



TRYLEIDIAG PRESS REVIEW

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TropIKA: Tropical Diseases Research to Foster
Innovation & Knowledge Application



EVENTS HIGHLIGHTS

7th Annual East African Regional Workshop: Cell Biology of Protozoan Parasites

*July 6th-19th 2008
Morogoro, Tanzania*

Sokoine University and Seattle Biomedical Research Institute are partnering with the American Society for Cell Biology to convene a special workshop on the Cell Biology of Protozoan Pathogens. An international faculty will lead a two-week workshop to train graduate students and young scientists from Africa in basic and applied research on protozoan pathogens, including malaria parasites and trypanosomes.

Especially outstanding students selected to participate will receive support for their travel, room and board. Applications should be received no later than **4 April 2008**. Applicants should include an abstract (1 page only) describing research that the student has performed or would like to perform on some aspect of protozoan pathogens.

More information: http://www.sbri.org/training/workshop_2008.asp

International Conference on Drug Design and Discovery for Developing Countries

*July 3rd-5th 2008
Trieste, Italy*

The aim of the Conference is to evaluate the state of the art of drug design methodologies and frontier applications. Particular focus will be given to drugs for diseases widely spread in developing countries (tropical and poverty-related diseases). Attention will be given to the presentations of researchers from developing countries and collaborative programmes. The Conference will include a poster session and discuss possible joint initiatives to be considered for inclusion in future ICS-UNIDO programmes.

More information: <http://www.ics.trieste.it/Portal/News.aspx?id=242>

2008 Global Ministerial Forum on Research for Health: Call for Abstracts

*November 2008
Bamako, Mali*

"Today, we have no architecture for global research for health," say representatives of the Bamako 2008 Steering Committee in a Comment published in *The Lancet*. Bamako 2008 will provide a unique platform for ministers of health, science and technology and social development to identify and discuss research priorities to tackle global health and development challenges.

The 2008 Global Ministerial Forum will assess progress over the last 20 years and commitments from earlier conferences. It subsumes the Global Forum's 2008 meeting, Forum 12. Bamako 2008 will look at current challenges and place health research and innovation within the wider context of research for development. While political momentum for strengthening research in and by low- and middle-income countries is growing, much remains to be done.

The three key objectives of the Forum are to:



- **Strengthen leadership** for health, equity and development
- **Engage all relevant constituencies** in research and innovation for health
- **Increase accountability** of research systems

More information:

http://www.globalforumhealth.org/Site/004_Annual%20meeting/000_Bamako%202008/002_Home.php

Congress 70th Anniversary of IPK, VII Cuban Congress of Microbiology and Parasitology, IV National Congress of Tropical Medicine

*From 8th to 11th December 2008
Havana, Cuba*

Last 7 December 2007, during the Closing Ceremony of the successful VIII Central America and Caribbean Congress of Parasitology and Tropical Medicine, held in Havana, Cuba, we had the pleasure of officially declaring the beginning of the activities related to the 70th Anniversary of the foundation of the 'Pedro Kourí' Tropical Medicine Institute (IPK). This Cuban institution, having at present an international scope, was founded on 8 December 1937 by Professor Pedro Kourí Esmeja. Nowadays, the work carried out by this center is not only related to Tropical Medicine and Parasitology, but also to research and human resources formation in Medical Microbiology, Infectology, Epidemiology of Communicable Diseases and to Social investigations.

As part of this group of activities, we have decided to hold the **Congress 70th Anniversary of IPK**, jointly with the **VII Cuban Congress of Microbiology and Parasitology**, and the **IV National Congress of Tropical Medicine**, from 8-11 December 2008, in Havana. The Congresses will deal with several important topics related to infectious and parasitic diseases. For this reason, we are inviting all the parasitologists, bacteriologists, mycologists, virologists, infectologists, zoonologists, tropicalists, and those specialists working on other related disciplines who may be interested in these topics, in order to present and discuss our experiences and results about this fascinating world of sciences.

More information: <http://www.ipk.sld.cu/eventosipk/cong2008/index.htm>

International Engagement Awards: Engaging with Global Health Research –The Wellcome Trust

International Engagement Awards support projects with grants of up to £30 000 that aim to achieve some or all of the following:

- to strengthen the capacity of people in developing countries to facilitate public engagement with health research
- to stimulate dialogue about health research and its impact on the public in a range of community and public contexts in developing countries
- to investigate and test new methods of engagement, participation, communication or education around health research
- to promote collaboration on engagement projects between researchers and community or public organisations
- to support Wellcome Trust funded researchers in developing countries in engaging with the public and policy makers.



Projects could involve:

- communities and members of the public (particularly those affected by or involved in health research)
- science communicators, health and science journalists
- healthcare professionals, educators, field workers, community workers
- policy and decision makers.

More information:

<http://www.wellcome.ac.uk/Funding/Public-engagement/Grants/International-Engagement-Awards/index.htm>



RESEARCH NEWS

A determination of the steady state lysosomal pH of bloodstream stage African trypanosomes.

McCann AK, Schwartz KJ, Bangs JD.

Department of Medical Microbiology & Immunology, University of Wisconsin School of Medicine & Public Health, Microbial Sciences Building, 1550 Linden Drive, Madison, WI 53706, USA.

Mol Biochem Parasitol. 2008 Feb 15

The lysosomal/endosomal system of African trypanosomes is developmentally regulated and is important in the pathogenesis associated with infection of the mammalian bloodstream. Long considered to be a target for drug development, the internal pH of the lysosome has been variously reported to range from <5.0 to >6.0. We have refined a flow cytometric technique using a pH-sensitive probe that specifically targets the lysosome, tomato lectin:Oregon Green 488 conjugate. The probe is delivered to the lysosome with fidelity, where it is shielded against external pH. Measurement of fluorescent output in the presence and absence of lysomotropic agent (NH₄)Cl then allows precise titration of steady state lysosomal pH (4.84±0.23). Using bafilomycin A1 to inhibit acidification we demonstrate that this method is responsive to pharmacological perturbation of lysosomal physiology. This work should facilitate future studies of the lysosomal function in African trypanosomiasis, as well as other parasitic protozoa.

