A splendid gift from the Earth: the origins & impact of Avermectin

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Nobel Prize in Physiology or Medicine

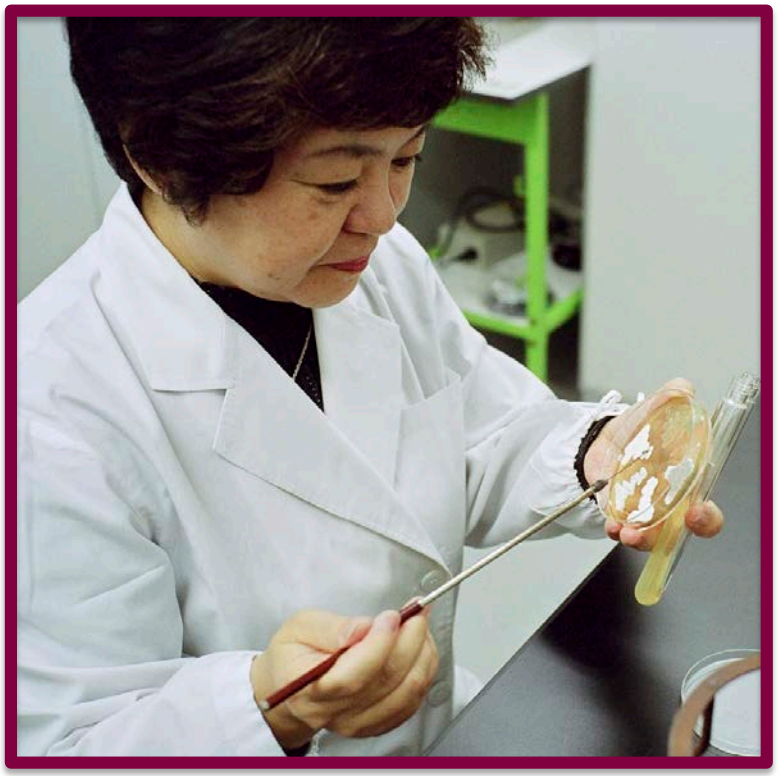
awarded for a discovery;

- **of major importance in Life Science or medicine**

&

- **that has changed the scientific paradigm and which confers the "greatest benefit on mankind"**

The first step of our research



Screening for new bioactive compounds

Source

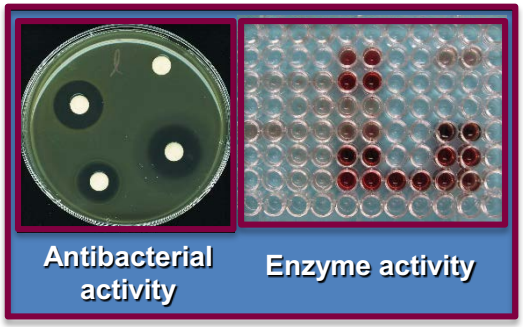
Colony

Pure culture

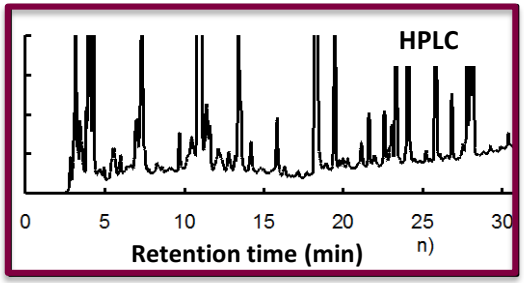
Strain

Liquid culture

Culture broth



Bioassay



Metabolite analysis

Jar fermenter

Compound

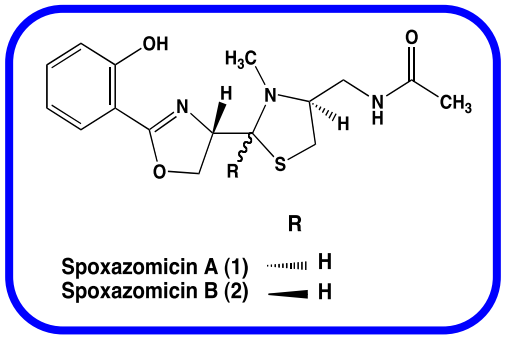
- Purification
- Structural analysis

Strain

- Identification
- Preservation

R & D

Actinomycetes (plant root & soil samples)



Anti-trypanosomals

***Streptosporangium oxazolinicum* sp. nov.**

***Phytohabitans suffuscus* gen. nov., sp. nov.**

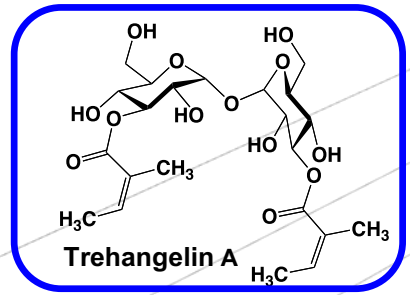
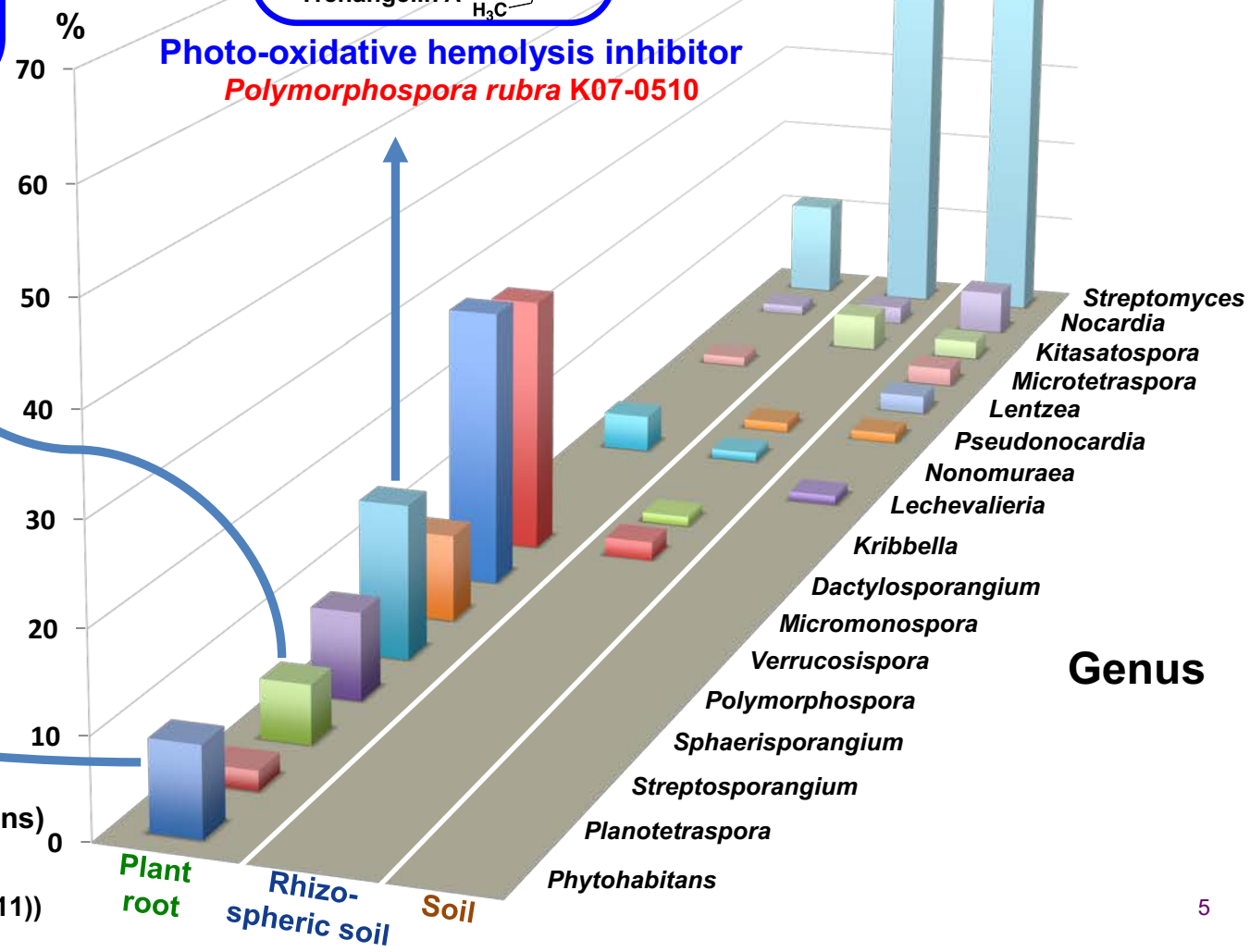


