# The Status of the Computer Aided Drug Design: Then, Now and Future

**G. Narahari Sastry**
**CSIR – North East Institute of Science and Technology,**
**Jorhat – 785006,**
**Assam, India**

IYBSSD2022
International Year
of Basic Sciences
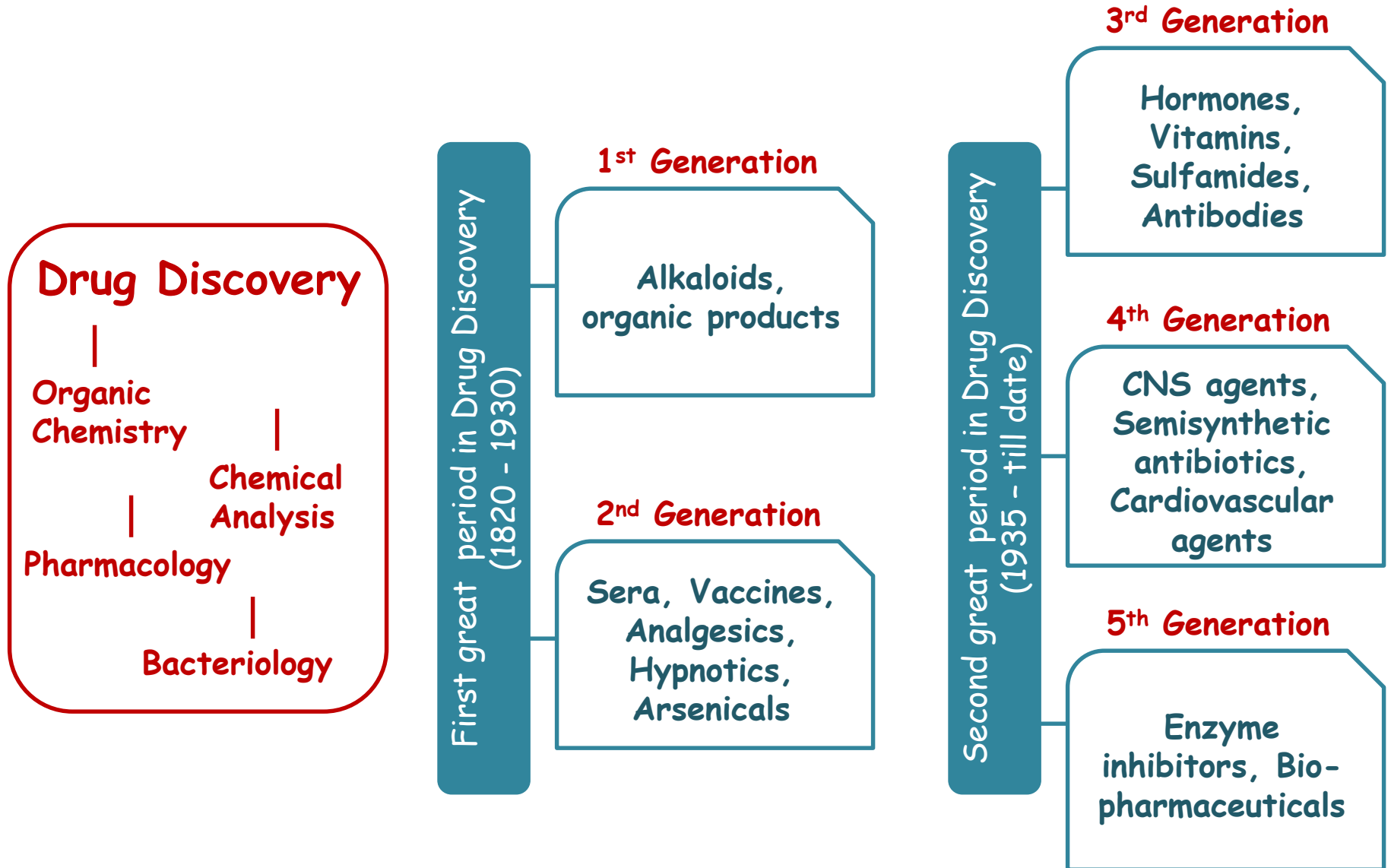for Sustainable Development

IBMC
Institute of Biomedical Chemistry

XXVIII Symposium on Bioinformatics and Computer-Aided Drug Discovery
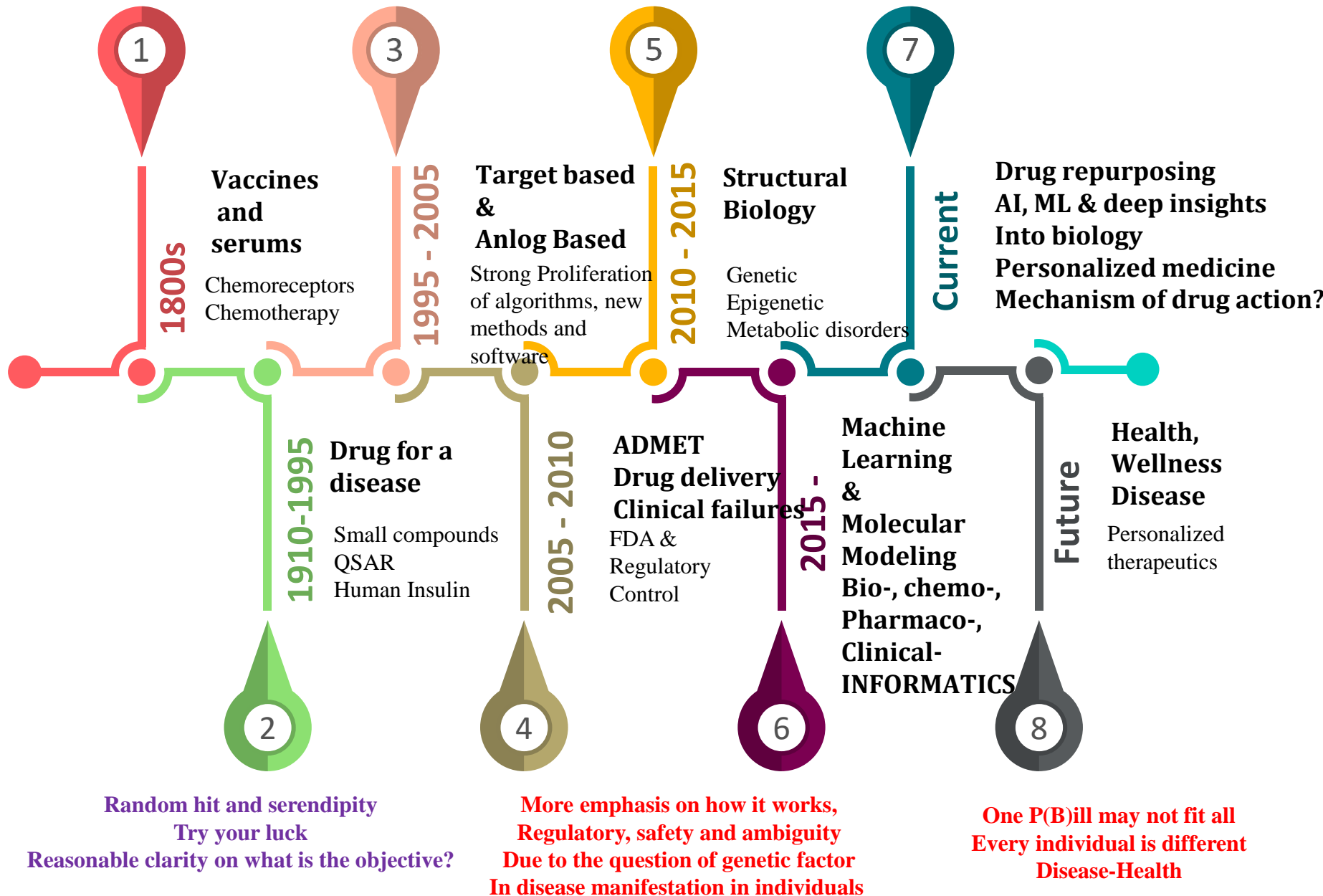26th May 2022, Moscow, RUSSIA

# Outline

- The evolution of drug discovery… A bird's eyeview

- Computer aided drug discovery

- Disease-Health

- Disease Specific Web Portal Development (MPDS)

