

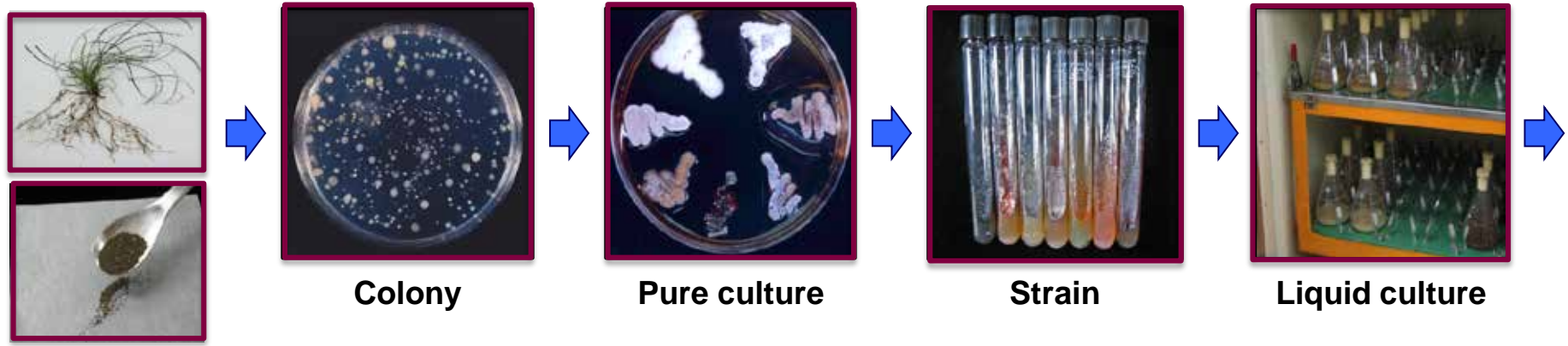
# 微生物創薬について

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大村 智





# Screening for new bioactive compounds



Source

Colony

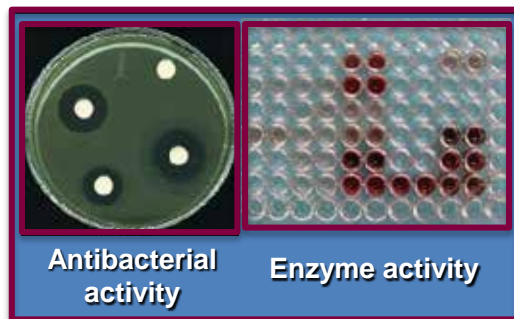
Pure culture

Strain

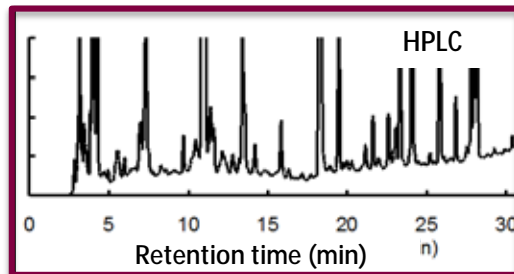
Liquid culture



Culture broth



Bioassay



Metabolite analysis



Jar fermenter

**Compound**

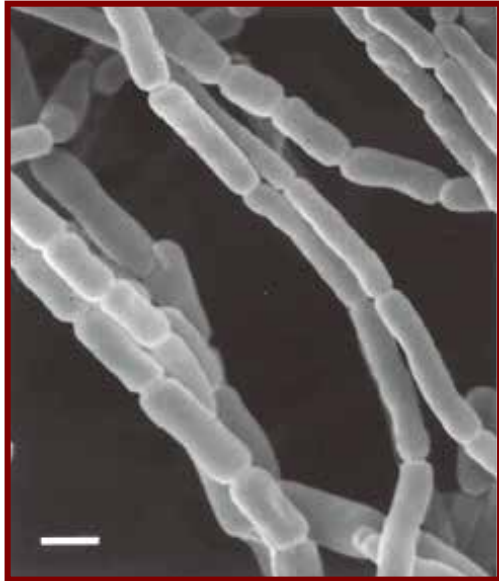
- Purification
- Structural analysis

**Strain**

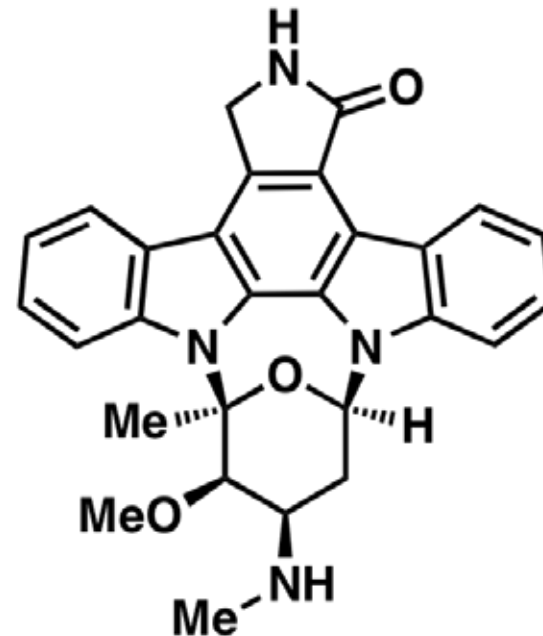
- Identification
- Preservation

R & D

# Staurosporine: 1<sup>st</sup> natural Indolocarbazole



*Saccharothrix aerocolonigenes* subsp.  
*staurosporeus* AM-2282<sup>T</sup>  
(*Lentzea albida* AM-2282)