Photo-oxidative hemolysis inhibitor

***Polymorphospora rubra* K07-0510**

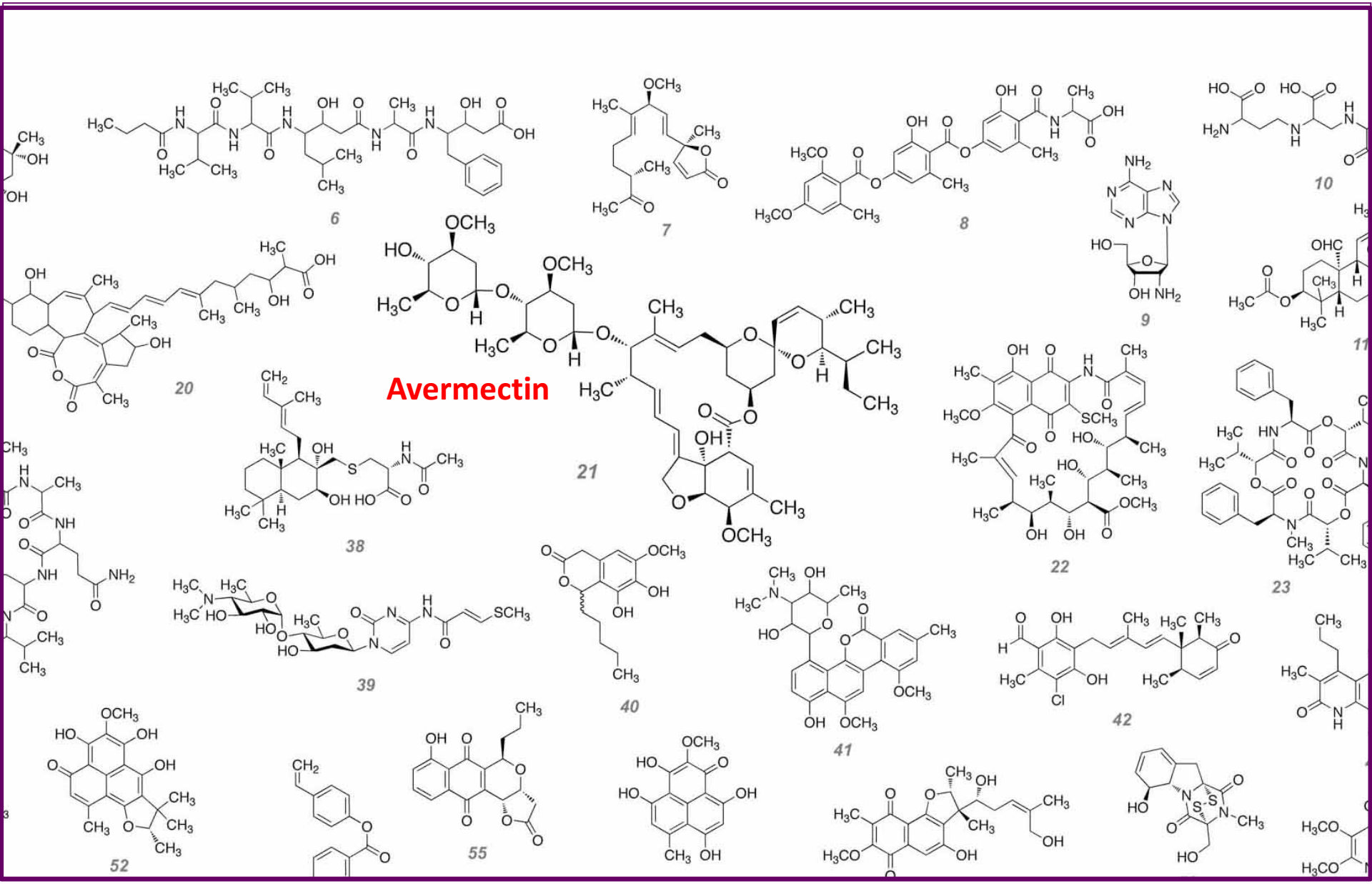


(after Takahashi, Y. & Inahashi, Y. (2011))

