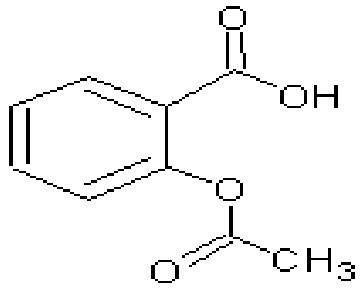
DRUG

Any chemical compound used in the treatment, or prevention of disease or other abnormal condition.

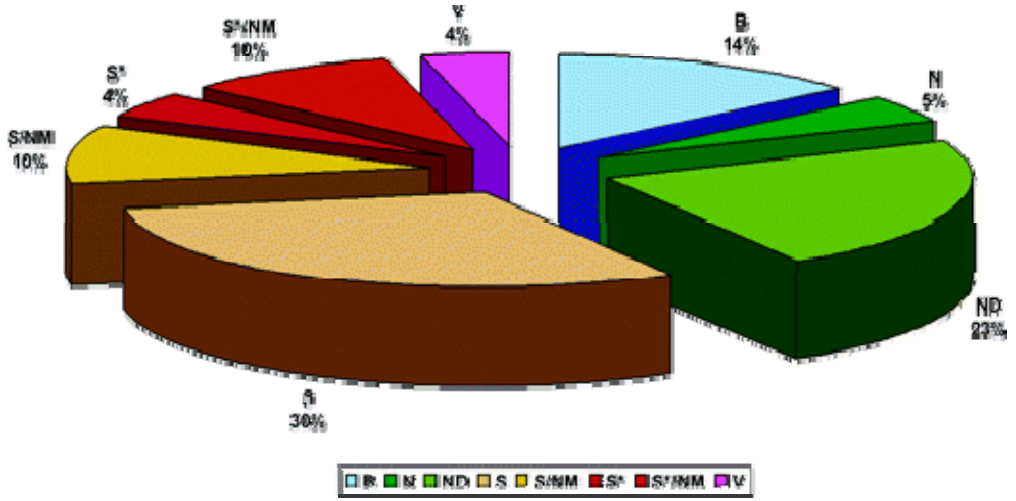


Aspirin

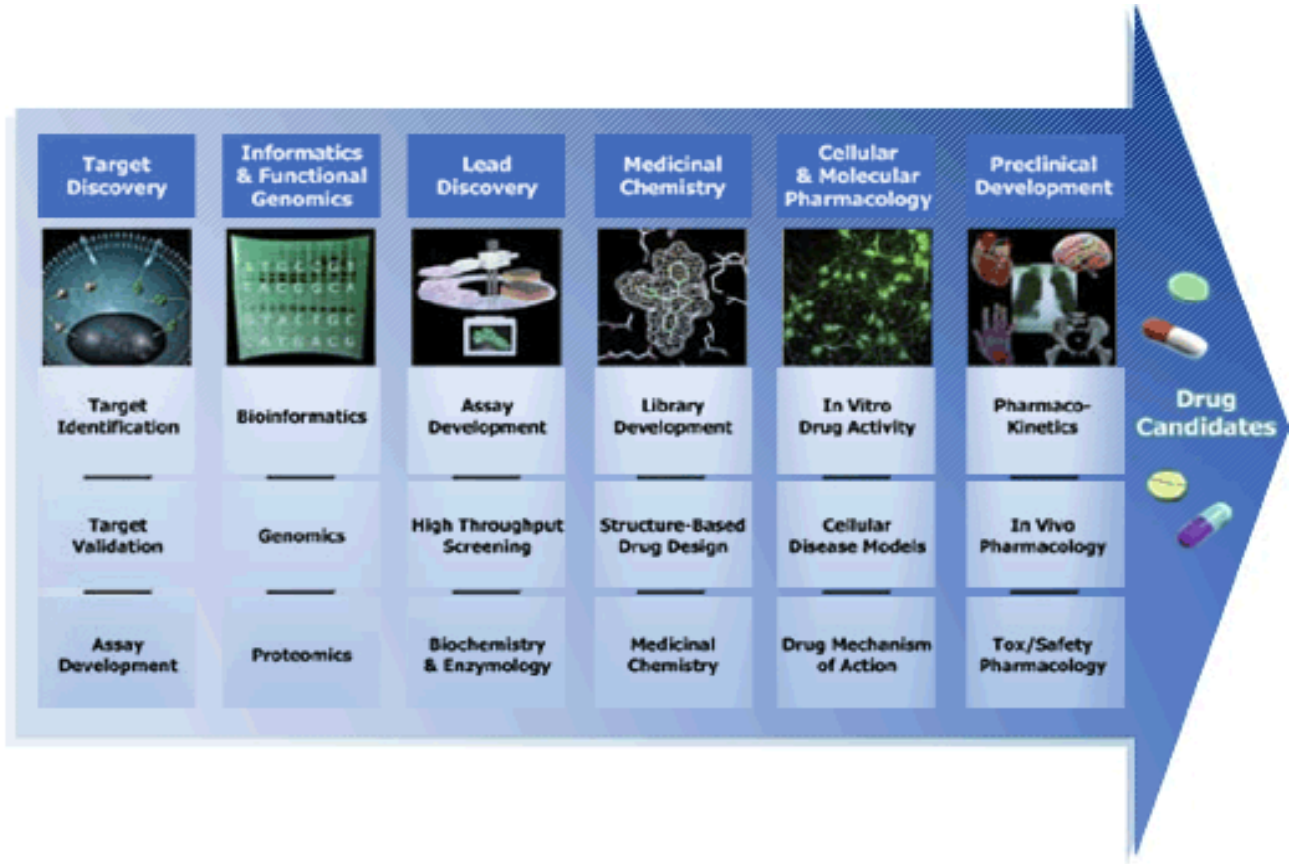
Acetylsalicylic Acid

$C_9H_8O_4$

All new chemical entities, 01/1981-06/2006, by source (*N* = 1184).



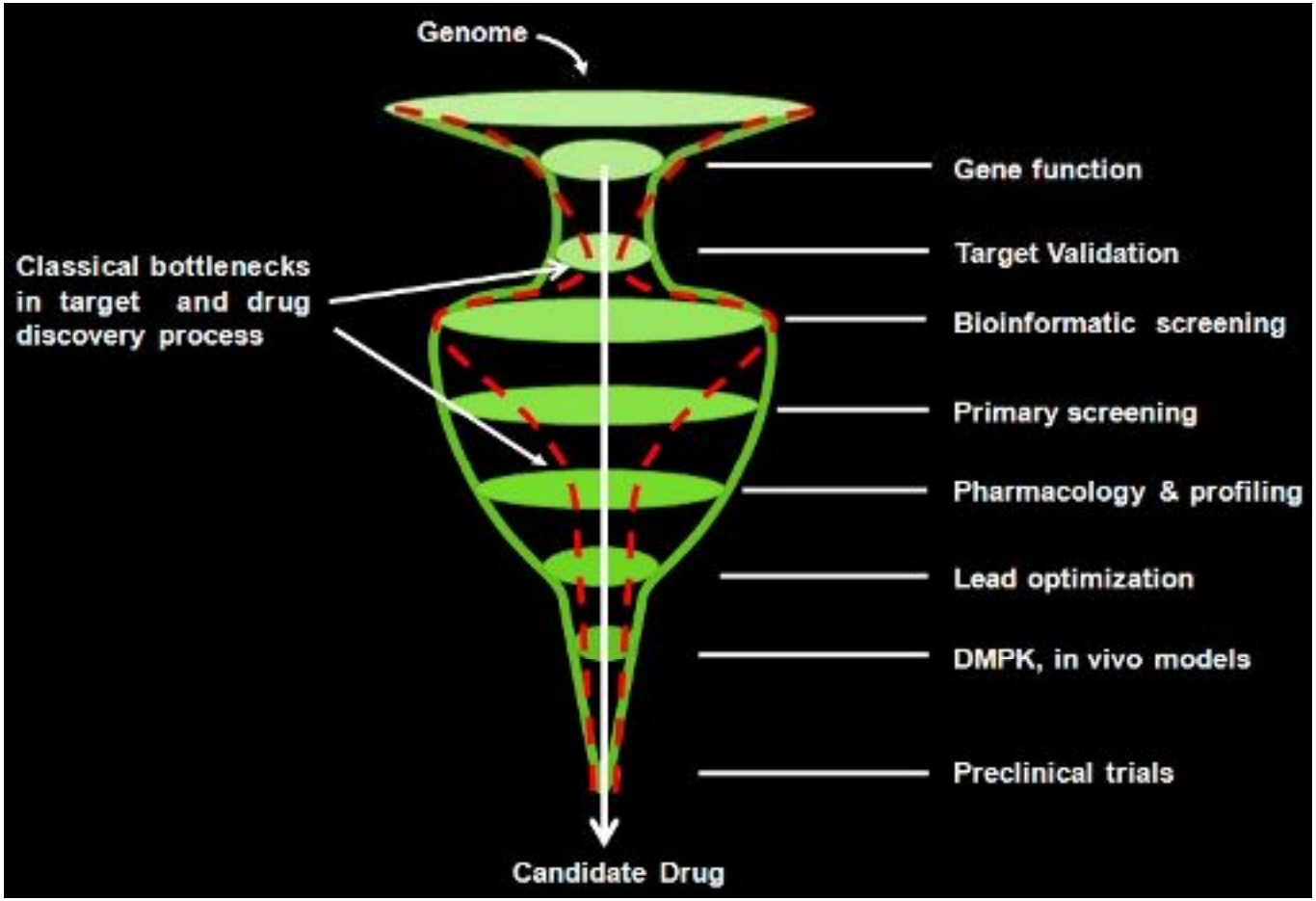
B" Biological; usually a large (>45 residues) peptide or protein either isolated from an organism/cell line or produced by biotechnological means in a surrogate host.
"N" Natural product.
"ND" Derived from a natural product and is usually a semisynthetic modification.
"S" Totally synthetic drug, often found by random screening/modification of an existing agent.
"S*" Made by total synthesis, but the pharmacophore is/was from a natural product.
"V" Vaccine.


