SYNERGY MEETING OF: FP7-HEALTH-2013-2.2.4-2
Drug Development for Neglected Parasitic Diseases

Modena 15-16th June 2016

ABSTRACTS BOOK

Subject: A-ParaDDisE project overview

Authors: Raymond J. Pierce

Organisation/Affiliation: CIIL, Inserm U1019 – CNRS UMR8204, Université de Lille, Institut Pasteur de Lille.

Consortium: Anti-Parasitic Drug Discovery in Epigenetics (A-ParaDDisE)

Abstract

Enzymes that "write" or "erase" epigenetic marks on chromatin are attractive targets for drug development in numerous pathologies, including Neglected Parasitic Diseases. Parasite-selective inhibitors may be designed to exploit key differences in parasite enzymes compared to human orthologues and species-specific sensitivities to the blocking of a particular enzyme activity can be exploited. These strategies are pursued during the A-ParaDDisE project, involving research teams in Europe, Brazil and Australia, targeting schistosomiasis, leishmaniasis, Chagas disease and malaria.

Subject: Project overview

Authors: Jane MacDougall

Organisation/Affiliation: IP Research Consulting SAS, Photeomix, Paris -France

Consortium: Kinetoplastid Drug Development: strengthening the preclinical pipeline (KINDReD)

Abstract:

The aim of KINDReD is to create a unique and powerful drug discovery platform with the common objective of advancing promising laboratory-driven discoveries into clinical utility.

•To implement a coherent (integrated) approach to populate and advance all stages of the anti-trypanosomatid drug pipeline.

•To establish an integrated global network of academic and industrial partners united by a central objective: to develop and apply innovative cutting-edge molecular and cellular tools that will enable us to populate and accelerate the preclinical pipeline for anti-kinetoplastid chemotherapeutics.

•To advance every aspect of the preclinical pipeline, by developing new technologies where necessary, from early target discovery, validation and screening through to advanced toxicology and animal testing.

•To bring forward one new Phase I clinical candidate for each trypanosomatid disease at the end or within a short time after the end of the project.

•In parallel, and where appropriate in partnership with likeminded bodies such as WHO, Wellcome Trust, DNDI etc. we will set up an association that will lobby industrial groups to take an active role in the further clinical development of our registered candidates (repurposed or new chemical entities) showing potency against these parasitic diseases after the conclusion of the funding period.

Subject: Project overview

Authors: Prof Maria Paola Costi

Organisation/Affiliation: Università di Modena e Reggio Emilia (UNIMORE)

Consortium: New Medicines for Trypanosomatidic Infections (NMTrypI)

Abstract:

NMTrypI project aims at obtaining new candidate drugs against Trypanosomatidic infections with appropriate efficiency from the lead phase to the final preclinical phase that are more accessible to patients. At least three main compound classes are developed: miltefosine derivatives, as multi target compounds, thiadiazoles derivatives and pteridines. Pteridine reductase and Dihydrofolate reductase are the main targets. A unified platform for compounds synthesis, animal studies and selection has been validated for compounds progression.

Subject: Project overview

Title : PDE4NPD: phosphodiesterase inhibitors to the NPD rescue?

Authors: Prof Dr Rob leurs

Organisation/Affiliation: Vrije Universiteit Amsterdam

Consortium: Phosphodiesterase Inhibitors for Neglected Parasitic Diseases (PDE4NPD)

Abstract:

The PDE4NPD project is an EU-funded platform to develop new chemical entities targeting parasitic PDEs. In this presentation the consortium as a whole will be introduced and the main approaches will be highlighted.

