Overview of the Workshop

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Motivation

- Computational drug design is an important approach for new drug discovery, and is also one of the most important applications of modern structural biology.

- Based on the estimate from graph theory and combinatorial chemistry, the number of biologically relevant chemical molecules is about $\mathbf{10^{60}}$. However, the total number of curated chemical compounds from natural products or synthetic chemistry so far is only about $\mathbf{10^{10}}$, which highlights the importance of accurate prediction of the properties of a chemical compound that still does not exist, and thereby carrying out drug design on a specific disease with a selected target.

- Accuracy of prediction is no doubt the most important issue in current researches of computational drug design.

How to predict accurately?

- Computational methods based on **statistical physics** and **quantum chemistry** are rooted in **universal principles**, and therefore could serve as the tools of **best predictive power** to derive the properties of chemical compounds that still do not exist in this world.

- However, calculations based on such rigorous approaches used to be carried out only on huge supercomputers, required very long time for computation, and can only be applied to systems with small numbers of atoms. In the past decades, theoretical physical chemists relentlessly explored effective hierarchical strategies to achieve computations or simulations of systems of much larger scales.

- Currently, due to the advances in modern supercomputers, it is already possible to carrying out the all-atom explicit solvent simulations of the spatial scale of the cell for hundreds of nanoseconds, with about $\mathbf{10^9}$ atoms in the whole system. Thanks to the recent development and popularization of GPU-based scientific computations, it is now possible to carry out **free energy calculations** based on structural biology and statistical physics to resolve important issues in the challenges from virtual screen of large chemical libraries for drug discovery.

Good education is essential

- Harnessing structural biology, statistical physics, and quantum chemistry to perform computations for drug discovery requires large amount of background knowledge and trainings.
- It is thus the purpose of this workshop to provide the necessary trainings and educations for carrying out computational drug design.
- Besides, there are significant progresses in the field of deep learning and artificial intelligence, and computational drug design has also benefitted from the applications of these novel methods.
- We hope to explore the recent advances in these areas to offer good trainings and visions for young scientists who are interested in structure-based drug design.

舉辦動機

運用計算方法來進行藥物設計是一個新藥開發的一個重要方法，也是現代結構生物學最重要的應用之一。根據圖論與理論組合化學估計，與生物相關的化學分子數目約為10^{60}，然而目前已自天然物中發現以及化學合成的分子數則尚不到10^{10}，因此能對絕大多數尚未在世上存在的化學分子的性質做準確的預測，並對特定的疾病與藥物標靶進行藥物設計，是現在計算藥物領域最重要的課題。

基於統計物理及量子化學的計算因根據的是最有普適性的原理，顯然是最具有預測尚未存在的分子的性質的理論工具。然而，這類計算過去常常需要倚賴大型超級電腦，而且需要很長的計算時間，只能應用在系統的原子數目不大的系統，因此大多是在基礎課題上的研究。過去數十年來，理論物理化學家一直在探索有效的層秩式策略(hierarchical strategy)，以達到更大尺度的系統的模擬計算。目前由於先進超級電腦的發展，我們已能對細胞尺度大小約十億原子的系統，進行全原子的分子動力學約百奈秒時間尺度模擬。也由於近年來GPU用於科學計算的快速進展與普及化，我們運用統計物理以結構生物為基礎來從事自由能計算，已在許多例子中顯示可有效解決超大化學資料庫藥物虛擬篩選面臨的挑戰。

然而，運用結構生物及統計物理及量子化學來進行計算與藥物設計，關係到許多高複雜性的背景知識與訓練，而且在目前國內並沒有適當的嚴謹課程以提供年輕學子來接受完整的訓練。此外，近年來由於深度學習等人工智慧的演算法有相當大的進展與突破，在藥物分子性質預測上也有亮眼的成果。因此，本課程的設計希望能提供國內年輕科學家及學生在計算藥物領域一定的基礎訓練，並對這領域最新進展有所掌握。

A grand challenge problem for science and the human society

- There are many diseases that **still do not have any medications** to treat or to prevent because of **very little financial incentive** from the view of the private sector or pharmaceutical industries. Such diseases could be **rare diseases** (according to US criteria, diseases that affect fewer than 200,000 people) or **common diseases that have been ignored** (such as tuberculosis, cholera, typhoid, and malaria) because they are far more prevalent only in developing countries than in the developed world.
- Besides, there are also **many infectious diseases that do not have any clinically applicable therapeutics**, e.g., **dengue virus disease**, and even for those diseases having some therapeutics also suffer from the **drug resistance** issues, which surely call for more efficient and effective approaches for drug discovery.
- Many infective diseases would lead to **world-wide pandemics**, which are apparent threats to human health and global stability.

The limitation of current status

- To efficiently explore the drug-like chemical space, **computational approaches are the only promising directions**.
- Currently, there are about **679-million** commercially available compounds curated by the UCSF ZINC database (http://zinc15.docking.org/tranches/home/), which is **impossible to be physically maintained by any single laboratory or any pharmaceutical company**.
- Even with computational approaches, it is a daunting task to screen the entire ZINC chemical library and huge computational resource is demanded.
- Yet, most current computational methods are of approximate nature and thus **a majority of computationally identified hits are false-positives**. These issues hindered the effective discovery of good small molecules for further drug development.

THE JOURNAL OF PHYSICAL CHEMISTRY B

Article

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

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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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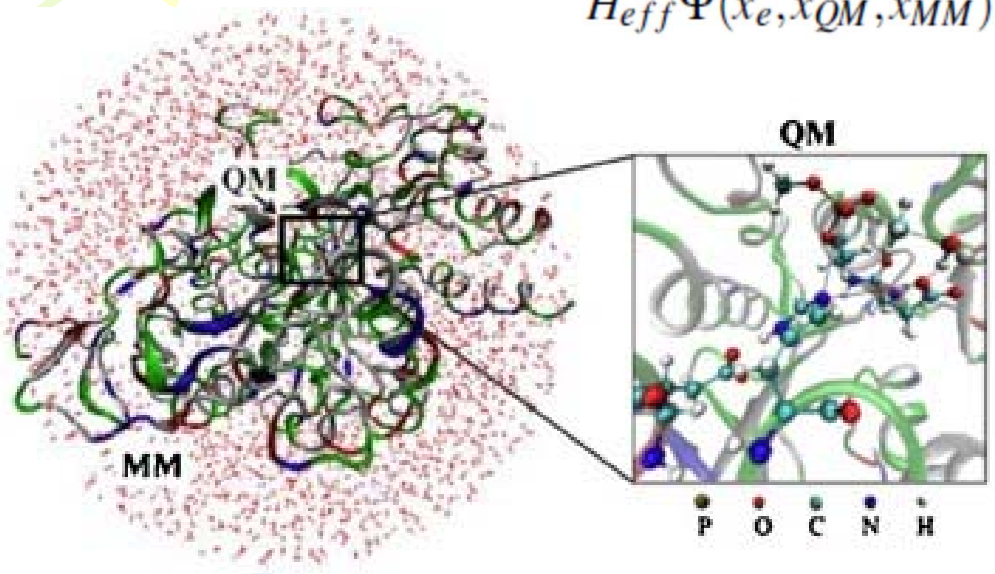
The critical problems that hinder advancement

Most of current virtual screening computational tools are based on grid-based energetic calculations and simple linear free energy models, which are **too crude approximations** for general protein-ligand interactions and the **accumulated errors** in the free energy calculations lead to **huge number of false-positive** hits in virtual screening campaigns against very large chemical libraries.

