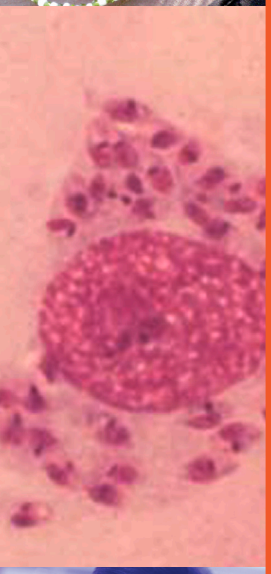

World Leish 4, Lucknow, India, February 2009

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Ongoing Studies on Improved Treatments
Tuesday, February 3, 2009 - Auditorium 1: 11.30-13.30

Challenges for and Potential in Early-Stage R&D
Wednesday, February 4, 2009 - Room A2: 11.00-13.00

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Welcome to the DND*i* Symposia at the 4th World Congress on Leishmaniasis

Tuesday, February 3, 2009
Auditorium 1: 11.30-13.30

"Improved Treatments for Visceral Leishmaniasis – Status of Ongoing Studies, and Challenges & Opportunities Ahead"

Wednesday, February 4, 2009
Room A2: 11.00-13.00

"Challenges for and Potential in the Early-Stage R&D Pipeline to Develop New Antileishmanial Drugs"

DND*i*, as a sponsor of WorldLeish4 and organiser of two treatment-related symposia, is honoured to have you here with us today as you will have a chance to share your knowledge and wisdom in the field of visceral leishmaniasis with those of us who are aiming to develop better treatments to meet the needs of patients suffering from this potentially life-threatening disease.

As this gathering of worldwide 'leishmaniacs' is convened, we are excited to see the variety of partners who are among us: representatives of national and local authorities, pharmaceutical firms, health-related NGOs, academics, and research institutes.

We would like to especially thank the organisers of WorldLeish4, as well as our distinguished chairs and speakers who will bring some exciting research and expertise that we hope will ignite audience discussion. It's also important to recognize the many public and private donors who not only make such meetings possible, but also make our research & development possible. We are pleased to see their presence here as well!

We look forward to future engagements as we work together to make a true difference in delivering adequate treatments to the most neglected patients.

Best regards,

Bernard Pécoul, MD, MPH
Executive Director, DND*i*

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DND*i* IN 2009

DND*i* (Drugs for Neglected Diseases *initiative*) is a collaborative, patients' needs-driven, not-for-profit drug R&D organisation that is currently developing new treatments against visceral leishmaniasis (VL), malaria, sleeping sickness (human African trypanosomiasis, HAT), and Chagas disease. The initiative's primary objective is to deliver six to eight new treatments by 2014 for these diseases and to establish a robust R&D pipeline. In doing so, DND*i* also works to use and strengthen existing capacities in disease-endemic countries, and to raise awareness and advocate for the need to develop new treatments for the most neglected diseases.

DND*i* was established in 2003 by Institut Pasteur and Médecins Sans Frontières along with four publicly-funded research organisations in neglected disease-endemic countries – the Indian Council for Medical Research (ICMR), the Kenya Medical Research Institute (KEMRI), the Oswaldo Cruz Foundation (Fiocruz) in Brazil, and Malaysian Ministry of Health. DNDi is supported by a balanced mix of public and private funding.

Working in partnership with industry and academia, DND*i* has built the largest ever R&D portfolio for the kinetoplastid diseases and currently has seven clinical and four preclinical projects. DND*i* has successfully delivered two fixed-dose antimalarials ("ASAQ" and "ASMQ") to Africa and Latin America, respectively. In December 2008, DND*i* and partners released promising clinical trial results on an improved combination therapy, "NECT," for human African trypanosomiasis.

Learn more about DNDi's activities and partners at www.dndi.org.

DND*i* IN INDIA

With support from DND*i*'s founding member, the **India Council of Medical Research (ICMR)**, DND*i* opened the **regional support office** in India in 2005 to support and catalyse DND*i*'s operational activities, namely in the field of two diseases, malaria and visceral leishmaniasis (VL). These two diseases are prevalent in India and affect more than 3 million Indians each year, according to Indian government estimates.

India has been the increasing 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. Consequently, no one can deny that India has become an emerging pharmaceutical hub where research costs are low and pools of skilled medical research and drug development experts are abundant. These elements make India a key country in the fight to address neglected diseases and are reasons why DND*i* has been active in the country since its 2004. In fact, DND*i* is currently carrying out more than 30% of its R&D activities in India.

Learn more about DNDi's activities and partners in India at www.dndiindia.org.

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DND*i*s AIMS AND ACTIVITIES IN VISCERAL LEISHMANIASIS

DND*i* forms its disease objectives by first assessing the needs of the patients in the field. For patients with visceral leishmaniasis, **the ideal product is oral, safe, effective, low cost, and short course (≤10-day).** Ideally, this treatment will be effective against all forms of the disease and will be adapted for use in rural health settings.

As it can take 10 years to bring a compound through the preclinical and clinical phases of development, DNDi intends to build on previous research by extending the registration and availability of current drugs, while maximizing their potential and minimizing their drawbacks.

DNDi also aims to accelerate the development and registration of new VL drugs by building on already existing preclinical and early clinical data (on safety and efficacy). Several products including buparvaquone, new amphotericin B formulations and aminoquinolines are considered and could be made available to patients as early as 2014.

In addition, DNDi has a lead optimization programme (with support from the Bill&Melinda Gates Foundation) which will also bring new candidates into clinical development during this timeframe. All of these new drugs can also be considered for combination therapy.

