Workshop on Fundamental Research for Tuberculosis

Organized by the Stop TB Partnership Research Movement
in collaboration with NIAID, NIH and TAG

Workshop Report
18-19 March 2010, Bethesda, Maryland, USA

Recognizing fundamental science as an integral part of an aggressive, transformational research response to the continuing global TB epidemic is one of the most pressing issues of our time. To re-define the scope and contribution of fundamental research for TB control, the TB Research Movement of the Stop TB Partnership, in collaboration with NIAID/NIH and TAG, have organized a workshop to identify fundamental research questions that underpin development of new diagnostics, drugs and vaccines that are needed to meet the goal of elimination of TB by 2050.

Objectives of the workshop:

The ***overall goal*** of the workshop was to define the most pressing priority questions that need to be addressed to drive the innovation needed for expedited development of new drugs, diagnostics and vaccines for TB control.

The ***specific objectives*** were:

1. to identify the fundamental research questions that are critical for the development of new drugs, diagnostics and vaccines to control TB;
2. to identify technical and intellectual gaps in basic research that impede answers to these fundamental questions;
3. to gather input into the development of a roadmap for the contribution of fundamental research towards the goal of elimination of TB by 2050;
4. to outline methods to estimate the funds needed to adequately support fundamental research to meet the objective of elimination of TB by 2050.

The first day of the workshop was aimed at highlighting key knowledge gaps in the natural history and epidemiology of TB, the pathogen, the host, the host-pathogen interaction and the overall dynamic nature of development of TB disease. These gaps were then broadened on the second day of the workshop, to address how they impact the development of new drugs, vaccines and diagnostics and why addressing these questions is critical to make a quantum leap in the development of new tools for TB control.

<u>DAY ONE</u>:

1. Opening Session:

Anthony Fauci, Head, National Institute of Allergy and Infectious Diseases, NIH, opened the meeting by reminding us that although TB has a huge public health impact, innovations in TB science have not followed due to lack of resources. Global investment in TB lags well behind many other diseases. In his keynote address at the Pacific Health Summit in Seattle in June 2009, Dr Fauci mentioned MDR/XDR TB as important areas of focus and concern, but stressed that fundamental research needs are much broader and have to include all aspects of TB. While NIAID is already supporting a comprehensive

research agenda, the details of biomedical research in TB the scientific work is a work in progress and will be influenced by the outcome of this meeting. TB, together with Malaria and HIV, is and remains a high priority in NIAID's Global Health Research Agenda. A clearly focused, collaborative fundamental global research agenda is the key to engaging funders and stakeholders in the continued support for this disease.

Marcos Espinal, Executive Secretary, Stop TB Partnership, expressed that, to eliminate TB as a public health concern, the community needs new tools, many of which are currently in the experimental stage. The overall mission of the Stop TB Partnership is to reduce the incredible social and economic toll of TB which poses a significant burden on individuals and societies. The Stop TB partnership is an open, global organization that established focused working groups that define and address key TB research and control questions to help coordinate efforts and drive the needed advances forward. The Global Plan to Stop TB is the business plan for the efforts of the Stop TB Partnership to halve mortality from and prevalence of TB by 2015. At its half way point, the current Global Plan is being revised to highlight, for the first time, the importance of fundamental science as a critical component in the development of new tools.

Christian Lienhardt explained the role and objectives of the TB Research Movement, which is part of the Stop TB Partnership and is the driver for this workshop. He reminded that the Global Plan to Stop TB 206-2015 outlines strategic directions for all activities needed to control and eventually eliminate TB by 2050, and proposes costs and funding needs to achieve these goals. While global TB control achievements are on track with the Millennium Development Goals, control efforts are lagging behind for many high burden countries, particularly in sub-Saharan Africa. At the current rate of decline of global TB incidence (about 1% a year), the target of elimination of TB (defined as less than 1 case per 1,000,000 population) will not be achievable by 2050. The current trajectory of decline can only be improved through novel tools used in combination with existing and continuously improved control strategies. The goal of the TB Research movement is to analyze the current gaps in fundamental knowledge that underpins the development of new tools and strategies for TB control, identify needs for funding, and promote the integration of global biomedical science agendas that address the continuum of research needed in TB. This is the first meeting ever in which the Stop TB Partnership addresses the importance and need for integration of fundamental research into the global TB control agenda, so outputs from this workshop are highly anticipated.