Title : Discovery of Anti-Trypanosomal and Anti-Leishmanial Compounds from Natural Sources for the NMTrypI Project

Authors: Stephen Wrigley,[1] Deepa Karunakaran,[1] Bethlehem Kebede,[1] Carolina B. Moraes,[2] Bruno S. Pascoalino,[2] Laura M. Alcantara,[2] Caio H. Franco,[2] Claudia P. Bertolacini,[2] Vanessa Fontana,[2] Kaliandra Goncalves,[2] Denise Pilger,[2] Tereza C. Lima,[2] Lucio H. Freitas-Junior,[2] Sheraz Gul,[3] Markus Wolf,[3] Asaad K.M.A. Ahmed[4]
Organisation/Affiliation: [1]Hypha Discovery Ltd., Uxbridge, Middlesex, UK; [2] Laboratório Nacional de Biociências (LNBio), Centro de Pesquisa em Energia e Materiais (CNPEM), Campinas-SP, Brazil; [3]Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Hamburg, Germany; [4]Medical Biochemistry Research Unit, Medicinal and Aromatic Plants Research Institute, National Center for Research, Khartoum, Sudan.
Consortium: NMTrypI

Abstract

To identify new anti-parasitic compounds from natural sources, Hypha's MycoDiverse™ library of fungal fermentation extracts and fractions together with an HPLC fraction library generated from extracts of Sudanese medicinal plants were screened in phenotypic assays against *Trypanosoma brucei*, *T. cruzi* and *Leishmania infantum*. The approach taken to prioritise and dereplicate hits will be described and progress in the assay-guided purification of compounds with promising properties presented.

Subject: Chemical library of small molecule modulators of epigenetic enzymes

Title : Chemistry of histone modifying enzyme inhibitors and focused libraries

Authors: Antonello Mai

Organisation/Affiliation: Sapienza University of Rome, Italy

Consortium: A-PARADDISE

Abstract

Epigenetic regulation of gene expression involves covalent modification of DNA or histones. Its aberrations can be reversed by the use of DNA methyltransferase, histone acetyltransferase, deacetylase, methyltransferase or demethylase inhibitors. We show here our library of epi-drugs, involving inhibitors or activators of virtually each known epigenetic target. They have been or will be studied for their effects in both human and parasite epi-targets, to assess their parasite-selectivity, the real challenge of the use of epi-drugs in parasites.

Title: Profiling of flavonol derivatives for the development of anti-trypanosomatidic drugs

Authors: Chiara Borsari and Maria Paola Costi

Organisation/Affiliation: UNIMORE

Consortium: NMtryPI

Abstract

Trypanosomatids are causative agents of Chagas' disease, sleeping sickness and Leishmaniasis. Starting from a natural products library, we combined a target-based screening on pteridine reductase 1 with a phenotypic screening on *Trypanosoma brucei*. Flavonols were identified as hits and a related library of sixteen compounds was synthesized and biologically evaluated. Crystallographic studies and docking analysis of PTR1 complexes allowed SAR elucidation. A wide range of *in-vitro* early ADME-Tox properties were assessed to guide compounds selection.

Title: 2-amino-1,3,4-thiadiazoles as PTR1 inhibitors for the treatment of Trypanosomiasis

Authors: **Pasquale Linciano and Maria Paola Costi**

Organisation/Affiliation: UNIMORE

Consortium: NMtryPI

Abstract

Pteridine reductase 1 (PTR1) is an enzyme responsible for the reduction of biopterin and folic acid in Trypanosomatidae spp. Several nonfolate compounds based on a thiadiazole core structure were investigated as parasitic PTR1 inhibitors. We solved the crystal structures of four TbPTR1-inhibitor complexes and used these to develop new thiadiazole derivatives. The compounds obtained display antitrypanosomal activity in vitro (phenotypic screening) and are able to synergize with methotrexate, a dihydrofolate reductase (DHFR) inhibitor.

Subject: Data Management

Title: Data management for NMTrypI and Synergy.

Authors: Wolfgang Mueller

Organisation/Affiliation: HITS Heidelberg

Consortium: NMTrypI

Abstract

NMTrypI data management is based on the openSEEK system. This system built in the FAIRDOM project for systems biology data management is open source, versatile, and extensible. It allows storage and cataloguing of any type of data, models, and experimental procedures, it is extensible to allow advanced visualisation and interaction with the data stored in SEEK.
We shortly describe the system and show how some examples on how the system is used in NMTrypI and for the Synergy projects and how we intend to interface with other systems.

Subject: Hit generation

Title : A-ParaDDisE: Targeting histone modifying enzymes for drug development.