Communicable diseases in the immigrant population attended to in a tropical medicine unit: Epidemiological aspects and public health issues.

Manzardo C, Treviño B, Gómez I Prat J, Cabezos J, Monguí E, Clavería I, Luis Del Val J, Zabaleta E, Zarzuela F, Navarro R.

Tropical Medicine and International Health Unit "Drassanes", Institut Català de la Salut, Av. Drassanes 17-21, 08001 Barcelona, Spain.

Travel Med Infect Dis. 2008 Jan-Mar;6(1-2):4-11.

For geographical and historical reasons, Spain is receiving an increasing number of immigrants. The aim of this study was to evaluate some epidemiological aspects and the main public health issues of communicable diseases in Barcelona's immigrant population. From 2001 to 2004, a population of immigrants from tropical, subtropical regions and Eastern Europe was attended to in our centre. Each patient was offered a complete screening for tropical and common diseases. The prevalence and demographical characteristics of eight diseases with a potential risk of transmission in our setting were studied: latent and active tuberculosis, syphilis, human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), Chagas disease, *Giardia intestinalis* and *Entamoeba histolytica/Entamoeba dispar*. In all, 2464 immigrants mainly from sub-Saharan Africa were seen. Among the patients who underwent the screening, 46.5% had a positive tuberculin skin test (10mm), incidence of active tuberculosis was 324.7/100,000 immigrants in the period of the study, 6.4% had a



positive syphilis serology, 7.7% had a positive HBsAg, 3.1% had a positive serology for HCV and 2.8% were HIV positive, 41 patients from Latin America with risk factors for American Trypanosomiasis were screened for Chagas disease by immunofluorescence assay and 34% had a positive result; 5.4% of stools parasitological tests were positive for *G. intestinalis*; 4.2% for *E. histolytica*/*E. dispar*. Communicable diseases in immigrant population could lead to emerging and re-emerging infections in the European Union with important issues for public health. European countries may have to establish guidelines for screening of infectious diseases in immigrants from low-income countries.

Diagnosis, Management and Treatment of Chronic Chagas' Heart Disease in Areas Where *Trypanosoma cruzi* Infection Is Not Endemic.

Gascón J, Albajar P, Cañas E, Flores M, Gómez I Prat J, Herrera RN, Lafuente CA, Luciardi HL, Moncayo A, Molina L, Muñoz J, Puente S, Sanz G, Treviño B, Sergio-Salles X; Working Group of the second workshop on "Imported Chagas' Disease, a New Challenge in Public Health". Consensus document of the Spanish Society of Tropical Medicine and International Health (SEM-TSI).

Secció Medicina Tropical-Centre Salut Internacional. IDIBAPS. Hospital Clínic. Barcelona. España. jgascon@clinic.ub.es.

Enferm Infecc Microbiol Clin. 2008 Feb;26(2):99-106. [Article in Spanish]

Chagas' disease, or American trypanosomiasis, is a parasitic zoonosis found only in the Americas. Under natural conditions, *Trypanosoma cruzi* is transmitted by insects belonging to different species of *Triatoma*. However, several routes of transmission that do not involve insect vectors have also been described, such as transmission via blood products or transplantation of infected organs, and vertical transmission. At present, the number of people infected with Chagas' disease worldwide is estimated to be about 10-12 million. The process of urbanization in Latin America and migratory population movements from endemic countries have led to the disease being diagnosed in non-endemic areas. It is estimated that 20-30% of individuals infected with *T. cruzi* will develop symptomatic heart disease at some point during their lives. The specific differential characteristics of chronic chagasic cardiopathy, lack of knowledge of the disease among many healthcare workers, and the fact that arrhythmia or sudden death is frequently the first manifestation of disease all make it essential that diagnostic and therapeutic protocols for the disease are developed and disseminated. The aim should be to improve patient care by increasing understanding of the condition by physicians and other healthcare professionals who may be involved in its detection and treatment.

The anti-oxidant defence response in individuals with the indeterminate form of Chagas disease (American trypanosomiasis).

Pérez-Fuentes R, Torres-Rasgado E, Salgado-Rosas H, Zamora-Ginez I, Sánchez-Guillén MC.

Laboratorio de Investigación en Fisiopatología de Enfermedades Crónicas, Centro de Investigación Biomédica de Oriente, Instituto Mexicano del Seguro Social, km 4.5 Carretera Federal Atlixco-Metepec, Puebla, C.P. 62340, Puebla, Mexico; Facultad de Medicina, Benemérita Universidad Autónoma de Puebla, 13 Sur 2901 Colonia Volcanes, Puebla, C.P. 72000, Puebla, Mexico.



Ann Trop Med Parasitol. 2008 Apr;102(3):189-197.

In previous studies in animal models, *Trypanosoma cruzi*-induced oxidative stress and damage have sometimes been controlled by the host's anti-oxidant defence responses. The role of the anti-oxidant defence responses, such as the activities of the anti-oxidant enzymes glutathione peroxidase (GPx) and superoxide dismutase (SOD), in protection against inflammation and damage have now been investigated in humans infected with *T. cruzi*. The subjects were 32 asymptomatic but seropositive individuals with the indeterminate form of Chagas disease, 18 symptomatic and seropositive patients with the chronic disease, and 50 seronegative and apparently healthy controls. The inflammatory process was explored using serum concentrations of tumour necrosis factor (TNF) and NO. The serum concentrations of GPx in the patients in the indeterminate phase of infection were similar to those in the controls but much higher than those in the chronic cases ($P=0.001$). The serum concentrations of SOD in the patients in the indeterminate phase of infection were not only significantly higher than those in the cases of chronic Chagas disease ($P=0.0004$) but also significantly higher than those in the controls ($P<0.001$). The seropositive subjects had significantly higher serum concentrations of TNF and NO than the controls ($P<0.01$ for each) and the cases of chronic Chagas disease had significantly higher serum concentrations of TNF and NO than the subjects with the indeterminate form of the disease ($P<0.01$ for each). It therefore appears that the host's anti-oxidant defence responses (at least in terms of elevated concentrations of SOD) may inhibit inflammation during the indeterminate phase of Chagas disease.

