EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

Exploratory Workshop Scheme

Standing Committee for the European Medical Research Councils (EMRC)

ESF Exploratory Workshop on

Multidisciplinary consortium for the development of effective, but non-toxic drugs against MDRTB and XDR-TB

Lisbon (Portugal), 30 November – 4 December 2010

Convened by:

Leonard Amaral, Stephen Gillespie and Dick van Soolingen

Local Organisers: Miguel Viveiros and Isabel Couto

SCIENTIFIC REPORT

Co-sponsored by

SANITATEM QUAERENS IN TROPICOS
INSTITUTO DE HIGIENE E MEDICINA TROPICAL
UNIVERSIDADE NOVA DE LISBOA

Executive summary:

The ESF Workshop EW09-007 was held at the Institute of Hygiene and Tropical Medicine, Universidade Nova de Lisboa, Rua Junqueira 100, 1349-008 Lisbon, Portugal, from 1-3 December 2010. The Workshop was organised with the intent of providing an atmosphere where discussions were to be encouraged and collaborations between the participants would be facilitated. To this extent, the surroundings selected were a small auditorium that accommodated 50 persons, with comfortable seats and proximity to the speaker. To further increase the needed collaborative atmosphere, lunches and dinners were held in small restaurants that provided good examples of Portuguese culture and cuisine. The number of participants totalled 23, eight females and 15 males, and came from Argentina, Austria, Denmark, France, Germany, Holland, Hungary, Ireland, Portugal, Spain, Turkey and the UK. Of these, 20 provided 30 minute presentations of their interests, work and involvement in studies of multi-drug resistant infections of tuberculosis, therapy, drug-discovery, and descriptions of expected collaborative work with identifiable participants. Because of the informal atmosphere of the surroundings and obvious willingness of the convenors to seek collaborative situations, many participants within the 3 day period of meetings and discussions, organised future collaborative projects in drug-discovery as well as participation in future ESF type of proposals, suggested by the ESF raporteur Professor B. Petrunov.

The main objective of the ESF Workshop EW09-007 was to provide the platform for interaction of European Scientists from a variety of disciplines for the formulation of a plan that may result in the creation of effective anti-MDR/XDR TB because the rates of active pulmonary tuberculosis in certain parts of Europe continue to rise. However, this is only the “tip of the iceberg” with respect to the impact of this serious infection. A far greater and more significant threat to the health status of Europe is the rising advent of multi-drug resistant tuberculosis (MDRTB) infections despite intense attention from the health authorities in European countries. Within the period of 2003-2007 there were more than 2500 cases of MDR-TB in the European Union, of which 10% were the more serious and expensive to treat XDR/ MDR TB.

The rising rate of new MDRTB cases in the past 15 years has not yet resulted in the development of any new and effective drug. Although there are many reasons for the absence of an effective response from the pharmaceutical environment, it must be said that hundreds of compounds are reported each year as having *in vitro* activity against MDRTB. Nevertheless, most of these compounds are toxic, and very few are shown to be active at the site where *M tuberculosis* resides; mainly within the non-killing macrophage of the human lung. If any compound is to be effective against intracellular *M. tuberculosis*, effective drugs must penetrate the pulmonary macrophage, reach the phagosome-encapsulated *Mycobacterium*, remain effective at this site and reach a concentration level that inhibits the replication of the micro-organism, and even better, kill it. This is a high demand for any drug, unless the design of the drug incorporates the qualities needed to be effective.

The group of participants selected for the ESF Workshop EW09-007 were consisted of infectious disease specialists, laboratory clinical mycobacteriologists who could assess and evaluate compounds for *in vitro, ex vivo* and *in vivo* activities against MDR/XDR Mtb, biochemists and chemists that specialised in chemical manipulation of active anti-TB drugs, plant chemists that isolated compounds with promising anti-TB properties, physiologists who were experts aspects of cellular infection produced by Mycobacterium tuberculosis, geneticists who applied molecular biological techniques for the

characterisation of antibiotic resistant strains of Mtb, structural biologists that could provide the basis for identification of drug sensitive component of a target molecule, and clinicians with experience in conducting clinical trials. In short, the group consisted of those specialists needed for a concerted, collaborative effort for rapidly obtaining drugs that could prove effective against MDR/XDR Mtb and which were devoid of any significant negative side effects.

