The 2015 Nobel Prize in Physiology or Medicine

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Dr. Satoshi Omura of Kitasato Univerisity and his collaborator, Dr. William C. Campbell of Merck, were awarded the 2015 Nobel Prize in Physiology or Medicine "for their discoveries concerning a novel therapy against infections caused by roundworm parasites". What they discovered is the breakthrough medicine ivermectin[(1)] which cures onchocerciasis[(2)], an insect-borne disease caused by the parasite *Onchocerca volvulus*.

Onchocerciasis is estimated to affect 18 million people every year primarily in tropical regions such as West and Central Africa. Once infected, intense itching, rash, scarring and visual impairment occur, and in severe cases blindness is resulted. It is estimated nearly 300,000 people lose their eyesight to every year to onchocerciasis.

Onchocerciasis is also called "river blindness" because the blackfly abundant near tropical riversides transmits the disease. The infection cycle begins by the blackfly ingesting microfilaria upon stinging a carrier of onchocerciasis. Microfilaria grows to larvae in the blackfly. When the blackfly stings a healthy person, larvae enter the skin and become an adult in lymphatics after over a year. An adult filaria spread thousands of eggs containing microfilaria every day and numerous microfilariae migrate inside the body through skin, lymph, blood vessel and eventually reaches eye tissue.

Mectizan, the Merck brand name of ivermectin, presents striking efficacy when 150 mg per 1 kg of body weight is taken orally once a year. Ivermectin has additional outstanding features. It has fewer side effects than other common antimicrobial drugs and it can be administered in tablet form which eases distribution, particularly in undeveloped areas. Lastly, there have been no reports of resistance to ivermectin since its introduction in 1987. Ivermectin is nearly an ideal drug.

Ivermectin (Fig. 1(a)) is a dihydro derivative of avermectin (Fig. 1(b)) found by Dr. Omura. These two compounds are very similar to each other. Only the difference is at positions 22 and 23 where these two carbon atoms are fully hydrogenated in ivermectin compared to avermectin. Avermectin is a natural organic compound produced by actinomycetes living in soil. Researchers in Dr. Omura's laboratory at Kitasato Institute carried plastic bags no matter where they went. The particular actinomycetes was found in soil sampled near the scenic golf course "Kawana" in Shizuoka Prefecture. When the soil was screened back in the laboratory, an unknown actinomyces was identified and names as *Streptomyces avermitilis*. This sample was sent to Merck, as usual, with data including its antimicrobial activity profile against various microorganisms. When a cultured solution of *S. avermitilis* was fed to mice infected with parasites, it showed strong antiparasitic activity. The research groups of Dr. Omura and Merck extracted and isolated the active ingredient and named it avermectin. Avermectin was refined to ivermectin through optimization by synthesizing various derivatives and successive studies.

The detailed action mechanism of ivermectin is still being elucidated. The targets of ivermectin are the glutamate-gated Cl^- channels that are invertebrate-specific members of the Cys-loop family of ligand-gated ion channels. Glutamate-gated Cl^- channels are also

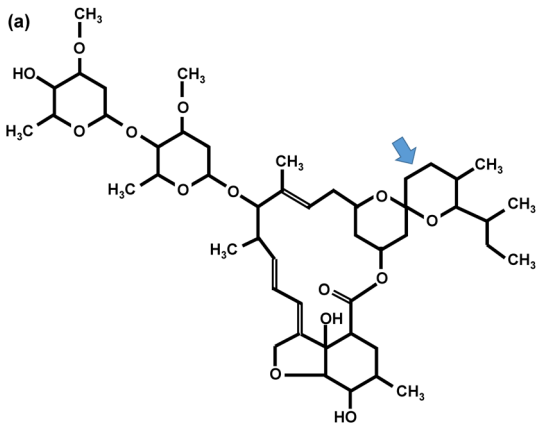

Fig. 1(a). Ivermectin B_{1a}.

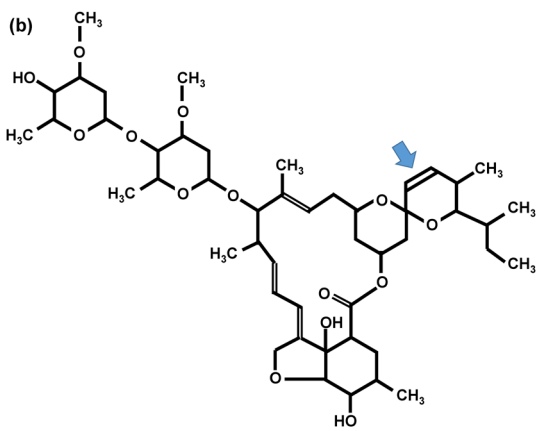

Fig. 1(b). Avermectin B_{1a}.

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present in neurons in mammals however ivermectin cannot cross the blood–brain barrier into the mammalian central nervous system where these receptors are located. This model explains why ivermectin paralyzes nematode but is not toxic to mammals.

Currently, it is estimated that the number of people spared from onchocerciasis by taking ivermectin is at least 200 million worldwide and may be even 300 million. The reason ivermectin has helped so many people is the groundbreaking decision by Merck to donate Mectizan. Usually endemic diseases occur in economically poor regions and it is not expected that a drug developer could recover its costs from the patients. This is why it is difficult for pharmaceutical companies to develop drugs for endemic diseases no matter how many people are suffering. At the beginning of the ivermectin development, Merck anticipated that governments would purchase the medicine once the development was completed. What is unique in this case, is that Merck, even after they determined that governments in onchocerciasis-prevalent regions had not intention to purchase the drug, continued the development project. This is a rare example where the policy "to get the drug to people who need it" was given priority over the pursuit of making profit that is essential to viability of a private company. Merck is well known as one of the so-called "Mega Pharmas". Not only it is financially sound, but also it has attracted much respect as a good citizen. Merck was selected as the "The most respected company in the world" in the US business magazine Fortune 7 years in a row since 1987. What made the reputation of Merck immovable was the donation of Mectizan.

An additional contribution of ivermectin to human society has been an increase in food production. Initially, the contract between Dr. Omura and Merck was limited to the development of veterinary drugs. Thus, ivermectin was first launched as an antiparasitic drug for commercial livestock such as cattle. Ivermectin contributed to an increase in animal food production by restoring the appetites of livestock. It also contributed to an increase in the harvest of crops by enabling people to stay and cultivate fertile riverside areas that were previously avoided for fear of "river blindness".

Onchocerciasis, which has been a scourge of mankind for centuries in certain areas, is being eliminated country by country. The idealism of Dr. Omura in "contributing human to society" and the idealism of Merck donating Mectizan, is achieving a triumph that seemed to be absolutely impossible 25 years ago. Considering the direct and indirect impact in the improvement of the life of human beings, the value of the development of ivermectin is immeasurable.

Among the Nobel Prize winners of 2015, Dr. Omura has the closest relationship to Rigaku. In a search of the Cambridge Structure Database, 38 structures were found under Dr. Omura as of October, 2015 and at least 13 of them were analyzed by Rigaku single crystal systems such as an AFC5R or Mercury CCD. We are proud to have helped Dr. Omura in his quest to alleviate human pain and suffering.

References

(1) A. Crump and S. Ōmura: *Proc Jpn Acad Ser B Phys Biol Sci.,* **87** (2011), 13–28.

(2) http://www.who.int/blindness/causes/priority/en/index2.html for example.