The effects of bee (*Apis mellifera*) venom phospholipase A2 on *Trypanosoma brucei brucei* and enterobacteria.

Boutrin MC, Foster HA, Pentreath VW.

Centre for Parasitology and Infectious Diseases, Biomedical Sciences Research Institute, School of Environment and Life Sciences, University of Salford, The Crescent Salford, Lancs M5 4WT, United Kingdom.

Exp Parasitol. 2008 Feb 9

The potential role of phospholipases in trypanosomiasis was investigated using bee venom phospholipase A2 (bvPLA2) as a model. The effects of bvPLA2 on the survival of *Trypanosoma brucei brucei*, 2h and 12h cultures of *Enterobacter cloacae*, *Escherichia coli*, *Citrobacter freundii* were studied. About 1mgml⁻¹ bvPLA2 was trypanocidal after 30min. Some growth occurred at lower concentrations up to 2h after treatment but viability decreased up to 8h. Even very low concentrations of bvPLA2 (10⁻¹²mgml⁻¹) had some trypanocidal activity. Bee venom PLA2 was bactericidal to 2h bacterial cultures but bacteriostatic to 12h ones. Minimum bactericidal concentrations were 10⁻⁵-10⁻⁶mgml⁻¹. The results showed that bvPLA2 had significant trypanocidal and antibacterial effects on Gram-negative bacteria. The relationship to events occurring during infection is discussed. Phospholipases may play a role in increased endotoxin levels in trypanosomiasis.

Inhibitory Effects on Cytochrome P450 Enzymes of Pentamidine and Its Amidoxime Pro-Drug.

Bürenheide A, Kunze T, Clement B.

Department of Pharmaceutical Chemistry, Pharmaceutical Institute, Christian-Albrechts-University of Kiel, Kiel, Germany.



Basic Clin Pharmacol Toxicol. 2008 Mar 16

Pentamidine is an antimicrobial drug, intravenously used in the treatment of trypanosomiasis, leishmaniasis or pneumocystis pneumonia. To elucidate potential drug interactions with pentamidine and N,N cent-dihydroxypentamidine, respectively, the cytochrome P450 (CYP450) inhibitory properties of these compounds were determined. The study was performed in vitro by using human liver microsomes and marker substrates of several CYP450 isoenzymes. Marker activities were investigated by high-performance liquid chromatography in presence of known selective inhibitors or at different concentrations of pentamidine and N,N cent-dihydroxypentamidine, respectively. No or only minor influence on CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4 marker activities could be observed, suggesting that neither of the tested substances would exert a significant effect on hepatic CYP450 isoenzymes responsible for the metabolism of co-administrated drugs in vivo. However, in vivo studies are needed before final conclusions can be drawn.

Kinesin Motor Domain of Leishmania Donovanii as future vaccine candidate.

Dey A, Sharma P, Redhu NS, Singh S.

Department of Laboratory Medicine, All India Institute of Medical Sciences, New Delhi-110029, India; Immunology Group, International Centre for Genetic Engineering and Biotechnology, New Delhi-110067, India.

Clin Vaccine Immunol. 2008 Mar 19

Visceral Leishmaniasis (VL) is one of the important parasitic diseases placing approximately 350 million people at risk. Due to non-availability of an ideal drug, development of a safe, effective and affordable vaccine could be a solution for control and prevention of this disease. The present study was carried out to examine the immunological potential of kinesin protein from the microtubule locus of *Leishmania donovani* as suitable vaccine candidate. In-silico analysis of this region revealed clusters of MHC-I & II binding epitopes in its motor domain region. A recombinant protein was expressed from this region and named as rLvacc. The antigenicity and immunogenicity studies of this protein by western blot analysis revealed that rLvacc is strongly recognized by sera from acute VL patients. En route for its immunogenicity, the peripheral blood mononuclear cells (PBMC) from cured VL patients were separated and lymphocyte proliferation assay was carried out in presence of rLvacc. After lymphocyte proliferation, the pooled culture supernatant was assayed for anti- rLvacc antibody titers using ELISA. The results showed that IgG2 subtype antibodies were predominant while IgG1 subtype antibodies were produced in very low titers. On the basis of these ex-vivo preliminary findings, its immunogenicity was studied in Balb/C mice. Vaccination with the DNA construct generated good cellular immune response with significant increase in IFN-gamma and IL-2 cytokines levels (Th-1), but no increase in IL-4 levels (Th-2). Taken together, our findings suggest that kinesin motor domain region of *L. donovani* could be a potential vaccine candidate against visceral leishmaniasis.

Dendritic Cell Differentiation State and Their Interaction with NKT Cells Determine Th1/Th2 Differentiation in the Murine Model of Leishmania major Infection.

Wiethe C, Debus A, Mohrs M, Steinkasserer A, Lutz M, Gessner A.



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J Immunol. 2008 Apr 1;180(7):4371-81.

Recent reports demonstrated that dendritic cells (DC) sense inflammatory and microbial signals differently, redefining their classical subdivision into an immature endocytic and a mature Ag-presenting differentiation stage. Although both signals induce DC maturation by up-regulating MHC class II and costimulatory molecules, only TLR signals such as LPS are able to trigger proinflammatory cytokine secretion by DCs, including Th1-polarizing IL-12. Here, we explored the murine *Leishmania major* infection model to examine the CD4(+) T cell response induced by differentially matured DCs. When partially matured TNF-DCs were injected into BALB/c mice before infection, the mice failed to control *L. major* infection and developed a Th2 response which was dependent on IL-4R α signaling. In contrast, injections of fully matured LPS+CD40-DCs induced a Th1 response controlling the infection. Pulsing DCs with a lysate of *L. major* did not affect DC maturation with TNF- α or LPS+anti-CD40. When the expression of different Notch ligands on DCs was analyzed, we found increased expression of Th2-promoting Jagged2 in TNF-DCs, whereas LPS+CD40-DCs up-regulated the Th1-inducing Delta4 and Jagged1 molecules. The Th2 polarization induced by TNF-DCs required interaction with CD1d-restricted NKT cells. However, NKT cell activation by *L. major* lysate-pulsed DCs was not affected by blockade of the endogenous glycolipid, suggesting exchange with exogenous parasite-derived CD1 glycolipid Ag. In sum, the differentiation stage of DCs as well as their interaction with NKT cells determines Th1/Th2 differentiation. These results have generic implications for the understanding of DC-driven Th cell responses and the development of improved DC vaccines against leishmaniasis.