Short term: better use of existing treatments through geographical extensions and new combinations

- **Combination of existing therapies for VL in each endemic continent (Africa, Asia, Latin America)**: combinations can reduce course, toxicity, and cost of treatments
  - A clinical study of a **paromomycin + SSG combination in East Africa**
  - A clinical study examining **3 possible combination therapies in India**
    - AmBisome & miltefosine
    - AmBisome & paromomycin
    - Miltefosine & paromomycin

Long term: new drugs and improved research capacity

- **Improved formulations of buparvaquone and of amphotericin B**: compounds which could improve upon route and length of current treatments
- **New drugs** developed from compounds identified in discovery activities progressed through **VL lead optimisation consortium**
- **Multi-country, multi-partner "Leishmaniasis East Africa Platform" (LEAP)** to strengthen regional research capacity

By 2014, DND*i* aims to deliver from its VL-specific portfolio:

- 2 new co-administrations recommended by WHO
- a robust pipeline
- 1 new drug registered
- 2 geographical extensions in endemic regions outside India by 2014

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Tuesday, February 3, 2009
Auditorium 1: 11.30-13.30

"Improved Treatments for Visceral Leishmaniasis – Status of Ongoing Studies, and Challenges & Opportunities Ahead"

Leishmaniasis has a worldwide distribution across Central and South America, southern Europe, North and East Africa, the Middle East, and the Indian subcontinent. The visceral form of leishmaniasis (VL) has an estimated incidence of 500,000 new cases and 60,000 deaths each year, with the majority of cases currently occurring in Sudan and India. The few therapeutic options registered for visceral leishmaniasis include liposomal/amphotericin B, antimonials (sodium stibogluconate or SSG/glucantime), miltefosine, and paromomycin. All have limitations such as price, feasibility, safety, efficacy, and drug resistance. With the limitations of current treatments including toxicity, need for hospitalisation, growing resistance, and high costs, patients urgently need new and improved treatments.

This symposium will examine the status of current clinical research on improved VL treatments, including an East African clinical research platform and early results from its ongoing clinical study being conducted with the Drugs for Neglected Diseases *initiative* (DND*i*), the use of liposomal amphotericin B by Médecins Sans Frontières under routine programme conditions in Bihar, India, and the potential of combination therapies in India and beyond, including an ongoing clinical study on combination therapies being conducted by DND*i* and its partners.

Symposium Chairs

Dr. Shyam Sundar, MD
Professor of Medicine, Institute of Medical Sciences, Banaras Hindu University, India;
Director, Kala-azar Medical Clinic, Muzaffurpur, India

Dr. Sundar is a Professor of Medicine at the Institute of Medical Sciences, Banaras Hindu University, where he uses immunology and molecular biology techniques to study the mechanisms of drug resistance of visceral leishmaniasis (VL). Notably, Prof Sundar established and is also the Director of the Kala-azar Research Centre, the first centre dedicated to the research and treatment of visceral leishmaniasis. This centre is at the forefront of the diagnosis and treatment of the disease in Muzaffarpur in the Indian state of Bihar. For two decades, Dr. Sundar has been involved in the study and treatment of VL, and has authored over 250 publications on this subject.

Prof. Eltahir Awad Gasim Khalil, MD, FRCP
Director, Institute of Endemic Diseases, University of Khartoum, Sudan;
Head, Clinical Pathology & Immunology, Institute of Endemic Diseases, University of Khartoum, Sudan

Prof. Khalil has served as the Director of the Institute of Endemic Diseases in Sudan. A haematologist by training, Prof. Khalil graduated from medical school at the University of Khartoum in Sudan in 1981 and is also a Fellow of the Royal College of Pathologists in the UK. With research interests in vaccines for visceral leishmaniasis, extrapulmonary tuberculosis, and sickle cell disease, Prof Khalil has over 60 publications and is the current President of the Sudanese Association of Clinical Biologists. He is also an active LEAP member.

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"Improved Treatments for Visceral Leishmaniasis – Status of Ongoing Studies, and Challenges & Opportunities Ahead"

Chaired by Drs. Sundar and Khalil

Topic	Speaker
Keynote address and introduction of Chairs	**Dr. Nirmal K. Ganguly** Kenya Medical Research Institute; Drugs for Neglected Diseases *initiative* Africa Nairobi, Kenya
The Leishmaniasis East Africa Platform (LEAP): addressing the challenges and opportunities of conducting clinical research on visceral leishmaniasis in East Africa	**Dr. Monique Wasunna** Kenya Medical Research Institute; Drugs for Neglected Diseases *initiative* Africa Nairobi, Kenya
New treatments for visceral leishmaniasis in East Africa: The story so far	**Dr. Ahmed Mudawi Musa** Institute of Endemic Diseases University of Khartoum Khartoum, Sudan
Experience of Médecins Sans Frontières after 1 year of using liposomal amphotericin B (AmBisome®) treatment for Indian visceral leishmaniasis under routine programme conditions in Bihar, India	**Dr. Nines Lima** Médecins Sans Frontières – Spain Barcelona, Spain
Combination therapy for visceral leishmaniasis: why, what, and where?	**Dr. Johan van Griensven** Institute of Tropical Medicine, Antwerp Antwerp, Belgium
Combination therapy for visceral leishmaniasis (VL) in the context of DNDi's R&D strategy to improve treatment of VL	**Dr. Manica Balasegaram** Drugs for Neglected Diseases *initiative* Geneva, Switzerland
Discussion / Q& A – started by expert intervention of Jorge Alvar	**Audience**

Expert Intervention

"Meeting the global challenges of visceral leishmaniasis, what are the next steps?"

Dr. Jorge Alvar

Medical Officer, Leishmaniasis Control Programme, Communicable Diseases, Neglected Tropical Diseases Control, World Health Organisation (WHO), Geneva, Switzerland

Dr. Alvar currently leads a major WHO- and Spanish government-funded initiative to improve VL control measures in Ethiopia and Sudan. Dr. Alvar has extensive experience in the field of microbiology, specifically in virology and parasitology, which he gathered from many years of work at the National Microbiology Centre, Carlos III Institute of Health, Madrid, prior to his move to the WHO.

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Keynote Introduction

Prof. Nirmal K. Ganguly, MD, MBBS
Distinguished Biotechnology Fellow and Advisor, Translational Health Science and Technology Institute, India

Prof. Nirmal K. Ganguly was most recently the Director General of the Indian Council of Medical Research, New Delhi. He has also served as the General President (Elect) of the Indian Science Congress Association for the year 2004-2005 and was Acting Director at the Post Graduate Institute of Medical Education & Research, Chandigarh, and at the National Institute of Biologicals, NOIDA. His major research areas have been tropical diseases, cardiovascular diseases, and diarrhoeal diseases. He has authored over 725 publications and won over 100 awards internationally and nationally, including a nomination for the Dr. U.C Chaturvedi IAMM Lifetime Achievement distinction in 2007. On January 26, 2008, he was honoured with the prestigious Padma Bhushan Award by her Excellency, the President of India, in the field of medicine.