The QM/MM Hybrid Approach

$$H_{eff}\Psi(x_e, x_{QM}, x_{MM}) = E_{eff}(x_{QM}, x_{MM})\Psi(x_e, x_{QM}, x_{MM})$$

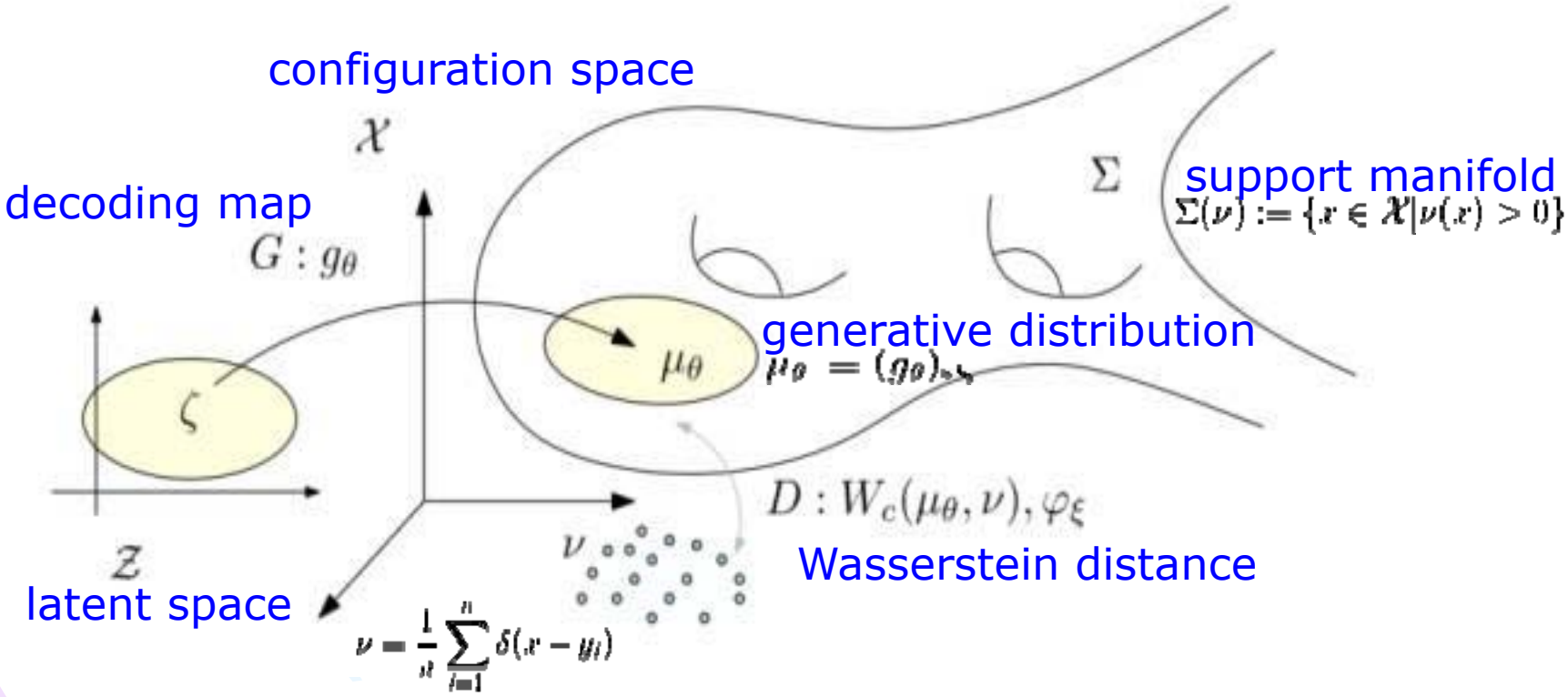


$$E_{eff} = \langle \Psi | H_{QM} + H_{QM/MM} | \Psi \rangle + E_{MM}$$

$$H_{QM/MM} = \sum_q \sum_m \left[Q_m h_{electron}(x_e, x_{MM}) - Q_m Z_q h_{core}(x_{QM}, x_{MM}) + \left(\frac{A}{r_{qm}^{12}} - \frac{B}{r_{qm}^{6}} \right) \right]$$

Wasserstein Generative Adversarial Network

Arjovsky et al. arXiv:1701.07875 (2017)



v(x): the probability that x presents a true instance

Wasserstein GAN

Martin Arjovsky[1], Soumith Chintala[2], and Léon Bottou[1,2]

[1]Courant Institute of Mathematical Sciences
[2]Facebook AI Research

Times Cited: 457 (2018/3/15)

Drug Discovery Today • Volume 00, Number 00 • February 2018 REVIEWS

Reviews • INFORMATICS

The rise of deep learning in drug discovery

Hongming Chen[1], Ola Engkvist[1], Yinhai Wang[2], Marcus Olivecrona[1] and Thomas Blaschke[1]

[1] Hit Discovery, Discovery Sciences, Innovative Medicines and Early Development Biotech Unit, AstraZeneca R&D Gothenburg, Mölndal 43183, Sweden
[2] Quantitative Biology, Discovery Sciences, Innovative Medicines and Early Development Biotech Unit, AstraZeneca, Unit 310, Cambridge Science Park, Milton Road, Cambridge CB4 0WG, UK

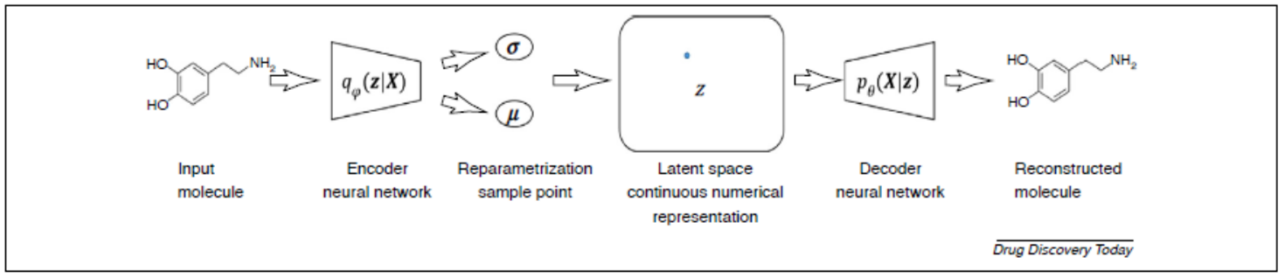


FIGURE 4

The illustration of a variational autoencoder (VAE) method. The encoder neural network (NN) converts a discrete molecule into Gaussian distribution deterministically. After the latent variables are reparameterized against the gaussian distribution with given mean and variance, a new point is sampled and fed into the decoder NN. In the generation mode, only the decoder is used to generate a new molecule from the sampled latent point.

Review

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molecular informatics

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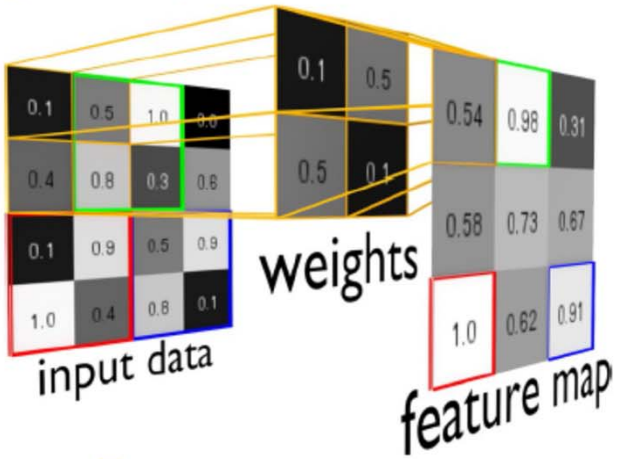
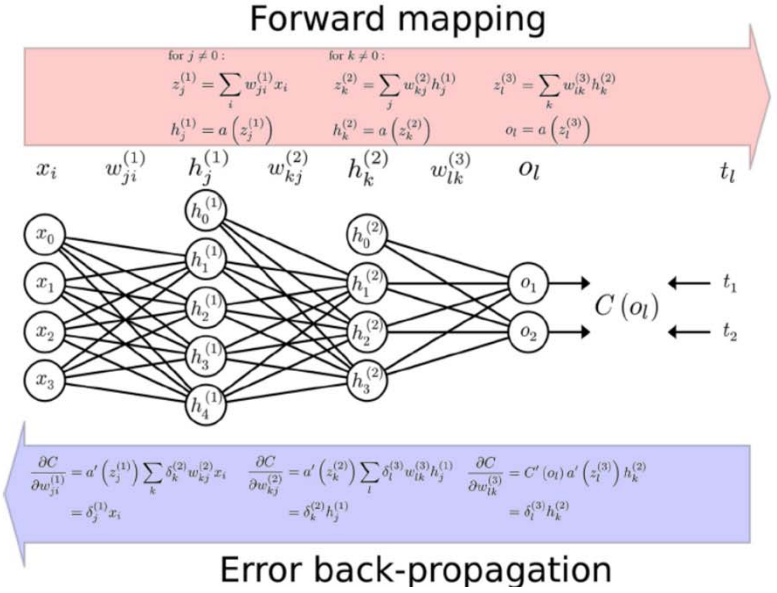
Deep Learning in Drug Discovery

Erik Gawehn,[a] Jan A. Hiss,[a] and Gisbert Schneider*[a]

Abstract: Artificial neural networks had their first heyday in molecular informatics and drug discovery approximately two decades ago. Currently, we are witnessing renewed interest in adapting advanced neural network architectures for pharmaceutical research by borrowing from the field of "deep learning". Compared with some of the other life sciences, their application in drug discovery is still limited. Here, we provide an overview of this emerging field of molecular informatics, present the basic concepts of prominent deep learning methods and offer motivation to explore these techniques for their usefulness in computer-assisted drug discovery and design. We specifically emphasize deep neural networks, restricted Boltzmann machine networks and convolutional networks.

