NIH Request for Information on a Strategic Framework for Tuberculosis Research

Analysis of Public Comments

September 26, 2018

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Executive Summary

The National Institute of Allergy and Infectious Disease (NIAID) has developed the *NIAID Strategic Plan for Tuberculosis Research* to advance tuberculosis (TB) research and development for the next five years and beyond. This effort aligns with a concerted global effort, led by the World Health Organization (WHO) and supported by the United States (U.S.) Government, to reduce TB deaths by 95 percent and to reduce TB disease incidence by 90 percent by 2035 (relative to 2015 levels). To solicit input from the public on a draft framework of the plan before it was finalized, NIAID released a *Request for Information (RFI): Inviting Comments and Suggestions on a Framework for the NIAID Tuberculosis Strategic Plan* (NOT-AI-18-043; see Appendix 1). The NIAID Tuberculosis Research Strategic Plan Working Group carefully considered the suggestions and where appropriate, incorporated them into the final strategic plan.

The RFI gathered input from the research community, advocacy groups, and other interested stakeholders on significant knowledge gaps and barriers, resource deficiencies, and areas of emerging technologies relevant to TB research. Interested parties could submit comments through a web-based form from June 27 to July 16, 2018. NIAID received a total of 69 submissions from a range of organizations and individuals. Three of these responses were submitted via email after web-based submissions closed.

The responses reflected a wide array of scientific perspectives and comments on TB research needs. Many respondents were enthusiastic in their support of the framework. Most comments either highlighted specific topics within the framework that warranted more intensive study or suggested additional concepts to include. From the analysis of the responses, several cross-cutting scientific areas and principles of collective significance were identified.

Many comments emphasized the importance of supporting fundamental research to improve the understanding of bacterial diversity, drug resistance, molecular mechanisms of TB latency, and the role of host genetic diversity in host-pathogen interactions. Other responses suggested studying TB disease in specific contexts, including in latency, with specific comorbidities (e.g., diabetes) and coinfections (e.g., HIV coinfection), during pregnancy, and in childhood. Other prominent themes included the need for biomarkers for different stages of TB disease; better TB vaccines (preventive and therapeutic); safe and effective drug regimens of shorter duration; and rapid, point-of-care diagnostics that can detect different forms of *Mycobacterium tuberculosis* (*Mtb*) using a variety of sample types in diverse populations. Several resources considered to be crucial to facilitating TB research were identified, including improved small animal and non-human primate models for varying manifestations of TB (e.g., latent TB infection); a larger, diversified and cross-disciplinary research workforce; mechanisms for product development; and expanded biosafety level 3 (BSL3) facilities. Finally, some respondents pointed out the importance of adherence and implementation science research to develop methods that ensure rapid and effective uptake of new interventions.

Report on RFI Results

Introduction

Tuberculosis (TB) is a modern-day scourge caused by the bacterium *Mycobacterium tuberculosis* (*Mtb*). In 2017, 10 million people, including 1 million children, became ill with TB disease, and [1.6 million people with TB disease died](#), making it the leading infectious cause of death in the world. Globally, approximately 1.7 billion people, [including 13 million people in the U.S.](#), are living with *Mtb* infection, known as latent TB; they have a [lifetime 5 to 10 percent chance of developing active disease](#). HIV coinfection poses additional challenges, as the risk of progressing from latent to active disease is [20 times higher](#) in people living with HIV (PLWH), and the compatibility of TB drug regimens with antiretroviral therapy must be considered.

To address the global health emergency that TB represents, [the World Health Organization (WHO) End TB Strategy](#) established ambitious goals [to reduce TB deaths by 95 percent and to reduce TB disease incidence by 90 percent by 2035](#) (relative to 2015 levels). The U.S. Government endorsed the vision of the End TB Strategy and formed the [U.S. Government Global Tuberculosis Strategy](#) and the [National Action Plan for Combating Multidrug-Resistant Tuberculosis](#), which align with and complement the End TB Strategy by proposing reinvigorated efforts in fundamental research, diagnosis, prevention, and treatment of TB; strengthened patient care; and improved policies and support systems to benefit patients.

To support and align with global and domestic TB research goals, the National Institute of Allergy and Infectious Diseases (NIAID) developed a strategic plan to advance tuberculosis research for the next five years and beyond. In 2017, NIAID convened a trans-NIAID working group to develop the plan that included members from six NIAID divisions and the NIAID Office of the Director. These NIAID subject matter and policy experts developed a strategic framework intended to revitalize the NIAID TB research approach and take steps to close critical knowledge gaps, as well as advance research for needed tools to end the TB pandemic. The framework outlined five areas of research opportunity in TB, including improving fundamental knowledge, diagnosis, prevention, treatment, and research resources.

NIAID sought input using a Request for Information (RFI) ([NOT-AI-18-043](#); see [Appendix 1](#)) from stakeholders in the scientific research community and the general public regarding the proposed framework. Comments were submitted through a web-based form from June 27 to July 16, 2018 or by email on, but not limited to, the following three topics in TB research:

- Significant research gaps and/or barriers not identified in the framework
- Resources required or lacking that may be critical to advancing the areas of research opportunity
- Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

NIAID staff categorized the responses into cross-cutting themes when possible or otherwise summarized the responses by each of the three topic areas identified above.

Characteristics of Respondents:

NIAID received 69 responses to the RFI, including three late responses that were emailed after the online comment period closed. Most responses were from individuals at academic institutions (37) and

several responses were submitted on behalf of advocacy organizations (9). Other respondents included unaffiliated individuals (8), government employees or contractors (7), and individuals employed by private companies (6). One response was from a NIAID-supported clinical trial group and one was anonymous.

Cross-Cutting Themes

Several themes emerged from comments submitted on the topic areas identified in the RFI. Overall, the submissions were positive and supportive of the framework. Many comments detailed the need for expanding fundamental basic research to further our understanding of bacterial diversity, drug resistance, molecular mechanisms of latent TB infection, and the role of host genetic diversity in host-pathogen interactions. Several respondents called for new or improved drug regimens, including increased drug discovery using modern approaches (e.g., high-throughput screening of small molecule inhibitors), better drug delivery methods, and more effective drugs that could be administered for shorter duration with fewer side effects. Another group of comments focused on the need for improved TB diagnostics and biomarkers, including rapid diagnostics to directly detect *Mtb* in point-of-care settings, and accurate biomarkers of TB disease, particularly for latent TB.

Numerous responses highlighted the need for additional research resources for TB. Respondents particularly emphasized the importance of developing additional resources to study *Mtb*-HIV coinfection, including the development of animal models (e.g., non-human primate [NHP] models). Stakeholders encouraged NIAID to take steps to expand and revitalize the cadre of TB

Box 1. Cross-Cutting Themes
• *Fundamental research on bacterial and host diversity, drug resistance, and latent TB*
• *New and improved drug regimens, TB diagnostics, and biomarkers*
• *Resources to study* Mtb-*HIV co-infections*
• *Expansion of cadre of TB researchers*
• *Implementation and adherence research*

researchers by funding scientists with novel ideas to advance innovation and discovery, especially physician scientists, mid-career researchers, and those conducting pediatric clinical research.

Several respondents encouraged the inclusion of implementation science and research on adherence in the strategic plan. The suggested implementation science topics included research to demonstrate feasibility, acceptance, and cost-effectiveness of treatment strategies. Respondents remarked on the need for healthcare providers to utilize state-of-the-art best practices to improve the quality of care for people with TB, especially for specialized groups, such as those who are also subject to malnutrition, indoor smoke exposure, and social instability. Respondents who voiced support for adherence research underscored the need for new methods to measure adherence and development of interventions to improve adherence in high-burden and resource-limited settings.

Significant Research Gaps and/or Barriers Not Identified in the Framework

While numerous respondents characterized the proposed framework as comprehensive, several submissions identified gaps and barriers that were absent from or not emphasized in the framework. Specifically, comments focused on pharmacokinetic research and drug development. Respondents cited the need to define drug-drug interactions between TB drugs and antiretroviral therapies for treatment of people coinfected with *Mtb* and HIV, and to establish best practices for safe TB medication co-administration with hormone-based contraception and opioid substitution therapies. As the drug approval process was cited as a barrier, NIAID was encouraged to support product development all the way through the approval process, possibly through collaborations with the U.S. Food and Drug Administration (FDA), and public-private partnership mechanisms.

Box 2. Significant Research Gaps and/or Barriers
• *Pharmacokinetic research on new and existing drugs*
• *Drug development*
• *Inclusion of special populations in clinical trials*

Other respondents cited the importance of inclusion of special populations in clinical trials, such as pregnant women, children and adolescents, and PLWH.

Resources Required That May Be Critical to Advancing the Areas of TB Research

Respondents identified several resources that are key to progress in TB biomedical research. Suggestions included forging strategic partnerships between NIAID and other government partners, such as the U.S. Centers for Disease Control and Prevention (CDC), the U.S. Agency for International Development (USAID), and NIH/Fogarty International Center, to encourage scientific collaboration and foster infrastructure development.

Many research resources were cited as lacking, including animal models of TB infection using both NHP and smaller mammals. For instance, several respondents considered animal models necessary for exploring the genetic basis of TB drug resistance. Correspondingly, additional laboratories with the appropriate Animal Biosafety Level (ABSL) were also mentioned as a needed resource.

Centralized technology resource cores for multi-omics approaches, and computational methods, such as machine learning and artificial intelligence, were suggested. Respondents also highlighted the critical need to develop consolidated specimen repositories or enhance existing repositories to facilitate collaboration and information-sharing among NIH-funded TB researchers.

There were numerous comments indicating the need for an increase in funding for TB research. Specifically, respondents suggested augmenting investments in TB research to levels similar to HIV/AIDS funding. Others proposed developing new grant mechanisms explicitly for research in resource-limited and high burden countries.

Box 3. Resources Required or Lacking
• *Strategic partnerships*
• *Research and laboratory resources*
• *Centralized technology cores and specimen repositories*
• *Increased funding for TB research*

Additionally, trusted healthcare providers, as well as mechanisms to provide social and community empowerment, were cited as critical resources that are lacking in the fight against TB.

Emerging Scientific Advances or Techniques in Basic, Diagnostic, Therapeutic, or Vaccine Research That May Accelerate NIAID Research Priorities

NIAID provided an opportunity to RFI respondents to identify any new developments in the areas of basic, diagnostic, therapeutic, or vaccine research that would accelerate NIAID TB research priorities. Several emerging advances in basic research were suggested, such as expanding studies of TB host-pathogen interactions to mouse models beyond common strains, developing bioengineered 3D tissue culture systems of lung and solid organ granulomas, and employing bacterial genome-wide association studies (GWAS) on TB clinical isolates.

Many responses to this topic focused on techniques that generate big data, such as next-generation sequencing, and analysis of gene expression and immune profiles for TB infection and protective immune responses. Other basic research techniques cited include single-cell genomics and genome-scale Clustered Regularly Interspaced Short

Box 4. Emerging Scientific Advances or Techniques
• *Animal models, 3D tissue culture, GWAS*
• *Big data approaches, CRISPR-Cas9*
• *Rapid DNA sequencing, non-sputum* Mtb *testing*
• *Injection-free regimens for MDR-TB, novel vaccine strategies*
• *Patient-centered models of healthcare*

Palindromic Repeats (CRISPR)-Cas9 based genetic manipulation methods. Utilization of several analytic techniques were suggested, including mass spectrometry and flow cytometry.

Emerging advances in diagnostics research, such as technology allowing the rapid sequencing of DNA in high-burden TB settings and methods to detect secretory *Mtb* peptides, or antibodies in latently infected people, were cited as having high value. New methods of non-sputum testing for detecting TB disease were also highlighted.

Respondents suggested several therapeutic and vaccine advances with the potential to accelerate NIAID TB research priorities, including a bedaquiline-based injection-free regimen for multidrug-resistant TB (MDR-TB), host T-cell therapy, and the development of therapeutic and mucosal vaccine candidates. Respondents cited the need for novel vaccine strategies and therapies, such as those targeting non-traditional targets in *Mtb*.

