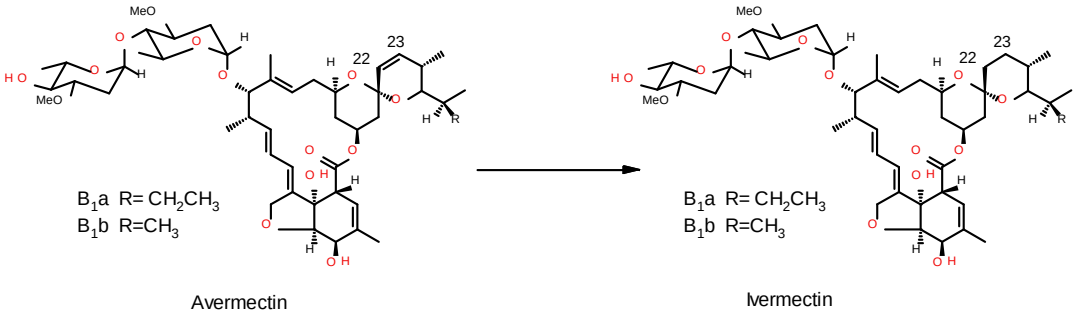
2015 NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE
William C. Campbell/Satoshi Ōmura and Youyou Tu

Walter Cabri
VP I&D Region Generic API
Fresenius Kabi Anti-Infectives
Cernusco sul Naviglio (MI)
walter.cabri@fresenius.com

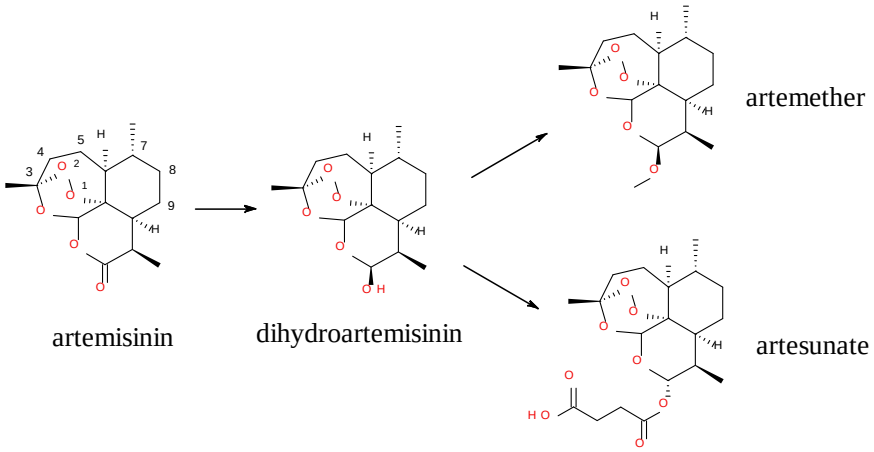
The 2015 Nobel Prize in Physiology and Medicine was awarded, with one half, jointly to William C. Campbell and Satoshi Ōmura for their discoveries concerning a novel therapy against infections caused by roundworm parasites (Onchocerciasis and Lymphatic Filariaris) and, the other half, to Youyou Tu for her discoveries concerning a novel molecule for the therapy against malaria. Neglected tropical diseases are a symptom of poverty and disadvantage. Those most affected are the poorest populations often living in remote, rural areas, urban slums or in conflict zones. With little political voice, neglected tropical diseases have a low profile and status in public health priorities. Thanks to the drug discovery and development work sponsored by international organizations and Foundations against some of these diseases, Malaria Onchoerciasis (river blindness)/Lymphatic Filariaris (elephantiasis) cannot be considered anymore neglected. Interestingly all these therapies are based on natural products isolated from fermentation or plant extraction.