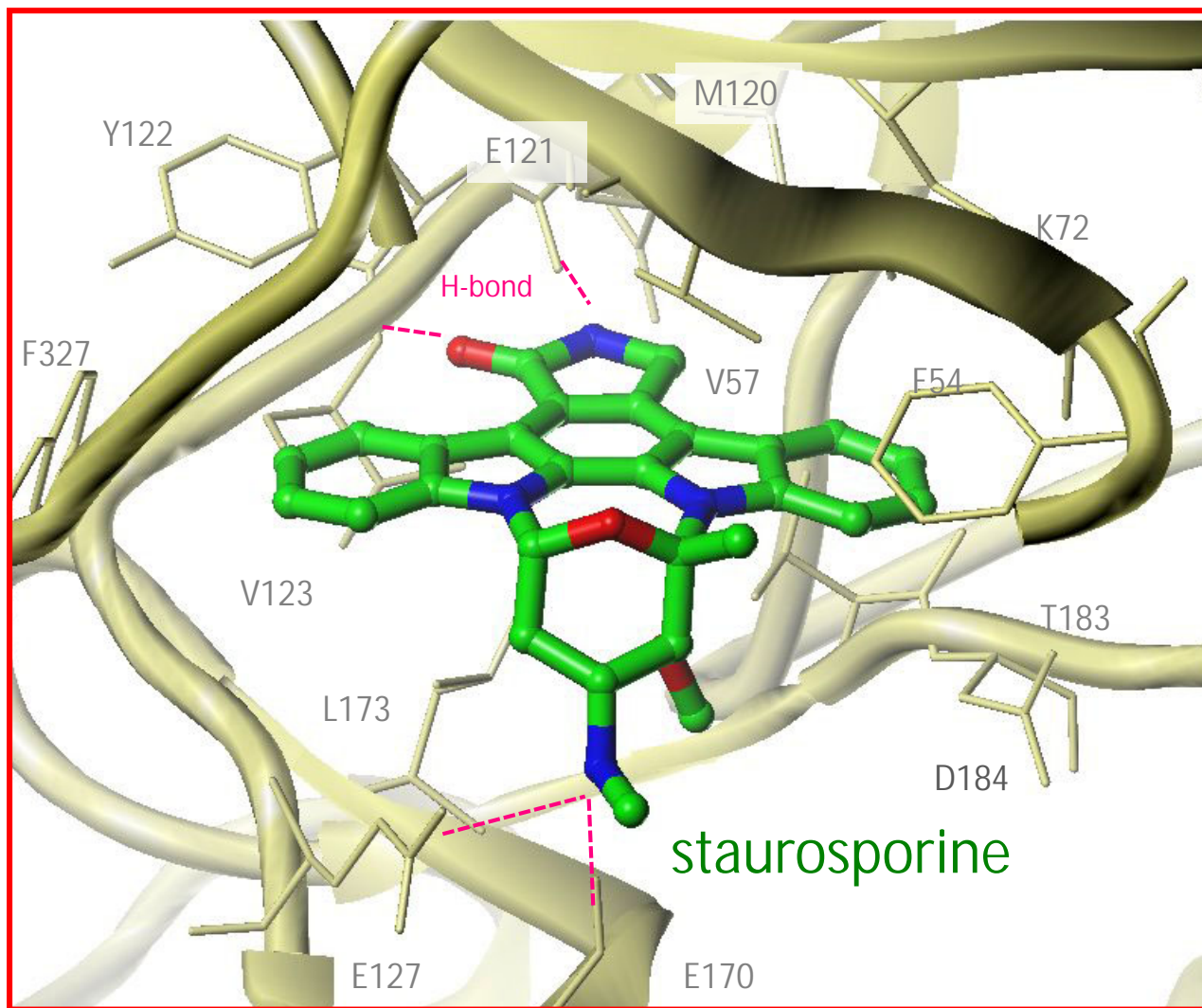


**Staurosporine**  
(Inhibitor of protein kinases)

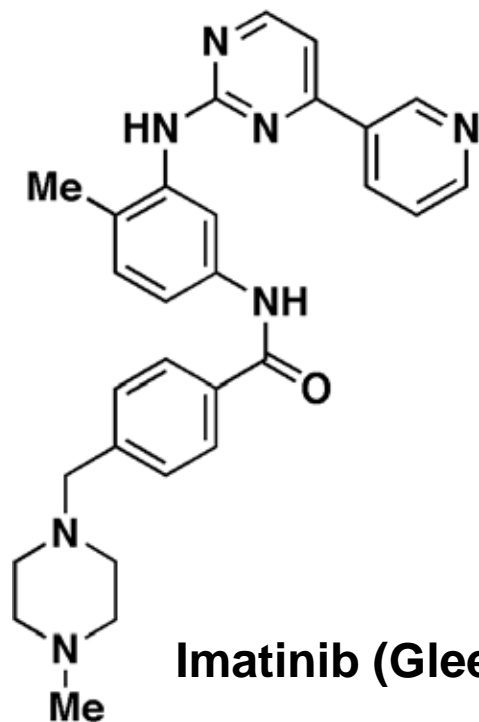
S. Ōmura *et al.*, *J. Antibiot.* **30**, 275 (1977)

T. Tamaoki *et al.*, *Biochem. Biophys. Res. Comm.*, **135**, 397 (1986)

# Complex structure of staurosporine with the catalytic sub-unit of cAMP-dependent protein kinase

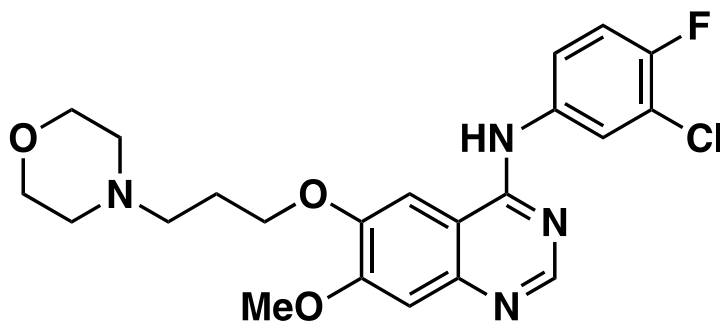


(courtesy of Dr H. Gouda)