Many respondents advocated for healthcare advances that would benefit the fight to end the TB epidemic, such as innovative, patient-centered models of care and the use of information technology to deliver services to TB patients.

Other Comments

Several respondents commented that the framework was robust, and one group noted that the plan was consistent with principles outlined by the TB vaccine research and development community in the Global Plan to End TB 2016-2020. Other suggestions and concerns focused on increasing patient access to interventions and products resulting from NIAID-supported research, especially in resource-limited settings.

Several respondents suggested that NIAID create a funding mechanism for translational and preclinical product development to bridge the gap between early phase product development where industry investment is low (pre-investigational drug application through Phase 1) and later stages of development.

Conclusion

NIAID solicited feedback using an RFI ([NOT-AI-18-043](#)) on a draft strategic framework to advance TB research and development for the next five years and beyond. The responses were submitted by a wide array of stakeholders, including scientists, patient advocacy groups, and members of the general public. Most of the remarks included strong support for efforts to identify the knowledge and tools needed to end TB globally. They also provided numerous suggestions and commentary that informed the development of and reinforced the TB research priorities detailed in the strategic framework. The NIAID Tuberculosis Research Strategic Plan Working Group carefully considered the suggestions and incorporated them, where appropriate, in the *NIAID Strategic Plan for Tuberculosis Research*.

Acknowledgements

Request for Information (RFI): Inviting Comments and Suggestions on a Framework for the NIAID Tuberculosis Strategic Plan

Notice Number: NOT-AI-18-043

Key Dates
Release Date: June 27, 2018
Response Date: July 16, 2018

Related Announcements
None

Issued by
National Institute of Allergy and Infectious Diseases (NIAID)

Purpose

This notice is a time-sensitive Request for Information (RFI) inviting comments and suggestions on the framework for an NIAID Tuberculosis Strategic Plan.

NOTE: It is important to read this entire RFI notice to ensure an adequate response is prepared and to have a full understanding of how your response will be utilized.

Background

In response to the U.S. Government's alignment with the concerted global effort led by the World Health Organization (WHO) to end the tuberculosis (TB) epidemic, NIAID is developing a strategic framework to advance tuberculosis research and development for the next five years and beyond.

The NIAID strategic framework is also aligned with NIAID's ongoing efforts to intensify TB research and innovation in support of the U.S. Government Global Tuberculosis Strategy and the National Action Plan for Combating Multidrug-Resistant Tuberculosis, which share and complement the WHO commitment to reduce TB deaths by 95% and reduce TB incidence by 90% by 2035 through advancing TB research and innovation.

The NIAID TB strategic framework aims to progress five areas of research opportunity vital to advancing understanding, prevention, and treatment of TB, and highlights research gaps critical to achieving the aspirational goal of ending TB.

Areas of Research Opportunity

Fundamental Research

- Understand the factors that determine the course of *Mycobacterium tuberculosis* (*Mtb*) infection and progression to, and manifestation of disease, including:

- Bacterial and host factors
- Host-pathogen interactions
- Understand factors that determine *Mtb* transmission
- Understand the epidemiology of TB (e.g., drug-resistant TB, impact of co-infection

Detection/Diagnosis

- Discover novel biomarkers or biosignatures for TB diagnosis and prediction of treatment outcomes
- Improve/develop accurate and rapid diagnostics (including point-of-care, non-sputum based, speciation, and drug-sensitivity) for all forms of TB, in all age groups

Prevention/Vaccines

- Support discovery, design, development, and evaluation of novel vaccine candidates, antigen/adjuvant combinations, and delivery approaches to:
- Prevent activation of latent *Mtb* infection
- Prevent new *Mtb* infections
- Enhance the breadth/durability of protective immune responses
- Identify correlates of immune protection
- Discover, develop, and/or improve interventions that interfere with TB transmission

Treatment/Therapeutics

- Discover, develop, and evaluate new and improved therapeutic interventions and regimens, including therapeutic vaccines and host-directed therapies
- Develop improved regimens to shorten treatment duration (e.g., chemopreventative regimens for drug-resistant and drug-sensitive TB)
- Better understand/characterize existing TB drugs (e.g., in situ pharmacokinetics/dynamics)
- Identify strategies to rapidly assess and prevent permanent disability due to drug adverse events

Resources

- Characterize and optimize existing animal models and develop novel animal models (along with supporting reagents) that represent the human disease state and better predict human responses to support product development
- Develop and standardize assays and reagents to assess vaccine efficacy
- Develop tools to assess bacillary burden in humans
- Improve/develop resources to promote sharing of animal/clinical samples and data sets
- Leverage and expand existing clinical and preclinical capacity to test promising vaccine candidates

Information Requested

This RFI seeks input from stakeholders throughout the scientific research community and the general public regarding the above proposed framework.

The NIAID seeks comments on any or all of, but not limited to, the following topics in TB research:

- Significant research gaps and/or barriers not identified in the framework above
- Resources required or lacking that may be critical to advancing the areas of research opportunity

- Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework above

How to Submit a Response

All comments must be submitted electronically on the submission website. **Responses (no longer than 500 words in MS Word or pdf format) must be received by 11:59:59 pm**

(ET) on July 16, 2018. You will see an electronic confirmation acknowledging receipt of your response.

Responses to this RFI are voluntary. **Do not include any proprietary, classified, confidential, trade secret, or sensitive information in your response.** The responses will be reviewed by NIH staff, and individual feedback will not be provided to any responder. The Government will use the information submitted in response to this RFI at its discretion. The Government reserves the right to use any submitted information on public NIH websites, in reports, in summaries of the state of the science, in any possible resultant solicitation(s), grant(s), or cooperative agreement(s), or in the development of future funding opportunity announcements.

This RFI is for information and planning purposes only and shall not be construed as a solicitation, grant, or cooperative agreement, or as an obligation on the part of the Federal Government, the NIH, or individual NIH Institutes and Centers to provide support for any ideas identified in response to it. The Government will not pay for the preparation of any information submitted or for the Government's use of such information. No basis for claims against the U.S. Government shall arise as a result of a response to this request for information or from the Government's use of such information.

We look forward to your input and hope that you will share this RFI document with your colleagues.

Inquiries

Please direct all inquiries to:

Email: niaidtbstrategicpla@niaid.nih.gov

Or

Elizabeth Walsh, Ph.D.
National Institute of Allergy and Infectious Diseases (NIAID) Telephone: 301-
761-7932
Email: elizabeth.walsh@nih.gov

Appendix 2: RFI Responses[1]

Significant research gaps and/or barriers not identified in the framework

We advocate for the inclusion of vulnerable populations in TB research. Pregnant women are at high risk of TB, and their families are at high risk of poor outcomes from it. Yet pregnant women are routinely excluded from clinical trials. Without proper data and guidance resulting from research, these women are either denied access to treatment or prevention, or treated in the absence of data. Both situations pose a risk of a poor outcome for the mother and her pregnancy. As women are of child-bearing potential for the majority of their life course, a drug is truly safe only if it can be administered to women, including those who are already and/or have the potential to become pregnant. We urge NIAID to include pregnant women and women of child-bearing potential in all research capacities within the Tuberculosis Strategic Plan. NIAID should work with NIH to establish a mandate for research networks, institutions, and independent investigators that receive funding from the NIH to institute a standing protocol to allow for the enrollment of pregnant women in the studies they conduct, or provide a justification for the exclusion of these women as part of their funding proposal (i.e., the default should be to safely include pregnant and post-partum women, making inclusion of pregnant and postpartum women opt-out, as opposed to opt-in). We welcome the efforts NIAID has taken to appropriately include children and adolescents in research, and to ensure people with HIV (PLHIV) are included in TB clinical trials. We appreciate the inclusive nature of NIAID's stated intent in the Strategic Plan to "improve/develop accurate and rapid diagnostics for all forms of TB, in all age groups," and recommend this be furthered by explicitly including all age groups, as well as PLHIV and pregnant women, in the preceding point, "discover novel biomarkers or biosignatures for TB diagnosis and prediction of treatment outcomes," as well as inclusion of children and people with HIV in the section on vaccines, as presentation and progression of disease, and immune response, may differ in these populations. Finally, while we commend NIAID's efforts to include PLHIV in TB clinical trials, NIAID must also use this plan to increase efforts to include people with TB in HIV clinical trials. Critical safety and dosing information on drug-drug interactions come far too late, as evidenced by the widespread roll out of dolutegravir in advance of understanding of how it could be delivered with rifamycin-based TB therapy. As HIV trials are usually larger and better resourced, NIAID's leadership in getting them to include people with TB to answer these important questions could avoid the current common situation of scrambling to catch up to ensure that innovations for preventing and treating HIV can work on the sizable number of people with both HIV and TB. NIAID should continue to support pharmacokinetic work to define drug-drug interactions between TB drugs and antiretroviral agents. It is also important to establish the safety of co-administering TB medicines with hormone-based contraception and opioid substitution therapies.

Resources required or lacking that may be critical to advancing the areas of research opportunity

NIAID is the world's leading funder of TB research and development (R&D), playing a historically crucial leadership role in spurring life-saving innovations, as well as leveraging additional investments from other donors. Yet resources for TB research — which hover at about one-third of the global projected need— still fall short of sums needed to close the deadly gaps in TB prevention, diagnosis, and treatment. Even NIAID, and the U.S. government more broadly, are in a position to do more. Our fair-share methodology projects that if each country dedicates less than 0.1% of its gross annual expenditure on all forms of R&D to TB, we can effectively close the vast global TB research funding gap. According to

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[1] Some RFI responses have been modified to remove identifiable information

this methodology, total U.S. government contributions to TB R&D annually should be $444,500,000. However, U.S. government investments in TB research in 2016 have totaled $316,471,566 – leaving tremendous potential for the government to build on its leadership and contribute additional resources to advance research. We recommend that NIAID, as the leading U.S. agency funding TB research, be empowered to substantially increase its annual investments in TB R&D, both to close this gap and to meet all the priorities detailed in the Tuberculosis Strategic Plan. Expanded contributions through NIAID also ensures fulfillment of our nation's ambitious vision in the National Action Plan to Combat Multidrug-Resistant TB by funding the research strategy necessary to give public health the new tools needed to eliminate this deadly disease. In addition to fiscal resources, NIAID can leverage other resources vital to efficient, collaborative research by continuing to forge strategic partnerships with other research networks and agencies involved in TB research, such as the U.S. Centers for Disease Control and Prevention's Tuberculosis Trials Consortium, and the U.S. Agency for International Development. NIAID should explore ways of supporting and synergizing on TB research efforts funded by other U.S. government agencies, such as the Biomedical Advanced Research Development Authority, the Department of Defense (including its Congressionally-directed Medical Research Program), and the National Science Foundation. A sorely lacking resource in TB research is clinical trial capacity. This point is noted in relation to vaccine research, but lack of trial capacity is a problem for TB drug trials as well. This had led to slow enrollment and lengthy trial timelines, with ethical implications as results are delayed and new standards of care emerge, which can complicate ongoing trials. Investments in building site capacity for TB vaccine and drug/drug regimen candidates are critical. Another vital resource NIAID should include is its knowledge on engagement of affected communities in research design and implementation. NIAID has been a leader in ensuring effective engagement of communities in HIV research and has mobilized its network of community representatives for TB research. More can be done to ensure that representatives are aware of the unique challenges and opportunities in TB research, to work with other research sponsors to support their community engagement work, and build communities of practice across clinical trial sites and networks.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Whole genome sequencing (WGS) presents a major scientific advance with great opportunity for applicability for TB, particularly if more cost-effective and less resource-intensive tools for it can be developed. NIAID should include WGS in its priorities for TB diagnosis to ensure the rapid developments in WGS are applicable to TB and readily adoptable in countries where TB has the highest burden.