Keywords: bioinformatics · cheminformatics · drug design · machine-learning · neural network · virtual screening





INNOVATION

Automating drug discovery

Gisbert Schneider

Abstract | Small-molecule drug discovery can be viewed as a challenging multidimensional problem in which various characteristics of compounds — including efficacy, pharmacokinetics and safety — need to be optimized in parallel to provide drug candidates. Recent advances in areas such as microfluidics-assisted chemical synthesis and biological testing, as well as artificial intelligence systems that improve a design hypothesis through feedback analysis, are now providing a basis for the introduction of greater automation into aspects of this process. This could potentially accelerate time frames for compound discovery and optimization and enable more effective searches of chemical space. However, such approaches also raise considerable conceptual, technical and organizational challenges, as well as scepticism about the current hype around them. This article aims to identify the approaches and technologies that could be implemented robustly by medicinal chemists in the near future and to critically analyse the opportunities and challenges for their more widespread application.

Figure 2 | **Automated drug discovery facilities. a** | Millions of compound samples are stored in compact high-capacity facilities and handled by robots. **b** | Robot systems perform both high-throughput and medium-throughput screening of up to ten thousand samples per day to determine the activity against the biological target of interest. Multiple arms and flexible workstations enable fully automated liquid dispensing, compound preparation and testing. These storage and screening systems have become cornerstones of contemporary drug discovery. **c** | A prototype of a novel miniaturized design–synthesize–test–analyse facility for rapid automated drug discovery at AstraZeneca is shown. Images **a** and **b** courtesy of Jan Kriegl, Boehringer–Ingelheim Pharma; image **c** courtesy of Michael Kossenjans, AstraZeneca.

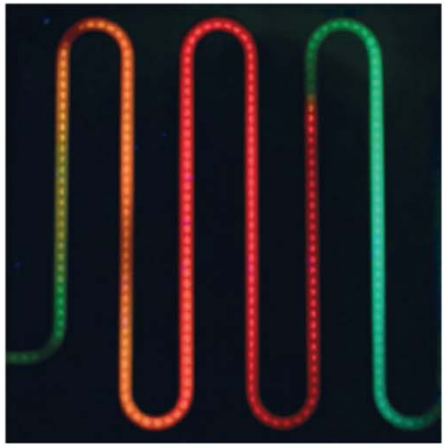
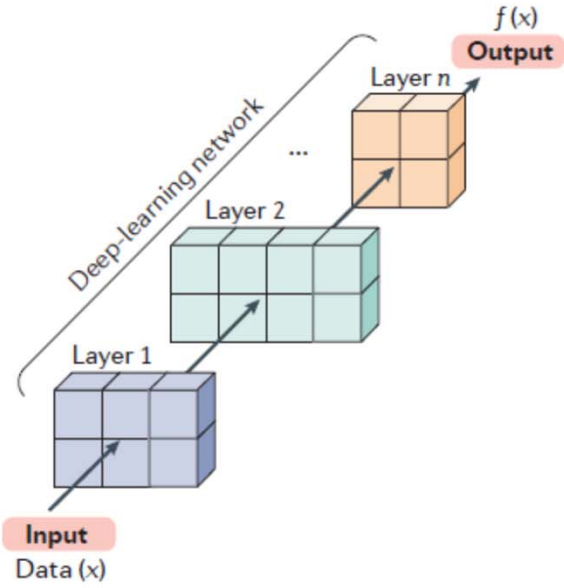


Figure 5 | **Chemical synthesis in microfluidics droplet reactors.** The image shows a microreactor channel with droplets containing multinary $(Cs/FA)Pb(Br/I)_3$ perovskite nanocrystals[123].



Journal of Medicinal Chemistry

Article

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Discovery of Potent Non-Nucleoside Inhibitors of Dengue Viral RNA-Dependent RNA Polymerase from a Fragment Hit Using Structure-Based Drug Design

Fumiaki Yokokawa,*[,†] Shahul Nilar,[†] Christian G. Noble,[†] Siew Pheng Lim,[†] Ranga Rao,[†] Stefani Tania,[†] Gang Wang,[†] Gladys Lee,[†] Jürg Hunziker,[†] Ratna Karuna,[†] Ujjini Manjunatha,[†] Pei-Yong Shi,[†,‡] and Paul W. Smith[†]

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Supporting Information

ABSTRACT: The discovery and optimization of non-nucleoside dengue viral RNA-dependent-RNA polymerase (RdRp) inhibitors are described. An X-ray-based fragment screen of Novartis' fragment collection resulted in the identification of a biphenyl acetic acid fragment 3, which bound in the palm subdomain of RdRp. Subsequent optimization of the fragment hit 3, relying on structure-based design, resulted in a >1000-fold improvement in potency in vitro and acquired antidengue activity against all four serotypes with low micromolar EC_{50} in cell-based assays. The lead candidate 27 interacts with a novel binding pocket in the palm subdomain of the RdRp and exerts a promising activity against all clinically relevant dengue serotypes.

DOI: 10.1021/acs.jmedchem.6b00143
J. Med. Chem. 2016, 59, 3935−3952

RESULTS AND DISCUSSION

A fragment screen of the Novartis fragment collection using X-ray crystallography identified a single hit, a biphenyl acetic acid fragment, 3 (IC_{50} 734 μM, SPR-K_d 613 μM, LE 0.24), which bound in the palm subdomain (Figures 1, 3).[21] A related analogue from the Novartis archive, 4 (IC_{50} 769 μM, SPR-K_d > 200 μM, LE 0.26), was also found to bind in the same pocket using X-ray crystallography but it bound with the opposite orientation of the carboxylic acid moiety, suggesting that the binding was mainly from the biphenyl moiety. Each carboxylic acid formed an H-bond interaction with the priming loop (Figure 3).

