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Prof. John Beddington
chief scientific officer, UK

Vaccine makers get 5-month WHO breathing space

More R&D factories on the horizon

DNDi champions the cause of infectious diseases

Nobel Prize for Glowing Protein Researchers

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■ Bio Business ■

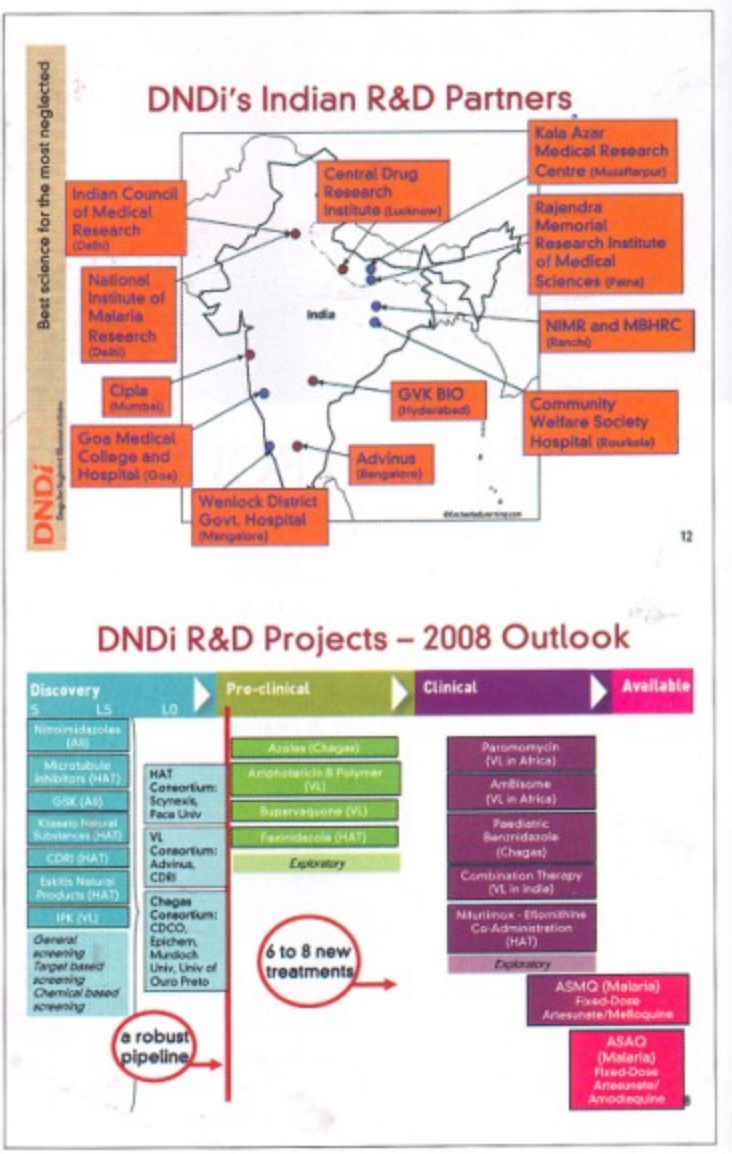
DNDi: Championing the cause of infectious diseases

While cancer and diabetes might be on the rise in the past few years, the proportion of infectious diseases that plague the developing world cannot be ruled out.

The world's pharma biggies might be focusing all their attention on lifestyle and non-communicable diseases in the light of the increasing effects of globalization, but it seems that does not undermine the danger that infectious diseases present. A new study by the World Health Organization (WHO) outlining the global burden of disease reveals that four out of the top 10 causes of death globally are infectious diseases. The report outlines the leading causes of death globally as heart disease, stroke, pneumonia, chronic respiratory disease, diarrhea, HIV/AIDS and tuberculosis as according to Colin Mathers, Coordinator for Epidemiology and Burden of Disease at WHO and lead author of the study.

India is also not untouched by the burden of infectious diseases. Malaria and Visceral leishmaniasis are largely prevalent in India and affect more than 3 million Indians each year, according to government estimates. India has been increasing the focus of medical research as it bears a large burden of two types of diseases: on the one hand, that of neglected tropical diseases, which represent major health problems, and on the other, an increase in non-communicable lifestyle diseases. These along with India emerging as a pharmaceutical hub with low research costs and large pools of skilled medical research and drug development manpower were some of the reasons why DNDi (Drugs for Neglected Diseases initiative) has been active in the country since 2004. It recently opened its office in India to further its commitment to the cause.