Other comments

In keeping with the need to ensure applicability and accessibility of innovations, and human rights principles, we also urge NIAID to make an explicit part of its Tuberculosis Strategic Plan a commitment to ensuring the availability, affordability, accessibility, and acceptability of interventions resulting from research funded by NIAID (and therefore, ultimately, the public). Products of publicly -funded research should be considered public goods. This includes NIAD leveraging its investments to secure commitments to data sharing, collaboration, appropriate pre-approval access (also called "compassionate use" or "expanded access"), product registrations in trial-site and high TB burden countries, and affordable pricing. We thank NIAID and its leadership for the remarkable investments and stewardship of them to date which have enabled high quality, high impact research, and look forward to more.

Significant research gaps and/or barriers not identified in the framework

We applaud NIAID for developing this Strategic Plan for TB Research and are grateful for the opportunity to submit comments through this RFI process. The research framework presented by NIAID to advance tuberculosis (TB) research and development for the next five+ years is an extraordinary achievement and is critical to outlining the path forward to achieving the aspirational goal of ending TB. Basic research to help us understand the human response to TB has been woefully underfunded for decades. Diagnostic tools have improved somewhat, but otherwise, we are taking care of our TB patients much the same way we were 40 years ago – when we didn't know what caused AIDS, a disease we can now treat, thanks to basic and applied research, much of which was supported by NIAID. To have this same level of effort and investment in TB research, led by NIAID and articulated in this TB Strategic Research Plan, is desperately needed and very appreciated by the TB control community. Although much of the essential research is outlined in the framework, we believe it important to provide greater specificity as to the research gaps challenging those who are on the frontlines providing care and treatment for those with TB (active and TB infection) in the US. Bottom line -- we need to develop new strategies to diagnose and treat TB. Antibiotics work, but the bacterium is too smart for us and antibiotic resistance, now about 25% of culture confirmed cases in some jurisdictions of the United States, is an increasing challenge. Research is needed to determine how best to overcome the protective strategies the bacterium uses to evade killing by our human immune responses. Specific research questions include (a) how the bacterium adapts; (b) how it tricks our innate and adaptive responses, and (c) survives! Research focused on the host-pathogen interaction and immunology is imperative. Also essential is a real diagnostic test that can differentiate infection from disease, is administered and reported out at the point of care, which can accurately predict the likelihood of progressing from infection to disease. The current diagnostics for latent TB infection (LTBI) are woefully inadequate. The absence of a diagnostic "gold standard" contributes to the private provider community's unwillingness to treat LTBI. A diagnostic test which gives consistent results and accurately predicts who would progress to disease would be a game-changer for TB control efforts, in the United States and globally. With the recent exception of Bedaquiline and Delamanid, the drugs used to treat TB are decades old, have devastating side-effects, regimens and pill combinations are far too complicated and lengthy. TB needs the same focused R&D efforts and investments in pharmaceuticals like in HIV/AIDS which resulted in new classes and types of anti-retroviral drugs. We need the development of new antibiotics or other antimicrobials to target the protective nature of the TB bacterium. Finally, the importance of the discovery of a successful vaccine – one that conveys lasing immunity in all ages and against all strains of TB –

Resources required or lacking that may be critical to advancing the areas of research opportunity

The existing ATCG and TBTC are strong TB clinical trials programs and the TB control community in the US is grateful to recent findings which resulted in the introduction of rifapentine, a 12-week course for the treatment of LTBI. However, significantly lacking in the current TB research framework, and not explicitly identified in the proposed NIAID framework, is the essential inclusion of vulnerable populations (specifically, pregnant and lactating women, and children) in clinical trials focused on TB. This needs to change and needs to change rapidly. Also lacking from the framework is TB research that focuses on implementation science or operational research. The possibilities are limitless but one such study would better define the essential components of successful TB case management. Quality TB care is imperative; however, with the decreased funding for TB programs, we see devastating impacts in cuts

to shift care away from highly trained nurses and a shift away from directly observed therapy, the traditional TB public health standard of care. Additionally, funding programmatic research would leverage the data collected by US-based TB programs and provide answers to programmatically relevant questions. For example, "did TB patients on intermittent therapy have worse treatment outcomes than TB patients on daily therapy during xx period?" is a study question which could be easily be answered by pooling individual patient-level data across US-based TB programs and could be accomplished with a strong consortium model, great collaboration, and a research infrastructure erected with relatively little investment in research funding. These types of research opportunities, combined with those included in the strategic plan which are more focused on basic science and pharmaceutical or vaccine development, would significantly advance our efforts to eliminate TB.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

TB research could be accelerated by the development of data repositories, housing de-identified demographic, clinical and biological specimens from those with latent TB infection, drug sensitive TB, and MDR- or XDR-TB. These repositories in both clinical and epidemiological research agendas would contribute significantly to our understanding of basic, diagnostic,therapeutic, or vaccine research.

Other comments

Our organization's members would be those individuals who implement the findings of the TB research agenda so elegantly articulated by this NIAID Tuberculosis Strategic Plan. It is important to note that a significant and long overdue infusion of funding into TB research would accelerate considerably the US research and development efforts and would provide the United States with the opportunity to be leaders in the development of new tools to benefit both domestic, and global, TB. The United States can be way-makers in this fight to eliminate TB, the number one infectious disease killer. Our own challenges with combatting the disease here in the United States would benefit greatly from the five areas of research opportunity identified by NIAID and additional implementation science and operational research alluded to in these comments. NIAID's development of this TB Research Strategic Plan is an important step towards identifying areas where research can advance our understanding, prevention, and treatment of TB.

Significant research gaps and/or barriers not identified in the framework

The research framework outlined by NIAID provides a comprehensive strategy for advancing TB vaccine research and development (R&D) from fundamental research to preclinical research, and reflects many of the objectives that were agreed upon by the TB vaccine R&D community when it contributed to the development of the Global Plan to End TB 2016-2020. While the research areas outlined in the research framework will be essential to the successful development of new, more effective vaccines, there should be concomitant emphasis on human trials conducted in parallel with fundamental and preclinical research. Human data and samples from human trials are the only way to identify biomarkers and correlates of protection and determine which preclinical models are predictive of human protection and which preclinical biomarkers are also useful in humans. Clinical trials are the only way to determine the efficacy in humans of vaccine candidates, delivery platforms, and immunologic and antigenic approaches. The field also lacks a human challenge model for TB, a significant gap that, if filled, would enable much faster and cost-efficient triaging of candidates, regimens and approaches. The field of TB vaccine R&D is at the beginning of a fundamental transformation due to recent advances in clinical

research and the availability of human data and biospecimens from large efficacy trials. Results of a Phase 2 trial to evaluate prevention of infection showed that it may be possible to prevent high-risk populations from becoming infected with *Mtb* by BCG revaccination or potentially an improved subunit vaccine, and these results need to be confirmed. Results of a Phase 2b prevention of disease trial in *Mtb*-infected African adults evaluating another subunit vaccine will be published soon. If vaccine efficacy is demonstrated, it would be the first time a subunit vaccine has demonstrated protection of already infected adults from getting TB disease. Clinical trials are now underway to evaluate the efficacy of TB vaccines in prevention of disease recurrence, another novel trial design that can help to demonstrate biologic effect prior to advancing to larger scale trials while also providing human data to contribute towards potentially improving treatment regimens and adding to the body of learning on key scientific issues such as immune mechanisms of action and biomarkers. Another under-recognized but important aspect of TB vaccine development is development of models (whether in vitro, animal, controlled human infection or mathematical – analogous, for example, to PK/PD modeling of drugs) that would help streamline vaccine dose and regimen optimization. Due to this gap, many vaccines (across disease areas) are advanced and even licensed with a potentially suboptimal dose and/or regimen. A comprehensive framework for TB vaccine research must emphasize the full continuum of TB research activities, from fundamental research through to late stage clinical trials, and support an iterative cycle of learning.

Resources required or lacking that may be critical to advancing the areas of research opportunity

Arguably the greatest barrier to advancing TB R&D is insufficient, sustained financial resources. The funding gap for TB R&D is estimated to be $1.3 billion per year. Although researchers and product developers have been able to make progress despite the funding gap, chronic underfunding of TB R&D severely limits scientific advances, and may even impact the number of researchers willing to enter or stay in the field. To successfully enhance fundamental understanding of TB, as well as develop new products, approaches and technologies to control TB, funding is needed to stimulate the discovery of novel ideas and approaches, elucidate mechanisms of action, translate innovative ideas into viable product candidates, and advance product candidates through the development pipeline towards licensure. The most efficient and effective way to support a robust preclinical and clinical portfolio, accelerate R&D pipelines, and maximize the likelihood of success is to support multiple projects and clinical trials simultaneously, allowing for comparison of results and the ability to advance the most promising candidates. However, this approach is not possible in the current constrained funding environment for TB R&D. Potentially promising projects are sidelined due to lack of funding to evaluate or further develop them. Although multiple TB vaccine candidates are potentially approaching large-scale trials - which would offer numerous learnings that could inform both research and development, including a better understanding of human immune responses, the ability to evaluate the efficacy of a diverse set of delivery platforms, and the evaluation of vaccine candidates in different target populations and regions - at current funding levels, the field may face the scenario where only one candidate may be tested in a large trial at a time. This would result in a lost opportunity to evaluate and compare multiple vaccines and approaches in different target populations and regions, compare vaccines with different mechanisms of action (induced immune responses), and drastically slow progress. There is also a need to invest in the infrastructure to conduct mid- and late-stage clinical trials. There are multiple promising candidates potentially approaching large efficacy trials but there is insufficient global clinical trial site capacity in many TB endemic countries. Building the necessary capacity includes not only specific human resource and lab capacity at sites, but also epidemiology

studies in trial site communities to support appropriate clinical trial design and ensure robust results. New TB vaccines, drugs, and diagnostics will be essential to meeting global targets to end TB – in fact, these targets will not be met without these new tools. Failure to increase investment in TB R&D now will further delay development of these new tools, resulting in tremendous economic and human costs worldwide.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

There are numerous scientific advances and techniques in the field of TB vaccine R&D that may accelerate NIAID research priorities and TB vaccine R&D globally. For example:

- Collaborative efforts are underway globally to develop a controlled human infection model (CHIM) for TB. CHIMs have been pivotal in accelerating vaccine development for other major infectious diseases, such as malaria, RSV and influenza, as they enable early, small-scale human testing of a vaccine protective ability before commencing lengthy, expensive, large-scale clinical trials. Work conducted by a consortium of investigators is promising with preclinical proof of concept data expected to be available in 2018.
- The CMV-TB candidate, based on an attenuated version of Cytomegalovirus (CMV), a common virus that infects humans and is found throughout the world, may represent a completely new approach to TB vaccine development by inducing novel and lifelong persistent immune responses. It has shown the strongest protection seen to date of any novel candidate evaluated within a stringent non-human primate challenge model. CMV-based vaccines have also shown promising preclinical data for HIV vaccines. Research is ongoing to understand the basis of protection against TB and whether this mechanism can be induced in humans. This candidate could enter clinical trials in early 2019.
- Recent findings that intravenous delivery of BCG (IV BCG) in rhesus macaques is far more protective than intradermal and/or aerosol delivery and induces a qualitatively different set of immune responses. Similar protection results with IV BCG have been seen in a mouse model and suggest a potential role for trained innate immunity in protection. These studies and their follow-up could not only advance understanding of vaccine-induced protective immune responses and mechanisms of action, but also lead to identification of potential biomarkers of protection that could then be evaluated as human biomarkers of protection.
- Novel clinical trial designs, including prevention of infection (POI), prevention of recurrence (POR), and other prevention of disease (POD) trials in select high risk populations (e.g., healthcare workers, household contacts, miners) could help determine potential efficacy of TB vaccine candidates prior to entering large-scale clinical trials at lower cost and earlier in the development process. The first POI study to be completed reported results in early 2018 for the H4:IC31 candidate and a second arm evaluating BCG revaccination, demonstrating that vaccination can reduce the rate of sustained TB infections (measured by sustained QuantiFERON conversions) in a high-transmission setting.
- Despite positive indicators that new TB vaccines are achievable, vaccine development is inherently risky and costly. To address this, a set of 'stage gate criteria' have been developed for each stage of the development process to ensure that only promising candidates are advanced to the next stage of development. These stage gates are proposed as part of a portfolio

management process to mitigate risk, increase overall probability of success, and ensure that limited resources are directed to the most promising candidates.