Mario Raviglione, head of WHO's Stop TB Department, provided the perspective of the WHO TB control strategy. The component 6 of the strategy calls for more research, including research to develop new diagnostics, drugs and vaccines and programme-based operational research to introduce new tools into practice. Dr. Raviglione articulated that high quality research data, as well as transfer of technologies to high burden countries are key for successful implementation of new and improved TB control strategies. To facilitate improvements in TB control, the WHO provides norms,

standards and policies. This workshop on fundamental research is considered to be a key component for promoting the importance of research for new strategies for TB control.

Christine Sizemore provided a summary of the overarching goal of the workshop – the definition of fundamental questions in TB that need to be addressed to drive innovation and ultimately improve human health. Fundamental research questions underlie all aspects of TB care and control and are addressed through studies in basic, translational, clinical, epidemiological and operational research disciplines. Answers to fundamental questions in TB provide the knowledge needed to develop new diagnostics, treatment regimens, and preventive strategies, most importantly, vaccines. A roadmap of key overarching fundamental questions is urgently needed to provide a unifying framework for all areas of science, independently of product development goals. For this, participants in this workshop are asked to articulate and discuss knowledge gaps and provide common ground for the development of global fundamental research agenda for cross disciplinary research.

Gilla Kaplan started the scientific sessions of the workshop by suggesting how to define the types of fundamental research questions that provide a common framework for scientific disciplines. Since TB is driven by the close relationship of the pathogen and the host, four basic research questions emerge:

1. Why do only some persons get disease and others don't – this question outlines the importance of the study of the natural history and epidemiology of TB.
2. How do we identify those who are infected and those persons at highest risk of developing disease – this question provides the foundation for the development of preventive and diagnostic strategies.
3. Why do not all persons respond fully to treatment – answers to this questions will shed light onto the current action and mechanisms of TB drugs, the importance and utility of regimens and how these can be improved.
4. How to we interrupt progression from exposure to infection and from infection to disease – an understanding of what constitutes successful control of infection by the host versus development of disease is critical for the development of diverse vaccination and other TB prevention strategies.

These fundamental questions are complex and cannot be addressed without close coordination and collaboration among research communities and disciplines. While each scientific discipline can make significant contributions to each question, we, as a community need to put the "big picture" of TB back together to understand this human disease scientifically through collaborative activities.

2. Setting the stage : the Epidemiology of TB

The scientific sessions on both days provided much more detailed information than can be summarized here. Fundamental questions that were defined and discussed are listed in annex 1.

Chris Dye began his summary of key epidemiologic issues in TB by discussing the decline in TB incidence in Alaskan Eskimos in early 50's. In this community, cases decreased by an unprecedented 13% per year, deaths by 30% a year. This decline was only possible through an increase in the combined efforts in intensive case finding, treatment, BCG vaccination of infants and preventive therapy. With the current tools for control of TB, it will require similar combinations of activities to reduce global TB incidence to below 1/1,000,000. Currently, global TB is focused on expansion of DOTS in high burden countries to arrive at the target of curing 85% of all enrolled and treated patients. In the public sector, most persons with TB are treated in DOTS programs who strive to meet similar global targets each year. In this environment, 10 million new cases are expected in 2010 and rates are still increasing despite the current control efforts. The most spectacular increase in TB rates since 1980s is seen in Africa due to the co-epidemic of HIV, and in Eastern Europe due to the increase in drug resistant TB. Two thirds of global TB cases are occurring in SE Asia which reports a slow, but likely insignificant decrease in incidence. *Why can we not achieve at global levelcase reduction rates as those seen in the Alaskan Eskimo population?* Dr. Dye posits that the main problem facing TB control is persistent transmission due to delayed treatment for several reasons: 1) Difficulty accessing health care; 2) Ineffective prevention of infection progressing to disease; 3) new risk factors for TB; 4) different dynamic of transmission of Mtb strain types; and 5) different economic factors. To eliminate TB by 2050, a rate of decline of about 16% per year would be needed, more than what was reached in the Eskimo population under optimal conditions. We need to combine interventions that improve diagnosis of TB, prevent infection through a pre-exposure vaccine, prevent active disease through preventive therapy and rapidly treat active disease, while at the same time reducing the varied risk factors for TB.