Keynote address

Leishmania donovani infection in India has changed its demographic pattern and now occurs in the poorest of the poor (Musharraf S.G.). This same community is affected in Bangladesh and Nepal. They can not afford the drugs and hospitalisation needed for the most effective treatment of *Leishmania*. Inadequate treatment, thereby leads to drug resistance and death, which pushes this population even further below the poverty line. Responding to this dire need, miltefosine was pushed through clinical trials in a short period of time, providing an antileishmanial treatment option to the poor. Miltefosine, however, has several shortfalls; it lowers haemoglobin levels, can not be given to expecting women and women of child bearing age, and causes many other debilitating side effects. Paromomycin, an injectable drug, has a similar treatment course, however, drug resistance has developed quickly. A lower cost version of AmBisome is currently in development and could provide an advance in treatment for this demographic group. By pairing several of the treatments in this VL landscpe, DND*i* has demonstrated the potential of several combinations in clinical trials: AmBisome + paromomycin; AmBisome + miltefosine; paromomycin + miltefosine *vs*. amphotericin B deoxycholate (the standard), but will need more robust data on post kala-azar treatment surveillance. Promoting accessibility, each of the aforementioned drugs are already individually used and accepted under current drug policies, uniformly in India, Bangladesh, and Nepal. Since an antileishmanial vaccine is not going to be available in the near future and elimination of the disease is still a goal, low cost combinations, with shorter lengths of treatment, also usable for women and children, may provide viable and important treatment options that will not develop cross resistance. The future outlook of the VL landscape will be discussed in the symposium.

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Dr. Monique Wasunna
Kenya Medical Research Institute, Nairobi, Kenya;
Drugs for Neglected Diseases initiative *Africa, Nairobi, Kenya*

Dr. Monique Wasunna is the acting Director of the Kenya Medical Research Institute (KEMRI), a Government parastatal charged with the mandate of carrying out biomedical research in Kenya. KEMRI, a founding partner of DND*i*, hosts the Africa Liaison office in Nairobi, Kenya, which Dr. Wasunna heads. She is a physician by training and an infectious disease specialist. Dr. Wasunna is a founding member and a former chair of the *Leishmania*sis East Africa Platform (LEAP). Her research interests have been primarily focused on clinical trials in Visceral *Leishmania*sis (VL), as well as malaria and HIV. In addition to DND*i* and LEAP, she collaborates with WHO/TDR. Dr. Wasunna was appointed a member of the International Bioethics Committee (IBC) of UNESCO (2008-2011) by the Director General, UNESCO, and is a member of the IBC Working Group on Social Responsibility and Health.

The Leishmaniasis East Africa Platform (LEAP): addressing the challenges and opportunities of conducting clinical research on visceral leishmaniasis in East Africa

Monique Wasunna on behalf of members of the *Leishmania*sis East Africa Platform

LEAP, the Leishmaniasis East Africa Platform, is a regional clinical research network that brings together experts from leishmaniasis-endemic East African countries, including Ethiopia, Kenya, Sudan, and Uganda. The platform incorporates partners from across the spectrum of clinical research and disease control organisations/institutions working in leishmaniasis in these countries. Founded in Khartoum, Sudan in 2003, LEAP serves to strengthen clinical research capacity, which is lacking in part due to the remoteness and geographic spread of the patients (most of whom are in the most impoverished regions of Africa). LEAP also serves as a base for ongoing educational cooperation between countries in the Eastern African region and for standardisation of procedures and practices as much as is possible within the confines of local regulations. Collaborating among member countries, LEAP facilitates clinical testing and registration of new treatments for VL in the Eastern African region; evaluates, validates, and registers improved treatment options that address regional needs for VL; and provides capacity strengthening for drug evaluation and clinical studies in the region. The platform's achievements include a multi-country clinical study, the establishment of clinical trial sites in remote areas across East Africa, and the training of study personnel. In the short term, LEAP is conducting a multi-country clinical study and has provided partners with a mechanism by which they can discuss and develop a cohesive strategy that is key to the coordinated implementation of integrated control strategies. Training and methodology workshops have been conducted, and infrastructure has been built or strengthened that will help LEAP to complete the ongoing clinical trial comparing paromomycin and sodium stibogluconate in East African patients. In the long term, LEAP will facilitate the design and implementation of new trials needed to ultimately make available new tools for the diagnosis and treatment of VL. The sharing of information and experiences gained, including methodologies as well as both positive and negative results, remains of critical importance, especially in terms of influencing policy change.

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Dr. Ahmed Mudawi Musa
Department of Immunology and Clinical Pathology, Institute of Endemic Diseases
University of Khartoum, Khartoum, Sudan

Dr. Ahmed Mudawi Musa, Assistant Professor at the Institute of Endemic Diseases (IEND), University of Khartoum, is a specialist in immunology, tropical medicine practice and research. He has headed the leishmaniasis research group of the IEND since 2004. Dr. Musa is an expert on post kala-azar dermal leishmaniasis (PKDL), leishmaniasis immunochemotherapy, and therapeutic leishmaniasis vaccine studies. He has led the IEND team to Western Sudan (Darfur), Southern Sudan (Bantiu) and Eastern Sudan (Kassala), is principal investigator for DND*i* at the treatment centres in Kassab and Dooka, and advises the Gedaref State Ministry of Health and DND*i*. Dr. Musa is also a WHO/TDR temporary advisor for clinical trials. Dr. Musa is the current chair of the Leishmaniasis East Africa Platform (LEAP).

