Computer Aided Drug Design

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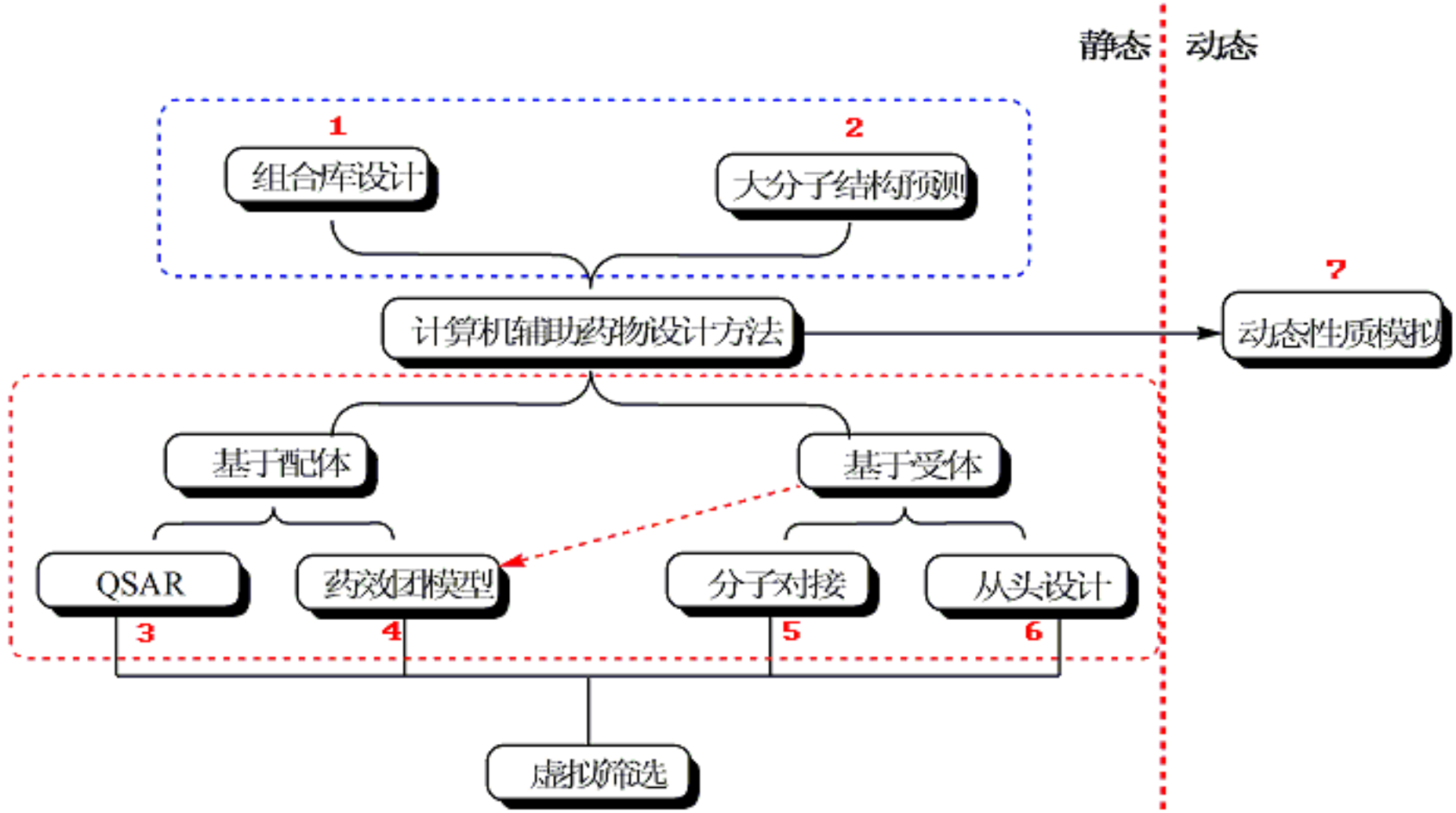
Textbook

- 分子模拟与计算机辅助药物设计
  - 魏冬青等编著，上海交通大学出版社
- 计算机辅助药物分子设计
  - 徐筱杰等编著，化学工业出版社
- 计算机辅助药物设计导论
  - 叶德泳著,化学工业出版社
- Textbook of Drug Design and Discovery, Third Edition, by Povl Krogsgaard-Larsen, published by Oxford University Press
- Computational Medicinal Chemistry for Drug Discovery，by Patrick Bultinck, et. al，published by Marcel Dekker，2003
- Molecular Modeling for Beginners，by Alan Hinchliffe，published by John Wiley and Sons，2002

Course Outline

- Introduction and Case Study
- Drugs
  - Combinatorial library
  - Pharmacophore
  - De novo Drug Design
  - QSAR
- Molecular Docking
- Drug Targets
  - Sequence analysis
  - Protein structure prediction
    - Homology modeling
    - Model Evaluations
    - structural/functional databases of proteins
  - Molecular simulation


静态
动态
1
组合库设计
2
大分子结构预测
7
计算机辅助药物设计方法
动态性质模拟
基于配体
基于受体
QSAR
药效团模型
分子对接
从头设计
3
4
5
6
虚拟筛选

What is a drug?

- Defined composition with a pharmacological effect
- Approved by the Food and Drug Administration (FDA)
- Most drugs are small molecules, and the interactions they make with proteins determine their effects, side effects and toxicity, to the human body

U.S. Department of Health and Human Services

U.S. Food and Drug Administration

Protecting and Promoting *Your* Health

A to Z Index | Follow FDA | En Español

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Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

Drugs

Home > Drugs

Spotlight

- Find Information about a Drug
- Search Drugs@FDA
- Orange Book Search
- National Drug Code Directory
- Drug Shortages

Recalls & Alerts

- Drug Recalls
- MedWatch: The FDA Safety Information and Adverse Event

CFDA 国家食品药品监督管理总局
China Food and Drug Administration

首 页 | 信息公开 | 公众服务 | 许可服务 | 专题专栏 | 数据查询

机构职能 | 总局领导 | 公开专栏 | 图片新闻 | 时政要闻 | 最新动态 | 地方动态 | 法规文件 | 公告通告 | 征求意见 | 专题发布与访谈 | 网上办事
送达信息 | 申请表及软件下载 | 行政许可事项申办须知 | 行政许可综合事项查询

站内文章检索： 搜索 高级搜索 数据速查： 国产药品 提交 2015年9月12日 星期六

食品药品监管总局在京举办“中国食品安全法宣传介绍会议”

时政要闻 | 最新动态 | 地方动态 更多

领导活动 | 领导讲话 | 工作动态 | 新闻发布

- 国家食品药品监督管理总局关于药物临床试验机构... (2015-09-09)
- 郭文奇会见英国环境食品农村事务部首席兽医官那... (2015-09-11)
- 食品药品监管总局召开食用农产品市场销售监督管... (2015-09-10)
- 国家食品药品监督管理总局关于启用新版《药品生... (2015-09-09)
- 食品药品监管总局关于做好《药品生产许可证》和... (2015-09-09)
- 关于78批次白酒和1批次花生油不合格的通告（... (2015-09-08)
- 2014年国家药物滥用监测年度报告发布 (2015-09-08)