The Agenda of the ESF Workshop EW09-007 therefore consisted of presentations by 20 of the participants that detailed what they could provide with respect to the main objective of the Workshop-namely, rapidly obtain compounds that could be evaluated for in vitro, ex vivo and in vivo activities against MDR/XDR Mtb and for those very active, non-toxic compounds, organise the needed clinical trials.

Conclusions: The results of the three day meeting indicated that the main objective of the ESF Workshop EW09-007 could be readily satisfied with follow-up collaborations made possible by proposals to be submitted to the ESF for Networking, Networks of Excellence, FP7/8 and possibly one for a Cost Action support.

2. Scientific content of the event

Wednesday 1 December 2010

Welcome: Leonard Amaral thanked the participants for attending and participating at the ESF Workshop EW09-007 especially at a time when they are busy with family activities in preparation for the holiday winter season. A special note was made that identified two individuals who were unable to attend: Firstly, Villy Frolund Thomsen, M.D. (Denmark) who, with Jette E Kristiansen, M.D. D.Sc. (participant from Denmark) was foremost responsible for many of the subjects that will be discussed concerning the application of common medicinal compounds for therapy of infectious diseases. Dr. Thomsen's active support during the early years (1980-1995) made it possible for studies that supported the use of non-antibiotics for reversal of antibiotic resistance and possible therapy of MDR infections. Secondly, Joseph Molnar, M.D., Ph.D., D.Sc. (Hungary) conducted the early studies showing that phenothiazines had the potential to cure a variety of therapeutically difficult bacterial infections. We are indebted to these physician-scientists for much of what will transpire during these three days of intensive discussions.
The participants received badges and a packet of material that consisted of addresses and telephone numbers of the Portuguese convenor and local organisers, maps of the region, the Agenda and Programme of the Workshop with scheduled presentations, writing utensils, pads and ticket for each of the three daily lunches and two daily coffee breaks of sufficient length to promote discussions.

Welcome: Prof Petrunov, M.D., Ph.D., raporteur for the ESF, provided a detailed presentation that identified and described the various programmes offered by the European Science Foundation some of which are supported by other European Commission programmes such as the Cost Action and FP7 programmes. His presentation included what he expected from the ESF Workshop EW09-007 in terms of scientific content as well as plans that would further the objectives of the Workshop. Finally, he provided a summary of the items that would constitute his report to the ESF.

Moderator of the programme of 1 December 2010: Leonard Amaral presented the rules for the participants and their presentations of no more than 25 minutes. The amount of time for discussion could vary depending upon the participation of the participants. During this first day, some of these discussion periods lasted over 30 minutes due to the interest and excitement generated by the presentations. This resulted in the extension of the day's presentations to 7 pm.
The following are the presentations made by the participants of the Workshop and brief summary of its contents.

"The role of the clinical TB laboratory in drug development." Professor Dick van Soolingen, Ph.D., Director of the TB National TB Reference Laboratories of The Netherlands presented a detailed description of what is expected from a TB laboratory for the evaluation of compounds for in vitro, ex vivo and in vivo activity against MDR and XDR Mtb. During his presentation he made it clear that there is a distinct problem for the definition that distinguishes XDR from MDR. Professor van Soolingen is involved in developing vitally needed laboratory facilities in areas of the world where such facilities do not exist or do not exist at the levels required for the identification and therapy of MDR/XDR TB infections. In particular, he described what constituted hospital and laboratory facilities in Central Asian countries where MDR/XDR TB is expected to kill many thousands this coming year. Lastly, he provided descriptions of essential laboratory methods, instrumentation, molecular biological tools needed for support of

programmes for control of TB, the identification, characterisation, antibiotic susceptibility of the causative organism and the support required during therapy of the TB infection. He suggested that a panel of MDR and XDR Mtb strains be designed for the evaluation of compounds obtained from the collaboration of the participant chemists. His presentation resulted in a question and answer period of 20 minutes.

