The Driving Force
Behind New Drug Discovery

Partnership with TB Alliance for anti-tuberculosis drug discovery from natural products

November 19, 2021

Isshin Tanaka

Applied Microbiology Group
Biological Research Department

DAIICHI SANKYO RD NOVARE CO., LTD.

My working experience in drug discovery from natural products

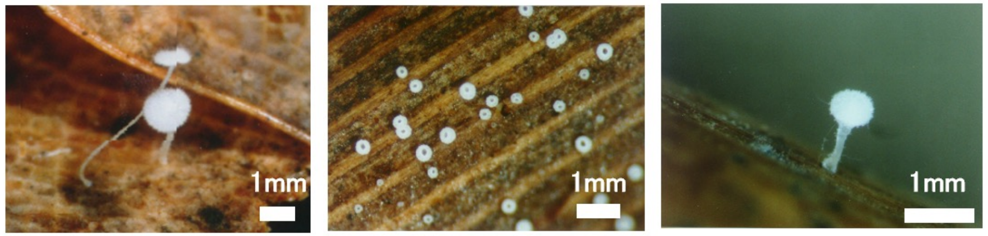
1995–2007	Sankyo Co., Ltd.
2007–2011	Daiichi Sankyo Co., Ltd.
2011 to present	Daiichi Sankyo RD Novare Co., Ltd.

Developed and commercialized natural product-derived pravastatin as a cholesterol-lowering drug

My initial task:

- Curating a microorganism library

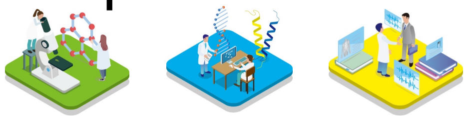
Basidiomycetes that form minute basidiocarp



Mycena *Seticyphella* *Physalacria*

My current task:

- Finding an effective use of the microorganism library and microbial extract libraries
- Developing new technologies for drug discovery from natural products



What is Daiichi Sankyo RD Novare?

DAIICHI SANKYO RD NOVARE CO., LTD.

Daiichi Sankyo RD Novare was established in 2011 with a mission of playing a role in the global R&D function of the Daiichi Sankyo Group by building an advanced technological foundation that supports innovative drug discovery and a high-quality clinical development process

Our Business

Business Overview

Drug Discovery Research Unit

A drug discovery platform that maximizes the process of creating new drugs.

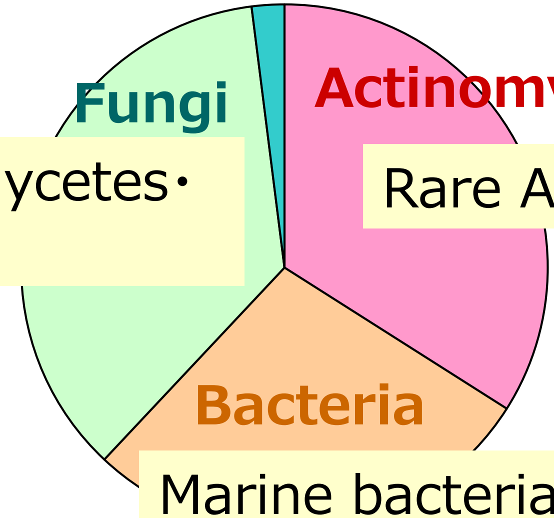
Translational Research Unit

Revolutionizing the drug discovery process though understanding of the disease.

Clinical Development Unit

Clinical trial operations that leverage collaboration.

Microorganism library of Daiichi Sankyo RD Novare



Fungi

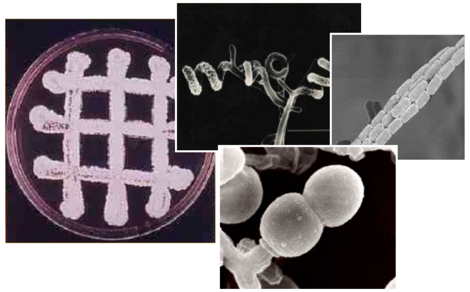
Discomycetes・Basidiomycetes・
Endophytes

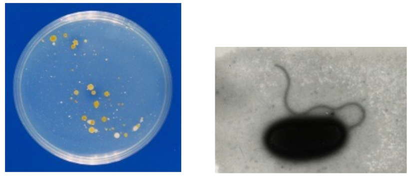
Actinomycetes

Rare Actinomycetes

Bacteria

Marine bacteria





Characteristic microorganisms of each group

- Contains a large number of strains isolated from terrestrial and marine environments in Japan
- Organized by molecular systematics based on rDNA
- Utilizing the crude fermentation extracts derived from the microorganism library in our research
- This library and research function were inherited by Daiichi Sankyo RD Novare from Sankyo