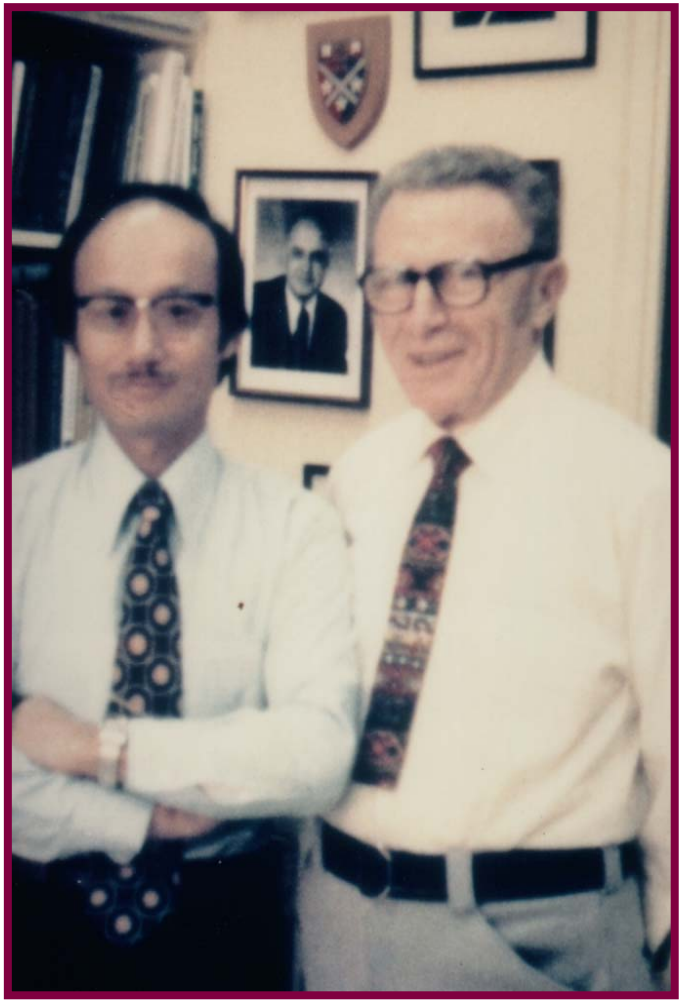
Discovery

- **Microorganisms:**
  - **New genera** **13**
  - **New species & sub-species** **52**
- **New compounds** **476**
- **Useful compounds** **26**
- **Targets for total syntheses** **>100**