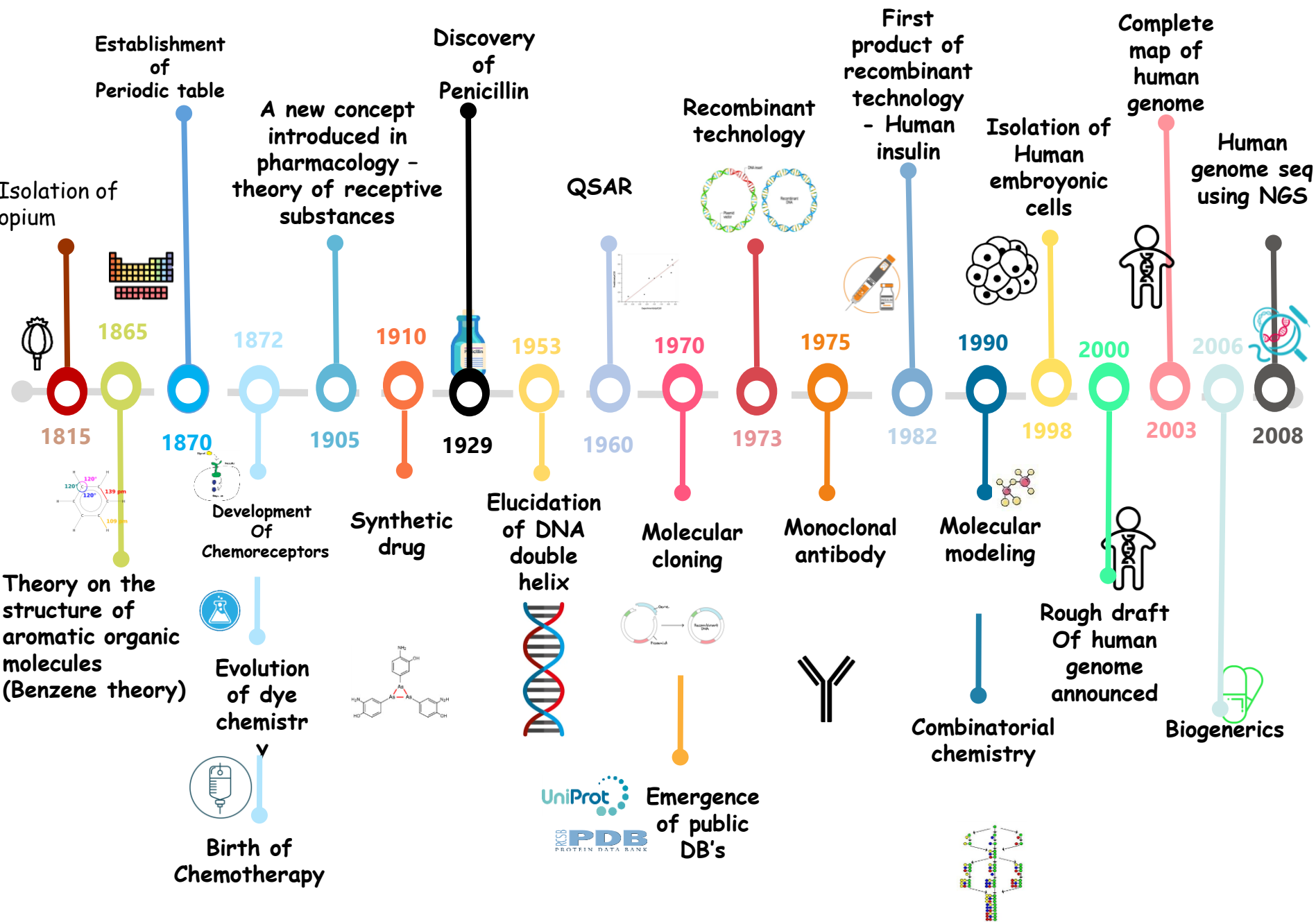- Some thoughts on how things may evolve
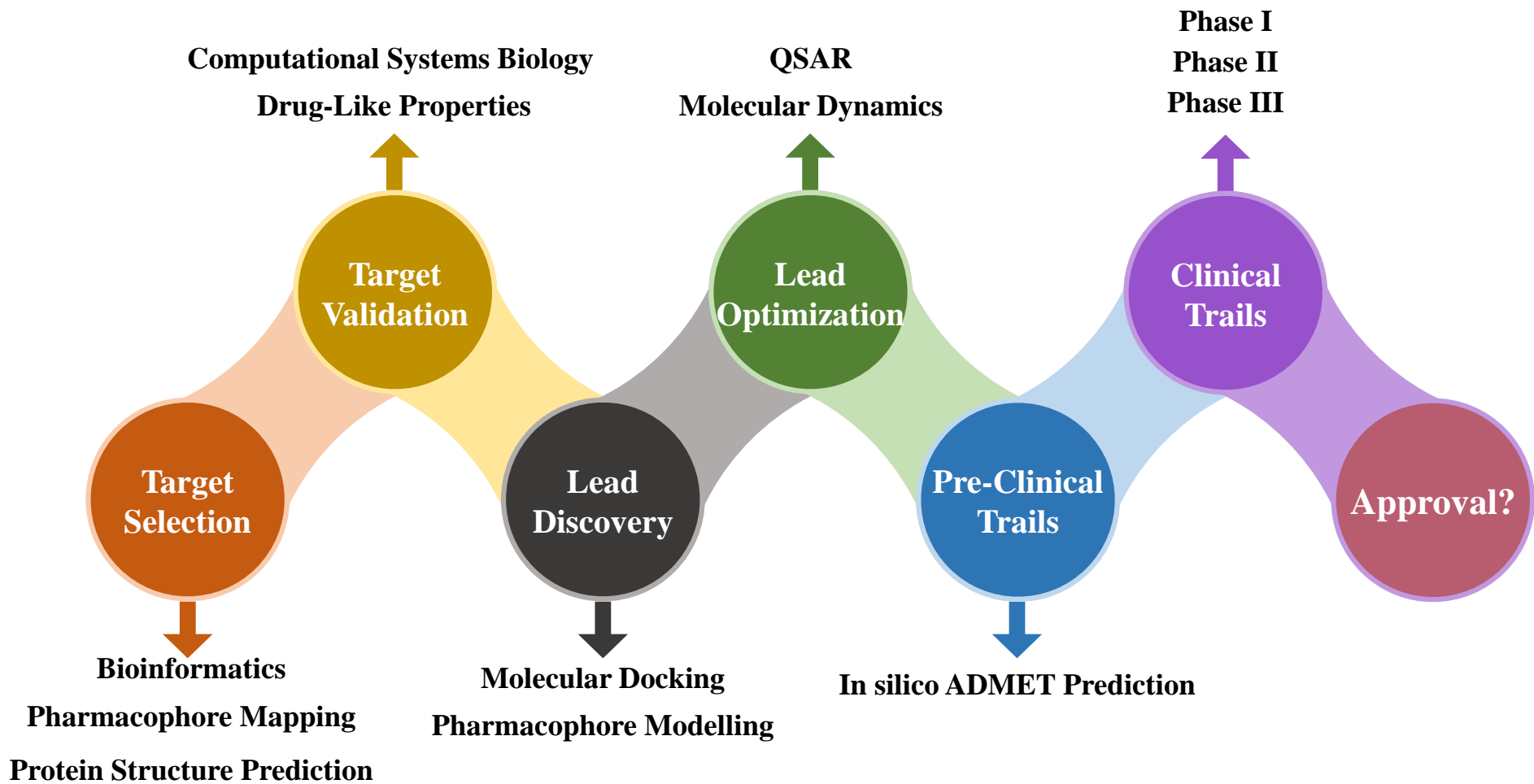
# Diffferent Stages in Drug Discovery

**Drug Discovery**
|
**Organic Chemistry**
|
**Chemical Analysis**
|
**Pharmacology**
|
**Bacteriology**

**First great period in Drug Discovery (1820 - 1930)**

**1st Generation**
Alkaloids, organic products

**2nd Generation**
Sera, Vaccines, Analgesics, Hypnotics, Arsenicals

**Second great period in Drug Discovery (1935 – till date)**

**3rd Generation**
Hormones, Vitamins, Sulfamides, Antibodies

**4th Generation**
CNS agents, Semisynthetic antibiotics, Cardiovascular agents

**5th Generation**
Enzyme inhibitors, Bio-pharmaceuticals

# Drug Discovery….the evolution

**1** — **1800s**

**Vaccines and serums**

Chemoreceptors
Chemotherapy

**2** — **1910-1995**

**Drug for a disease**

Small compounds
QSAR
Human Insulin

Random hit and serendipity
Try your luck
Reasonable clarity on what is the objective?

**3** — **1995 – 2005**

**Target based & Anlog Based**

Strong Proliferation of algorithms, new methods and software

**4** — **2005 – 2010**

**ADMET Drug delivery Clinical failures**

FDA & Regulatory Control

More emphasis on how it works,
Regulatory, safety and ambiguity
Due to the question of genetic factor
In disease manifestation in individuals

**5** — **2010 – 2015**

**Structural Biology**

Genetic
Epigenetic
Metabolic disorders

**6** — **2015 -**

**Machine Learning & Molecular Modeling Bio-, chemo-, Pharmaco-, Clinical- INFORMATICS**

**7** — **Current**

**Drug repurposing AI, ML & deep insights Into biology Personalized medicine Mechanism of drug action?**

**8** — **Future**

**Health, Wellness Disease**

Personalized therapeutics

One P(B)ill may not fit all
Every individual is different
Disease-Health

# Looking Back...A cursory look at how things evolved



Isolation of opium

Establishment of Periodic table

1865

1815

Theory on the structure of aromatic organic molecules (Benzene theory)

1870

Development Of Chemoreceptors

Evolution of dye chemistry

Birth of Chemotherapy

A new concept introduced in pharmacology – theory of receptive substances

1872

1905

Synthetic drug

Discovery of Penicillin

1910

1929

1953

Elucidation of DNA double helix

QSAR

1960

Molecular cloning

Emergence of public DB's

UniProt
PDB
PROTEIN DATA BANK

Recombinant technology

1970

1973

Monoclonal antibody

First product of recombinant technology - Human insulin

1975

1982

Molecular modeling

Combinatorial chemistry

Isolation of Human embryonic cells

1990

1998

2000

Rough draft Of human genome announced

Complete map of human genome

2003

Biogenerics

Human genome seq using NGS

2006

2008

# Computational Drug Discovery

# Conceptual map on experimental and computational methodologies for drug discovery process

Molecular Dynamics

Molecular Modelling

Protein Structure Predication

X-ray Crystallography

Assay Development

Biochemical Pathway Analysis

Lipinski's rule of 5

Chemical Similarity Search

Pharmacophore search

Molecular Docking

Low/High-Throughput Screening

De novo Design

Target Identification and Characterization

Hit identification

Viral Combinatorial Chemistry

Scaffold Hopping

QSAR Modelling

Quantum Mechanics

Lead Generation and Optimization

Experimental ADMET Analysis

In silico ADMET analysis

Physiologically Based Pharmacokinetic Modelling

Pre-clinical Studies

Clinical trials

FDA Approval

# Disease Pathophysiology



Disease manifestation in any organism is inhenerently dependent on number of factors: Unravelling the working strategy is key?

# A drug development cycle



- Is expensive, prolonged and risky affair?!