食 品
保健食品
药 品
化 妆 品
医疗器械

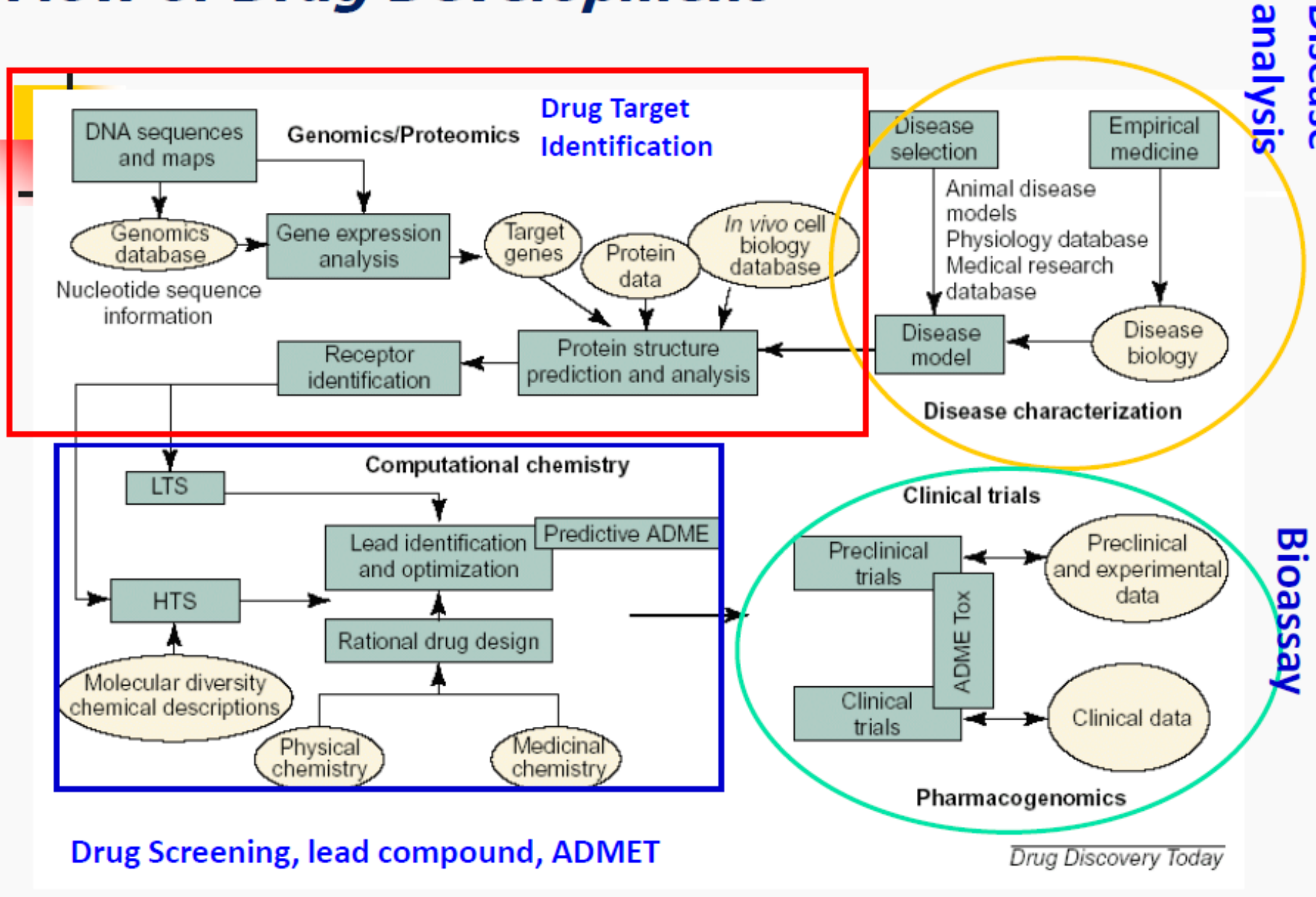
Sources of Drugs

- Small Molecules
  - Natural products
    - fermentation broths(发酵液）
    - plant extracts
    - animal fluids (e.g., snake venoms蛇毒)
  - Synthetic Medicinal Chemicals
    - Project medicinal chemistry derived
    - Combinatorial chemistry derived
- Biologicals
  - Natural products (isolation)
  - Recombinant products
  - Chimeric or novel recombinant products

Drug Discovery and Drug Development

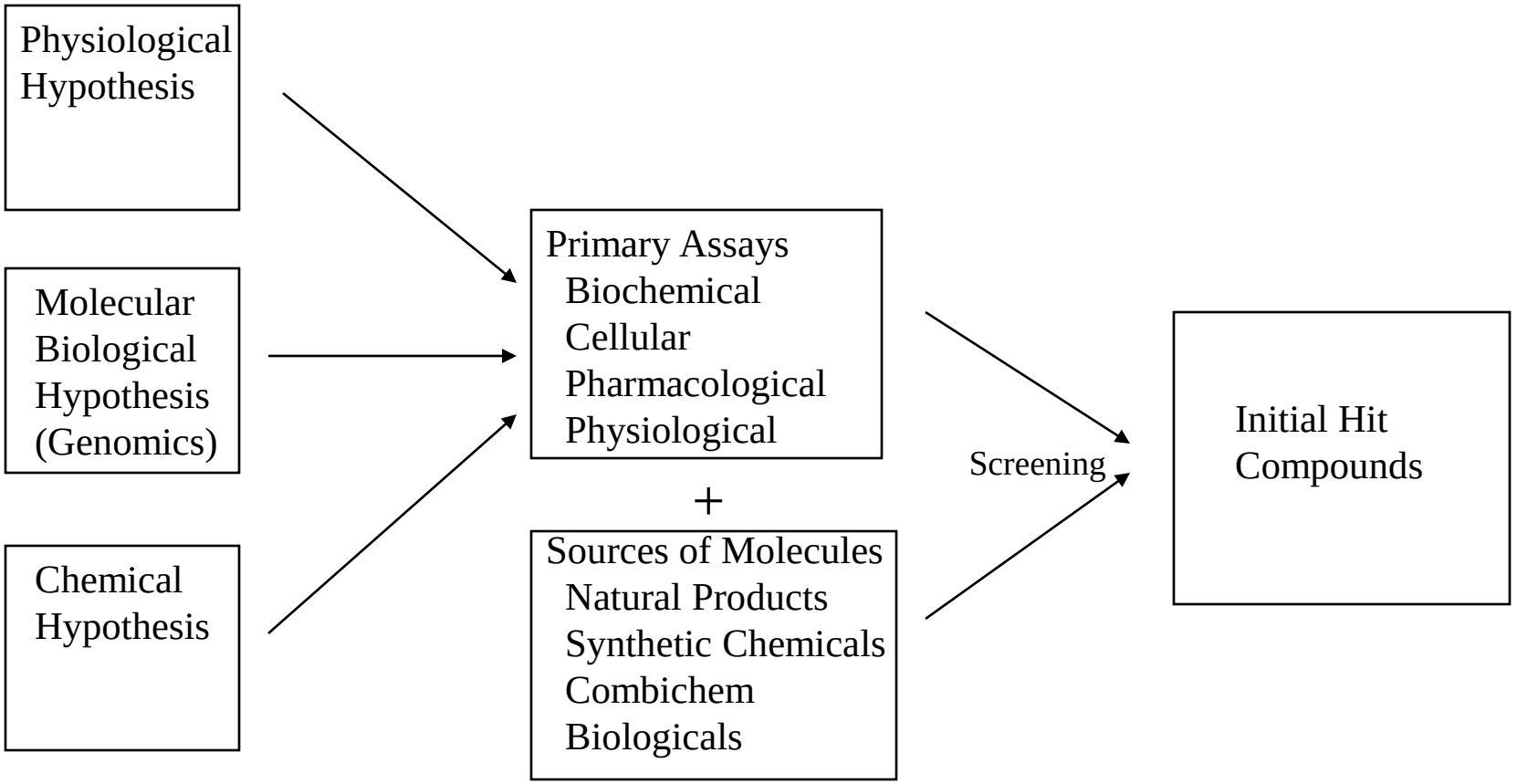
- Drug Discovery
  - Concept, mechanism, assay, screening, hit identification, lead demonstration, lead optimization
  - In Vivo proof of concept in animals and concomitant demonstration of a therapeutic index (=LD50 / ED50, 治疗指数=半数致死量/半数有效量)
- Drug Development
  - Begins when the decision is made to put a molecule into phase I clinical trials

Flow of Drug Development

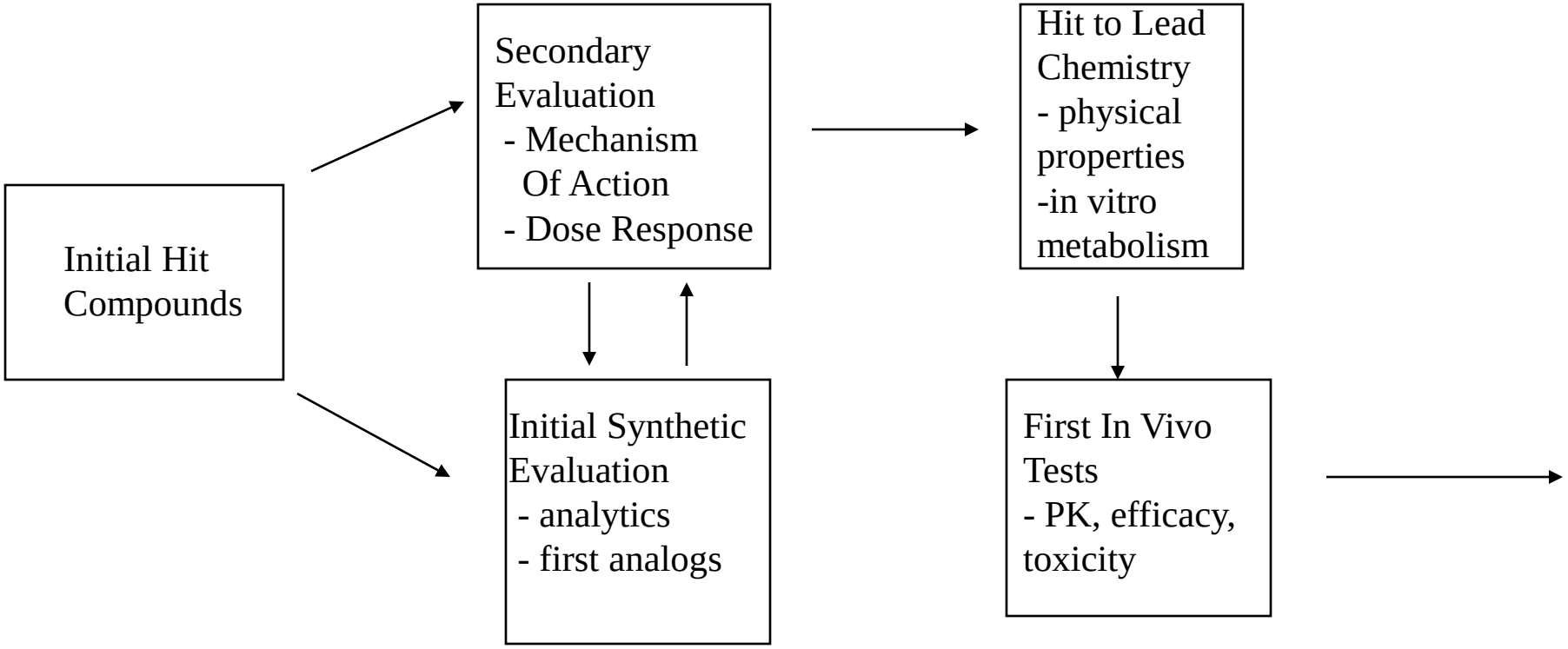


Drug Discovery Today 7: 315-323 (2002)