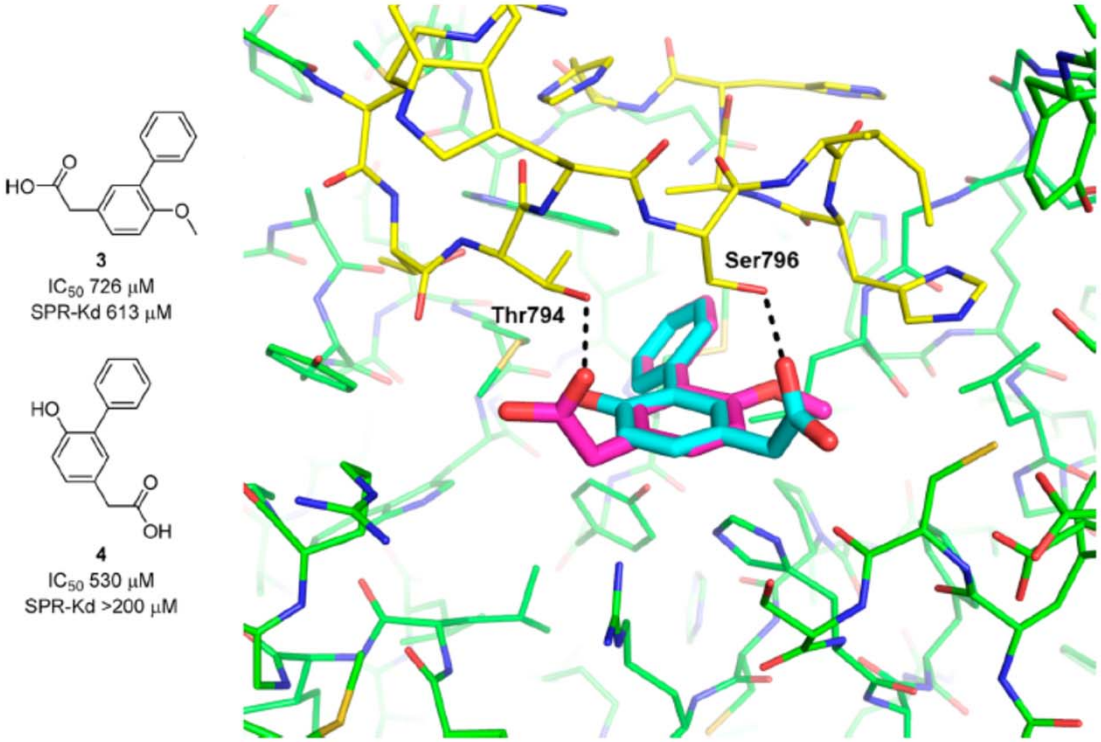
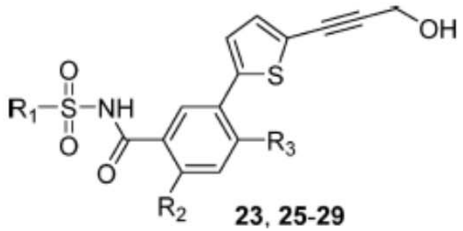
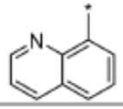


Figure 3. Overlay of co-crystal structures of 3 (magenta) and 4 (cyan) bound to the RdRp domain of DENV3 NS5. The compounds are shown as sticks and the protein as lines. The residues in the palm and thumb subdomains are green and in the priming loop yellow. H-bond interaction of carboxylic acid groups with the priming loop is shown by dotted lines.

Table 4. Enzyme Inhibition, SPR-K_d, cellular potency, log *D*, pK_a, and Caco-2 Data for Acyl Sulfonamide Analogues 23 and 25–29



23, 25-29

Cpd	R_1	R_2	R_3	D4 IC_{50} (μM)[a]	D4 SPR *Kd* (μM)[b]	EC_{50} (μM, A547 cells)[c]				logD (pH 7.4)	pKa	Caco-2[d] (cm/s x10^{-6})
						D1	D2	D3	D4			
23	Me	Me	OMe	0.34	0.12	>50	>50	>50	>50	0.8	4.0	0.5
25	Ph	Me	OMe	0.17	ND	31	34	18	41	1.7	3.8	0.5
26	Ph	OMe	OMe	0.25	0.09	15	37	7.3	14	1.5	4.8	10.8
27	3-MeOPh	OMe	OMe	0.17	0.07	1.8	2.3	1.8	1.8	1.6	4.7	3.91
28	3-MeOPh	OMe	Cl	0.14	0.01	6.8	13	5.5	7.0	0.9	3.8	ND
29		Me	OMe	0.023	0.007	6.3	14	3.8	10	1.5	4.4	2.57

[a]Enzyme IC_{50} values were determined as described in the Experimental Section. [b]K_d values were determined by SPR as described in the Experimental Section. [c]EC_{50} values were determined as described in the Experimental Section. [d]Apical to basal permeability at pH 7.4. D1 = DENV1, D2 = DENV2, D3 = DENV3, D4 = DENV4.

DOI: 10.1021/acs.jmedchem.6b00143
J. Med. Chem. 2016, 59, 3935–3952

Journal of COMPUTATIONAL CHEMISTRY WWW.C-CHEM.ORG REVIEW

Deep Learning for Computational Chemistry

Garrett B. Goh,*[a] Nathan O. Hodas,[b] and Abhinav Vishnu[a]

Wiley Online Library

Journal of Computational Chemistry **2017**, *38*, 1291–1307

Editorial

www.molinf.com

molecular informatics

Generative Models for Artificially-intelligent Molecular Design

Gisbert Schneider[a]

Gisbert Schneider

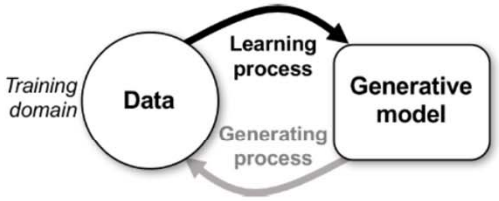
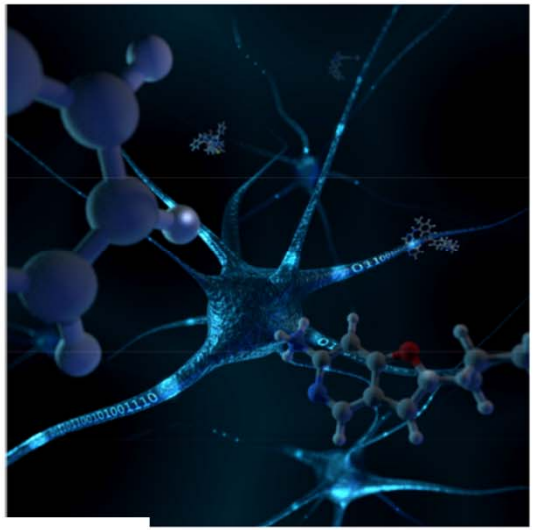


Figure 1. Schematic of generative modeling. Data distributions are learned by a generative model, which is able to generate new data instances based on the learned internal representation of the training domain. Such an approach may be considered artificially-intelligent, bearing promise for drug design.



Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

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ANI-1: an extensible neural network potential with DFT accuracy at force field computational cost†

J. S. Smith,[a] O. Isayev*[b] and A. E. Roitberg*[a]

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Accepted 7th February 2017

DOI: 10.1039/c6sc05720a

rsc.li/chemical-science

Deep learning is revolutionizing many areas of science and technology, especially image, text, and speech recognition. In this paper, we demonstrate how a deep neural network (NN) trained on quantum mechanical (QM) DFT calculations can learn an accurate and transferable potential for organic molecules. We introduce ANAKIN-ME (Accurate NeurAl networK engINe for Molecular Energies) or ANI for short. ANI is a new method designed with the intent of developing transferable neural network potentials that utilize a highly-modified version of the Behler and Parrinello symmetry functions to build single-atom atomic environment vectors (AEV) as a molecular representation. AEVs provide the ability to train neural networks to data that spans both configurational and conformational space, a feat not previously accomplished on this scale. We utilized ANI to build a potential called ANI-1, which was trained on a subset of the GDB databases with up to 8 heavy atoms in order to predict total energies for organic molecules containing four atom types: H, C, N, and O. To obtain an accelerated but physically relevant sampling of molecular potential surfaces, we also proposed a Normal Mode Sampling (NMS) method for generating molecular conformations. Through a series of case studies, we show that ANI-1 is chemically accurate compared to reference DFT calculations on much larger molecular systems (up to 54 atoms) than those included in the training data set.