Target Discovery
Informatics & Functional Genomics
Lead Discovery
Medicinal Chemistry
Cellular & Molecular Pharmacology
Preclinical Development
Target Identification
Bioinformatics
Assay Development
Library Development
In Vitro Drug Activity
Pharmaco-Kinetics
Target Validation
Genomics
High Throughput Screening
Structure-Based Drug Design
Cellular Disease Models
In Vivo Pharmacology
Assay Development
Proteomics
Biochemistry & Enzymology
Medicinal Chemistry
Drug Mechanism of Action
Tox/Safety Pharmacology
Drug Candidates

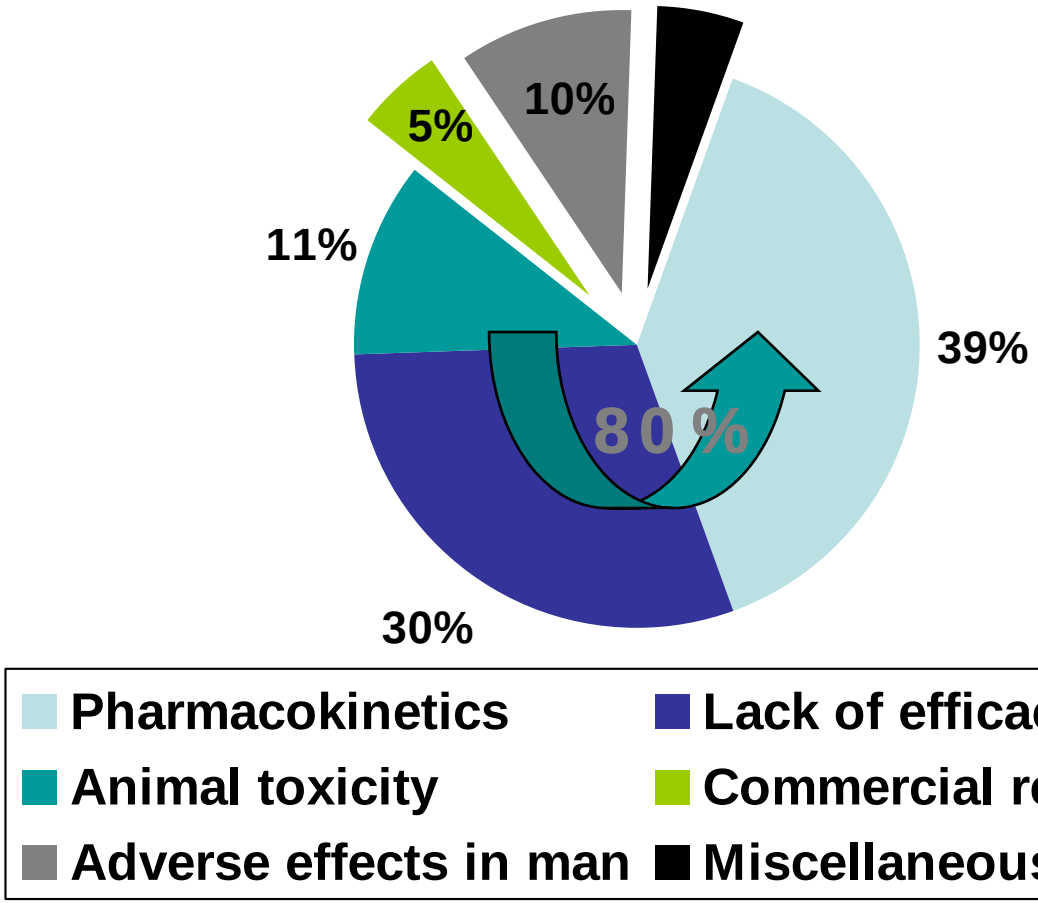
- **Average time from project inception to drug launch: 13-14 year**

- **Average total investment per LAUNCHED drug = $1 billion**

- **Average chance of project success:**
  - 1-3% at inception
  - 7-8% if drug reaches preclinical testing


Genome
Gene function
Target Validation
Classical bottlenecks in target and drug discovery process
Bioinformatic screening
Primary screening
Pharmacology & profiling
Lead optimization
DMPK, in vivo models
Preclinical trials
Candidate Drug

Reasons For Drug Failure



80% can be detected in preclinical phase

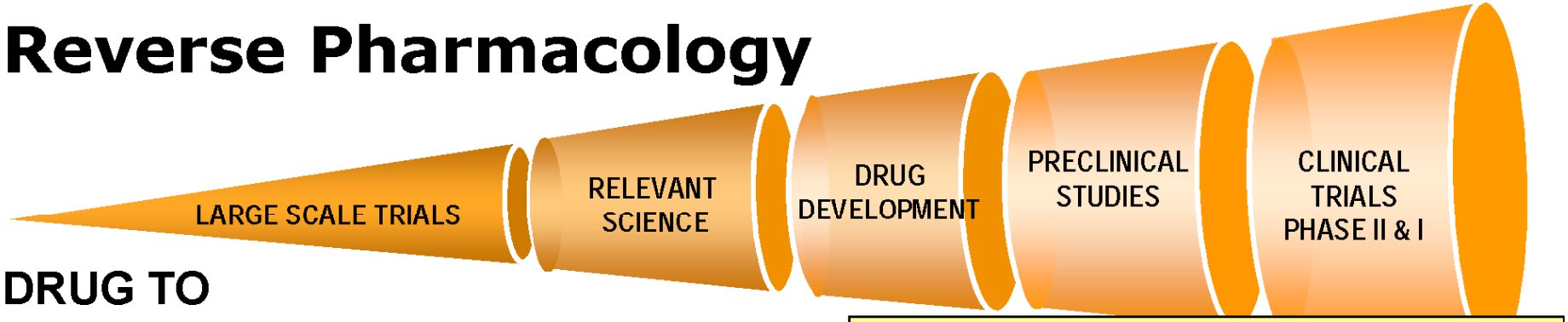
Source: 198 NCEs in clinical development by large UK companies, 1964–1985.