Authors: Jamal Khalife

Organisation/Affiliation: CIIL, Inserm U1019 – CNRS UMR8204, Université de Lille, Institut Pasteur de Lille.

Consortium: A-ParaDDisE

Abstract

The objective of the A-ParaDDisE project is to develop new drugs against Neglected Parasitic Diseases based on optimized epigenetic inhibitors targeting histone modifying enzymes. One strategy pursued involves the phenotypic screening of focused inhibitor libraries against the four parasites studied in the project. Assays have been performed on more than 500 compounds, generating hits for all the parasites. The results will be presented.

Subject: Validation

Title : "Advancements of hits and targets towards the trinity "

Authors: Terry K Smith, Louise Major, Emily Dickie & Kindred consortium

Organisation/Affiliation: University of St Andrews, Scotland

Consortium: Kindred

Abstract

An overview of some of the targets that have been genetically and chemically validated.
A selection of potent inhibitory compounds found via various biophysical screening tolls as well as enzymatic assay and how these have been taken forward through the drug discovery pipeline.

Subject: Hit generation

Title : Complementation of protozoan and helminth phosphodiesterases in a model parasite, Trypanosoma brucei, allows rapid functional and pharmacological studies in a cellular system

Authors: Prof. Dr. Harry de Koning

Organisation/Affiliation: University of Glasgow, UK

Consortium: PDE4NPD

Abstract:

The PDE4NPD consortium aims to identify new cAMP phosphodiesterase (PDE) targets in pathogenic parasites and develop inhibitors for these enzymes. PDE-encoding genes were identified from parasite genomes and cloned from DNA or cDNA, as appropriate.

In order to assess catalytic activity and allow characterisation in a cellular system, the PDEs were expressed in a modified T. brucei strain conditionally dependent on the heterologous PDE expressed in it, as the essential T. brucei PDE-B1 is expressed only under control of a tetracycline-inducible promotor.

Title: Recombinant expression and 3D-structure analysis of epigenetic targets from eukaryotic parasites

Authors: Martin Marek, Tajith Shaik and Christophe Romier

Organisation/Affiliation: IGBMC-GIE, Illkirch, France

Consortium: A-ParaDDisE

Abstract

Epigenetic mechanisms underlie the morphological transformations and shifts in virulence of eukaryotic parasites, and therefore the targeting of epigenetics-driven cellular programmes represents a new therapeutic strategy how to control parasitic infections. Today, zinc-dependent histone deacetylases (HDACs) belong to the most explored epigenetic drug targets in eukaryotic parasites. Here, we describe optimized protocols for the large-scale overproduction and purification of recombinant HDAC8 from *Schistosoma mansoni* (smHDAC8). Finally, crystallographic analyses of smHDAC8 will be **presented**.

Title : Searching for novel drugs to treat schistosomiasis

Authors: Dr Carmen Gil

Organisation/Affiliation: The Spanish National Research Council (CSIC), Madrid

Consortium: PDE4NPD

Abstract:

The PDE4NPD consortium is searching for new drugs to treat schistosomiasis based on target- and phenotypic-based approaches. The target-based approach was focused on phosphodiesterases (PDEs) as innovative targets. A sequence analysis with different PDEs has been done in order to develop an accurate model for SmPDE to perform virtual screening campaigns and discover new hits.

The second approach was phenotypic screening from our library of PDE inhibitors (and analogues thereof), as a source of new hits.

Subject: Technologies: the large NTD platform

Title : IOTA & Phosphodiesterase R&D: providing FBDD and MIPS technology to underpin NPD drug discovery"

Author: Dr. David Bailey

Organisation/Affiliation: IOTA Pharmaceuticals, UK

Consortium: PDE4NPD

Abstract: IOTA is an SME dedicated to early-stage drug discovery in the anti-infective and oncology therapy areas. We deploy fragment-based drug discovery (FBDD) approaches, informed by biochemical, biophysical and molecular structure information, coupling this to mechanism-informed phenotypic screening (MIPS) for chemotype definition.

In the PDE4NPD programme, we have applied FBDD to generate new chemical series for PDE medicinal chemistry, and MIPS to explore novel lead/phenotype relationships.