Times Cited: 46 (2018/3/15)

Program

Day 1

09:00-10:10	**Registration**
10:10-11:10	**Overview of the workshop [Speaker: Jung-Hsin Lin]**
11:10-11:30	Break
11:30-12:30	**Fundamentals in structure biology [Speaker: Jung-Hsin Lin]**
12:30-14:00	Lunch
14:00-15:30	**Introduction to Protein Data Bank (PDB) and molecular graphics (PyMOL) [Speaker: Ching-Shu Suen]**
15:30-16:00	Break
16:00-18:00	**Molecular graphics (UCSF Chimera) and analytics for biomolecule-drug interactions (Molprobity, PDB2PQR, LigPlot+, etc.) [Speaker: Pei-Ying Chu]**

Program

Day 2

09:00-10:30	**Quantum chemical calculations of drug-like molecules [Speaker: Jung-Hsin Lin]**
10:30-11:00	Break
11:00-12:30	**Hands-on tutorials of quantum chemical calculation with Gaussian and visualization of molecular orbitals and chemical spectra (GaussView) [Speaker: Ching-Yu Chou]**
12:30-14:00	Lunch
14:00-15:30	**Principles of molecular docking [Speaker: Jung-Hsin Lin]**
15:30-16:00	Break
16:00-18:00	**Hands-on tutorials of AutoDock 4.0 and AutoDock vina [Speaker: Pei-Ying Chu]**

Program

Day 3

09:00-09:40	**Deep learning approaches in computation drug discovery [Speaker: Jung-Hsin Lin]**
09:40-09:50	Break
09:50-10:30	**Improving Scoring-Docking-Screening Powers of Protein–Ligand Scoring Functions using Random Forest [Speaker: Yingkai Zhang]**
10:30-11:00	Break
11:00-11:30	**Hands-on Tutorial of Δ_{vina} [Speaker: Yingkai Zhang, Pei-Ying Chu]**
11:30-12:30	**Hands-on Tutorial of Gnina and DeepChem [Speaker: Pei-Ying Chu]**
12:30-14:00	Lunch
14:00-15:30	**Molecular dynamics simulations for drug-target complexes [Speaker: Jung-Hsin Lin]**
15:30-16:00	Break
16:00-18:00	**Hands-on Tutorial of AMBER16 (xLEaP, sander, pmemd, cpptraj) [Speaker: Ching-Yu Chou]**

Program

Day 4

09:00-10:30	**Quantum mechanical/molecular mechanical molecular dynamics simulations [Speaker: Yingkai Zhang]**
10:30-11:00	Break
11:00-12:30	**Hands-on Tutorial of AMBER16 (sqm, sander, pmemd) [Speaker: Ching-Yu Chou]**
12:30-14:00	Lunch
14:00-14:40	**Potential of mean force and free energy calculations [Speaker: Jung-Hsin Lin]**
14:40-14:50	Break
14:50-15:30	**Gaussian accelerated molecular dynamics simulation (GaMD) [Speaker: Yinglong Miao]**
15:30-16:00	Break
16:00-18:00	**Hand-on Tutorial of AMBER16 (sander, pmemd, WHAM, UI) and Gaussian accelerated molecular dynamics (GaMD) [Speaker: Yinglong Miao, Ching-Yu Chou]**

Program

Day 5

09:00 - 09:45 **Keynote 1: David Salamoni**

09:45 - 10:30 **Keynote 2: David T. Jones, University College London**
"Applying deep learning to the prediction of protein structure and function"

10:30 - 11:00 Coffee break & Group Photo

11:00 - 11:45 **Alexandre M. J. J. Bonvin, Utrecht University**
"HADDOCK goes small molecules. Integrative modelling of biomolecular interactions from fuzzy data"

11:45 - 12:30 **Yingkai Zhang, New York University**
"Computational modulator design to target protein-protein interactions"

12:30 - 14:00 Lunch

14:00 - 14:45 **Yinglong Miao, Kansas University**
"Accelerated computer simulations and drug discovery of G-protein-coupled receptors"

14:45 - 15:30 **Carmay Lim, Academia Sinica**
"Principles governing biological Processes: Applications to drug design and drug target identification"

15:30 - 16:00 Coffee break

16:00 - 16:40 **Jung-Hsin Lin, Academia Sinica**
"Harnessing structures and dynamics of biomolecules for polypharmacology-guided computational drug design"

The Drug

Statins: the Aspirin of the 21st century?

Last Updated: Monday, November 10, 2008 | 3:23 PM ET Comments 17 Recommend 37
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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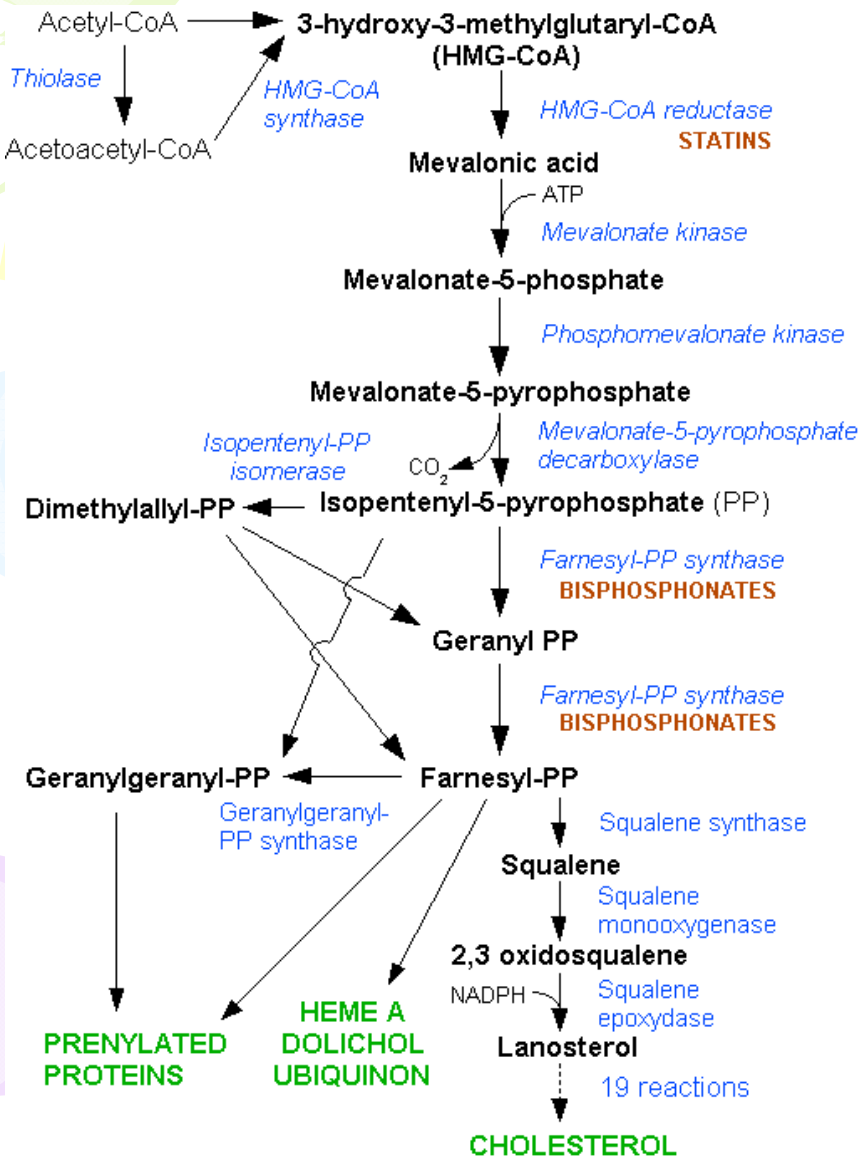
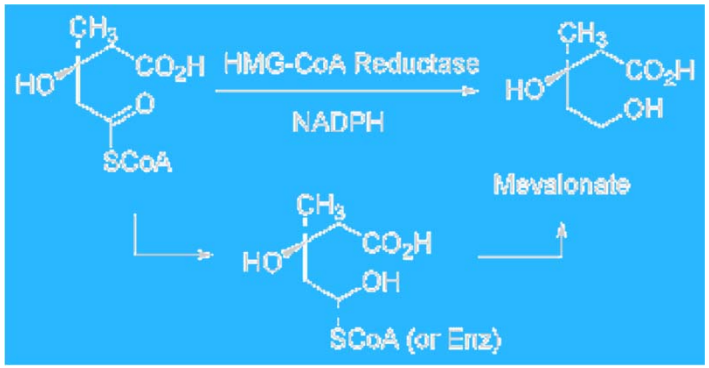
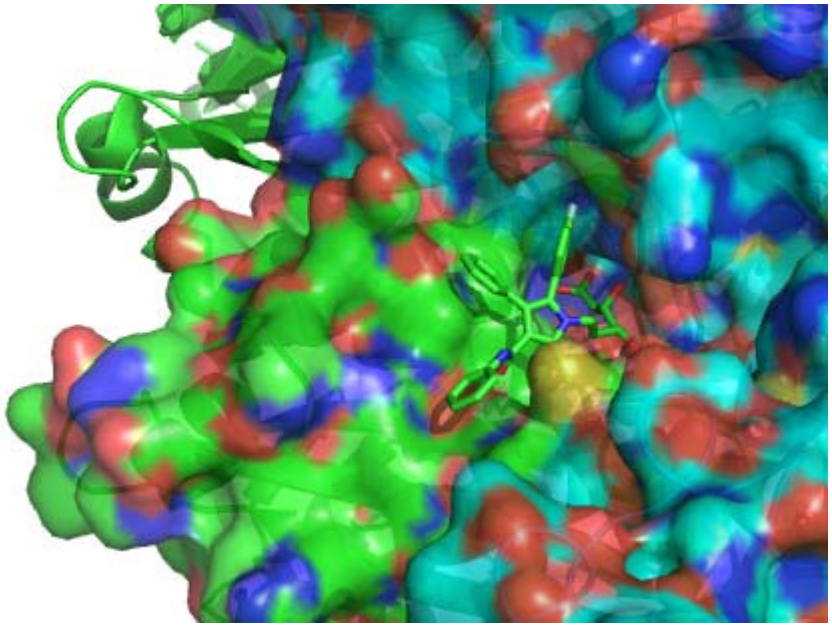
- Staying social may keep seniors' motor skills sharp 1 | 0
- Dog, cat bites could spread MRSA 2 | 5