Drug Discovery and Development Process

Expensive, time consuming, numerous bottlenecks

Economical, time sparing, least bottlenecks

Reverse Pharmacology



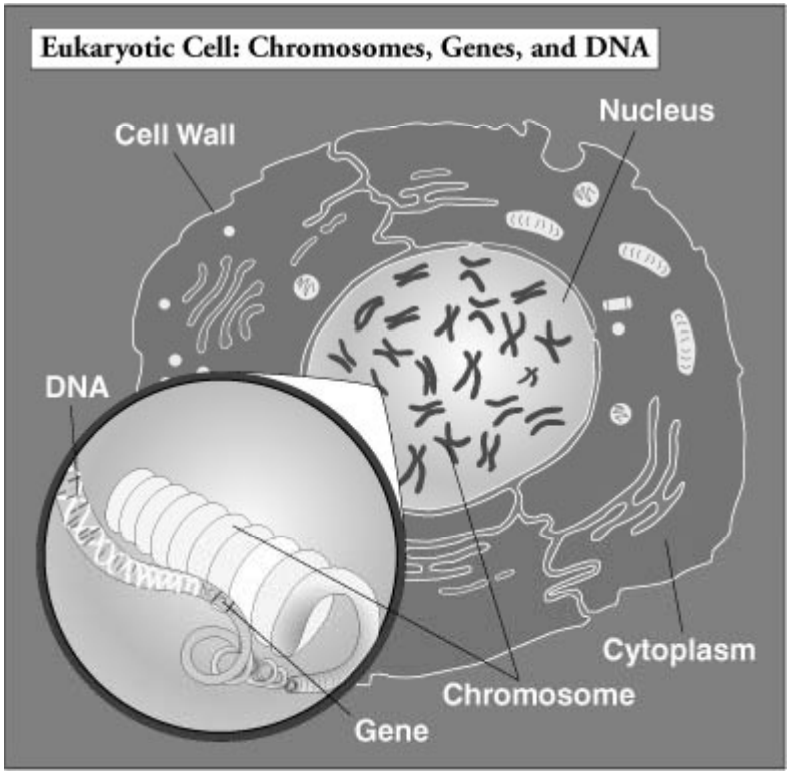
Courtesy: Dr Ashok Vaidya, SPARC, Mumbai

Disease Mechanism

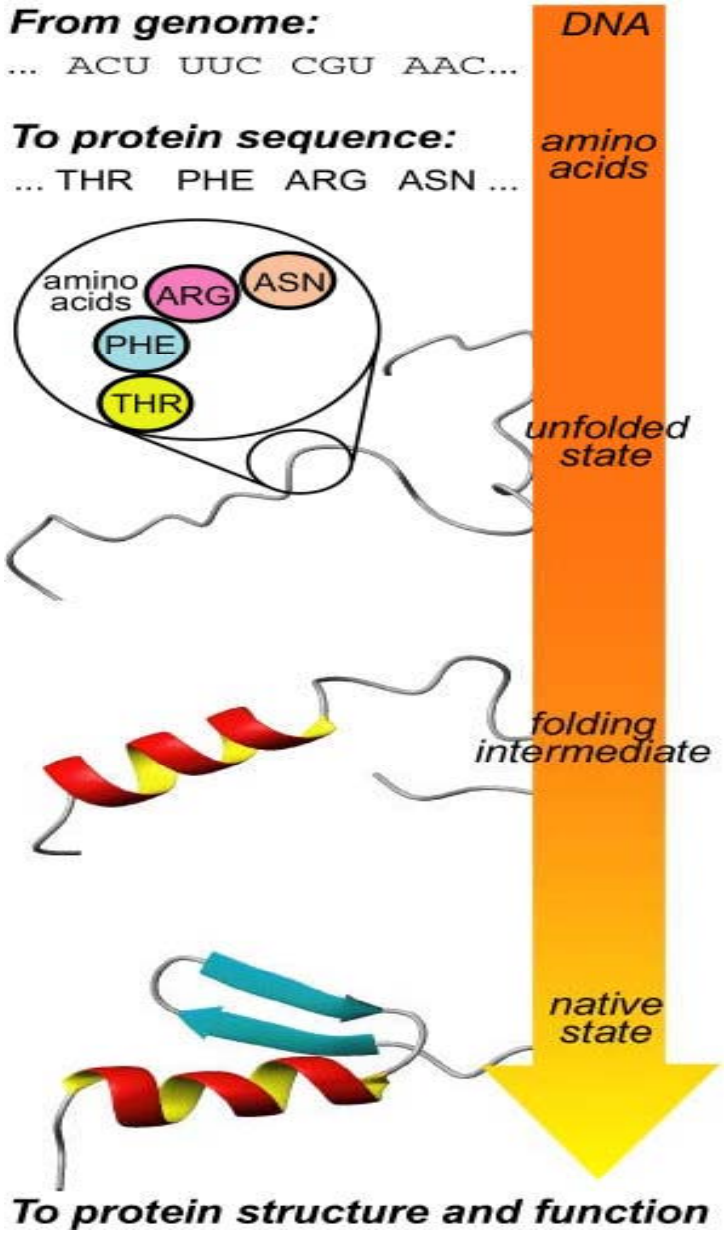
Understanding the disease mechanism directs research and formulates a possible treatment to slow or reverse the disease process.

Disease mechanisms can be broadly classified into the following groups

- **Defects in distinct genes—genetic disorders**
    - **Infection by bacteria, fungi, or viruses**
    - **Immune/autoimmune disease**
    - **Trauma and acute disease based on injury or organ failure**
    - **Multicausal disease**



Genes - A gene is a section of the DNA strand that carries the instructions for a specific function.


From genome:
... ACU UUC CGU AAC...
To protein sequence:
... THR PHE ARG ASN ...
DNA
amino acids
amino acids
ARG
ASN
PHE
THR
unfolded state
folding intermediate
native state
To protein structure and function

Target Type and ‘Drugability’

Targets for therapeutic intervention can be broadly classified into these categories:

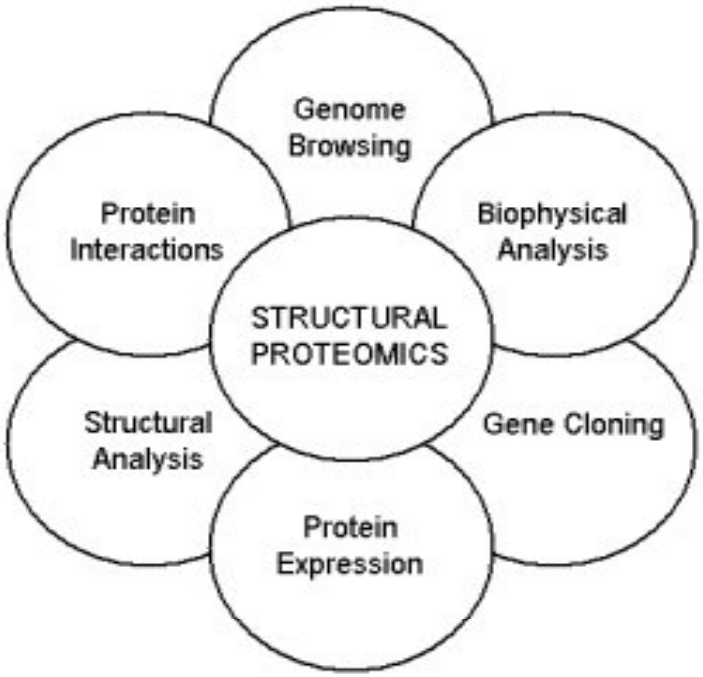
- **Receptors**
- **Proteins and enzymes**
- **DNA**
- **RNA and ribosomal targets**

Target Validation

Requires a demonstration that a molecular target is critically involved in a biological process

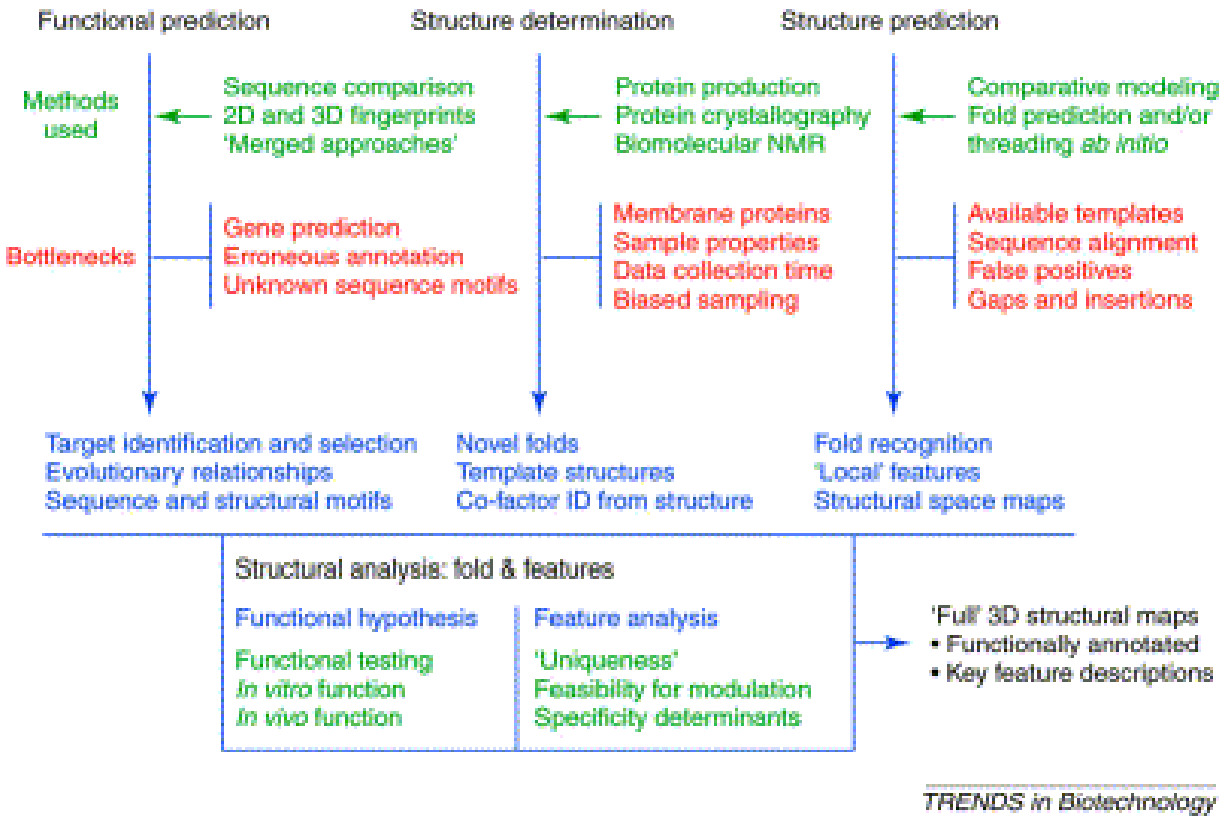
- **Knock-out/Knock-in/Gain-of-function, Transgenic Models**
- **Pathways**
- **Clinical Data**
- **Antisense DNA/RNA and RNAi**