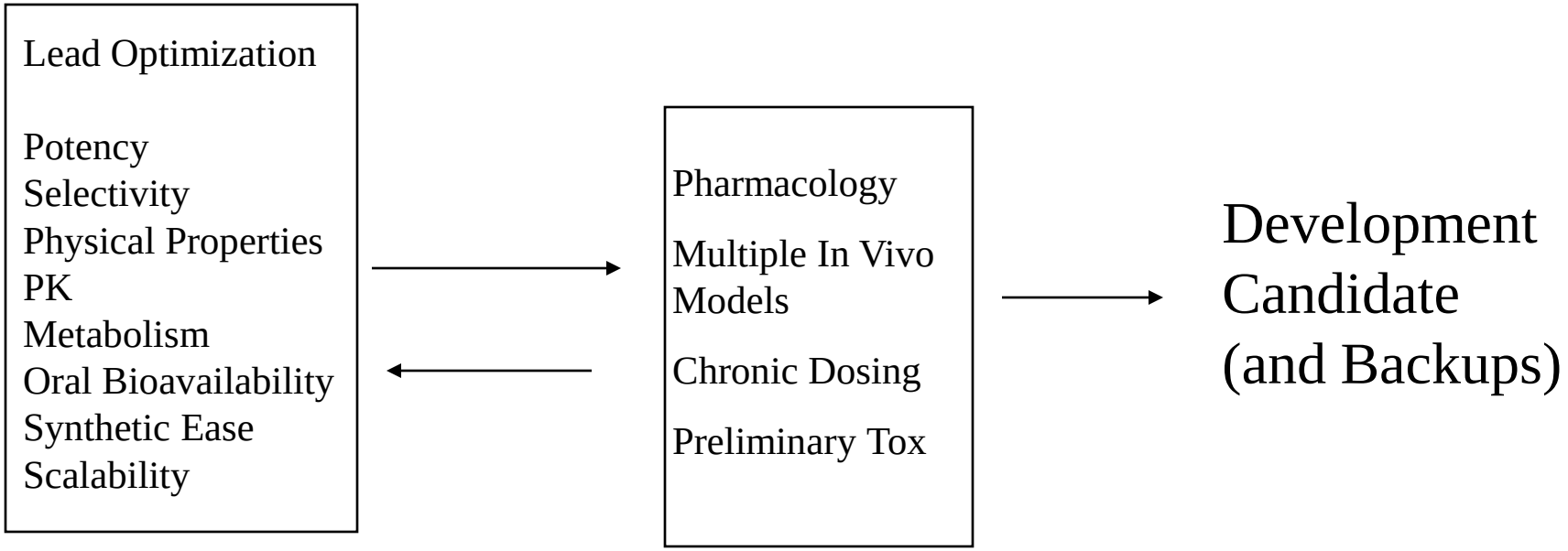
Drug Discovery Processes



Drug Discovery Processes - II



Drug Discovery Processes - III



Issues in Drug Discovery

- Hits and Leads - Is it a “Druggable” target?
- Resistance
- Pharmacodynamics 药效学
- Pharmacokinetics 药物代谢动力学
- Delivery - oral and otherwise
- Metabolism
- Solubility, toxicity
- Patentability

Issues in Drug Discovery

药物代谢动力学（Pharmacokinetics, PK）

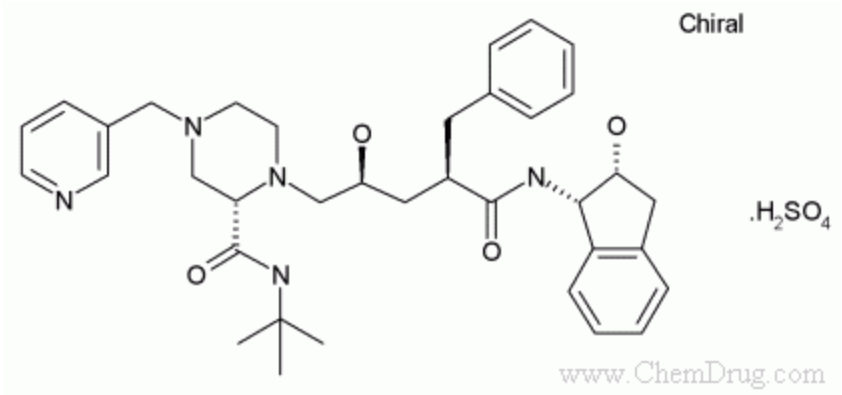
- A (Absorption)：药物从作用部位进入体循环的过程
- D (Distribution)：药物吸收后通过细胞膜屏障向各组织、器官或者体液进行转运的过程
- M (Metabolism)（Biotransformation）：药物在体内受酶系统或者肠道菌丛的作用而发生结构转化的过程
- E (Excretion)：药物以原型或者代谢产物的形式排出体外的过程
- T (Toxcity)：药物对机体的毒性

Drug Discovery Disciplines

- Medicine
- Physiology/pathology
- Pharmacology
- Molecular/cellular biology
- Automation/robotics
- Medicinal, analytical,and combinatorial chemistry
- Structural and computational chemistry
- Bioinformatics

Successful drug developments

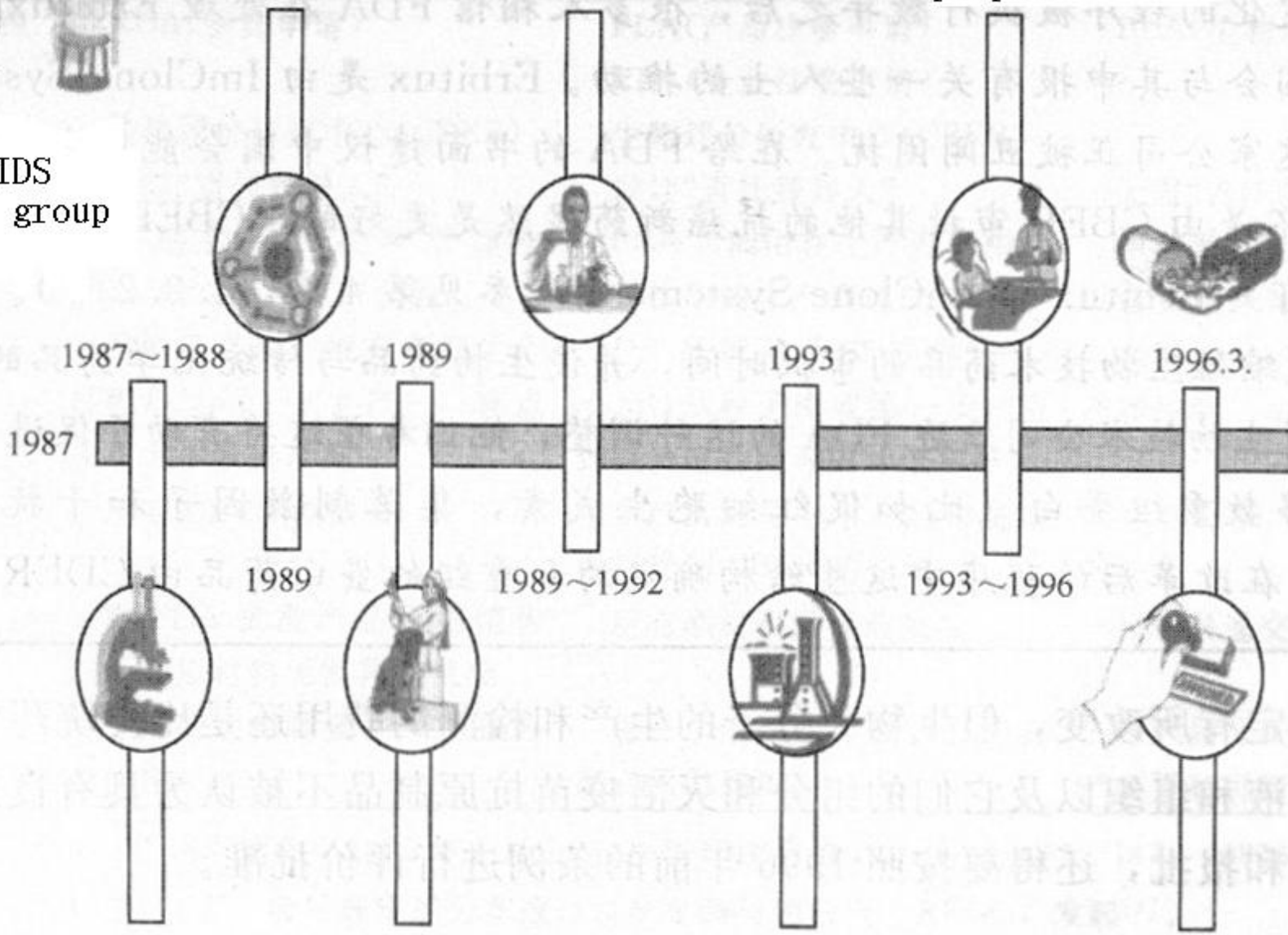
- HIV-1 Protease Inhibitors in the market:
  - Inverase (Hoffman-LaRoche, 1995)
  - Norvir (Abbot, 1996)
  - Crixivan (Merck, 1996)
  - Viracept (Agouron, 1997)