Other comments

The NIAID Framework focuses on the scientific elements of advancing TB research broadly; this response focuses primarily on TB vaccine research specifically, and the challenges and risks posed by chronic underfunding. In this response we would also like to acknowledge and address the importance of community engagement in TB vaccine R&D. Community engagement is essential to ensure that those who will participate in the trials that evaluate new tools and will ultimately use the resulting products are meaningfully engaged in their development. Effective community engagement programs establish important relationships between researchers and stakeholders within communities where clinical trials take place, and provide a platform for the local community to partner with the scientific community. Community engagement has shown to benefit research by boosting retention rates and study outcomes, increasing public visibility and recruiting study participants, helping to disseminate results, and generating a sense of community ownership of the trials. Researchers and study sponsors should make a concerted effort to develop community engagement plans and include affected communities in TB R&D. Engage multi-faceted programs (e.g., Community Partners) to promote effective representation of diverse communities where the NIH HIV/AIDS clinical trials networks conduct research. These programs provide learning materials specifically developed for community-based audiences and users, support Community Advisory Boards, help provide platforms for community input into clinical research, and support a cross-site network to coordinate community input, share experiences and resources and address challenges in clinical research. Engaging communities through these types of programs should be considered integral to TB vaccine research, and particularly to clinical evaluation of new TB vaccine candidates.

Significant research gaps and/or barriers not identified in the framework

If we are to ultimately control TB in humans, work on animal and zoonotic TB diagnosis, vaccine prevention and understanding overall differences and similarities in the disease processes must be initiated. This should include understanding differences in virulence factors between *Mtb* and *M. bovis* and the differences in disease pathogenesis caused by these species.

Resources required or lacking that may be critical to advancing the areas of research opportunity

"Small" animal models and in vitro assays that can definitively demonstrate the differences and similarities in human and large animal pathogenesis caused by *Mtb* and *M. bovis* need to be developed. The in vitro assay development should include tests that rapidly and accurately speciate *Mtb* and *M. bovis* from clinical samples from multiple extrapulmonary sites (i.e. not just from sputum and blood).

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Logical alternatives to the current immunologically-based diagnostics. These types of diagnostics (TST, IGRA, Ig) are indirect responses and are not assessing the infection status in real time. More funds to test repurposed drugs against *Mtb*. This is faster, easier and less expensive than assessing new classes of drugs. Therapeutic and mucosal vaccines as opposed to traditional sterilizing vaccines delivered via the parenteral route.

Other comments

The areas of research opportunity outlined above are excellent!

Significant research gaps and/or barriers not identified in the framework

Gaps: implementation science, operational capacity building, updated recommendations for TB diagnosis, treatment and prevention for clinicians and patients, support next generation of Tb researchers and infrastructure development; collaborate with Fogarty

Resources required or lacking that may be critical to advancing the areas of research opportunity

Global funding investment for vaccine developement and clinical trials; TB cores (similar to CFAR model), biobank and data repositories/ Emerging sci advances: use of bio signatures to identify persons at risk of progressing from latent infection to active TB; Implementation studies of short course and ultra-short prevention regimens

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

Increasing funding for investigator-proposed, cross disciplinary international conferences that cover a span of bench to implementation science, with a focus on engaging early-investigators and international collaborators on future TB research conducted in moderate to high-incidence settings.

Significant research gaps and/or barriers not identified in the framework

Analyze the transcriptomic, proteomic, metabolomic glycomic and lipidomic correlates of host-*Mtb* interaction, using in vivo models (mice, humanized mice, guinea pigs, nonhuman primates); Make investment into understanding amphiphilicty, its impact on host immune recognition and persistence, its incorporation into the development of biomarker discovery and measurement approaches;need for valid biomarkers: 1. to diagnose TB in general, and in children and extra pulmonary TB in particular (diagnostic biomarkers); 2. to distinguish those latently infected individuals who should receive preventive treatment (prognostic biomarkers of TB risk); 3. to select and evaluate the most promising vaccine candidates at an early stage; and 4. to monitor and triage for predicting treatment outcomes.

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

I would like to emphasize the need for support for fundamental research on both the pathogen and the host response to Mycobacterium tuberculosis. A significant amount of money has been invested in quick translational ideas despite fundamental gaps in knowledge regarding what sort of immune responses

are protective or how the bacteria respond to immune responses and antibiotic therapy. The trend has been a movement away from mechanistic dissection in model systems and towards descriptive studies and rushed translation, even though everything in history that has been developed to effectively fight infectious disease has come from basic science findings.

Resources required or lacking that may be critical to advancing the areas of research opportunity

I think the NIAID resource that allows investigators to submit antimycobacterial compounds that they have discovered to be tested against various strains in various assays and models is really good and helps to add consistency to antimycobacterial development. I think that this resource should continue. I also think that the structural biology resources would be very helpful, although it has not been as clear to me how one accesses those unless they are part of the initial collaboration.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Multiple areas of TB research require an in-depth understanding of the biology of the granuloma, the site at which pathogen and host interact and where the decisive host immune responses are generated that decide infection outcome. Granuloma composition also contributes to antimicrobial penetration and efficacy. Despite decades of work, granuloma composition and evolution remain incompletely characterized. Little doubt exists that granuloma studies require spatial characterization, since the local milieu of cellular types and phenotypes and the distribution of extracellular signaling molecules determine the fate of this lesion.

Resources required or lacking that may be critical to advancing the areas of research opportunity

Multiscale imaging methodologies are rapidly emerging: they include multiparameter fluorescence microscopy for protein and RNA detection, mass-spectrometry-based imaging by MALDI, and mass-spectrometry-based omics spatially targeted by laser capture microscopy. Our investigators are at the forefront of these approaches. Furthermore, the rapid evolution of single-cell transcriptomics and its increasingly feasible application to cells isolated from tissues makes it possible to generate a holistic, unbiased atlas of cellular composition and cellular phenotypes associated with stages of granuloma maturation. Such techniques will circumvent the limitations of rabbit and guinea pig studies in terms of animal-specific immunological reagents.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

NIH should invest more in clinical research for novel drugs, regimens, vaccines and diagnostics.

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Optimal formulations for latent tuberculosis are critical for achieving the USG Tb strategy and Action Plan for combating MDR-Tb as well as for meeting the objectives of the NIAID strategic framework. Recently CDC updated LTBI guidelines, expanding the use of 3HP to 2–17 years; those on ART with acceptable drug-drug interactions with rifapentine; and for self-administered therapy. Research is needed for the development of pediatric friendly fixed dose combination to support Tb prevention programs. To completely elucidate the real-life effectiveness and tolerability of these regimens in patients with concurrent diseases, additional focus is needed on drug interactions studies including TDM and blood levels studies to determine the impact of concurrent use of other medications. AntiTb drugs can cause CYP450 interactions therefore more information on real-life concurrent use with other medications is important. Post approval bioequivalence studies can also support more extensive use of multisource generics as they are developed.

Resources required or lacking that may be critical to advancing the areas of research opportunity

Funding for new FDC formulation development, drug quality studies, and post approval studies.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Recently there has been reports of shortages of key Tb medicines including isoniazid, capreomycin, and kanamycin primarily due to manufacturing issues and limited supply of active pharmaceutical ingredients. Also SLD like clofazimine that are off-patent and off exclusivity does not have generic equivalent and Tb indications in their approval. Recently South Africa became the first country to roll out bedaquiline-based injection-free MDR-Tb regimen. Several key areas for support related to the above include - 1. Support to generic manufacturers to diversify sources of approved products and mitigate shortages 2. Support for shelf life extension studies 3. Drug formulation issues to support reduced pill burden for eventual deployment of bedaquiline-based injection-free MDR-Tb regimen. 4. Active pharmacovigilance and post approval safety studies to complement FDA mandated post marketing requirements and commitments PMR/PMC.

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

One of the main challenges with the strategic plan is how it will fit into the existing NIH structure given that NIH is geared more towards fundamental research and less to the development of products and regimens, especially with yet unapproved products. I suggest that, especially for a poverty-related disease facing full market failure, NIAID takes a bigger role in addressing the critical need for novel product and regimen development and support moving products all the way to (and through) approval. The process NIH follows to fund projects makes drug development challenging. There are no effective mechanisms to shorten regimens with novel unapproved drugs, yet significant funding is invested once drugs are approved. While this is important, it means significant delays until optimized treatments become available for patients. More funding needs to be directed to product development in TB where the commercial market is not going to fill in the gaps in the development pipeline. Because of the traditional NIH timeline, it is hard to get access to new chemical entities, which means being limited to non-rate limiting studies. However, product development partnerships such as the TB Alliance (that I know well) and others may be interested to partner with NIH on late stage discovery and clinical work on novel products (drugs, diagnostics and vaccines) as long as an efficient mechanism for collaboration and funding can be devised ensuring no unnecessary delays in the pathway to registration. Current NIH mechanisms, including ACTG are often focused on academic collaborations. I suggest NIAID adds programs focused around product developers as key partners. This would ideally include a possibility to initiate programs by developers that may have access and co-funding requirements set by NIH. Finally, a clear gap in the research strategic priorities is the one linked to development of new rapid diagnostics/markers for latent infection (unless the term "all forms" also includes latency. This could have tremendous implications for control.

Resources required or lacking that may be critical to advancing the areas of research opportunity

A collaborative mechanism for NIAID to work with product developers on clinical trials and toxicity and other relevant issues in product development based on pre-set criteria for advancement of work in the product portfolio, with short and efficient approval mechanisms

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Accelerating the development of new tools for TB is essential. One area where this can be significantly approved is the current time frame for review and approval, which for projects on the critical path to approval would delay progress of studies through the pipeline. Collaboration between the NIH and the FDA as part of this strategic plan is essential, especially in light of the suggested increased focus outlined in the response above regarding the need for NIH to focus specifically on product development for unapproved drugs, diagnostics and vaccines. In new product development, including for neglected infectious diseases like TB, time is of the essence—and this includes getting the products all the way to the finish line and into the hands of health care workers for immediate use. The use of targeted next-generation sequencing could be highlighted as a top priority for DST. Digital technologies, big data, AI could also complement research on how to best link precision medicine necessary today to handle DR-TB with precision PH and programmatic functions.

Other comments

TB is operating in a field of market failure. While private sector engages, it is not the type of sustained commitment that exists for diseases with an existing or future commercial market. Therefore, the public

sector MUST step up and use its resources and expertise to ensure that new products are developed and made avalable for use. This means developing more structural collaborations with product development (both for- and not-for-profit) and funding as well as partnership mechanisms that are more predictable in allocating resources and funding to ensure the quickest route to approval and optimization of products. This could be achieved by pre-approving grants for products that meet strict pre-set stage gate criteria and get FDA approval for studies, for those products aiming at IND filing and in clinical trials. The recently launched Centers of Excellence for Translational Research (CETR) call for product development work in translational development is a good example of an approach worth broader use in pre-clinical as well as clinical stages of development (the phases before and after the scope for CETR).

Significant research gaps and/or barriers not identified in the framework

The following points may be implied but are not well captured in the outline, and in my opinion are important enough to be included as explicit areas of interest: - Better understanding of the spectrum and biology of (human) latent tuberculosis infection, and means to detect people most likely to progress from latent infection to active tuberculosis disease. - Better understanding of the biology of tuberculosis infection and disease specifically in the context of HIV infection. - Investigation of the roles and biological nature of "persister" bacteria that appear to arise in the face of antibiotic treatment.