Microbial metabolites discovered



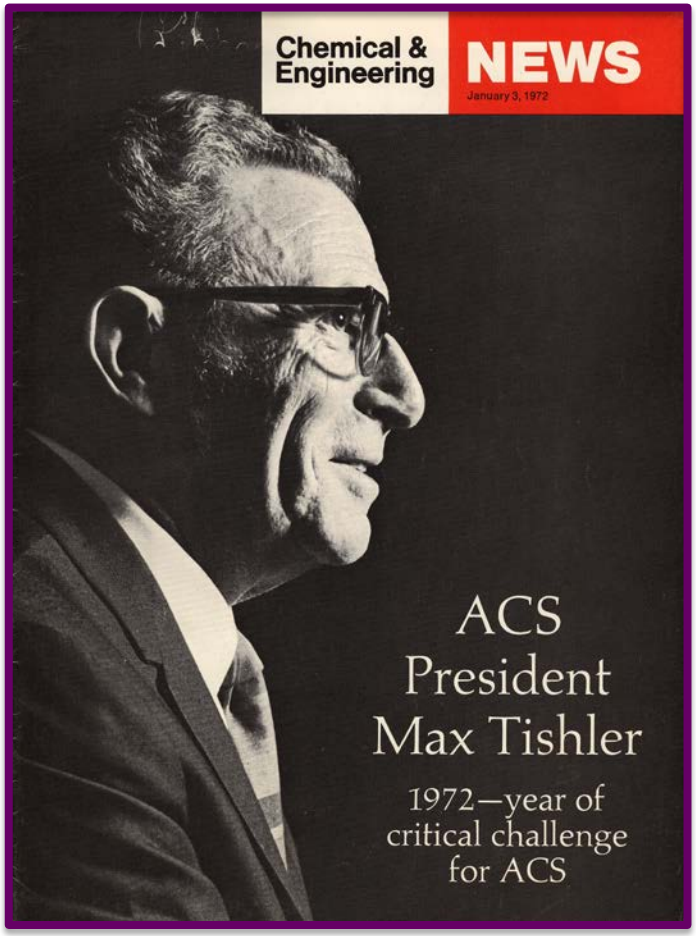
Ivermectin: the beginning



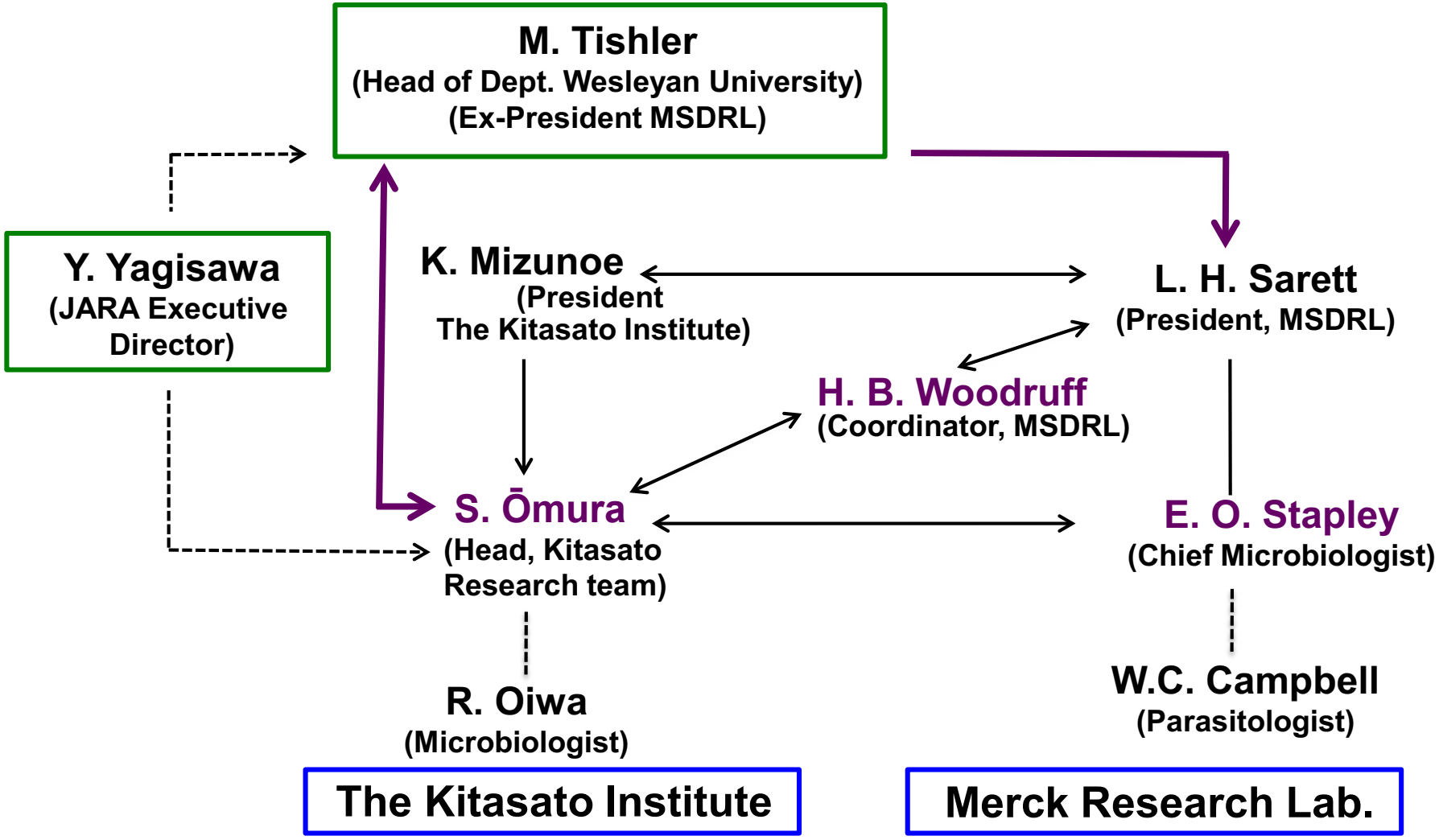
Satoshi Ōmura

Max Tishler (1906-1989)

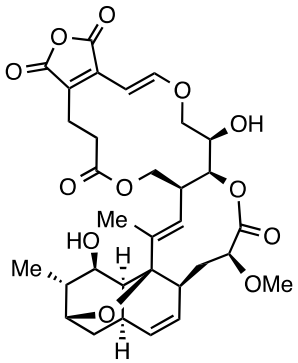
Wesleyan University
USA (1972)



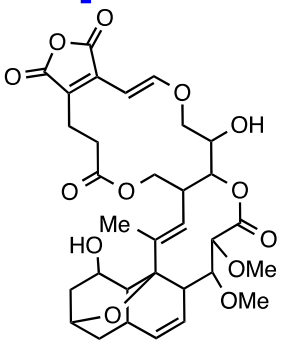
Kitasato - MSDRL Collaboration (1973)