HIV protease

people

erck AIDS
esearch group



HIV
Protease
sequence

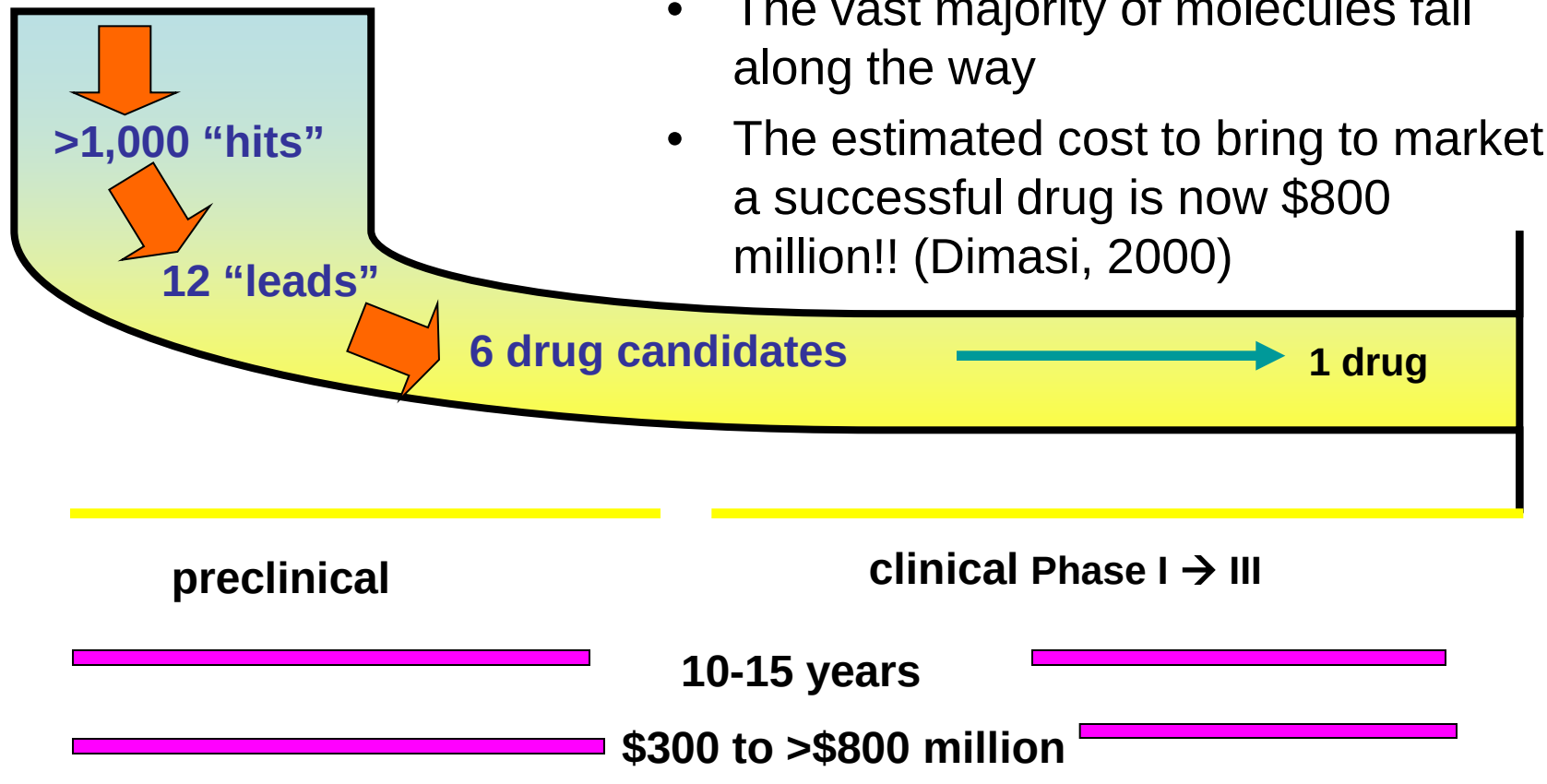
Toxicol
assay

Human assay

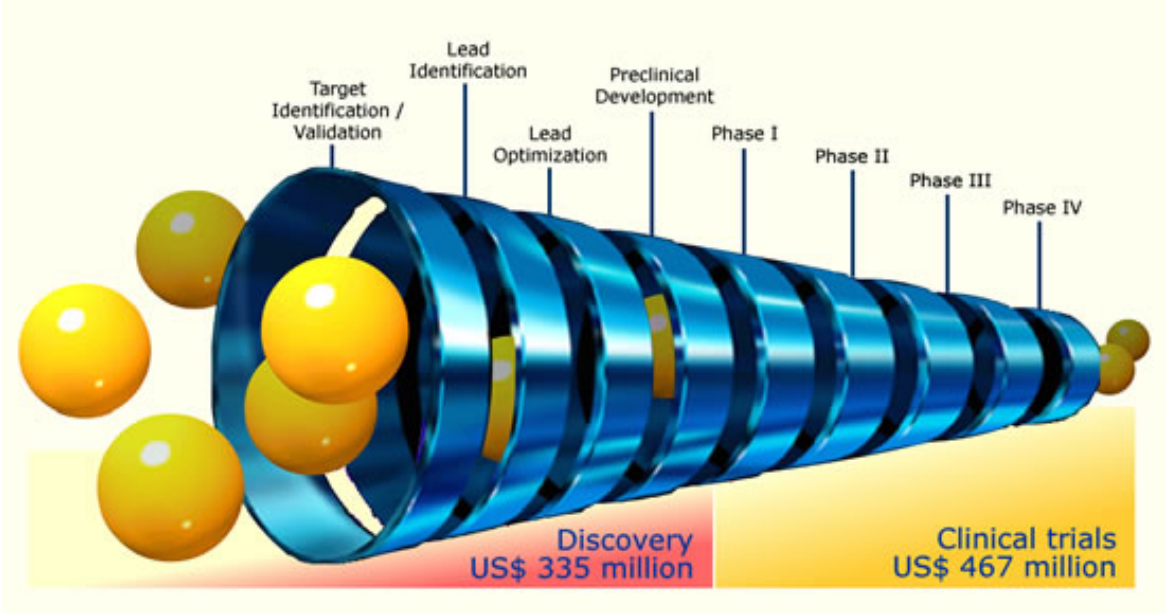
FDA approval
Crixivan after
42 days of Merck
NDA

Costs of drug discovery and development

- The time from conception to approval of a new drug is typically 10-15 years
- The vast majority of molecules fail along the way
- The estimated cost to bring to market a successful drug is now $800 million!! (Dimasi, 2000)