Protein-structure and -function prediction is one of the most important fields in the post-genomic era.

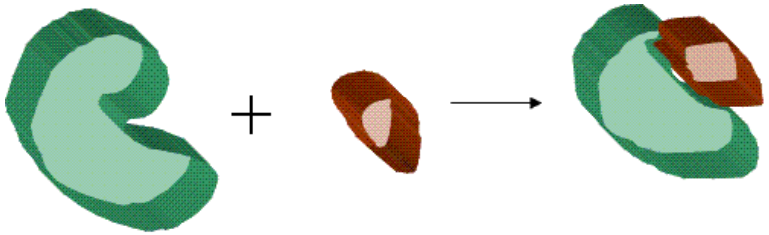

Genome Browsing
Protein Interactions
Biophysical Analysis
STRUCTURAL PROTEOMICS
Structural Analysis
Gene Cloning
Protein Expression

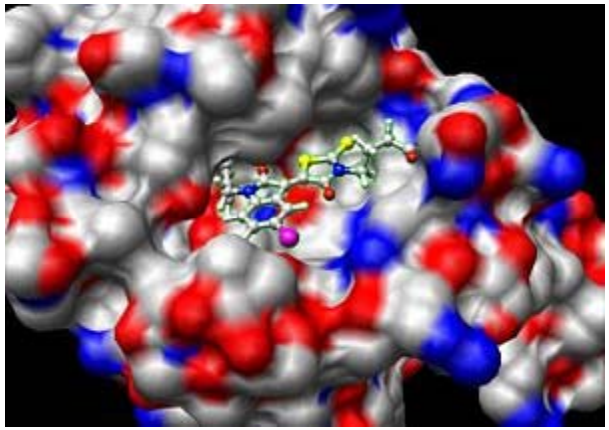
Overview of key factors impacting research programs in structural proteomics

as well as their desired outcome.

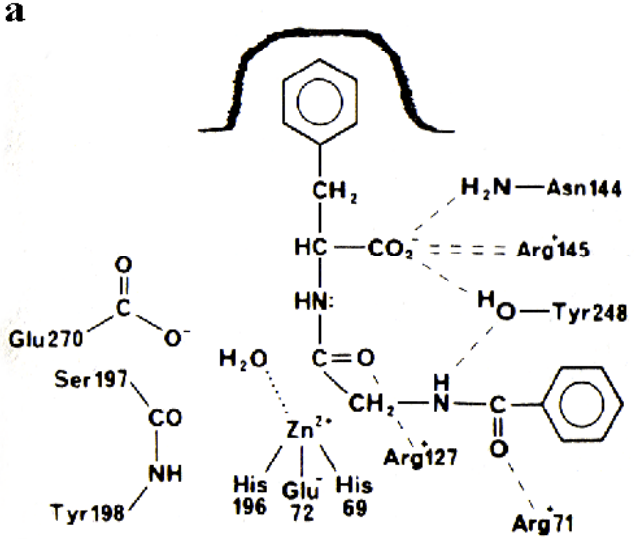


- **Strategies employed for Designing Drugs**

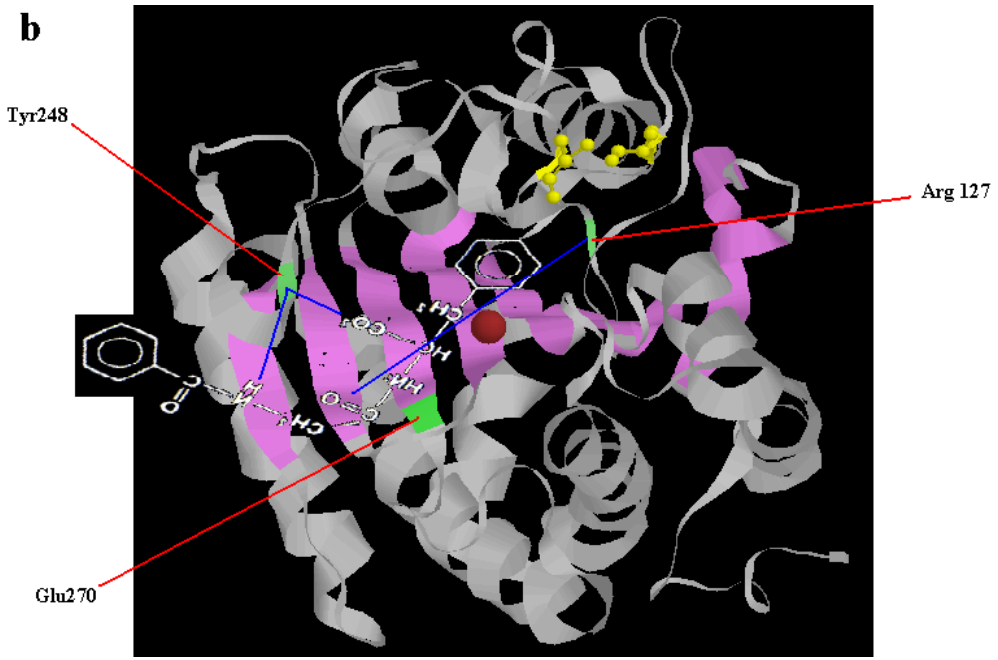




a

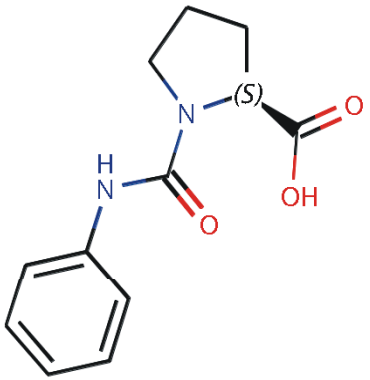

Glu270
Ser197
CO
NH
Tyr198
CH2
HC
CO2-
HN:
C=O
H2O
Zn2+
His 196
Glu- 72
His 69
CH2
H
N
C
O
Arg127
H2N—Asn144
Arg145
H
O—Tyr248
Arg71

b

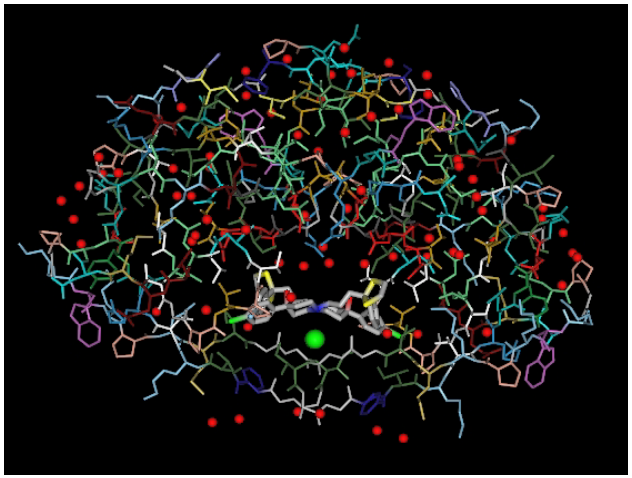

Tyr248
Arg 127
Glu270

Part I Screen in a nut shell

known active(s)
(ligand based design)



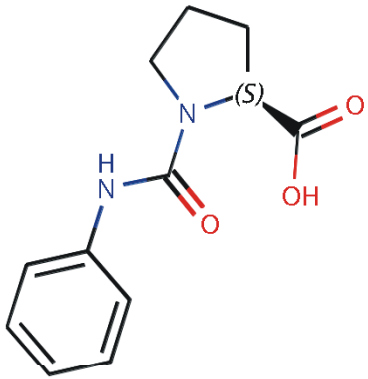
known receptor
(structure based design)