Comment on: Cutaneous leishmaniasis in Nepal: *Leishmania major* as a cause.

Kalra NL, Arya SC.

A-38, Swashtya Vihar, Delhi, India.

Trans R Soc Trop Med Hyg. 2008 Mar 17

Distribution of sand flies in El-Nekheil province, in Al-Madinah Al-Munawwarah region, western of Saudi Arabia.

El-Badry A, Al-Juhani A, Ibrahim EK, Al-Zubiany S.

Faculty of Medicine, Cairo university, Cairo, Egypt
aymanbb@hotmail.com

Parasitol Res. 2008 Mar 19

An entomological survey for sand flies was conducted at an area of cutaneous leishmaniasis-El-Nekheil in Northeast Al-Madinah Al-Munawwarah, Saudi Arabia. Standardized sampling with Centers for Disease Control (CDC) light traps and sticky traps was employed to determine monthly trends in species composition, density, sex ratio, and reproductive status and *Leishmania* infection rate of vector sand flies. A total of 621 sand flies were collected from March 2006 to November 2007. Six



species representing two genera were identified, three *Phlebotomus* species: *P. papatasi*, *P. sergenti*, and *P. bergeroti*; and three *Sergentomyia* species: *S. antennata*, *S. sergenti*, and *S. shewtzi*. *Phlebotomus papatasi* was the predominant anthropophilic species found and comprised more than 70% of the sand fly population. A population peak (June) was observed for this species. The density of *P. papatasi* intra-domiciliary was higher than extra-domiciliary stations and inflated by a greater proportion of female flies. Of 189 dissected *Phlebotomus* females, 43% were blood-fed. No *Leishmania* parasites were found. The proportion of gravid *P. papatasi* increased progressively during the 5-month period from May to September and averaged 38%. Proportions of gravid flies may be a valid indicator of the physiological age and epidemiologic importance of the vector sand fly population at this focus.

Treatment assessment by monitoring parasite load in skin biopsies from patients with cutaneous leishmaniasis, using quantitative nucleic acid sequence-based amplification.

Van der Meide WF, Peekel I, van Thiel PP, Schallig HD, de Vries HJ, Zeegelaar JE, Faber WR.

KIT Biomedical Research, Royal Tropical Institute, Amsterdam, The Netherlands.

Clin Exp Dermatol. 2008 Mar 16

Background. Current diagnostic methods for cutaneous leishmaniasis (CL) have low sensitivity or are not useful for treatment follow-up. We previously described the quantitative nucleic acid sequence-based amplification (QT-NASBA) method as a sensitive and specific assay for detection and quantification of *Leishmania* parasites in skin biopsies. This assay could be a valuable instrument for monitoring response to treatment of CL and identifying treatment failures at an early stage. **Aim.** QT-NASBA results of skin biopsies at the end and 6 weeks after treatment from patients with proven CL on various treatment regimens were compared with clinical outcome. **Methods.** The QT-NASBA assay measured the parasite load in skin biopsies before, at the end and 6 weeks after treatment. The results were compared with treatment outcome (clinical cure, delayed healing response or treatment failure) up to 6 months after treatment. **Results.** In total, 137 skin biopsies were obtained from 53 patients. A positive QT-NASBA result 6 weeks after treatment was significantly associated with treatment failure/delayed healing up to 6 months ($P < 0.001$). The positive predictive value (PPV) was 100% and the negative predictive value (NPV) was 92% (95% CI 82-100%). QT-NASBA results at the end of treatment and clinical outcome showed a less significant association ($P < 0.05$), with a PPV of 46% (95% CI 16-75% and an NPV of 89% (95% CI 79-99%). **Conclusions.** The QT-NASBA assay is a useful instrument to monitor parasite load in skin biopsies of patients with CL 6 weeks after treatment and can help to predict clinical outcome.

Visceral leishmaniasis in pregnancy - the role of amphotericin B.

Topno RK, Pandey K, Das VN, Kumar N, Bimal S, Verma RB, Siddiqui NA, Singh D, Kumar R, Kumar P, Ranjan A, Das P, Sinha PK.

Rajendra Memorial Research Institute of Medical Sciences, Agamkuan, Patna - 800007, Bihar, India.

Ann Trop Med Parasitol. 2008 Apr;102(3):267-70.



Pregnancy enhances the innate immune response in experimental cutaneous leishmaniasis through hormone-modulated nitric oxide production.

Osorio Y, Bonilla DL, Peniche AG, Melby PC, Travi BL.

*Department of Medicine, University of Texas, Health Science Center, San Antonio, Texas, USA
Centro Internacional de Entrenamiento e Investigaciones Medicas-CIDEIM, Cali, Colombia
Research Service, Department of Veterans Affairs Medical Center, South Texas Veterans Health Care System, San Antonio, Texas, USA*

