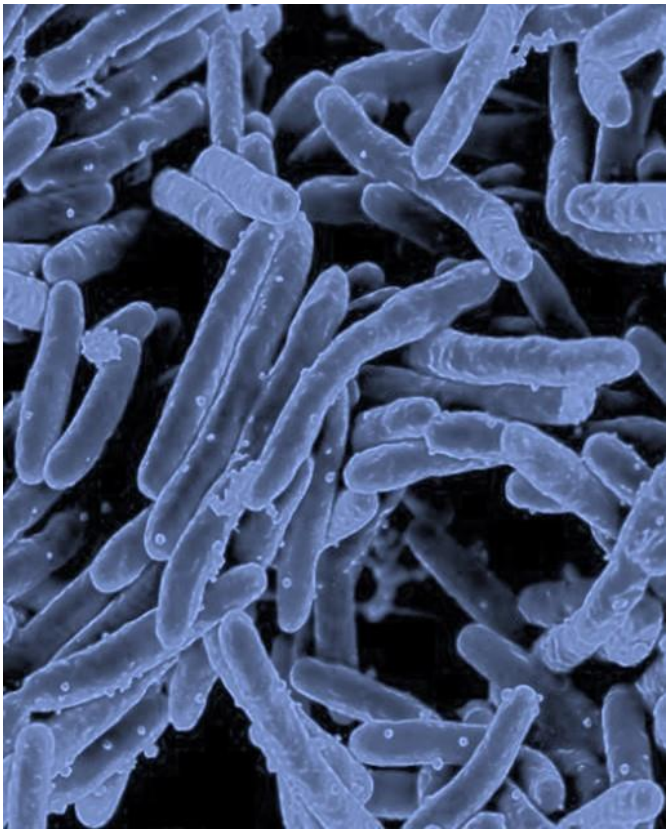
NIAID STRATEGIC PLAN FOR TUBERCULOSIS RESEARCH



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NIH National Institute of Allergy and Infectious Diseases

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Executive Summary

The National Institute of Allergy and Infectious Diseases (NIAID) at the United States (U.S.) National Institutes of Health is committed to reinvigorating and accelerating its research efforts to prevent, diagnose, and treat tuberculosis (TB) (Box 1, Figure 1). This *NIAID Strategic Plan for Tuberculosis Research* proposes building on current trans-NIAID efforts to understand better the immunology and pathogenesis of TB and expanding resources to quickly develop new tools to more effectively combat this disease. These tools include preventive vaccines and therapies, less-toxic treatment regimens of shorter duration, and rapid, accurate, easily implementable, point-of-care diagnostics to detect all forms of TB, including latent, disseminated, and drug-resistant (DR) TB, in the diverse populations and age groups affected.

In 2017, 10 million people, including 1 million children, became ill with TB, and 1.6 million people with TB 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 asymptomatic *Mtb* infection, known as latent TB; they have a lifetime 5 to 10 percent chance of developing active disease.

Efforts to halt the spread of TB domestically and globally are critical to reducing TB-related morbidity and mortality. The total global economic burden associated with TB from 2000 to 2015 was an estimated $617 billion. The societal benefit of implementing TB control and prevention measures for the U.S. from 1995 to 2014 was valued at $14.5 billion. To address the global health emergency that TB represents, the World Health Organization (WHO) End TB Strategy sets ambitious goals for 2035 to reduce TB deaths by 95 percent and to reduce TB disease incidence by 90 percent (relative to 2015 levels)

Box 1. NIAID Strategic Plan for TB Research Mission

Accelerate basic, translational, and clinical research to improve understanding of TB and expedite the development of innovative new tools and strategies to improve diagnosis, prevention, and treatment to end the TB pandemic

In support of this goal, the WHO, the U.S. Government Global TB Strategy, and the National Action Plan for Combating Multidrug-Resistant TB, outline paths to end the TB pandemic, including a strong emphasis on reinvigorating research efforts to advance fundamental knowledge of TB and enable the development of improved diagnostics as well as treatment and prevention strategies. The WHO End TB Strategy also proposes objectives to strengthen patient care and improve policies and support systems to immediately benefit patients. The United Nations General Assembly held its first-ever high-level meeting on TB in September 2018 to discuss a unified approach to address the TB pandemic.