Mechanism of Statins







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

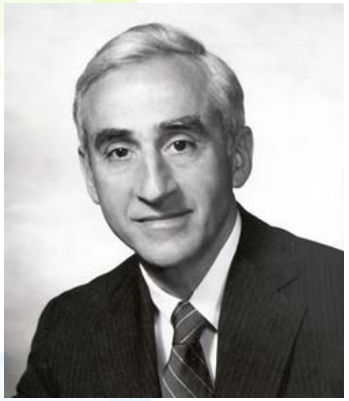
Discovery of first statin, mevastatin

- 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.

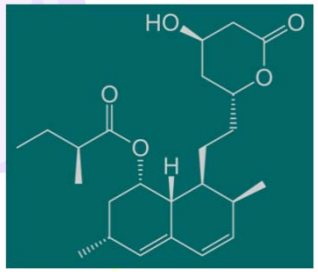
Endo studied 6,000 compounds, of which three extrolites from a *Penicillium* mold showed an effect. One of them, **mevastatin**, was the first member of the statin class of drugs. Soon after, lovastatin, the first commercial statin, was found in the *Aspergillus* mold. Although mevastatin never became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

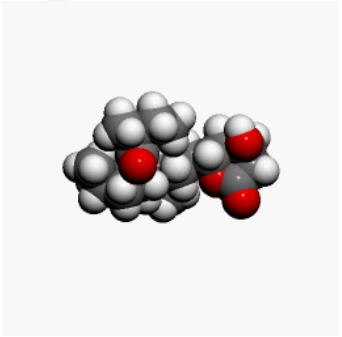
Discovery of lovastatin

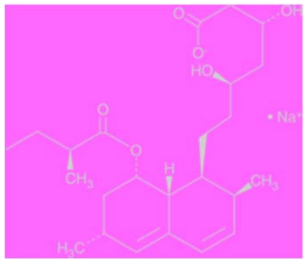


P. Roy Vagelos (born October 8, 1929 in Westfield, New Jersey), was president and chief executive officer (1985) and chairman (1986) of the multinational pharmaceutical company Merck.

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**





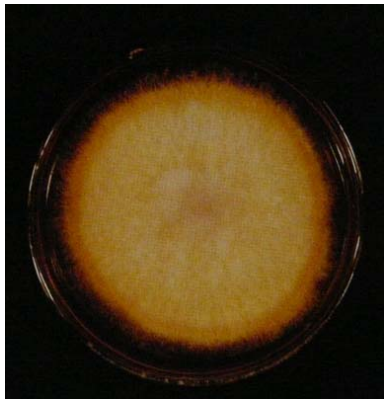


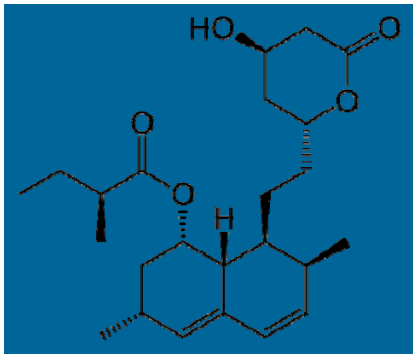
Aspergillus terreus

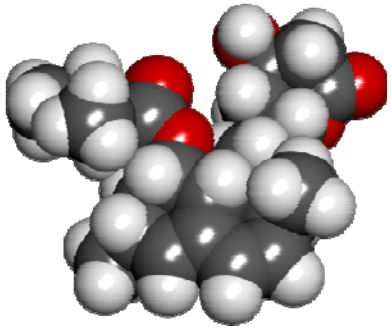
土麴黴, 髮菌科麴菌屬下的一個種

Red Yeast Rice (紅麴米、紅曲米)

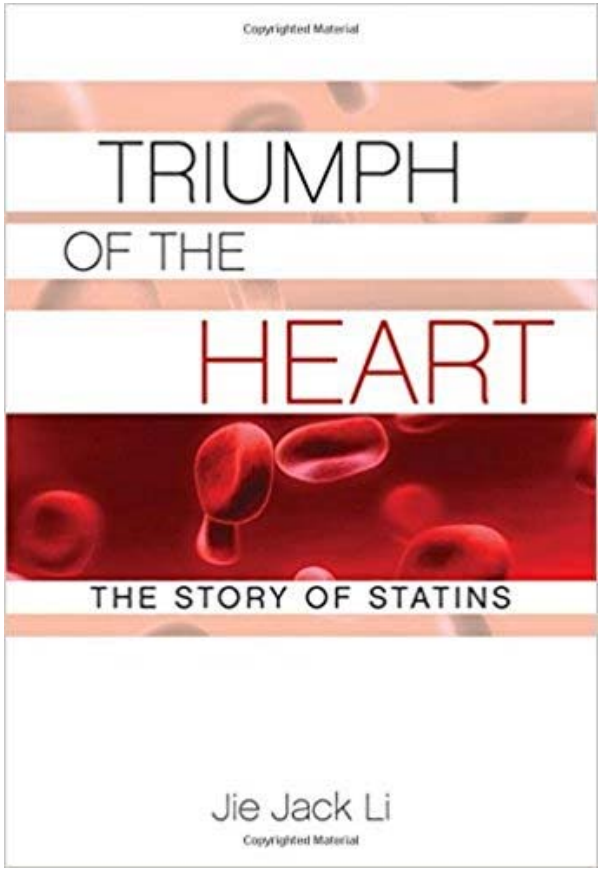
- Red yeast rice is a bright reddish purple fermented rice, which acquire its color from being cultivated with the mold *Monascus purpureus*.
- In addition to its culinary use, red yeast rice is also used in traditional Chinese herbology and traditional Chinese medicine.
- Its use has been documented 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.