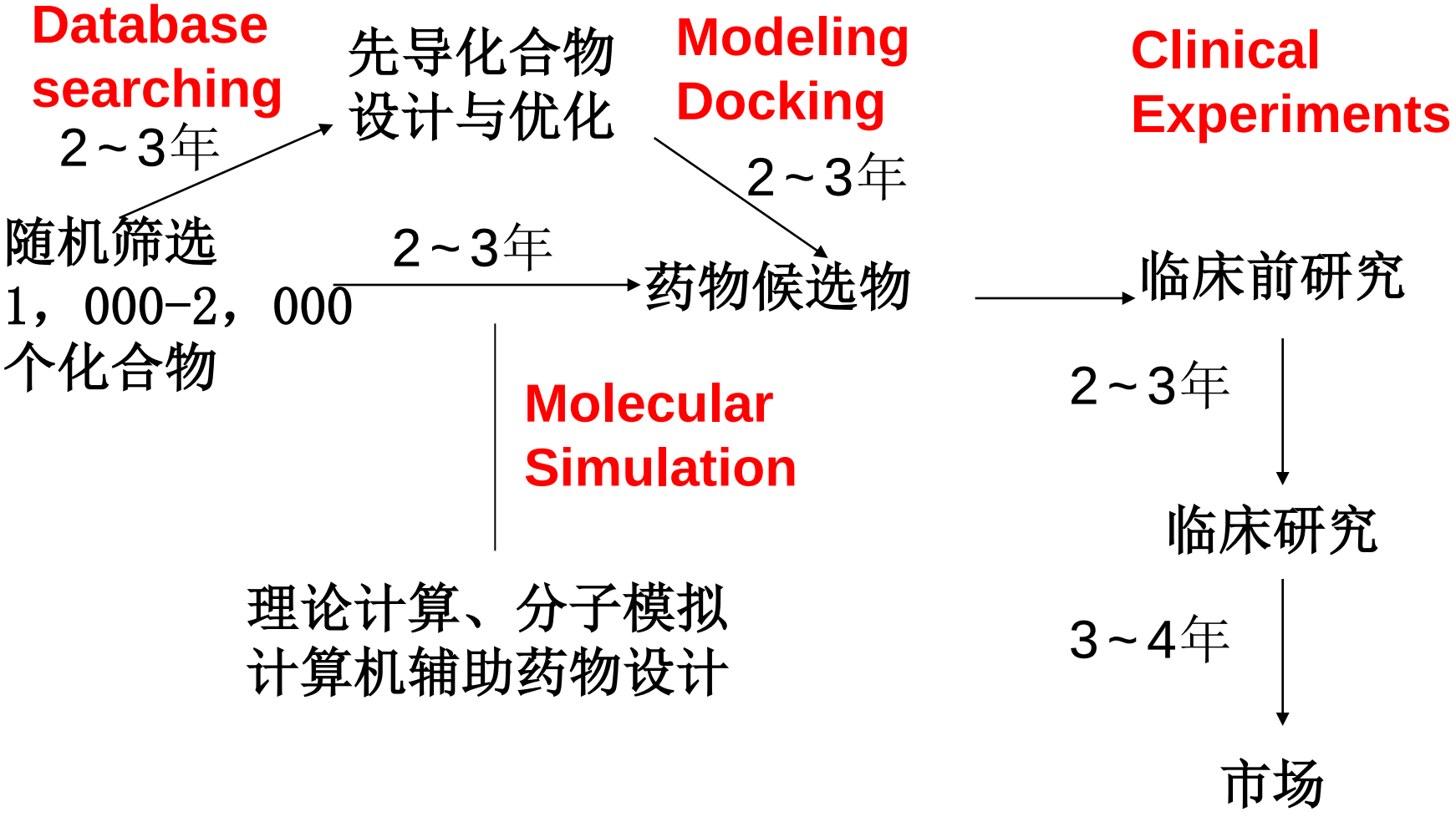


Costs in the Drug Discovery Pipeline

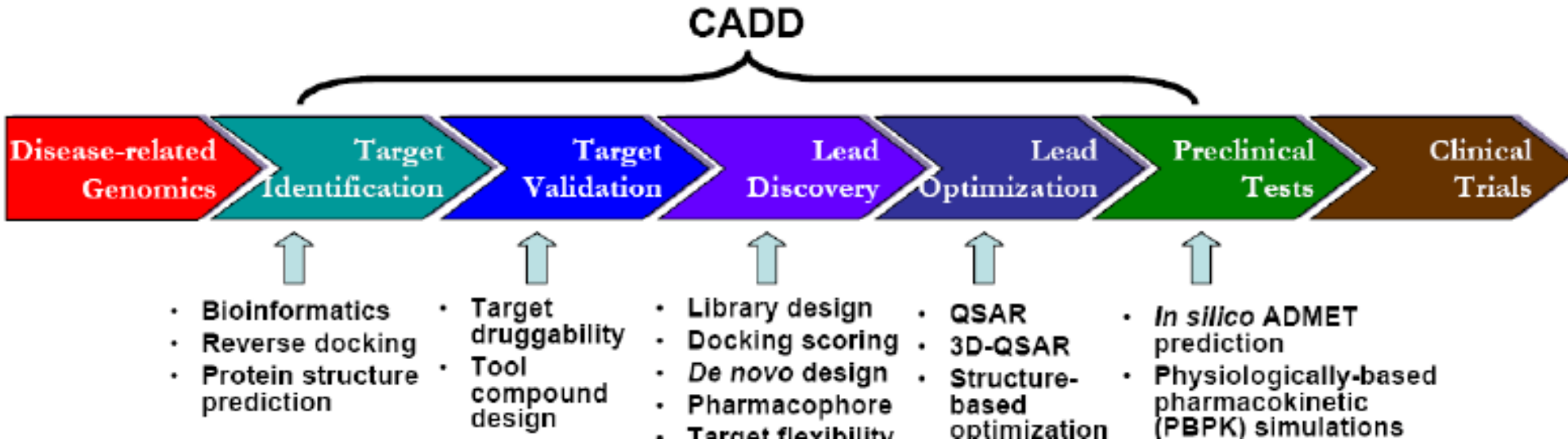


- Clinical trials are most expensive part of the pipeline – if failure can be predicted before this point, it saves time and money

Why we need computers?



CADD in various stages of drug discovery



A Little History of Computer Aided Drug Design

- 1960’s - Viz - review the target - drug interaction
- 1980’s- Automation - high throughput target/drug selection
- 1980’s- Databases (information technology) - combinatorial libraries
- 1980’s- Fast computers - docking
- 1990’s- Fast computers - genome assembly - genomic based target selection
- 2000’s- Vast information handling - pharmacogenomics

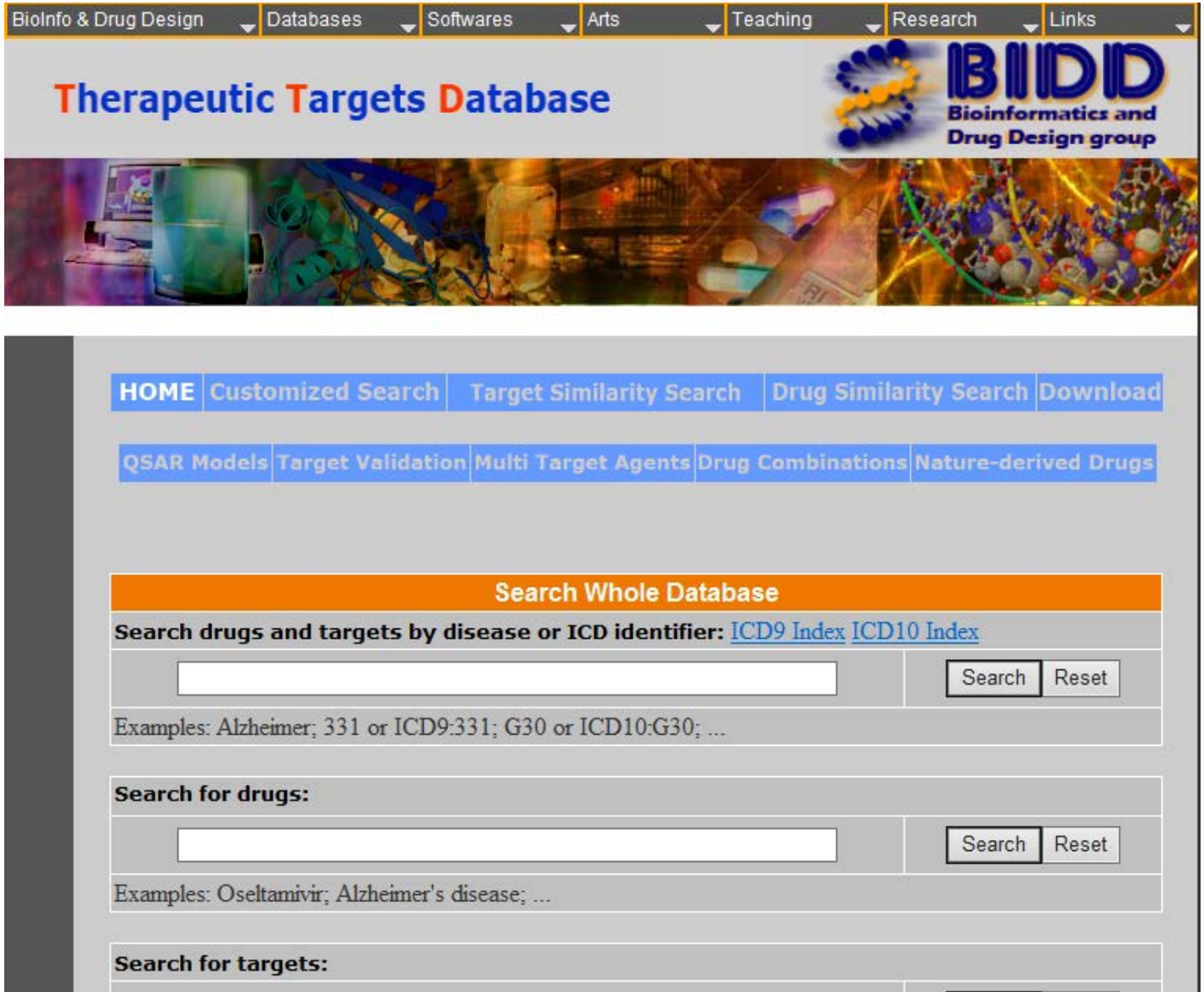
Drug Targets

- Proteins
  - Receptor
  - enzyme
  - ion channel
- Nucleic acid
- Therapeutic Target Database (TTD)

  http://bidd.nus.edu.sg/group/ttd/ttd.asp

Biomacromolecules that can interact with drug molecule and generate physiological effect

Therapeutic Target Database (TTD)



Therapeutic Target Database (TTD)

You are searching for: 'aids'
All drugs with indication or ICD9 containing the above word(s) will be displayed.

<<First <Previous Page 1 of 1 Next> Last>>

Search Result

Disease Entry	**diagnostic aids for mydriasis**		
ICD9	379.43	**ICD10**	H57.0
Target	TTDS00005 Muscarinic acetylcholine receptor M4		
Drug	DAP000345 Tropicamide	**Status**	Approved

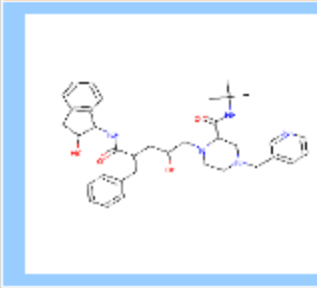
Disease Entry	**aids-related kaposi's sarcoma**		
ICD9	176	**ICD10**	C46
Target	TTDS00492 Interferon-alpha/beta receptor		
Drug	Not Available	**Status**	Not Available

Disease Entry	**aids related dementia**		
ICD9	042, 290-294	**ICD10**	B20, F01-F07
Target	TTDR00950 Kynureninase		

Therapeutic Target Database (TTD)

You are searching for: 'Crixivan'

<<First <Previous Page 1 of 1 Next> Last>>

Structure	Search Result	
	Drug Name	**Indinavir**
	Drug Status	Approved
	Disease	HIV infection
	TTD Drug ID	DAP000168 Drug Info