"Geo-epidemiology of MDR/XDR TB." Nalin Rastogi, Ph.D., Director of TB laboratories of the Pasteur Institute, Guadalupe, France, presented a detailed programme for the genetic characterisation of MDR strains of *Mycobacterium tuberculosis* at the Global level. Because of the mobility of populations from areas of the globe where TB is still common place to areas where TB within the national population is initially infrequent, the spread of TB and its antibiotic resistant forms readily takes place. Plotting the movement of these strains from region to region and locale to locale, provides an important tool for understanding the spread of the infection, its evolution in terms of antibiotic resistance and virulence, and identification of effective drugs for therapy of given strain specific infections. Dr. Rastogi works closely with many TB laboratories of the world, including those directed by Dr van Soolingen. The question and answer period was extensive given the importance of genetic characterisation and the specialised tools and instrumentation required. Dr Rastogi proposed to create a panel of genetically characterised strains that represented 95% of the global distribution of such strains.

"Defining XDR TB at the genetic and molecular biology levels." Professor Isabel Portugal, Ph.D., University of Lisbon, presented her studies that genetically characterised XDR Mtb of the Lisbon, Portugal area, and demonstrated that resistance to specific antibiotics must be defined beyond that normally provided by the TB clinical laboratory for the identification of XDR TB patient, inasmuch as retrospective studies such as the ones she has conducted in Lisbon, show that XDR TB infections have been present for many decades and that with respect to Lisbon, Portugal, more than 50% of the MDR Mtb strains isolated during these decades are XDR. There is a distinct need for the identification of mutations relevant to the second line of defence agents used to treat MR and XDR TB. The discussion centered on molecular genetic methods for identification of mutations responsible for the XDR phenotype of clinical isolates and therefore the selection of targets that could be evaluated for drug discovery was proposed and this topic would be further covered by other presenters of the programme.

"Efflux pumps of *Mycobacterium tuberculosis*." Professor José Ainsa, Ph.D. of the University of Zaragoza, one of the pioneers in the field of efflux pumps of mycobacteria gave a review of his work and the need for the identification of over-expressed efflux pumps of MDR and XDR Mtb clinical isolates. As of the time of his presentation, the identification of the main efflux pump and its structure of Mtb remain to be elucidated. Nevertheless, the use of molecular genetic methods has provided insight into the function of these of pumps and because they may be the cause for resistance of MDR clinical isolates to agents used for therapy of XDR TB, there is a need for further work in the field of drug discovery for agents that may be used as adjuncts for therapy of efflux pump mediated MDR and XDR TB infections. Discussions centered on the type of efflux pumps present in Mtb since the organism stains as a Gram positive yet has a periplasmic space and porins reflective of Gram negative bacteria. Discussions pointed out certain features of efflux pumps of Mtb that suggest an ABC type transporter identity.

Recap of morning session. Leonard Amaral led the discussion which had to be abbreviated due to lengthy discussions following the morning's presentations.

"Targeting efflux pumps of mdr *Mycobacterium tuberculosis*." Professor Miguel Viveiros, Ph.D., Director of the Mycobacteriology Unit of the IHMT, Universidade Nova de Lisboa, presented a review of the work conducted by his Unit that defined the response of efflux pumps of mycobacteria to various agents known to have activity against efflux pumps of other bacteria. The work presented demonstrated the basis for inducing specific over-expression of efflux pumps by prolonged exposure to a given agent, and the evaluation of agents for inhibition of the efflux pump system via a real-time efflux method developed in his laboratory. The work described the use of mutants deleted for different efflux pump genes and porin genes for defining the physiological activity of the pumps and mechanisms by which agents can target such activities. The discussion of this topic presented opportunities for the chemists to suggest various compounds in their possession and indeed, some of these participants has already collaborated in past and on-going projects that identified potential candidates as adjuncts with antibiotics that are initially extruded by the over-expressed efflux pump system of mycobacteria.