**CADD Service Providers**
*Distribution by Year of Establishment*

- Pre-1991
- 1991-1995
- 1996-2000
- 2001-2005
- 2006-2010
- 2011-2015
- Post-2015
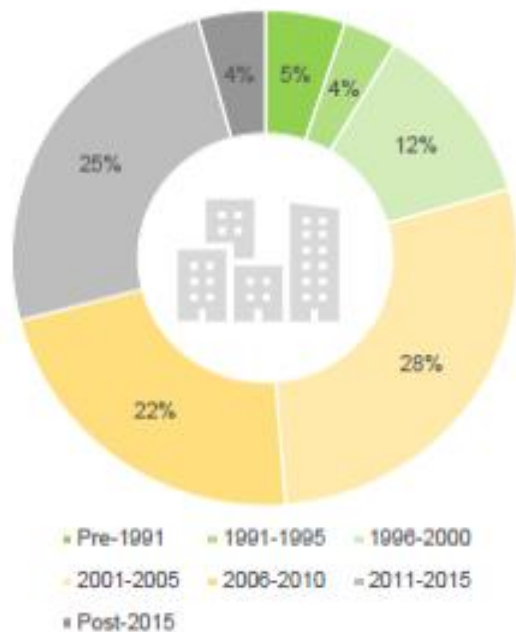
Given its potential to offer significant cost and time-related benefits, many companies focused on providing a variety of CADD services for drug discovery have been established in last decade (2008-2018) alone

**CADD Service Providers**
*Distribution by CADD Approaches[1]*

Ligand-based Drug Design

Structure-based Drug Design

Fragment-based Drug Design
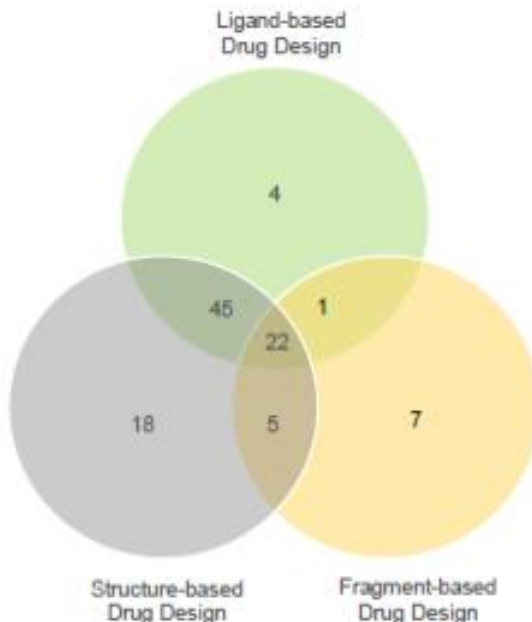
Prominent examples of large companies that offer services based on all the abovementioned approaches include AMRI, Charles River Laboratories, ChemDiv, Evotec, Jubilant Biosys and Pharmaron

**CADD Service Providers**
*Distribution by Drug Discovery Steps[2]*

- Lead Optimization — 111
- Hit-to-Lead — 109
- Hit Generation — 109
- Target Validation — 20
- Target Identification — 31
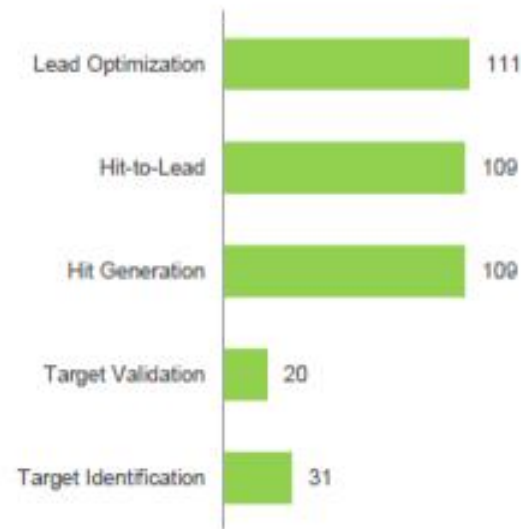
Lead optimization, hit-to-lead and hit generation are amongst the most popular drug discovery steps that can now be accomplished in silico; in contrast, target based drug discovery requires extensive experimental support

The market landscape is highly fragmented with several new entrants; majority of the companies offer structure-based drug design focused on early stage drug discovery.

Source: Computer-Aided Drug Discovery Services Market, 2018-2030 (2018).

CADD Services Market
Distribution by Drug Discovery Steps
2018 and 2030

USD Billion

- Target Identification
- Target Validation
- Hit-to-Lead
- Lead Identification
- Lead Optimization
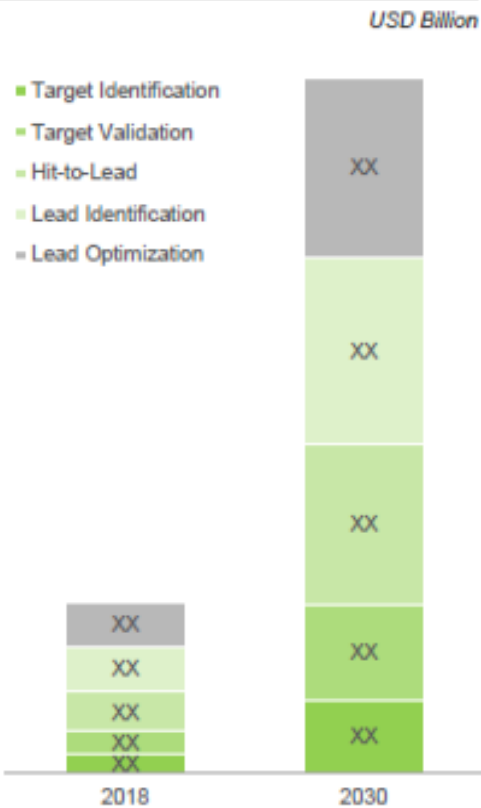
CADD Services Market
Distribution by Type of Molecules
2018 and 2030

USD Billion

- Small Molecules
- Biologics
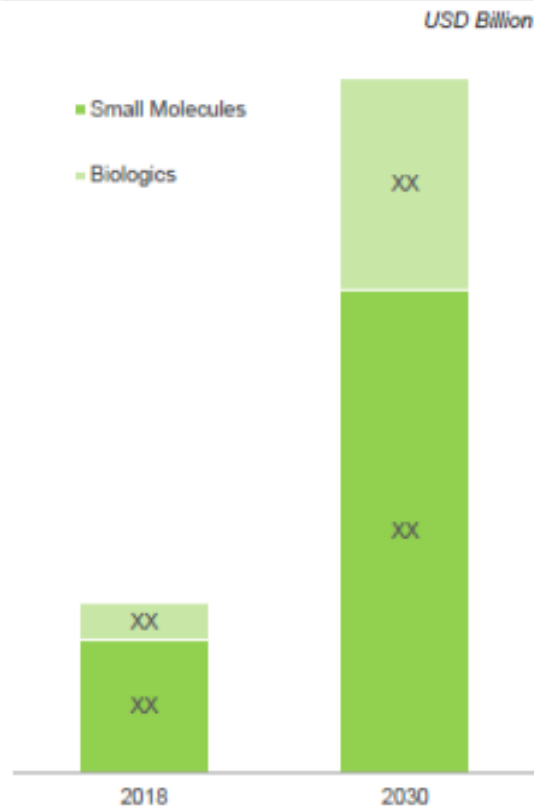
CADD Services Market
Distribution by Type of Sponsor
2018 and 2030

USD Billion

- Academic / Research Institutes
- Pharmaceutical / Biotechnology Companies
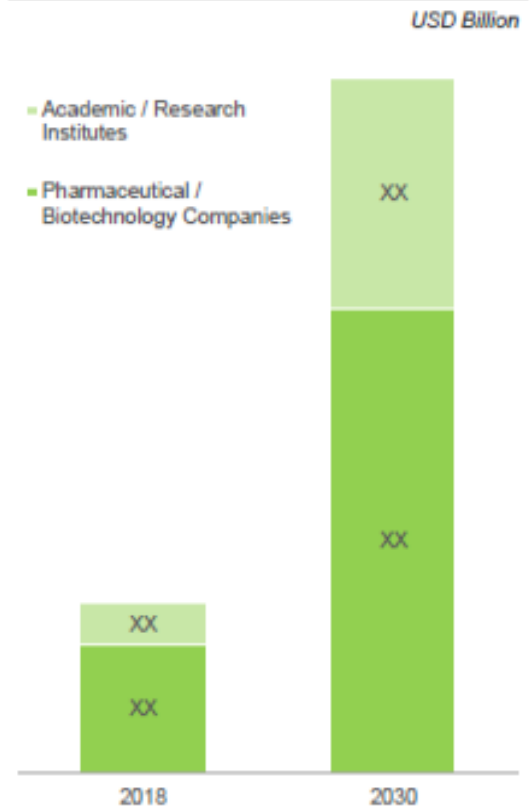
The overall opportunity is anticipated to be well-distributed across the various steps of drug discovery steps, type of molecules and the concerned sponsors

Source: Computer-Aided Drug Discovery Services Market, 2018-2030 (2018).

**CADD Services Market**
Distribution by Regions / Countries, 2018-2030

Legend — North America | Europe | Asia-Pacific

Note: The size of the bubble represents the likely market share in the long-term (2030)

The majority share is expected to be held by North America and Europe; however, Japan, China and certain other emerging markets are likely to grow at faster rate.

Source: Computer-Aided Drug Discovery Services Market, 2018-2030 (2018).

# Data Science - A Game changer in Drug Discovery???

# Bottlenecks in Drug Discovery – In recent times!

# Drug Product Profile & Challenges



– Delivery route
• Oral, parenteral, topical, inhaled….