To support and align with the global and domestic TB research goals outlined in the formal plans listed above, NIAID's strategic plan has a specific translational TB Research Mission (Box 1). The plan includes five strategic priorities that capitalize on recent advances in the field and are critical to the development and evaluation of the knowledge and tools needed to end TB globally:

1. **Improve fundamental knowledge of TB** to understand host and bacterial factors (and their interplay) that drive *Mtb* pathogenesis, transmission, and epidemiology. Elucidate the immune mechanisms responsible for limiting or failing to limit *Mtb* infection and disease

2. **Advance research to improve the diagnosis of TB**, including research to identify biomarkers and biosignatures for different forms of TB that can facilitate the development of accurate, rapid, and easily implementable diagnostic and prognostic tests for use in all populations
3. **Accelerate research to improve TB prevention** by supporting science to design, develop, and evaluate preventive vaccines and chemoprevention, and to identify markers of protective immunity that can predict vaccine efficacy
4. **Support research to improve treatment for all forms of TB in all populations and age groups**, including research to develop less toxic regimens of shorter duration for safe and effective treatment, host-directed therapies (HDTs), and therapeutic vaccines
5. **Develop tools and resources to advance research in understanding, preventing, diagnosing, and treating TB,** including human cohorts and clinical capacity; animal models representative of human disease; and assays, reagents, and tools to assess vaccine, therapeutic, and diagnostic candidates

To accelerate research for these five strategic priorities, NIAID will leverage current resources and global collaborations, including existing NIAID-supported clinical trials networks (Appendix 1). NIAID also will promote a more multidisciplinary approach to TB research, drawing on expertise from fields within and outside of TB research to facilitate studies of complex biological questions and encourage the application of state-of-the-art technologies used successfully in other fields. Additionally, NIAID will provide critical support for training the next cadre of TB researchers to accelerate an aggressive research agenda. With these research efforts and an emphasis on rapid translation of results to patients—facilitated through collaborations within the U.S. Government and with other key partners—new TB prevention and control strategies can and will be developed and implemented both domestically and abroad to end TB.

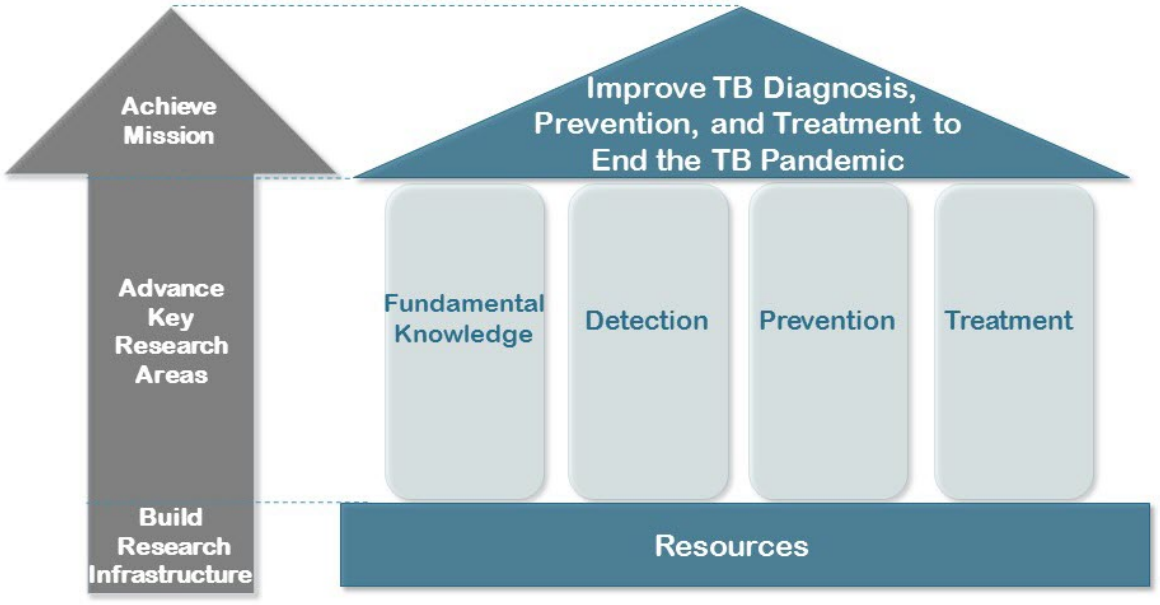

Figure 1. The NIAID Strategic Plan for TB Research proposes to build on an existing foundation of research and resources to advance five TB research priorities targeted at 1) improving fundamental knowledge, 2) advancing diagnosis, 3) preventing initial infection or progression to active disease, 4) improving treatment for all forms of TB in all populations and age groups, and 5) building resources to advance understanding and tool development in priorities 1 through 4.

