



New opportunities in Natural Product Drug Discovery

Kappei Tsukahara, Ph.D.

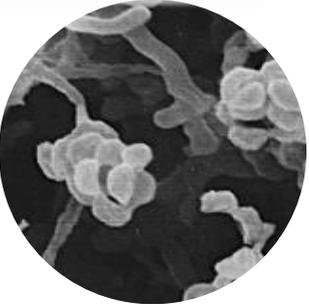
Eisai Co., Ltd.

April 9th, 2019

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



Material access



Marine-organism

Micro-organism



NP database

Natural Samples
(tens of thousands samples)

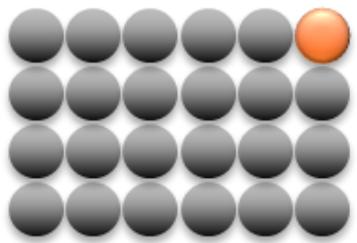
Bioactive natural product

Clinical trial

Screening

Purification

Optimization
Scale up production

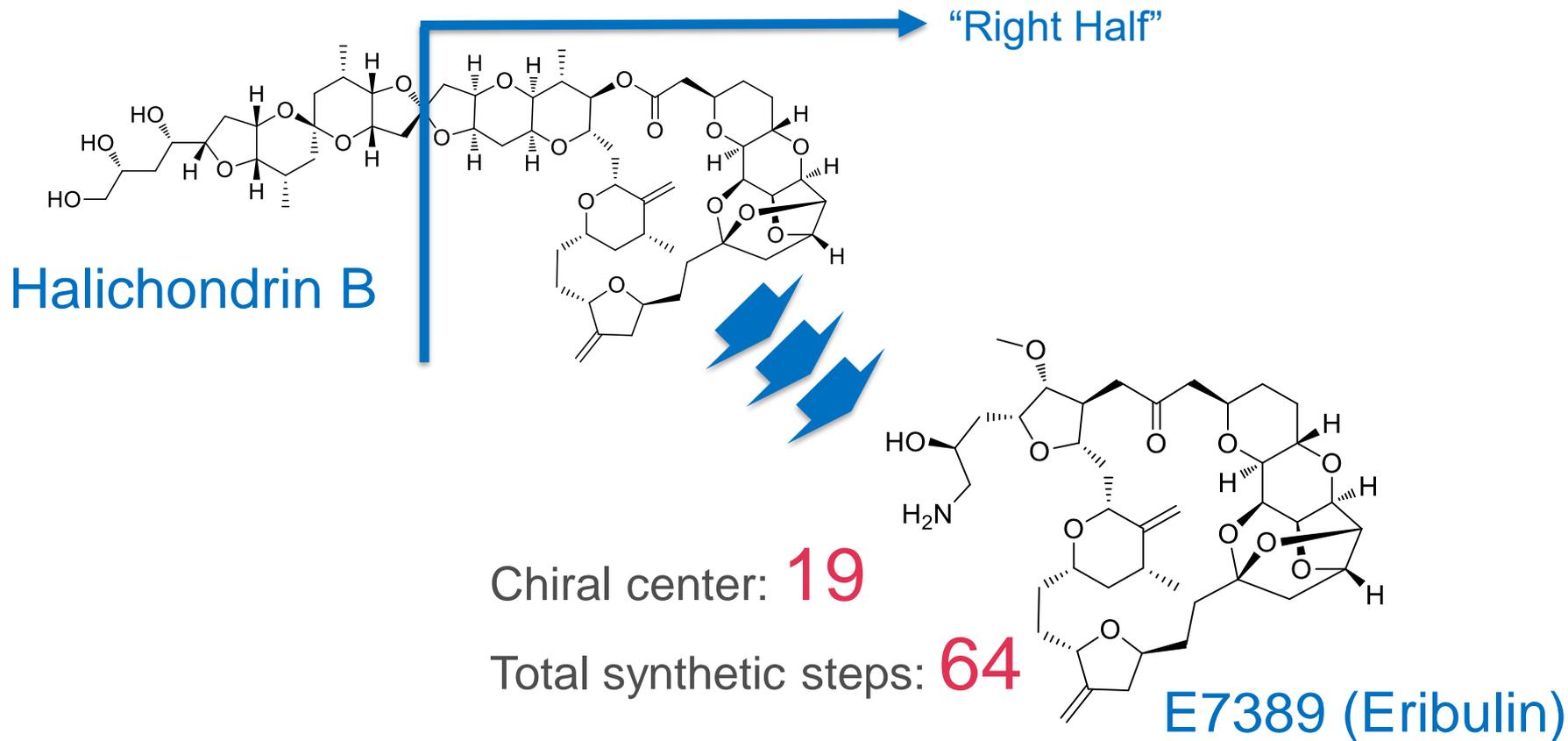


Find a hit extract (●)



Drug candidate

Chemical beauty of Eribulin enabled by powerful synthetic chemistry



Pladienolide B as a unique "Drug Lead"