"Secretory targets of *Mycobacterium tuberculosis*." Dr. Young-Hwa Song, Ph.D., from EMBL, Hamburg, Germany, presented her most recent work that identified a large series of proteins secreted by Mtb. These proteins have been purified, characterised and some have has their structures defined. The presentation resulted in a prolonged period of questions, answers and discussions on the pertinence of these secretory proteins to progression of latent infection to active TB disease. Because of the novelty of these proteins, discussions also centered on the possible use of these proteins in the manner that the skin test PPD is used for identification of a latent TB infection, with the possibility that the limitations of the PPD test may not be present with the use of secretory proteins as so indicated.

"The human macrophage." Professor Elsa Anes, Ph.D. from the University of Lisbon gave a review that centered on her work with mouse, human and human cell lines of macrophages during phagocytosis of Mtb and eventual formation of a the phagolysosome. The review provided insight into the immunology of infection and therefore identified potential targets that could assist in the therapy of MDR/XDR infections. Among the targets identified were cathepsins. This work is crucial for the development of drugs that are to have activity where the mycobacterium resides in the pulmonary system-namely, the pulmonary macrophage of the alveoli. The presentation set the stage for the presentation that followed and therefore, a prolong discussion of the details of the intracellular process of infection ensued.

"Targeting the macrophage for enhanced killing of intracellular *Mycobacterium tuberculosis*." Marta Martins, Ph.D., University College of Dublin, presented her work that defined the manner by which non-killing human macrophages are activated to kill intracellular MDR and XDR Mtb by a variety of compounds that inhibit the activity of the K+ transporter of the phagolysosome. This presentation unified the presentations by Drs. Ainsa, Viveiros and Anes as well as suggest that the skeleton of phenothiazines is ideal for the creation of derivatives that enhance the killing activity of non-killing human macrophages of the lung. Discussions on efflux pump targets for drug discovery, namely, derivatives of thioridazine was intensive for 20 minutes. In effect, because the discussion involved presentations by the morning and afternoon speakers, it provided the moderator to opportunity to use it for **Recap of morning and afternoon sessions.**

The first day of the workshop ended at 18:30 hrs. The participants were gathered at the Hotel venue of the Workshop and transported to the Ferry that took them across the

Tagus river to a picturesque traditional Portuguese restaurant. The traversing of the Tagus provided photo opportunities of the village of Belem, its monuments and famous Monastery of St Geronimo. Dinner ended at 22:30 hrs. Participants arrived at the Hotel at 23:00 hrs where discussions continued on topics presented during the course of the day.

Thursday, 2 December 2010

Moderator: Dick van Soolingen.

General Plan for day´s activities. Presentations are to be held to the allotted 25 minutes and discussions limited to one or two questions since the programme for today must be completed on time if Dinner reservations are to be met. The presentations have been divided into two parts: a) Providers of compounds, drug discovery, target verification and qualitative structure-activity relationships (QSARS) and b) Medical aspects related to current therapy of MDR/XDR TB and future that of the near with thioridazine and related compounds.

"**Plants as sources for anti-TB compounds."** Professor Franz Bucar, Ph.D., University of Graz, Austria provided a lecture on compounds isolated from plants that have been shown to have significant *in vitro* activity against Mtb and related antibiotic resistant strains. The compounds described may be used as lead compounds for the creation of derivatives that may have improved anti-TB characteristics. His lecture focused on the attention that is needed to traditional medicine claims which, when investigated further show that the claims are justified and that the degree of cure provided by traditional medicine can be vastly improved simply by increasing the amount of compound administered, an amount that cannot be achieved from the ingestion of the plant alone.