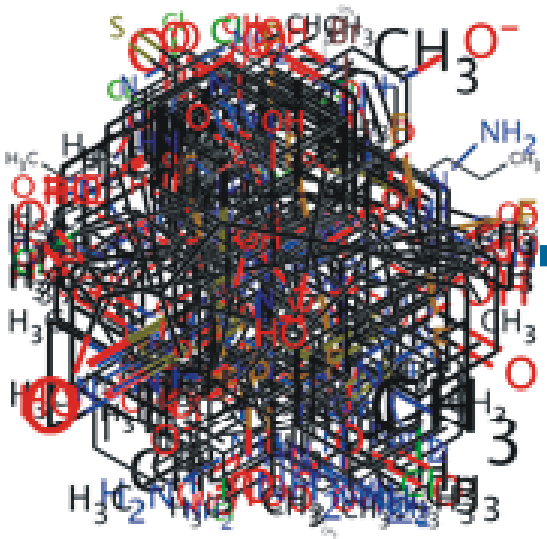


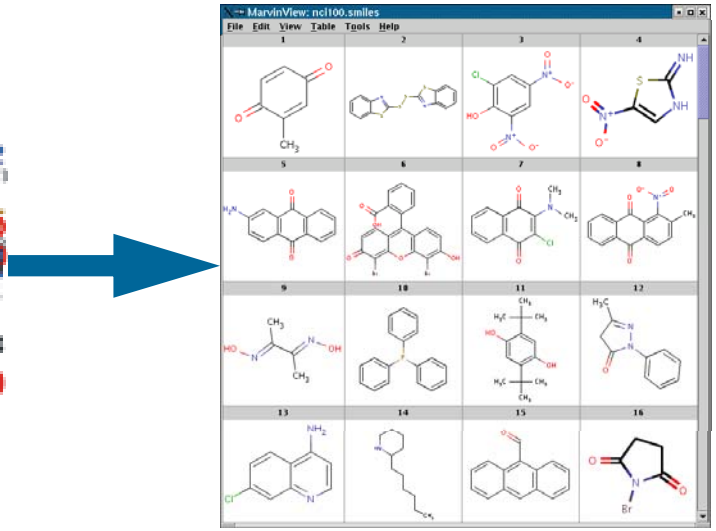
Aim: find ‘better’ structures

- higher activity
- not toxic
- fewer side effects
- etc.

The need for virtual screening



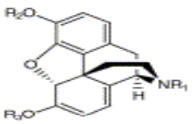




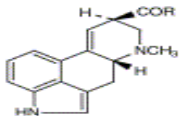
query structure
(known active)

corporate
database (targets)

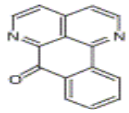
structures found
(virtual hits)



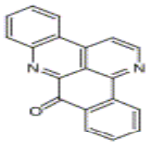
Thebaine R_1=R_2=R_3=CH_3
Northebaine R_1=H R_2=R_3=CH_3
6-Acetylmorphine R_1=CH_3 R_2=H R_3=CH_3CO
Diamorphine R_1=CH_3 R_2=R_3=CH_3CO



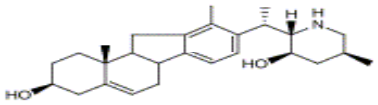
Lysergamide R=NH_2
Lysergic acid R=OH



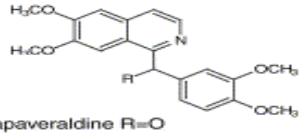
Sampangine



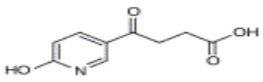
Benzosampangine



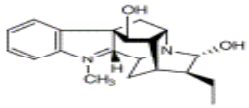
Veratramine



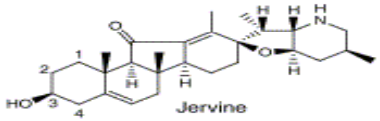
Papaveraldine R=O
(*S*)-Papaverinol R=OH
(*S*)-Papaverinol *N*-oxide R=OH, *N*-oxide



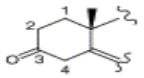
4-[(6-Hydroxypyridine)-3-yl]-4-oxobutyrate



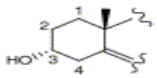
Ajmaline



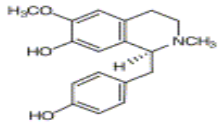
Jervine



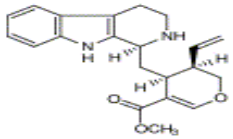
Jervinone



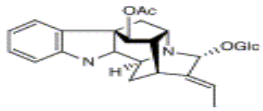
3-*Epi*-jervine



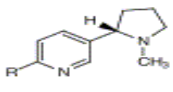
(*S*)-*N*-Methylcoclaurine



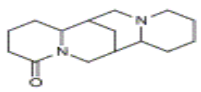
Strictosidine



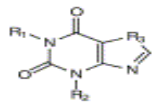
Raucaffricine



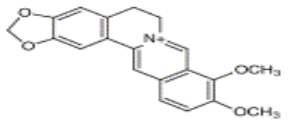
(*S*)-Nicotine R=H
6-Hydroxy-(*S*)-nicotine R=OH



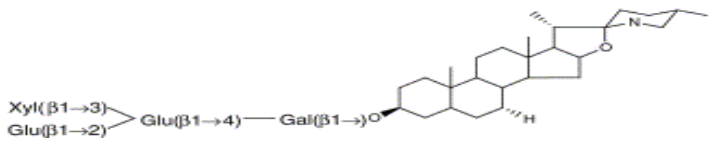
Lupanine



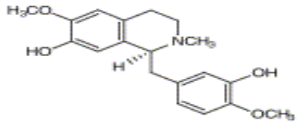
Caffeine R_1=R_2=R_3=CH_3
Theobromine R_1=H R_2=R_3=CH_3
Theophylline R_1=R_2=CH_3 R_3=H