<<First <Previous Page 1 of 1 Next> Last>>

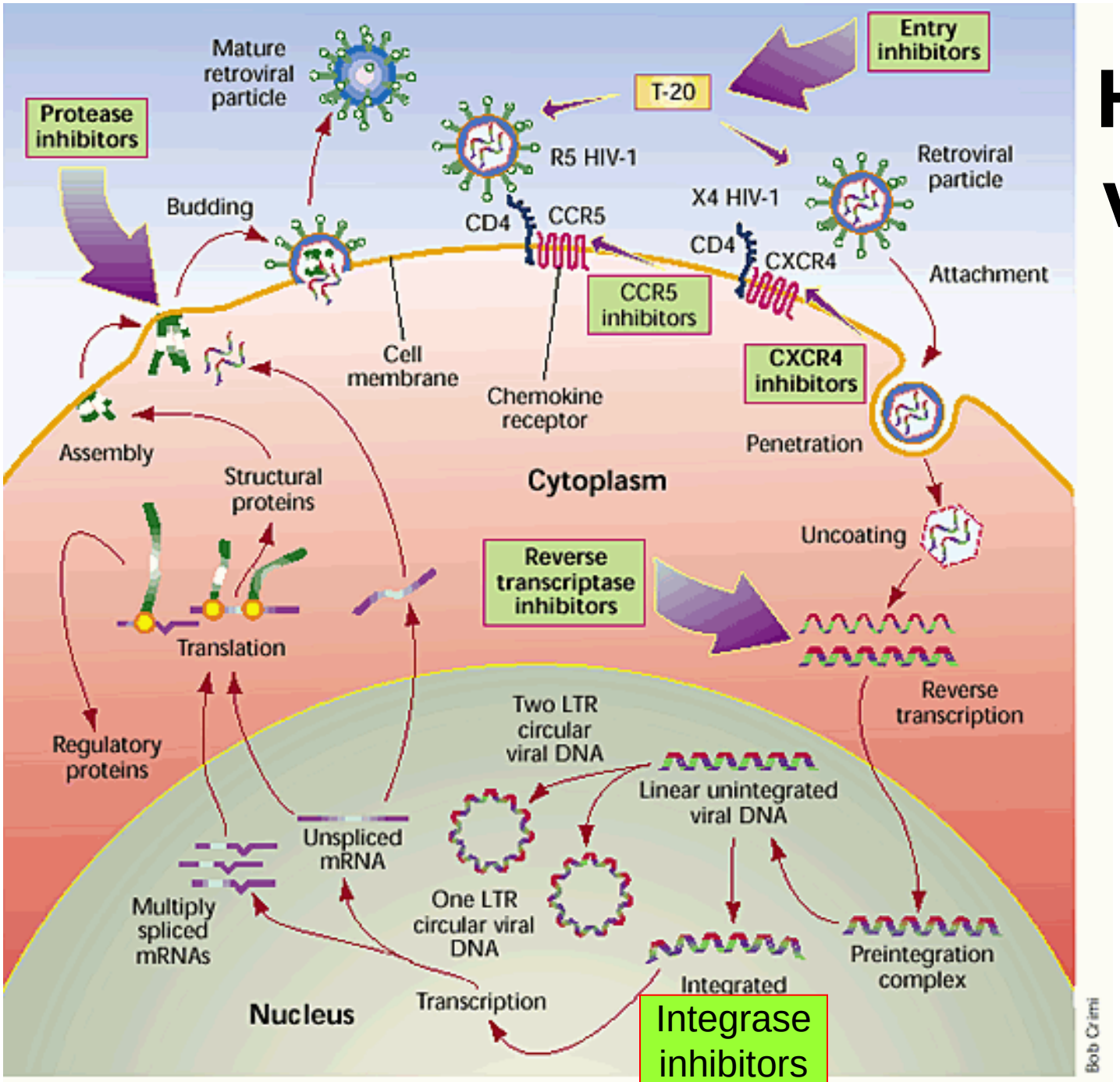
Drugs and targets

- One drug on one target
- Multi target agents
  - One drug on multiple target
  - Side effects
  - Serendipity in Drug Discovery
- Drug combinations
  - Complexed biological metabolism
  - Interference between drugs
  - Cock tail to overcome Drug resistance
- Nature derived drugs, traditional medicine

Serendipity in Drug Discovery

- Surprised effect of one drug designed for other proposes
  - Tamoxifen (birth control and breast cancer)
  - Viagra (hypertension 高血压 and erectile dysfunction 勃起功能障碍)
  - Salvarsan (Sleeping sickness and syphilis 胎传性梅毒)
  - Interferon-α (hairy cell leukemia 多毛细胞白血病 and Hepatitis C丙肝)

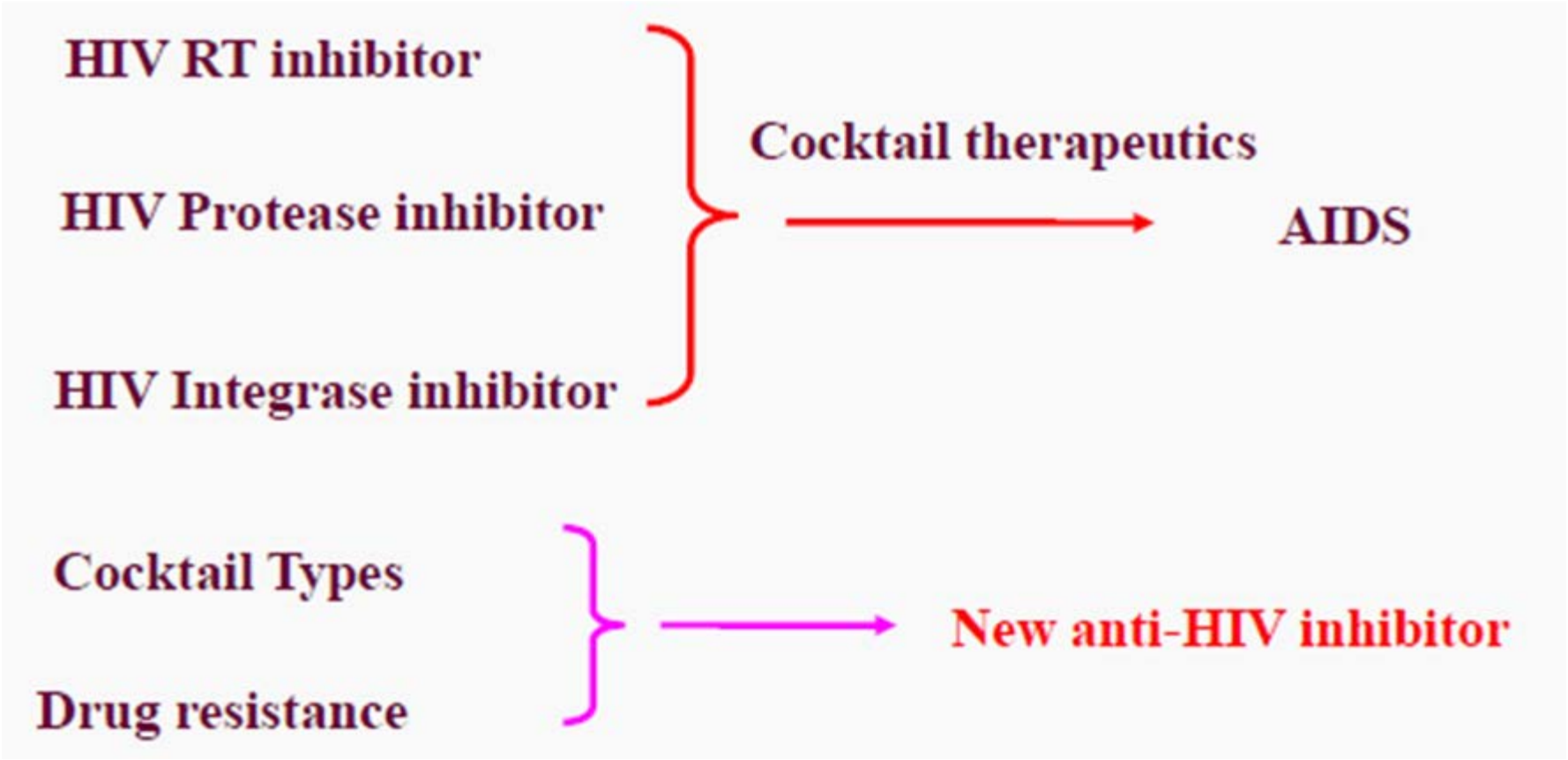
Cocktail therapy of AIDS



HIV-1 virus

Nature Medicine 5, 740 - 742 (1999)

Cocktail therapy of AIDS



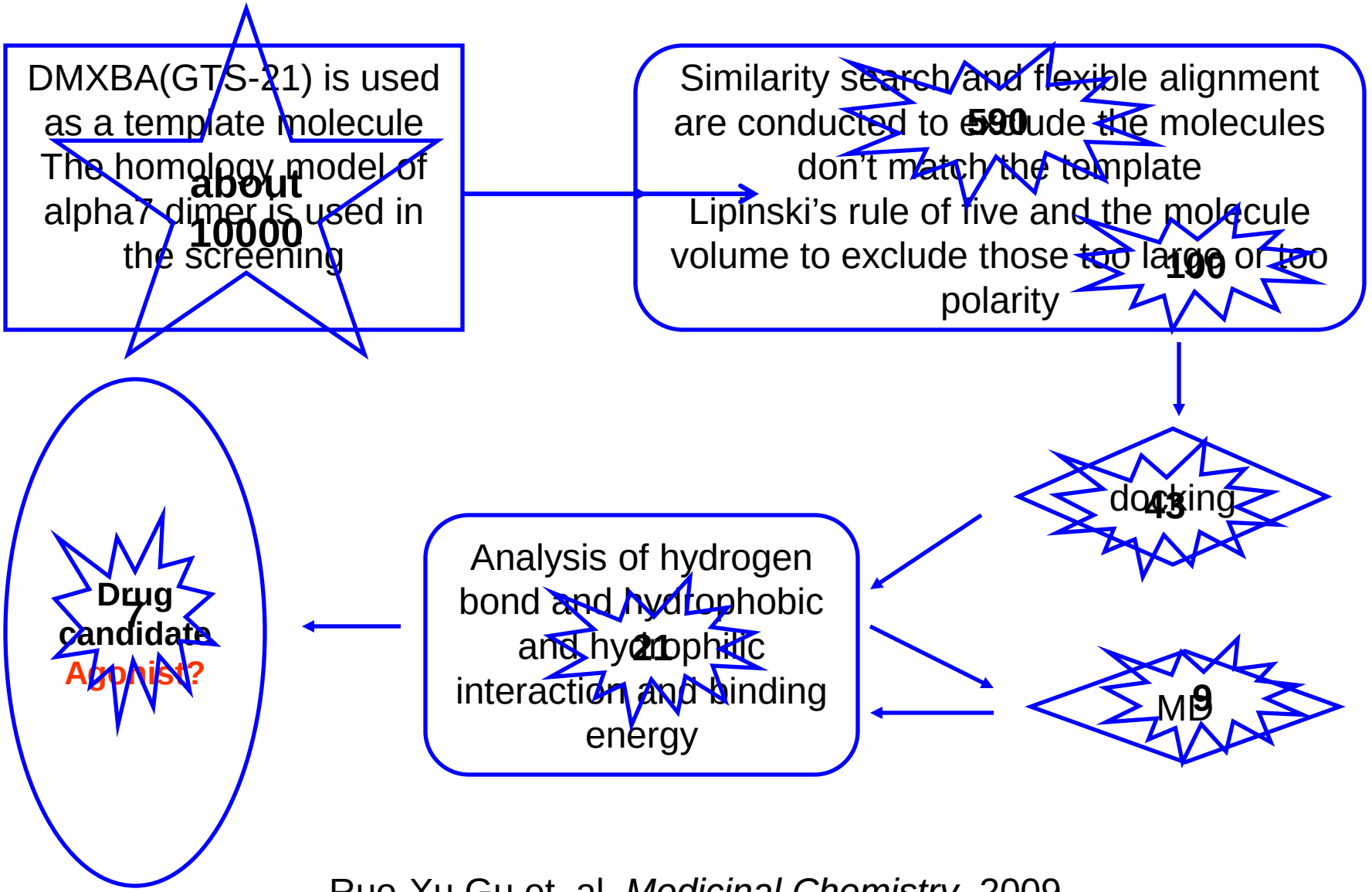
Types of Drug Combinations

Pharmacodynamically

- Synergistic（协同）
  - due to anti-counteractive actions
  - due to complementary actions
  - due to facilitating actions
- Additive （叠加）
- Antagonistic（颉抗 ）
- Potentiative（增效）
- Reductive（降效）

