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Drugs for neglected diseases: part I

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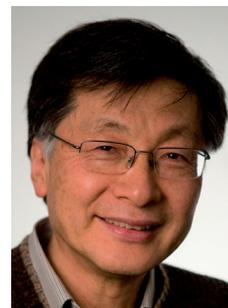
This and the next issue of *Future Medicinal Chemistry* will focus on neglected diseases, defined by the WHO as those that affect almost exclusively poor and powerless people living in rural parts of low-income countries [101]. The WHO's Special Programme for Research and Training in Tropical Diseases lists as its target diseases: Chagas (American trypanosomiasis), dengue fever, helminths (diseases caused by worms), human African trypanosomiasis (sleeping sickness), leishmaniasis (kala-azar), leprosy, lymphatic filariasis (elephantiasis), malaria, onchocerciasis (river blindness), schistosomiasis, sexually transmitted infections, TB/HIV co-infection and TB [102]. Patients of these diseases suffer physically as well as psychologically, since they are often marginalized in society. The nature of the diseases and the lack of access to treatment make them doubly scourging to patients because treatment of these diseases is often limited not only by the lack of proper medical care, but also because certain drugs are not efficacious or have severe adverse effects. For instance, although there are some alternative drugs available, the arsenic-containing drug melarsoprol is still used in late-stage human African trypanosomiasis. It is an old drug, discovered in 1949, and must be given by injection. Its toxicity is such that there is approximately 8% treatment-related mortality and the treatment failure rate is also relatively high [1,2]. This is just one example; but looking across other neglected tropical diseases, the situation is similar and could benefit from the fruits of modern medicinal chemistry. Such an effort is undoubtedly ongoing in a few research laboratories around the world but the number is extremely small and research funding is woefully inadequate.

According to a recent Oxfam publication, neglected tropical diseases receive only US\$1 out of every \$100,000 spent worldwide on biomedical research and development [103]. The exact dollar ratio may vary depending how

neglected tropical diseases are defined, but a similar picture can be obtained from the fact that out of 1559 new drugs developed worldwide from 1975 to 2004, only 21 were for patients with neglected tropical diseases [3]. Research results from these laboratories are being published in major journals, but it is difficult to get an overview of the current status of the field, especially if one is interested in medicinal chemistry efforts.

To respond to this, in these two special issues, we have asked representatives of the four major not-for-profit product-development partnerships (PDPs), Drugs for Neglected Diseases Initiative, Medicine for Malaria Venture, Institute of One World Health and the Global Alliance for TB Drug Development (TB Alliance) to summarize their current status and the major challenges facing their own field, as well as to offer a discussion of the chief functions of their organization. We have also asked academic and public research laboratories to present their latest contributions to neglected disease research; contributors include those from the University of California, San Francisco Sandler Center, Northeastern University, St Louis University Center for World Health and Medicine, University of Bern, University of Cape Town, and the National Institute of Health. Finally, we are also happy to feature two contributions from industry partners, Scynexis/Anacor and Tibotec/Johnson & Johnson, which have exciting new drugs under development.

It is important to remember that given the risks and attrition rates in drug development, the drug pipeline for neglected diseases is still too weak to guarantee novel drugs for future treatment. We need to stress the need for more funding, a more coordinated approach to research, increased involvement of pharmaceutical companies, and an importance of greater research capabilities in the developing countries. The involvement of big pharmaceutical



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companies in recent years is heartening because they have the majority of medicinal chemistry expertise at their disposal and there is no reason why it should not be utilized. For example, several companies are donating compounds for screening, actively seeking opportunities to work with not-for-profit PDPs, and making their databases and patents available to external researchers. The companies are, however, not focused on neglected diseases *per se* because there is little return on investment. For that we need to rely on the innovative research in academic and governmental laboratories to identify new drug targets and to increase basic knowledge of disease physiology. We, therefore, need to strengthen the mechanisms (including, but not limited to PDPs) for the coordination and seamless transition from basic research to drug discovery and development. An eight-point declaration was recently produced to enhance the speed and effectiveness of solving neglected tropical diseases [4].

In this issue

This issue features an interview with Professor McKerrow, Director of the Sandler Center for Basic Research in Parasitic Diseases at the University of California, San Francisco [5]. His experiences and views on the research on neglected diseases set the tone for this issue. In a commentary, Peter Ruminski discusses how an organization such as his is designed to fill the gap between basic scientific discoveries in academic settings and clinically relevant drug candidates [6]. The research spotlight by Ann Ginsberg, Chief Medical Officer of TB Alliance, discusses the function and the portfolio of this organization [7].

In an industrialized world we often do not think of diarrheal diseases as life-threatening but they do have a high mortality rate that

could be prevented by rehydration therapies. The review by de Hostos *et al.* outlines their efforts to reduce the high mortality of children caused by diarrheal diseases [8]. The research paper by Jacobs *et al.* discusses oxaborols as novel agents against sleeping sickness [9]. This is the first disclosure of experimental details of their compounds. Pollastri and Campbell present their concept of target repurposing as a way to efficiently discover new drugs against neglected diseases by overcoming the lack of research resources [10]. Seebeck *et al.* present their work into another repurposing approach, in this case taking advantage of the structural similarity between human and protozoan phosphodiesterases [11]. Robertson and Renslo explain the operation at Sandler Center in the University of California, San Francisco, where they carry out both drug repurposing and lead-optimization exercises [12].

We hope that the articles published over these two special issues provide valuable insights into the current contributions of medicinal chemistry efforts to neglected disease research.

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