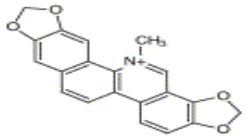
Berberine



α-Tomatine



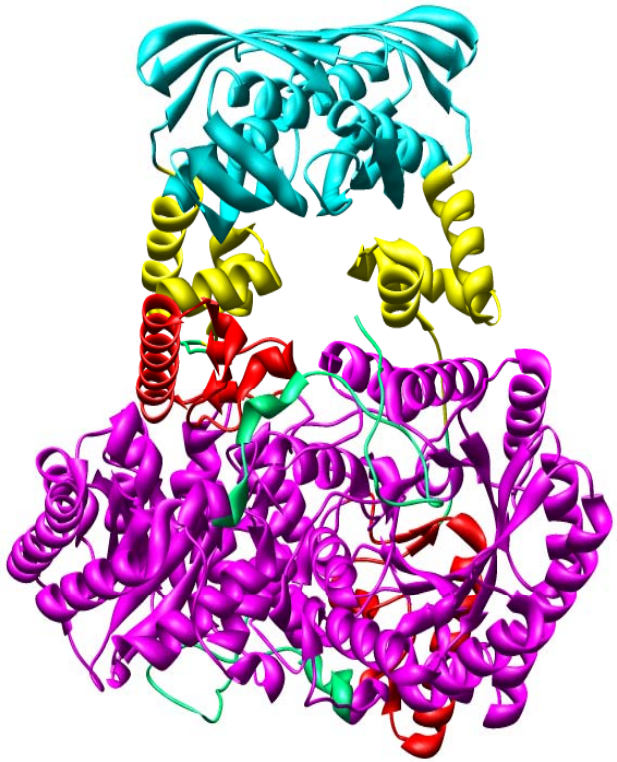
(*S*)-Reticuline



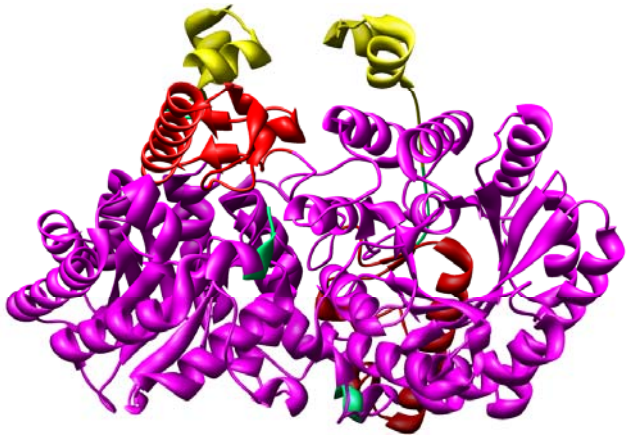
Sanguinarine

Current Opinion in Microbiology

Natural Products as drugs



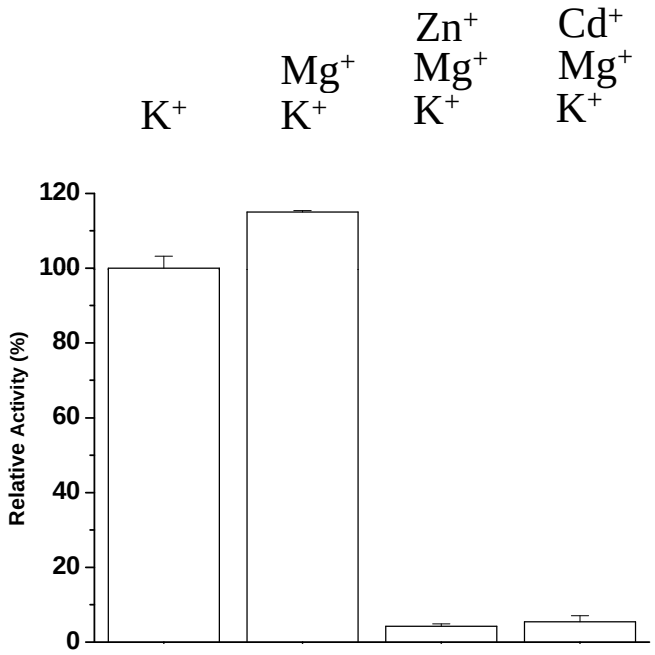
MtαIPMS



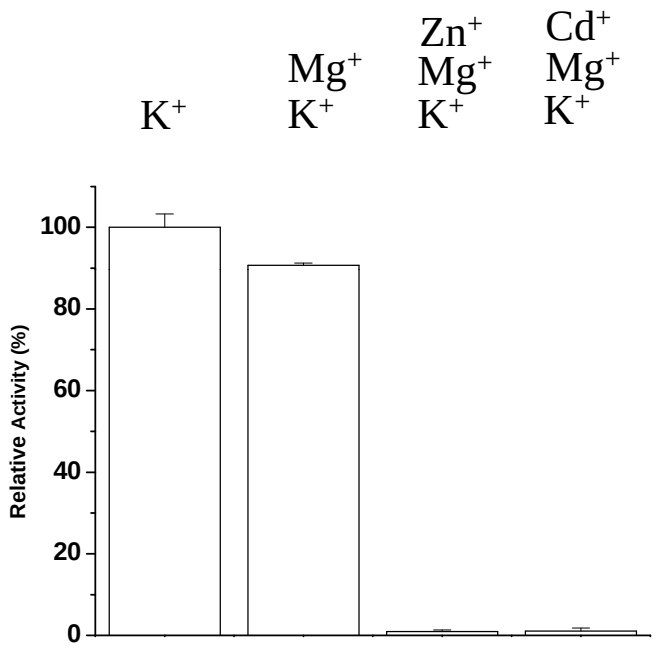
TIM barrel domain

TIM barrel domain (magenta), subdomain I(red) subdomainII(yelow), regulatory domain (cyan)

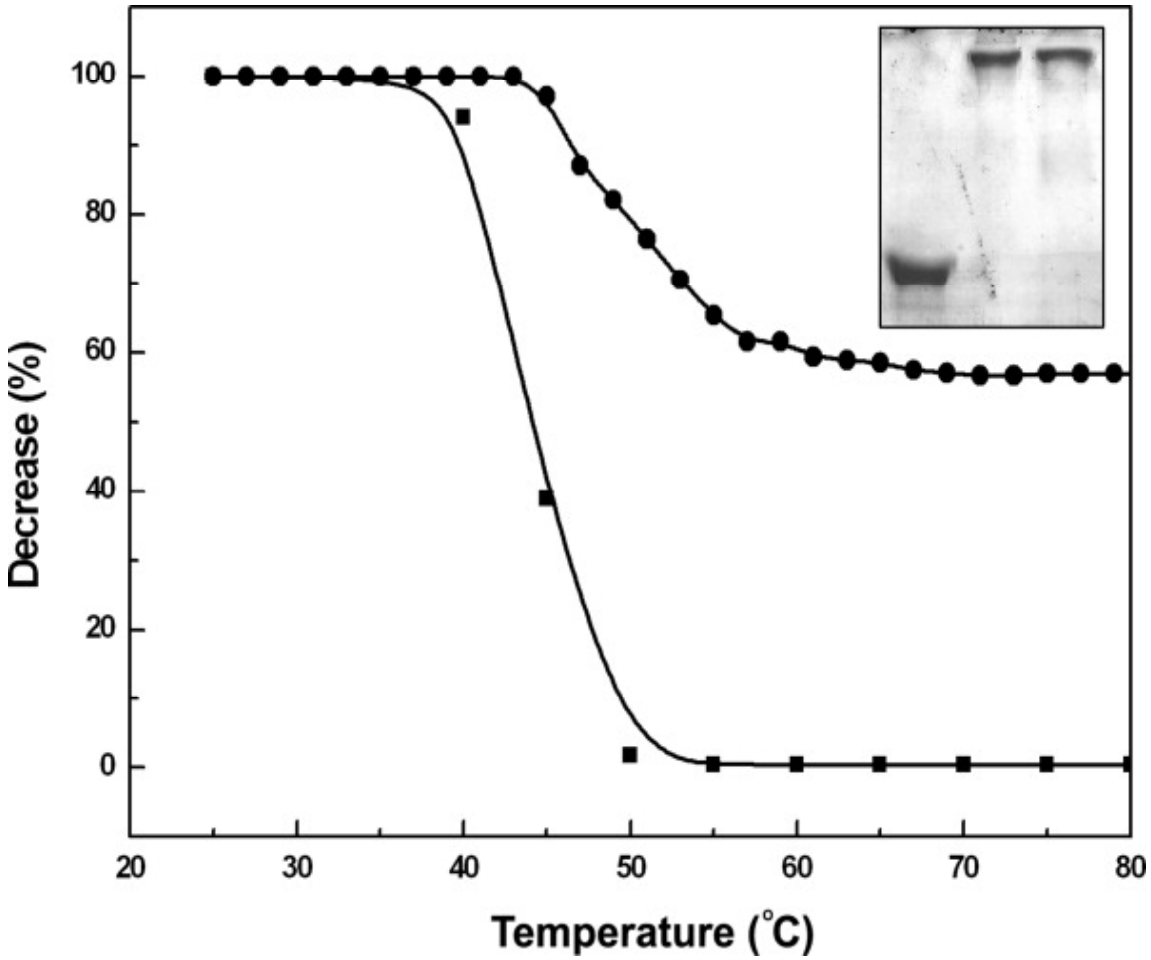
Metal cations induced differential effect on the functional activity of MtαIPMS and TIM barrel domain

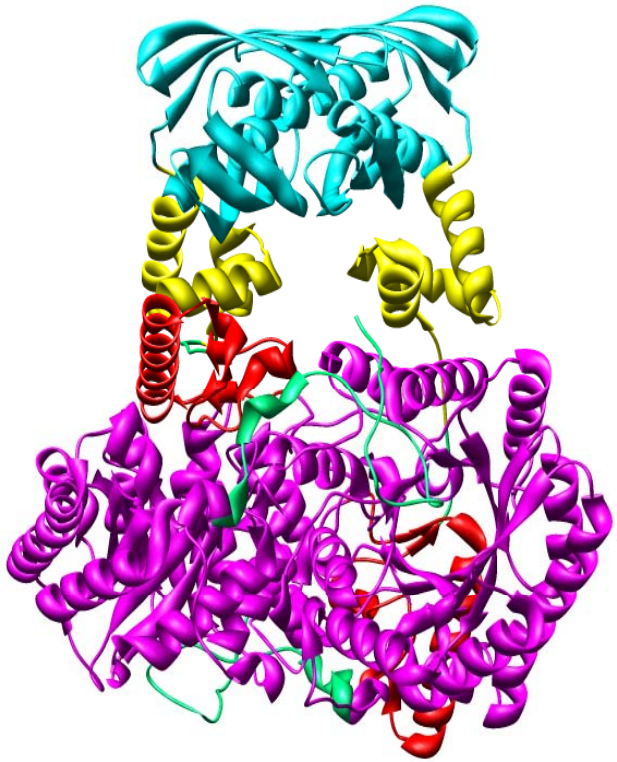


MtαIPMS

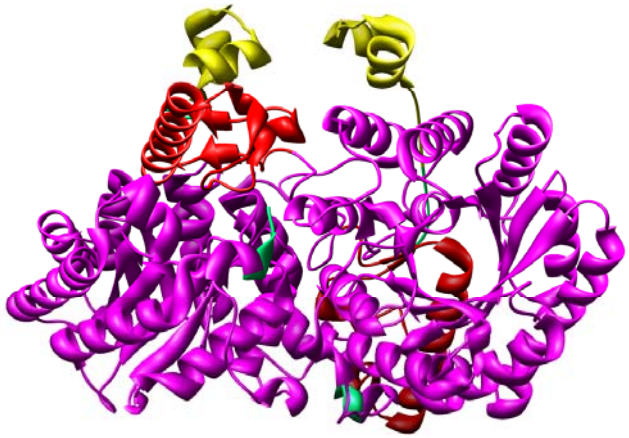


TIM barrel domain


Decrease (%)
100
80
60
40
20
0
20
30
40
50
60
70
80
Temperature (°C)

