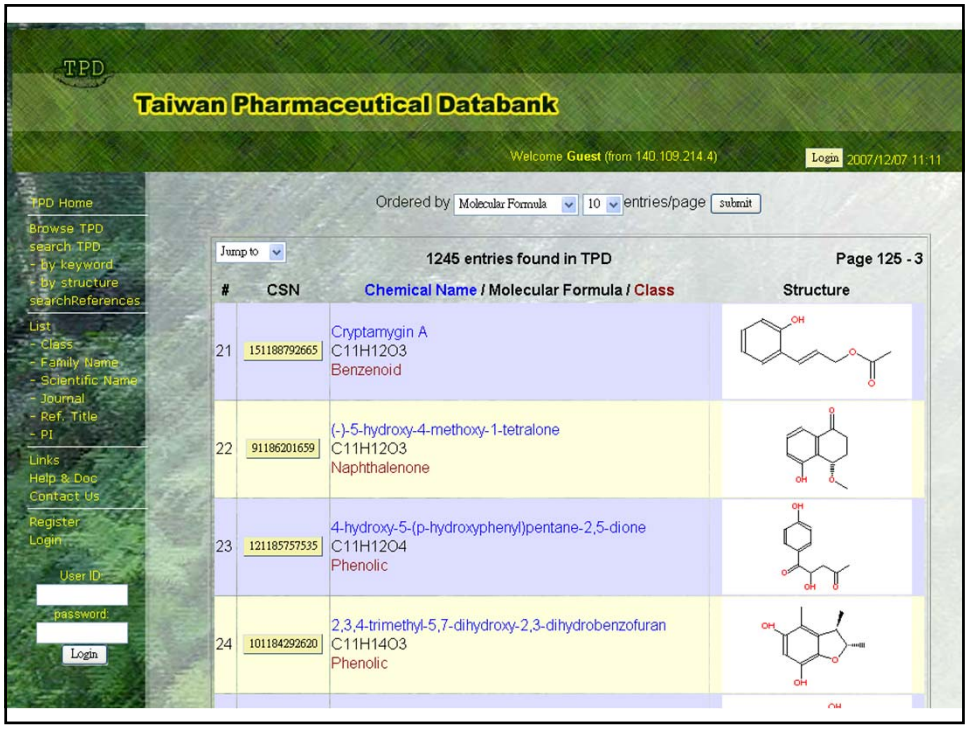




Taiwan Pharmaceutical Databank

The information for each compound entry includes:

- Structure and Nomenclature
  structure (still image and interactive presentation), compound's class
  chemical name, IUPAC name, synonym, CAS Registry Number
- Physical and Chemical Properties
  molecular formula, molecular weight, melting point, solubility, store condition
- Biological Activity and Toxicity
  text and/or image
- Spectrum Analysis
  text and/or image
- Natural Sources
  family name, scientific name, part used, collected time and location
- Amount in the lab
- References
  reference information and links to PubMed and/or DOI if available
- External links
  Chemical Structure Lookup Service, ChemSpider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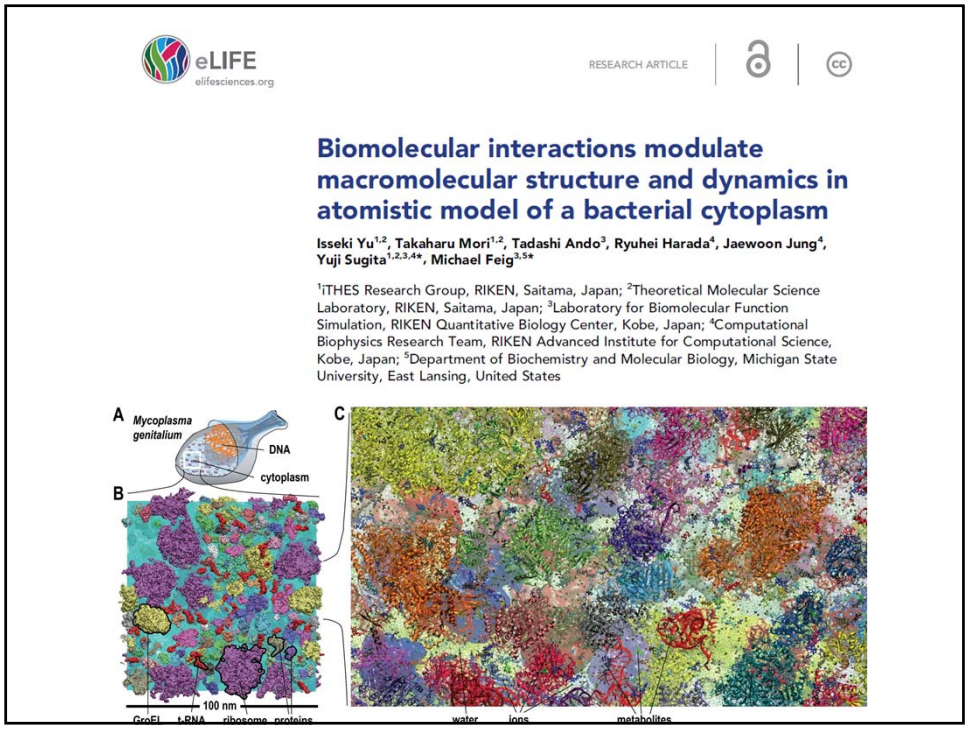
1245 entries found in TPD
Page 125 - 3
CSN Chemical Name / Molecular Formula / Class Structure
21 151188792665 Cryptamygin A C11H12O3 Benzenoid
22 91186201659 (-)-5-hydroxy-4-methoxy-1-tetralone C11H12O3 Naphthalenone
23 121185757535 4-hydroxy-5-(p-hydroxyphenyl)pentane-2,5-dione C11H12O4 Phenolic
24 101184292620 2,3,4-trimethyl-5,7-dihydroxy-2,3-dihydrobenzofuran C11H14O3 Phenolic