J Leukoc Biol. 2008 Mar 17

The maintenance of host defense during pregnancy may depend on heightened innate immunity. We evaluated the immune response of pregnant hamsters during early infection with *Leishmania (Viannia) panamensis*, a cause of American cutaneous leishmaniasis. At 7 days post-infection, pregnant animals showed a lower parasite burden compared with nonpregnant controls at the cutaneous infection site ($P=0.0098$) and draining lymph node ($P=0.02$). Resident peritoneal macrophages and neutrophils from pregnant animals had enhanced *Leishmania* killing capacity compared with nonpregnant controls ($P=0.018$ each). This enhanced resistance during pregnancy was associated with increased expression of inducible NO synthase (iNOS) mRNA in lymph node cells ($P=0.02$) and higher NO production by neutrophils ($P=0.0001$). Macrophages from nonpregnant hamsters infected with *L. panamensis* released high amounts of NO upon estrogen exposure ($P=0.05$), and addition of the iNOS inhibitor L-N⁶-(1-iminoethyl) lysine blocked the induction of NO production ($P=0.02$). Infected, nonpregnant females treated with estrogen showed a higher percentage of cells producing NO at the infection site than controls ($P=0.001$), which correlated with lower parasite burdens ($P=0.036$). Cultured macrophages or neutrophils from estrogen-treated hamsters showed significantly increased NO production and *Leishmania* killing compared with untreated controls. iNOS was identified as the likely source of estrogen-induced NO in primed and naïve macrophages, as increased transcription was evident by real-time PCR. Thus, the innate defense against *Leishmania* infection is heightened during pregnancy, at least in part as a result of estrogen-mediated up-regulation of iNOS expression and NO production.

Present situation of vector-control management in Bangladesh: A wake up call.

Mondal D, Alam MS, Karim Z, Haque R, Boelaert M, Kroeger A.

Parasitology Laboratory, Laboratory Sciences Division, International Centre For Diarrhoeal Disease Research, Mohakhali, Dhaka 1212, Bangladesh.

Health Policy. 2008 Mar 12

OBJECTIVES: Kala-azar or visceral leishmaniasis is one of the major vector-borne diseases in Bangladesh. The disease is transmitted by sandfly. The incidence of the disease, which has been increasing since the early eighties, must be reduced by taking adequate vector-control measures. The objective of the present study was to identify the favorable factors and the constraints of present vector-control management in Bangladesh. **METHODS:** Purposively selected senior entomologist and retired senior entomologist at central level, civil surgeons, entotechnicians, health inspectors and



spray men from kala-azar-endemic districts, community leaders, and NGO representatives were key informants of the study. A household survey to learn about knowledge and perceptions of the people about kala-azar vector was carried out, using a structured questionnaire, in 202 randomly selected households. RESULTS: Practically, there was no vector-control activity in the nine most kala-azar-endemic districts of Bangladesh. Inadequate human resources, lack of logistics, and unavailability of funds for vector control were the major constraints. Community perception about kala-azar vector was poor. However, the use of bednets in the community was high. No private organization was involved in kala-azar vector control. Knowledge of the spray men about the insecticide-spraying technique was also unsatisfactory. CONCLUSION: Kala-azar vector control in Bangladesh needs immediate attention of policy-makers and donors, otherwise, elimination of kala-azar from the country by 2015 may not be achievable.

Human resistance to African trypanosoma infections

Perez-Morga D.

Laboratoire de Parasitologie Moléculaire, Institute de Biologie et Médecine Moléculaires IBMM, ULB, Gosselies, Belgique. David.Perez-Morga@ulb.ac.be

African trypanosomes (prototype: *Trypanosoma brucei*) are protozoan flagellates that infect a wide range of different mammals. In humans, these parasites have to counteract innate immunity because human serum possesses efficient trypanolytic activity. Resistance to this activity has arisen in two *T. brucei* subspecies, termed *T. b. rhodesiense* and *T. b. gambiense*, allowing them to infect humans where they cause sleeping sickness in East and West Africa respectively. The study of the mechanism by which *T. b. rhodesiense* escapes lysis by human serum led to the identification of the trypanolytic factor, which turned out to be an ionic pore-forming apolipoprotein associated with some HDL particles.

Prodrugs for the treatment of neglected diseases.

Chung MC, Ferreira EI, Santos JL, Giarolla J, Rando DG, Almeida AE, Bosquesi PL, Menegon RF, Blau L.

Lapdesf - Laboratório de Desenvolvimento de Fármacos, Departamento de Fármacos e Medicamentos, Faculdade de Ciências Farmacêuticas - UNESP Rodovia Araraquara-Jaú Km 1, 14801-902, Brazil. chungmc@fcar.unesp.br

Molecules. 2007 Mar 19;13(3):616-77.

Recently, World Health Organization (WHO) and Medicins San Frontieres (MSF) proposed a classification of diseases as global, neglected and extremely neglected. Global diseases, such as cancer, cardiovascular and mental (CNS) diseases represent the targets of the majority of the R&D efforts of pharmaceutical companies. Neglected diseases affect millions of people in the world yet existing drug therapy is limited and often inappropriate. Furthermore, extremely neglected diseases affect people living under miserable conditions who barely have access to the bare necessities for survival. Most of these diseases are excluded from the goals of the R&D programs in the pharmaceutical industry and therefore fall outside the pharmaceutical market. About 14 million people, mainly in developing countries, die each year from infectious diseases. From 1975 to 1999, 1393 new drugs were approved yet only 1% were for the treatment of neglected diseases[3]. These numbers have not changed until now, so in those countries there is an urgent need for the design and synthesis of new drugs and in this area the prodrug approach is a very interesting field. It



provides, among other effects, activity improvements and toxicity decreases for current and new drugs, improving market availability. It is worth noting that it is essential in drug design to save time and money, and prodrug approaches can be considered of high interest in this respect. The present review covers 20 years of research on the design of prodrugs for the treatment of neglected and extremely neglected diseases such as Chagas' disease (American trypanosomiasis), sleeping sickness (African trypanosomiasis), malaria, sickle cell disease, tuberculosis, leishmaniasis and schistosomiasis.

Human IgG antibody response to *Glossina saliva*: an epidemiologic marker of exposure to *Glossina* bites.

