












“Drug Discovery Using Natural Compounds in Thailand: An Update”

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Herbal Extracts

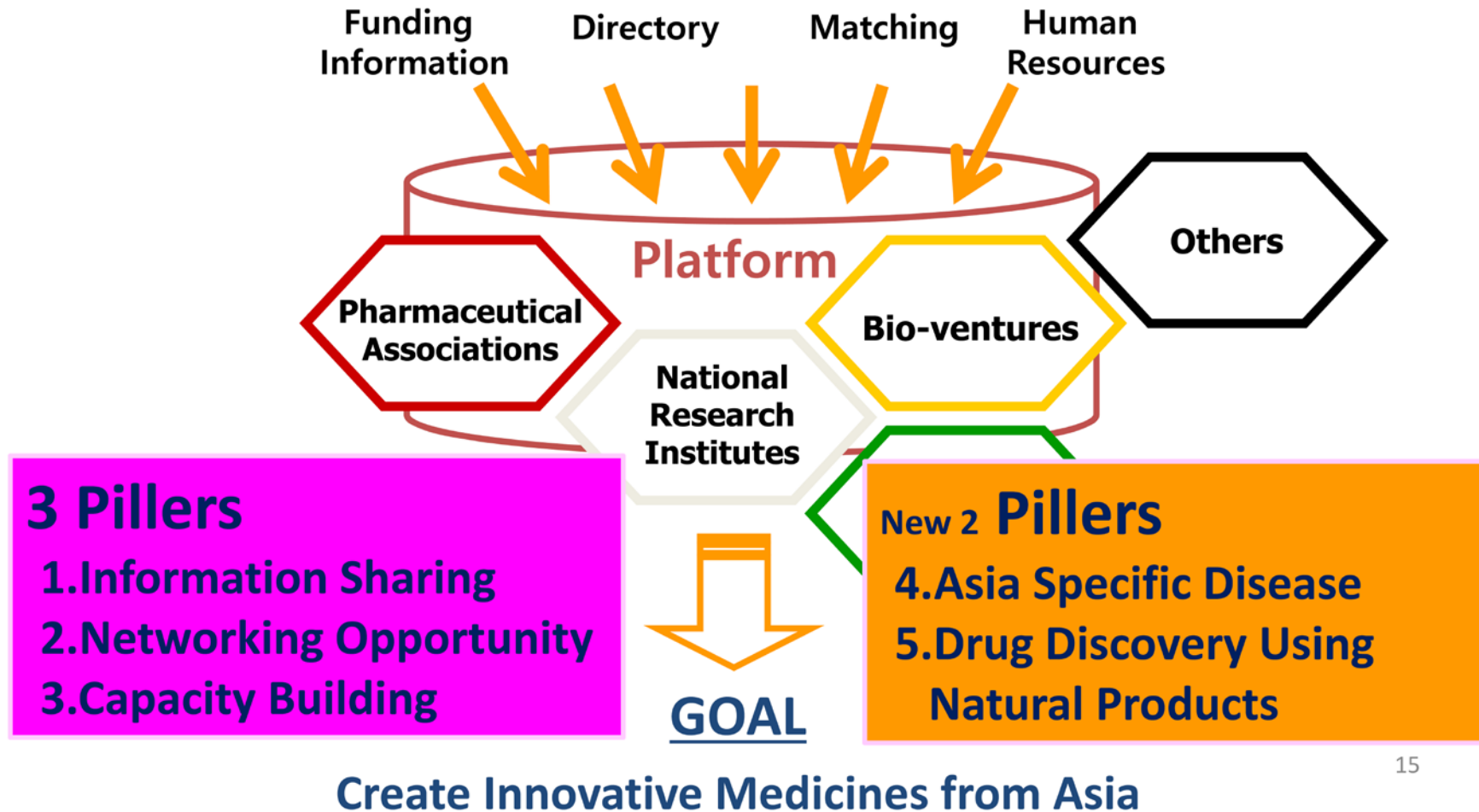
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Bangkok, Thailand