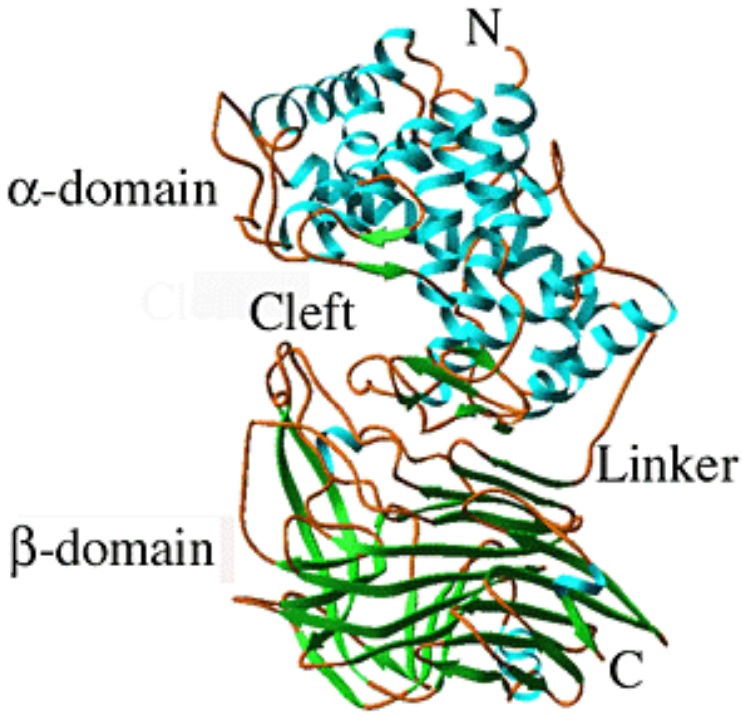


MtαIPMS

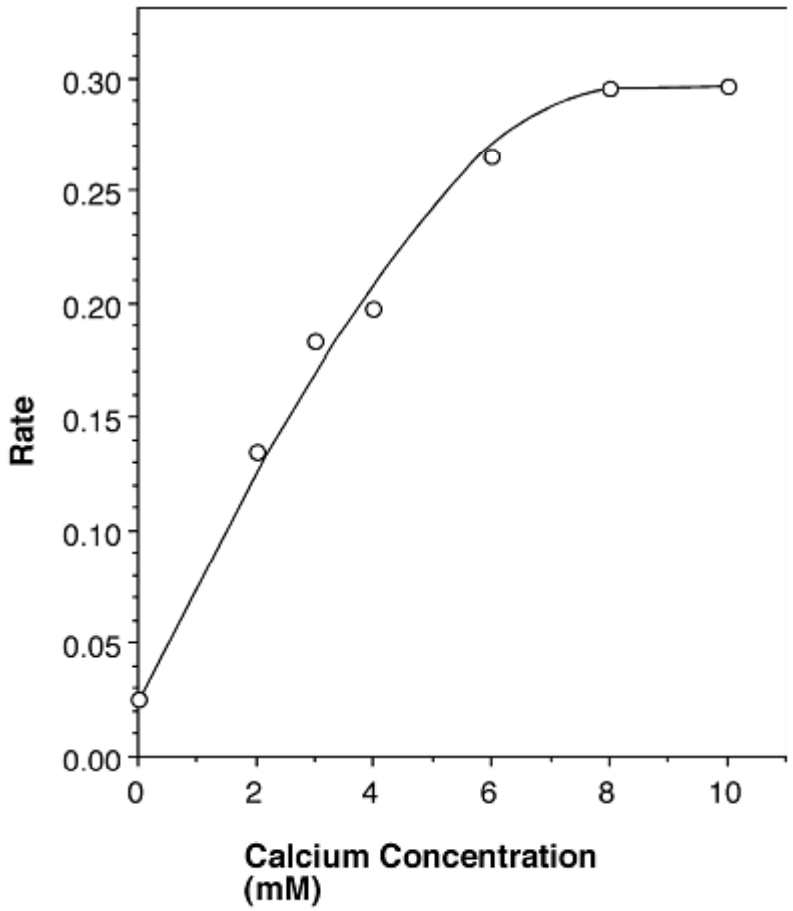


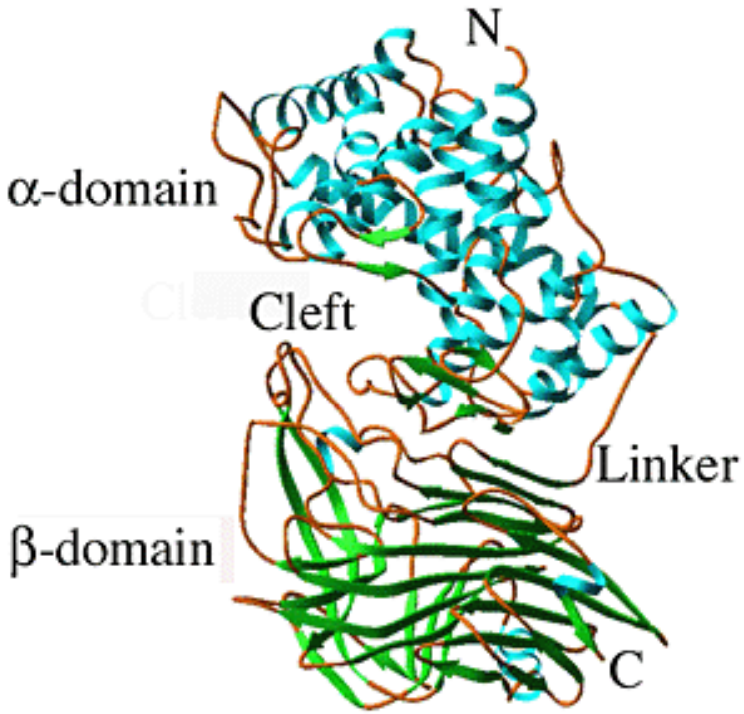
TIM barrel domain

TIM barrel domain (magenta), subdomain I(red) subdomainII(yelow), regulatory domain (cyan)


N
α-domain
Cleft
Linker
β-domain
C

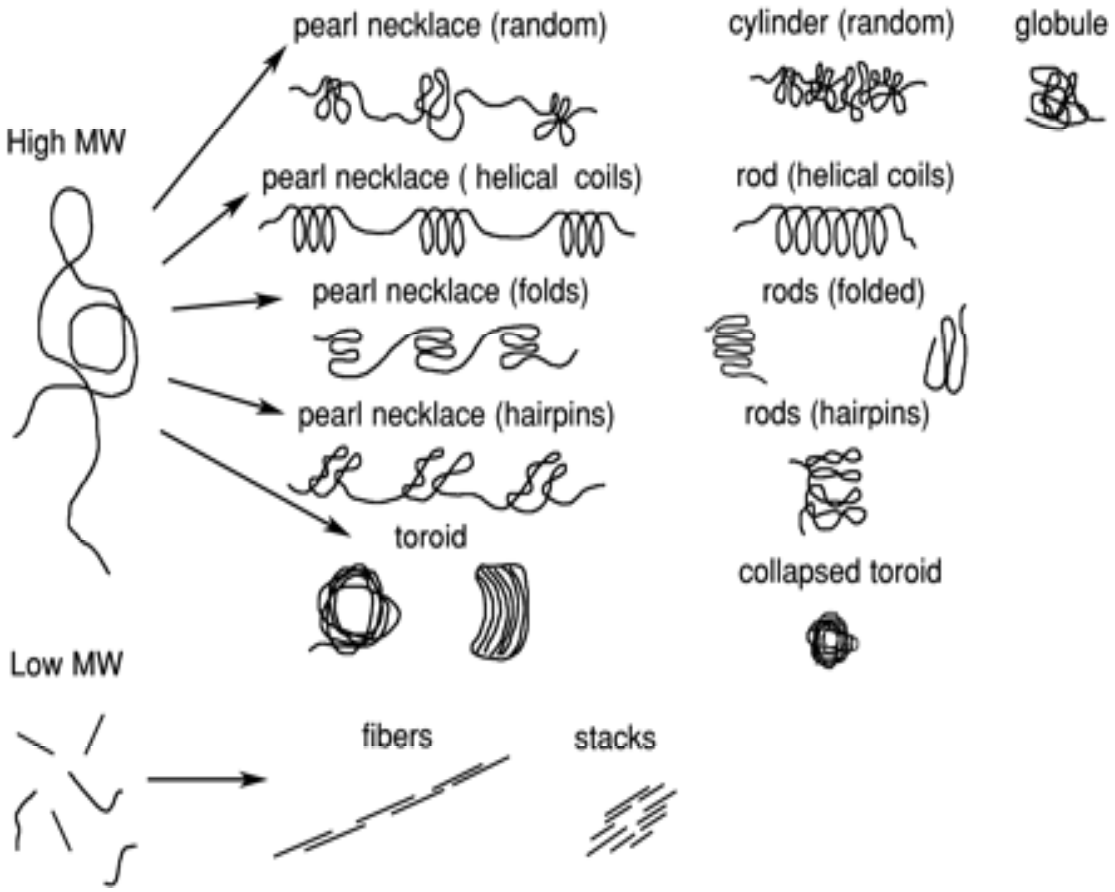
Calcium ions essential for functional activity of HL