eLIFE
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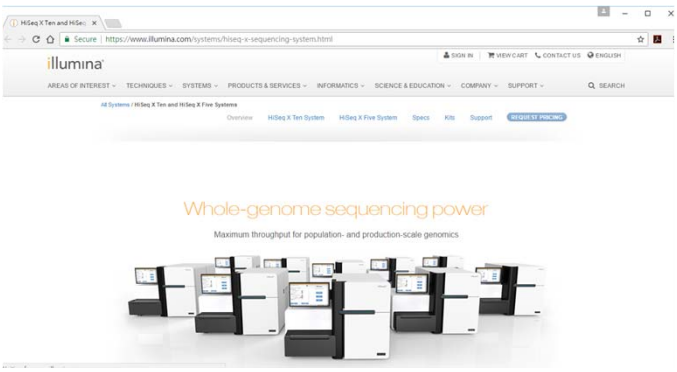
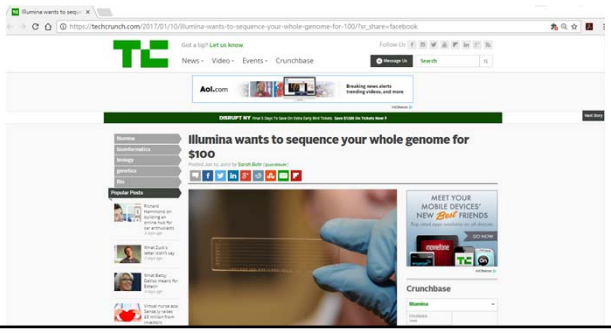
RESEARCH ARTICLE
Biomolecular interactions modulate macromolecular structure and dynamics in atomistic model of a bacterial cytoplasm
Isseki Yu[1,2], Takaharu Mori[1,2], Tadashi Ando[3], Ryuhei Harada[4], Jaewoon Jung[4], Yuji Sugita[1,2,3,4*], Michael Feig[3,5*]
[1]iTHES Research Group, RIKEN, Saitama, Japan; [2]Theoretical Molecular Science Laboratory, RIKEN, Saitama, Japan; [3]Laboratory for Biomolecular Function Simulation, RIKEN Quantitative Biology Center, Kobe, Japan; [4]Computational Biophysics Research Team, RIKEN Advanced Institute for Computational Science, Kobe, Japan; [5]Department of Biochemistry and Molecular Biology, Michigan State University, East Lansing, United States
A
Mycoplasma genitalium
DNA
cytoplasm
B
C
100 nm
GroEL
tRNA
ribosome
proteins
water
ions
metabolites





The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 21, 2008 VOL. 359 NO. 8

SLCO1B1 Variants and Statin-Induced Myopathy — A Genomewide Study

BACKGROUND

Lowering low-density lipoprotein cholesterol with statin therapy results in substantial reductions in cardiovascular events, and larger reductions in cholesterol may produce larger benefits. In rare cases, myopathy occurs in association with statin therapy, especially when the statins are administered at higher doses and with certain other medications.