Latest List of DA-EWG Members

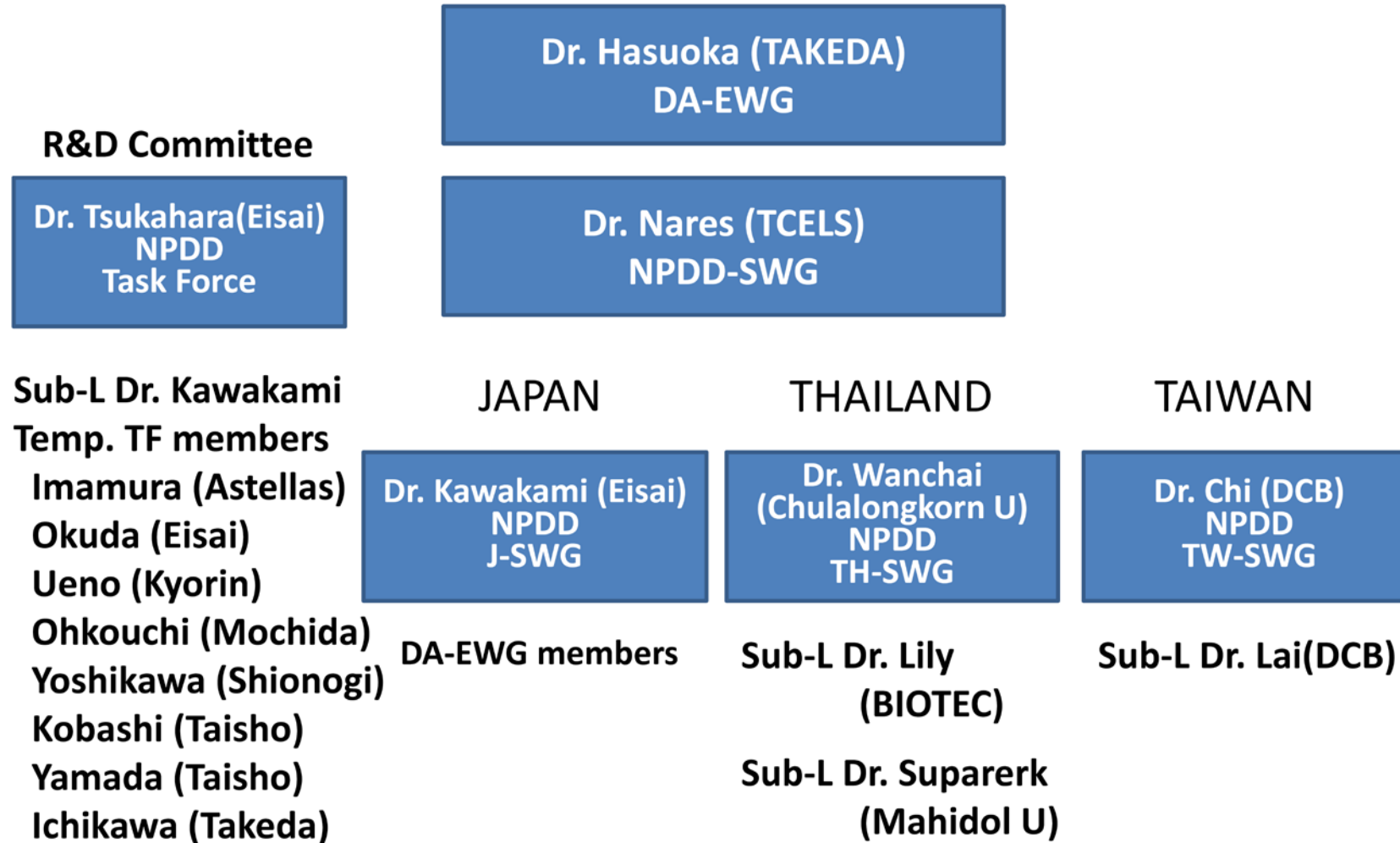
	Japan	South Korea	Taiwan	China	Hong-Kong	Singapore	Malaysia	Thailand	India
									
International R&D type Association	JPMA	KRPIA	IRPMA	RDPAC	HKAPI	SAPI	PhAMA	PreMA	OPPI
Domestic R&D type Association		KPMA	TRPMA	PhIRDA					
National Research Institute	(OCCI)	KDDF	DCB	SIMM		EDB	BIOTECH CORP	TCELS	NCBS
Academia			Academia Sinica		HKU pharmacy program				

Open Innovation APAC Aimed in Asia

APAC leverages its open innovation platform and supports the development and implementation of government policy through collaboration among member countries



Management System



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Three natural products related facilities in Thailand



Thailand National Chemical Bank of Natural Products, Chulalongkorn University

Consolidating the natural product library of nine Thai universities in the Chulalongkorn university from August, 2016.
Started as a plan of 40 million baht fiscal year 2016 for the cooperation of TCELS.
Scheduled to be screened at ECDD

Excellent Center for Drug Discovery (ECDD), Mahidol University

Just stood up in August, 2016, and it exists in the preparation stage like the installation of the HTS/HCS screening device etc. now.
Scheduled to become a screening center of Thailand in the natural product library.

BIOTEC/Thailand Bioresource Research Center (TBRC)

Biggest microbial culture collections in Thailand and ASEAN established in 1986.
60% of collected sample (>90,000 strains) is fungi, and various kinds like the insect pathogenic, water, marine, and leaf mold etc. are collected.
One of the features is a collection of the insect pathogenic fungus.
An organization that does permission and licensing of the use of natural resources by the ABS practice based on the domestic law.
Sharing of knowledge and tools as the ASEAN data center for microbial.

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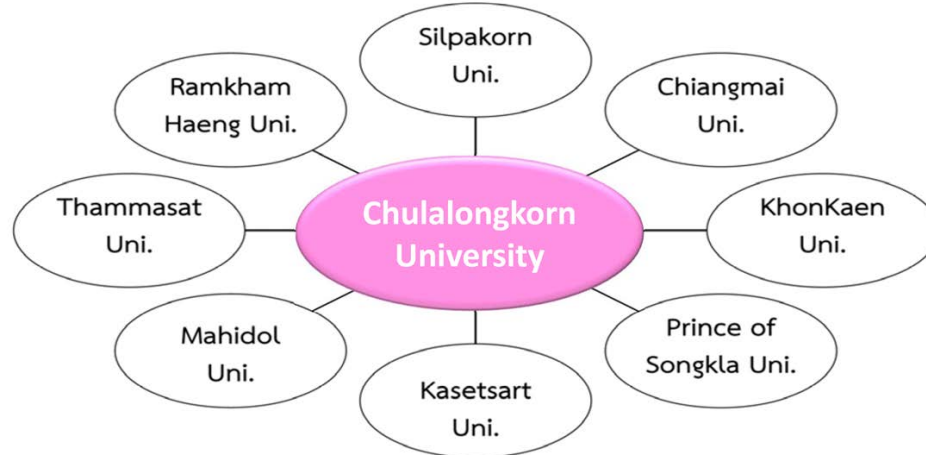