Resources required or lacking that may be critical to advancing the areas of research opportunity

Very few groups in the U.S. have the infrastructure and capabilities to conduct tuberculosis research with non-human primates, which is now an important research approach. To its credit, NIAID/NIH is expanding its capabilities for NHP research within its intramural research program. While extramural collaborations will take place, intramural researchers may not be in a position to respond to all requests for NHP-related collaboration. A means to also make TB NHP research capabilities accessible to extramural researchers, on an occasional or by-application basis, would be welcome. Some kind of resource-sharing plan sponsored by NIAID may be a way to amplify ideas of others who would like to pilot an idea in NHP studies but whose institutions are unlikely to be able to stand up and sustain a full-blown TB NHP program.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Not a single bullet point presented addresses latent TB infection (LTBI), likely because it has been historically difficult to study, I propose the following be added to the strategic framework: Active *Mtb* infection is only part of the problem. Reduction of TB incidence by 90% cannot be fully addressed without reduction in the huge global LTBI reservoir. Therefore, it is critical to develop tools to easily identify individuals with LTBI so they can be treated and the reservoir size reduced. • Understand the molecular mechanisms *Mtb* uses to establish and maintain latent tuberculosis; apply the power of genome scale approaches toward these once intractable issues • Develop biomarkers for latent

tuberculosis for better diagnosis and creative treatment regimens that harness the unique nonreplicating persistent state of *Mtb* in LTBI

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

The research priorities of the NIH for TB eradication should include: 1) the elucidation of a comprehensive transcriptional, genetic and metabolic map of *Mtb* persistence. 2) the development of strategies to prevent persistence formation or to kill persisters. 3) the development of testor strains of *Mtb* that could distinguish killing of actively growing *Mtb* or killing of persisters. 4) the elucidation of the mechanism of slow growth of *Mtb*. 5) The elucidation of the mechanism by which *Mtb* prevents the formation of antibodies that mediate antibody-dependent cellular killing.

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

The "Areas of Research Opportunity" is well-considered. I underscore the importance of targeting research in new drugs to control TB, especially drug-resistant TB, that can cure TB in less time than the current 6 months for regular TB and 18-24 months for MDR-TB, and with less side-effects. We also need advanced diagnostics, even better than what's already been developed, that can identify drug resistance quickly (minutes to hours), accurately, at low cost, and better yet if the machines are portable and easy to set up. Although NIH has usually emphasized "scientific" research and not "sociological" research, there are sociological barriers to TB treatment and control that need to be studied and addressed. What does it take to get doctors, presented with the symptoms and indicators for TB, to recognize the possibility of a TB diagnosis and order the tests? What does it take to get persons suffering from early stages of TB to seek treatment right away, when it might mean missing a day of work to go to a clinic, or losing their job or their community status, if it were known that they have TB? Ultimately these social factors can play a huge role in determining how quickly we bring TB and MDR-TB under control.

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

Shortening the course of treatment, both the full course to cure, and the intermediate point where a TB patient is not infectious, improve public health by freeing up scarce human and financial resources to deploy against other health issues.

Significant research gaps and/or barriers not identified in the framework

(Submitter left answer blank)

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

As a urologist, I've had occasion to see several cases of extra pulmonary TB, while working in this country. Please make sure there is significant investment in clinical research for novel drugs, easily transported assays for use in the field, vaccines, and drug regimens. It is essential that we forward progress with TB.

Significant research gaps and/or barriers not identified in the framework

Understanding of the mechanisms underlying TB heterogeneity will require advancements in systems biology approaches, including technologies that simultaneously capture 'omics' of both host and pathogen from the same infected cell/tissue; the development of single cell analytics; and novel methods, algorithms and tools to accurately model TB heterogeneity

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

One of the main challenges with the strategic plan is how it will fit into the existing NIH structure given that NIH is geared more towards fundamental research and less to the development of products and regimens, especially with yet unapproved products. We strongly suggest that, especially for a poverty related disease facing full market failure, NIAID takes a bigger role in addressing the critical need for novel product and regimen development and support moving products all the way to (and through)

approval. The process NIH follows to fund projects makes drug development challenging. There are not effective mechanisms to shorten regimens with novel unapproved drugs, yet significant funding is invested once drugs are approved. While this is important, it means significant delays until optimized treatments become available for patients. More funding needs to be directed to product development in TB where the commercial market is not going to fill in the gaps in the development pipeline. Because of the traditional NIH timeline, it is hard for them to get access to new chemical entities, which means they are limited to non-rate limiting studies. However, product development partnerships and others will be very interested to partner with NIH on late stage discovery and clinical work on novel products (drugs, diagnostics and vaccines) as long as an efficient mechanism for collaboration and funding can be devised to collaborative ensure no unnecessary delays in the pathway to registration and patients occur. Current NIH mechanisms, including ACTG are often focused on academic collaborations. We strongly suggest NIAID adds programs focused around product developers as key partners. This would ideally include a possibility to initiate programs by developers that may have access and co-funding requirements set by NIH.

Resources required or lacking that may be critical to advancing the areas of research opportunity

A collaborative mechanism for NIAID to work with product developers on clinical trials and toxicity and other relevant work in product development based on pre-set criteria for advancement of work in the product portfolio, with short and efficient approval mechanisms.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Accelerating the development of new tools for TB is essential. One area where this can be significantly approved is the current time frame for review and approval, which for projects on the critical path to approval would delay progress of studies through the pipeline. Collaboration between the NIH and the FDA as part of this strategic plan are essential, especially in light of the suggested increased focus outlined in the response above regarding the need for NIH to focus specifically on product development for as yet unapproved drugs, diagnostics and vaccines. In new product development, including for neglected infectious diseases like TB, time is of the essence—and this includes getting the products all the way to the finish line and into the hands of patients whose lives depend on them.

Other comments

TB is operating in a field of market failure. While private sector engages, it is not the type of sustained commitment that exists for diseases with an existing or future commercial market. Therefore, the public sector MUST step up and use its resources and expertise to ensure that new products are development and make them into the hands of patients who need them most. This means developing more structural collaborations with product developments (both for- and not-for-profit) and funding and partnerships mechanisms that are more predictable in allocating resources and funding to ensure the quickest route to approval and optimization of products. This could be achieved by pre-approving grants for products that meet strict pre-set stage gate criteria and get FDA approval for studies, for those products aiming at IND filing and in clinical trials. The recently launched Centers of Excellence for Translational Research (CETR) call for product development work in translational development is a good example of an approach worth broader use in pre-clinical as well as clinical stages of development (the phases before and after the scope for CETR).

Significant research gaps and/or barriers not identified in the framework

Please increase significantly the amount for clinical research for new diagnostics, novel drugs, and regimens, and new TB vaccines.

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

(Submitter left answer blank)

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

NIH should invest more in clinical research for novel drugs, regimens, vaccines and diagnostics.

Significant research gaps and/or barriers not identified in the framework

(Submitter left answer blank)

Resources required or lacking that may be critical to advancing the areas of research opportunity

Money invested in clinical research for novel drugs, regimens, vaccines, and diagnostics.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

(Submitter left answer blank)

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

NIH should invest more in clinical research for novel TB drugs, regimens, vaccines, and diagnostics.

Significant research gaps and/or barriers not identified in the framework

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

1. TB blood test. A TB blood test has been developed that monitors the production of IgG, IgM or IgA antibodies in latently infected individuals, among BCG vaccinated infants and during mycobacterial infections (TB, leprosy and mycobacterioses). This ELISA test is very useful in rural areas. 2. Rapid test Flowthrough. a rapid test for pathogen detection, useful at point-of-care, has been developed. It allowed investigations on the value of the BCG vaccine. The test was proposed to FIND and turned down on the ground that it needed a cabinet. This objection is unacceptable. The test needs an improvement at the level of solubilisation of sputum. 3. Therapy adjuvants A food supplement (much cheaper than drugs) able to stimulate the production of Nitric Oxide (the first response of macrophages to an invasion) has been shown very effective in the treatment of AIDS patients. The active principle, uleine, was shown to be effective also against TB.

Other comments

The TB challenge has worsened since 2016. Let us hope you will be able to improve the situation.

Significant research gaps and/or barriers not identified in the framework

For pulmonary TB. While noted generally under Treatment/Therapeutics phamacokinetics/pharmacodynamics (PK/PD), there is room for advancement of mathematical modeling and simulation that builds on the current PK/PD framework. This includes (1) more precise conventional PK/PD models that better account for the individual patient, (2) more detailed mechanistic or semi-mechanistic modeling of drug combinations, and (3) moving beyond conventional PK/PD methods to include advanced models and statistical methods for dose-exposure-response relationships focused on details of disease in the lungs (lesion structure and formation, drug penetration, differing bacterial subpopulations, phenotypic variation) However, there is generally a lack of experimental support for such an approach, with the main hurdle being the current approaches to experimental design that are based on standard hypothesis testing rather mathematical model development. For example, in vitro and in vivo dose-response studies may be aimed at determining whether a new compound is more efficacious than a control compound, with experimental design based on a statistical power calculation to answer that question. A mathematical model (even perhaps only a simple model) however, that is based on a conceptual understanding of the physiological and biochemical processes involved would require data to precisely specify the model parameters throughout the time course of the experiment, and also to discriminate between more than one model type. These issues could be addressed by focusing on model-based experimental design - i.e, designing the experiment to develop and test hypothesized dynamic mathematical relationships that are conceived prior to the start of the experiment.

Resources required or lacking that may be critical to advancing the areas of research opportunity

The main barrier to model based experimental design in tuberculosis drug development is the lack of detailed and precise experiments to support such an approach.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Fundamental Research: Identify host biomarkers (using an omics approach, identify targets for therapy and vaccines; identify correlates of protection and risk to progressing; methods to quantify *Mtb* bacilli in vivo

Better Diagnostics/Clinical trial for ultra-short preventive TB therapy

Therapeutics: Shorten Tb drug treatment/ Better vaccines/Optimization of treatment of TB and other comorbidities, particularly diabetes mellitus (DM)

Adherence/Resources: Vaccine research in NHP

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

(Submitter left answer blank)

Resources required or lacking that may be critical to advancing the areas of research opportunity

My one suggestion here is to consider centralizing a resource core for image analysis, machine learning, and artificial intelligence to automate and streamline research and diagnostic methods that rely on visual interpretation. The resource could geared towards any type of medical or research images, possibly algorithm tools that people could access, or shared image databases (say of granulomas) which can be challenging to access.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Thanks for the opportunity. The framework is very thorough. My only suggestion - really food for thought - may be worth adding or specifying that research focused on biomarkers and predictive modeling (whether it be disease progression, treatment responses, or vaccination responses) use cross-

disciplinary computational expertise for data analyses, and testing for accuracy using independent data sets. My impression is that biomarker studies often end up being descriptive statistics.

Other comments

Maybe consider support of developing bioengineered 3D tissue culture systems of lung and solid organ granulomas?

