New opportunities in Natural Product Drug Discovery

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Overview of the drug discovery process from natural products ~ a long journey ~

Material access

Natural Samples
(tens of thousands samples)

Screening

Purification

Optimization
Scale up production

Bioactive natural product

Drug candidate

Clinical trial

NP database

Find a hit extract (○)

Hit Extract

Material access

Marine-organism

Micro-organism

NP database
Natural products drug discovery in Eisai

Halichondrin B

Total synthetic halichondrin B analog

E7389 (Eribulin)

Approved (anti-tumor drug)

Pladienolide B

Semi-synthetic pladienolide D derivative

E7107

H3B-8800 (clinical trial ongoing)
Why Halichondrin B?

*Halichondria okadaii* (marine sponge)

Halichondrin B

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**Why NOT Halichondrin B as a drug?**

- Extremely limited material supply from natural sources required for discovery research, clinical development and commercial production

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*B-16 Mouse Melanoma Model*

Median Survival Time (days)

0 ug/kg, 2.5 ug/kg, 5 ug/kg

T/C = 244%

in vivo activity confirmed at NCI (natural material) and at Eisai (synthetic material)

Chemical beauty of Eribulin enabled by powerful synthetic chemistry

Halichondrin B

Chiral center: 19
Total synthetic steps: 64

“Right Half”

E7389 (Eribulin)
Pladienolide B as a unique “Drug Lead”

Streptomyces platensis Mer-11107

- Novel chemical structure
- Unique mechanism of action
- Highly potent *in vitro* & *in vivo*
- Complete remission was observed *in vivo* xenograft model

From Pladienolide B to E7107 with microbial and chemical conversion technologies

Purification

Micro-organism
Streptomyces platensis
Mer-11107

Pladienolide B

Optimization

Bio-conversion
Improve the aqueous stability

Pladienolide D

Optimization

Semi-synthesis
Enhance *in vivo* activity

E7107
New technology reveals precise binding mode of E7107 to the target protein

Cryo-EM technology enabled protein structure analysis of huge and dynamic target complex like spliceosome

The overall structure of the four-protein complex with E7107.

The cryo-EM map shows that E7107:
- binds at the interface of SF3B1 and PHF5A
- competes with U2 snRNA in the BPA region
- stabilizes SF3B1 to a non-functional conformation

New insights into novel drug design

New opportunity for NP drug discovery
Natural product meets new demands and technologies

- **Mid-size molecules**: Targeting protein complex as well as protein-protein interaction
- **Assay technology**: Phenotypic screening system such as iPS cell-derived human disease models
- **Synthetic biology**: Natural products are “Genetic products” that can be modified by genetic manipulation

New era of “NP” Drug Discovery
Discover new NPs through APAC NPDD Consortium
Constructing unique and sustainable collaboration mechanism in Asia

Japan
JPMA members with N^2PC and IMC

- Technology transfer
- Technical support
- Consultation

1. **Capacity building** of young researchers in Asian countries

2. **Drug discovery** using natural products in Asian countries

**Asian countries: one of the most biodiversity rich areas in the world**

N^2PC: Technology Research Association for Next generation natural products chemistry

IMC: Institute of Microbial Chemistry