METHODS

We carried out a genomewide association study using approximately 300,000 markers (and additional fine-mapping) in 85 subjects with definite or incipient myopathy and 90 controls, all of whom were taking 80 mg of simvastatin daily as part of a trial involving 12,000 participants. Replication was tested in a trial of 40 mg of simvastatin daily involving 20,000 participants.

N. Engl. J. Med. **359**: 789 -799 (2008)

Drug Induced Adverse Immunological Response

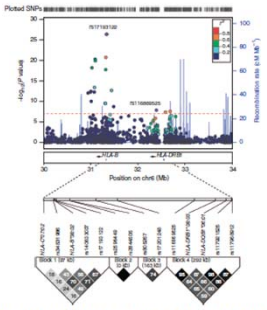


Figure 1 | Regional plot of association signals and LD patterns at the HLA region. (Top panel): The x axis shows chromosomal positions. The left *y* axis shows $-\log_{10}P$ values from the GWAS. Colours of the dots indicate the LD relations hip between rs17193122 or rs116869525 and their neighbouring SNPs in the 4-Mb region (30–32 Mb for rs17193122 and 32–34 Mb for rs116869525) based on our own data (969 samples). The red dashed line indicates the significance threshold (9.56×10^{-8}). The right *y* axis shows the recombination rate between SNPs calculated based on Asian-ancestry population data from the 1000 Genomes Project. (Bottom panel): LD map based on r^2 in the associated regions using genotype results from our own data (969 samples). We construct the plot using the Haploview software version 4.2, and r^2 (×100) values are depicted in the diamonds.

outliers (Supplementary Figs 3 and 4). We identified two independent association signals at the HLA region (Table 1, Figs 1 and 2, Supplementary Table 4). The first signal was represented by rs17193122 ($P_{\text{first stage}} = 8.18 \times 10^{-8}$, $P_{\text{second stage}} = 1.15 \times 10^{-24}$, $P_{\text{combined}} = 4.29 \times 10^{-27}$). The second association signal was represented by rs116869525 ($P_{\text{first stage}} = 3.88 \times 10^{-5}$, $P_{\text{second stage}} = 8.24 \times 10^{-5}$, $P_{\text{combined}} = 1.27 \times 10^{-8}$). In addition to the HLA region at chromosome 6p21, the results also revealed one non-HLA locus showing borderline GWAS association signals, represented by rs56343172 at chromosome 3q13 ($P_{\text{first stage}} = 1.71 \times 10^{-5}$, $P_{\text{second stage}} = 7.32 \times 10^{-4}$, $P_{\text{combined}} = 7.75 \times 10^{-8}$).

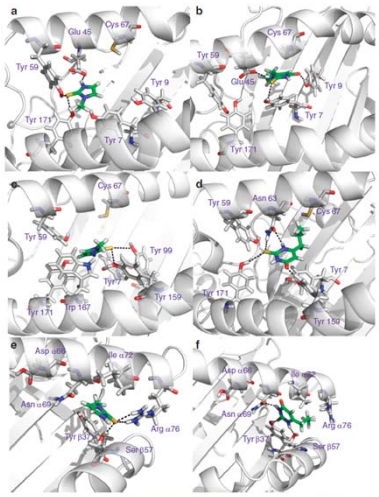
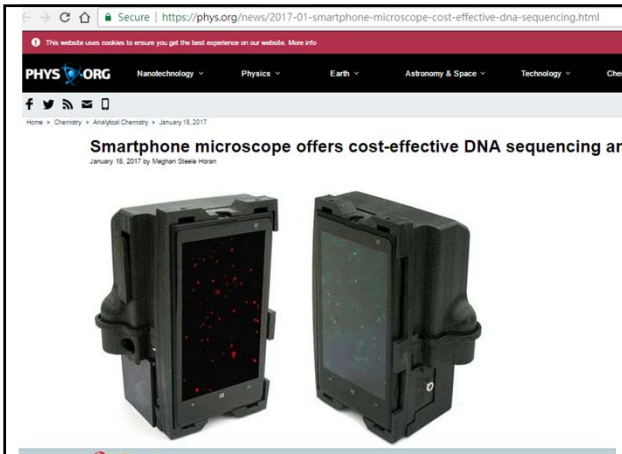


Figure 4 | Specific protein-ligand interactions between thionamide drugs and the HLA proteins identified in this work. (**a**) Methimazole-HLA-B*38:02. (**b**) Propylthiouracil-HLA-B*38:02. (**c**) Methimazole-HLA-B*38:01. (**d**) Propylthiouracil-HLA-B*38:01. (**e**) Methimazole-HLA-DRA/DRB1*08:03. (**f**) Propylthiouracil-HLA-DRA/DRB1*08:03 complexes. The predicted binding affinities are within the range between −4.48 and −6.36 kcal mol^{-1}.