Subject: Hit to Lead development

Title : HTS of epigenetic enzymes from parasites and follow-up testing of hit compounds

Authors: Johan Schultz

Organisation/Affiliation: Kancera AB

Consortium: A-ParaDDisE

Abstract

The A-PARADDISE project develops small-molecule inhibitors of parasitic enzymes involved in epigenetic processes against four Neglected Parasitic Diseases: schistosomiasis, malaria, leishmaniasis and Chagas disease. The strategy is target-based, and both virtual screening (VS) and high-throughput screening (HTS) approaches are employed to identify suitable starting points for chemistry development. In this talk, HTS and the follow-up testing of hit compounds will be described.

Subject: Presentation Hit ID

Title : "A GSK Contribution to NTD: Three Kinetoplastids Boxes"

Authors: J. M. Coterón (Cote)

Organisation/Affiliation: Kinetoplastid DPU, DDW-GSK

Consortium: None

Abstract

GSK aims to discover innovative medicines to combat NTDs working together with public and private partners. Since 2010, GSK devotes a full Drug Discovery Unit at Tres Cantos to Diseases of the Developing World under the "Open Innovation, Open Collaboration" principle. A recent GSK contribution is three compound sets identified from phenotypic HTS against parasites responsible for Visceral Leishmaniasis, Chagas disease and HAT. Each "box" contains around 200 high-value hits made available to the wider scientific community as an open resource for future lead discovery programmes to fight these three kinetoplastid diseases.

The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents

Title "Systems biology strategies for target and biomarker identification in Kinetoplastids."

Authors **Joachim Clos**

Affiliation: **Bernhard Nocht Institute for Tropical Medicine (BNI) -Hambourg**

Consortium: **NMTrypI**

Abstract

It is of utmost importance to identify the targets and biochemical pathways that are affected by lead drugs. In Kinetoplastid protozoa, with their complete lack of regulated RNA synthesis, this necessitates the use of non-RNA-based strategies, namely comparative proteome analysis, functional cloning, next generation sequencing, ribosome footprinting and in silico network building. Here we show how these basic research tools can be combined into a genome-wide search for lead targets, biomarkers and resistance pathways.

Subject: Hit-to-lead

Title : Structure-based design and bioguided optimization of epigenetic inhibitors for anti-parasitic therapy

Authors: Sippl, Wolfgang

Organisation/Affiliation: Martin-Luther-Universität Halle-Wittenberg

Consortium: A-ParaDDisE

Abstract

A novel approach for targeting eukaryotic parasites is to tackle their epigenetic machinery that is necessary for the extensive phenotypic changes during their life cycle. We identified S. mansoni histone deacetylase 8 (smHDAC8) for antiparasitic therapy.1-3 We present results from virtual screening, in vitro testing and X-ray studies of smHDAC8 inhibitors. Chemical optimization resulted in highly potent smHDAC8 inhibitors that are able to kill the parasite in cell cultures.

References:

1 M. Marek, S. Kannan, et al. Structural Basis for the Inhibition of HDAC8, a Key Epigenetic Player in the Blood Fluke Schistosoma mansoni. Plos Pathogen 9(9):e1003645, 2013.

2 S. Kannan, J. Melesina, et al. Discovery of Inhibitors of Schistosoma Mansoni HDAC8 by Combining Homology Modeling, Virtual Screening and In Vitro Validation. J Chem Inf Model, 54, 3005-19, 2014.

Title: Targeting the parasitic folate pathway by a structure-based drug design approach

Authors: Ina Poehner, Joanna Panecka, Talia Zeppelin, Rebecca C. Wade

Organisation/Affiliation: HITS gGmbH

Consortium: NMTrypI

Abstract

Dihydrofolate reductase (DHFR) is an established target providing crucial educts for DNA synthesis by folate reduction. Trypanosomatids appear resistant to DHFR inhibition due to a metabolic bypass via pteridine reductase 1 (PTR1) - a target for blocking the Trypanosomatid folate pathway.
We present a structure-based drug design approach involving mapping of target binding pocket properties (PTR1, parasitic DHFR) in comparison with off-targets, virtual screening, fragment-based design and lead optimization to discover selective folate pathway inhibitors.