Frank Cobelens continued the discussion by reminding us that the first step in controlling TB must be to stop transmission. To understand how best to achieve this , we must collect more information about why not every patient with TB is diagnosed and why this diagnosis is often late and what factors prevent patients with persistent cough from seeking care. The current focus on smear positive TB greatly limits our ability to detect cases. This focus is in part based on the lack of availability of diagnostic tools to detect smear negative TB and the lack of scientific data that guide the recommendation for isoniazid preventive therapy (IPT) for all affected persons, including those with co-infections and co-morbidities. To simplify recommendations for preventive therapy, identification of persons with the highest probability of developing active disease is needed. Epidemiologists recognize that the transmission of TB is driven by specific environments and likely also strain types. To identify settings with highest transmission and define the best courses for intervention, more epidemiological data and collaborations with other scientific disciplines to explain these epidemiologic phenomena is needed.

3. The Natural history of TB:

Peter Donald gave an extensive summary of key aspects of human TB with insight into the complex biological underpinnings of this disease. Currently we place primary emphasis for diagnosis and transmission on sputum smear positivity of the patient (since this indicates the presence of large numbers of bacteria in transmissible secretions), but questions remain on the number of bacteria needed to establish disease, the role of the infectiousness of the strain, the state of the transmitting patient and the receptive host, etc. Taken together, this presentation highlighted that no single aspect of TB can be studied in isolation and that approach to TB must be multi-disciplinary.

Philip Hopewell pointed out that a focus on studying the natural history of TB allowed for bridging epidemiology with basic science. Studying the natural history of a disease provides the focal point for all fundamental research questions of biological relevance. TB is a complex disease that is difficult to understand. The bacterium is not very pathogenic, the risk of infection is highly variable, infection progresses to disease in multiple phases influenced by complex host and pathogen factors. Since it is difficult to measure transmission and its impact on outcomes of disease in humans, we have relied on studying pathogenicity as a surrogate for transmission, thus limiting our understanding of the importance of this aspect of TB.

4. The Germ:

Clifton Barry discussed several scientific dogma that currently influence the direction of biomedical research in TB.

- *Dogma 1:* Geographically segregated clades of Mtb influence the dynamics of TB transmission and pathogenicity. To study whether the genetic differences between strains that are hypothesized to have diverged from a theoretical prototuberculosis strain are stable and affect how TB develops, we first need to understand the fundamental, common characteristics of TB. The biological processes underlying the development of active TB and cavitation are poorly understood due to the complex interaction between host and pathogen. To prove that genetic differences in Mtb affect clinical disease, one needs to determine whether the natural response of Mtb to evolutionary pressure is genetically determined. Rather than assuming that genetically different strains have evolved and drive disease globally, evolutionary pressures imposed on Mtb through disease control interventions may continually select and define the prevalence and stability of strains circulating in high burden settings.
- *Dogma 2:* Various populations of Mtb with differences in their physiological characteristics exist within microenvironments in the host and respond differentially to chemotherapy. To explain the need for prolonged treatment to stably cure TB patients, it has been hypothesized that different populations of Mtb exist or develop that have have limited sensitivity to TB chemotherapy and necessitate prolonged treatment. However, the presence and location of these populations have to date only be inferred

from limited animal studies and have not been confirmed in humans. To prove that these populations exist and display differential sensitivity to chemotherapy, we need to be able to measure small quantities of bacteria in situ in human TB lesions. This approach is limited by our lack of understanding of where Mtb resides in tissues during TB and what proportion of bacteria are extracellular versus intracellular. We have started to understand that different lesions respond differently during the course of chemotherapy but we do not know whether this is a stochastic event or whether different types of antibiotics affect the adaptation of Mtb within host microenvironments, and thus lead to systematic evasion of antimicrobial action.