New treatments for visceral leishmaniasis in East Africa: The story so far

Ahmed Mudawi Musa on behalf of the LEAP0104 Study Group

The available treatment options for visceral leishmaniasis (VL) in East Africa are far from satisfactory, as they are either expensive (AmBisome®) or toxic (sodium stibogluconate, SSG). Therefore, new and improved treatment options are urgently needed to replace or complement existing ones. Under the auspices of the Drugs for Neglected Diseases *initiative* (DND*i*), leishmaniasis experts in East Africa created a research body to test new treatments for VL: the *Leishmania*sis East Africa Platform (LEAP).

An ongoing clinical trial in East Africa (Sudan, Ethiopia, Kenya, and Uganda) is testing the efficacy and safety of paromomycin (PM) *vs.* SSG and the combination of SSG/PM *vs.* SSG. PM alone, at a dose of 15mg/kg per day for 21 days, has shown variable efficacy rates in five study sites; the lowest efficacy observed in Eastern Sudan, and highest in southern Ethiopia.

To improve the efficacy of PM alone, a dose-finding study was conducted in Sudan. As a result of that study, a PM dose of 20mg/kg/day for 21 days was selected to replace the original PM dose. The observation that the original PM dose showed variable efficacy rates in five study sites has also necessitated an investigation into the variability of the *Leishmania* species causing VL in the region, as well as possible host factors.

This presentation will review the early results and ongoing activities of the PM *vs.* SSG and SSG/PM *vs.* SSG clinical trial.

Dr. Nines Lima
Tropical Disease Advisor, Médecins Sans Frontières (MSF) Spain

Nines Lima works as a Tropical Disease Advisor with Médecins Sans Frontières (MSF) Spain. She is a medical doctor whose research interests include Chagas disease, human African trypanosomiasis, malaria, viral haemorrhagic fever, and visceral leishmaniasis. In April 2007, Nines served on the scientific committee that developed the treatment protocol for visceral leishmaniasis patients in Vaishali district, State of Bihar, India. Currently, she acts as an advisor to the MSF-supported visceral leishmaniasis treatment programme in India, which aims to identify and provide the most tolerable and effective treatment possible for primary visceral leishmaniasis patients. She is particularly interested in helping to generate evidence regarding optimum treatment dosage for Liposomal Amphotericin B.

Experience of Médecins Sans Frontières after 1 year of using liposomal amphotericin B (AmBisome®) treatment for Indian visceral leishmaniasis under routine programme conditions in Bihar, India

M.A. Lima on behalf of the MSF/RMRI AmBisome Study Group

In Bihar, India, Médecins Sans Frontières (MSF) treats people living amid the world's highest concentration of visceral leishmaniasis, also known as kala-azar. Transmitted between both people and animals by the bite of certain types of sandflies, the parasitic disease, in its most severe form, kills nearly everyone within one to four months, if medical attention is not received.

Project implementation started in July 2007 at the Sadar Hospital in Hajipur, which is the referral hospital for more than 2 million people living in Bihar's Vaishali district. On average, the MSF team tests 310 patients monthly and admits 140 to Sadar Hospital in Hajipur. Complicated cases, such as those co-infected with tuberculosis or HIV, are transferred to and treated with AmBisome free of charge at the Rajendra Memorial Research Institute of Medical Sciences (RMRIMS) in Patna, whose kala-azar ward MSF helped to rehabilitate.

In a one-year period, a total of 4,250 patients have received consultation in the MSF programme with 2,013 admissions[1] (45% female). Treatment of patients, initially children (Five admissions on the first day), began on 16 July 2007. On the 27 July 2007, MSF began to treat adults as well.

Outcome indicators are very satisfying in the overall cohort due to the comprehensive and diligent care the team has been providing (an efficient referral protocol and system; life-saving services, such as blood transfusions to a high proportion of those in need; early detection; and complete treatment for coinfections, including severe acute malnutrition, HIV, tuberculosis, pneumonia, etc.)

Initial cure rate at discharge: 98.5%
Defaulter rate: 0.7%
Death rate: 0.7%

Key challenges remain:

- Integration of comprehensive and free of charge (early diagnosis) treatment of kala-azar (and co-morbidities) into the Ministry of Health system.
- Maintenance of the highest standard of service at all levels: referral, in-patient care, early detection, and treatment of co-infections, blood transfusion, etc.

1 MSF has also provided AmBisome® as a "rescue treatment" for 257 patients with severe kala-azar in eight other highly endemic districts of Bihar (Muzaffarpur, Saran, Gopalganj, Purbi Champaran, Araria, Purnia, Madhepura, and Saharsa).

Johan Van Griensven, MD, PhD
Institute of Tropical Medicine, Antwerp, Belgium

Dr. Griensven was trained as a specialist in Internal Medicine in Leuven, Belgium and South Africa, with subsequent training in Epidemiology at the London School of Hygiene and Tropical Medicine. In 2004, he obtained his PhD degree after performing basic research on HIV in the Laboratory of Molecular Virology and Gene Therapy at the Rega Institute for Medical Research (Leuven, Belgium). For the last four years, he has been working in Africa, both as a clinician and researcher. Between 2004-2005, he was working for the Institute of Tropical Medicine-Antwerp (ITM-A) in Botswana, supporting the national antiretroviral treatment programme. In 2005-2007, he worked for the HIV programme of MSF in Rwanda. Subsequently, he joined Family Health International-Rwanda. Since October 2008, he has been a postdoctoral researcher at the ITM-A, working on neglected tropical diseases.

Combination therapy for visceral leishmaniasis: why, what, and where?