Three natural products related facilities in Thailand

National Network for Chemical Bank of Natural Products



**BIOTEC's
Thailand
Bioresource
Research Center**




**Opening July 8, 2016
Excellent Center for
Drug Discovery**

Start from System Design in 2017



**National Center for
Genetic Engineering
and Biotechnology**



National Research Council of Thailand



Thailand Center of Excellence for Life Sciences



Action Plan on the Establishment of the National Chemical Bank of Natural Products and Herbal Extracts

2017 Phase 1:

April 21

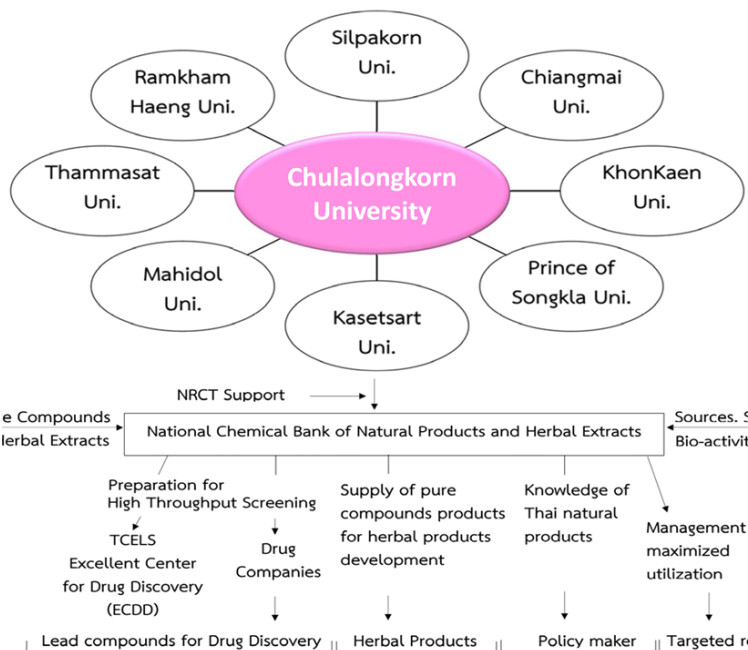
System Design of the Chemical Bank

All member meeting (All academia, TCELS, BIOTEC, CRI, NRCT) about the action plan

June (early)

International expert group meeting in Bangkok, including:

- Chinese National Compound Library, Shanghai, China
- Korea Chemical Bank, Korea Research Institute of Chemical Technology
- Drug Discovery Initiative, The University of Tokyo, Tokyo Japan
- Compound Australia, Griffith University, Australia
- Center for Drug Discovery Innovation University of California San Diego, USA
- IRBM Compound Collection (EU) IRBM Science Park, Pomezia (RM), Italy



Jun - Sep

A series of meeting among the working group members to come up with:

- Best practice of the Chemical Bank
- Local/Regional networking among universities and national centers
- Agreements between researchers and the Chemical Bank
- IP issues
- Action plan, etc

2018 Phase 2:

Implementation (start from Oct 2017)

Worldwide Public Compound Libraries

National Public Compound Libraries

	USA	Japan	China	Australia	EU	EU	Korea
Center	NIH/NCI MLP (2004~2013)	U.Tokyo/DDI (2006~)	NCDS/CNCL 2012(1997)~	Compound Australia 2008(2001)~	IMI/ELF 2013~2017	EU-OpenScreen (2015~)	Korea Chem. Bank (2000~)
Library Size	MLSMR Chemical Lib. 370,000	8 Univ. Chemical Lib. 230,000	Core & Satellite Lib. 1,800,000	Chemical Lib. 400,000 Natural product Lib. >200,000 (72,000) (Nature Bank)	JECL Chemical Lib. (500,000)	ECBL Chemical Lib. (300,000)	Chemical Lib. 400,000
HTS Center	9 MLPCN	U.Tokyo & 6 Univ.	NCDS		ESC (30 Industry-Academia Consortium)	EU Members &	Korean Researchers
DB	PubChem (Open to public)					ECBD	Chem-Bio SAR DB

- > **NIH/MLP**: Nation Institute of Health/ Molecular Libraries Program
- > **MLSMR**: Molecular Libraries Small Molecular Repository
- > **MLPCN**: Molecular Libraries Probe Production Center Network
- > **DDI**: Drug Discovery Initiative, formerly OCDD (Open Innovation Center for Drug Discovery)
- > **NCDS**: National Center for Drug Screening, **CNCL**: Chinese National Compound Library
- > **IMI/ELF**: Innovative Medicines Initiative/ European Lead Factory Program
- > **JECL**: Joint European Compound Library, **ESC**: European Screening Center
- > **ECBL**: European Chemical Biology Library, **ECBD**: European Chemical Biology DataBase

Characteristics of Japan's DDI and Korea's KCB Compound Libraries

Drug Discovery Initiative DDI Drug Discovery Initiative

Components of Chemical Library (March 2016)