The origin of our collaboration with TB Alliance in 2014

- TB Alliance planned to conduct anti-tuberculosis drug discovery research from natural products in Japan and had been surveying Japanese research institutes through the GHIT Fund
- Daiichi Sankyo RD Novare was seeking a chance to expand utilization of microorganism library

We received an explanation from the GHIT Fund and understood the significance of collaboration

- Strong needs for Novare’s microorganism library
- Supported research costs by GHIT Fund and PDPs
- Expected contribution to global health through our expertise in drug discovery research

Screening project started in 2015

〜1980s **Former company Sankyo did drug discovery research.** Since the 1980s, the company's research had been shifting to other areas of unmet medical needs

Research suspended over 30 years

Technology has advanced during this period

- Molecular phylogenetics
- Increased understanding of microbial genomes
- Development of synthetic biology

2015 **Screening project started**

<u>Differences from screening 30 years ago</u>

- Use expanded and more diverse microorganism library organized by molecular systematics
- Use *Mycobacterium tuberculosis*, not *Mycobacterium smegmatis*, for phenotype screening

Status of GHIT-sponsored projects with TB Alliance

Drugs / Vaccines	Target Research	Screening	Hit-to-Lead	Preclinical
Diagnostics	Target Research			Product Design

Not Awarded from GHIT (2017) ★
Hit-to-Lead project

★ Awarded from GHIT (2019)
Hit-to-Lead project

DAIICHI SANKYO RD NOVARE CO., LTD.
TB Alliance

Screening
2015～2019

Hit-to-Lead
2019～

Discovery of novel active compounds

Completed PJ

Active PJ

A new project started based on the achievements so far

DAIICHI SANKYO RD NOVARE CO., LTD.
TB Alliance

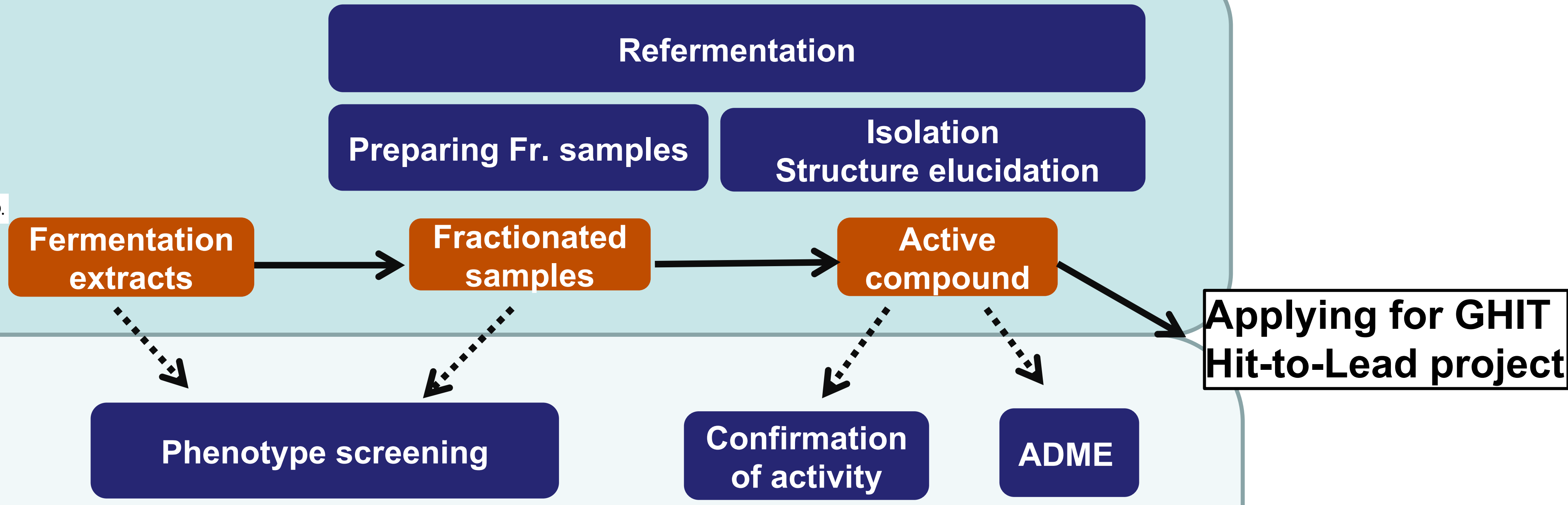
Screening
2021～

Roles in the screening project

Daiichi-Sankyo

RD Novare

DAIICHI SANKYO RD NOVARE CO., LTD.



Refermentation

Preparing Fr. samples

Isolation
Structure elucidation

Fermentation extracts → Fractionated samples → Active compound → Applying for GHIT Hit-to-Lead project

Phenotype screening

Confirmation of activity

ADME

TB Alliance

TB Alliance

University of Illinois Chicago
(USA)

BioDuro-Sundia
(China)

Japan Anti-Tuberculosis Association
(Japan)

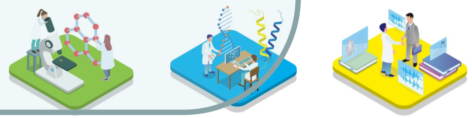
Biotranex
(USA)

Evotec
(USA)

Texas A&M University
(USA)

🟧 Research material

🟦 Research activity



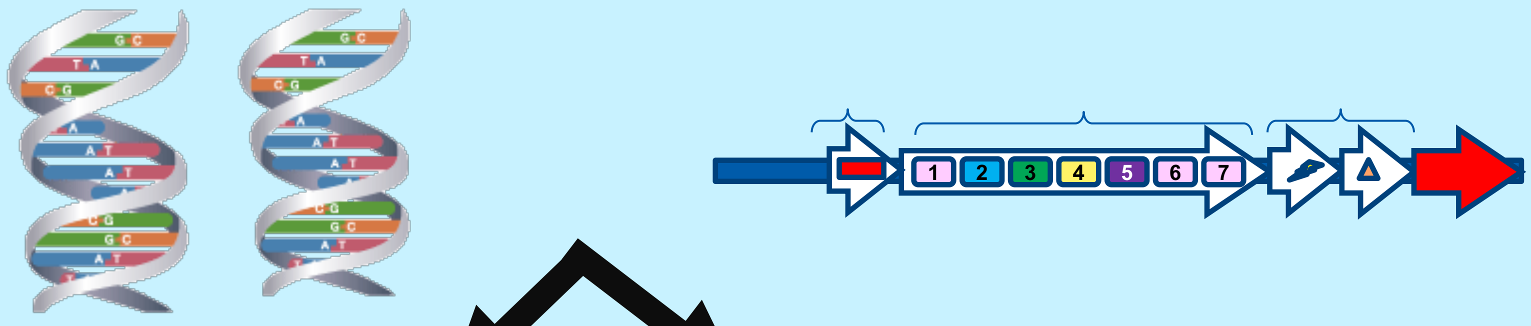
Role of Daiichi Sankyo RD Novare in the Hit-to-Lead project

- Make the derivatization plan with TB Alliance
- Provide the parent or analog compounds used for derivatization
  - Gram-scale compounds are needed
  - Analogous compounds or basic skeletons of the compounds useful for diversification of semi-synthesis