- *Dogma 3*: Animal models reliably reflect aspects of human disease. Since our understanding of human TB is at best limited, many hypotheses in biomedical science have developed from animal studies without ever having been proven in humans. While the current animal models are excellent for testing the effect of chemotherapeutic candidates against Mtb grown in vivo, more complex studies of the dynamics of human TB require continues cross-evaluation in humans and readjustment of hypotheses and interpretation of model data. Only through an iterative process of validation of animal model data/hypotheses in human studies will we be able to define the true value of animal studies for the selection and potential impact of new drugs and vaccines against human TB disease.

Eric Nuermberger reminded us that *"all models are wrong; some are useful"*, especially in complex diseases such as TB. A major challenge for the biomedical research community is to define and agree upon what are the useful aspects of each animal model. It is understood that the complexity of human TB is not reflected in the current animal models, particularly since these were developed on the basis of reliably producing disease, not to reflect the ability of most hosts to contain disease. It has been tempting to use data from mouse models to predict the efficacy of candidate drugs against clinical aspects of TB. However, the relationship between pathology and response to therapy needs to be defined better if one wishes to study drug efficacy beyond bacterial kill. Currently, we are relying on measuring the reduction in bacterial load in animals as a surrogate for “clinical response”. However, as also indicated by other speakers, since we do not yet understand how bacterial numbers and their location in human hosts affect disease dynamics, animal data on the reduction of bacterial loads in lung and/or spleen need to be interpreted carefully. Until we better understand natural history in humans, animal model data have to be carefully analyzed and interpreted in the appropriate context.

5. The Host:

Douglas Young: Elimination of TB 2050 will require multiple approaches focused on prevention and treatment of disease, combined with efforts to reduce transmission. Since Mtb infection engenders a spectrum of possible responses by the host, any intervention that interferes with the kinetics of disease progression will be useful. The definition of this spectrum requires to develop markers that indicate who harbors live

Mtb bacteria and who has cleared them. Mtb infection does not simply develop into active pulmonary disease but transitions through various stages, many of which may result in natural clearance of the pathogen. Our current knowledge about the dynamic nature of TB is derived from epidemiological studies that indicate that not everyone infected develops disease and that persons with Mtb infection but absence of clinical symptoms (latent TB) do not always progress to active disease. Furthermore, the heterogeneity of TB lesions seen in humans has not been fully appreciated for their impact on disease progression. Investigation of this impact will also offer opportunities to study whether physiologically different bacterial populations exist in humans and how these may affect progression of TB. At any rate, to understand the complexity of TB and to identify markers that characterize the most critical stages along the spectrum, translational and iterative research in humans and animal models is critical.

Henry Boom addressed that to understand transmissible, human TB, we need to focus more on the immune responses occurring in the lung. While most current immune studies in TB are conducted with peripheral blood, we need to increase our focus on the innate host immune responses mounted at the time of exposure to Mtb, as well as how Mtb evades immune killing and successfully establishes in lung lesions. We recognize that both host and pathogen factors play a role in these events, but the relative contribution of these is poorly understood. Furthermore, immune responses to Mtb infection change with age and infant TB develops differently from adult TB, pointing to the critical contribution of the failure of the innate immune response to contain TB. To better understand immune evasion by Mtb, we need to characterize the dynamic nature and role of granuloma formation and dissect whether they serve to contain the pathogen or whether they develop as a result of immune adaptation of Mtb. Also, to this day, we only have a rudimentary understanding of the activity and mechanism of immune protection by BCG and why it fails to protect adults. Without this knowledge, it will be difficult to compare new vaccine candidates against BCG and/or improve on the activity of the current BCG vaccine.

