Japanese Society of Parasitology

New Approaches to Overcoming Neglected Tropical Diseases (NTDs)

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Position and Situations of Neglected Tropical Diseases (NTDs)

Infectious diseases are nowadays discussed as a global problem from various aspects including not only medicine but also politics, economy, society, and culture. In particular, HIV/AIDS, malaria, and tuberculosis are the infectious diseases acknowledged as urgent issues by international society. On the other hand, there is a group of infectious diseases called NTDs, which spread widely in developing countries in tropical regions and are excluded from the attention of international society despite the tremendous burden they are imposing on society.[1] The World Health Organization (WHO), based on the recognition that NTDs are a factor preventing the growth of many developing countries, is waging a campaign to strengthen international collaboration against these diseases including the participation of developed countries.

NTDs are Infectious diseases with complex backgrounds, and the solution of this problem requires multifaceted approaches. Because many NTDs are chronic diseases, as is the case with parasitic diseases, they usually do not provoke panic among people and are rarely featured as a subject of advanced medical studies in developed countries. NTDs may be regarded as the diseases of socially vulnerable people. Although they are not given a high priority on the administrative agenda in endemic areas, these diseases actually require the application of advanced medical studies to disease control efforts involving developed countries.

International Strategy for NTD Control and the Role of Japan

Among developed countries, Japan is the country that has been making the most important contribution to NTD control. Since Japan expressed the commitment to play a central role in the management of soil-transmitted parasitic diseases at the G7 Summit conference in 1996, the country has been increasing its collaborative efforts as the largest supporter to the NTD control activities of the WHO. Japan has been actively leading the promotion of human resources development and application studies targeted at parasite control in Asia and Africa.

The Centers for International Parasite Control (CIPACs) supporting human resources development and projects for parasite control in developing countries were established and operated as official development assistance (ODA) projects. After the JICA projects were terminated, these Centers were operated independently and continued to play central roles in the international promotion of parasite control (**Fig. 1**). While the objective of CIPACs was to transfer the successful experience of Japan in parasite control to endemic areas, the most important pillar of their activities was the inhabitant-centered disease control projects pivoted on school health.[2] The aim is to disseminate the public health system of Japan, in which parasite control measures worked as an entry point to the improvement of community health, through seminars and small-scale pilot practices so that it may eventually be incorporated in national plans.

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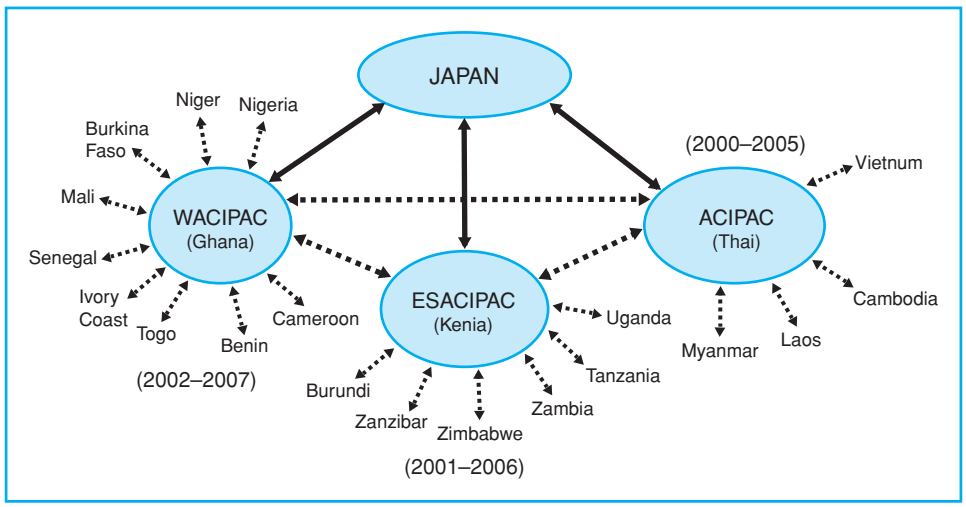

