

REVIEW ARTICLE

Professor Hamao Umezawa opened up a new road for the development of molecularly targeted therapeutic drugs for cancers

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This issue is dedicated to Prof Hamao Umezawa in appreciation of his great contributions to pioneering research on antibiotics targeting oncogenes.

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Professor Hamao Umezawa was a pioneer in cancer chemotherapy. In 1953, Professor Umezawa isolated the first antitumor compound, sarkomycin, from *Streptomyces*.¹ The compound showed strong cytotoxic activity against several tumor cell lines but was not sufficiently effective *in vivo* for clinical use. Afterwards, Prof Umezawa continued to search for cytotoxic antitumor compounds of microbial origin and their synthetic derivatives, and by the mid 1980s, he had identified more than 20 novel compounds. Among these, bleomycin, aclacinomycin, peplomycin and pirarubicin have been the most outstanding successes and are used clinically for treating patients with several types of cancer.

At that time, Professor Umezawa pioneered a new approach for the development of anticancer drugs that target oncogenes. One great achievement of these efforts was the re-discovery of herbimycin A² (Figure 1). By the early 1980s, oncogenes had been well characterized at the molecular level, and the results from studies in the field had provided new insights into the understanding of neoplastic transformation.³ In Rous sarcoma virus (RSV)-transformed cells, the functional expression of p60^{src} (the *src* gene product) was shown to be required for manifestation of the oncogenic event.⁴ On the basis of these findings, in 1984 Professors Uehara, Hori, Takeuchi and Umezawa screened for compounds that were active in converting the transformed morphology of RSV-infected rat kidney cells to a normal morphology, which resulted in the identification an active compound produced by *Streptomyces* sp. MH237-CF8, herbimycin A.^{5,6} In addition to p60^{src}, herbimycin A was observed to inactivate oncogene functions of the p60^{src} family. In particular, it showed differentiation-inducing activity against chronic myelogenous leukemia cell line K562,⁷ in which ABL is activated by chromosomal translocation (Philadelphia translocation). Furthermore, herbimycin A showed *in vivo* antitumor activity against FDC-P2 cells expressing BCR/ABL.⁸ It was then revealed that herbimycin A binds to heat shock

protein HSP90 and destabilizes and decomposes members of the p60^{src} family.⁹

Additional pioneering research of Professor Umezawa, in which the author took part in from the beginning, was the discovery of erbstatin. In 1979, the oncogene product p60^{src} was discovered to catalyze tyrosine phosphorylation as a new type of protein modification.¹⁰ Following this discovery, ligand binding was observed to induce a rapid increase in epidermal growth factor (EGF) and platelet derived growth factor receptor tyrosine kinase (RTK) autophosphorylation.^{11–13} These findings suggested an important role of tyrosine phosphorylation in growth factor-mediated proliferation signals and in the *src* family oncogene-mediated signaling pathway for oncogenesis.

The discovery of the growth factor receptor and oncogene products associated with tyrosine kinase prompted us to screen for a compound that suppresses tyrosine kinase from the secondary metabolites of microorganisms. We did so using the membrane fractions of EGF receptors overexpressing the human epidermoid carcinoma cell line A431 as a source of tyrosine kinase. As a result, in 1986, a novel natural product named erbstatin was isolated as an inhibitor of EGF receptor tyrosine kinase from the cultured broth of *Streptomyces* sp. MH435-hF3 by the author, Dr Sawa, Dr Takeuchi and Professor Umezawa¹⁴ (Figure 1).

Erbstatin has a structure resembling tyrosine and shows a pattern of competitive inhibition with the protein to be phosphorylated.¹⁵ It is a broad spectrum tyrosine kinase inhibitor that also inhibits other receptor tyrosine kinases, such as Her-2, and non-receptor type tyrosine kinases, including Fyn and Lck. Although erbstatin is unstable in the presence of serum, it shows antitumor effects on leukemia cell line L1210 and breast cancer cell line MCF-7-bearing cancer mice by administering it in combination with a stabilizer.¹⁶ Following this epochal discovery, numerous inhibitors of tyrosine kinase were synthesized worldwide beginning in the late 1980's. In particular,

Structures of compounds featured in this article

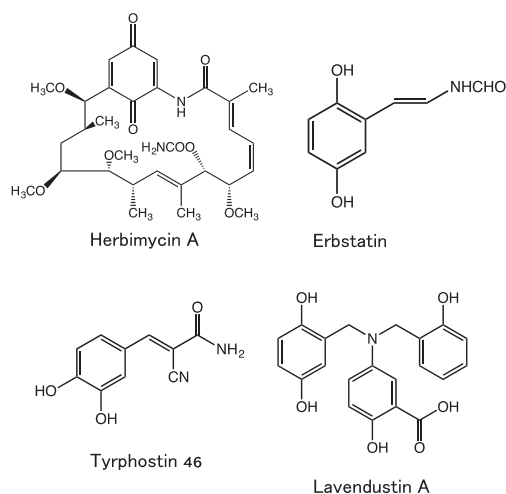


Figure 1 Structures of compounds featured in this article.

Professor Tatsuta *et al.* and Prof Umezawa synthesized several erbstatin analogs,^{17,18} and Yaish *et al.* synthesized a group of tyrosine kinase inhibitors called tyrophostins (Figure 1) using erbstatin as a model.¹⁹ Although Professor Umezawa passed away in 1986, the screening of tyrosine kinase inhibitors was succeeded by his first son, Professor Kazuo Umezawa, who discovered a novel compound, lavendustin A (Figure 1), from *Streptomyces griseolavendus* in 1989.²⁰

Today, many tyrosine kinase inhibitors, such as gefitinib and imatinib, are clinically used to treat patients with several types of cancer. Thus, the discovery of erbstatin by Professor Umezawa has greatly contributed to the subsequent study of the development of molecularly targeted therapeutic drugs for different cancers.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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