Introduction

Over the course of history, TB has killed more people than any other infectious disease. Over the past 200 years, it is estimated that at least 1 billion people have died from TB—more than the number of deaths resulting from malaria, smallpox, HIV/AIDS, cholera, plague, and influenza combined. TB remains the deadliest infectious disease in the world. In 2017, the WHO estimates that TB claimed the lives of 1.6 million people, including 230,000 children.

Mycobacterium tuberculosis (*Mtb)*, the bacterium that causes TB, is transmitted through the air and primarily infects the lungs, although it can also affect other parts of the body, including the brain. An estimated 1.7 billion people globally, including 13 million people in the U.S., are thought to be latently infected with *Mtb*; they carry the bacterium, but do not show any symptoms of disease. People with latent TB infection have a 5 to 10 percent lifetime risk of developing active TB disease. Activation of latent disease most often manifests in its most contagious form, pulmonary TB, characterized by an array of symptoms including cough, fever, weight loss, and night sweats. HIV infection, young age, and conditions that weaken the immune system significantly increase the risk of developing TB disease in all forms. Left untreated, severe complications can develop that lead to death in about half of people who progress to active TB disease.

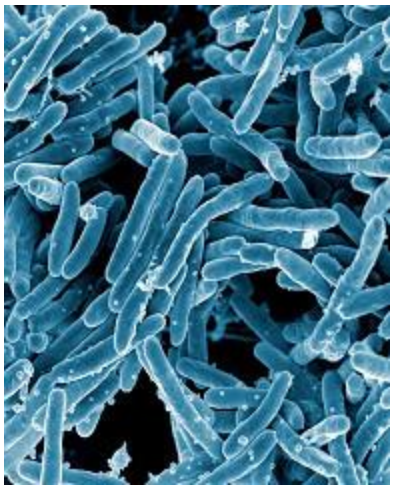

Figure 2. Scanning electron micrograph of Mycobacterium tuberculosis*, the bacterium that causes tuberculosis. Image credit: NIAID.*

Although drug-sensitive (DS) TB is treatable, curative therapy typically requires a cumbersome six-month, four-drug regimen with well-described toxicities. Inadequate treatment can lead to multidrug-resistant TB (MDR-TB), which is resistant to the two most effective anti-TB drugs, rifampin (RIF) and isoniazid (INH), and also to extensively drug-resistant TB (XDR-TB), which is resistant to many additional TB drugs. Standard treatment of MDR-TB can take more than 2 years, including painful daily injections for 6 months, and can be prohibitively expensive. XDR-TB therapy is even more complex and often fails. Some of these treatments often result in long-lasting or permanent toxic side effects. The significant challenges of effectively treating DS-, MDR- and XDR-TB underscore the critical need for shorter, safer, and more effective drug regimens that are easily tolerated and can be delivered to patients in all care settings. Recently completed and ongoing clinical trials of drug regimens of shorter duration have shown significant promise of better treatment options for patients.

For those infected with *Mtb*, HIV co-infection poses additional challenges. The risk of progressing from latent to active TB disease is estimated to be 20 times higher in people living with HIV (PLWH), and each disease increases the severity of the other. Additionally, TB drug regimens need to be compatible with HIV antiretroviral therapy (ART) and vice versa, which further complicates treatment. Unfortunately, many regions of the world with high HIV prevalence, particularly sub-Saharan Africa, also have a high burden of TB. Despite significant efforts to improve the care of patients, TB is the leading cause of death in PLWH worldwide, highlighting the urgent need for improved diagnosis and optimized treatment strategies that are also suitable for these populations.

Each year an estimated 40 percent of patients with active TB disease, or approximately 4 million people, go undiagnosed or unreported. These missed TB patients, some of whom harbor drug-resistant (DR)

strains, account for a significant portion of TB deaths and continue to fuel the pandemic. A person with active TB disease may infect an additional 10 to 15 people per year. New technologies for rapid and accurate diagnosis in point-of-care and/or low-resource settings and for all ages and populations are needed to help identify and facilitate prompt treatment of TB patients.

Effective vaccination strategies are needed to change the trajectory of the TB pandemic. The Bacillus Calmette–Guérin (BCG) vaccine, administered to neonates and infants throughout most of the world, provides protection against meningitis and disseminated disease in children; however, it insufficiently protects against disease in adolescents and adults. Although more intensive efforts are needed to better understand the fundamental requirements necessary to develop a highly effective TB vaccine, recent animal studies and human clinical trials provide promising indications that more efficacious vaccines are within reach.