Fig. 1 Global network for parasite control initiative

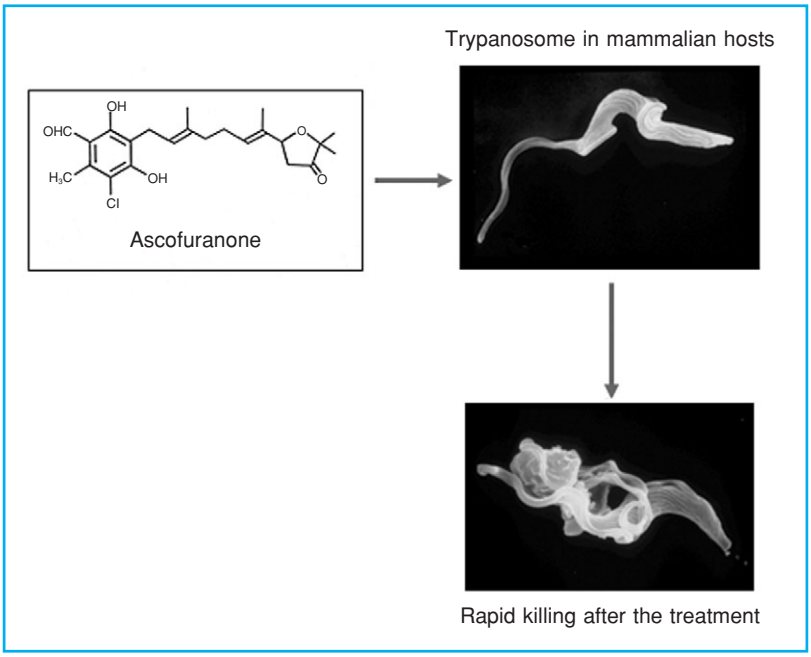

Fig. 2 Ascofuranone: a new drug for African trypanosomiasis

Basic Study Contributing to NTD Control—Development of a new antitrypanosomal agent

It has been pointed out that a factor preventing the solution of NTD problems is the delay in the development of vaccines and new therapeutic agents. No vaccines against parasitic diseases have been brought into practical use. On the other hand, the development of anthelmintics other than those for malaria has been disappointing internationally.

Japan is a major source of information on the development of new drugs that can effectively support the medical treatment of NTDs. Here we look at the development of two drugs. One is

ascofuranone, a new therapeutic agent for African trypanosomiasis. African trypanosomiasis is a protozoan infection caused by *Trypanosoma brucei gambiense* or *T. b. rhodesiense* occurring widely in the sub-Saharan Africa continent. It gradually develops central nervous system symptoms in the early stages of infection, and typical cases progress to a comatose condition known as "sleeping sickness" frequently resulting in death. At present, several tens of thousands of people contract this disease every year in Africa. At the same time, the disease also affects millions of domestic animals. The therapeutic arsenal against this disease still frequently depends on drugs with severe adverse effects and insufficient efficacy, such as arsenic drugs.

The African trypanosoma protozoa differ completely from mammals in that they depend on the glycolysis pathway for energy generation. Trypanosome alternative oxidase (TAO) is the end oxidation enzyme required for the working of this glycolysis pathway, and ascofuranone was discovered to be a specific inhibitor of this enzyme.[3] The major advantages of ascofuranone are its safety and effectiveness. Unlike conventional protozoan agents, ascofuranone was found to kill the protozoa 100% within 60 minutes in vitro. Furthermore, in vivo tests using mice demonstrated complete cure after oral administration at 100 mg/kg (**Fig. 2**). Studies in large domestic animals also showed similarly high cure rates without causing serious adverse reactions in mammalian hosts. This is an epoch-making agent in these respects.

Generating high expectations as a safe new drug against African trypanosomiasis, ascofuranone has been given much attention in the Drugs for Neglected Diseases Initiative (DNDi), an international collaboration scheme aiming at the development of drugs against NTDs, and approved for programs such as a research grant.

Prospects for Development of New Schistosomiasis Drugs

Another important contribution next to ascofuranone is the study for the development of anti-schistosomiasis drugs. Although schistosomiasis is a tropical parasitic disease comparable to malaria in importance, it is a typical example of an NTD. The number of victims decreased after the development of the specific drug praziquantel, and the priority of this disease as a health problem decreased accordingly. However, the continued use of a single drug has sometimes caused the emergence of praziquantel-resistant strains, and the need for the development of alternative drugs has been voiced. Although artemisinin-based drugs were found to deliver high efficacy,[4] these are antimalarial agents based on a traditional Chinese medicine and hence have drawbacks of limited supply quantity and high prices.

Table 1 Two different active phases of N-89 against Schistosoma mansoni in vivo

	2 weeks PI	5 weeks PI
Parasite killing	+++	none
Egg production	?	+++

N-89 is a cyclic peroxide compound that shares the same endoperoxidase activity with artemisinin and exerts high efficacy against malaria. Furthermore, evaluation of the effect on schistosomiasis demonstrated that the agent has a potent parasiticidal effect against schistosomes.[5] Similarly to artemisinin-based agents, it kills schistosome larvae in the early stages of infection and suppresses the fecundity of adult schistosomes, and the effects of this drug have been confirmed to be different from those of praziquantel (**Table 1**). Because N-89 can be synthesized chemically in large quantities, it is expected to be useful for the prevention and treatment of schistosomiasis, complementing the drawbacks of artemisinin.

Future Visions

The WHO campaign has been successful in raising international interest in NTDs. The harmonized development of both developed and developing countries is an essential prerequisite for the solution of global issues such as CO_2 reduction, and the overcoming of NTDs is an important step to the social development of developing countries. The efforts of Japan taking the lead among developed countries in NTD control measures have realized a certain level of achievement, but there still remain considerable unsolved problems, such as how current programs can be continued for the future and how developing countries can independently establish and operate such pro-

grams. Japan's international contribution to infection control is also a major part of the country's policy agenda. In the field of NTDs, it is necessary to continue international cooperation building on past efforts towards vaccine development, new drug development, operation of control measures, etc.

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