Subject: Hit-to-lead

Title : PDE inhibitors as new therapeutic entries for Chagas diseases?

Authors: Prof. Dr. Iwan de Esch & Dr. Maria de Nazare Corrreia Soeiro

Organisation/Affiliation: Vrije Universiteit Amsterdam, NL / Fiocruz, Brazil

Consortium: PDE4NPD

Summary:

Current therapy for Chagas disease (CD) presents important limitations besides the epidemiological shift due to the migration of infected individuals to non-endemic areas, bringing to light the relevance of building private and academic efforts.
Fiocruz contributes to the identification of novel agents for CD performing phenotypic screens regarding the activity and selectivity of PDE inhibitors against different forms and strains of Trypanosoma cruzi (in vitro and in vivo) assessed through a standardized phenotypic flow chart, besides also contributing to target validation.

Subject: X-ray crystallography for NMTrypI

Title : Crystallographic contributions to design and development of antiparasitic drugs in the frame of NMTrypI consortium

Authors: Manuela Benvenuti, Lucia dello Iacono, Flavio di Pisa, Giacomo Landi, Cecila Pozzi, Stefano Mangani*

Organisation/Affiliation: University of Siena – Department of Biotechnology, Chemistry and Pharmacy

Consortium: NMTrypI

Abstract

X-ray crystallography contributions to a drug discovery program involve the description of new targets, the understanding of enzyme mechanism and inhibition and the discovery of new lead compounds. However, relevant advances can be achieved only by integrating different techniques and expertises like phenotypic screens, bioinformatics, proteomics, spectroscopy, biochemistry and chemical synthesis. The information provided by the structures of lead compounds bound to the targets chosen by the NMTrypI consortium will be analysed and critically reviewed.

Subject: Technologies: the large NTD platform

Title : The minimum information about a bioactive compound exemplified by the PDE4NPD and NMTrypI consortia compounds

Authors: Dr. Sheraz Gul

Organisation/Affiliation: Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Hamburg, Germany.

Consortium: PDE4NPD/ NMTrypI

Abstract:

Recent years have witnessed an expansion in the disciplines encompassing Drug Discovery outside the pharmaceutical industry [1,2]. An archetypal small molecule Drug Discovery project will aim to identify chemical starting points that modify the functions of genes, cells, or biochemical pathways. In some but not all instances, these functions may be linked to disease processes, and an opportunity will exist to further develop the chemical starting points into novel therapeutic agents. In small molecule Drug Discovery, the ultimate aim is to identify new therapeutics, an activity that has historically been conducted within the commercial sectors [3]. Screening using miniaturised microtitre plate formats remains the most widely utilised methodology for identifying novel chemical starting points that are capable of modulating target function in a meaningful, biologically relevant manner [4]. The active compounds identified from screening campaigns (Hits) would subsequently optimised to yield Lead and Candidate compounds with the latter entering clinical trials.

This presentation will discuss the strategies that have been adopted by the PDE4NPD and NMTrypI consortia to progress targets and the associated compounds from a small molecule therapeutic perspective. Particular focus will be given to compound profiles in terms of in-vitro off target liabilities, in-vitro toxicity and in-vitro ADME and safety profiles in order to improve their probability of progressing in the Drug Discovery value chain [5].

References

[1] Frearson JA and Collie IT. HTS and hit finding in academia - from chemical genomics to drug discovery. Drug Discov Today 2009;14:1150.
[2] Baker M. Academic screening goes high-throughput. Nat Meth 2010;7:787.
[3] Goodman M. Market watch: Pharma industry performance metrics: 2007-2012E. Nature Rev Drug Discov 2008;7:795.
[4] Macarron R, et al. Impact of high-throughput screening in biomedical research. Nat Rev Drug Discov 2011;10:188.
[5] Orchard S, et al. Minimum information about a bioactive entity (MIABE). Nat Rev Drug Discov 2011:10:661.

Subject: **Toxicity and ADME assays**

Title : **KINDRED ADME-Tox strategy.**

Authors: Roura, M., Kortazar, D., Valcarcel, M., Ramos, I.