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Am J Trop Med Hyg. 2008 May;78(5):750-3

The evaluation of human antibody response specific to arthropod saliva may be a useful marker of exposure to vector-borne disease. Such an immunologic tool, applied to the evaluation of the exposure to *Glossina* bites, could be integrated in the control of human African trypanosomiasis (HAT). The antibody (IgG) response specific to uninfected *Glossina fuscipes fuscipes* saliva was evaluated according to the vector exposure and trypanic status in individuals residing in an HAT-endemic area. A high level of anti-saliva IgG antibodies was only detected in exposed individuals, whether infected or not by *Trypanosoma brucei gambiense*. In addition, the evaluation of specific IgG response represented spatial heterogeneity according to studied sites. These results suggest that the evaluation of anti-saliva IgG could be an indicator of *Glossina* exposure and thus could be integrated in other available tools to identify populations presenting risks of HAT transmission.

Neglected diseases in the news: a content analysis of recent international media coverage focussing on leishmaniasis and trypanosomiasis.

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PLoS Negl Trop Dis. 2008 May 14;2(5):e234.

BACKGROUND: Although the pharmaceutical industry's "neglect" of neglected tropical diseases (NTDs) has been investigated, no study evaluating media coverage of NTDs has been published. Poor media coverage exacerbates the neglect. This study aimed to investigate, describe, and analyse international media coverage of "neglected diseases" in general and three specific NTDs-African trypanosomiasis, leishmaniasis, and Chagas disease-from 1 January 2003 to 1 June 2007. **METHODS:** Archives of 11 leading international, English-language media were searched. A content analysis was done, coding for media organisation, date, author, type of report, slant, themes, and "frames". Semi-structured interviews with journalists and key informants were conducted for further insight. **PRINCIPAL FINDINGS:** Only 113 articles in a 53-month time period met the inclusion criteria,



with no strong trends or increases in coverage. Overall, the BBC had the highest coverage with 20 results, followed by the Financial Times and Agence France Presse. CNN had the least coverage with one result. The term "neglected diseases" had good media currency and "sleeping sickness" was far more widely used than trypanosomiasis. The disease most covered was leishmaniasis and the least covered was Chagas. Academic researchers were most commonly quoted as a main source, while the World Health Organization (WHO) and pharmaceutical industry were the least quoted. Journalists generally agreed NTDs had not been adequately covered, but said a lack of real news development and the need to cater to domestic audiences were major obstacles for NTD reporting. All journalists said health agencies, particularly WHO, were not communicating adequately about the burden of NTDs. CONCLUSIONS: Public health agencies need to raise priority for NTD advocacy. Innovative strategies, such as reporting grants or creating a network of voices, may be needed.

Novel Markers for Treatment Outcome in Late-Stage Trypanosoma brucei gambiense Trypanosomiasis.

Lejon V, Roger I, Mumba Ngoyi D, Menten J, Robays J, N'siesi FX, Bisser S, Boelaert M, Büscher P.

Clin Infect Dis. 2008 May 13.

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Background. To date, no biological marker for treatment outcome in human African trypanosomiasis (HAT) has been described. The accuracy of biological markers for prediction of treatment outcome of HAT caused by *Trypanosoma brucei gambiense* was assessed. Methods. Cerebrospinal fluid (CSF) white blood cell (WBC) count and immunoglobulin M (IgM), trypanosome-specific antibody, total protein, and interleukin-10 levels were determined before and up to 24 months after treatment of late-stage HAT. Results. Treatment failure was experienced by 48 of 260 patients. Pretreatment CSF WBC counts ≥ 102 cells/ μ L, IL-10 concentrations ≥ 37 pg/mL, LATEX/IgM end titers $\geq 1:32$, LATEX/T. b. *gambiense* end titers $\geq 1:2$, and protein concentrations ≥ 674 mg/L were associated with treatment failure. Six months after treatment, patients with CSF WBC counts ≤ 5 cells/ μ L were at low risk of HAT recurrence (negative predictive value, >0.93). After 12 months, the combination of CSF WBC count ≥ 8 cells/ μ L and LATEX/IgM end titer $\geq 1:4$ predicted treatment failure with 97% specificity and 79% sensitivity. Eighteen months after treatment, each marker accurately predicted treatment outcome. The combination of CSF WBC count ≥ 8 cells/ μ L and LATEX/IgM end titer $\geq 1:4$ was 100% specific for treatment failure after 18 and 24 months. Conclusions. HAT-affected patients with elevated pretreatment CSF levels of WBC, interleukin-10, IgM, trypanosome-specific antibody, and total protein are at risk of treatment failure. Six months after treatment, patients with CSF WBC counts ≤ 5 cells/ μ L can be considered to be cured. The assessment of a combination of CSF WBC count and LATEX/IgM level allowed accurate prediction of outcome beginning at 12 months after treatment, as did each individual marker at 18 months after treatment.

High Failure Rates of Melarsoprol for Sleeping Sickness, Democratic Republic of Congo.



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Emerg Infect Dis. 2008 Jun;14(6):966-967.

A retrospective chart review of 4,925 human African trypanosomiasis patients treated with melarsoprol in 2001-2003 in Equateur Nord Province of the Democratic Republic of Congo showed a treatment failure rate of 19.5%. This rate increased over the 3 years. Relapse rates were highest in the central part of the province.

High Levels of Genetic Differentiation between Ugandan *Glossina fuscipes fuscipes* Populations Separated by Lake Kyoga.

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PLoS Negl Trop Dis. 2008 May 28;2(5):e242.

BACKGROUND: *Glossina fuscipes fuscipes* is the major vector of human African trypanosomiasis, commonly referred to as sleeping sickness, in Uganda. In western and eastern Africa, the disease has distinct clinical manifestations and is caused by two different parasites: *Trypanosoma brucei rhodesiense* and *T. b. gambiense*. Uganda is exceptional in that it harbors both parasites, which are separated by a narrow 160-km belt. This separation is puzzling considering there are no restrictions on the movement of people and animals across this region. **METHODOLOGY AND RESULTS:** We investigated whether genetic heterogeneity of *G. f. fuscipes* vector populations can provide an explanation for this disjunct distribution of the *Trypanosoma* parasites. Therefore, we examined genetic structuring of *G. f. fuscipes* populations across Uganda using newly developed microsatellite markers, as well as mtDNA. Our data show that *G. f. fuscipes* populations are highly structured, with two clearly defined clusters that are separated by Lake Kyoga, located in central Uganda. Interestingly, we did not find a correlation between genetic heterogeneity and the type of *Trypanosoma* parasite transmitted. **CONCLUSIONS:** The lack of a correlation between genetic structuring of *G. f. fuscipes* populations and the distribution of *T. b. gambiense* and *T. b. rhodesiense* indicates that it is unlikely that genetic heterogeneity of *G. f. fuscipes* populations explains the disjunct distribution of the parasites. These results have important epidemiological implications, suggesting that a fusion of the two disease distributions is unlikely to be prevented by an incompatibility between vector populations and parasite.