Drug - Drug interactions

Differentiation from current therapies
(Safety, Cost, Efficacy )

Dosing frequency
(Every day, every week)

Cost of Drugs

Risk of Misuse/Controlled substances

Tolerable side effects

Safety in pregnant/breastfeeding populations

Dose adjustment in pediatric patients

Monitoring – specialist use, liver function tests,…
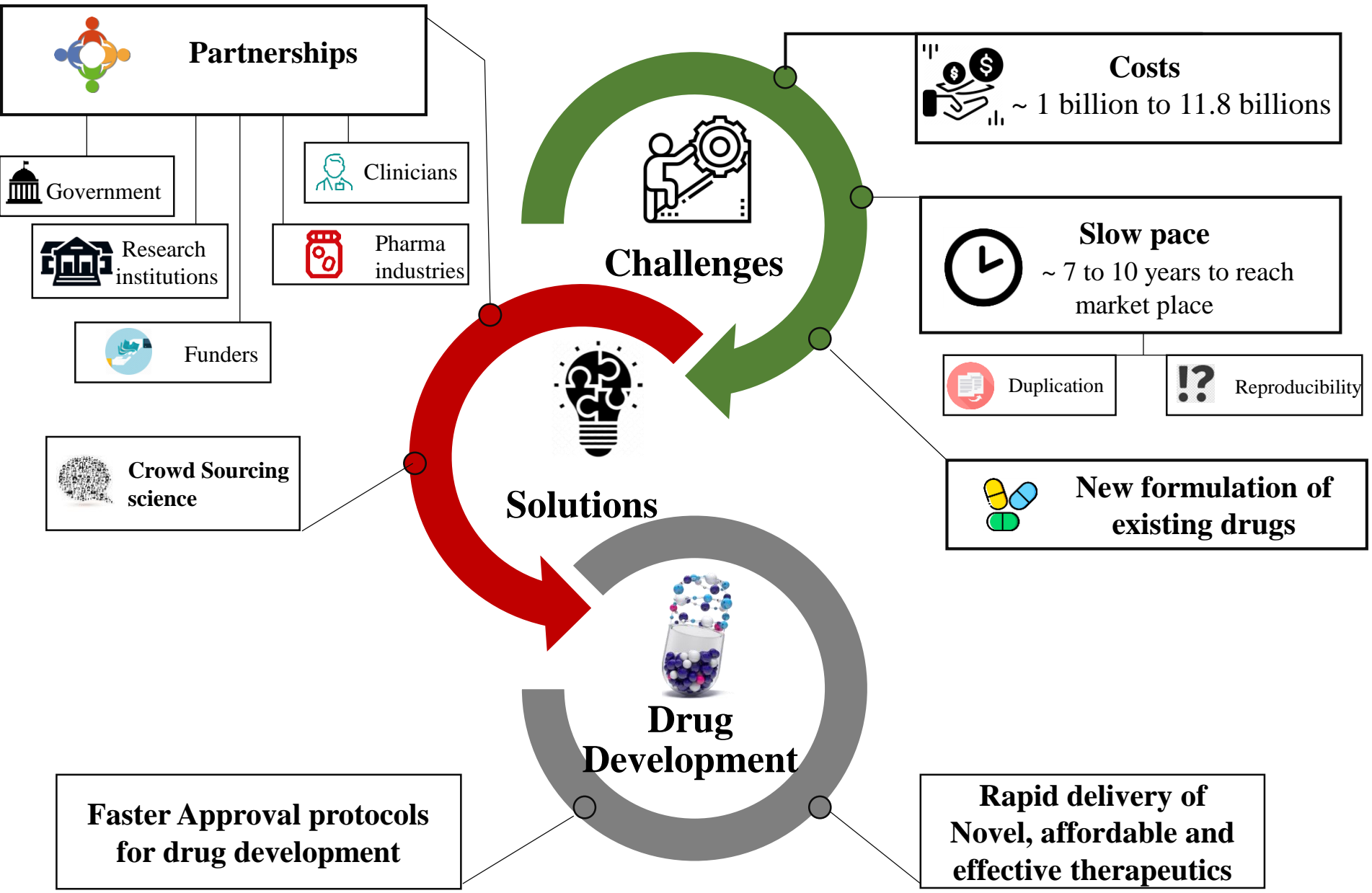
## Drug Product Profile & Challenges
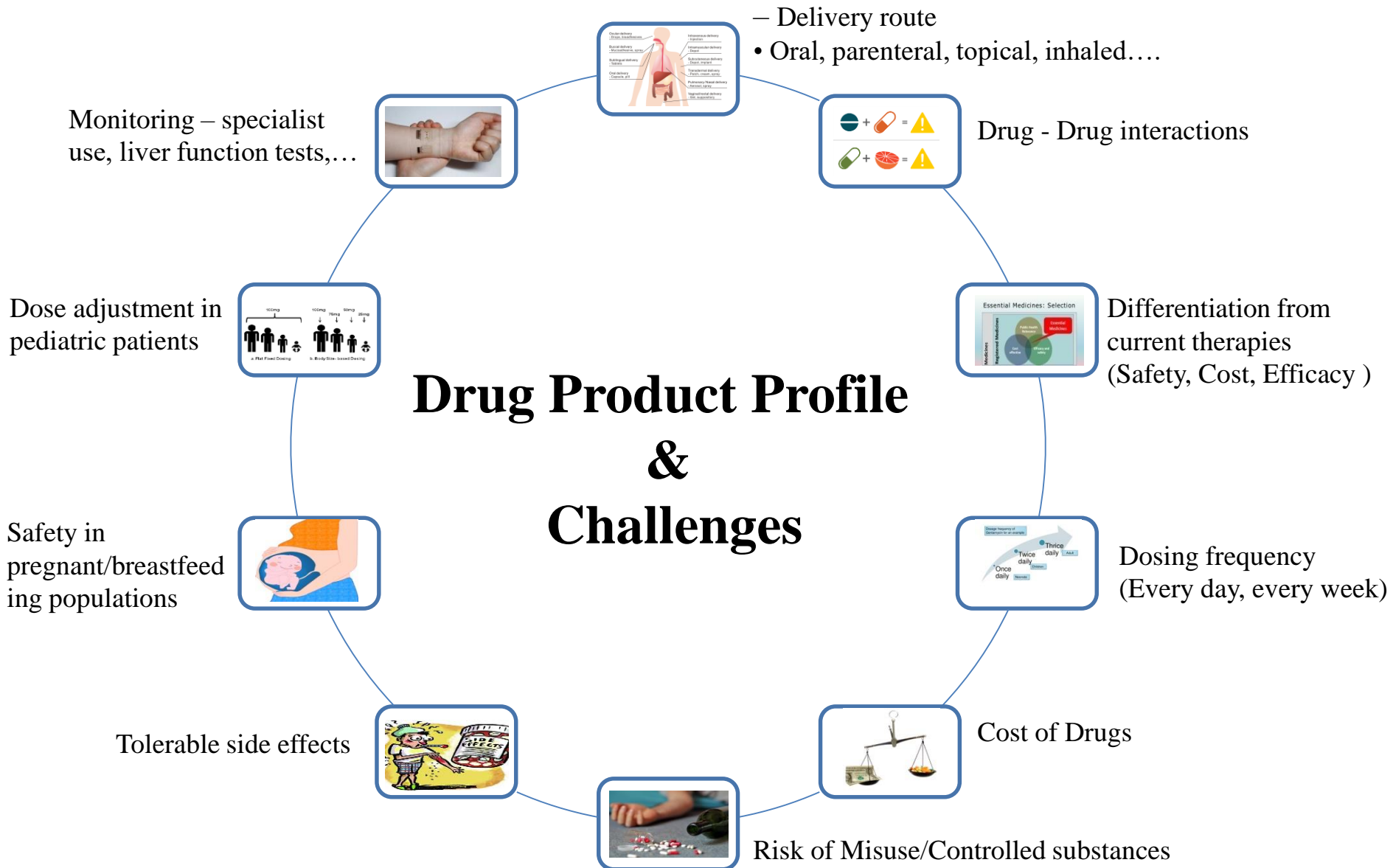
# Disease – A Perturbation in Health: A Mathematical Model

**WHO Definition for Health**
Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity
**Post-COVID WHO Definition for Health !**
Health is a state of complete physical, mental, social, **emotional** and **spiritual** well-being and not merely the absence of disease or infirmity