Figure 3. Needle syringe and vaccine bottle. Image credit: NIAID.

WHO recently developed the End TB Strategy that aspires to end the TB pandemic by 2035. A fundamental component of this strategy is intensified research and innovation to develop new tools to combat TB. NIAID, the major global funder of TB biomedical research and development supporting nearly one-third of the global TB biomedical research effort, has a responsibility to develop the critical tools needed to achieve the global goal of ending the TB pandemic.

NIAID recently conducted a portfolio analysis (see summary in Appendix 3) to map current investments, held extensive internal discussions to outline critical areas of focus, solicited input from the public, and subsequently developed this strategic plan. The plan emphasizes five strategic priorities that support basic, translational, and clinical research focused on enhancing the fundamental knowledge, diagnosis, prevention, and treatment of TB (Figure 1). NIAID will accelerate efforts to develop preventive vaccine candidates, while continuing to support the development of safer, shorter, more effective drug regimens and improved diagnostics.

Several themes, outlined below, cut across the strategic plan to maximize the use of resources and accomplish the plan's objectives:

- Advances in **basic TB research, diagnostics, prevention, and treatment** will be translated into interventions for the benefit of both the U.S. and global populations
- Existing NIAID-supported and collaborative **human cohorts and preclinical resources** (Appendix 1) will be expanded and adapted to expedite research and maximize usage across the research spectrum
- **State-of-the art tools and techniques** (including improved animal models) will be applied to TB research by encouraging **cross-disciplinary research collaborations**
- Collaborative **domestic and international efforts** will be intensified to foster rapid development of new diagnostics, vaccines, and therapeutics that are applicable to patients in high- and low-TB burden settings, including the U.S.

The plan highlights the need to better understand human *Mtb* infection and the factors that affect TB disease development for the purpose of facilitating new interventions and treatment strategies. The plan also outlines the research resources and tools needed to advance the strategic research priorities. Modern, 21st century tools and technologies have the potential to provide improved insight into the

complex nature of TB pathogenesis and to create highly effective preventive and therapeutic interventions for implementation both in the U.S. and abroad.

Advances guided by the five strategic priorities are expected to be interdependent and complementary. Broad, multidisciplinary biomedical collaboration and coordination is vital, as is training the next generation of TB scientists to capitalize on emerging scientific opportunities. NIAID expects this plan to serve as a foundation for its future research investments and to guide a comprehensive effort toward the successful development of the diagnostic, prevention, and treatment tools necessary to end the TB pandemic.

Research Plan

Strategic Priority 1: Improve Fundamental Knowledge of TB

TB infection can manifest in two forms: latent, asymptomatic infection and active, symptomatic disease. Although these classifications drive treatment decisions, they inadequately describe the intricate dynamics of disease. The development of improved diagnostics, vaccines, and therapeutics requires a more detailed understanding of the dynamics of bacterial and host biology involved in initial *Mtb* infection, the factors that lead to control or progression to active TB disease, and the basis for the requirement of prolonged treatment.

Detailed molecular analyses of pathogen and host factors, as well as a more comprehensive understanding of host-pathogen dynamics, are needed to better understand how they affect host responses to TB infection and potentially, subsequent disease outcomes. Emerging technologies offer the potential to characterize *Mtb* heterogeneity and determine how the ability of the pathogen to exist in different metabolic states and cellular niches mediates survival and susceptibility to antibiotics. Equally important, advanced technologies have the potential to rapidly improve our understanding of the quality, quantity, and diversity of host immune responses required to effectively eliminate or control *Mtb* in diverse cellular and tissue environments. Since host-pathogen interactions are likely modulated by age, sex, ethnicity, host genetics, comorbidities (such as diabetes), and co-infections (such as HIV), more comprehensive and integrative approaches to studying TB will be required. NIAID has placed a priority on TB research in the context of HIV to specifically address the interplay of these two co-pandemics.

Box 2. Strategic Priority 1 Focus Areas
• *Develop a comprehensive view of the dynamics and complexity of Mtb pathogenesis, immunity, transmission, and epidemiology* • *Advance diagnostics, preventive measures, and therapeutics through characterization of TB disease with modern tools* • *Promote interdisciplinary programs and engage new researchers to study complex biological phenomena*

NIAID will leverage existing research activities, resources, and human cohorts to achieve the scientific objectives outlined below. Collaborative research conducted in TB-endemic countries will provide novel insights into the impact of co-infections and comorbidities on TB and how immune responses and other host-pathogen interactions may differ among people residing in these settings. NIAID will support research to study the heterogeneity of TB disease in the context of its diverse disease manifestations, co-infections, comorbidities, and microbial genetics to determine their impact on disease outcomes and transmission.