Significant research gaps and/or barriers not identified in the framework

Gaps: validation of new anti-mycobacterial drugs; method of detection that can be employed in resource-limited setting

Opportunities in Fundamental Research: Animal and cellular models to investigate latent *Mtb* and *Mtb* in granulomas

Prevention/Vaccines: Identify *Mtb* antigens and protective antibodies;

Therapeutics: Validation of anti-*Mtb* activity in novel compounds and identify combinations ofsynergistic compounds

Resources required or lacking that may be critical to advancing the areas of research opportunity

Resources: Support novel means to deliver drugs to POC

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

With the increasing incidence of Type 2 Diabetes (T2DM), both among children and adults it is important to investigate the influence of metabolic disorders, impact of nutritional status on reactivation of latent tuberculosis. For treatment/therapeutics, it will be important to evaluate anti-TB activity of drugs which are already approved by FDA for other intracellular pathogens or respiratory disorders, to reduce the regulatory timeline for a new therapeutic to reach to the market/patient. The above framework does not include: - Effect of non-infectious co-morbidities on primary or reactivation of latent tuberculosis. - Repurposing of drugs for TB treatment -More efforts on clinical research network programs including both physician and basic research scientists -Focus on all forms of TB including TB meningitis since this remains mis-diagnosed

Resources required or lacking that may be critical to advancing the areas of research opportunity

There has been an increasing interest in single cell-genomics, it is important to have resources available to community and concerted efforts to validate the genomics data with their functional outcome and have an understanding to what extent it modulates immune or vaccine response to TB. More efforts on clinical research network programs including both physician and basic research scientists. Development of low cost diagnostics that may be used in resource limiting settings. TB granuloma may be considered as solid tumor, resources are needed to characterize similarity / dis-similarity of TB granuloma with cancer.This will help to develop newer host-directed therapeutic approaches.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Identifying and characterize the vaccine induced factors such as suppressor cells (e.g. myeloid derived suppressor cells) that may inhibit vaccine induced protective immune response. Utilization of flow cytometry based immunoassay approaches for high throughput and simultaneous study of proteins and RNAs.

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Key signalling pathways subverted by Mycobacterium tuberculosis infection. Host mediated therapies.

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Fundamental research and therapeutics: understanding the mechanisms underlying drug tolerance and transient drug resistance, and using this information to design drugs to target tolerant and/or transiently resistance bacterial populations.

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

The NIAID TB Research Strategy appears robust in terms of preventing, detecting and treating TB; however, many of these efforts will be for naught as long as TB treatment is protracted and patients fail to complete these regimens. The Strategy is notably devoid of any objectives related to improving treatment adherence and completion. Without adequate measures to support and monitor patients until treatment completion, treatment failure and acquired drug resistance will continue. As an example, the newly approved, highly effective oral medications for MDR-TB provide a rare opportunity to achieve TB elimination goals; however, strict adherence will be critical to avoid promotion of M. tuberculosis strains that are resistant to these drugs as well. Addressing adherence can be accomplished

through the development and evaluation of individual (e.g., increasing health literacy, adherence monitoring and support), structural (e.g., food and housing security, customizable drug formulations that are easier for patients to take and minimize side effects), and social (e.g., reducing stigma, increasing awareness of treatment benefits to the community) interventions.

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

The 5 areas for research for TB is already extensive. I think that more resources should be allocated for basic research particularly the discovery of an effective vaccine. In the area on treatment, an effective, less toxic and short regimen for drug resistant must be prioritized.

Resources required or lacking that may be critical to advancing the areas of research opportunity

Laboratory capacity has to be increased especially in high burden countries to ensure research advancement.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

In my opinion the heterogeneity of TB disease (lesion types, host cells infected, bacterial phenotypes, organs, ect..) represents the biggest hurdle to all elements of diagnostics, vaccines, and control. This is similar to what the cancer field is describing with tumor heterogeneity. For example: Disease progression appears to be determined at the individual lesion or host cell level. Diagnostic analysis of bulk specimens (eg, blood, urine) are essentially average measurements of a whole organism response. These approaches are likely not sensitive or percise enough to predict disease outcome. Likewise, immune control of TB is seemingly determined at the individual lesion or host cell level. Immunology has not defined what host response is truly protective (immune correlates) and how this plays out at the lesion level. It is also likely that the prolonged treatment with TB drugs is required to eradicate different populations of bacteria. These different populations of bacteria also likely contribute to the development of drug resistance. We need to understand how lesion/tissue/host cell heterogeneity impacts our current drug treatments and going forward we need to incorporate this knowledge into TB drug development. In my opinion all aspects of the above framework could be strengthened if they incorporate the concepts of TB disease heterogeneity. Acknowledging the heterogeneity of TB disease

certainly complicates our view of the disease but I really think that by not addressing this we are holding back progress.

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Other comments

Given that TB now kills more people than AIDS, is it time to have a dedicated TB study section and research focus?

Significant research gaps and/or barriers not identified in the framework

1. Lack of understanding of key anatomical barriers and innate host responses that prevent about 60% of humans from getting infected nor triggered a memory adaptive response after close *Mtb* exposure.

2. Lack of understanding of the biology of HUMAN granuloma and its different stages in the containment, tolerance, clearance, and failure to contain *Mtb* infection.

3. Lack of understanding of *Mtb* immune evasion and immune tolerance mechanisms in humans.

4. Role of *Mtb* bacterial diversity and key bacterial factors in pathogenicity and transmission

5. Lack of reliable systemic human biomarkers of initial infection, containment and protection, and containment and non-protection state.

6. Lack of funding in recent decades to clinical investigators with translational training in TB leading to a reduced capacity, interest and expertise in translational TB research in the US. Young investigators commonly take other research pathways due to a very difficult extramural funding environment, which also affect US-international research collaborations.

Resources required or lacking that may be critical to advancing the areas of research opportunity

1. Funding to support protective time to mid career researchers, and pediatric investigators

2. Funding for new US-international research effort to create research capacity and sustainable infrastructure in high TB endemic areas and high TB transmission settings.

3. NIAID improved role to support research efforts by reaching out potential young and mid career investigators, and providing technical and research tools that are usually not available without funding in most academic institutions (eg, gene expression analysis and bioinformatics core support, etc)

4. Level up funding of TB research to AIDS research

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Emergent gene expression and field-based immunoprofiling human data to better characterize TB infection states and risk of reactivación and likelihood of protection. Presence of secretory *Mtb* peptides in serum protein in patients with TB infections. Novel vaccine strategies with non conventional and conventional immune protection against initial infection and TB reactivation.

Other comments

Happy to discuss over the phone or in person

Significant research gaps and/or barriers not identified in the framework

We do not know what epitope peptides are presented to CD4 or CD8 T cells by M. tuberculosis-infected cells - there are reasons to believe that the peptides presented by dendritic cells to prime naive T cells differ from those presented by dendritic cells and macrophages later in infection. New methods for sensitive detection of peptides bound to HLA molecules on cells from biohazardous (M. tuberculosis-infected) samples are needed.

Resources required or lacking that may be critical to advancing the areas of research opportunity

1. A BSL3 facilities equipped with advanced microscopic imaging capabilities, specifically, multiphoton intravital microscopy with appropriate biocontainment. 2. Additional ABSL3 facilities for TB research in nonhuman primates. Considering the priority given to use of nonhuman primates in TB research, there need to be more than two or three institutions/facilities/investigators available for collaborative studies. 3. Support to develop new small animal (especially rodent) models that better mimic the distinct stages/outcomes of human infection with M. tuberculosis AND that include opportunities for genetic manipulation that currently only apply to limites strains of mice.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

1. Support to acquire equipment needed for single-cell RNA studies in BSL3/ABSL3 facilities. 2. Need support to develop embryonic stem (ES) cells from diverse strains of mice suitable for TB immunology and vaccine research, so that targeted deletions and modifications can be made.

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Implementation science for diagnostic algorithms and novel testing modalities, including triage testing, that may accelerate TB treatment and improve outcomes.

Resources required or lacking that may be critical to advancing the areas of research opportunity

More RFAs for clinical and implementation sciences, particularly for HIV/TB co-infected patients.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Need more understanding of implementation science to merge existing tools with novel diagnostic and therapeutic options.

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Adherence, linkage and retention in care for patients with DR-TB. Short course regimens remain quite toxic and have substantial treatment-related adverse effects. Further, 9 months remains a very long duration and loss to follow-up is substantial. Innovative models of care are needed to decentralize treatment to primary care facilities - thereby increasing access to care. Symptom management strategies for DR-TB treatment.

Resources required or lacking that may be critical to advancing the areas of research opportunity

Funding

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Innovative (differentiated) models of care are needed to decentralize treatment to primary care facilities - thereby increasing access to care.

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

What are the barriers in early suspecting, diagnostics time period, treatment adherence and positive prevention

Resources required or lacking that may be critical to advancing the areas of research opportunity

No investment on above topics at all entire TB research investment is on medical aspect not on social and community empowerment aspect.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Include patient perspective along with medical perspective equally

Other comments

PLHIV can be utilized as an TB champions for positive prevention and treatment adherence

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Significant research gaps and/or barriers not identified in the framework

The notion that TB has a very strong human genetic determinism was unambiguously established in the 1930s. Evidence is compelling for anyone who wants to read these papers. What is missing is the identification of the causal genes that account for a significant proportion of cases. I don't refer to weak GWAS signals that were predicted and shown to be insignificant. I refer to causality -- cause and effect. The reason these genetic disorders have not been identified yet is that TB, like all human phenotypes, shows genetic heterogeneity. Even SCID or Fanconi can be caused by mutations in >20 genes. Obviously, TB will be caused my mutations in >100 genes, each gene being causal in a small but not negligible proportion of cases. Our preliminary data strongly suggest that this model is correct. This is the fundamental problem in the field of TB pathogenesis. I think your call should make it explicit.

Resources required or lacking that may be critical to advancing the areas of research opportunity

What is lacking is money to fund WES and WGS, and the accompanying biochemical and immunological experiments, which provide for the first time in human history the opportunity to tackle the problem of genetic heterogeneity underlying human TB. Human TB should be studied genetically like any genetic disorder: with patient- and family-based studies. Patients can and should ideally be recruited in populations, but they should be studied one by one, or in small groups, because of genetic heterogeneity. There is no need to re-do the GWAS mistake with NGS. The same causes produce the same consequences: a wrong genetic model failed once, it will fail twice. Genetic heterogeneity can only

be tested by patient- and family-based studies, following the spectacular tradition of 100 years of clinical genetics.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

WES and WGS.

Other comments

Understanding TB should be the priority. Understanding why only a small proportion of exposed individuals develop life-threatening TB. Understanding the human genetic and the immunological mechanism underlying inter-individual variability. Although TB can be prevented by hygiene and cured by antibiotics, this is unlikely to work forever. Understanding TB, its pathogenesis, and especially its genetic and immunological determinism, is the only way to develop host-directed preventive and therapeutic approaches.

Significant research gaps and/or barriers not identified in the framework

- Understanding the impact of TB lineage (and sub-lineage, family, clade etc) on , pathogen virulence, transmission, clinical phenotype and outcomes.

- Understanding the role of host diversity in host-pathogen interactions, as TB strains have co-evolved with humans, resulting in phylogeographic restriction of certain lineages

- Develop mechanism to ensure that strains from countries like India which are underrepresented in molecular studies are obtained for vaccine studies

Resources required or lacking that may be critical to advancing the areas of research opportunity

Long-read sequencing of P-E and P-P-E regions that are not analyzed by Illumina based short-read sequencing. Most WGS analyses exclude these regions, which may be valuable for understandng the role of antigen variation in host-pathogen interactions.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Use of MALDI-TOF or LC-MS to identify resistance

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Under "Treatment/Therapeutics" there is no mention of the importance and value of efforts to improve the adherence of patients with active TB to treatment regimens that have been shown, when correctly implemented and completed, cure greater than 95% of patients with drug-sensitive (DS) TB. The WHO, In its most recent (April 2017) guidelines for the treatment of DS TB contain the first-ever WHO evidence-based recommendations on the use of, among other approaches, electronic medication monitors to help patients adhere to TB medication and deliver TB care. (Recommendations 2.1.2 and 2.1.3). However the WHO recommendations indicate that the confidence Level (Strength of Evidence) for these recommendations is "Low".