General Library

Drug-like compounds with chemical diversity

Including university compounds

To discover new pharmacophores
To cover diverse chemical space

Core Library

9,600 diverse compounds for random pilot screening

Fragment/Scaffold Library

Collection of partial structures of drugs and drug candidates

Validated Compound Library

Known bioactives for checking assay systems or repositioning

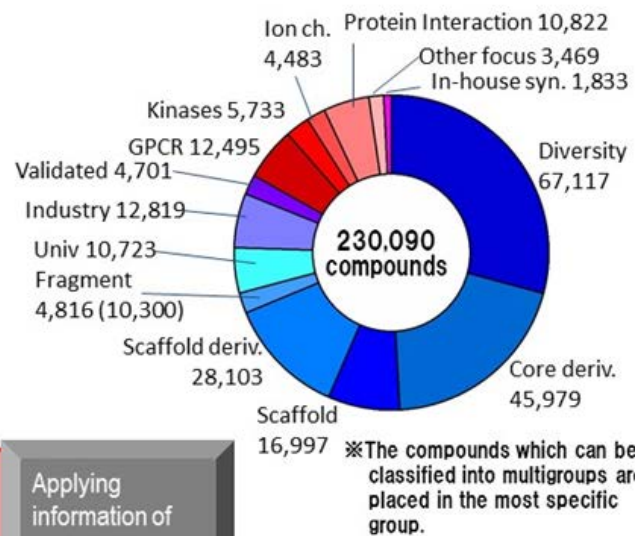
Samples from Industry

Focused Library

In silico prediction of candidates for ligands of targeted proteins

Applying information of protein structure

To improve hit rates



Korea Research Institute Chemical Technology

Compound Library Status of KCB

Composition of KCB Library

- Library size : 400,000 of diverse structures
- Synthetic small organic compounds
- Single-component natural products
 - medicinal herbs, soil and marine microbes, fungi

Collection of KCB Library

- Collected from domestic research groups since year 2000
 - Compounds voluntary donated from academia and biotech. ventures
 - Compounds mandatory deposited from government funded-projects
- Specially designed skeleton compounds by on-demand CRO synthesis
- Purchased from international vendors

Characteristics of Compounds Australia and EU's IRBM Compound Libraries



Compounds Australia provides compounds in assay-ready microplates without structures for screening.

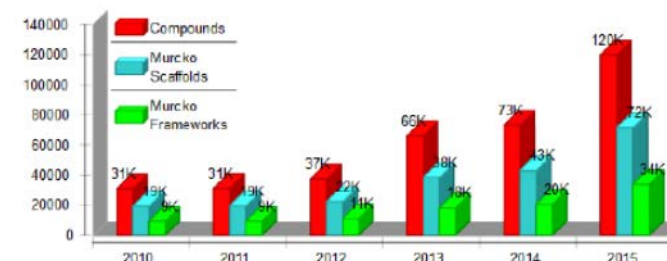
Collection	Number and Format	Ownership	Sample Information
Open Academic	> 19,500 pure compounds in microtubes	Academic Groups	Log P, MW, HBA, HBD, PSA, chiral centres, chemical fingerprint
Open Scaffolds (https://www.griffith.edu.au/science-aviation/compounds-australia/our-libraries/?a=564443)	> 33,000 pure compounds in microtubes	Purchased	Log P, MW, HBA, HBD, PSA, chiral centres, chemical fingerprint, structure
Open Drugs	>2,500 FDA Approved pure compounds in microtubes	Purchased	Log P, MW, HBA, HBD, PSA, chiral centres, chemical fingerprint, structure



IRBM Compound Collection



- Collection of 150K compounds for screening / collaborations
 - Grown from 30K initial compounds with foStucus on structural diversity
 - commercial compounds
 - contributions from external institutions
 - in-house synthesis
- Library is high quality and balanced between lead-like and drug like compounds
 - Reasonable average molecular weight,
 - Low % undesirable compounds (PAINS, / REOS / in-house solubility model prediction)
- Automated generation of statistics in real-time <http://ultron.irbm.it:8080/birt/frameset?report>



Characteristics of UCSD's CDDI and Thailand's TBRC Collections

Center for Drug Discovery Innovation, UC San Diego Available Compound Libraries

Pure marine natural products

A unique diversity set of marine algal, cyanobacterial and sponge natural products from the Scripps Institution of Oceanography with its 50-year history in pioneering marine natural products chemistry

Pure terrestrial natural products

This library is comprised of 720 pure natural products of terrestrial origin, selected to represent a broad chemical space

