# TB Alliance Screening Projects with GHIT

GHIT R&D Forum, 12/08/2017, Takushi Kaneko

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

# What Do We Want in a New TB Drug?

- Novel mechanism of action:  No cross-resistance with the existing TB drugs
- Active against both drug-sensitive and drug-resistant *Mycobacterium tuberculosis* (Mtb)
- Potential to shorten the treatment duration (as indicated by, for example, activity against non-replicating Mtb)
- Given orally (dose size < 0.5 g, once daily)
- No (or little) DDI with other TB drugs or ARV drugs
- Safe since treatment is long
- Low cost of goods

# What is TB Alliance?

- TB Alliance (Global Alliance for TB Drug Development) is a not-for-profit organization dedicated to the discovery and development of better, faster-acting, and affordable tuberculosis drugs/regimens
- Founded in the year 2000 and based in New York and Pretoria, South Africa
- Virtual organization with about 50 employees, we do not have any laboratories
- Major funders include the Bill and Melinda Gates Foundation, US and foreign governments
- Product development partnership (PDP) collaborating with academic laboratories and major pharmaceutical companies
- Harnessing the power of global innovation, expertise, and partnerships…
  - AbbVie, Eli Lilly, Glaxo SmithKline, Janssen Pharmaceuticals, Merck, Roche Pharmaceuticals, Sanofi
  - Institute of Materia Medica, Johns Hopkins University, Medical Research Council at University College London, National Institute of Health, Schrödinger, Stellenbosch University, TB Drug Accelerator Program, University of Auckland, University College London, University of Dundee, University of Illinois at Chicago, Yonsei University, and others
- …to develop novel regimens effective against both drug-sensitive and -resistant TB

# GHIT Sponsored Activities

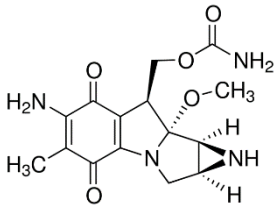
## HTS of Corporate Compound Collections-Synthetic Compounds

- Phenotypic Screens
  - Astellas, Daiichi-Sankyo, Dainippon-Sumitomo Pharma, Mitsubishi-Tanabe Pharma, Shionogi, and Takeda
  - Screens carried out either at Japan Anti-TB Association (JATA) or University of Illinois at Chicago (UIC) (Requires BSL-3 labs)
  - Three hit-to-lead projects (Daiichi-Sankyo, Shionogi, and Takeda) in progress
  - Other additional screens being negotiated (including target-based or virtual screens)

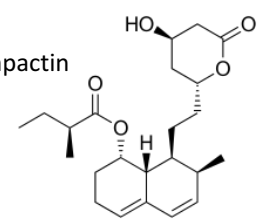
# Natural Product-Based Screens

NP = One of the strengths of Japanese Pharma and Research Organizations

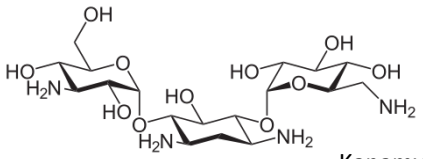
- Among the anti-bacterial and anti-cancer agents, a large percentage of the drugs are derived from natural products
- Historical Examples
  - Mitomycins (1955) Dr. Toju Hata, Kitasato Institute/Dr. Shigetoshi Wakaki, Kyowa Hakko
  - Kanamycin (1957) Dr. Hamao Umezawa, Institute of Microbial Chemistry
  - Compactin (1978) Dr. Akira Endo, Sankyo and Tokyo Noko University
  - Avermectin (1978). Dr. Satoshi Omura, Kitasato University, Merck
  - Halichondrins (1985). Drs. Daisuke Uemura and Yoshimasa Hirata, Nagoya University, Eribulin/Eisai