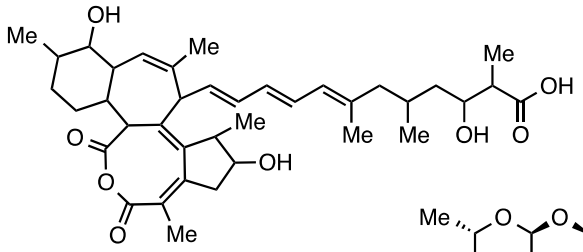
Compounds discovered in collaboration



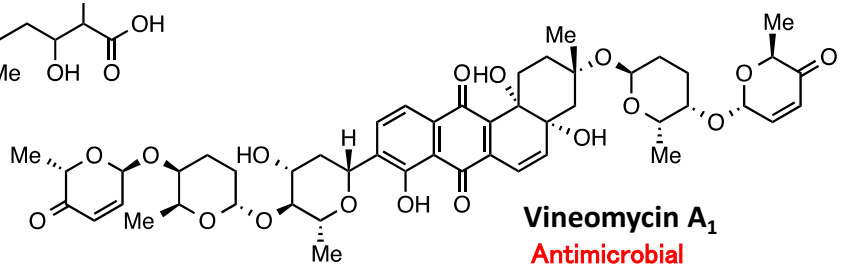
Luminamicin
Antimicrobial



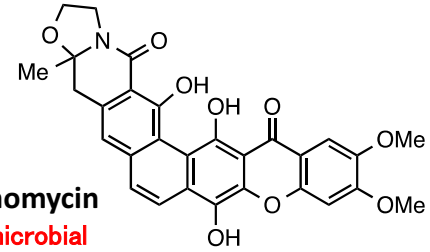
Lustromycin
Antimicrobial



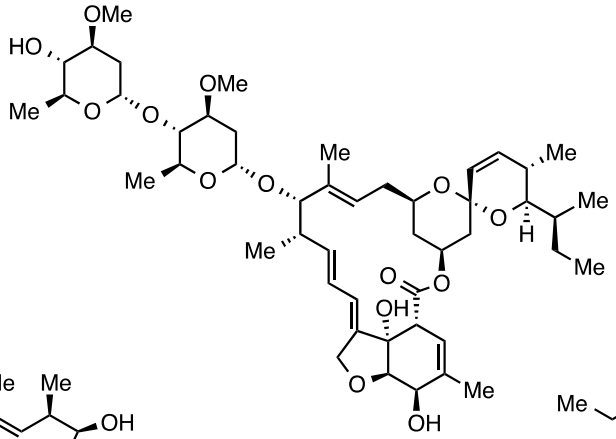
Aurantinin A
Antimicrobial



Vineomycin A_1
Antimicrobial

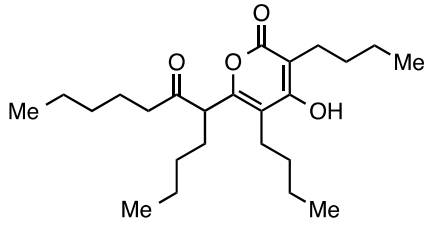


Cervinomycin
Antimicrobial

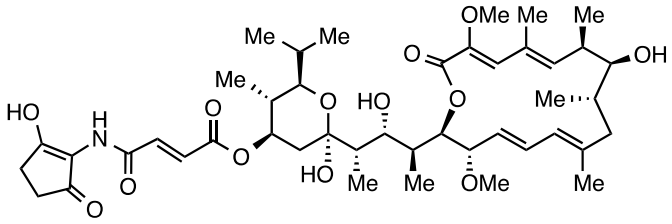


Avermectin B_{1a}
Anthelminitic

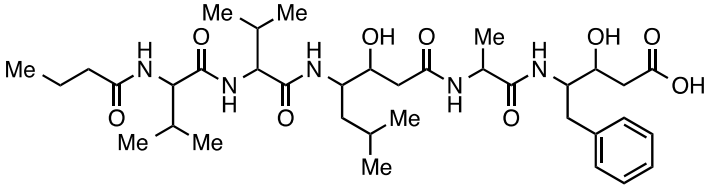
Endectocide



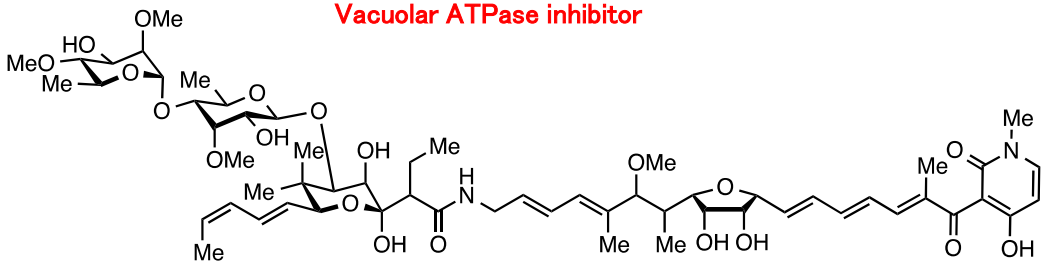
Elasnin
Elastase inhibitor



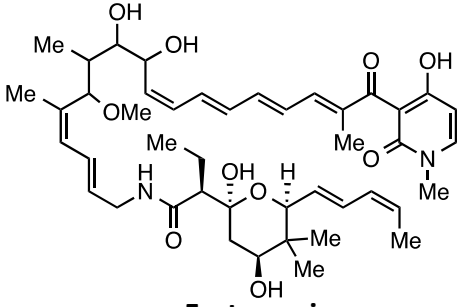
Setamycin
Vacuolar ATPase inhibitor



Ahpatinin
Renin inhibitor

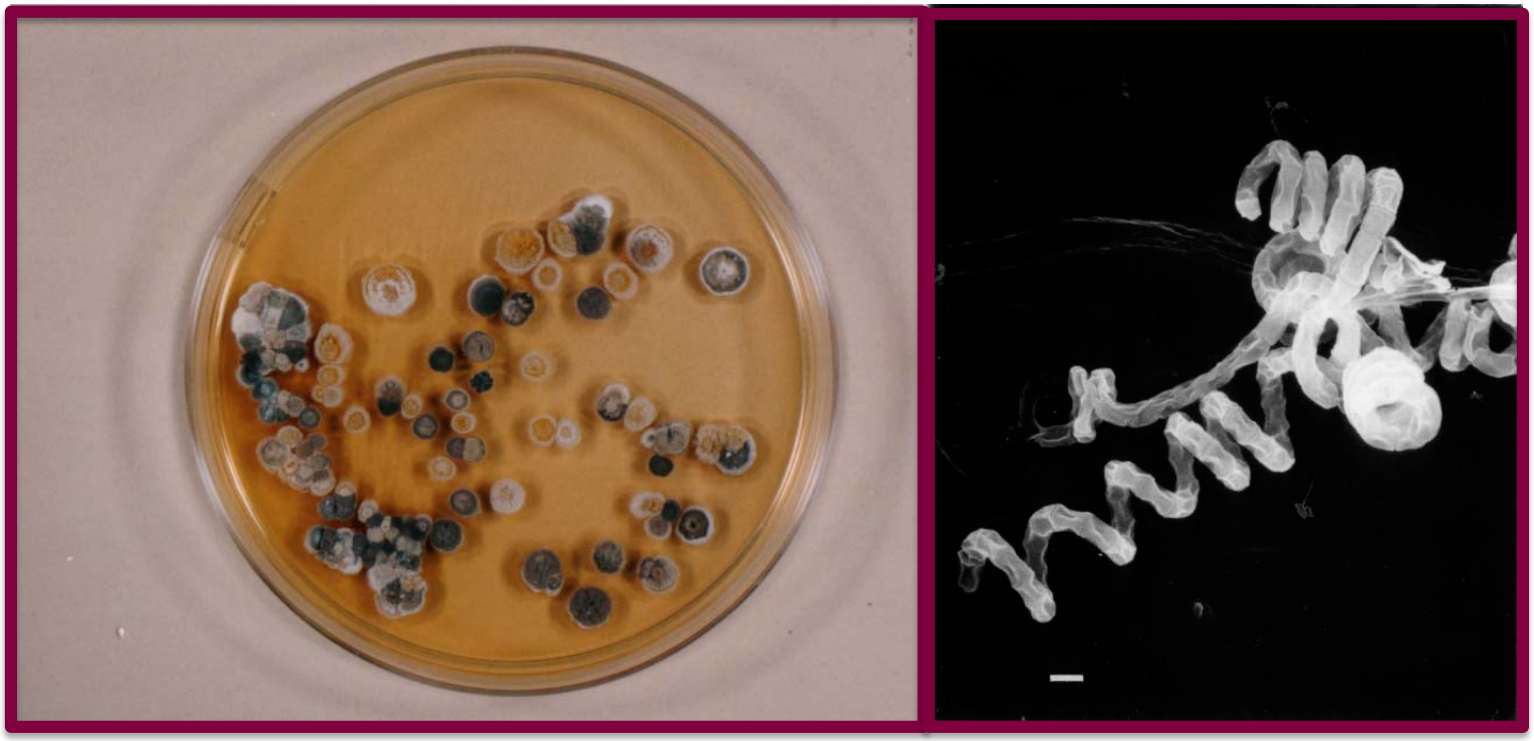


A-73A
Antimicrobial



Factumycin
Antimicrobial

The avermectin producing strain



Streptomyces avermectinius (S. avermitilis)

(white bar: 1 ⁄m)

Human health goals : Onchocerciasis (River blindness)

- Caused by filarial worms, transmitted by *Simulium* black flies
- Females release millions of immature worms; migrate to skin & eyes - skin disease, unbearable itching & blindness.

- People at risk 120 million
- People infected 18 million
- Blinded / disabled 770,000
- Disease burden (DALY) 1.1 million
- Countries affected 36
- No safe drugs available

(data~1987)

(Source: UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases (TDR))

Ivermectin: world's most effective drug donation

S. Ōmura

P. R. Vagelos

The Kitasato Institute (1989)

Ivermectin : the solution

- Taken once annually
- Very safe - taken without medical supervision

Ivermectin Distribution

Key partners for Mass Drug Administration (MDA)

- ✓ Merck & Co. Inc. & Mectizan Donation Program
- ✓ The Kitasato Institute
- ✓ World Health Organization (WHO)
- ✓ TDR (Special Programme for Research & Training in Tropical Diseases)
- ✓ Onchocerciasis Control Programme - West Africa (OCP)
- ✓ African Programme for Onchocerciasis Control (APOC)
- ✓ World Bank
- ✓ Endemic country governments
- ✓ Non-Governmental Organizations (NGOs)
- ✓ Affected communities & volunteer drug distributors

Onchocerciasis impact

Asubende, Ghana (2004)

Lymphatic filariasis

- **Caused by parasitic worms of the species, *Wuchereria bancrofti* (90%) & *Brugia malayi* (10%), transmitted by various species of mosquitoes**

Infection causes filarial fever, elephantiasis, male genital damage & severe social stigma

- **People at risk > 1.3 billion**
- **People infected 120 million**
- **Countries affected 83**

(data ~2000)

(Source: Global Alliance to Eliminate Lymphatic Filariasis (GAELF), 2010)

Thanks to *Streptomyces avermectinius*

Ivermectin treatments approved (2014):

Onchocerciasis	110 million
Lymphatic filariasis	218 million
Sub-total =	328 million
Combined treatments	73 million
TOTAL =	255 million

Ivermectin treatments administered (2013)

Onchocerciasis	107 million
Lymphatic filariasis	120 million
TOTAL =	227 million

Total treatments approved:

- Onchocerciasis (1987-2014) = 1.4 billion
- Lymphatic filariasis (2000-2014) = 1.2 billion

(Source: MDP, WHO(WER), APOC)

Global elimination goals

2020 Lymphatic filariasis **2025** Onchocerciasis

Ivermectin : commercial human use

- **Strongyloidiasis**
  - caused by *Strongyloides stercoralis*
  - >300 million people infected worldwide
- **Scabies**
  - infestation of *Sarcoptes scabiei* affects >130 million people at any one time
- **Head Lice** *(Pediculosis capitis)*
  - household-wide treatment effective in preventing infestation spread

(Source: WHO)

Ivermectin Mass Drug Administration

Secondary benefits: Africa (4-country study)

Health:

- 55.7% improved vision
- 54% dewormed
- 50.3% better skin
- 44.4% reduced itching
- 31.4% less head lice
- Less ill health, less high blood pressure, less epilepsy
- Better fertility & improved libido

Social:

- 75.6% reported improved ability to work
- 28.3% improved self respect/esteem
- 26.4% better peer acceptance
- 15.6% improved school attendance
- 9.1% better home relationships

(Source: Okeibunor, J.C. *et. al*. (2011))

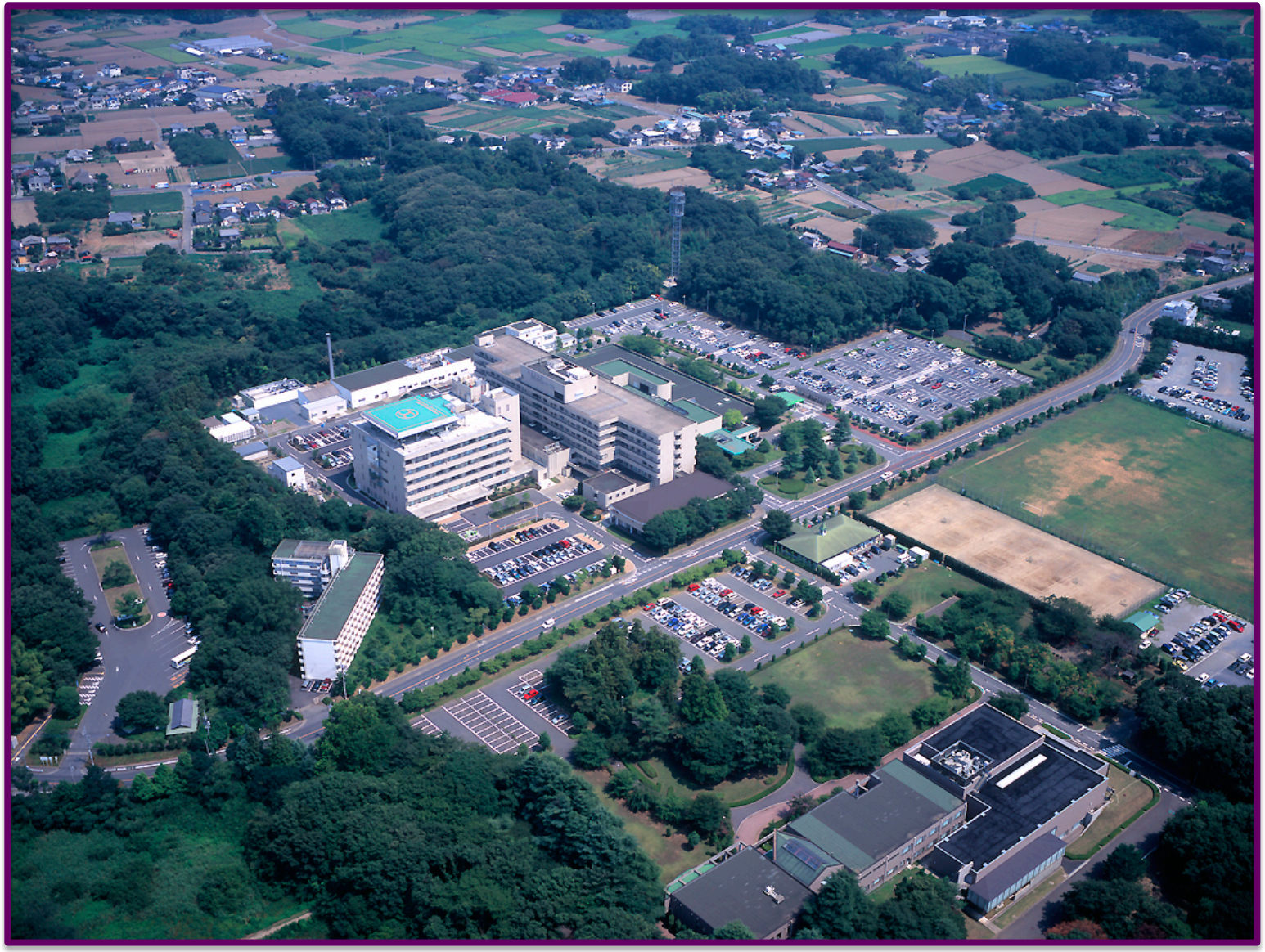
Avermectins & Neglected diseases

- **Avermectins – action on parasites & insect vectors**
  (mosquitoes, Tsetse flies, triatomine bugs, sandflies, etc.)