"Heterocyclics as good sources of anti-TB drugs." Professor Georgy Hajos, Ph.D., Director of Chemistry Insitute of the Hungarian Academy of Science, Budapest, that have anti-TB activity for the creation of derivatives with improved activities. Because he has been collaborating with the Portuguese TB groups, a large number of anti-MDR/XDR TB compounds, some of which appear to be non-toxic, have progressed from *in vitro* through *ex vivo* study. One particular compound, SILA 421 generated a huge amount of interest and has resulted in collaborations between the Portuguese, Hungarian and Dutch participants. This topic will be the subject of discussion during the 3rd day of the Workshop.

"New molecules for consideration." Professor Ismail Yalcin, Ph.D., University of Ankara, Turkey presented a large listing of apparently unrelated molecules that have been prepared and studied for anti-TB properties. Because some of these molecules were used as lead compounds for further derivatives, the generated series of derivatives provided the basis for QSARS, and this in turn has generated "intelligently designed" molecules that he can provide to the participants for *in vitro, ex vivo* and *in vivo* study.

"Anti-TB Drug Discovery Program at IPK." Zaesung No, Ph.D., Director of the Institute of Pasteur-Korea, Seoul, S Korea, described the anti-TB drug discovery programme of IPK. The description of the facilities and the invitation extended to the participants provided the basis for collaborations that would yield "medicinal chemistry" data that is required for pre-clinical trials. Discussions that resulted in collaborations

were conducted during the lunch break with recap to be provided on the 3rd day of the Workshop.

"QSARs for further drug design." Jean-Marie Pagès, Ph.D., Chimiorésistance et Drug-Design, Facultés de Médecine et de Pharmacie, University of Marseille, presented a lecture on the use of Qualitative Structure-Activity Relationships (QSARs) for development of new anti-TB compounds. The targets for drug discovery centered on efflux pumps of mediate MDR phenotypes of bacteria. Consequently, a major component of the lecture provided detail presentation of transport, structural aspects of transporters, affinities for substrates, use of molecular genetics for assisting drug- target aims, and for the use of substrates that bind irreversibly to relevant transporters that extrude given antibiotics prior to their reaching their intended targets, and hence, the inhibition that results from said binding provides the opportunity to use antibiotics for which initial resistance made them "fall by the wayside". Discussion was left for the lunch break.

"Therapy of MDR/XDR TB." Martin Boeree, M.D., The Netherlands, presented the therapy currently in use for MDR and for XDR TB and demonstrated the difficulties involved for therapy of the latter infection. He reviewed the status of various clinical trials that examine the efficacy of new compounds as well as the current clinical trials he is conducting in Africa with high doses of rifampicin for therapy of MDR TB. Because he is aware of the effects of thioridazine on the activity of antibiotics against MDR strains of Mtb, he is anxious to test whether thioridazine can reduce the dose level of ripampicin for therapy of MDR TB. This idea is important since rifampicin even at normal levels of use for therapy of antibiotic susceptible TB infections is hepatotoxic. Dr Boeree's enthusiasm over the possible use of the phenothiazine thioridazine carried over into the audience and further discussions were scheduled for the last day of the Workshop since time could not be extended for such discussions following his presentation.

"Successful Therapy of XDR TB with combinational therapy: Thioridazine and second line of defence drugs. Eduardo Abbate, M.D., Argentina, presented his study that proved that a combination of thioridazine with three antibiotics to which the patient did not respond, produced 10 out of 12 cures. He further illustrated that the problems associated with thioridazine and possible prolongation of QTc interval did not materialise due to the initial administration of the agent at low dose level, with increasing dose taking place bi-weekly. Because this presentation followed that of Dr Boeree, there was much need for discussion. However, after one question, it was decided that further discussion should take place on the last day of the Workshop.