These studies will help inform the breadth of assays and studies that must be undertaken to develop and evaluate products for use in diverse care settings and populations.

By expanding the focus of TB research to the characterization of pulmonary, extra-pulmonary, and disseminated TB using modern tools, including imaging technologies, multidisciplinary systems biology, and computational modeling, NIAID will help define factors that determine whether pulmonary or extra--pulmonary TB occurs in a given patient. This distinction is necessary to expand diagnostic tests to patients with extra-pulmonary TB. Furthermore, NIAID will support research on tissue-specific and systemic immunity to *Mtb* and the factors involved in localization of the pathogen to various organs and its evasion of the immune system. Gaining insight into the mechanisms that lead to disease will facilitate the design and interpretation of animal models that better represent human disease.

Objective 1.1: Understand the host and pathogen drivers that underlie the dynamics and pathophysiology of latent TB in humans

Following *Mtb* infection, the majority of people can control the infection without displaying symptoms. For those who become infected, the roles of bacterial genetics and epigenetics in the virulence and fitness of *Mtb* during early stages of infection need to be characterized in more detail in humans and animal models, as do the types of host cells that are infected, the extent of bacterial exposure needed to establish infection, and the way infection spreads through the body. In-depth analysis of host immune mechanisms that eliminate or control *Mtb* in its latent form may prove to be important in developing improved vaccine strategies.

Currently, the only readily available tools, in addition to radiographic imaging, to determine whether a patient is infected are blood or skin tests that measure immune responses against *Mtb* proteins, or time-consuming sputum culture tests that detect the presence of *Mtb*. These tests are not able to distinguish between latent infection and active disease. Research to identify biomarkers that can predict the risk of progression to active disease is ongoing. Current efforts show promise; however, additional research is needed to rapidly identify and treat patients latently infected with *Mtb* in order to prevent symptomatic disease.

NIAID will foster cross-disciplinary programs that bring together basic and clinical researchers with expertise in bacteriology, pathology, immunology, systems biology, and other relevant disciplines to study these highly complex and dynamic aspects of TB pathophysiology. Animal models that recapitulate latent infection will be valuable tools to create hypotheses that can be tested in humans, where it may not be possible to fully study the natural history of infection.

Objective 1.2: Understand the host and pathogen drivers that underlie the dynamics and pathophysiology of active TB in humans

Mtb has co-evolved with humans over millennia, and research efforts are focused on delineating how the body controls the pathogen, or the circumstances under which *Mtb* successfully evades immune control and induces disease. Although pulmonary TB is the primary and most transmissible form of TB, extra-pulmonary or disseminated TB that spreads to other organ systems outside the lung, including the brain, also can occur. Patients with extra-pulmonary TB are difficult to diagnose because current strategies are optimized for identifying pulmonary TB. An increased understanding of the pathology of extra-pulmonary TB will help define the spectrum of TB and why each type of TB develops, and will facilitate diagnosis and appropriate treatment of patients who do not present with classic TB symptoms.

Modern imaging technologies, such as positron emission tomography/computed tomography (PET/CT, Figure 4), provide sophisticated insights into the dynamics of TB pathology in humans, particularly the development and evolution of pulmonary granulomas, which are pockets of infection walled off by the host immune response. Data emerging from the application of state-of-the art technologies suggest that biomarkers can be identified to more effectively classify and predict the course of the patient's disease and the susceptibility of the pathogen to antibiotics. Currently, no method exists to track *Mtb* throughout its life cycle in the host. Novel methods to quantify *Mtb* directly or indirectly through biomarkers or microbially directed imaging probes are critical to better determine the response to therapy. Potentially, such techniques could identify patients who are either curable with shorter course therapy or who may experience relapsing disease. Additionally, the ability to quantify live *Mtb* in the host would improve the ability to develop drugs that are active against *Mtb* in different metabolic states and would contribute to assessing the efficacy of novel vaccine candidates in human clinical trials.

A better understanding of the nature and dynamics of host-pathogen interactions at the molecular and cellular level that result in active TB is critical to developing improved diagnostics, vaccines, and therapeutics. Further studies are needed to determine the factors that lead to the establishment of *Mtb* infection, how the genetic makeup of both *Mtb* and the host affect the course of infection, the other host and microbial factors that contribute to *Mtb* infection control or evasion of the immune system, and the host-pathogen interactions that eventually trigger active disease.