Pentamidine dosage: a base/salt confusion.

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PLoS Negl Trop Dis. 2008 May 28;2(5):e225.

Pentamidine has a long history in the treatment of human African trypanosomiasis (HAT) and leishmaniasis. Early guidelines on the dosage of pentamidine were based on the base-moiety of the two different formulations available. Confusion on the dosage of pentamidine arose from a different labelling of the two available products, either based on the salt or base moiety available in the preparation. We provide an overview of the various guidelines concerning HAT and leishmaniasis over the past decades and show the confusion in the calculation of the dosage of pentamidine in these guidelines and the subsequent published reports on clinical trials and reviews. At present, only pentamidine isethionate is available, but the advised dosage for HAT and leishmaniasis is (historically) based on the amount of pentamidine base. In the treatment of leishmaniasis this is probably resulting in a subtherapeutic treatment. There is thus a need for a new, more transparent and concise guideline concerning the dosage of pentamidine, at least in the treatment of HAT and leishmaniasis.

Sleeping sickness in West Africa (1906-2006): changes in spatial repartition and lessons from the past.

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Trop Med Int Health. 2008 Mar;13(3):334-44.

OBJECTIVE: To review the geography and history of sleeping sickness (Human African trypanosomiasis; HAT) over the past 100 years in West Africa, to identify priority areas for sleeping sickness surveillance and areas where HAT no longer seems active. **METHOD:** History and geography of HAT were summarized based on a review of old reports and recent publications and on recent results obtained from medical surveys conducted in West Africa up to 2006. **RESULTS/CONCLUSIONS:** Active HAT foci seem to have moved from the North to the South. Endemic HAT presently appears to be limited to areas where annual rainfall exceeds 1200 mm, although the reasons for this remain unknown. There has also been a shift towards the south of the isohyets and of the northern distribution limit of tsetse. Currently, the most severely affected countries are Guinea and Ivory Coast, whereas the northern countries seem less affected. However, many parts of West Africa still lack information on HAT and remain to be investigated. Of particular interest are the consequences of the recent political crisis in Ivory Coast and the resulting massive population movements, given the possible consequences on HAT in neighbouring countries.

Identification of Leishmania parasites in clinical samples obtained from cutaneous leishmaniasis patients using PCR-RFLP technique in endemic region, Sanliurfa province, in Turkey.

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Parasitol Res. 2008 May 30. [Epub ahead of print]

Antroponotic cutaneous leishmaniasis (ACL) is an endemic disease and one of the major health problems in Sanliurfa province located in the southeastern region of Turkey. *Leishmania tropica* is confirmed as the causative agent of ACL in this region. In Sanliurfa city alone, the recorded total cases of ACL were 6,817 between 2001 and 2006. We aimed to determine the effectiveness of a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method for identification and differentiation of the *Leishmania* parasite in comparison to direct microscopic examination of clinical samples. The lesion exudates were collected from 51 ACL suspected patients and used for smear-slide preparations and DNA isolation. The isolated DNA was amplified by PCR, including primers selected on repetitive DNA for identification of a *Leishmania* subgenus, and the amplified DNA was restricted by *HaeIII* restriction endonuclease. The PCR-RFLP results showed that only *L. tropica* exists in this province. It is also determined that the positivity rate with PCR was higher (96%) than by microscopic examination (64%) in the diagnosis of ACL. Our results indicate that the PCR-RFLP method is more sensitive and specific for the detection and differentiation of agents of ACL in this area.



Political and regulatory

The impact of climate changes on neglected tropical diseases is itself neglected

March 4th

Source: TropIKA

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Former Vice President Al Gore, the Nobel Peace Prize winner for 2007, delivered a major speech on global warming at New York University Law School in September 2006, calling for an immediate freeze on carbon dioxide emissions to fight the effects of global warming. In his address he said, 'This is an opportunity for bipartisanship and transcendence, an opportunity to find our better selves and, in rising to meet this challenge, create a better brighter future.'

The potential impact of global warming on the transmission of the neglected tropical diseases has received insufficient attention from researchers. Most studies on the impact of global warming on the transmission of tropical diseases have focused on malaria, and an early estimate suggested that its epidemic potential may increase by 12–27% as a direct consequence of higher temperatures. Very few studies have been carried out regarding the neglected tropical diseases, although some reviewers have discussed the situation as regards vector-borne diseases. Most of the vector-borne diseases considered by these reviewers are neglected tropical diseases, including filariasis, leishmaniases, trypanosomiasis, schistosomiasis, and arboviral diseases, (e.g. dengue, yellow fever, Japanese encephalitis).

There is an urgent need for researchers to investigate further the potential impact of climate changes on the transmission of neglected tropical diseases. The findings of such research are required so that populations might be able to adapt or, if necessary, migrate to overcome increased risks for transmission of neglected tropical diseases caused by climate changes.

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TDR Business Plan 2008-2013 Visceral Leishmaniasis Elimination

Overall Objective

To develop intervention tools and generate evidence for influencing policies for elimination of visceral leishmaniasis.

Specific Objectives

- Play a stewardship role to define needs, priorities and provide technical guidance to research for elimination of visceral leishmaniasis.



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- Generate evidence on most cost-effective elimination strategies using optimal interventions across treatment and vector control.
 - Develop and evaluate new and improved diagnostics, drugs and combination therapies.
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Contact

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About the TropIKA

The Special Programme for Research and Training in Tropical Diseases (TDR) has established *TropIKA.net* as a global knowledge management electronic portal to share essential information and to facilitate identification of priority needs and major research gaps in the field of infectious diseases of poverty.