Impure fraction libraries

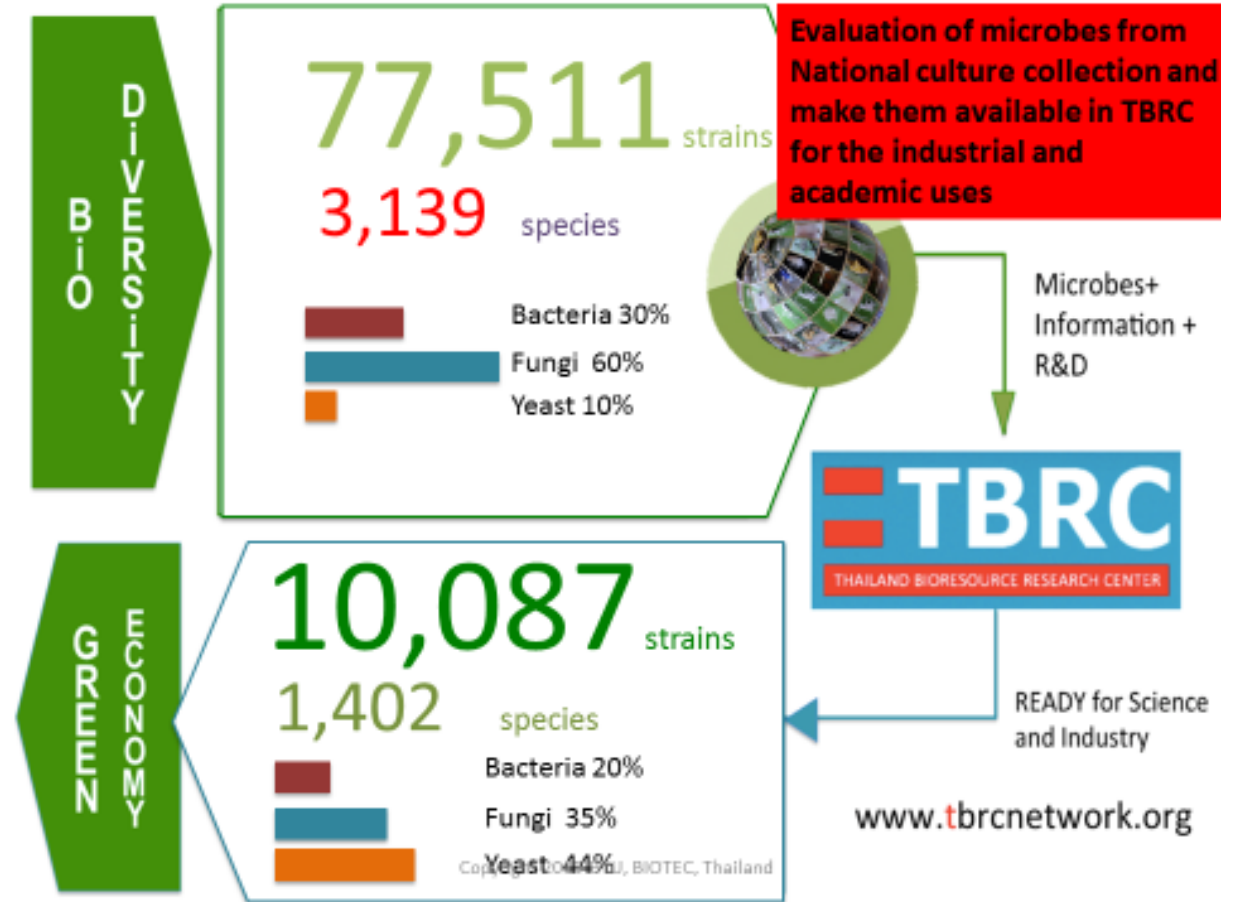
Numbering close to 4000 materials, this exceptionally high diversity set is comprised of partially purified fractions deriving from algal, cyanobacterial and sponge samples. Identification of active materials is by interaction with the providing laboratory; all samples prescreened by LCMS/MS such that active compound identities are readily deduced.

Synthetic compound library

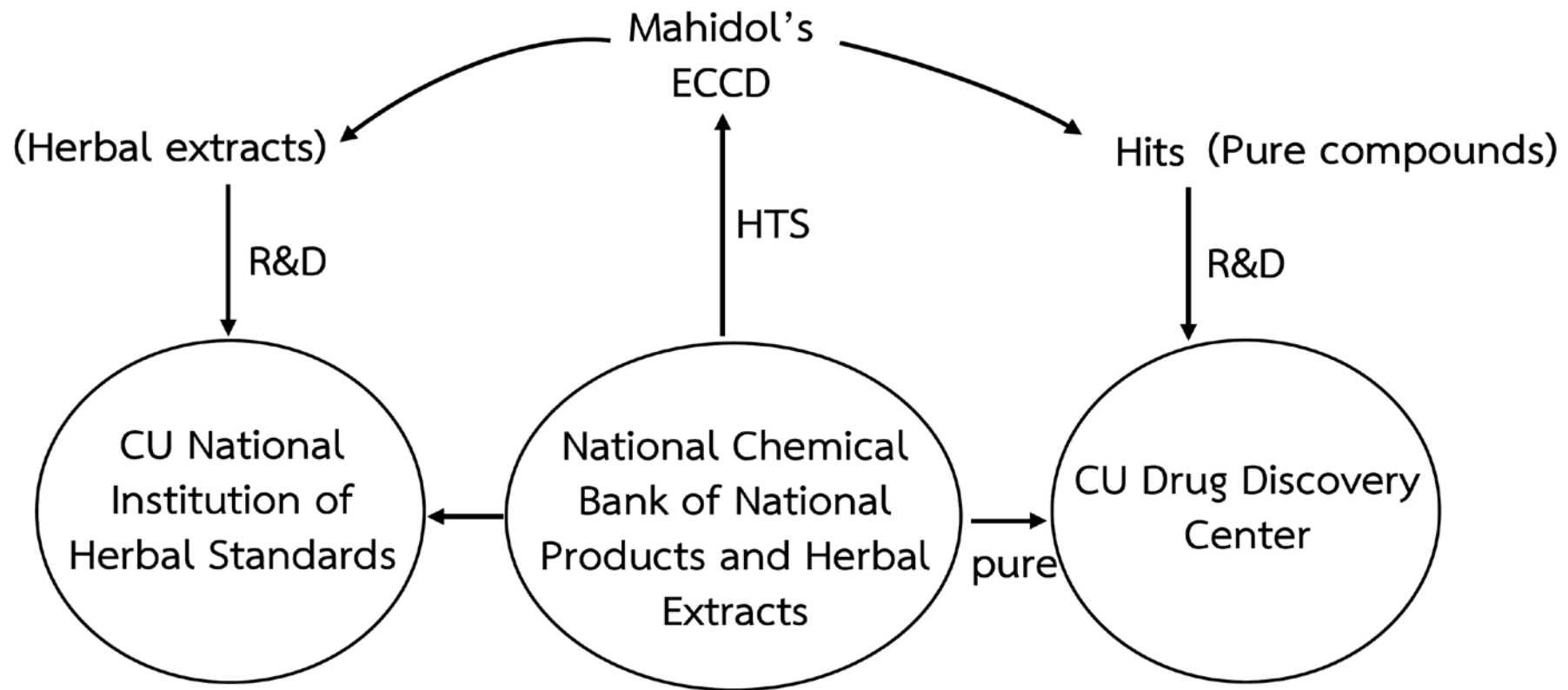
This library captures the incredible materials synthesized by synthetic organic chemists at UCSD over the past 50 years, largely in the area of natural products synthesis, and represents intermediates as well as end products