Johan van Griensven, Marleen Boelaert
Institute of Tropical Medicine, Antwerp, Belgium

Despite the progress of recent years, the number of drugs available for the treatment of visceral leishmaniasis remains limited, with antimonials (SSG), paromomycin (PM), amphotericin B (AmB), liposomal amphotericin B (L-AmB) and miltefosine (MF) as the main options. Costs, requirement of prolonged hospitalisation, and drug-toxicity are additional challenges for successful treatment and disease control/elimination. Combination therapy has been pursued for a number of reasons. First, the gradual increase in resistance to SSG in the Indian subcontinent has demonstrated the risk of emergence of drug resistance with monotherapy. Combination therapy could be a means to prevent/delay drug resistance, as has been successfully employed for malaria, tuberculosis, and HIV. Second, combination therapy could improve treatment efficacy for complicated cases, like HIV-coinfection. Third, combining two drugs could allow for the reduction of treatment duration and/or total drug doses, resulting in lesser toxicity, higher compliance, less burden on the health system, and, by reducing overall costs, a more cost-effective option. The main combinations currently under consideration in India are L-AmB + MF, L-AmB + PM, MF + PM. L-AmB + SSG and SSG + PM combinations are being studied in Africa. The first Phase 2 results from India revealed several short combination therapies of low dose L-AmB and MF (7-14 days) that merit further exploration. Over the next few years, efficacy and safety results from several trials of combination therapies will become available, which hopefully will provide a number of safe and effective options. However, other factors will be important in determining which combination therapy to select within a given context. Regional differences in drug susceptibility will have to be considered. Local health infrastructure and capacity will determine the feasibility and effectiveness of specific drug combinations (eg, hospitalisation, effective contraception while exposed to MF). Cost-effectiveness assessments will need to be conducted to decide on the most rational choice. It will require long term observation to determine whether combination therapy truly prevents resistance.

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Dr. Manica Balasegaram
Clinical Project Manager, DNDi, Geneva, Switzerland

Dr. Balasegaram manages DND*i*'s clinical research projects for the treatment of visceral leishmaniasis in East Africa. He has a background in internal/ emergency medicine. Prior to joining DND*i* in January 2008, he was Head of the Manson Unit, a medical research and implementation unit of Médecins Sans Frontières (MSF) – UK and has worked in the field in Uganda, Sudan, the Republic of Congo, Ethiopia, and India. Dr. Balasegaram has clinical and research experience in tropical medicine, including malaria, sleeping sickness, and visceral leishmaniasis. He was the Principal Investigator at Um el Kher, one of the two Sudan sites involved in the DND*i* paromomycin trial for the treatment of visceral leishmaniasis.

The use of combination therapies for managing primary visceral leishmaniasis

There are few therapeutic options registered for visceral leishmaniasis. These include liposomal/ amphotericin B, antimonials (sodium stibogluconate or SSG/ glucantime), miltefosine and paramomycin. All have limitations that include price, feasibility, safety, efficacy, and drug resistance.

Antimonials are cheap (20 USD per treatment) and given intramuscularly. However, SSG efficacy has declined in India to below 70% due to drug resistance. Efficacy in Africa and South America remains good, but treatment is long (maximum 30 days), adding to hospital and patient costs.

Amphotericin B requires intravenous usage (15 injections in 30 days) and is associated with nephrotoxicity. The liposomal formulation (AmBisome) is safe and effective, but prohibitively expensive. Even at a preferential price (20 USD per vial) for the public/ not-for-profit sector in the developing world, monotherapy is over 300 USD (40kg adult) and is given as staggered intravenous doses over 20 days to one month.

Paromomycin (PM) is a cheap (15 USD per treatment) antibiotic that has been shown to be effective and relatively safe for VL in India. It offers a real alternative in areas of antimony resistance. However, treatment still requires three weeks of daily intramuscular injections. Moreover, efficacy in Sudan (the principal endemic country of Africa) is much lower than that of India, and the drug is not likely to be effective against *L.chagasi* and *L.infantum*.

Miltefosine is the first available oral anti-leishmanial drug. It is expensive, but is now available at a preferential price of 65 USD per adult treatment. It has been demonstrated to be effective and reasonably safe in India, where it is registered. However, it requires a 28-day treatment course, and with some (usually minor) gastrointestinal toxicity, this may affect compliance. Resistance through the LDMT transporter has been shown *in vitro* and *in vivo* in mice. Efficacy in South America and Africa has not been firmly established.

These problems can be addressed by the development of combination treatments. Treatments that are currently under/ planned for evaluation include SSG & PM (for 17 days), AmBisome & miltefosine (7-14 days), AmBisome & PM (for 10 days), AmBisome & SSG (for 10 days). AmBisome is given as a one dose infusion (5-10 mg/kg), with the advantage of being cheaper, safe, and effective. The single 5 mg/kg dose is over 90% efficacious in India. These combinations offer to minimise toxicity, delay development of resistance, improve feasibility, and remove some opportunity costs, providing an effective option in the treatment and control of VL.

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Wednesday, February 4, 2009
Room A2: 11.00-13.00

"Challenges for and Potential in the Early-Stage R&D Pipeline to Develop New Antileishmanial Drugs"

There are few drugs currently registered to treat visceral leishmaniasis (VL), a disease with 500,000 new cases each year (the majority of which are currently occurring in India and Sudan) and which kills 60,000 people each year. The limitations of these current treatments include toxicity, need for hospitalisation, growing resistance, and high costs. New and improved treatments are needed.

The priority for DNDi's drug development programme in VL is an oral, safe, effective, low-cost, and short-course (10-day) treatment that could replace current treatments, thereby improving and simplifying current case management. Ideally, this treatment will be effective against all forms of the disease and be adapted for use in rural health centres. In order to develop such a treatment, a large amount of research must be coordinated and time must be invested, as there is high attrition in the drug development process.

This symposium will cover current opportunities, including emerging antileisihmanial approaches and technologies from early-stage discovery research identifying potential antileishmanial compounds to a disease-specific lead optimisation consortium led by Advinus, one of DNDi's Indian partners, to develop the most 'druggable' candidates. Challenges, including the variability of the *Leishmania* species causing the disease and drug sensitivity testing, will also be discussed.

Symposium Chairs

Simon L. Croft, PhD
Professor of Parasitology, Head of the Department of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, UK

Dr. Croft trained as a parasitologist at the Liverpool School of Tropical Medicine and spent post-doctoral periods researching anti-parasite drug mechanisms and the transmission of African trypanosomiasis, before moving onto research on anti-protozoal chemotherapy. His expertise and knowledge on anti-protozoal chemotherapy was developed while working for five years with the Wellcome Research Laboratories, Beckenham, UK in the 1980s. Following his return to academia, Dr. Croft focused his research on the identification and evaluation of novel drugs and formulations for the treatment of kinetoplastid diseases and malaria. This research included projects on miltefosine, AmBisome, and topical paromomycin, all of which reached clinical trials for the treatment of leishmaniasis. Other research interests include drug-immune response interactions and PK PD relationships in leishmaniasis and malaria. From 2004 to 2007, he was the first R&D Director of the Drugs for Neglected Diseases initiative (DNDi), Geneva.