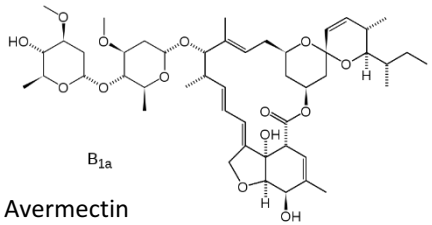
Mitomycin C



Compactin

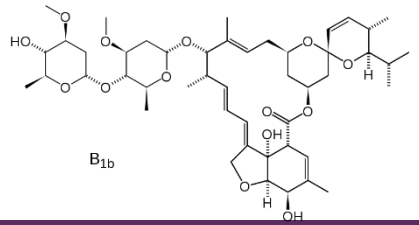


Kanamycin

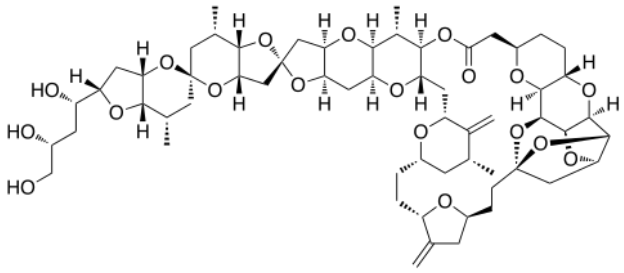


$B_{1a}$

Avermectin



$B_{1b}$



Halichondrin

# GHIT-Sponsored Natural Product Screens at TB Alliance

- Chugai
  - 813 Purified natural products
- Daiichi-Sankyo RD Novare
  - Terrestrial and marine microorganism fermentation extracts (28,000 extracts) and 639 purified natural products
- HyphaGenesis and Toyama Prefectural University
  - 37,000 Fungal extracts
- OP Bio Factory
  - Marine microorganism fermentation extracts (11,187 extracts) and 549 purified natural products

❖ With each organization above we have at least one series we are currently pursuing

# One of the Series We are Pursuing at Daiichi-Sankyo RD Novare

- The producing organism is Actinomadura sp.
- The active components have been purified and their structures determined
- Completely novel structures as anti-TB agents and appear to be specifically active against Mycobacteria

| | MIC against Mtb H37Rv (µg/mL) | | Cytotoxicity (µg/mL) |
|---|---|---|---|
| | MABA* | LORA* | Vero cells |
| Compound 1 | <0.125 | >32 (80%) | >32 |
| Isoniazid | 0.45 | >128 | |

- Possess high stability in H/M liver microsomes and high aqueous solubility
- Its MOA, not MmpL3 or DprE1, but still under investigation
- Currently we are working on the possibility of demonstrating their *in vivo* efficacy

- MABA= Microplate Alamar Blue Assay, one method to measure drug activity against replicating Mtb: *LORA=Low Oxygen Recovery Assay, one method to measure drug activity against non-replicating Mtb

# Summary

- From the GHIT-sponsored screens we have identified compounds/extracts with sufficient potency and stability and we are working toward demonstrating their *in vivo* efficacy
- Influence of partnerships
  - It has been great to work with the talented and dedicated scientists from all the organizations we collaborated. Each organization has a slightly different emphasis on how to approach drug discovery
  - We were able to tap into the corporate cumulative knowledge base of natural products (Daiichi-Sankyo RD Novare)
  - We were able to work with other organizations such as Japan Agency for Medical Research and Development (AMED) to get additional contacts

- The expertise and the knowledge of natural product science = the area Japan can use to contribute toward global health

# Acknowledgements

GHIT Fund
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astellas

Innovation all for the patients
CHUGAI
Roche A member of the Roche group

Daiichi-Sankyo

DAIICHI SANKYO RD NOVARE CO., LTD.
Passion for Innovation. Compassion for Patients.®

DAINIPPON SUMITOMO PHARMA

HyphaGenesis

Mitsubishi Tanabe Pharma

Okinawa Natural Products
OP Bio Factory

SHIONOGI

Takeda

TOYAMA Prefectural University