"Designing and Conducting Clinical Trials." Ruben Thanacoody, UK, presented the lecture that was to be given by Co-convenor Stephen H Gillespie, M.D. who was unable to attend due to the closing of the airports in London due to snow and impossible travel from Scotland to London. The contents of the_ reflected the current regulations governing clinical trials by UK based groups in the UK and anywhere in the globe. The details of these regulations are addressed by Dr Gillespie's pending publication of his manual on how to conduct a clinical trial. The knowledge provided by the presentation would be used during the last day of the Workshop for establishing clinical trials for the therapy of MDR/XDR TB with thioridazine in combination with antibiotics.

The second day of the Workshop ended at 17:30 hrs and the participants collected at 19:00 hrs at the venue Hotel and taken to a restaurant in the Chiado district of Lisbon for dinner and Fado entertainment.

Friday, 3 December 2010

General Plan for day´s activities. Leonard Amaral presented an over-all plan for the activities of the last day of the Workshop which included:

1. Presentation by the ESF raporteur Professor Petrunov that would provide and assessment of the Workshop and his suggestions pertinent to the options he had presented on the opening day of the Workshop. Based upon a very positive review of the two days of the Workshop, he suggested the following:
    a) Proceed with a drug development plan that exploits the development of thioridazine and no more than two other drugs for anti-MDR/XDR TB therapy.
    b) Consider the creation of a Networking proposal to be submitted to the ESF in March 2011.
    c) Consider the creation of an FP7 proposal for development of the three drugs for anti-MDR/XDR TB therapy.
2. An Open discussion for establishing Future PLANs for DRUG DEVELOPMENT as per Professor Petrunov's recommendations.
3. Organisation of participants into three Working Groups for the creation of proposals recommended by Professor Petrunov.

The Groups organized were:

Group I: Chemists and biochemists
Group II: Laboratory specialists and physiologists,
Group II: Clinicians to be involved in clinical trials.

The three groups were to meet separately and elect a representative.

Group I was charged with the responsibility of selecting active anti-MDR/XDR TB compounds for modification.

Group II was charged with the responsibility of establishing a series of laboratory based assays and procedure for evaluation of compounds provided by **Group I.**

Group III was charged with developing plans for establishing clinical trials for therapy of MDR/XDR TB.

The groups met for two hours and the representatives of each group provided a report to the participants of the Workshop.

Groups I and II were fused for discussions of targets, validation, QSARs and the

items needed for further development of plans presented by Professor Dick van Soolingen. The following was suggested and accepted by the Participants:

Professor Leonard Amaral would coordinate a Networking proposal for drug development as per the recommendations made by Professor Petrunov.

Professor Dick van Soolingen would coordinate the development of the FP7 proposal for drug development of three compounds-thioridazine, SILA 421 and a third to be chosen

later. Professor van Soolingen will appoint Group Leaders for each component of the FP7 plan (Work Packages).

Report from Group III-by Dr. Ruben Thanacoody.

1. A global group of TB specialists, led by Professor Amaral would coordinate the use of thioridazine in combination with three antibiotics for therapy of non-responsive XDR TB patients whose prognosis is serious and there is nothing else available that will be effective. This Compassionate basis for therapy is to take place in India, Peru and Africa and at the time of this writing is already in effect in Peru and India.
2. Thioridazine would be introduced into existing MDR clinical trials in Africa by Dr Martin Boeree, pending renewal of his clinical trial programme.

The participants of the Workshop agreed to the proposed activities recommended.

The third and last day of the Workshop came to a close at 13:30 hrs and participants were to be picked up at 19:30 hrs for Dinner.

3. Assessment of the results, contribution to the future direction of the field, outcome

Plans for Collaborations that resulted during the Workshop

Due to the presentations, common interests in specific areas of TB and drug development were identified. These resulted in the following:

a) Provision of SILA 421 by Professor Amaral and Professor Hajos to Dr Boeree for evaluation in the MDT/XDR TB infected mouse.
b) Evaluation of a series of active derivatives prepared by Professor Hajos and Professor Yalcin for QSARs by Dr Pages.
c) Agreement by Participants to participate in the proposed TB Centre to ECCMID.
d) Agreement by the Medical Participants to organise a Global programme for therapy of the non-responsive XDR TB patient with thioridazine on "Compassionate" basis. This already begun Peru at the time of this writing.
e) Agreement by the Medical Participants to introduce thioridazine into existing MDR clinical trials directed by Dr Boeree.
f) Agreement by the Participants that an FP7 proposal would be designed and coordinated by Professor van Soolingen for drug-discovery of new, effective and non-toxic anti-MDR/XDR compounds.
g) Agreement to participate in a proposal to be submitted to the ESF for Networking that would facilitate the main goal of the Workshop- drug-discovery of new, effective and non-toxic anti-MDR/XDR compounds.
h) Agreement of Clinical TB laboratorians to assist Professor van Soolingen in developing TB laboratories in Central Asia countries that have huge numbers of MDR/XDR TB patients.

4. Final programme

WorkShop EW09-007

"Multi-disciplinary consortium for the development of effective, but non-toxic drugs against MDR-TB and XDR-TB"

Programme

Tuesday, 30 November: Arrival of participants.

Wednesday, 1 December 2010

8:30-9:00 **Registration/Attendance**

9:00-9:15 **Welcome**
Leonard Amaral

9:15-9:30 **Welcome**
Prof Petrunov

9:30-10:00 **The role of the clinical TB laboratory in drug development.**
Dick van Soolingen

10:00-10:30 **Geo-epidemiology of MDR/XDR TB.**
Nalin Rastogi

10:30-11:00 ***Coffee Break/discussions.***

11:00-11:30 **Defining XDR TB at the genetic and molecular biology levels.**
Isabel Portugal

11:30-12:00 **Efflux pumps of *Mycobacterium tuberculosis*.**
José Ainsa

12:00-12:30 **Recap of morning session.**
Leonard Amaral

12:30-14:00 ***Lunch.***

14:00-14:30 **Targeting efflux pumps of mdr *Mycobacterium tuberculosis*.**
Miguel Viveiros

14:30-15:00 **Secretory targets of *Mycobacterium tuberculosis*.**
Young-Hwa Song

15:00-15:30 ***Coffee Break/discussions.***

15:30-16:00 **The human macrophage.**
Elsa Anes

16:00-16:30 **Targeting the macrophage for enhanced killing of intracellular *Mycobacterium tuberculosis*.**
Marta Martins

16:30-17:00 **Recap of afternoon session.**
Leonard Amaral

19:00-22:00 ***Dinner.***

Thursday, 2 December 2010

9:00-9:30 **General Plan for day´s activities.**
Leonard Amaral

9:30-10:00 **Plants as sources for anti-TB compounds.**
Franz Bucar

10:00-10:30 **Heterocyclics as good sources of anti-TB drugs.**
Georgy Hajos

10:30-11:00 **New molecules for consideration.**
Ismail Yalcin

11:00-11:30 ***Coffee Break/discussions.***

11:30-12:00 **Anti-TB Drug Discovery Program at IPK**
Zaesung No

12:00-12:30 **QSARs for further drug design.**
Jean-Marie Pagès

12:30-13:00 **Recap of morning session.**
Leonard Amaral

13:00-14:30 ***Lunch.***

14:30-15:00 **Therapy of MDR/XDR TB.**
Martin Boeree

15:00-15:30 **Successful Therapy of XDR TB with combinational therapy: Thioridazine and second line of defence drugs.**
Eduardo Abbate

15:30-16:00 ***Coffee Break/discussions.***

16:00-16:30 **Designing and Conducting Clinical Trials.**
Stephen H Gillespie

16:30-17:00 **Recap of afternoon session.**
Leonard Amaral

19:00-22:00 ***Dinner.***

Friday, 3 December 2010

9:00-9:30 **General Plan for day´s activities.**
Leonard Amaral

9:30-13:00 **Open discussion for establishing PLAN for DRUG DEVELOPMENT.** *(Coffee available during session).*

Organisation of participants into Working Groups:

WG1 (Sources of compounds)
WG2 (Mol Biol, Gen Biol., Structural Biol, Biochem).
WG3 (Clinical Laboratory Mycobacteriologists)
WG4 (*In Vitro*, *Ex Vivo*, *In Vivo* Evaluators of compounds).