DAY TWO

Key questions identified on the first day of the workshop were used to stimulate discussions on day two that were aimed at defining how fundamental research questions in TB will influence and guide tools development and translational research. Four discussion sessions were held to define critical knowledge gaps in product development science to create the level of innovation needed to make a quantum leap in the development of new tools for TB control:

1. Biomarkers (chair: Eric Rubin)
2. TB diagnostics (chair: Gerhard Waltz)
3. Drugs - (chair: Carl Nathan)
4. Vaccines - (chair: Mark Doherty)

Each session was conducted as an interactive discussion. Not all questions and comments raised during these sessions can be captured here. We attempted to select the most pressing issues, and cluster them into the following categories that can be addressed sequentially or concurrently:

1. How best to characterise human TB?
2. What are the key molecular features of host/pathogen interaction?
3. What are the essential questions to expedite development of new tools for TB control?

We then grouped suggested research questions according to specific sub-objectives in each of these categories. For each of these sub-objectives, we propose a series of research activities, set targets for 2015 and beyond (long-term goals), and potential indicators for success to arrive at summary recommendations to be included in the revision of the Global Plan to Stop TB 2006-2015. These summary recommendations are the first step towards the establishment of a roadmap that outlines how and where fundamental research efforts will be critical to fill the gaps towards the goal of elimination of TB by 2050.

The 3 main objectives and sub-objectives are listed there-under. Key research activities arising from these discussions can be found in **Annex 2** of this report described in a simplified logical framework. The more detailed logical framework that lists all parameters above is available upon request.

Objective 1: To improve the characterization of human TB using modern biomedical and clinical/epidemiological approaches.

Sub-objectives:

1. To define the overall spectrum of TB in humans and identify suitable markers of these stages
2. To identify key microbiological characteristics that correlate with disease outcomes
3. To define key epidemiological characteristics of TB in various settings

This was the most important priority identified by workshop participants, since it will ultimately provide tools and knowledge for all subsequent research areas. While many studies have been conducted in humans and animal models, our understanding of the nature of TB in humans is incomplete. To reach this goal, researchers from many scientific disciplines have to work together to better understand the nature and life of the pathogen, how humans respond to it, how disease develops and how it eventually spreads to others. Since TB is a chronic disease and not every infected person develops TB in the same manner, it is critical to characterize the steps that lead from first contact with the pathogen to established infection and then from infection to disease, and how

both the host and the pathogen contribute to these processes. This will ultimately help us understanding how TB occurs and is transmitted in communities, including in those who are also affected by HIV/AIDS and other epidemics, and will help shape strategies to combat this disease worldwide. The comprehension of the overall *spectrum of TB* and the identification of *bacterial* and *host markers of transition* between the main stages of human TB are key to understand where an individual is placed on the spectrum and identify who will progress from one phase of the spectrum to the other and why.

Objective 2: To address key molecular features of host/pathogen interaction:

Sub-objectives:

1. To define the contribution of the *pathogen* to the dynamic nature of TB
2. To define the contribution of the *host* to the dynamic nature of TB
3. To define the *host-pathogen interaction* in the dynamic nature of TB

The fine comprehension of the host-pathogen interaction at the molecular level in the dynamic nature of TB requires to define the respective contribution of the *germ* and the *host* and then their *interaction*. To understand TB from the perspective of the *pathogen*, it has been suggested that different populations of Mtb exist in humans during disease and that these populations differ in how they respond to drug treatment. These populations remain to be confirmed in human patients, and it has to be determined where they reside and to what extent they influence the timeline and outcome of TB. Furthermore, we need to understand whether bacteria that remain after the initial two months of drug treatment are different from the bacteria that were eliminated during the intensive phase of therapy. This will then allow us to develop drug regimens that are optimized for elimination of bacteria at all stages of disease. Ultimately, we need to develop highly sensitive methods to determine when all bacteria are eliminated from patients or when bacterial numbers are low enough to consider patients cured.

To understand TB from the perspective of the *patient*, we need to define how the immune system is able to eliminate Mtb in most infected individuals while this mechanism fails in those who develop TB. It is suggested that a combination of human and bacterial genetics but also location of bacteria and overall immune status and health play a major role. However, how these factors contribute to the development of TB is not yet fully understood.

Objective 3: To define essential questions to expedite development of new tools for TB control.