**Disease = Health + Perturbation**

**Health = PW + MW + SW**

PW = Physical well-being
MW = Mental well-being
SW = Social well-being

**Disease ≠ Sickness ≠ Illness ≠ Malady**

# Health-Ageing-Disease Relationship
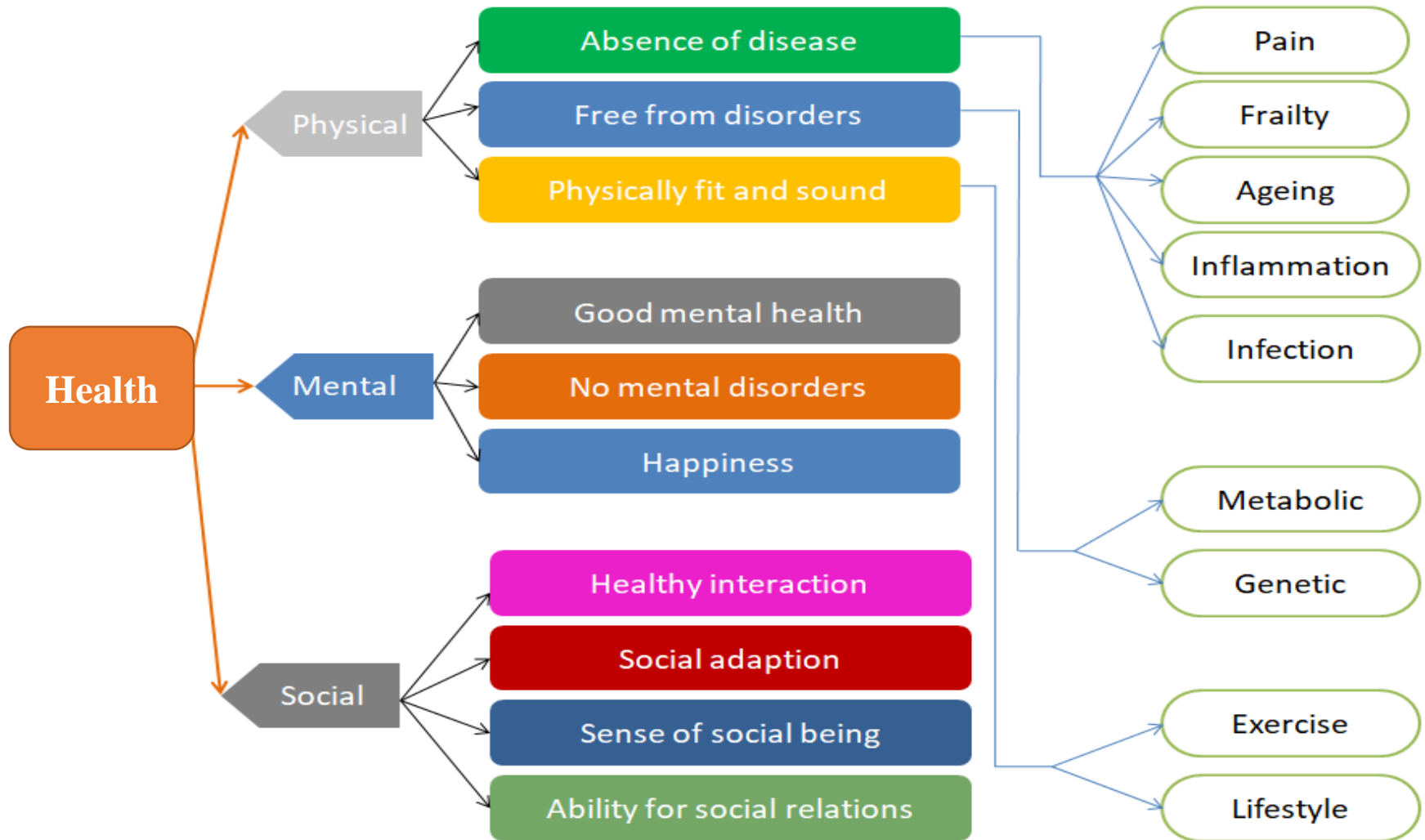


**Physical**
- Absence of disease
- Free from disorders
- Physically fit and sound

**Mental**
- Good mental health
- No mental disorders
- Happiness

**Social**
- Healthy interaction
- Social adaption
- Sense of social being
- Ability for social relations

- Pain
- Frailty
- Ageing
- Inflammation
- Infection

- Metabolic
- Genetic

- Exercise
- Lifestyle

"Health is a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity"

# Data driven, structural biology and molecular modeling
# Unraveling the pathophysiology of degenerative diseases and disease progression

## Physical
- Nutrition
- Exercise
- Sleep
- Alcohol and Drugs
- Weight Management

## Mental
- Skills, Behaviors, and Knowledge
- Self-confidence, Awareness, and Self Perception

## Social
- Public Health
- Family Relationships
- Peer Relationship

H E A L T H

Life Style diseases

Congenital and genetic diseases

Genetic factors

Nutrient deficiency

Life style

Aging

Environmental factors

Psychological factors

Infectious Diseases

Neurodegenerative diseases

Biological Age, Chronological Age, Psychological Age

Interactions between Genes and the Environment and Their Effects on Health

Genetic Determinants

IMMUNITY INFLAMMATION
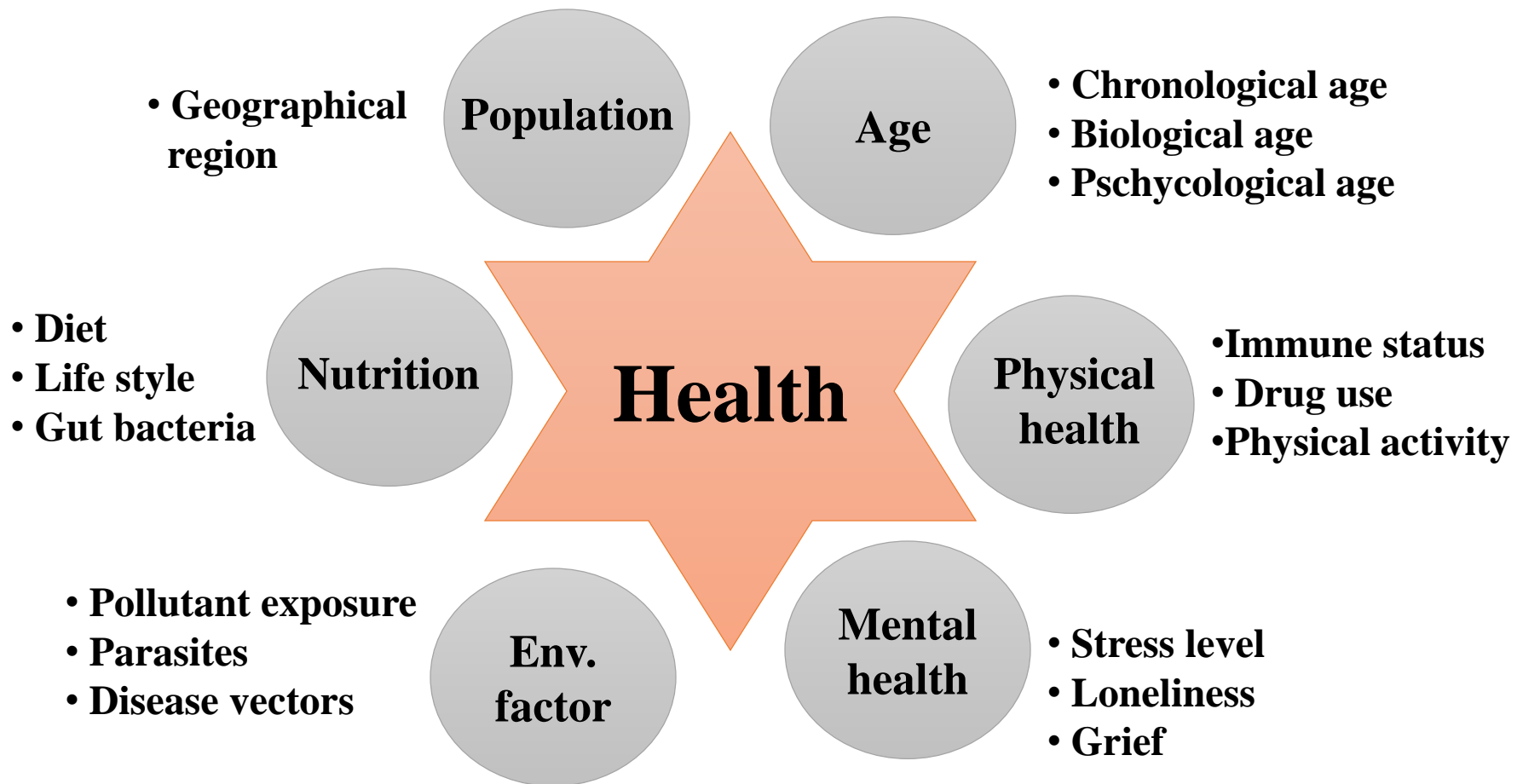
Altered:
- Macrophage activation
- T – cell-antigen-specific expansion
- Antibody production

Ageing

Genetic Factors

Physical Factors

Environmental Factors

Nutrition & Life style

Cognitive Factors
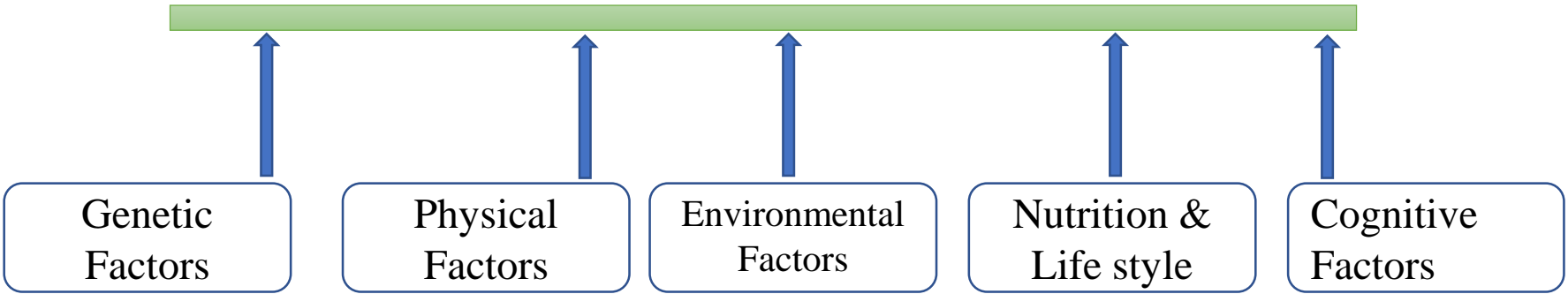
Age associated Diseases

# Factors Connecting Rare Diseases, Metabolic Disorders, Lifestyle Diseases, And Infectious Diseases
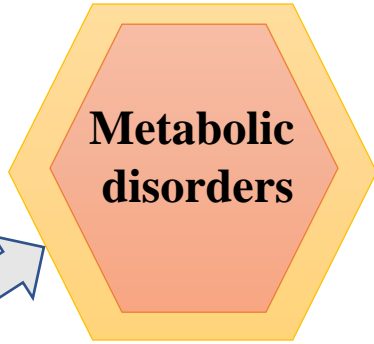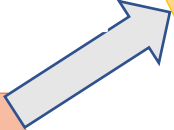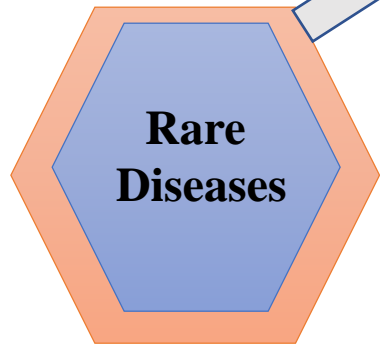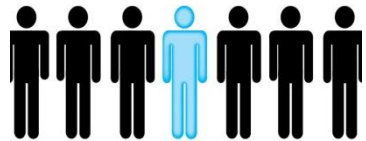
# Genesis of Molecular Property Diagnostic Suite: MPDS

**MPDS idea was conceived by GNS in 2004**

**While MPDS Team started working in 2011**

Various brainstorming MPDS workshops were held at, CSIR- IICT, CSIR-NCL and CSIR-NAL in the years 2014-2016
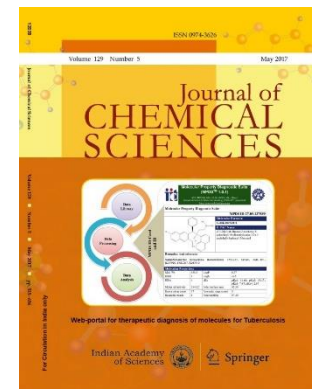