Resources required or lacking that may be critical to advancing the areas of research opportunity

Rigorous additional research is now needed to demonstrate the Feasibility (Relative ease of implementation and operation of the technology within existing health systems, technology infrastructure, and supply chains), Acceptance (relative satisfaction of patients and providers with the necessary technology), Effectiveness (e.g., improvement in average adherence and the extent to which the technology positively impacts treatment outcomes as well as positive impact on relapse as compared to standard of care) and Cost Effectiveness (an assessment of cost-effectiveness/comparative cost-effectiveness of the proposed technology-enabled intervention versus the standard of care in the relevant geographical and clinical context. To accomplish these goals, funding of various technologies and implementation research is badly needed.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

There are now at least 3 relatively inexpensive technologies (electronic dose monitoring, video-observed therapy, and "99DOTS" (in which daily phone call-in is used) as well as other technologies (ingestible sensors, "smart" apps, etc.) that are currently under study in several settings. To allow and promote scale up of of one or more of these adherence interventions in high-burden, resource-limited settings, considerable additional improvements in the technology and its interface with local and national TB control programs, and especially more implementation research is needed. The ultimate goal is demonstrating to payers (governments and other funders of TB therapy) the scalability and cost-effectiveness of these adherence interventions.

Other comments

I have been involved in large-scale efforts to study and improve patient adherence in TB and HIV for almost 30 years. There are numerous other approaches to determining the adherence to medications of patients with HIV, TB and many other chronic conditions. The 2 most important limitations of virtually all of the methods to measure adherence, such as pill counts, measures of drug or biomarkers in plasma or dried blood spots or in other matrices such as hair, is that they are retrospective, and cannot be used to improve the adherence of an individual patient. Moreover, they are generally much more expensive to implement than the technologies mentioned above.

Significant research gaps and/or barriers not identified in the framework

1) What are the mechanisms of drug tolerance in TB? What TB genes are involved (efflux pumps, toxin-antitoxins, etc.), and how does the host immune system promote drug tolerance? 2) Related to point 1 above: what are the mechanisms that enable TB to persist in a clinically latent state? 3) Are there additional common mechanisms of drug resistance left to be discovered in TB? This has important implications for molecular diagnostics. 4) Related to point 3 above: although there is limited genetic diversity in TB, this diversity seems to be important (including for reasons other than drug resistance). What is the impact of this genetic heterogeneity? 5) Better understand/characterize existing TB drugs (e.g., in situ pharmacokinetics/dynamics)– to this I would add a better understanding of the mechanisms of action (MOA) of existing antituberculars, including the hundreds if not thousands of pre-clinical anti-TB drugs which we know to be TB bioactive, but for which we do not know how they work. 6) The comprehensive application of genetics to promote early stage TB drug discovery: target identification, target validation, MOA determination, drug-target synergy discovery, etc.

Resources required or lacking that may be critical to advancing the areas of research opportunity

See below.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

There are a number of emerging scientific advances that may accelerate these NIAID research priorities: 1) The development and application of genome-scale CRISPR based genetics has the potential to dramatically accelerate TB research (full disclosure: this is the primary thrust of my research program). Genetics has long been a barrier to progress in TB, and CRISPR enables us to ask critical questions that would be impossible with any other current method. The development of transposon-site hybridization (TraSH) was a landmark event for the TB field- CRISPR promises to be a similarly, if not more, impactful advance. 2) The expansion of TB host-pathogen interactions to mouse models beyond the standard BALB/c and C57BL/6 has great potential to model human genetic diversity in a relevant, tractable, and affordable small animal model. 3) Bacterial GWAS studies with TB clinical isolates has proven to reliably identify mutations associated with TB drug resistance. While few new common mutations have so far been identified that seem to contribute to drug resistance, it is now time to extend these studies to identify mutations associated with other important bacterial phenotypes (e.g. drug tolerance).

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

It is disappointing to not see implementation research in the framework. Research to date has led to significant advances in diagnostics and in treatment for MDR TB and LTBI. Yet, studies have consistently shown there has been poor uptake of novel tools and that the overall quality of TB care is poor worldwide. The impact of new tools developed through this framework will be mitigated unless there is also investment in research to improve care delivery and quality.

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Gaps in preventing TB spread: "An interruption of continuity" had been created by the so call ICE immigration policy, actually, by not screening any person entering the USA. This is a health problem caused by not having an organized-political-health discipline on the nation; putting at risk the dissemination of controlled diseases such as Tuberculosis that could be introduce by new people coming into the USA. It is very important that a proper Federal or local government create or incorporate a local organism per state or at a Federal level to deal with the crises causing the ill designed immigration department to avoid, unintentionally, affect the control of the health of the inhabitant of USA. On the above reasoning, and because politics is taking over decisions pertaining to other department, it is

important that ICE be abolished and a well designed project be establish to avoid the spreading of diseases on the USA population by incompetent organisms.

Resources required or lacking that may be critical to advancing the areas of research opportunity

Congress must and should establish proper new laws in reference to USA immigration and invest the most money in any department created to help in the watch and assist the Immigration Dept. ICE is not the proper one to handle this situation that end up in abuses to foreigners entering this NATION and that could turn in future harm to the USA inhabitants.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

TB is most abundant in poor nations. In well organized cities, there is less possibilities of a person acquiring TB. Tuberculosis vaccines are not used for anyone set to stay, temporally or not in USA territories due to the disorganized way the government is controlling immigration. ...again, ICE is not the proper department to work in immigration problems in the USA. ...Congress have to enact new laws establishing the safeguard of USA inhabitants. ...up to now, it seems, but not medically shown, that the health of new incoming immigrants are mishandled by the Federal Government ...even new immigrants are exposed to acquire TB when entering the USA, Mycobacterium Tuberculosis is a disease, not an ethnic illness and actually, children immigrants are at risk, for their IG has not yet develop enough to protect them from local USA diseases.

Other comments

Source: https://en.wikipedia.org/wiki/Tuberculosis Presently, one-third of the world's population is thought to be infected with TB.[1] New infections occur in about 1% of the population each year.[11] In 2016, there were more than 10 million cases of active TB which resulted in 1.3 million deaths.[3] This makes it the number one cause of death from an infectious disease.[3] More than 95% of deaths occurred in developing countries, and more than 50% in India, China, Indonesia, Pakistan, and the Philippines.[3] The number of new cases each year has decreased since 2000.[1] About 80% of people in many Asian and African countries test positive while 5–10% of people in the United States population test positive by the tuberculin test.[12] Tuberculosis has been present in humans since ancient times

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Significant research gaps and/or barriers not identified in the framework

(Submitter left answer blank)

Resources required or lacking that may be critical to advancing the areas of research opportunity

Per "Improve/develop resources to promote sharing of animal/clinical samples and data sets", some of the recent NIAD DAIT RFAs and FOAs reference data repositories of record to note where data sets are to be deposited for sharing, If existing repositories (e.g. NCBI GEO/SRA/dbGAP, ImmPort, PATRIC, PRIME) are adequate, the TB Strategic Plan RFA should note which repositories should be used for sharing of data sets. If the repositories are not adequate, either the TB SP RFA should note development of new repositories or enhancement of existing repositories.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

(Submitter left answer blank)

Resources required or lacking that may be critical to advancing the areas of research opportunity

A global biomedical workforce of physician scientists able to work bench-to-bedside and back is severely lacking in TB. This, as well as significant NIH investment and deep pharmaceutical engagement are the three factors crucial to the rapid generation of transformative breakthroughs in HIV that have been lacking to date in TB. A funding mechanism that links the BRICS R&D network to the best of the NIH, including a Fogarty-like mechanism specifically focused on training the next generation of global TB leaders in biomedical discovery and translation is sorely needed. Please invest heavily in the global R&D workforce as it will also serve the American people well in the context of flu and other pandemic diseases. Please ensure that specimen collection is fully funded in all NIH-sponsored clinical trials (see comments on Precision Medicine and development of a "new taxonomy of TB" below).

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Please ensure that breakthroughs in immuno-oncology are rapidly translated into TB through collaboration and cross-talk between NIH-funded TB groups (TBRU, REPORT, HVTN, ACTG) and PACT (Partnership for Accelerating Cancer Therapies) as well as other Cancer Moonshot activities. Please ensure that the principles outlined in All of Us (Precision Medicine) are uniformly applied to all NIH-funded TB trials (does the microbiome matter to TB vaccine response? do parasitic co-infections impact TB drug treatment response? do immunogenetics matter in response to either drugs or vaccines, or both?). Our database of clinical observations in the modern era is too narrow to build innovative solutions upon; we need to learn more from every TB patient we study...

Other comments

This is stupendous, I cannot thank you enough.

Significant research gaps and/or barriers not identified in the framework

Supporting efforts that bridge between chemical biology tools and drug discovery hits and leads and development candidates.

Resources required or lacking that may be critical to advancing the areas of research opportunity

Supporting research at the interface of fields such as chemistry and biology, computation and chemistry, computation and biology.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

Thank you for supporting tuberculosis research.

Significant research gaps and/or barriers not identified in the framework

One area that is not specifically addressed is the identification of biomarkers that predict cure of latent TB...besides waiting for time to pass. Since latent TB is the reservoir for active TB, tackling new therapeutics that can eliminate latent TB organisms with fewer safety (or convenience) issues would be beneficial to degrade the reservoir and to patient welfare. But the current therapeutic LTBI regimens rely on time to subsequent active disease, which is not amenable to new drug development by industry. The number of patients treated for latent TB yearly in the U.S. make it a compelling market opportunity for drug developers, but lack of a near-term biomarker is impeding efforts. A drug that could eliminate latent TB organisms safely and efficiently could also be used in active TB therapy. Otherwise, the list of items to tackle with research seems pretty comprehensive.

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

(Submitter left answer blank)

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

This is in no way critical of NIAID, who have been excellent. Our experience has been that there is major difficulty in persuading external investors or industrial partners that TB represents a good disease for conventional drug development paradigms- raise A series to fund pre-IND, IND & Phase 1, then raise B series to fund Phase 2a etc. The 'valley of death' appears to be the inability to raise series A sums of money (6-10M US) to get Phase 1 done in particular. Thinking of ways to address this particular 'valley of death' could be very productive in advancing science to the clinic. Of course, the sums of money are large (6-10M US for Phase 1 alone), and so rigorous review (for example, multiple replications of in vivo data in mouse models at a minimum) and phased funding, as well as other controls to ensure the wisest possible uses of this funding. NIAID could also use standardized processes and contracts for pre-IND, IND development, Phase 1 performance etc, and might be able to achieve economies of scale, but also prevent the wasted time and money that small companies often go through as they develop their expertise to actually be able to know what they have to do to get through Phase 1, find consultants who need to get up to speed in TB, find appropriate vendors etc.

Significant research gaps and/or barriers not identified in the framework

While it is important to develop new tools to end the TB epidemic, we must also work to use our existing tools more effectively in high TB burden areas. We need to fund studies that look at ways to measure the implementation of existing TB tools. Implementation should be a specific area of investigation in whatever effort the NIAID is developing to address ending the TB epidemic. Any new tool that is developed will suffer the same fate as the old tools if we do not understand how to implement them.

Resources required or lacking that may be critical to advancing the areas of research opportunity

We need a dedicated and sustained focus on funding the study implementation to identify best practice for TB screening, diagnostic testing, treatment, transmission control and how to spread these best practices widely.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

The entire field of implementation science is rapidly advance in methods and techniques to conduct the analyses need to close the "know-do" gap. The NIAID should recognize the importance of this field in ended the TB epidemic because efforts to end TB are unlikely to be successful without it.

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Our diagnostics (TSTs and IGRAs) cannot differentiate between TB states and even these are not very accurate. We need a reliable (and cost-effective) test that can identify infection from disease. Is there hope for the LAM assay?

Resources required or lacking that may be critical to advancing the areas of research opportunity

It was all-hands-on-deck when HIV reached its zenith. Dozens of useful drugs were developed. TB is still using decades-old drugs with myriad side-effects and toxicity issues. We need new antibiotics and antimicrobials that address the protective nature of the TB bacilli.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

LAM for non-sputa testing for TB.

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Mycobacterial culture remains the gold standard for detection of TB, but it is too slow and time consuming. Nucleic acid amplification methods led by Cepheid GeneXpert technique significantly shorten the turnaround time, but the sensitivity is about 90% in comparison to culture. DNA-based testing can be used for clinical therapy monitoring.