Answers to fundamental questions addressed in objectives 1 and 2 will naturally contribute data for the development of specific tools for TB control, i.e. diagnostics, drugs and vaccines, but will also highlight key questions that need to be addressed for product development.

1. How to diagnose patients with infection and disease at the earliest possible stage ? A key requirement for new diagnostic tools and strategies is to diagnose patients at risk at the earliest possible stage to provide the most appropriate care for prevention or treatment of TB. To identify persons who are infected with Mtb but who have not yet developed TB disease, it is essential to identify either components of the bacterium or characteristics of the host immune response that clearly point to the presence of live Mtb, irrespective of whether a person has TB in the lung or anywhere else in the body, and whether the person's immune system is healthy or compromised.

2. How to eliminate the pathogen ? A key requirement for new drugs and treatment strategies is to better understand the life cycle of Mtb in patients. For this, we need to combine studies and data from all areas of microbial science, from genetics to nutrient utilization to how the bacterium builds it cellular components, in a common strategy termed systems biology, to re-assemble the life of the pathogen from individual data sets. This comprehensive view will allow us to identify points of vulnerability of the pathogen, to which drugs can be directed, that may have eluded us with existing methods. In addition, until new drugs become available for patients, we must better understand how the currently used therapies eliminate Mtb and whether they can be recombined in a different manner to improve their effectiveness.

3. How to prepare the host immune system against Mtb infection and disease? Lastly, for vaccines, the key goal is to understand how to prepare the host immune system against Mtb infection and disease. For this, it needs to be determined what components of the host immune system are critical for the elimination of the bacteria and why prior infection and disease do not protect against recurrent TB. Since humans can develop TB more than once in their lifetime, the immune system does not recognize Mtb effectively and does not protect the body against re-infection or a second course of disease. This makes the development of an effective vaccine very challenging. To guide the development of new vaccines, we also need to understand the advantages and limitations of the current vaccine, BCG and whether its effectiveness can be improved.

NEXT STEPS:

1. Highlighting Fundamental Research as a separate component of biomedical R&D in the mid-term revision of the Global Plan to Stop TB 2006-2015.

In the Global Plan to Stop TB 2006-2015, fundamental research efforts were initially considered as part of the process for the development of new diagnostics, drugs, and vaccines. To address the importance of fundamental science as the driver of innovation in product development and TB control, it was essential to define the key fundamental

research questions that need to be addressed in order to contribute usefully to the development of new diagnostics, drugs and vaccines. Recognizing the importance of fundamental science as a key component of the global fight to eliminate TB will allow identification of research gaps to which the attention of global funders can be directed. To this end, we have now included a full section on Fundamental Research within the Update of the Global plan to Stop TB.

2. Costing Fundamental Research activities.

This is work in progress. With the help of several workshop participants and directions provided by Christopher Fitzpatrick, costs of specific research activities laid out in the detailed logframe are being determined. The update of the Global Plan will include a rough estimate of expected costs to support key fundamental research activities.

3. Development of a roadmap for the contribution of fundamental research towards the goal of elimination of TB by 2050.

The next step for the TB Research Movement is to further leverage the initial input gained from this workshop and organize more detailed discussions based on the initial logframe to define a global roadmap for the integration of fundamental research into TB Elimination Strategies. The objective of this roadmap is to identify critical research priorities that will have to be supported by major stakeholders (researchers and funding organizations) to facilitate those revolutionary discoveries that are needed to improve TB control strategies and bring us closer to the goal of elimination of TB by 2050.

4. Advocate for novel mechanisms of funding and multi-disciplinary large-frame studies.

4.1 To further highlight the need for integration of fundamental research into global TB elimination strategies, we intend to summarize the key findings of this workshop in a publication in a Medical Journal.

4.2 To facilitate comprehensive longitudinal studies in human patients, the TB Research Movement intends to call attention to the need for large comprehensive human cohort studies that should be jointly supported by key funders, as well as to highlight the need for including scientific analyses into clinical trials designed to test interventions. Particularly to define markers of response to therapy or immune protection, much benefit and savings can be derived by maximally leveraging ongoing human trials. It should be considered to consent volunteers to make clinical samples from trials available to the research community for further analysis.