MPDS-TB published in the year 2017

**More MPDS-Disease specific portal for HIV, Metabolic disorders, etc., were under development in the year 2017**

### Core developers
1. ANSHU BHARDWAJ
2. PRASAD V BHARATAM
3. M RAM VIVEK
4. NEHA TRIPATHI
5. RAKESH KUMAR
6. ARUN SHARMA
7. ANAMIKA SINGH GAUR
8. SRIDHARA JANARDHAN
9. LIJO JOHN

### Co-developers
1. CHINMAYEE CHOUDHURY
2. ANIRBAN BANERJI**
3. D. ARUN KUMAR
4. M. PRASANTHI
5. P. SRI SARANYA
6. S. HEMASRI
7. KARUNAKAR TANNEERU
8. NANDAN KUMAR
9. KUMARDEEP CHAUDHARY
10. SANDEEP SINGH
11. ASHEESH KUMAR
12. RUCHI MISHRA
13. SURESH KUMAR
14. CHARUVAKA MUVVA
15. ER AZHAGIYA SINGAM
16. CHINMAI MADHURI
17. DEEPAK PANDIT
18. VIJAY KHEDKAR
19. YOGESH JOSHI
20. ANMOL HEMROM
21. DEEPAK BHARTI
22. PANKAJ NARANG**
23. ABHAYSINH MORI
24. HARISH JANGRA
25. R VENKAT KRISHNAN
26. APARNA SINGH
27. REETU SHARMA
28. HARI SAILAJA
29. KAAMINI RAITHATHA
30. PRASUN DUTTA
31. NEERAJ K RAJPUT
32. UCA JALEEL
33. ANURAG PASSI

**PI:** Dr. G. NARAHARI SASTRY

### Co-Principal Investigators
Dr. G.P.S RAGHAV
Dr. ANSHU BHARDWAJ
Dr. PRASAD V BHARATAM
Dr. V SUBRAMANIAN

Dr. DEVESH KUMAR
Dr. M KARTHIKEYAN
Dr. UC ABDUL JALEEL
Dr. ANDREW LYNN

**Advanced AI modules for MPDS included in 2019**

**MPDS-Covid-19 and MPDS-MD developed in 2020**

Drug-like filters, toxicity filters, membrane permeability filters are developed for advanced AI modules in 2021

**MPDS disease-specific web portals are aimed to gather, find & discover all possible information on a particular disease from all possible resources along with CADD tools at one place.**

# Development of Open Source Drug Discovery Software

**Molecular Property Diagnostic Suite (MPDS) is being developed with the purpose of strengthening computational drug discovery in India.**

## Architecture of MPDS Disease-specific Web Portals



Galaxy Interface

Scripts in Perl, Python, C, C++ etc.

Search query

Get output

MySQL Database

Biological Space

Chemical Space

Disease-Specific Data

Server

Send Input

Get Output

Send query to server

Get data from server

Users

Web browser

XML script

Get output

Give input

Molecular Modeling, Chemoinformatics, Bioinformatics tools
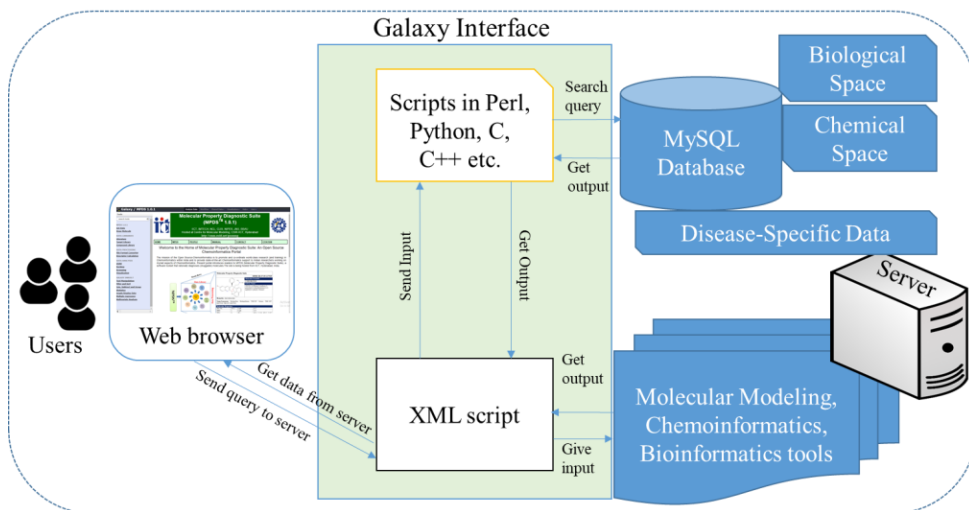
MPDS – Tuberculosis
MPDS – Diabetes
MPDS – COVID19
MPDS – Metabolic disorders
MPDS - HIV

## MPDS modules

**Data library**
- Target library
- Literature
- Gene library
- Compound library

**Data processing**
- File format converter
- Descriptor calculations

**Data analysis**
- Molecular docking
- 2D-QSAR
- Virtual screening
- Drug repurposing
- Visualization
- Active site prediction

**Advanced modules**
- Machine learning tools
- Text mining
- Predictive computing
- Multi-scale modeling

- Disease dependent
- Disease independent

http://mpds.neist.res.in

## PASS: prediction of activity spectra for biologically active substances

Alexey Lagunin, Alla Stepanchikova, Dmitrii Filimonov and Vladimir Poroikov

Laboratory of Structure-Function Based Drug Design, Institute of Biomedical Chemistry RAMS, Moscow, Pogodinskaya str., 10, 119832, Russia

## Abstract

**Summary:** *The concept of the biological activity spectrum was introduced to describe the properties of biologically active substances. The PASS (prediction of activity spectra for substances) software product, which predicts more than 300 pharmacological effects and biochemical mechanisms on the basis of the structural formula of a substance, may be efficiently used to find new targets (mechanisms) for some ligands and, conversely, to reveal new ligands for some biological targets. We have developed a WWW interface for the PASS software. A WWW server for the on-line prediction of the biological activity spectra of substances has been constructed.*
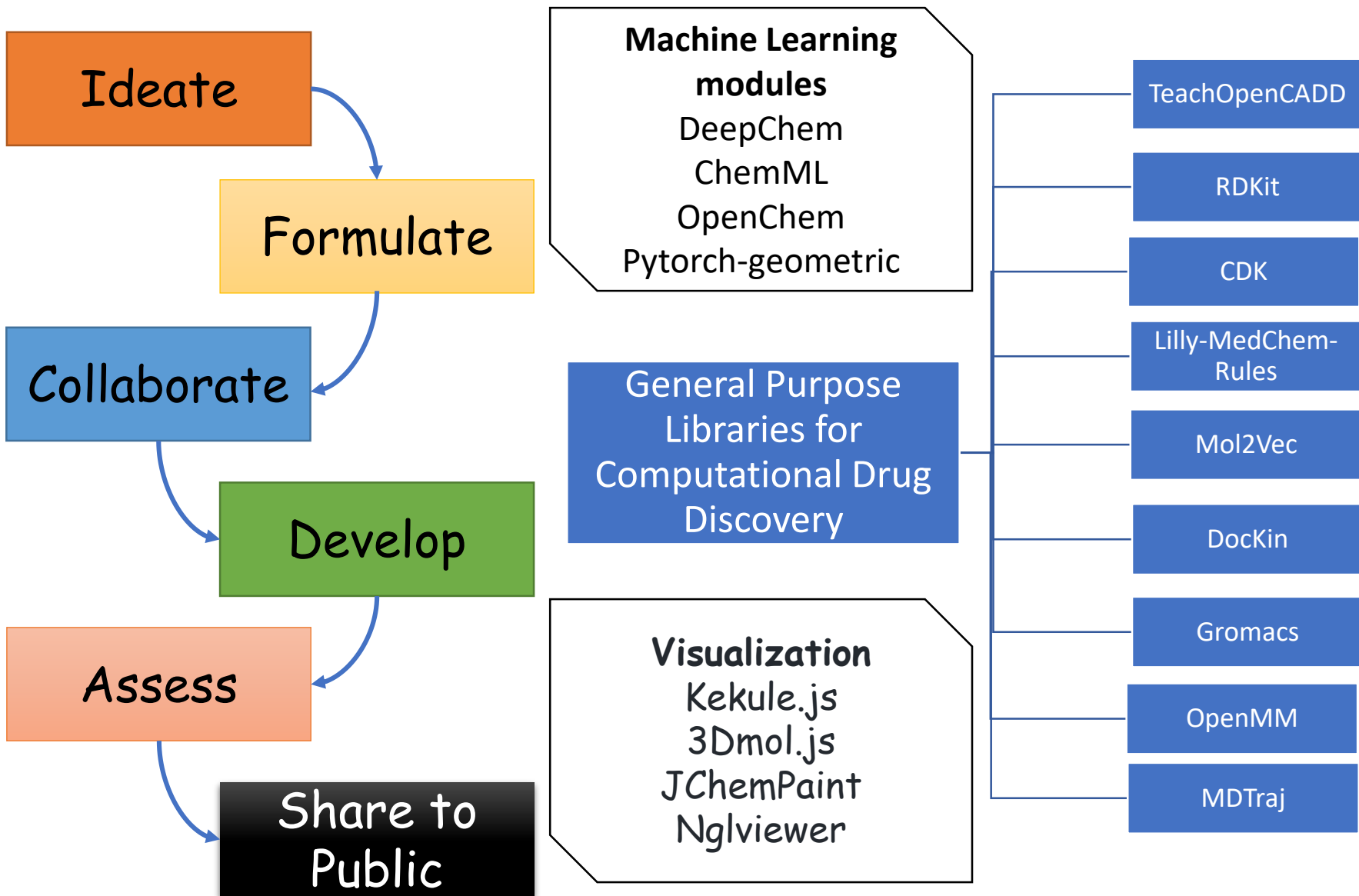
**Availability:** *http://www.ibmh.msk.su/PASS/*