Individual WGs meet (getting to know each other); Elect Group Leader.

WG1 (Sources of compounds) **meet** with **WG2** (Mol Biol, Gen Biol., Structural Biol, Biochem).

PURPOSE: PLAN FOR TARGET IDENTIFICATION.

WG3 (Clinical Laboratory Mycobacteriologists) with **WG4 (***In Vitro, Ex Vivo*, In Vivo Evaluators of compounds).

PURPOSE: PLAN FOR DRUG EVALUATION

13:00-14:00 ***Lunch.***

14:00-15:00 **WG Leaders present summary of meetings.**

15:00-15:30 ***Coffee Break.***

15:30-17:00 **Formulation of a possible FP7 proposal for 2011.**
Plan for Distribution of Labour.

17:00 **End of Workshop.**

19:00 ***Closing dinner.***

5. Final list of participants/gendre/affiliation

ARGENTINA

Eduardo Abbate (male)

Professor of Medicine

Division de Tisioneumonologia del Hospital FJ Muniz

AUSTRIA

Franz Bucar (male)

Professor

Institute of Pharmaceutical Sciences
Department of Pharmacognosy
Karl-Franzens-University Graz

DENMARK: Jette E Kristiansen (female)

Assoc Professor

South Danish University

FRANCE

Jean-Marie Pages (male)
Director
Chimiorésistance et Drug-Design
Facultés de Médecine et de Pharmacie

Nalin Rastogi (male)
Director
Unit of Tuberculosis and Mycobacteriology
Pasteur Institute Guadalupe

GERMANY
Young-Hwa Song (female)
Scientist
EMBL-Hamburg

HOLLAND

Martin Boeree (male)

Med Director

Nijmegen Medical Ctr

ULC Dekkerswald Nijmegen

Dick van Soolingen (male)
Director
Natl Mycobact Ref Laboratory of the Netherlands,

HUNGARY

Gyorgy Hajos (male)
Director & Professor Chemistry
Chem Res Ctr
Hung Acad Sci

Zsuszanna Reidl (female)
Professor
Chem Res Ctr
Hung Acad Sci

IRELAND

Marta Martins (female)

Post-Doctoral Fellow

Univ Coll Dublin

KOREA (INSTITUTE OF PASTEUR-KOREA)

Zeasung No (male)

Director

Institute Pasteur Korea

PORTUGAL

Elsa Anes (female)
Assistant Professor
Mol Pathogen Ctr
Univ Lisbon

Miguel Viveiros (male)
Associate Professor
Inst Hyg Trop Med
Univ Nova Lisboa

Isabel Portugal (female)
Professor of Pharmacy
Sch Pharm
Univ Lisbon

Isabel Couto (female)
Assistant Professor
Inst Hyg Trop Med
Univ Nova Lisboa

SPAIN

José Ainsa (male)

Permanent Lecturer

Dept Microbiol

Univ Zaragoza

Julia Gonzalez (male)
Professor of Medicine
Department of Microbiology
Hospital Clinic
University of Barcelona

TURKEY

Ismail Yalcin (male)

Professor of Chemistry

Fac Pharmacy

Ankara University

Esin-Aki Yalcin (female)

Professor of Chemistry

Fac Pharmacy

Ankara University

UK

Stephen Gillespie (male)
Professor Medicine
St Andrews University

Ruben Thanacoody (male)
Senior Lecturer
University of Newcastle-upon-Tyne

6. Statistical information on participants

Country of origin

Argentina	1	Austria	1	Denmark	1
France	2	Germany	1	Netherlands	2
Hungary	2	Ireland	1	Korea	1
Portugal	4	Spain	2	Turkey	2
United Kingdom	2				

Gender

Male: 14 Female: 8