Approved drugs library

This is a purchased library of 1440 approved drugs, and enables rapid translational opportunities when agents are found active to a new disease target



Positioning of Chulalongkorn University in Drug Discovery Research



Chula Drug Discovery and Development Research Center Proposal

□ Objective/Mission:

- **To help transfer research findings to programs with translational value and/or commercial potential**
 - Addressing fragmented research using integrative and industry-like process, platform and expertise

□ Guiding Principle:

- Milestone/product focused
- Comprehensive and system approach; Scientific driven
- Collaborative within and across functions
 - Partnership with key linkages internally and externally when possible
- Transparency and efficiency process

Chula Drug Discovery and Development Research Center – Scope

➤ Two-Parallel staged approach

- I. Discovery of New Compounds - Focus initially on known targets with high medical unmet need and/or high commercial value
- II. Development of New Drug Products with previously approved drugs with commercial potential

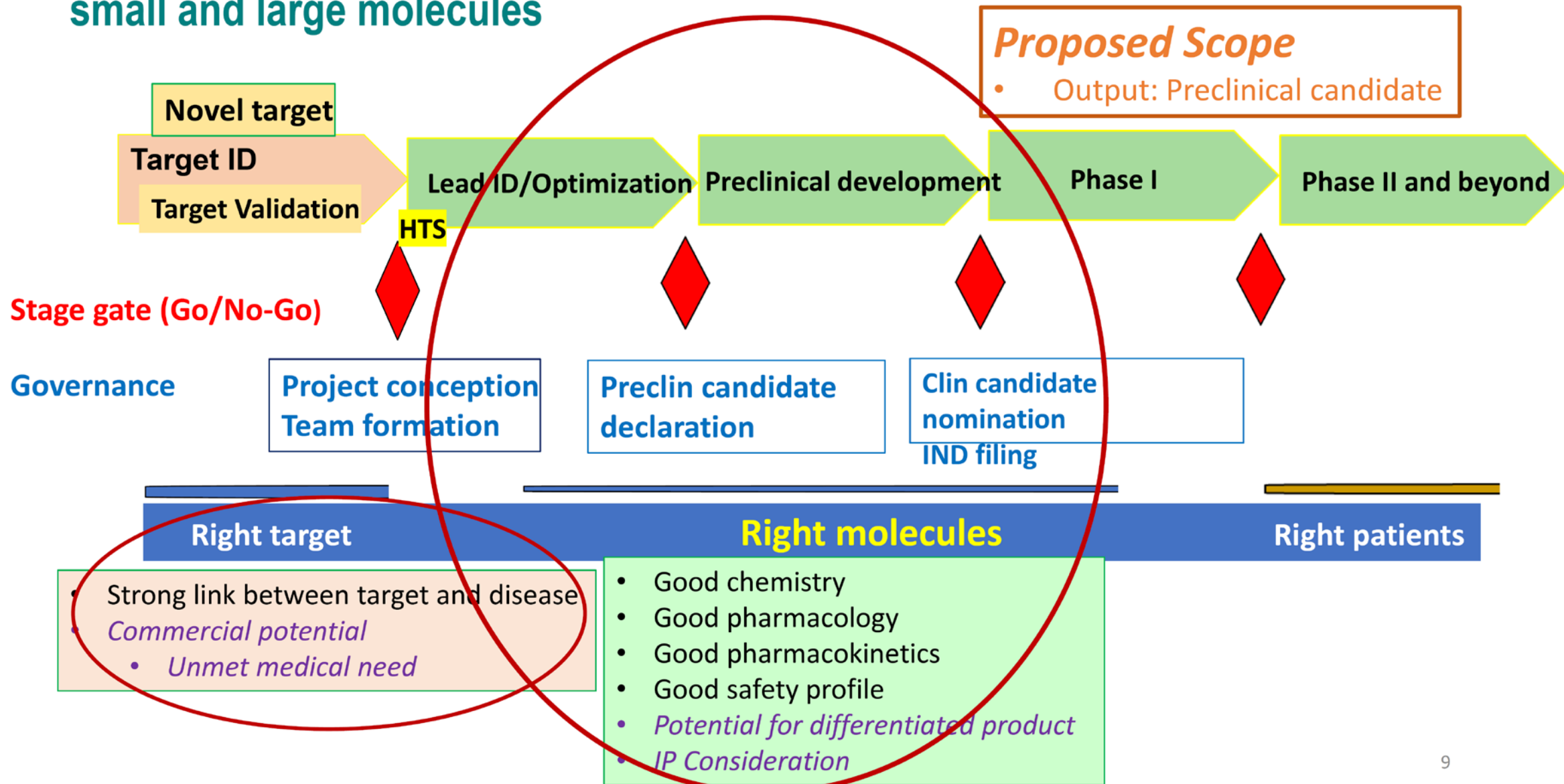
I. New compounds (Discovery program)