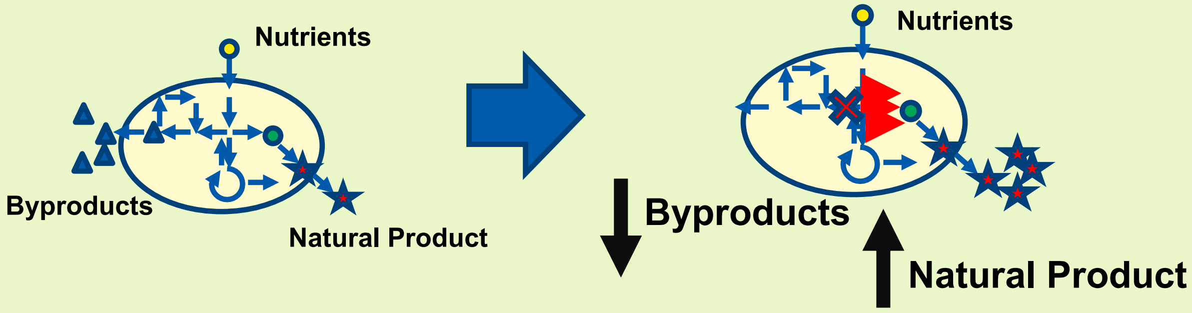
To provide the compounds efficiently, we wanted to utilize genomic information and biosynthetic genes of the producing microorganisms

Prospects for utilization of microbial genome

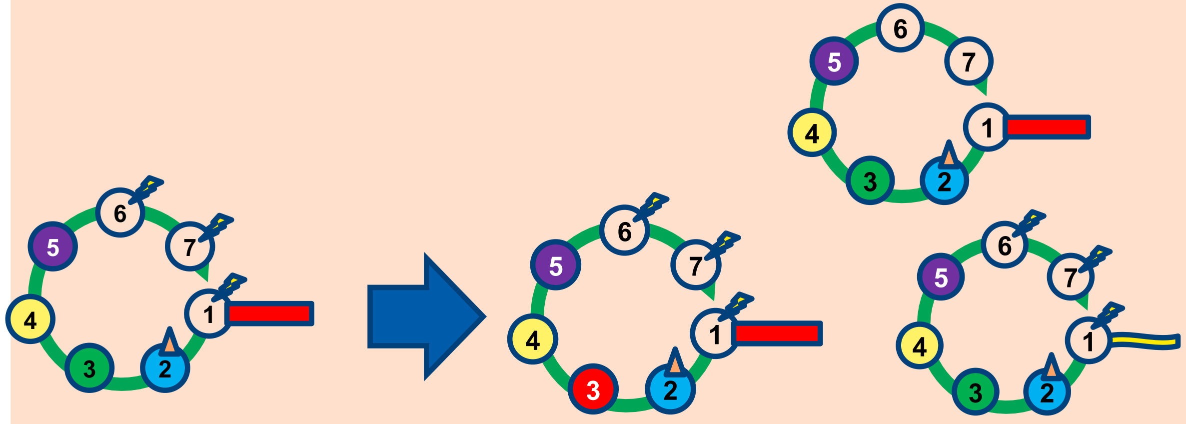
Microbial genome and biosynthetic genes



Productivity improvement



Generation of novel compounds



Take home message

1. Microorganism libraries are still an attractive source of new drug leads where new active compounds can be found
2. With support from GHIT Fund, this proven and limitless source can be put to great use for neglected diseases
3. A combination of the know-how accumulated within our organization and new approaches in microbial genomes and biosynthetic genes can generate novel leads

Acknowledgements

DAIICHI SANKYO RD NOVARE CO., LTD.

Biological Research Department

Yasunori Muramatsu
Youko Fujita
Tadaaki Morishita
Masaaki Kizuka
Takahiro Miyauchi
Yasunori Ono
Emi Kurosawa
Shinobu Abe
Tomio Ishikawa
Hanako Nishizawa

Organic & Biomolecular Chemistry Department

Marumoto Shinji
Hiroki Shimizu
Tetsunori Fujisawa
Hiroshi Maruoka

Pharmaceutical & ADMET Research Department

Yoshimine Fujii
Masaru Iwasaki

GHIT Fund

GHIT Fund Management teams

TB ALLIANCE

Dr. Takushi Kaneko
Dr. Nader Fotouhi
Zaid Tanvir

<Cross-sector partnerships of TB ALLIANCE>

Japan Anti-Tuberculosis Association

Dr. Norio Doi
Dr. Yasuhiro Horita

University of Illinois Chicago

Professor Scott G. Franzblau

Various other research institutes