Strategic Priority 2: Advance Research to Improve Diagnosis of TB

Prompt, accurate, and rapid diagnosis of TB infection is critical to determining the optimal treatment strategy. Most current diagnostic protocols, including nucleic acid amplification, microscopy, and bacterial cultures, require laboratory equipment and experienced personnel that are not always available in TB prevalent areas. Most of these protocols call for sputum-based samples, which are difficult to obtain from young children and PLWH who have low amounts of *Mtb* in their sputum (paucibacillary disease). Additionally, extra-pulmonary forms of TB cannot be detected using sputum samples.

The most commonly used diagnostic for active TB infection, microscopic detection by direct sputum smear, is only 50 to 60 percent accurate, does not provide critical information about drug resistance, and often cannot accurately establish the presence of active disease in people who have low levels of *Mtb*. Other tests, such as the Tuberculin Skin Test and the QuantiFERON®-TB Gold test, have low accuracy in immunocompromised people, are unable to distinguish individuals with latent TB infection from those with active TB disease, or can deliver false positive results in people vaccinated with the BCG vaccine (for additional information on the BCG vaccine, see Strategic Priority 3).

Recent advances in TB diagnostics, including the roll-out of the WHO-recommended Xpert® MTB/RIF diagnostic test, have provided significant improvements over traditional diagnostic tools. However, there is still a need for simple, easy-to-use, inexpensive, point-of-care diagnostics, including additional rapid diagnostics that identify drug resistance. The Xpert® MTB/RIF diagnostic test is accurate and rapid; however, it requires ready access to and proper storage of reagents and supplies, and trained personnel who may not be available in some resource-limited areas with high burden of TB disease.

Box 3. Strategic Priority 2 Focus Areas
• *Integrate biomarkers and biosignatures derived from fundamental TB research into technology platforms to facilitate the development of diagnostics* • Develop *rapid, accurate, and inexpensive point-of-care diagnostics and prognostics for all forms of TB* • *Accelerate clinical validation of diagnostic platforms in large patient cohorts*

Discovery of host and microbial biomarkers or biosignatures is rapidly advancing. However, there is still a need to identify individual markers or combinations of markers that indicate infection, risk of disease progression, response to therapy or predict disease recurrence. Furthermore, these markers and signatures need to be combined with suitable diagnostic platforms for testing in resource-rich and -limited health care settings. Ideally, these types of studies should leverage existing clinical trials, study protocols, and clinical cohorts supported by NIAID and other partners.

NIAID will support research to intensively profile bacterial signatures and human host responses using high-throughput genomic sequencing, "omics" technologies, and bioinformatics tools to identify biomarkers of infection, risk of disease progression, or risk of disease recurrence. NIAID also will support the integration of host biomarkers and biosignatures into diagnostic platforms suitable for use in diverse healthcare settings, and for the evaluation of innovative diagnostic algorithms using existing or novel TB diagnostics.

Objective 2.1: Discover novel biomarkers or biosignatures for TB prevention, diagnosis, and prognosis, prediction of treatment outcomes, and identification of drug resistance

To address the need for new and improved TB diagnostics, significant efforts will be required to identify biomarkers or biosignatures that can be integrated into suitable technologies to provide accurate, reliable, and actionable information to clinicians. Host-based biosignatures for latency and active disease must be identified to predict whether a latent infection will progress to active disease so that preventive therapy can be initiated. Additionally, there is a need to identify biomarkers or biosignatures that correlate with predictors of response to therapy and evolution of drug resistance.

In addition to serving as the basis for clinical diagnosis and prognosis, pinpointing microbial and host biomarkers will be essential to facilitate clinical trials and serve as surrogate endpoints for candidate preventive or therapeutic interventions. Surrogate endpoints may suggest whether a product is efficacious and should proceed to more advanced clinical testing. Due to the limitations of sputum-based approaches, it is preferable that biomarker signatures are identified from easily obtainable, non-sputum samples such as peripheral blood, urine, stool, or volatiles, such as compounds that may be measured in the breath.

Novel biomarkers will need to be validated in diverse populations according to geography, age, ethnicity, and comorbid conditions, including diabetes, HIV infection, parasitic worm infections, and other non-tuberculous mycobacterial infections.