Statins set a high standard in efficacy, safety, and benefits



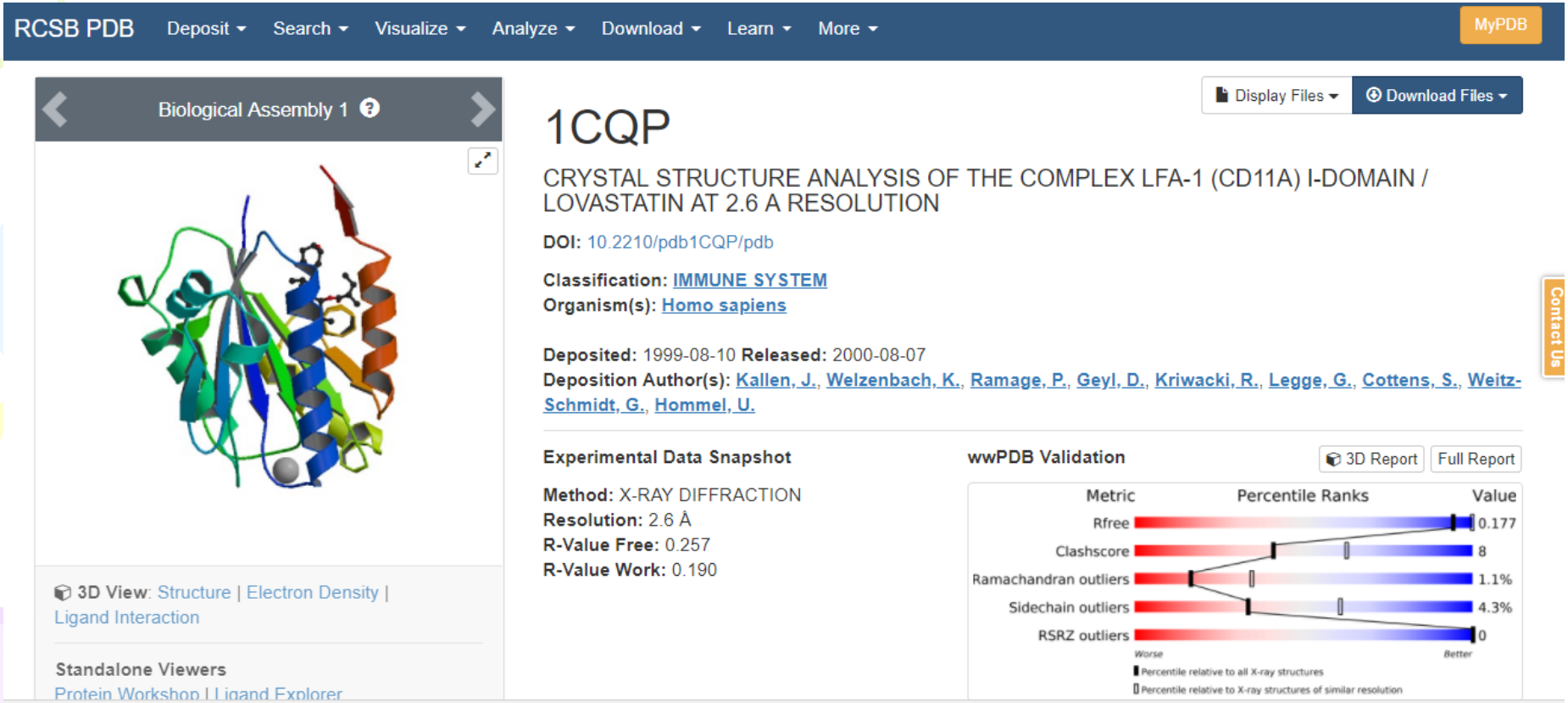
STATINS AND CANCER PREVENTION

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)

The Protein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CRYSTAL STRUCTURE ANALYSIS OF THE COMPLEX LFA-1 (CD11A) I-DOMAIN / LOVASTATIN AT 2.6 A RESOLUTION
DOI: 10.2210/pdb1CQP/pdb
Classification: IMMUNE SYSTEM
Organism(s): Homo sapiens
Deposited: 1999-08-10 Released: 2000-08-07
Deposition Author(s): Kallen, J., Welzenbach, K., Ramage, P., Geyl, D., Kriwacki, R., Legge, G., Cottens, S., Weitz-Schmidt, G., Hommel, U.
Experimental Data Snapshot
Method: X-RAY DIFFRACTION
Resolution: 2.6 Å
R-Value Free: 0.257
R-Value Work: 0.190
wwPDB Validation
3D Report
Full Report
Metric
Percentile Ranks
Value
Rfree
0.177
Clashscore
8
Ramachandran outliers
1.1%
Sidechain outliers
4.3%
RSRZ outliers
0
Worse
Better
Percentile relative to all X-ray structures
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J. Mol. Biol. (1999) 292, 1–9

JMB

COMMUNICATION

Structural Basis for LFA-1 Inhibition upon Lovastatin Binding to the CD11a I-Domain

J. Kallen[1], K. Welzenbach[1], P. Ramage[1], D. Geyl[1], R. Kriwacki[2] G. Legge[2], S. Cottens[1], G. Weitz-Schmidt[1] and U. Hommel[1]*

[1]*NOVARTIS PHARMA AG Preclinical Research, CH 4002 Basel, Switzerland*

[2]*The SCRIPPS Research Institute, Department of Molecular Biology, 10550 North Torrey Pines Road, La Jolla, CA, 92037, USA*

The lymphocyte function-associated antigen (LFA-1) belongs to the family of β_2-integrins and plays an important role in T-cell activation and leukocyte migration to sites of inflammation. We report here that lovastatin, a drug clinically used for lowering cholesterol levels, inhibits the interaction of human LFA-1 with its counter-receptor intercellular adhesion molecule-1. Using nuclear magnetic resonance spectroscopy and X-ray crystallography we show that the inhibitor binds to a highly conserved domain of the LFA-1 α-chain called the I-domain. The first three-dimensional structure of an integrin inhibitor bound to its receptor reveals atomic details for a hitherto unknown mode of LFA-1 inhibition. It also sheds light into possible mechanisms of LFA-1 mediated signalling and will support the design of novel anti-adhesive and immunosuppressive drugs.

PDB ID: 1CQP

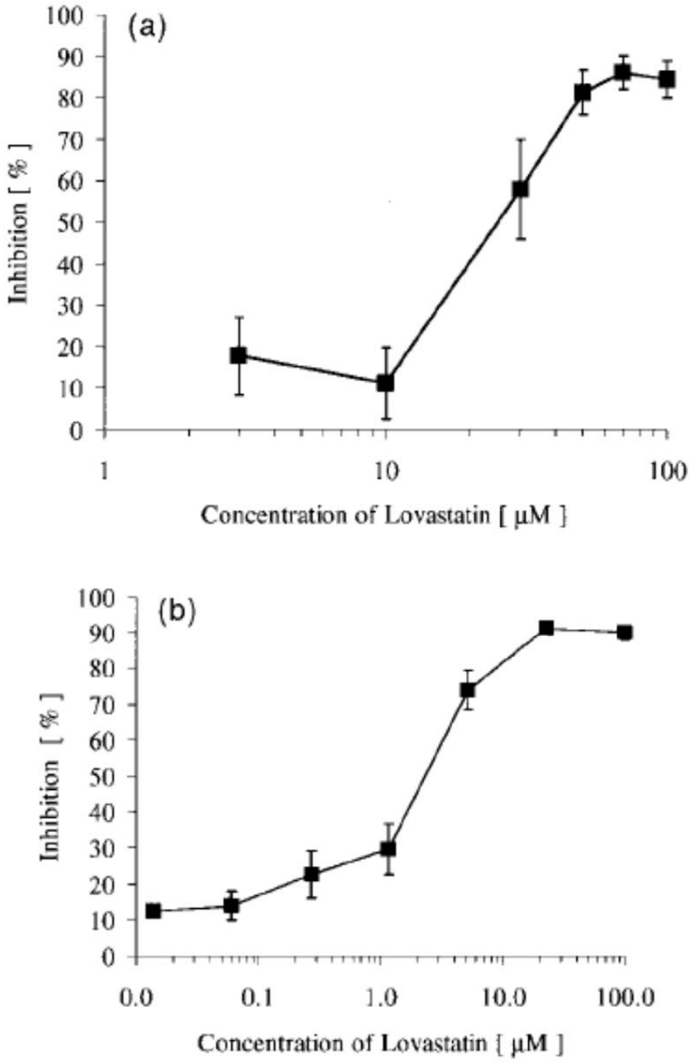

Figure 1. Inhibition of LFA-1/ICAM-1 interaction by lovastatin in the (a) cell-based adhesion assay and the (b) cell-free binding assay. For the Hut78/ICAM-1 adhesion assay microtitre plates were coated with goat anti-mouse Cκ monoclonal antibody (1µg ml^{-1}) in carbonate buffer (pH 8.5) for two hours at 37°C. Plates