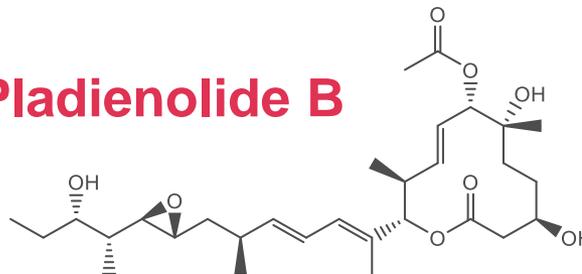
Micro-organism

Streptomyces platensis
Mer-11107

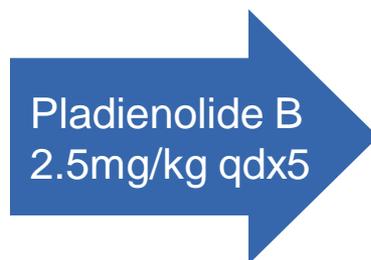


Purification

Pladienolide B



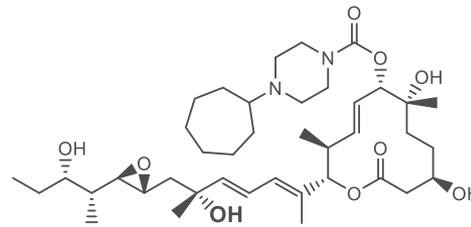
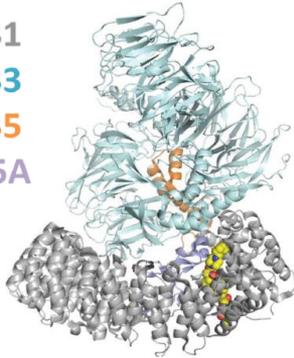
- ◆ Novel chemical structure
- ◆ Unique mechanism of action
- ◆ Highly potent *in vitro* & *in vivo*
- ◆ Complete remission was observed *in vivo* xenograft model



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

SF3B1
SF3B3
SF3B5
PHF5A

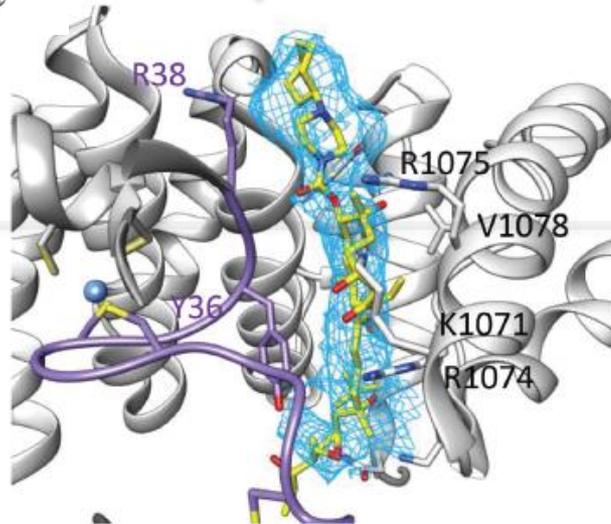


E7107

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

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



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

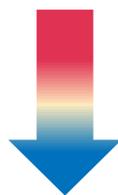
Discover new NPs through APAC NPDD Consortium

Constructing unique and sustainable collaboration mechanism in Asia



Japan

JPMA members
with N²PC and IMC

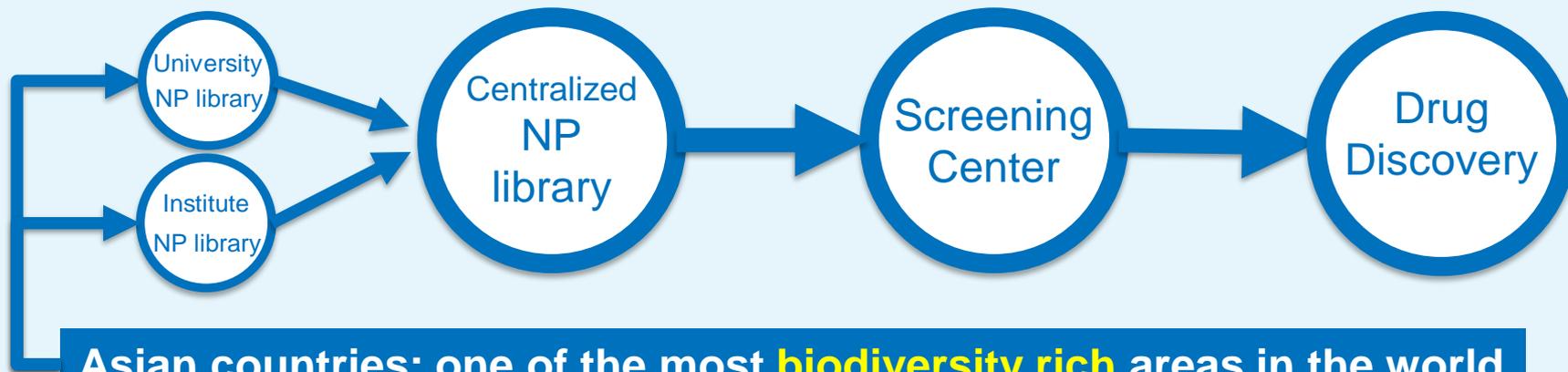


- Technology transfer
- Technical support
- Consultation

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

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

each **Asian country**



N²PC: Technology Research Association for Next generation natural products chemistry

IMC: Institute of Microbial Chemistry