**For use:**

**Chronic myelogenous leukemia  
(慢性骨髓性白血病)**



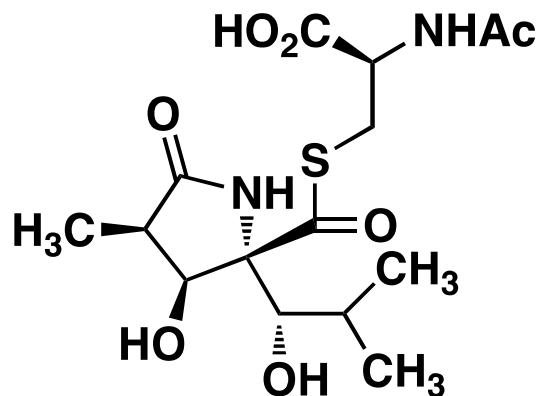
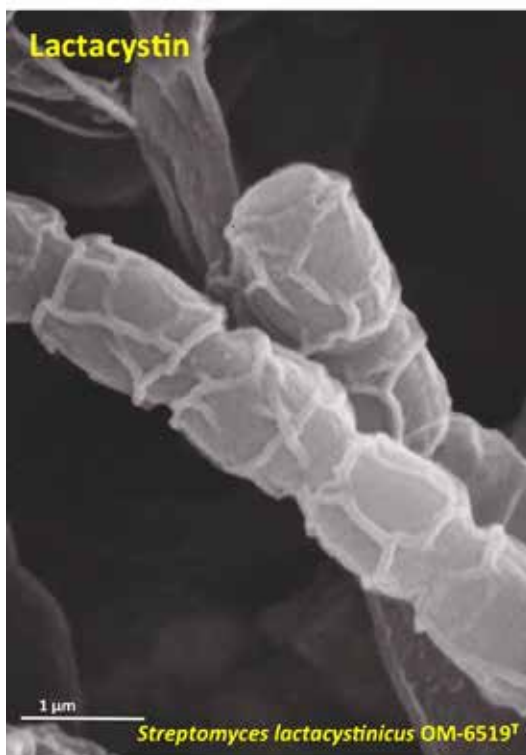
**For use:**

**Nonsmall-cell lung carcinoma  
(非小細胞肺癌)**

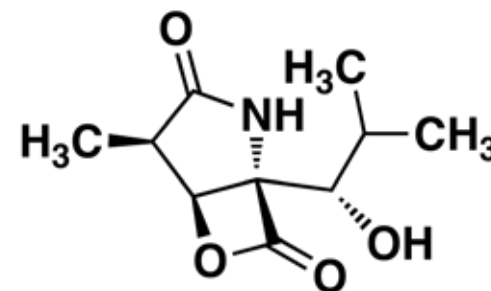
1) N. P. Shah *et al.*, *Oncogene* 22, 7389 (2003)

2) S. B. Bharate *et al.*, *Chem. Rev.* 113, 6761 (2013)

# Kitasato Institute : some key discoveries



**Lactacystin**  
(proteasome inhibitor)



**Omuralide**

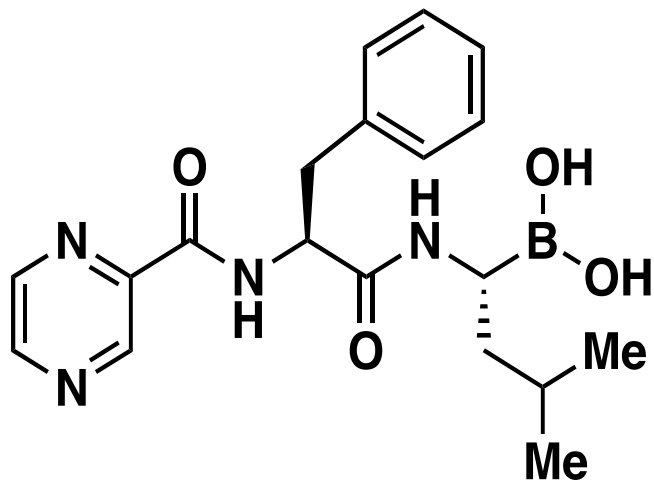
- S. Ōmura *et al.*, *J. Antibiot.*, **44**, 113, 117 (1991)  
G. Fenteany *et al.*, *Science*, **268**, 726 (1995)  
E. J. Corey *et al.*, *Chem. Pharm. Bull.* **47**, 1-10 (1999)





