Partnership with TB Alliance for anti-tuberculosis drug discovery from natural products
November 19, 2021
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DAIICHI SANKYO RD NOVARE CO., LTD.
My working experience in drug discovery from natural products

<table>
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<th>Period</th>
<th>Company</th>
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</thead>
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<tr>
<td>2011 to present</td>
<td>Daiichi Sankyo RD Novare Co., Ltd.</td>
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**My initial task:**
- Curating a microorganism library

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

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

Basidiomycetes that form minute basidiocarp

- Mycena
- Seticyphella
- Physalacria
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.
Microorganism library of Daiichi Sankyo RD Novare

- 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:

1. Strong needs for Novare’s microorganism library.
2. Supported research costs by GHIT Fund and PDPs.
3. 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
Differences from screening 30 years ago
- 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

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<th>Drugs / Vaccines</th>
<th>Target Research</th>
<th>Screening</th>
<th>Hit-to-Lead</th>
<th>Preclinical</th>
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<td>Diagnostics</td>
<td>Target Research</td>
<td></td>
<td></td>
<td>Product Design</td>
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</table>

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

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

**Discovery of novel active compounds**

**DAIICHI SANKYO RD NOVARE CO., LTD.**

**TB Alliance**

**Screening**
**2015〜2019**

**Hit-to-Lead**
**2019〜**

A new project started based on the achievements so far

**Completed PJ**

**Active PJ**

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**Screening**
**2021〜**
Roles in the screening project

**RD Novare**
- Fermentation extracts
- Preparing Fr. samples
- Fractionated samples
- Active compound
- Refermentation
- Isolation Structure elucidation

**TB Alliance**
- University of Illinois Chicago (USA)
- Japan Anti-Tuberculosis Association (Japan)
- Texas A&M University (USA)
- Biotranex (USA)
- Evotec (USA)
- BioDuro-Sundia (China)

Applying for GHIT Hit-to-Lead project

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.
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