Objective 2.2: Improve and develop accurate and rapid diagnostics

Predictive and diagnostic biomarkers need to be paired with appropriate technology platforms to establish and validate new diagnostic assays that are operable under broad environmental conditions and care settings and require minimal maintenance. One of the most urgent developmental needs is a non-sputum-based, rapid, sensitive, and inexpensive point-of-care diagnostic that also provides information about drug susceptibility. Ideally, this test should be suitable to detect TB infection in people who have paucibacillary disease, children, and HIV seronegative and seropositive populations.

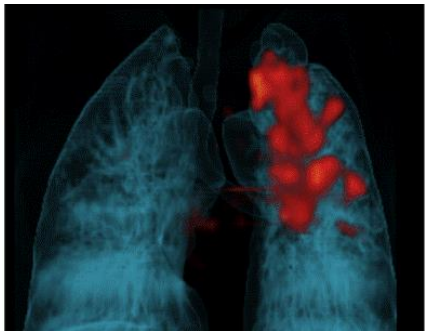

Figure 4. TB-infected lung PET/CT image used for diagnosis, monitoring, and prediction of treatment outcomes. Image credit: NIAID.

Newly developed or improved nucleic acid amplification-based technologies, rapid culture-based platforms, and other new technologies would ideally allow testing directly on patient samples with minimal or no sample processing and would yield results in a short time frame. In parallel with the development of the ideal point-of-care diagnostic, it will be beneficial to improve existing or make novel diagnostics for use in a point-of-care setting or a central laboratory. Novel, sophisticated diagnostic technologies will likely be expensive and not affordable for all patients and all geographic locations. Inexpensive triage or screening diagnostics that can be used with Xpert® MTB/RIF or other more sophisticated and expensive diagnostics would allow for more cost-effective integration of these tools into TB control programs. Microbial-based diagnostic tools remain important to confirm the identity and drug sensitivity of the infecting pathogen and have utility for surveillance of emerging drug resistance.

Strategic Priority 3: Accelerate Research to Improve TB Prevention

The medical approaches to prevent TB infection or disease involve vaccines and/or chemoprevention. There are two primary vaccination strategies for prevention of active pulmonary TB disease: 1) a vaccine given to individuals with latent infection that prevents progression to active clinical disease; and, 2) a vaccine given to uninfected individuals that prevents primary *Mtb* infection. Given the incidence of latent *Mtb* infection, the most effective tool to combat the TB pandemic would be a vaccine that prevents individuals with latent *Mtb* infection from progressing to active, transmissible disease. Vaccines that prevent initial infection or the establishment of latent disease would also have a significant impact.

The BCG vaccine, given to neonates throughout the world (although not common practice in the U.S.), provides moderate protection against severe complications of disseminated disease in children, but does not sufficiently protect against TB in adolescents and adults. Despite intensive efforts to improve upon BCG, success has been hampered in part by an incomplete understanding of the immunological mechanisms required to more effectively prevent TB. A recent clinical trial performed in adolescents at high risk of acquiring *Mtb* suggested that revaccination with BCG may offer at least temporary protection from infection. Researchers are planning an intensive immunological investigation to determine the implications of these results and whether this BCG revaccination strategy will translate to fewer people developing active TB.

To improve vaccine strategies, NIAID will invest in research and resources, including improved animal models, to support rational vaccine design. To guide the design and selection of preclinical vaccine candidates, it will be necessary to pinpoint opportunities for immunological analyses within vaccine

clinical trials to identify correlates of protection. Within these studies, it also will be important to consider how previous BCG vaccination and exposure to other types of mycobacteria may affect the efficacy of novel vaccine approaches.

Box 4. Strategic Priority 3 Focus Areas
• *Discover, develop, and evaluate new or improved vaccines and chemopreventive regimens* • *Improve understanding of protective immunity against* Mtb *and identify correlates of immune protection* • *Develop vaccines or chemopreventive regimens to block infection with* Mtb*, progression to active TB disease, or interrupt* Mtb *transmission*

In the absence of a highly effective vaccine, a regimen of antibiotics, referred to as chemopreventive therapy, can be used to prevent latently infected people from progressing to active TB disease. In the U.S., current standard treatments involve administering antibiotics for 3 to 9 months. Although effective in areas where there is a low TB burden, chemopreventive therapy does not provide lasting protection against repeated exposures that commonly occur in people who live in regions with high TB burden. Furthermore, given the requirement for long duration of treatment and difficulties with adherence associated with chemoprevention, there is a need for shortened regimens effective against all forms of DS- and DR-TB, particularly for people who are at higher risk of developing active TB, such as PLWH. Recent clinical trial results suggest that therapy as short as one month may be feasible.