Organisation/Affiliation: Innovative Technologies in Biological Systems SL (INNOPROT)

Consortium: KINDRED

Abstract

Drug development pipeline consists in a series of assays aimed to identify, validate and develop new therapeutic candidates. In each test, some molecules turn out to be under the acceptance criteria. Therefore, obtaining a potential hit is a very unlikely event. Typically the process starts with a high number of chemical entities that are firstly tested for efficacy in a suitable *in vitro* model. We propose a pipeline that includes the ADME-Tox analysis at an earlier stage, in order to use it for identification and validation of leads. In our opinion, this strategy would end up with better hits, optimizing the costs and resources in the process.

Subject: Lead to Drug

Title : "Miltefosine and similar compounds: Can we tell a better story?"

Authors: Theodora Calogeropoulou, Kyriakos Prousis, Marina Roussaki, Theano Fotopoulou, Pantelis Afroudakis, Georgios Magoulas and the NMTrypI consortium.

Organisation/Affiliation: National Hellenic Research Foundation, Institute of Biology,Medicinal Chemistry and Biotechnology, Athens, Greece

Consortium: NMTrypI

Abstract

Miltefosine, an alkylphosphocholine is currently the only oral drug available for the treatment of visceral and cutaneous leishmaniasis. However, at the therapeutically effective doses, severe gastrointestinal side effects and serious weight loss were observed while, teratogenicity remains a problem. We have demonstrated that ring-substituted alkylphosphocholines exhibit enhanced activity and reduced toxicity than miltefosine. In depth SAR studies led to the development of a phospholipid derivative possessing a drug lead profile.

Subject: **Pre-clinical studies**

Title : Pre-clinical studies using different animal models to discovery new drug against neglected disease.

Authors: Nuno Santarem, Anabela Cordeiro-da-Silva and Kindred&NmtrypI consorcia

Organisation/Affiliation: I3S/IBMC

Consortium: Kindred&NmtrypI

Abstract

Animal models are a pre-requisite in drug development before human clinical trials. Current animal models are used to investigate host–pathogen interactions, pathogenesis, Pharmacology: (pharmacokinetics / pharmacodynamics and toxicology/safety), *in vivo* maintenance of parasites and *in vivo* evaluation of drug candidates. Several models are used in drug development of new anti-trypanosomal: mice, golden hamster, dog and rhesus monkey. Advantages/disadvantages for different models used in drug development of negletected disease will be presented and discussed.

Subject: Pre-clinical studies

Title : Animal models in pre-clinical studies of NTD. Hamster and dog models of visceral leishmaniasis

Authors: María J. Corral, Juan J. Torrado, Mª Dolores Jiménez-Antón, Ana Isabel Olías, José Mª Alunda

Organisation/Affiliation: Universidad Complutense de Madrid, Instituto de Investigación Hospital 12 de Octubre, Madrid, Spain

Consortium: NMTrypI

Abstract

Development of a successful chemotherapeutic treatment for a human disease implies a number of complex and interactive steps including early safety/toxicity tests and predictive preclinical models. In visceral leishmaniasis, Syrian hamsters (*Mesocricetus auratus*) is an advanced rodent model of the human disease (e.g. chronicity). Dog is an excellent preclinical model for visceral leishmaniasis and also a target species (i.e. *Leishmania infantum*); thus clinical course, signs, lesions and outcome are very close to the human disease.

Subject: Animal models

Title: *Leishmania infantum* : Experimental infection in Non-Human Primates

Authors: Vasco Rodrigues, Sonia André, Calaiselvy Soundaramourty, Yasmina Fortier, Chloé Borde, Mireille Laforge, Bernard Krust, Jérôme Estaquier

Organisation/Affiliation: CNRS FR3636 Paris France

Consortium: Kindred

Abstract

Leishmania infantum causes a chronic infectious disease named visceral leishmaniasis (VL). Immunity fails to clear leishmania infection, ultimately leading to the chronic stage and can be fatal. We used rhesus macaques to decipher the immune events associated with parasite establishment and chronicity in particular in deep tissues. Our results provide evidence for the lack of splenic T follicular helper cell (Tfh) associated with a poor and short-lived production of *Leishmania*-specific antibodies. Further analyses have demonstrated the occurrence of exhausted T cells associated with the absence of parasite controls. Therefore, Non Human primates represent potent models to monitor new drug therapeutic interventions in relationship with immune response. Actually, we are evaluating the impact of miltefonis on parasite dissemination in deep tissues.