Resources required or lacking that may be critical to advancing the areas of research opportunity

Enhance detection methods based on metabolomics targeting TB-specific metabolites. Such techniques have been studied in H. pylori and Aspergillus detections.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

In the US where TB rate is relatively low, so promptly and correctly isolate TB patients in the hospital is a tough and critical work. We usually put the suspected patients on air-borne isolation while waiting for testing results from clinical microbiology lab. One way we can do is to put a "membrane" before the HEPA filters, and all volatiles can be absorbed and concentrated on the membrane which can be used for analysis by LC-MS-MS.

Other comments

No.

Significant research gaps and/or barriers not identified in the framework

The most significant barrier is NIAID's nepotism and preference for researchers who have been touting the same ideas for years and yet have failed to translate any of their animal studies into human subjects.TB is a disease that affects the poorest of the poor-there is a significant social/environmental context to this disease.Thus, teams that involve both physician-scientists as well as basic researchers have to collaborate.Early career physician-scientists with new ideas need to be encouraged and reviewers need to look beyond the "safe investment" mentality to fund more "high risk high reward" research. Please also keep in mind that good ideas can also come from "not so well known" settings.

Resources required or lacking that may be critical to advancing the areas of research opportunity

Country-specific consolidated sample repositories and clinical databases which allow multiple researchers to collaborate.These research groups have to include young and old researchers.The major high burden countries all have country-specific unique challenges and NIAID needs to recognize this. If possible, some grant mechanisms specific to high burden countries should be created-for e.g.malnutrition and diabetes and impoverished migrant labor populations in India,HIV in Africa etc. Currently, there is a lack of focus on improving treatment outcomes overall and in specialized groups which are not affected by HIV for e.g. subjects with malnutrition, indoor smoke exposure, social instability. Research into methods improving treatment outcomes in such groups is urgently needed.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Nanoparticle-based targeted therapy, Nanotrap-based diagnostics. T cell therapies as host-directed therapy

Other comments

The best diagnostics in Infectious Diseases are direct detection of the pathogen.Rapid methods to directly detect TB in point of care settings are urgently needed. Also, mechanisms and outcomes of INH resistance needs more research as it is one of the major causes of resistance in a high burden country like India.

Significant research gaps and/or barriers not identified in the framework

1. There is a need to explore issues related to adherence of care providers to treatment regimens particularly at private sector. This is imposed by the fact that many patients in developing countries uses private sector. It may not be the case in USA. 2. Patients compliance is another issue need to be explore and I think it has a lot to do with resistance

Resources required or lacking that may be critical to advancing the areas of research opportunity

Human resources is a key in treating a chronic case like tuberculosis. Patient may prefer to be treated and followed by the same provider

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

How to deliver services to TB patients using IT technology should be considered

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Better understanding of transcriptional regulators that enact virulence programs at the genetic level. Inhibiting transcription of genes associated with virulence factors may prevent M. tuberculosis from entering a latent state or reactivation after a period of latency. We need to dedicate a portion of funding towards a comprehensive understanding of global transcriptional network models. This entails elucidating the transcriptome of essential transcriptional regulators, such as the MtrAB and PrrAB two-component systems, as various stages of infection to better understand the essential genes they regulate in efforts to expand our repertoire of potential novel therapeutic targets. Furthermore, high-throughput screening of small-molecule inhibitors targeting transcriptional regulators should receive adequate funding in efforts to improve the spectrum of novel therapeutic targets against M. tuberculosis. Additionally, we will benefit from integrating multiple "omics" strategies (e.g. transcriptomics, metabolomics, etc.) to approach the development of treatment strategies, in the light of both in vitro and in vivo settings.

Resources required or lacking that may be critical to advancing the areas of research opportunity

Developing multi-omics tuberculosis research centers with research staff and faculty experienced in diverse high-throughput fields such as transcriptomics and metabolomics. Whereas high-throughput strategies provide important insights into the cause and progression of tuberculosis, they are seldom used in conjunction in many peer-reviewed publications. By integrating these techniques into large, well-devised experiments, we will obtain a global picture of how M. tuberculosis is able to persist as one of mankind's most efficient pathogens. This also entails using the same strategies described above to elucidate the systemic effects in humans, using patients experiencing acute, latent, and reactivated tuberculosis.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

We as a scientific community need to be open-minded as it relates to promising therapies targeting non-traditional targets in M. tuberculosis. For instance, providing a better understanding of how diarylthiazoles(e.g. fatostatin) inhibit M. tuberculosis growth. Skeptics argue that fatostatin also exhibits

pleiotropic effects not related to its anti-tuberculosis properties, such as anti-obesity, anti-cancer, and anti-osteoporosis properties. These side effects seem to have little negative outcome in patients (though fatostatin has only been tested in murine models), we should remain open-minded when it comes to the beneficial effect of certain small molecule inhibitors of tuberculosis and develop personalized treatment strategies in efforts to avoid the emergence of drug-resistant M. tuberculosis strains.

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Improving host immunity to M. tuberculosis among individuals infected with a pre-existing HIV infection.

Resources required or lacking that may be critical to advancing the areas of research opportunity

Further development of nonhuman primate models that can be used to explore ways to improve the immune function of HIV+/SIV+ individuals who are then exposed to M. tuberculosis.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

The TB strategic plan made no mention of HIV-*Mtb* co-infection, except as an epidemiological issue. This is a huge global health problem with large knowledge gaps.

Resources required or lacking that may be critical to advancing the areas of research opportunity

Support for developing models of co-infection are a critical first step to addressing the outstanding issues around *Mtb*/HIV co-infection.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Modeling both infections in nonhuman primates Single cell-based transcriptomics In vivo imaging Candidate TB vaccines that may afford some protection from *Mtb* in HIV-infected individuals

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Management and administration of TB programs and training of personnel

Resources required or lacking that may be critical to advancing the areas of research opportunity

Increase in support of TB programs in resource limited countries

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Response and management of Multdrug resistant TB and paediatric TB

Other comments

Robust mobilization of resources and support by beneficiary countries in terms of budgetary allocations

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Significant research gaps and/or barriers not identified in the framework

Much information has been discovered about mutations associated with resistance to the drugs used for treatment of TB. However, not all mutations cause resistance, some produce higher levels of resistance than others, and some cause resistance to some members of a class of drugs, while other drugs in the same class may still be effectively used. Primary mutations have been associated with drug resistance, but sometimes compensatory mutations occur which tend to restore the fitness of the TB bacteria and therefore are selected for in vivo. The impact of the compensatory mutations on minimal inhibitory concentrations (MIC) and drug effectiveness are also unknown. The impact of various mutations and combinations of mutations on MIC should be evaluated, as well as associations between these mutations and treatment success or failure also needs to be evaluated.

Resources required or lacking that may be critical to advancing the areas of research opportunity

Animal studies of the links between specific drug resistance-associated mutations/ combinations of mutation and treatment success or failure are needed. However, animal studies are expensive. Human trials have the limitation that combination therapy is universally used. However, when an organism has a specific mutation associated with resistance to a specific drug, and that mutation is linked to treatment failure when the drug in question is given, inferences can be made that the mutation leads to treatment failure. Thorough cataloguing of this kind of information is needed.

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Next generation and whole genome sequencing are yielding profound new information. However, these methods take excessive time and are not compatible with guiding treatment decisions. More rapid methods, informed by knowledge gained from WGS, need to be developed. These rapid methods will need to be robust and must include automated sample handling to be rolled out to high-burden TB settings where sophisticated laboratory staff may not be available. DNA arrays or real-time molecular beacon assays with melt curves may enable determination of specific DNA sequences in many cases. These need to be developed further.

Other comments

New and rapid TB diagnostic technologies need to be integrated into clinical practice and tuberculosis control in high burden settings. This requires intensive training of clinicians and TB control staff, as well as availability of second line drugs or new classes of drugs when resistance is found.

Significant research gaps and/or barriers not identified in the framework

Yes, there is a significant gap which represents a serious problem in fighting TB and many other diseases in general. 1- For many years researchers are looking for biomarkers but in vain. Million of Dollars has been spent. 2- Thinking out of the box, unfortunately, are not accepted by evaluators. The reason

sometimes is we do not like it. In conclusion, researchers who have power are only listening to themselves.

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Yes, I have a comprehensive diagnostic test for TB. It will be on the market this year. It is based on new discovery.

Other comments

I want to help, would you please give me this chance.

Significant research gaps and/or barriers not identified in the framework

Identification of one to two pathognomonic diagnostics for TB detection. Cause, detection of bacilli is nowadays almost impossible.

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Drug sensitivity tests across the full spectrum of available compounds used to wage war on TB. New, completely unrelated c ompounds from present day ones with higher efficacy but lower side effects.

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Biosocial, cultural, and environmental factors that stand as challenges to TB eradication thus far, i.e., high density living situations in impoverished communities with less than ideal work and housing conditions

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

I love NIH's national and International efforts to control tuberculosis. However, I am very very concerned how the US Taxpayer's dollars are utilized for worthless scientific questions which can contribute almost nothing to STOP the spread of tuberculosis. Sadly, the NIH funding goes to few groups who are only repeating things over and over again. However, new investigators have novel ideas but the

sizes of mountains are unbeatable for fresh scientists to emerge with novel sciences. NIH has to focus on new ideas instead of bogus screaming of the so called "established investigators". Why NIH gives more that TWO A01s for similar ideas, which are already known to be never anywhere?

Resources required or lacking that may be critical to advancing the areas of research opportunity

Support new ideas and help those who have ideas but may be not lucky enough to go forward due to the unfair networks of similar researchers for decades. It is really frustrating how new ideas emerge if we keep rewarding the failed ideas again and again!

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

NIH must listen to new ideas and suggest strategies and provide resources to come up with something new. NIH has more than enough funding but dumping everywhere for similar purposes poor questions.

Other comments

Create a human-like transmission and (natural control) of majority of the TB-exposed and uninfected family members of TB patients using Rhesus macaques. Cultivate researchers from other disciplines and make it easier for them to transition to TB research. For instance, if someone who previously worked on schistosomiasis and HIV would like to transition to TB, make a mechanism to support that. Somebody took few ideas out of a proposal I wrote, but the grant is still in my computer. I never try to beat the network of the reviewers to get a funding for my idea that I know is novel even if few scientists have told me that my idea is too big.

Significant research gaps and/or barriers not identified in the framework

This framework does not address patient-centered factors. TB will not be eliminated in the United States until the burden of LTBI is directly addressed. Shortened treatment regimens for LTBI are a significant step in the right direction but their potential cannot and will not be realized until clinicians have proven methods to assess patient readiness and willingness to start and complete treatment.

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Drug delivery towards TB infection

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

Drug delivery to the TB reservoirs

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

I LIVE IN A COUNTRY WITH ACTIVE TB. I AM AN INTERNIST ON SPECIAL FOCUS IN HIV/TB FELLOW OF THE AMERICAN COLLEGE OF PHYSICIANS

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Mtb divisome may represent therapeutic targets; break the latent state and induce cell division

Resources required or lacking that may be critical to advancing the areas of research opportunity

Cell division tools - solid state NMR to study transmembrane proteins

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Mathematical and computational modeling can assist with SP goals: identifying mechanisms of bacterial, host, and host-pathogen interactions,dsovery of biomarkers, design of novel prophylactics and vaccines, design testing and delivery of drugs

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

A core capability to promote understanding of mycobacterial lipids, integrating modeling with biophysics, biochemistry, host-pathogen biology, and measurement science is critical. Understanding

the metabolome and lipidome of *Mtb* in the context of the host – not as independent biomarkers – is critical.

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)

Significant research gaps and/or barriers not identified in the framework

Cell division tools - solid state NMR to study transmembrane proteins; *Mtb* divisome may represent therapeutic targets; break the latent state and induce cell division

Resources required or lacking that may be critical to advancing the areas of research opportunity

(Submitter left answer blank)

Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework

(Submitter left answer blank)

Other comments

(Submitter left answer blank)