# A Knowledge based approach to drug repurposing for socially important and rare diseases

*RSF/DST Project # 16-45-02012/ INT/RUS/RSF/12*

**Co-PIs:** G. Narahari Sastry, Ph.D. (CSIR - NEIST, jorhat)
Vladimir Poroikov, Dr. Sci. (IBMC, Moscow)

# Web Portals Integration



http://mpds.neist.res.in/

MPDS Compound Library with Properties and Drug likeness Filter

Galaxy Based Platform

Results Obtained from both the Web Portals

MySQL Database with Common Access

http://www.pharmaexpert.ru/passonline/

Biological Activity Prediction Tools in Way2Drug

Developed on Bootstrap Front-end Framework

Integrated Platform

http://www.way2drug.com/dr/dst/

# Integrated Web portal

MPDS          WAY2DRUG

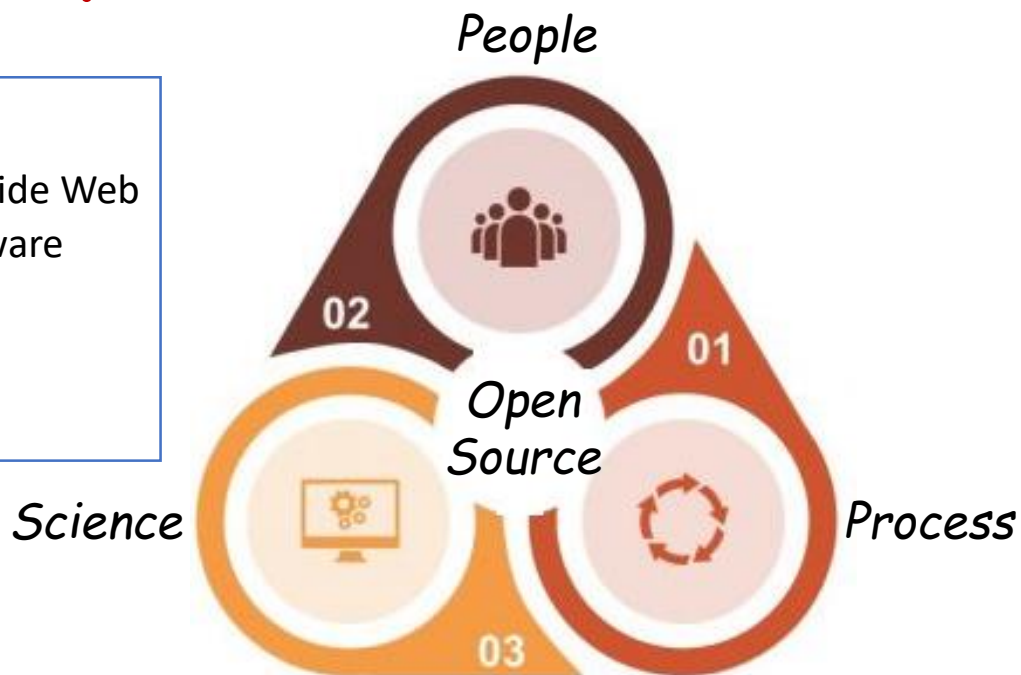**Available at: http://www.way2drug.com/dr/dst/**

# Instilling the mindset to write and develop software for drug discovery

# Learning from Successful Open Source Developments

**Few Successful Open Source Projects**

- Linux OS
- The World Wide Web
- Apache Software Foundation
- Android
- Python

People

Open Source

Science

Process

- Security
- Affordability
- Transparency
- Perpetuity
- Interoperability
- Flexibility

Transforming the features of Open Source Software for Tangible Benefits in Computational Sciences

- Chemical and biological data repositories
- High performance computing clusters
- Cloud computing
- Virtual Machine
- Containers

# Architecture of MPDS
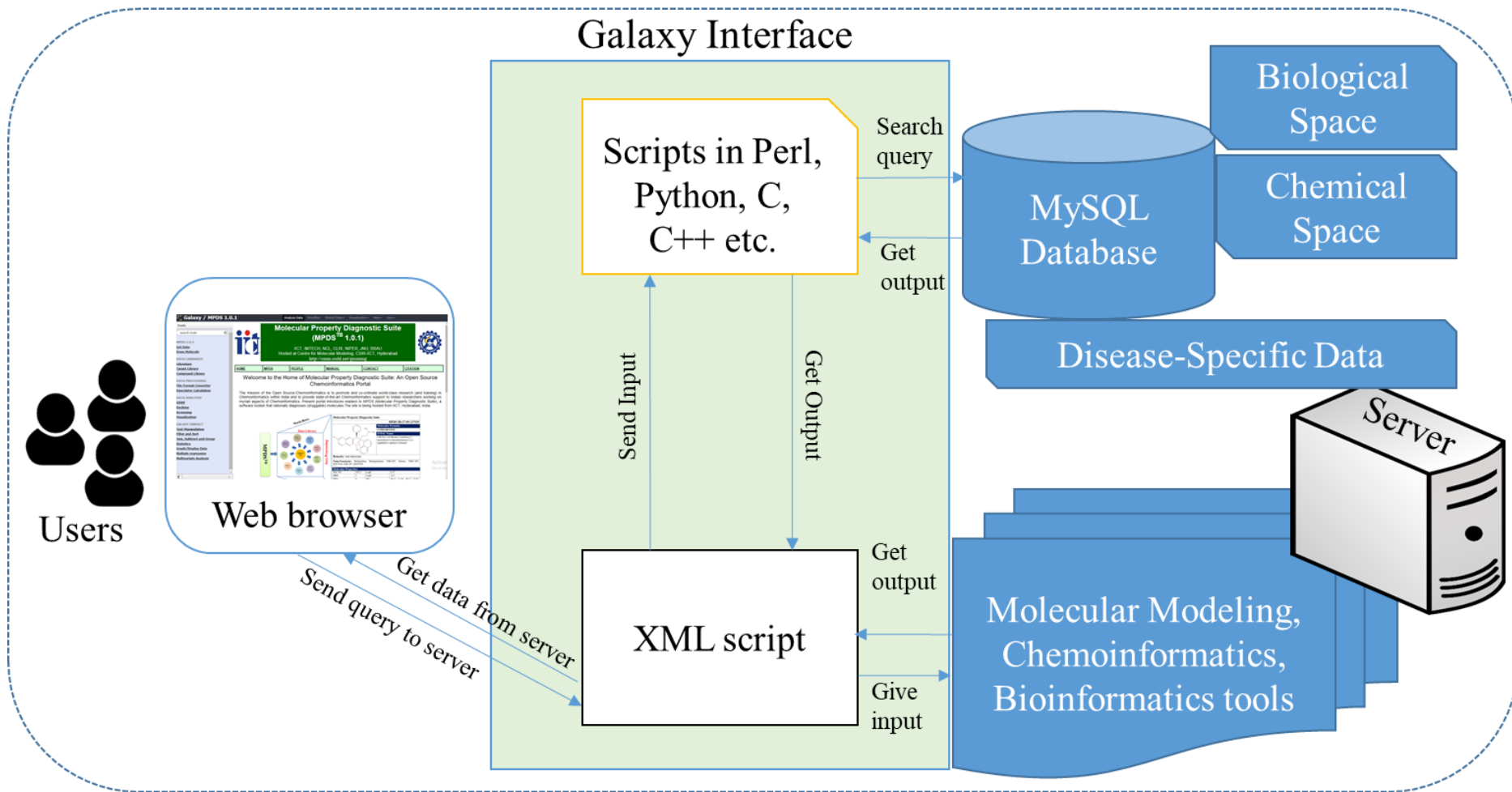
# Open source drug discovery tools in MPDS Platform
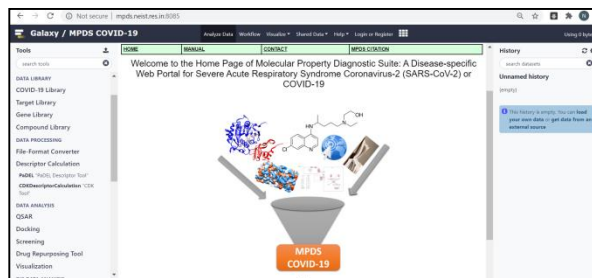
## Hosted @ CSIR - NEIST

**MPDS server**

**Galaxy**

**Indigenously developed Scripts**

**Open source drug discovery tools**
**Molecular docking**
**Virtual screening**
**DruLito**
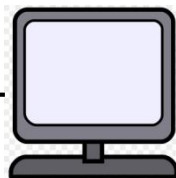**PASS analysis**
**PaDEL Descriptor**

**MPDS Homepage**

**USER INPUT**

**GET OUTPUT**

•Macromolecules
•Small molecules
•(different file formats)

•ADME Properties
•Drug likeness properties
•Docking score
•Docked complex

# Selected Publications of MPDS

Contents lists available at ScienceDirect

## Journal of Biomedical Informatics

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

### Molecular property diagnostic suite for diabetes mellitus (MPDS[DM]): An integrated web portal for drug discovery and drug repurposing

Anamika Singh Gaur[a], Selvaraman Nagamani[a], Karunakar Tanneeru[a], Dmitry Druzhilovskiy[b], Anastassia Rudik[b], Vladimir Poroikov[b], G. Narahari Sastry[a,*]

[a] Centre for Molecular Modeling, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500 007, India
[b] Institute of Biomedical Chemistry, Pogodinskaya Str., 10 Bldg. 8, Moscow, 119121, Russia

SAR AND QSAR IN ENVIRONMENTAL RESEARCH, 2017
VOL. 28, NO. 11, 913–926
https://doi.org/10.1080/1062936X.2017.1402819

Taylor & Francis
Taylor & Francis Group

### Molecular property diagnostic suite (MPDS): Development of disease-specific open source web portals for drug discovery[$]

S. Nagamani[a], A. S. Gaur[a], K. Tanneeru[a], G. Muneeswaran[a], S. S. Madugula[a], MPDS Consortium, D. Druzhilovskiy[b], V. V. Poroikov[b] and G. N. Sastry[a]

[a]Centre for Molecular Modeling, CSIR-Indian Institute of Chemical Technology, Hyderabad, India; [b]Institute of Biomedical Chemistry, Moscow, Russia

## ACS OMEGA

### Mycobacterium tuberculosis Cell Wall Permeability Model Generation Using Chemoinformatics and Machine Learning Approaches