Subject: **Development of a Clinical Candidate for Chagas Disease**

Title **"Development of a Clinical Candidate for Chagas Disease"**

Authors **James H. McKerrow PhD,MD**

Affiliation: **University of California San Diego**

Consortium: **KINDReD**

Abstract

The Kindred Consortium has completed preclinical evaluation of a new drug for Chagas Disease targeting the major protease of Trypanosoma cruzi. This protease inhibitor has now undergone testing in rodents, dogs, and monkeys for PK/PD and safety. It is orally bioavailable, effective and safe up to 100mg/Kg in all species. The proposed human dose is 10mg/Kg for 20 days.

Subject: Complementary Methods for post-therapeutic monitoring

Title: Cellular Immunology insights beyond the benefits of etiological treatment of Chagas disease.

Authors: Martins-Filho, AO & Teixeira-Carvalho A.

Organisation/Affiliation: Grupo Integrado de Pesquisas em Biomarcadores, CPqRR, FIOCRUZ

Consortium: KINDReD

Abstract

Challenges for short/late post-therapeutic monitoring in Chagas disease relays on low sensitivity of parasitological/molecular tests and persistent/residual seropositivity. Complementary cellular immunology methods have been developed in FIOCRUZ-Brazil for Chagas disease post-therapeutic monitoring showing early/late qualitative benefits of treatment for immunological status towards a sustained pro-inflammatory profile counterbalanced by modulatory events, even when parasitological/serological cure is not achieved. Cellular immunobiomarkers should be considered during rational search of novel therapeutic targets for Chagas disease.

Subject: Clinical trials

Title : Clinical trials in disease endemic countries

Authors: Ole F. Olesen, Ph.D

Organisation/Affiliation: European & Developing Countries Clinical Trials Partnership

Consortium: None

Abstract

The European & Developing Countries Clinical Trials Partnership (EDCTP) supports clinical trials on poverty-related diseases (PRDs) and capacity development for clinical trials in sub-Saharan Africa. All phases of clinical trials (phases I to IV) for new or improved medical interventions, as well as advanced testing and validation of new diagnostic tools can be supported under the second EDCTP programme (EDCTP2), which runs from 2014-2024 and has received a financial contribution from the European Union of 683 million EUR on condition that the European Participating States mobilise a similar contribution. While the first phase of EDCTP only included the three major infectious diseases (HIV/AIDS, malaria and tuberculosis), the second program also covers neglected and emerging infectious diseases, and thereby provides an unprecedented European initiative to support the clinical development of new medical interventions against tropical diseases.

Subject: KINDReD Association

Title : "A GSK Contribution to NTD: Three Kinetoplastids Boxes"

Authors: Jane MacDOUGALL)

Organisation/Affiliation: KINDReD

Consortium: KINDReD

Abstract

The KINDReD ASSOCIATION, an independent, charitable body, was set up in 2016 with the purpose of supporting promising preclinical candidates against Neglected Infectious Diseases (NIDs) to enter early phase clinical trials. The initial aim will be to promote a healthy portfolio of new clinical candidates, as the well-recognised high attrition rates in clinical trials means that many drugs may succumb to safety and efficacy issues. The Association will initially sponsor the molecules resulting from the European Community's Seventh Framework Programme under grant agreement No.602773 (Project KINDReD), which reaches term in August 2016. However, it is open to receive other advanced molecules from any source, and also against other neglected infectious diseases, on the understanding that there is absolute adherence to open source drug discovery with full freedom to operate accompanying any eventual intellectual property rights. New partners are invited to join and contribute to building the strengths already established by the 14 international partners of the FP7 KINDReD consortium over the past three years. Together with new partners and new molecules we will combine our expertise and experience to provide accessible treatment for those who need it most.