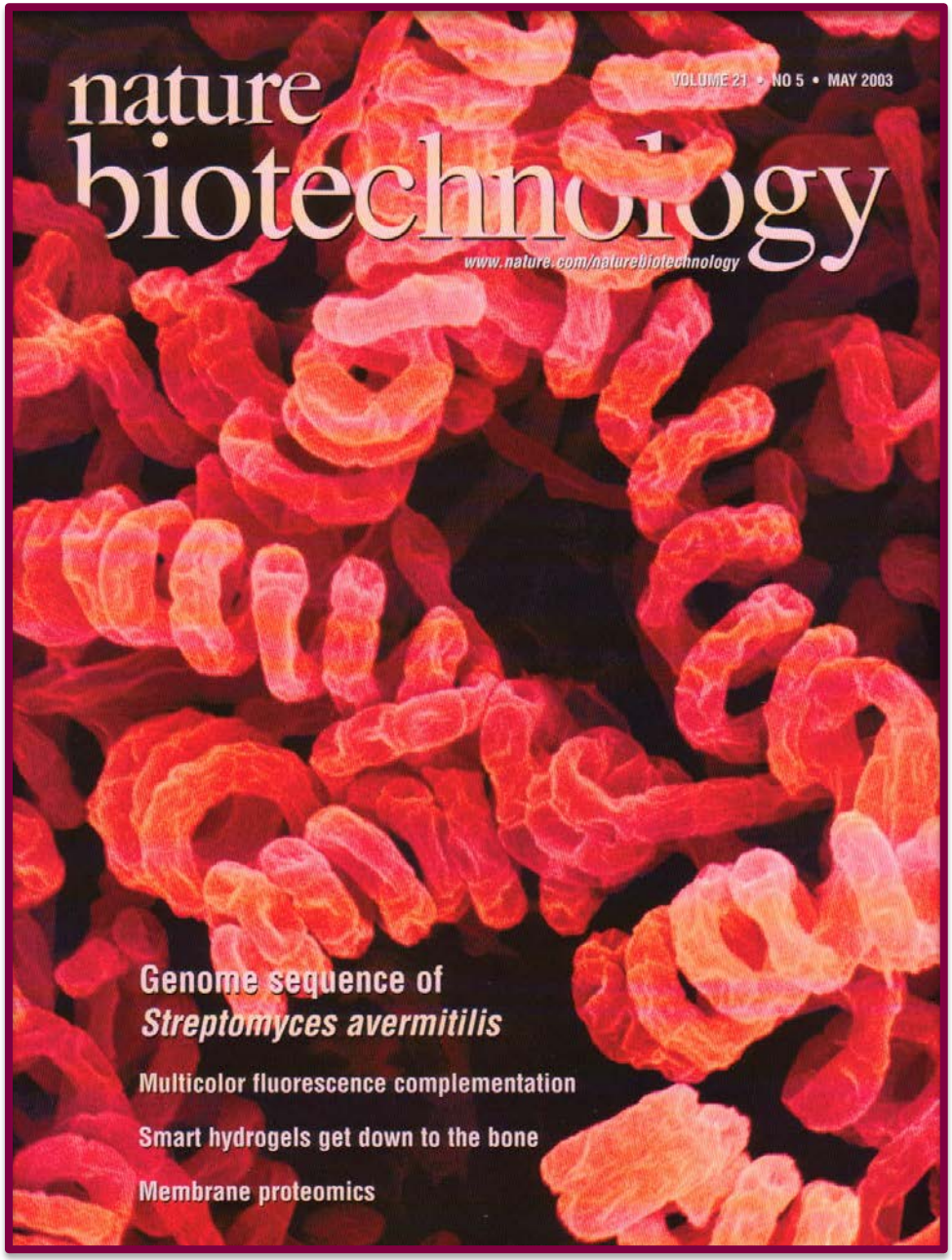
- **Ivermectin reported to be effective against:**
  - **Malaria**
  - **Tuberculosis**
  - **Leishmaniasis**
  - **Trypanosomiasis**
  - **Flaviviruses (Dengue & Yellow fever)**
  - **Trichinosis**
  - **Chlamydia**
  - **Leukaemia**
  - **Schistosomiasis**

(Source: Ōmura, S. & Crump, A. (2014))

Benefits to Japan



Avermectin : exploiting the source

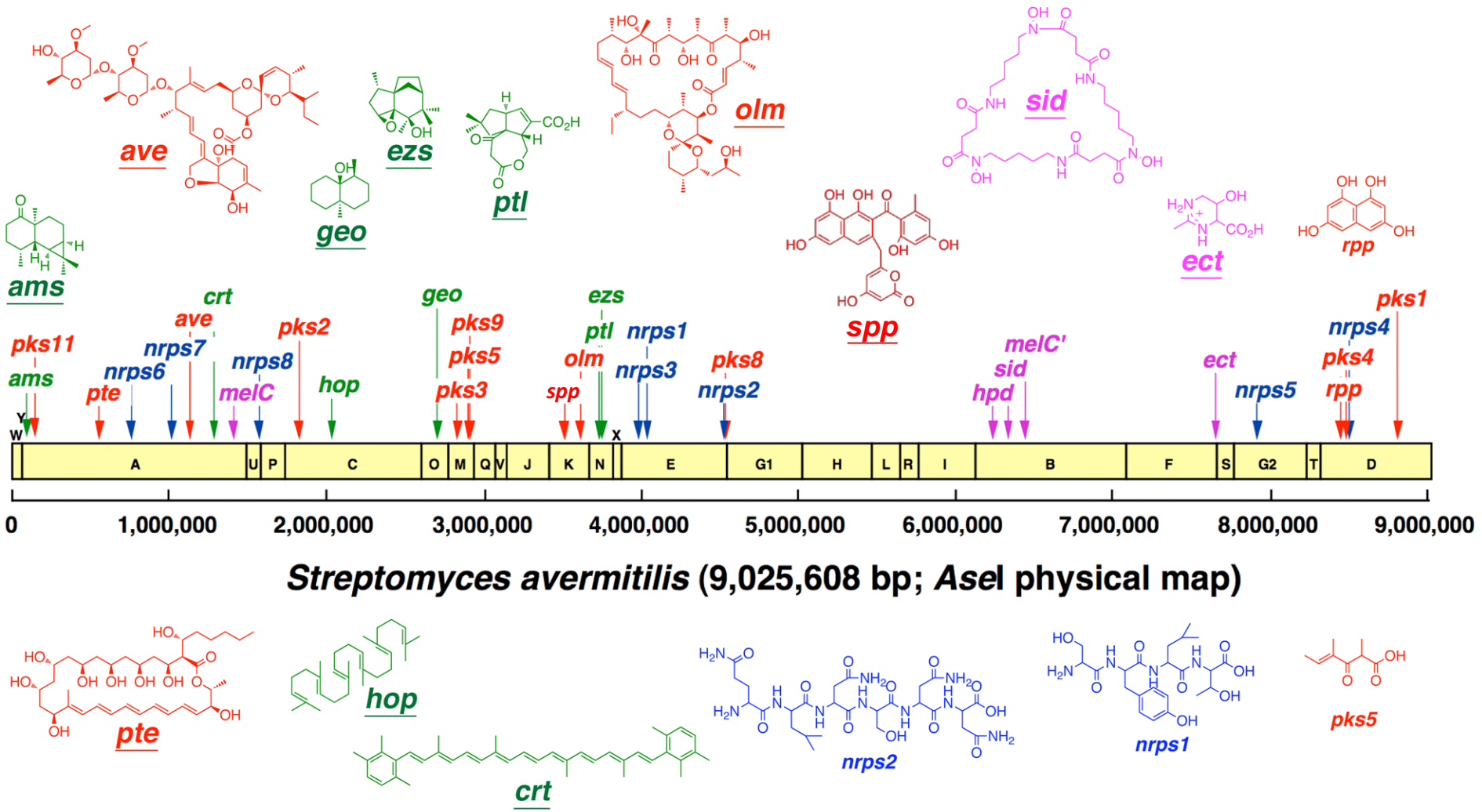


Publications:

Ōmura, S. *et al.*, (2001)
***Proc. Natl. Acad. Sci., USA*., 98, 12215**

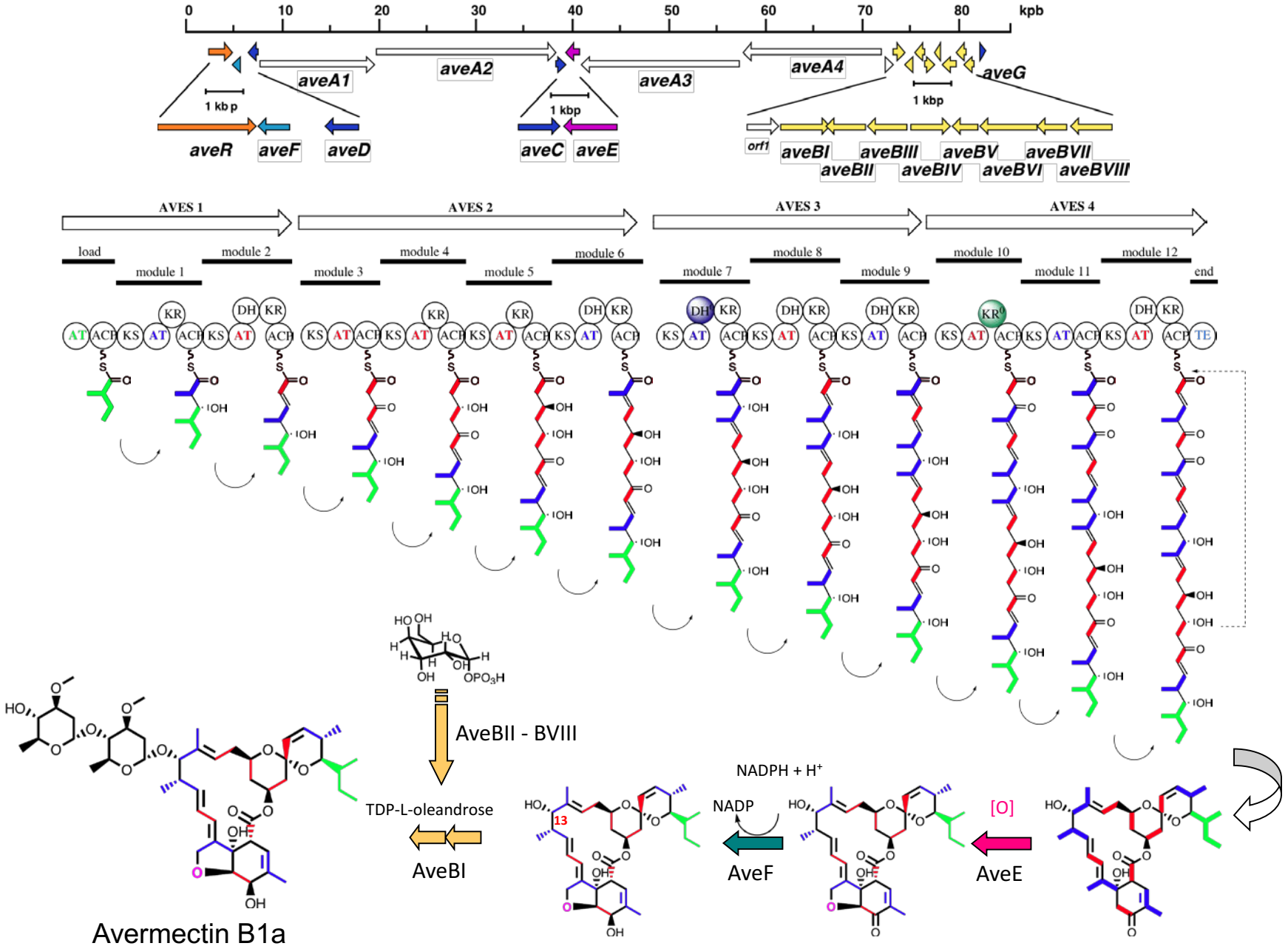
Ikeda, H. *et al.*, (2003)
***Nature Biotechnol*., 21, 526**

Distribution of gene clusters for secondary metabolite biosyntheses in *Streptomyces avermectinius* (*avermitilis*)



Streptomyces avermitilis **(9,025,608 bp; *Ase*I physical map)**

S. avermectinius : avermectin biosynthesis



Personal research philosophy

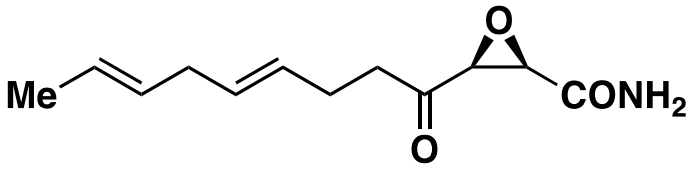
“to exploit the potential of microorganisms and microbial metabolites to advance scientific progress in all fields, including Organic Chemistry, Biochemistry and Medicine, as well as to accelerate and maximize improvements in human health and welfare worldwide”

Nature's bounty

Microbes do not produce useless metabolites:

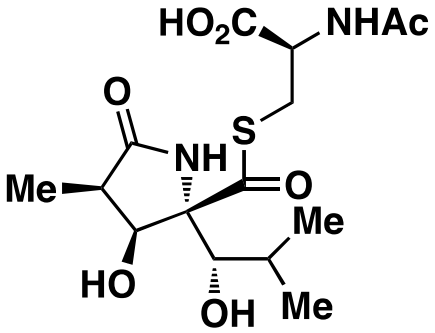
we just have little knowledge of their usefulness for mankind

Useful microbial metabolites for chemical biology & medicine



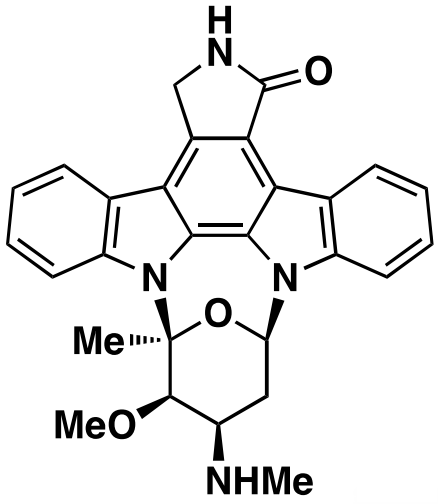
Cerulenin

(Inhibitor of fatty acid and polyketide syntheses)



Lactacystin

(Protreasome inhibitor)



Staurosporine

(Protein kinase inhibitor)

Tea ceremony (Chanoyu)

‘Ichi-go Ichi-e’ (一期一会) = “One encounter, one chance”

(expression emphasizing the profound respect and uniqueness embodied in each ceremony)

Acknowledgement

&

profound gratitude

Ωra

Thank you