4.3 One of the most critical outcomes of this workshop was the recognition that no one fundamental research question can be addressed in the absence of multi-disciplinary,

collaborative clinical studies that will require linking basic and translational studies with carefully planned and detailed large-scale, multi-site, epidemiological studies in populations in high exposure settings and with a high risk for disease progression. Such studies should lead to the development of high quality sample repositories of well characterized microbial and human samples for coordinated, collaborative development of biomarkers.

4.4 The TB Research Movement intends to continue discussions with funders and major stakeholders to define opportunities for targeted support of fundamental research projects. The TB Research Movement intends to hold additional, focused discussion meetings in 2011 and beyond to focus on well defined, critical, tangible research gaps and draft focused proposals for funding institutions.

Christian Lienhardt
TB Research Movement
Stop TB Partnership

29th June 2010

ANNEXES

Annex 1: Agenda of the workshop.

Workshop on Fundamental Research on TB
(jointly organized by the Stop TB Partnership TB Research Movement, NIH/NIAID and TAG)
March 18-19, Bethesda

AGENDA

Day 1	**The Need for Fundamental research: *where and how fundamental research can best feed the development of new tools for TB control ?***	
8h15 - 8h30	Registration	
8h30 - 8h40	Opening Comments	Dr A. Fauci (NIH/NIAID)
8h40 - 8h50	The Stop TB Partnership	Dr M. Espinal (Stop TB Partnership)
8h50 - 9h00	The Role of Research in the WHO Stop TB Strategy	Dr M. Raviglione (Stop TB - WHO)
9h00 - 9h10	The Global Plan to Stop TB and the TB Research Movement	Christian Lienhardt
9h10 - 9h30	Objectives of the Meeting	Christian Lienhardt
9h30 - 9h45	A Roadmap on Fundamental Research for TB?	Christine Sizemore
9h45 - 10h00	Defining Fundamental Research for TB	Gilla Kaplan
10h00 -11h15	The need for Fundamental Research for development of new tools for TB control: 1. The epidemiology of TB	**Chair: Carol Heilman** Presenter: Chris Dye Discussant: Frank Cobelens
11h15 -11h30	*Coffee break*	
11h30 -13h00	2. The natural history of TB	**Chair: Carol Heilman** Pres: Peter Donald Disc: Phil Hopewell
13h00 -14h00	*Lunch*	
14h00 - 15h30	3. The germ (where, what, dormancy, late responsiveness, animal models)	**Chair: Judy Hewitt** Pres: Clifton Barry Disc: Eric Nuermberger

15h30 -16h00	*Tea break*	
16h00 - 17h30	4. The host	**Chair: Judy Hewitt** Pres: Douglas Young Disc: Henry Boom
	Close day 1	

Day 2	**Defining the main fundamental knowledge questions for the development of new tools for TB control: *what do we need to know ?***	**Chair: Carl Nathan**
8h30 - 8h45	Summary of previous Day	C. Sizemore C. Lienhardt
8h45 - 10h30	Joint panel discussion: *define the 10 main questions that are critical for innovation in the field of:* 1. Biomarkers	Group discussion led by Eric Rubin
10h30 -11h00	*Coffee break*	
11h00 - 12h30	2. Diagnosis	Group discussion led by Gerhard Walzl
12h30 -13h30	*Lunch*	
13h30 - 15h00	3. Vaccines	Group discussion led by Mark Doherty
15h00 -15h30	*Tea break*	
15h30 - 17h00	4. Drugs	Group discussion led by Carl Nathan
17h00-17h30	Costing the needs for Fundamental Research: principles	Christopher Fitzpatrick
17h30 - 18h00	Feed-back and Summary *The critical challenges to research*	C. Sizemore C. Lienhardt
18h00-18h30	Conclusion and next steps (definition of core group to establish priorities and costs)	C. Sizemore C. Lienhardt
18h30	*Close day 2*	

Annex 2: List of Participants

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Annex 3: Simplified logical framework listing main fundamental research questions identifed at the workshop.