DNDi is a collaborative, patients' needs-driven, not-for-profit drug R&D organization that is currently developing new treatments against the world's most neglected infectious diseases such



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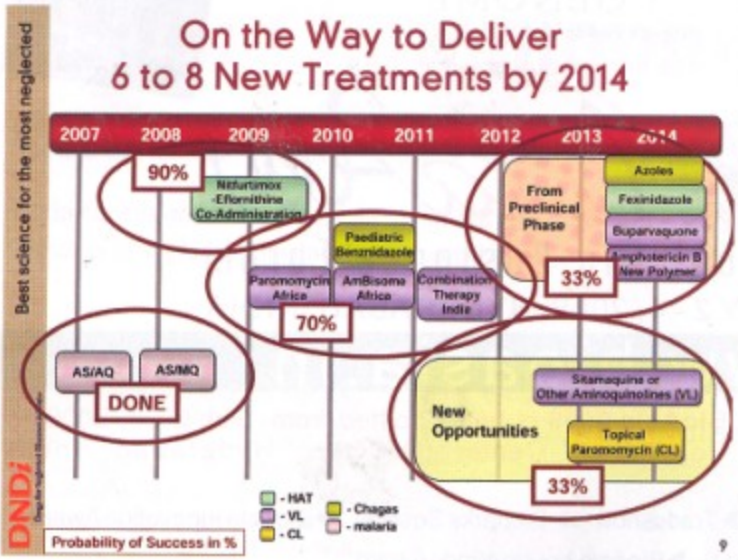

as sleeping sickness (human African trypanosomiasis, HAT), visceral leishmaniasis (VL), Chagas disease, and malaria. It was established in 2003 by Institut Pasteur and Médecines Sans Frontières along with four publicly-funded research organizations in neglected disease-endemic countries such as Kenya (Kenya Medical Research Institute (KEMRI), Malaysian MOH in Malaysia, Oswaldo Cruz Foundation Brazil and the Indian Council for Medical Research (ICMR) in India. WHO/TDR function as the permanent observer. Today, DNDi is a small team of permanent staff in Geneva along with four regional support offices in Kenya, India, Brazil, and Malaysia; an affiliate in North America, and two regional project support offices in the Democratic Republic of the Congo and Japan. Working in partnership with industry and academia, DNDi has built the largest ever R&D portfolio for the kinetoplastid diseases and currently has six clinical and four preclinical projects.

DNDi's activities in India

According to Dr Bernard Pécoul, executive director, DNDi, "The primary objective of DNDi is to deliver six to eight new treatments by 2014 for these diseases and to establish a strong R&D portfolio. In doing so, DNDi is also working to use and strengthen existing capacities in disease-endemic countries, and raise awareness and advocate for the need to develop new treatments for the most neglected diseases." DNDi opened the regional support office in India in 2005 with support from the India Council of Medical Research (ICMR) to support and catalyze its operational activities in the field of malaria and visceral leishmaniasis (VL). In fact, DNDi is currently carrying out more than 30 percent of its R&D activities in India. "India has an important role to play in the fight against infectious diseases. What is needed is a political leadership to start and sustain the efforts in "essential health R&D' and redefine the R&D priorities to initiate and stimulate research for neglected diseases."

Work on Visceral leishmaniasis

In December 2007, DNDi signed a five-year collaborative agreement with Advinus Therapeutics as primary partner in lead optimization consortium for VL. The project is to obtain optimized leads by processing "hit" molecules with good safety profiles and proven activity against Leishmania parasites. This consortium brings together expertise

Achievements

Malaria

ASAQ for treatment of malaria in sub-Saharan Africa; launched in March 2007; registered in 23 disease-endemic countries and ASMQ for treatment in Latin America and registered in Brazil in March 2008 and in use by Brazilian national authorities as part of ongoing intervention study (25,000 patients)

Visceral Leismaniasis (VL)

- Lead optimization partnership with Advinus and CDDRI Lucknow
- VL combination trial to evaluate safe and short-course combination therapy using existing drugs registered in region
- Paromomycin trial. Over 1,000 patients included in multi-centre trial in East Africa
- Leishmaniasis East Africa Platform—research capacity strengthening in Africa for VL

Human African Trypanosomiasis (HAT, sleeping sickness)

- Lead optimization partnership to progress molecules from early-stage screening research with Scynexis and Pace University
- Fexinidazole, first compound mining success from DNDi's nitroimidazoles project; finalizing preclinical studies; will enter first-in-human Phase I trials in early 2009
- Clinical trial of Nifurtimox-Eflornithine co-administration—promising study data being finalized; shows for NECT as easier to use, more practical, and safe therapy; full dossier will be submitted to WHO Essential Medicines List in 2008
- HAT Platform—research capacity strengthening in Africa for HAT

Chagas Disease

- Lead optimization partnership with Centre for Drug Candidate Optimization (CDCO),
- Epichem, and Murdoch University (Australia); Federal University of Ouro Preto (Brazil)
- Pediatric Benznidazole—agreement established with LAFEPE to develop first benznidazole formulation for children that is affordable.