gx50 - an example of computer aided drug design

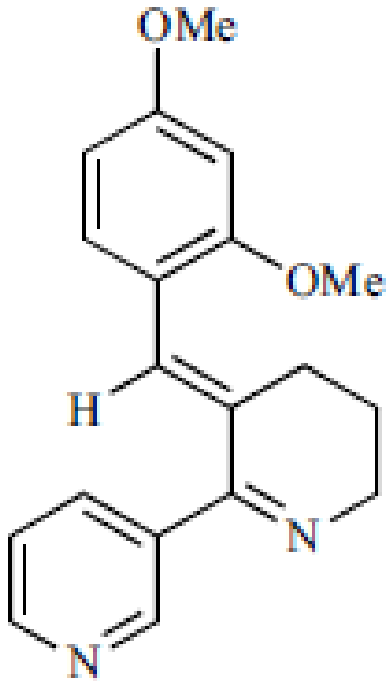
The screening 药物虚拟筛选



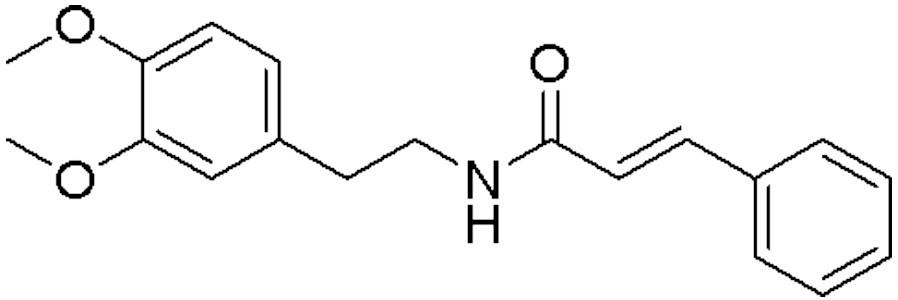
Ruo-Xu Gu et. al. *Medicinal Chemistry*, 2009

gx-50 – The Best molecule found in TCM Database

DMXBA(GTS-21)



gx-50



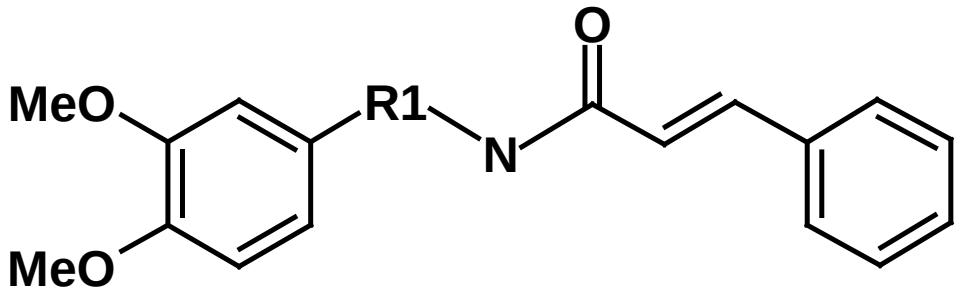
N-(2-(3,4-DIMETHOXYPHENYL)ETHYL)-3-PHENYLACRYLAMIDE

A molecule from Pricklyash Peel (Sichuan pepper)

Ruo-Xu Gu et. al. *Medicinal Chemistry*, 2009

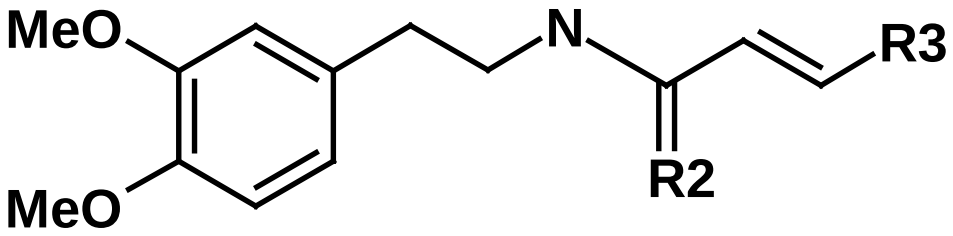
Maoping Tang et.al., Journal of Alzheimer's Disease 2013

Optimization and Modification of gx-50



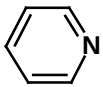
Original R1: -CH2-CH2-

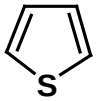
Modified R1: (1) -CH2- ; (2) -(CH2)3- ; (3) -(CH2)4- ; (4) -CH(CH3)CH2- ;
(5) -CH2CH(CH3)- ; (6) -C(CH3)=CH- ; (7) -CH=C(CH3)-

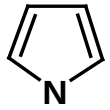


Original: R2=O, and R3= 

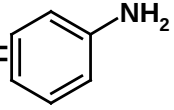
Modified:

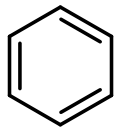
(8) R2=O, R3= 

; (9) R2=O, R3= 

;(10) R2=O, R3= 

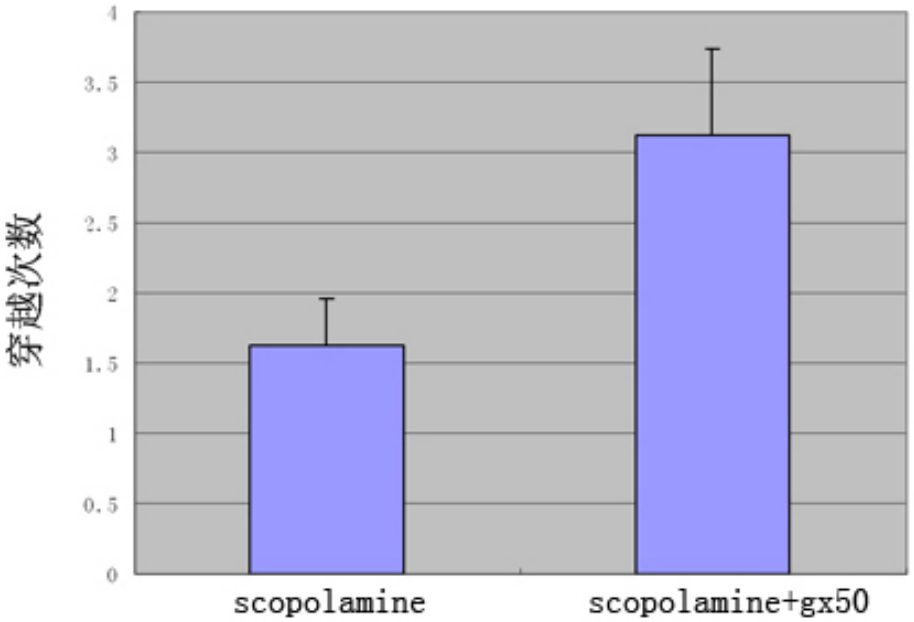
;