Chen, *et al. Nature Comms* 6, 7633 (2015)


Secure | https://phys.org/news/2017-01-smartphone-microscope-cost-effective-dna-sequencing.html

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Smartphone microscope offers cost-effective DNA sequencing and genetic mutation analysis

January 18, 2017 by Meghan Steele Horan

nature COMMUNICATIONS

ARTICLE

Received 21 Jul 2016 | Accepted 11 Nov 2016 | Published 17 Jan 2017 DOI: 10.1038/ncomms13913 OPEN

Targeted DNA sequencing and *in situ* mutation analysis using mobile phone microscopy

Malte Kühnemund[1,2,*], Qingshan Wei[3,4,5,*], Evangelia Darai[2], Yingjie Wang[3], Iván Hernández-Neuta[2], Zhao Yang[3], Derek Tseng[3], Annika Ahlford[2,6], Lucy Mathot[1], Tobias Sjöblom[1], Aydogan Ozcan[3,4,5] & Mats Nilsson[1,2]

The new device could be manufactured for much less than $500, while a typical microscope with multiple imaging modes would cost around $10,000, and higher-end versions, such as the one used to validate this mobile-phone microscope, would go for $50,000 or more.


SEPTEMBER 30, 2013
The Iran Opportunity By Fareed Zakaria / E-Cigarettes / $20K Homes
TIME
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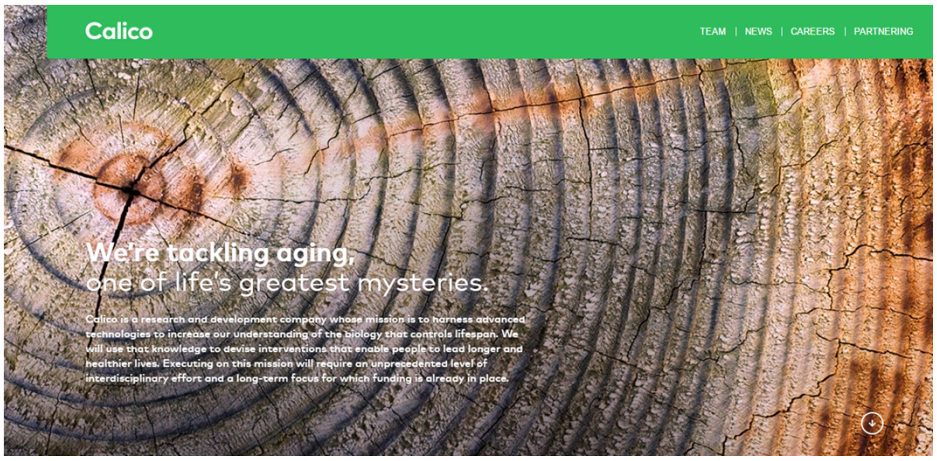
DEATH?
The search giant is launching a venture to extend the human life span.
That would be crazy—if it weren't Google
By Harry McCracken and Lev Grossman
time.com

Sep. 30, 2013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We're tackling aging,
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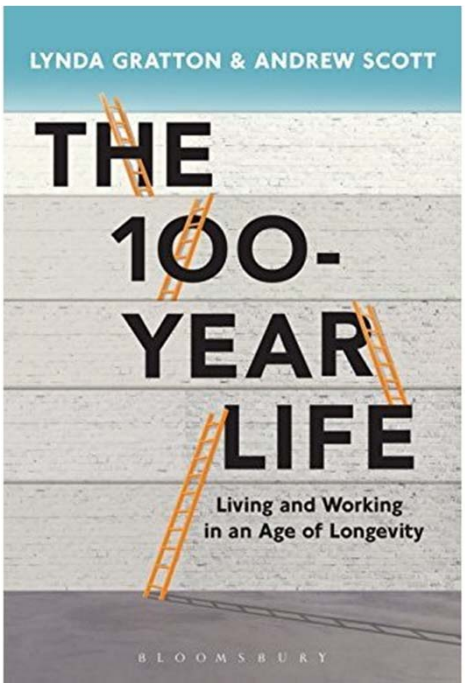
Calico is a research and development company whose mission is to harness advanced technologies to increase our understanding of the biology that controls lifespan. We will use that knowledge to devise interventions that enable people to lead longer and healthier lives. Executing on this mission will require an unprecedented level of interdisciplinary effort and a long-term focus for which funding is already in place.



Thank you very much for your attention.

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