Lovastatin binding to the LFA-1 I-domain

High throughput screening for small molecule antagonists of LFA-1 function using an LFA-1-dependent adhesion assay identified the fungal metabolite lovastatin (Mevinolin, Monacolin K) as an inhibitor of the LFA-1/ICAM-1 interaction (Figure 1). Lovastatin blocked LFA-1 binding in the cell-based Hut78/ICAM-1 assay with an IC_{50} of 25.0(±4.0) µM ($n = 5$). In an ELISA-type cell-free LFA-1/ICAM-1 binding assay lovastatin was found to have an IC_{50} of 2.4(±0.5) µM ($n = 6$). Lovastatin is known as a competitive inhibitor of 3-hydroxy-3′-methyl glutaryl coenzyme A (HMG CoA) reductase, a key enzyme of cholesterol synthesis (Alberts *et al.*, 1980; Corsini *et al.* 1995). Under physiological conditions the lactone ring of lovastatin may undergo hydrolysis, which leads to the generation of a δ-hydroxy acid. This hydroxy acid appears well suited to bind to the MIDAS motif of the αL I-domain and may thus represent the inhibitory principle behind lovastatin dependent LFA-1 inhibition. Consequently, we also tested the hydroxy acid form of lovastatin for its LFA-1 inhibitory activity. In both the cell-free and cell-based adhesion assay systems, the hydroxy acid showed impaired inhibition (cell free: IC_{50} 14.1(±2.3) µM ($n = 5$); cell-based: $IC_{50} > 100$ µM ($n = 2$)). These results indicate that the lactone form of lovastatin is responsible for its activities in our cell-based and cell-free assays and undermines the assumption that inhibition was conveyed in part by a carboxyl group binding to a divalent ion at the MIDAS motif.

Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site

GABRIELE WEITZ-SCHMIDT[1], KARL WELZENBACH[1], VOLKER BRINKMANN[1], TETSJI KAMATA[2], JOERG KALLEN[1], CHRISTIAN BRUNS[1], SYLVAIN COTTENS[1], YOSHIKAZU TAKADA[2] & ULRICH HOMMEL[1]

[1]*Novartis Pharma AG, Preclinical Research, Basel, Switzerland*
[2]*The Scripps Research Institute, Department of Vascular Biology, La Jolla, California, USA*
Correspondence should be addressed to G.W.-S.; email: gabriele.weitz@pharma.novartis.com

The β2 integrin leukocyte function antigen-1 (LFA-1) has an important role in the pathophysiology of inflammatory and autoimmune diseases. Here we report that statin compounds commonly used for the treatment of hypercholesterolemia selectively blocked LFA-1–mediated adhesion and costimulation of lymphocytes. This effect was unrelated to the statins' inhibition of 3-hydroxy-3-methylglutaryl coenzyme-A reductase; instead it occurred via binding to a novel allosteric site within LFA-1. Subsequent optimization of the statins for LFA-1 binding resulted in potent, selective and orally active LFA-1 inhibitors that suppress the inflammatory response in a murine model of peritonitis. Targeting of the statin-binding site of LFA-1 could be used to treat diseases such as psoriasis, rheumatoid arthritis, ischemia/reperfusion injury and transplant rejection.

Article No. jmbi.1999.3409 available online at http://www.idealibrary.com on IDEAL® J. Mol. Biol. (2000) 295, 1251–1264

JMB

NMR Solution Structure of the Inserted Domain of Human Leukocyte Function Associated Antigen-1

Glen B. Legge[1], Richard W. Kriwacki[1], John Chung[1], Ulrich Hommel[2] Paul Ramage[2], David A. Case[1], H. Jane Dyson[1]* and Peter E. Wright[1]*

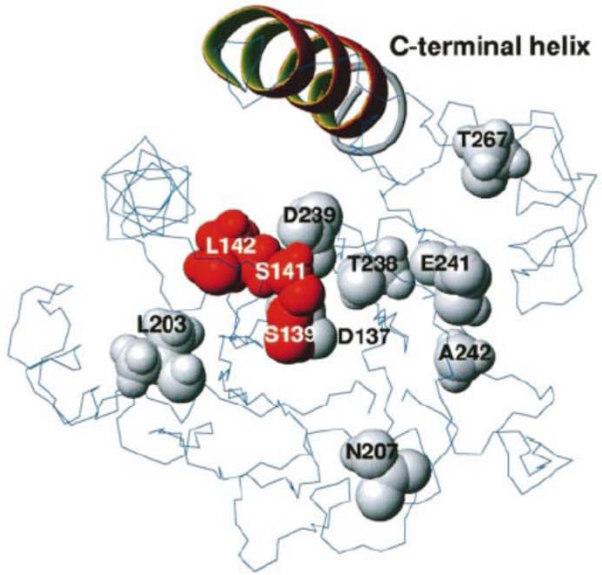

Figure 11. Backbone of the minimized mean NMR structure of the Mg^{2+} LFA-1 I-domain; the side-chains of residues whose ^{15}N and ^{1}H resonances differ the most between the Mg^{2+}-bound and Mg^{2+}-free forms of the protein shown in space-filling representation. The mean differences in the chemical shifts of ^{15}N and ^{1}H were calculated for each residue using the following formula:

$$\Delta\delta = \sqrt{\{[(\Delta H)^2 + (\Delta N/5)^2]/2\}}$$

Color coding: red, residues with $\Delta\delta \geqslant 2$ standard deviations over the mean value ($\Delta\delta \geqslant 0.285$); grey, residues with $\Delta\delta$ between 1 and 2 standard deviations over the mean value ($0.175 \leqslant \Delta\delta \leqslant 0.285$). The position of the C-terminal helix is shown. Figures were prepared with the program MOLMOL (Koradi *et al.*, 1996).

The interaction between the leukocyte function-associated antigen-1 (LFA-1) and the intercellular adhesion molecule is thought to be mediated primarily *via* the inserted domain (I-domain) in the α-subunit. The activation of LFA-1 is an early step in triggering the adhesion of leukocytes to target cells decorated with intercellular adhesion molecules. There is some disagreement in the literature over the respective roles of conformational changes in the I-domain and of divalent cations (Mg^{2+}, Mn^{2+}) in the activation of LFA-1 for intercellular adhesion molecule binding. X-ray crystallographic structures of the I-domains of LFA-1 and Mac-1 in the presence and absence of cations show structural differences in the C-terminal α-helix; this change was proposed to represent the active and inactive conformations of the I-domain. However, more recent X-ray results have called this proposal into question. The solution structure of the Mg^{2+} complex of the I-domain of LFA-1 has been determined by NMR methods, using a model-based approach to nuclear Overhauser enhancement spectroscopy peak assignment. The protein adopts the same structure in solution as that of the published I-domain X-ray structures, but the C-terminal region, where the X-ray structures are most different from each other, is different again in the solution structures. The secondary structure of this helix is well formed, but NMR relaxation data indicate that there is considerable flexibility present, probably consisting of breathing or segmental motion of the helix. The conformational diversity seen in the various X-ray structures could be explained as a result of the inherent flexibility of this C-terminal region and as a result of crystal contacts. Our NMR data are consistent with a model where the C-terminal helix has the potential flexibility to take up alternative conformations, for example, in the presence and absence of the intercellular adhesion molecule ligand. The role of divalent cations appears from our results not to be as a direct mediator of a conformational change that alters affinity for the ligand. Rather, the presence of the cation appears to be involved in some other way in ligand binding, perhaps by acting as a bridge to the ligand and by modulation of the charge of the binding surface.

[1]*Department of Molecular Biology MB2 and Skaggs Institute for Chemical Biology The Scripps Research Institute 10550 North Torrey Pines Road, La Jolla, CA 92037, USA*

[2]*Novartis Pharma AG CH-4002 Basel, Switzerland*

PDB ID: 1DGQ

List of software to be used in the hands-on sessions and should be installed on your laptop:

Molecular Graphics software and tools (Windows/linux/MacOS)

1. **pymol** https://sourceforge.net/projects/pymol/
2. **Chimera** https://www.cgl.ucsf.edu/chimera/download.html
3. **MGLTools** http://mgltools.scripps.edu/downloads

SSH and sftp clients for Windows

1. **putty** https://www.putty.org/
2. **WinSCP** https://winscp.net/eng/download.php
3. **MobaXterm** http://mobaxterm.mobatek.net/download.html

Please feel free to let us know if you have encountered any problems.