TropIKA is designed for the knowledge management component of the "Stewardship" function in the new *TDR Ten Year Vision and Strategy*, http://www.who.int/tdr/about/strategy/strategy_06.htm.

The new strategy will help focus global efforts on priority needs in infectious diseases research in disease endemic countries.

What Is TropIKA.net?

TropIKA.net (Tropical Disease Research to foster Innovation and Knowledge Application) is a web-based platform for the acquisition, review and sharing of current information and knowledge on:

- Public health research needs and scientific opportunities
- Research-based evidence in support of control and policy
- High profile research activities and control projects
- International research funding and support opportunities
- Potential innovations for interventions and control of infectious diseases of poverty.

Rationale for TropIKA.net

Priority research needs are unequally covered by the global research agenda. Several high-impact research areas are still neglected. There is a need to increase the engagement of disease-endemic countries in global research planning and agenda setting in infectious diseases which predominantly affect poor populations. Informed participation of disease endemic countries in the global research agenda setting is often prevented by limited access to scientific information and essential knowledge. Rapid advances in the field of information technology have made it possible to share and deliver information at higher speeds and lower costs and several initiatives aiming at enabling access to high quality, scientific information, via Internet, are now in place. However researchers and policy makers face the other problem of haphazard flow of scientific information for which they lack time to screen, awareness of what is relevant and essential for their domain of activities and skills for interpretation and application in health interventions.

Starting in 2004, the Special Programme for Research and Training in Tropical Diseases (TDR) with several partners, has carried out research on the needs of health researchers in order to find a solution to alleviate these problems. Conclusions from these research, survey and wide consultation with traditional and new stakeholders in infectious diseases of poverty underpin the development of this knowledge management platform (*TropIKA.net*). *TropIKA* is designed to enhance access and to share essential knowledge with health researchers and policy makers dedicated to improving control of infectious diseases of poverty.



Survey on needs of researchers in Infectious diseases of poverty

Several research, surveys and analysis conducted between 2004 and 2006 as part of efforts for developing *TropIKA.net* were also designed to gain a better understanding of how user needs, business model, and content would intersect to form the foundation of the platform. These activities included:

- **An online feasibility study.** In November 2004, TDR sponsored a follow-up to the initial feasibility study (conducted with AAAS in Jan-March 2004) to determine more precisely the requirement of the tropical disease research community for a proposed tropical diseases information web site. Of the 5,000 researchers who received the survey, 615 (roughly 13%) responded, providing a solid foundation for clarifying the content to be included in the *TropIKA* web site. In total 1,203 individual researchers responded to both surveys (March and November 2004). Some 71% of respondents had individual internet access with the incidence of shared computers and slow internet speed determined by the geographical region in which they were working. Asked to choose which information was essential, respondents selected: access to full text of journals (92%); research funding information (77%); research reports (67%); research news and related information (64%). This initial research has served as a key source of user research for the *TropIKA* platform.
- **Stakeholder interviews.** Dynamic Diagrams, a company to whom the information architecture design of the site was outsourced, interviewed five stakeholders, including members of the TDR Joint Coordinating Board, TDR communication and scientific staff, and the project manager of the WHO led Health InterNetwork Access to Research Initiative (HINARI) to assess organizational needs and expectations for *TropIKA*.
- **User interviews.** Four prospective users of the *TropIKA* site (three research scientists and one policymaker) were interviewed.
- **A review of web sites.** To gain a better understanding of the online landscape of which *TropIKA.net* would be a part, a number of existing web sites that might be considered either a model for or a prospective resource to include in the site were reviewed.
- **A Web Site Requirements Document.** Based on the findings from the activities above, a *Web Site Requirements Document* categorized the various *TropIKA* requirements in view of building the site

Based on these research, five business goals were identified:

1. Leverage existing articles and resources that are already online, offering a "one-stop shop" these material
2. Increase accessibility to full-text articles through collaboration with the HINARI initiatives, open access publishers (SciELO, PLoS) and the US, National Library of Medicine (PubMed)
3. Deliver information to users in a meaningful way. Present content in a way that has been sorted and consolidated by disease type, focusing on infectious diseases of poverty, and type of resources (scholarly literature, funding information, research reports, news, etc.)
4. Demonstrate unique value to users by providing original comprehensive and authoritative reviews and policy briefs on current research efforts in infectious diseases of poverty achieved by creating a dedicated Editorial Team guided by an international Editorial/Advisory Board.
5. Offer a new level of interactivity to users. The platform is expected to be an interactive venue for researchers and policy makers working in the field of diseases of poverty, through posting comments, moderated forums, blogs and communities of practice



The Primary goals of TropIKA.net are to

- Present up-to-date content in a context that makes sense for health researchers and policy makers
- Improve access to scientific information on infectious diseases of poverty
- Facilitate broad-based participation of disease-endemic countries in discussions and the formulation of current and emerging research priorities and agenda setting
- Provide health researchers and decision makers with a comprehensive resource about best practices and authoritative summaries of research findings that have implications for their efforts to meet the challenges of infectious disease control.
- Be used as an interactive knowledge platform for infectious diseases of poverty at health forums

Partners participating in the TropIKA.net initiative to date

- TDR (UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases)
- BIREME/PAHO/WHO, in Brazil: hosts and manages the portal
- HINARI: provides access to full text journals in specific countries
- The Global Health Library (GHL) and the Virtual Health Library (VHL)
- Public Library of Science Neglected Tropical Diseases (and PLoS in general) for sharing "open access" scientific content and technology
- SciELO journals and other open access journals

A glimpse at TropIKA.net information architecture

All content can be sorted by disease and then by types of resources:

- Research News
- Commissioned, Comprehensive Thematic Reviews
- Literature (research and review articles) with comments
- Virtual journals
- Policy and strategy briefs for infectious diseases of poverty
- Funding opportunities
- Networks (communities of practice, forums)
- Resources (training packages, factual databases, multimedia)
- Blogs