Selvaraman Nagamani and G. Narahari Sastry*

### Computers in Biology and Medicine
Volume 138, November 2021, 104856

### Molecular descriptor analysis of approved drugs using unsupervised learning for drug repurposing

Sita Sirisha Madugula [a, b], Lijo John [a, b], Selvaraman Nagamani [b, c], Anamika Singh Gaur [a, b, c], Vladimir V. Poroikov [d], G. Narahari Sastry [b, c]

# Some thoughts…

# > 5000 years of Knowledge/Wisdom

## &

# ~ 100 years of Modern Science

- Ethnopharmocology
- Health-nutrition-traditional practices.
- Can we gain by looking back in the not so recent past...(may be a few centuries of human existance)
- Sustainability...Asking the right questions

- **Doing things correctly vs. Doing correct things**

The discovery of bronze led to the creation of stronger weapons
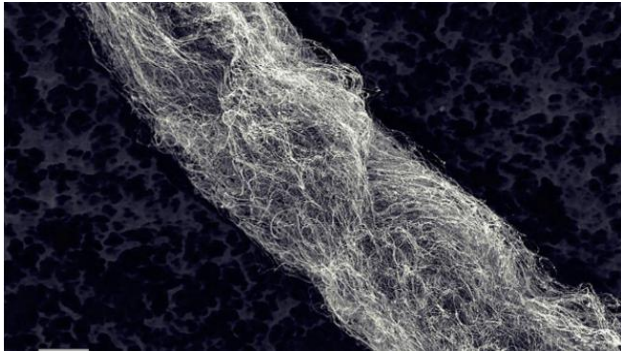

Fibrous material made from carbon nanotubes


Anaesthetics enabling advanced surgery

# Modeling & Computation is essential to design novel molecules for unmet needs of Science & Society


The invention of vulcanized rubber

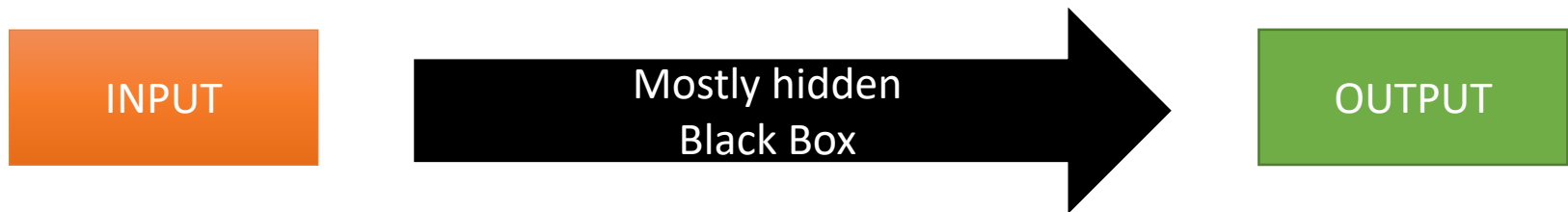
Fertilizers, are essential to modern food production


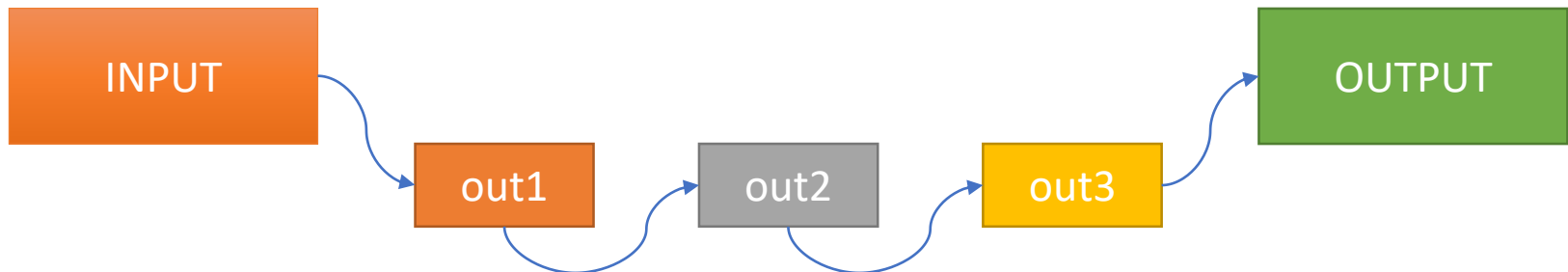Liquid crystals to control light and images

# On understanding…….

What contributes to better comprehension in understanding and analysing the computational drug discovery results ?

# Computational Intractability

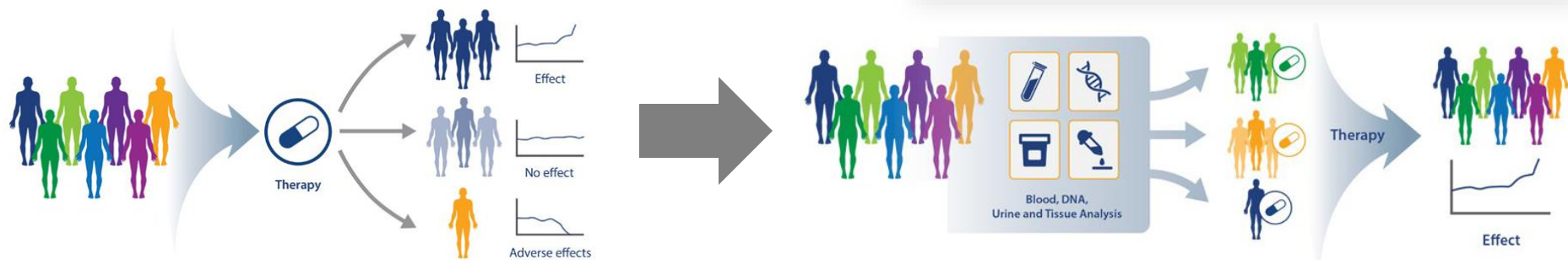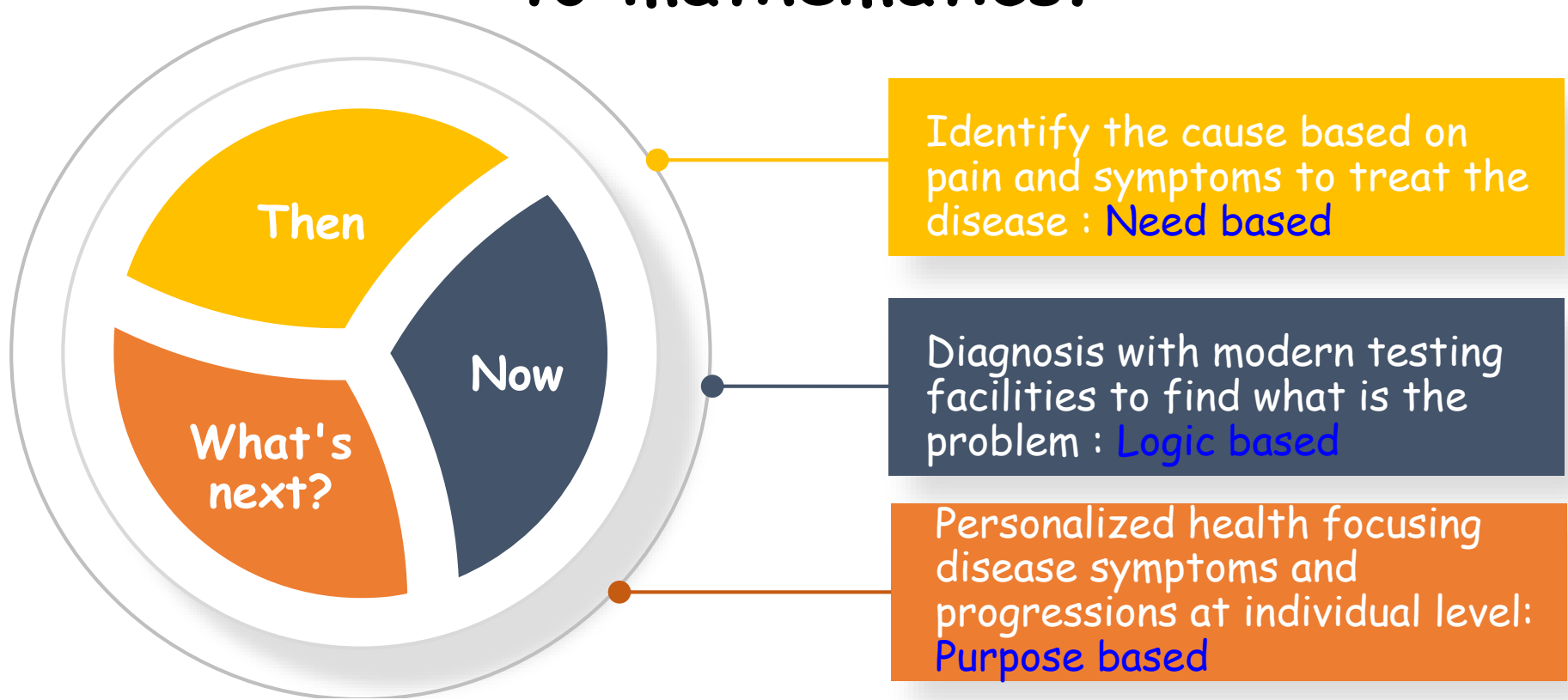Reality can only be measured to the limit derived by Heisenberg.

We attempt to model the reality of an analog world with digital computers.

Hence, our models, however accurate, will only be depicting the epistemological (and not ontological) reality. In other words, our models, however honest, will always be approximate.

Having said that, the innate motivation of any model has been to mimic the objective reality, as closely as it can be perceived.

# Computer Aided Drug Discovery
# How disease and health can be subjected to mathematics?

**Then**

**Now**

**What's next?**

Identify the cause based on pain and symptoms to treat the disease : Need based

Diagnosis with modern testing facilities to find what is the problem : Logic based

Personalized health focusing disease symptoms and progressions at individual level: Purpose based

"A Model must be wrong, in some respects, else it will be the thing itself. The trick is to see where it is right"!
---Henry A. Bent



I'm sorry for keeping it exceptionally real.

your e cards
someecards.com

Thank You!