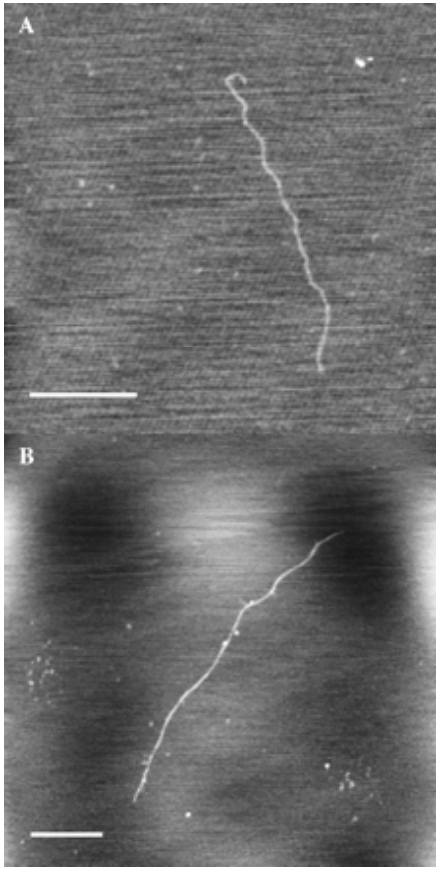


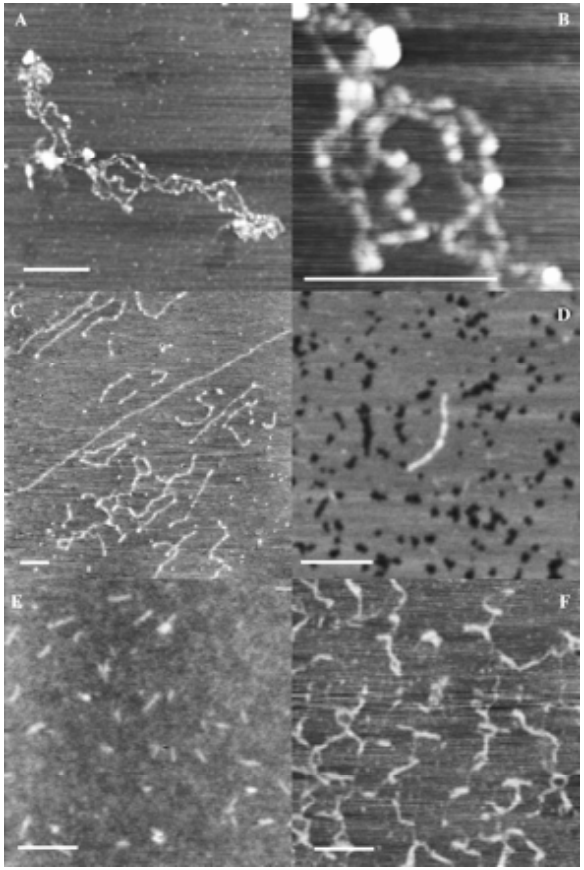


Calcium interacts with the C-terminal domain inducing outside movement relative to N-terminal domain

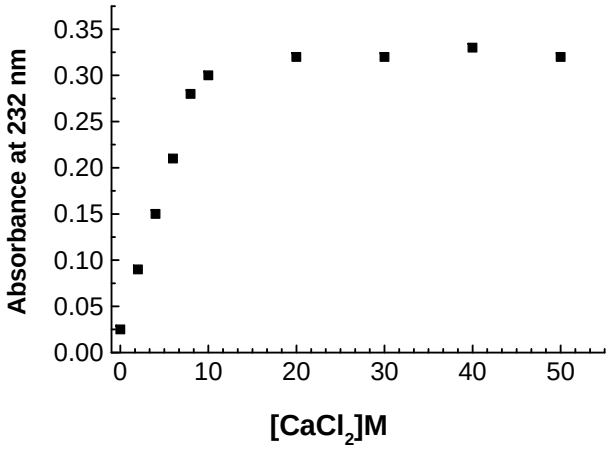
Possible Polyelectrolyte Condensation Modes for Hyaluronan

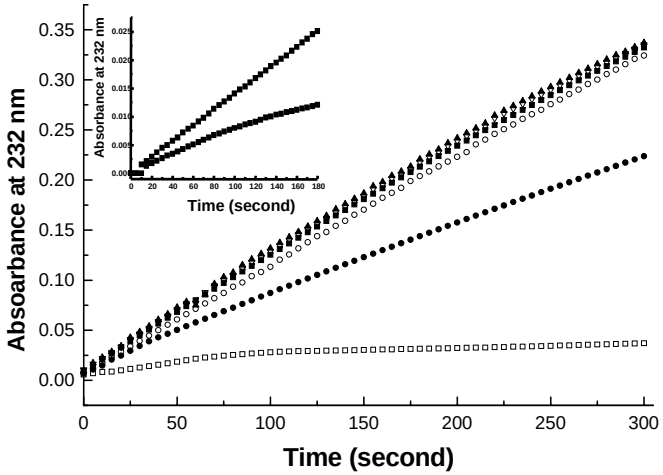


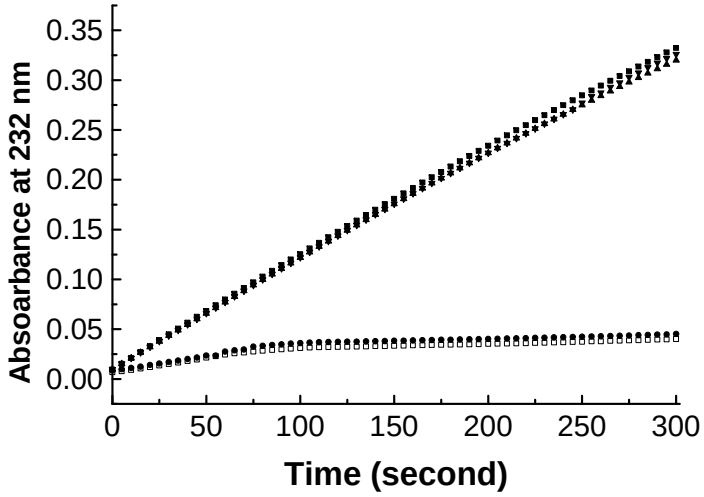

A
B


A
B
C
D
E
F

Why Ca^{++} dependent activity?







	Activity
SagHL + HA + $CaCl_2$	100%
SagHL + HA + $CaCl_2$ + NaCl	60%
SagHL + HA + $CaCl_2$ + EDTA	3%
SagHL + HA + EDTA	3%
SagHL + HA	3%
SagHL + $HA_{6\text{-}10}$ ± $CaCl_2$ / ± NaCl / ± EDTA	100%

Akhtar MS, Krishnan MY & Bhakuni V (2006) ***J. Biol. Chem*** 281, 28336-28344

Screening

- **In vitro/Cell-based**
- **In vivo/Animal Models**
- **HTS**

Test optimized leads in animals

[NOTE: Rats are not just “small humans”]

- Nevertheless, must establish safety in animals (mice, rats, pigs, dogs, etc…)
- Check for metabolism of drug
- Check for toxicity, adverse reactions
- Perhaps, check for signs of efficacy.
- Get indication of dosage ranges (mg/kg)