- Focus on Hit to Preclinical candidate
- Start with Naturally derived compounds or chemically synthesized compounds
 - Biologics at later stage
- Emphasis on 2 key therapeutic areas
 - Infectious – **HBV** initially?
 - Oncology?

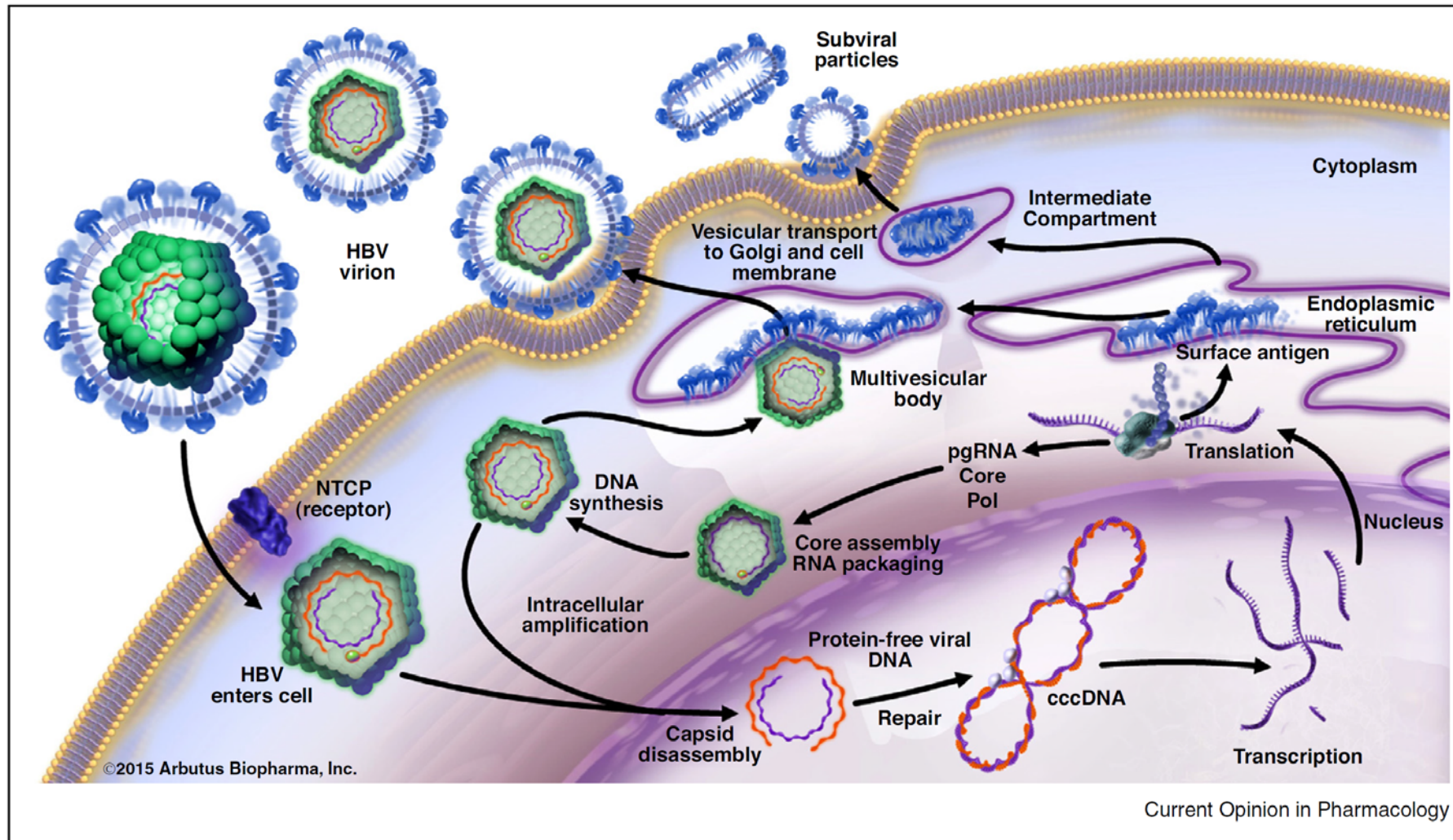
II. Previously approved compounds (Development program)