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Kasim Mookhtiar, PhD
Chief Scientific Officer and Business Head, Drug Discovery, Advinus Therapeutics, India

Kasim Mookhtiar is a co-founder of Advinus Therapeutics Pvt Ltd, a Tata Enterprise, and heads Advinus' Drug Discovery at Pune, India. Dr. Mookhtiar, a native of Mumbai, obtained the 5-year integrated MS in Chemistry at the Indian Institute of Technology, Bombay, a PhD at Florida State University, USA in Biochemistry, Protein Chemistry, Enzyme Kinetics and Inhibition, and completed postdoctoral studies at Yale University School of Medicine in Molecular Biology and Structural Biology (2D NMR). He then joined the Metabolic Diseases Drug Discovery group at the Bristol-Myers Squibb Pharmaceutical Research Institute in Princeton, NJ, USA, where he worked from 1992 to 2003. He pioneered the group's Diabetes and Obesity programmes, after which he formed and led the Department of Aging Research in Drug Discovery, a novel and cutting edge area for both basic and applied research. Prior to co-founding Advinus, he was Vice President, New Drug Discovery Research, at Ranbaxy Laboratories Limited, where he led a team of over 200 scientists from multiple disciplines.

"Challenges for and Potential in the Early-Stage R&D Pipeline to Develop New Antileishmanial Drugs"

Chaired by Drs. Croft and Mookhtiar

Topic	Speaker
Current and emerging approaches in antileishmanial research, with focus on Amphotericin B	**Denis Martin, PhD** Drugs for Neglected Diseases *initiative* Geneva, Switzerland
High-content/high-throughput screening for the discovery of new anti-leishmanial drugs	**Lucio Freitas-Junior, PhD** Institut Pasteur Korea Seoul, South Korea
Identifying the 2-substituted quinolines as potential treatment of leishmaniasis	**Alain Fournet, PhD** Director of Research Institut de Recherche pour le Développement (IRD) Paris, France
Experimental models for lead optimisation of novel antileishmanial agents	**Sunil Puri, PhD** Central Drug Research Institute Lucknow, India
Developing and optimizing the 2-substituted quinolines for the treatment of leishmaniasis	**Vadiraj Gopinath, PhD** Advinus Therapeutics Bangalore, India
Variation of Leishmania species causing visceral leishmaniasis in East Africa	**Dr. Asrat Hailu** Faculty of Medicine, Addis Ababa University, Addis Ababa, Ethiopia
Discussion / Q&A	**Audience**

Denis Martin, PhD
Senior Project Manager, DNDi, Geneva, Switzerland

Dr. Martin joined DND*i* in September 2006 as a senior project manager focusing on discovery and preclinical stage projects. Denis Martin earned his PhD in Physiology from the University of Grenoble and completed a postdoctoral fellowship at the University of South Alabama in the US. He previously served as the Vice President, Project Management at Pierre Fabre Laboratories. He has more than 20 years of experience in drug discovery and development at several international pharmaceutical companies, including Sanofi-Synthelabo. In his various roles, Dr. Martin has supervised the development of drugs for a wide range of therapeutic indications. These developments led to numerous registrations in France, Europe, or the United States.

Emerging approaches in antileishmanial research: focus on Amphotericin B

There has been significant improvement in the number of treatments available for VL during the past decade, with both new drugs and new formulations of old drugs either recently approved or under clinical assessment. Amphotericin B, under various formulations, has become one of the most efficient treatments for VL. The standard formulations (oily suspension) have limitations related to side effects. AmBisome, a liposomal formulation has overcome these limitations, but its cost and stability are serious limits to its wide-spread use. Recently, new formulations have emerged and are approved or under clinical development in India. However, their intravenous route of administration is still a barrier for appropriate use in the field. Studies aimed at replacing the lipid-based component with a narrow molecular weight polymer are ongoing, with the goal of developing a soluble complex, cheaper, and exhibiting increased thermal stability. The polymers can also prevent the systemic toxicity of AmB to which they are conjugated, still allowing the drug intracellular delivery.

Over the past months, two new formulations of amphotericin B – phospholipid-based cochleates and a lipid-based form with enhanced gastrointestinal tract absorption – have been reported to show activity as antifungals when administered orally in animal models. Early reports suggest that they also exhibit activity in murine models of visceral leishmaniasis. This presentation will review the ongoing activities in this highly active field.

Lucio Freitas Junior, PhD
Systems Biology of Pathogens, Institut Pasteur Korea, Seoul, South Korea

Dr. Freitas Junior is the leader of the Systems Biology of Pathogens Group at Institut Pasteur Korea. In 1999, he received his PhD in Microbiology, Immunology and Parasitology from the Federal University of São Paulo School of Medicine, Brazil, for his studies of *T. cruzi*. Dr. Freitas Junior performed his post-doctoral training at the Institut Pasteur, studying the antigenic variation in *Plasmodium falciparum* until 2003. He then served as a visiting professor in the University of São Paulo/ UNIFESP- Brazil Department of Microbiology, Immunology and Parasitology from 2003 until 2004. Dr. Freitas Junior's group is developing visual high-throughput screening assays to aid in the discovery of new drugs for malaria and leishmaniasis.

High-content/high-throughput screening for the discovery of new anti-leishmanial drugs

Jair Siqueira-Neto[1], Jiyeon Jang[2], Gyong Seon Yang[1], Seunghyun Moon[3], Jonathan Cechetto[2], Auguste Genovesio[3], Thierry Christophe[2], and **Lucio Freitas-Junior**[1]
[1]Systems Biology of Pathogens, [2]Screening Technology and Pharmacology and [3]Image Mining, Institut Pasteur Korea, Seoul, South Korea

High-content screening combined with high-throughput screening (HCS/HTS) and automated image analysis considerably speed up the drug discovery process and allow for the screening of a large number of compounds in complex phenotypic assays involving whole cells.