**Prof. Konrad Bloch**  
**1963 Nobel Laureate**

**Prof. E. J. Corey**  
**1990 Nobel Laureate**



**Bortezomib**  
**(Velcade®)**

**For use:**

**Multiple myeloma (多発生骨髓腫)**

**Mantle cell Lymphoma (マンترل細胞リンパ腫)**

P. Masdehors, S. Ōmura *et al.*, *Br. J. Haematol.*, 105, 752 (1999)

R. B. Shirtey *et al.*, *Neoplasia* 7, 1104 (2005)

## The avermectin producing strain

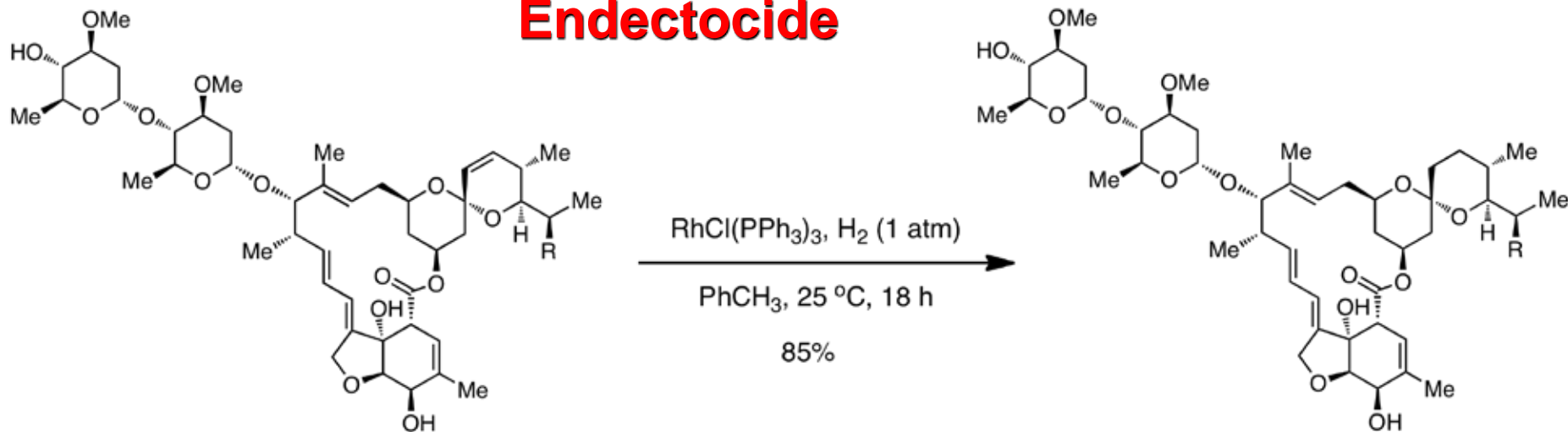


***Streptomyces avermectinarius (S. avermitilis)***

(—: 1mm)

# Ivermectin development

## Endectocide



**Avermectin B<sub>1a</sub>** : R = CH<sub>2</sub>CH<sub>3</sub>  
**B<sub>1b</sub>** : R = CH<sub>3</sub>

**Ivermectin**  
 ( 22,23-Dihydroavermectin B<sub>1a, b</sub> )  
 B<sub>1a</sub>; > 80%, B<sub>1b</sub>; < 20%

<b>Structure :</b>	<b>16-membered macrolide</b>
<b>Bioactivity :</b>	<b>Nematocidal and insecticidal</b>
<b>Mode of action :</b>	<b>Glutamate-gated chloride channel</b>

# Onchocerciasis: the helminth parasite



*Onchocerca volvulus* (microfilaria, 290  $\mu$ m)

# Onchocerciasis : the disease vector



*Simulium damnosum*