- Phase I: start with
 - Preclinical to Clinical candidates with new formulations, new route of administration
 - Clinical development of new dosage strength/dosing regimens
- Phase II: expansion to include
 - Preclinical development for New indications; chemical modifications (opportunistic)
 - Clinical development, in collaboration with external partners (e.g. local Pharma industry; GPO; international)

Drug Discovery and Development Process: General concept for both New small and large molecules




Discovery of hepatitis B virus (HBV) capsid assembly inhibitors

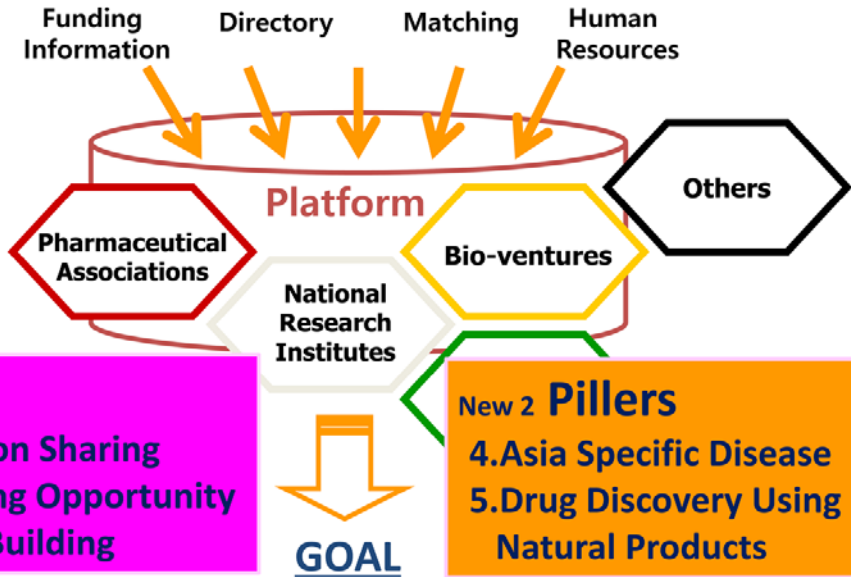


An illustration of the life cycle of HBV. Capsid assembly modulators target the process of core assembly and pgRNA packaging, influencing DNA synthesis, intracellular cccDNA amplification and the production of infectious virions. Graphic reproduced with the permission of Arbutus Biopharma, Inc.

Chula is fully involved in APAC Open Innovation Platform with various Collaborations

Open Innovation APAC Aimed in Asia 

APAC leverages its open innovation platform and supports the development and implementation of government policy through collaboration among member countries



The diagram shows a central 'Platform' box receiving inputs from 'Funding Information', 'Directory', 'Matching', and 'Human Resources'. It is connected to 'Pharmaceutical Associations', 'National Research Institutes', 'Bio-ventures', and 'Others'. Below the platform, a 'GOAL' arrow points to 'New 2 Pillars'.

3 Pillars

1. Information Sharing
2. Networking Opportunity
3. Capacity Building

New 2 Pillars

4. Asia Specific Disease
5. Drug Discovery Using Natural Products

GOAL

Create Innovative Medicines from Asia

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Drug Discovery Initiative DDI Drug Discovery Initiative

IRBM INTEGRATED RESEARCH BIOTECH MODEL **KRICT Korea Research Institute Chemical Technology**

 **Three natural products related facilities in Thailand**

National Network for Chemical Bank of Natural Products



The network diagram shows Chulalongkorn University at the center, connected to Ramkham Haeng Uni., Silpakorn Uni., Chiangmai Uni., Thammasat Uni., Mahidol Uni., Kasetsart Uni., KhonKaen Uni., and Prince of Songkla Uni.

Start from System Design in 2017

BIOTEC National Center for Genetic Engineering and Biotechnology

NRCT National Research Council of Thailand

ECDD Opening July 8, 2016 Excellent Center for Drug Discovery

TCELS Thailand Center of Excellence for Life Sciences

Comments, Opinions and Concerns of APAC Drug Alliance Expert Working Group and JPMA R&D Committee

Comments and Opinions

1. Expected much from NPDD
2. Establishment of the common chemical bank of natural products
3. Anxiety in Convention on Biological Diversity and Access and Benefit-sharing (CBD/ABS)
4. Avoiding crude extracts
5. Reproducibility

Demand of R&D Committee members

- 1. Establishment of the common chemical bank of natural products**
Services easy to use, Asian center of NP library
- 2. Screen with the assay system of the company**
Complement of the HTS/HCS owned by company
Smooth technology transfer
- 3. Creating a new framework of conclusion of a contract in accordance with CBD/ABS**
- 4. Supply purified natural products**
Avoid difficulty of assay using the extract or crude sample



Conclusion

1. Drug Discovery Using Natural Compounds In Thailand is progressing forward with the action of APAC Pillar 5 active movement
2. Pillar 5 NPDD Task Force has nicely summarized the potential of Thailand's 3 facilities: TBRC, ECDD, and National Chemical Bank of Natural Products
3. TCELS has strengthened the collaboration of the three facilities of the countries
4. Clear action plan on the establishment of Thailand National Chemical Bank has been implemented with international know-how supports
5. Chulalongkorn University is in the process of establishing a drug discovery and development research center with focusing on the steps of Lead identification/optimization and preclinical development
6. Primary focus may be in the infectious HBV disease