Aiming to develop new anti-leishmanials, we have adapted *Leishmania donovani* intramacrophagic amastigote culture to a HCS/HTS assay as a cellular model for leishmaniasis. We optimised infection of the human macrophage cell line THP-1 by *L. donovani* metacyclic promastigotes in order to obtain very high yields of amastigote-infected macrophages. The infected culture was seeded onto 384-well plates and incubated in the presence of serially diluted miltefosine or amphotericin B, as positive controls, and in the absence of drugs, as negative controls. After incubation period, parasites and cells were fixed, and DNA was stained with Draq 5 for reading in the automated confocal Opera (Evotec). Infection rates were assessed by an in-house built algorithm for the counting of *L. donovani* infected macrophages and the number of amastigotes per macrophage. Countings were normalised in relation to negative controls, thus obtaining confident and unbiased data on the leishmanicidal activity of the compound. The algorithm also simultaneously evaluated the cytotoxicity of compounds by analysing the viability of macrophages, thus eliminating false positive conditions. This assay was validated in the high-throughput format with 15 thousand points, including positive and negative controls as well as non-infected macrophages. Currently, we are screening 200,000 drug-like small compounds from a chemically diverse library, using the assay and the algorithm described above. We thank the Drugs for Neglected Diseases *initiative* for financial support.

Alain Fournet, PhD
Institut de Recherche pour le Développement (IRD), Paris, France

Dr. Fournet, a chemist-pharmacognosist, is the Director of Research, at the Institut de Recherche pour le Développement (IRD) in France, where he has worked since 1971. He received a PhD in Natural Sciences from the Faculty of Sciences of the University of Paris 11 in 1977, and in Pharmaceutical Sciences from the Faculty of Pharmacy of the University of Paris 11 in 1991. Dr. Fournet has extensive international experience, spending six years in the Congo, six years in French Guyana, eight years in Bolivia, and four years in Paraguay. His main research interest is in finding new antiparasitic drugs from plants used in traditional medicine to treat parasitic diseases, such as leishmaniasis and Chagas disease. Since 2000, Dr. Fournet has continued his research in the Faculty of Pharmacy of Paris 11 with the aim of analysing plant or crude extracts for their biological activity, isolating and quantifying their active molecules, and determining the structure of these molecules, in collaboration with several South American and South Pacific partners. He has 120 international publications and seven patents.

Identifying 2-substituted quinolines as potential treatment of leishmaniasis

IRD researchers conducted ethno-pharmacological studies in South America. These scientists, working with researchers from the French National Centre for Scientific Research (CNRS), the University of Paris-Sud, and the Institut Pasteur, have thus discovered and studied alkaloids of the quinoline chemical family with *in vitro* and *in vivo* antiparasitic properties. The quinolines, obtained by chemical synthesis, are analogues of quinolines initially isolated from *Galipea longiflora* (Rutaceae). In order to select the most active molecule (the least toxic and the easiest to synthesise), about 150 substituted quinolines were prepared and tested *in vitro* on different parasites, particularly those responsible for the cutaneous and visceral forms of leishmaniasis.

Further experiments were performed in order to choose the most promising compound as a potential drug candidate for the development of a new oral therapy. Two of these compounds were selected for their biological activity, their safety, and their ease of synthesis: 2n-propyl-quinoline (PRO) and the other, a propenyl chain functionalised at the position ether by an alcohol (OH).

Research work and development of these compounds active against leishmaniases are planned with the particular aim of perfecting their production on an industrial scale, especially to assess the pharmaceutical drugability of compounds PRO (salt) and OH, and also to select relevant formulations to secure their rational evaluation in animal models. The pharmacokinetic profiles of these new formulations and some toxicological studies have been performed (administration, distribution, and metabolism).

Recently, IRD and the Drugs for Neglected Diseases *initiative* (DND*i*), a non-profit product development partnership, have entered into a synergistic agreement to identify and develop new promising drug candidates against visceral leishmaniasis.

Sunil K Puri, PhD
Deputy Director and Head, Parasitology Division, Central Drug Research Institute, Lucknow, India

Dr. Puri is a research scientist at the Central Drug Research Institute, Lucknow with over 35 years of experience in experimental chemotherapy of parasitic infections including malaria and leishmaniasis. His research focuses on preclinical drug discovery, drug resistance, and immunoprophylaxis against parasitic infections and parasite biology in experimental laboratory models. Dr. Puri has been responsible for setting up the primate anti-malaria screening models, extensively employing laboratory-selected drug resistant rodent models. During the last 15 years, Dr. Puri has been actively involved in the development of second generation synthetic endoperoxide derivatives as alternatives to artemisinine based drugs, one of which has successfully completed preclinical studies. He is currently involved in studies on the mechanisms of drug resistance against artemisinin derivatives. Dr. Puri is also actively associated with DND*i*'s drug discovery consortiums for new therapeutic interventions for leishmaniasis and human African trypanosomiasis and has been associated as expert consultant with TDR and DND*i*. He has co-authored more than 140 peer-reviewed publications in international scientific journals and has more than 20 patents to his credit.

Experimental models for lead optimisation of novel antileishmanial agents

Sunil K Puri and Suman Gupta
Division of Parasitology, Central Drug Research Institute, Lucknow, India

An estimated 12 million people throughout the world suffer from the kinetoplastid disease leishmaniasis. Available therapeutic interventions for leishmaniasis have several limitations, including drug induced toxicity, emergence of resistant isolates, need for parenteral administration, and poor activity against some forms of the causative organism.

Convenient and reproducible assays, with acceptable predictive potential and capable of screening large numbers of compounds, are vital to support concerted efforts towards synthesis and lead optimisation with new prototypes. In the mammalian host, *Leishmania* parasites exist as 'amastigotes' that replicate within the macrophage cells. Currently available experimental models for selection of candidate antileishmanials rely mainly on screening of potential compounds in parasite multiplication assays, both *in vitro* and *in vivo.* Models designed to closely reflect the situation *in vivo* are labor-intensive and expensive, since they require an intracellular macrophage-amastigote system.