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Ongoing clinical trials on drugs for Malaria and Visceral leishmanisis

MALARIA

While clinical trials for ASAQ have been conducted, the clinical research for ASMQ has just started.

Malaria is present in over 100 countries and threatens half of the world's population. In sub-Saharan Africa, it is the single leading cause of death for children under five. It is unevenly distributed in India—80 percent of the population lives in low transmission areas and 20 percent in a high transmission belt. India holds 77 percent of the South-east Asia's malaria burden. The region also witnesses a large number of P. falciparum cases (up to 50 percent) and chloroquine resistance.

ASAQ: A clinical trial studying tolerability and effectiveness in real-life conditions has recently been conducted for ASAQ, the fixed-dose combination of artesunate (AS) and amodiaquine (AQ) for its eventual registration in India. The drug was launched in 2007 by DNDi in an innovative partnership with Sanofi-aventis. The study was carried out in partnership with the Indian Council of Medical Research (ICMR) and National Institute of Malaria Research (NIMR), namely in Orissa and Jharkhand regions and the study results were recently presented at the XVII International Congress on Tropical Medicine and Malaria.

Status

- Clinical trials in India (N=300)
- 2 sites (Ranchi and Rourkela) enrolled 300 patients
- Study completed in Q12008; Results presented at ICID and ICTM17 in 2008
- Consistent with previous studies with ASAQ in Africa
- Supports consideration of ASAQ as 1st-line therapy in India where appropriate

ASMQ: This new fixed-dose combination of artesunate (AS) and mefloquine (MQ), developed by DNDi and Farmanguinhos/Fiocruz, was successfully registered in Brazil in March 2008. To facilitate its future availability in Southeast Asia, upon approval from the ethics committee and the relevant national and local authorities, further clinical research is being conducted in the Goa and Mangalore regions in association with ICMR and NIMR. Further enabling the Southeast Asia expansion, Farmanguinhos/Fiocruz has agreed to the principle of technology transfer to the Indian pharmaceutical company, Cipla.

Status

- Clinical trials in India (N=84)
- Dec 2007: Enrolment started at2 sites (Goa; Mangalore). 77 patients enrolled (Sept 08)
- End of enrolment expected in Q42008
- Results expected by Q32009

VISCERAL LEISHMANIASIS (VL)

Clinical trials are on for VL combination therapies of Ambisome (lipid formulations of Amphotericin B), paromomycin, and miltefosine.

Leishmaniasis affects approximately 12 million people in 88 countries. The seven most affected countries represent over 90 percent of all reported new cases. India has about 1 lakh new cases of VL annually, of which approximately 90 percent are from Bihar. Until recently, pentavalent antimony complex was one of the very few standard VL treatments, despite all of its limitations: toxicity, lengthy treatment, and growing resistance. Presently, amphotericin B, paromomycin, and miltefosine have been evaluated and officially approved by all relevant authorities for the treatment of VL in India. All of these drugs have advantages and disadvantages with regards to cost, toxicity, length, and ease of administration. Therefore, to reduce the treatment period, to increase compliance, and to reduce the possibility of resistance developing, DNDi and its partners are investigating the use of combinations of these drugs to treat VL.

A clinical study to evaluate various drug combinations has been initiated in collaboration with ICMR and the Rajendra Memorial Research Institute (RMRI), at Patna, the Kala-azar Medical Research Centre (KMRC), and GVK Bio at Muzaffarpur. This project will be extended to Nepal and Bangladesh. The data collected will be used to make a recommendation to the national control programs in highly endemic areas of VL in the region. A total of 147 patients have been recruited so far out of the proposed 640 for clinical trials. Enrolment will continue through 2009 and the results are expected by early 2010.

in chemistry, screening, pharmacology, and pre-formulation in order to optimize a molecule's drug properties to be orally absorbed and reach the bloodstream, be distributed effectively to infection sites, remain intact in the body to kill the parasites, and yet not harm the patient. With a full team in place, Advinus Therapeutics in Bangalore has identified two promising series of compounds and conducted an assessment of the first series of synthetic compounds and initiated chemistry-biology activities. Screening at the Central Drug Research Institute (CDRI), in Lucknow, began in 2008 for in vitro and in vivo biological activities. ■

Shalini Gupta