Satoshi Ōmura, a Japanese microbiologist, has devised many novel methods for isolating, culturing and screening microorganisms, discovering during his career more than 470 compounds. In 1965 he began his career at the Kitasato Institute in Japan and in 1973 he started a collaboration with Merck Sharp & Dohme for the discovery of new drugs for animal health. He focused his attention on *Streptomyces. This class of soil microorganisms is able to produce a large variety of secondary metabolites that, in the last century, played a major role in drug discovery against bacterial infections, cancer and immunosuppressant agents*. Among thousand different cultures, Ōmura selected about 50 of the most promising, with the intent that they would be further tested and analyzed for their activity against harmful microorganisms. William C. Cambell (33 years spent in Merck 1957-1990) and his team at the MSD research center in Rahway found that, one of these strains later called *Streptomyces avermectinious*, was active against parasitic worms in a novel mice model. Thomas W. Miller separated and isolated the most potent metabolite Avermectin B_{1a}. Merck researchers John C. Chabala and Michael H. Fisher improved Avermectin B_{1a} pharmacological profile by a simple hydrogenation of the C22-C23 double bond generating Ivermectin that with the trademark of Ivomec® was successfully launched as a broad spectrum anti-parasitic drug in 1981. Campbell inspired by the fantastic results on animal models proposed in 1977 to test the molecules in clinical trials against human Onchoerciasis, a neglected disease. Merck CEO Roy Vagelos sponsored the development in connection with WHO and the first trials was conducted in Dakar 1982. Mectizan® the human version of Ivermectin was given by Merck for free through the Mectizan Development Program (MDP) to the WHO for the fight against Onchocerciasis since 1987. The numbers are impressive: 28 countries in Africa and 4 in South America are eligible to use Mectizan®; 1.5 billion treatments approved from 1987 to 2012 in 25 years of MDP; in 2015 South America endemic countries (Colombia, Ecuador, Guatemala and Mexico) will be declared free from the Oncocerchiasis, showing that with a good distribution of the drug it is possible to eradicate the disease. In 1998, Mectizan® in combination with albendazole donated by GSK was approved for the treatment of Lymphatic Filiarisis and since 2000 more than 665 million treatment have been approved in Yemen and 28 African countries. The number of treatments increases every year and now the Lymphatic Filiarisis Elimination (LFE) program has been launched. Merck earned several billion dollars with the sales of the Ivermectin veterinary drug in the rich countries and thanks to the work and intuition of William C. Campbell massive amount of Mectizan® was given for free to endemic countries for human treatment.



Avermectin Ivermectin

Malaria is the only disease with an Italian name Mala-aria and it is caused by a parasite Plasmodium that is spread by a mosquito, the Anopheles. There are five species of Plasmodium and the most dangerous one affecting mainly Africa and Asian countries is the Falciparum. During recent years three potent Artemisinin Combination Therapies (ACTs) have been registered for the treatment of malaria by Novartis, Sanofi-Aventis and Sigma-tau-MMV. All these combinations contain a derivative of Artemisinin respectively artemether, artesunate and dihydroartemisinin. 3.2 billion people are at risk of malaria. This leads to about 198 million malaria cases in 2013 (uncertainty range 124 million to 238 million) and estimated 584,000 deaths (uncertainty range 367,000 to 75,000). Because of the introduction of ACTs malaria mortality rates have fallen by 47% globally since 2000 and by 54% in the WHO African Region. Nowadays, the possibility to eradicate the disease in endemic countries is not a matter of drug availability but a matter of distribution of the drug. Nothing of this would be possible if, in early seventies, a team of Chinese scientists (saved from the Cultural Revolution) led by Youyou Tu didn't discover and isolate the precursor of the modern drugs, Artemisinin. Etnomedicine played a major role, in fact the effect of the extract of *Artemisia annua* against intermitted fever (Malaria) was described by a famous ancient pharmacist, Ge Hong (340 AD). Anyway, the first biological data were not reproducible. Ge Hong described a "gentle" extraction process to get the active compound from the leaves, in particular, a cold squeezed of the leaves in water. Youyou Tu used cold ethanol instead and the results of the extract became reproducible. In 1974 the Chinese team described the unique structure of Quinghaosu (Artemisinin) that contains a peroxo-ether, fragment at the basis of the biological activity and instability at high temperature.



The 2015 Nobel Prize in Physiology and Medicine focuses the attention on successful drug development devoted to third world diseases, showing to the public that, with a correct scientific approach and enough resources, the fight and the possibility to eradicate these plagues is possible.