(11) R2=O, R3= 

;(12) R2=S, R3= 

Ruo-Xu Gu et. al. *Medicinal Chemistry*, 2009

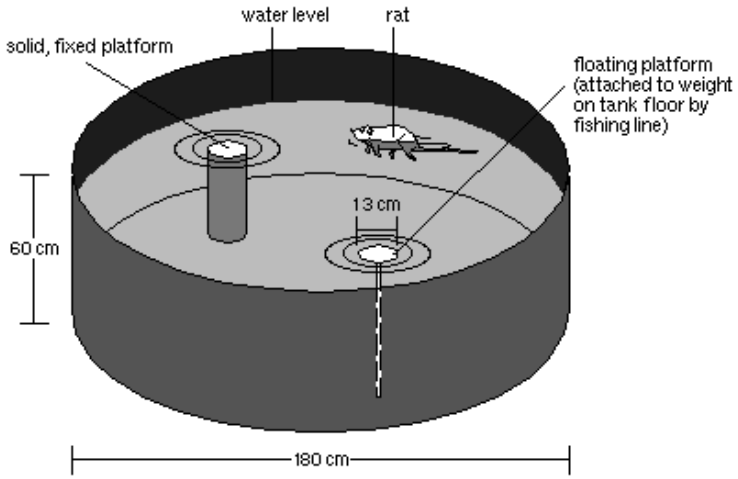
morris water maze

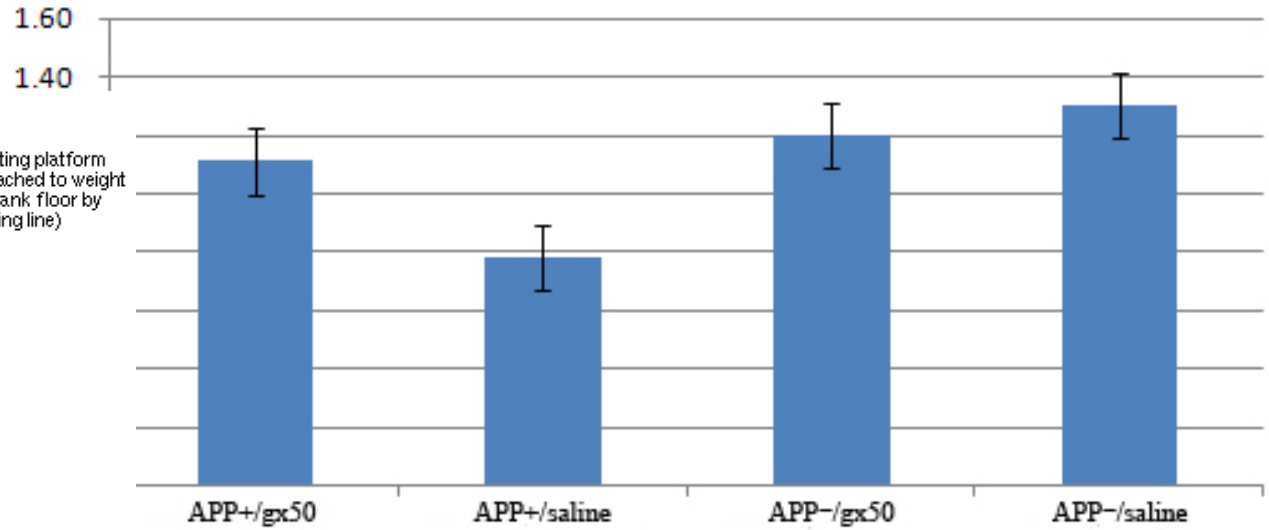


水迷宫实验

通过对东莨宕碱模型小鼠和APP转基因小鼠进行水迷宫实验，结果表明gx-50可以明显的改进小鼠的记忆力

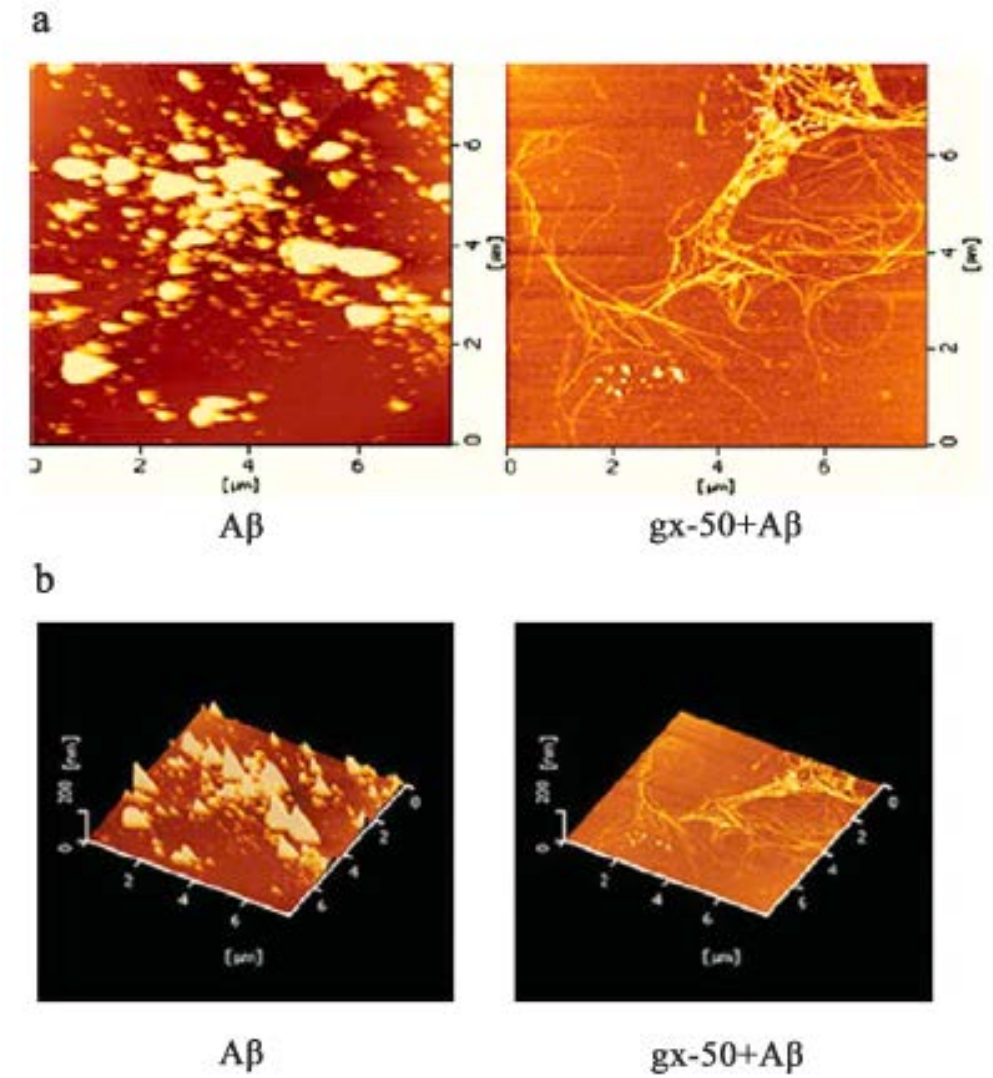
Morris water maze test demonstrated that gx50 could improve the memory ability of dementia mice





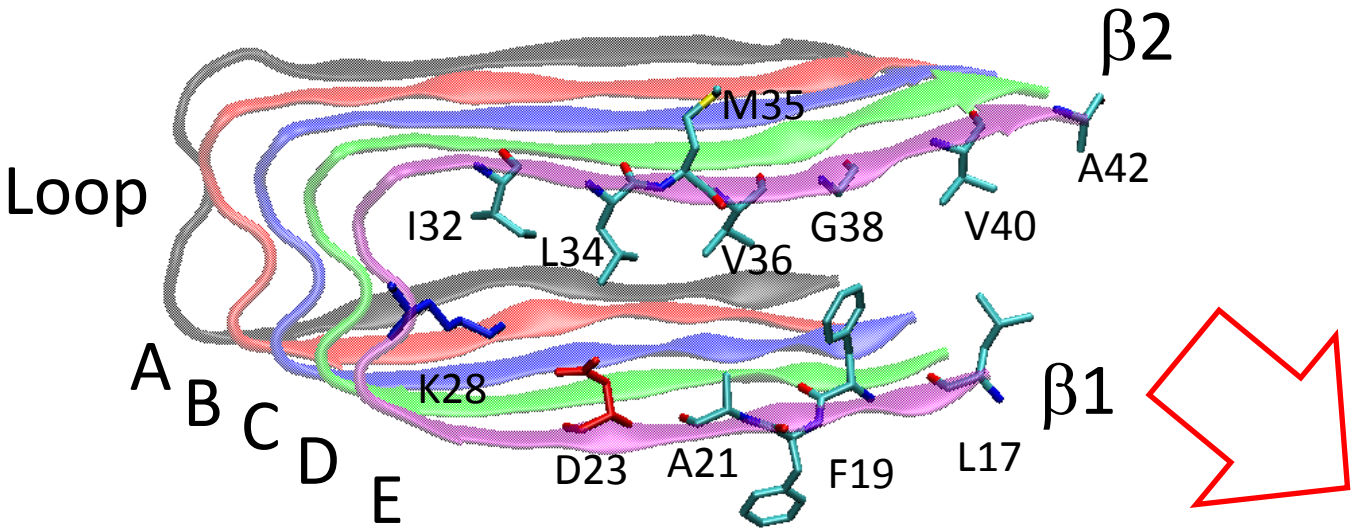
Aβ depolymerization-
Atomic Force Microscope（AFM）

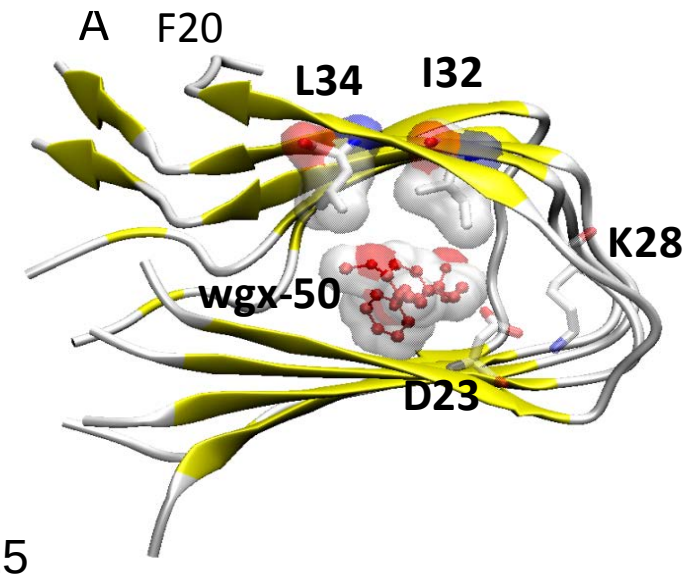
Aβ解聚实验–原子力显微镜

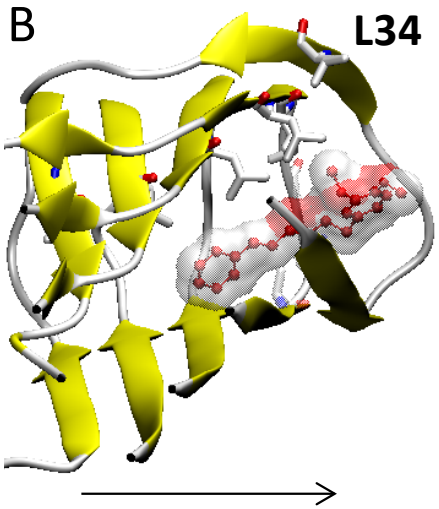


Maoping Tang et.al., Journal of Alzheimer's Disease 2013

Destabilization of Alzheimer's Aβ42 Protofibrils with Wgx-50 by Molecular Dynamics Simulations







Huaimeng Fan et. al. *JPCB* 2015