Availability of *Leishmania* cell lines expressing reporter genes (Luciferase /GFP) has opened up new possibilities for the development of ideal drug discovery assay systems. Drug discovery facilities at CDRI have developed *Leishmania donovani* cell lines expressing the firefly luciferase reporter gene (luc) as a part of an episomal vector, and established the suitability of these cell lines for *in vitro* screening of antileishmanial agents. The system has been adapted to evaluate compounds in a 96-well microplate format and is being employed for optimisation of leads by a consortium supported by the Drugs for Neglected Diseases *initiative*. A comparison of pre- & post-treatment parasite load, as determined in repeat biopsy samples from *L.donovani*-infected Golden hamsters, is the preferred criteria for *in vivo* efficacy validation.

Vadiraj Gopinath, PhD
Advinus Therapeutics, Bangalore, India

Dr. Gopinath is currently the Assistant Director of Advinus Therapeutics, a Tata Enterprise, in Bangalore, India. In his role, he has led the infrastructure development of 20 modular labs and the process development for the company's agro division. Dr. Gopinath received his MSc in Organic Chemistry and his PhD in Chemistry from the University of Mysore, Mysore, India. Dr. Gopinath then held the position of Research Officer in the R&D Division of GlaxoSmithKline Pharmaceuticals (India) Ltd from 1995 until 2002. To further his training, in 2002, he accepted a post-doctoral fellowship at the University of California, San Francisco in drug discovery of cystic fibrosis correctors. Dr. Gopinath re-entered industry in 2003, joining Aurigene Discovery Technologies Limited, Bangalore, India where he served as a scientist in their Medicinal Chemistry Group and as a project team leader for development of kinase inhibitors.

Developing and optimizing the 2-substituted quinolines for the treatment of leishmaniasis

Chimanines - structurally simple 2-substituted quinolines - were isolated by Fournet *et al.* in the early 90s from *Galipea longiflora*, a plant traditionally used by the Chimane Indians of Bolivia to treat cutaneous leishmaniasis. These products were eventually demonstrated to be active against *Leishmania* and *Trypanosoma cruzi* models in *in vitro* assays, and showed activity in murine models of the disease. Based on these early results, a focused analogous library of 200 2-substituted quinoline compounds was synthesised. These were tested *in vitro* against the intracellular form of *Leishmania donovani* at the Central Drug Research Institute, Lucknow. The initial optimisation strategy for the 2-substituted quinolines focused on optimisation of ring substitution, side chain, and semi-masking of double and triple bonds as fused rings to minimise non-specific reactions. These modified quinolines were significantly more effective than the parent compounds and a few compounds have shown >90% parasite killing at 3.0 µM. Metabolic stability, which is a known liability of this series, has been improved through the introduction of halogen substituents in more than ten compounds. The most promising compounds have been re-synthesised (1g scale) and will be assessed in a stringent hamster model of the disease.

Prof Asrat Hailu
Faculty of Medicine, Department of Microbiology, Immunology and Parasitology (DMIP), Addis Ababa University, Addis Ababa, Ethiopia

Prof Asrat Hailu is the Professor of Immunoparasitology and Head of the Department of Microbiology, Immunology and Parasitology at the Faculty of Medicine of Addis Ababa University (AAU). Engaged in leishmaniasis research and control activities in Ethiopia since 1982, he has served as Head of the *Leishmania*sis Research Unit of AAU for over ten years. Prof Hailu leads the *Leishmania*sis Research Group in Ethiopia, which has played a key role in setting up diagnostics and treatment programmes for leishmaniasis patients in both central and peripheral treatment centres. His main research interests are diagnostics, treatments, and vaccines for leishmaniasis.

Variation of *Leishmania* species causing visceral leishmaniasis in East Africa

The East/Horn of Africa is the epicentre of visceral leishmaniasis (VL) in Sub-Saharan Africa. Endemicity, often sporadic, is a characteristic feature of the disease in this region; however, historic epidemics have claimed the lives of many thousands in Sudan, Kenya, Somalia, and Ethiopia.

The species of phlebotomine sandfly involved in transmission depends on the two distinct ecologies of the disease in the region; 1) termite hill associated *Phlebotomus martini* and *P. celiae*, and 2) *P. orientalis* harbored by the black cotton soils of *Acacia-Balanites* woodlands.

Based on the multi-locus enzyme electrophoresis (MLEE) technique, the species of *Leishmania* causing visceral leishmaniasis in sub-Sahara Africa are *L. donovani*, *L. infantum,* and *L. archibaldi*. The latter two species are restricted to northern Ethiopia and eastern Sudan, whereas *L. donovani* is found in all foci. The validity of MLEE for identification of East African *Leishmania donovani* complex has been questioned (Jamjoom *et al*, 2004; Zemanova *et al*, 2004; Kuhls *et al*, 2005). Based on population genetic analyses, the non-existence of *L. archibaldi* and the absence of *L. infantum* in sub-Saharan Africa have been emphasised.

In an ongoing clinical trial of paromomycin (PM) in East Africa, significant geographical differences were observed in the efficacy of the drug, which prompted the researchers to study the molecular polymorphism within *Leishmania* species causing VL in the region. Geographical clustering of parasite populations (genetic isolation) was hypothesised to contribute to the observed variability of PM efficacy; and the distinctness of the two ecotypes of the disease.

In this study, 111 clinical isolates of *Leishmania* from VL patients (53 Sudan, 58 Ethiopia) were analysed by PCR, RFLP, and nucleotide sequences using four genetic markers, (i.e., ITS-1 sequences of ribosomal DNA, mini-exon sequences, repetitive DNA sequences (LEG), and CpbEF). By multi-locus analysis of RFLP and sequence patterns, genetic homogeneity of isolates in Southern Ethiopia and a contrasting heterogeneity in northern Ethiopia and eastern Sudan were found. Further, possible putative hybrids of *L. donovani* and *L. major* were discovered in eastern Sudan, where the overall diversity was also the largest.

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