In parallel with the development of improved vaccine and chemopreventive strategies, it is important to better understand the biological and epidemiological factors that drive the transmission of TB in order to facilitate the development of tools and approaches to maximally disrupt the spread of *Mtb*, particularly in high-risk groups.

Objective 3.1: Support the design and development of vaccine candidates that prevent infection or progression to active TB disease

Recent findings in animal models and human clinical trials provide promising signs that improved TB vaccines are achievable. Efforts to replicate and extend these results in clinical trials incorporating intensive immunological studies have the potential to transform the field. Studies to characterize all aspects of immune responses to *Mtb* infection will inform optimal vaccine design and routes of delivery. In parallel, studies to reverse-translate results from human studies back into animal models will enable a mechanistic understanding of immune responses required for protective immunity against TB and accelerate the development and selection of improved vaccine candidates. Vaccine candidates found to be active against pulmonary TB should also be tested for their effectiveness against other forms of TB.

State-of-the art technologies and bioinformatics tools can be used to discover new immunogens and immunogen/adjuvant combinations that can be rationally tested in diverse vaccine expression and delivery platforms. Multiple approaches, including iterative, head-to-head, preclinical and clinical evaluation of vaccine candidates using various dosing and administration strategies to maximize vaccine activity in target populations are important. Complementary research to identify and validate new assays and reagents will aid preclinical and clinical studies of vaccine candidates across the development pipeline.

Objective 3.2: Identify correlates of immune protection

Identifying correlates of immune protection would aid the development of an improved TB vaccine. Significant progress has been made in understanding the nature and magnitude of *Mtb*-specific immune responses, although the immune mechanisms that prevent *Mtb* infection or disease progression remain elusive. Animal studies have shown that T-cells limit the extent of infection or TB disease, although emerging evidence suggests that other components of the immune system also may contribute to protection.

Vaccine studies in animal models and small Phase 1 clinical trials, coupled with in-depth immunological analyses, can significantly improve understanding of the types of immune responses desired from a TB vaccine candidate. However, identifying correlates of immune protection will require the analysis of samples from larger efficacy trials demonstrating a protective effect. A systematic evaluation of immune response data from a recent BCG revaccination trial is planned. Significant effort should be made to thoroughly evaluate samples from this and future trials to identify mechanisms of protection that can guide the design and selection of vaccine candidates to advance into clinical trials.

Finally, comprehensive immunological characterization of individuals with latent TB infection who do or do not progress to active disease is needed to understand the immunological parameters that impact progression to active disease or containment of infection. This knowledge may help identify correlates of risk that, in turn, may inform the development of vaccines that may prevent progression to active TB disease.

Objective 3.3: Investigate regimens to shorten course of chemopreventive treatments for drug-resistant and drug-sensitive TB

Chemopreventive strategies are needed as an immediate solution to protect people with latent TB infection from progressing to active disease. Adherence to the standard 6- and 9-month INH- or RIF-based treatment regimens has been problematic because of the long duration of treatment and associated drug toxicities; thus, shorter drug regimens must be developed to address this issue. A once weekly dose of INH and rifapentine for 3 months has been shown to be equally effective at preventing active TB as the 9-month INH regimen and is recommended by the WHO and CDC as an alternative to the longer INH treatment regimen.

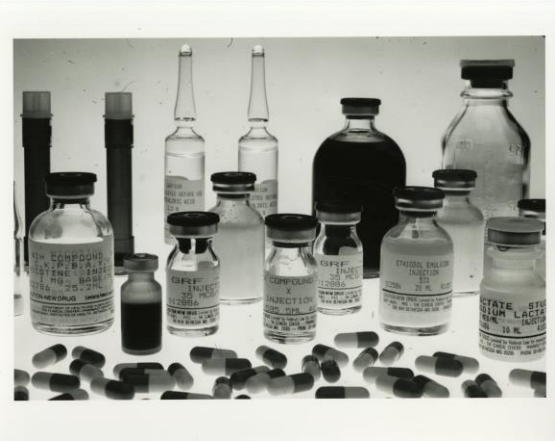

Figure 5. Drugs and vaccines. Image credit: NIH.

Results from a recent NIAID-supported clinical trial demonstrated that 1-month antibiotic regimens to prevent active disease in PLWH with latent TB were non-inferior to the 9-month INH regimen currently provided in many countries and were associated with fewer adverse events. Although these advances indicate a major step forward in reducing treatment duration and the occurrence of drug-related adverse events, there is still room for improvement. Developing regimens that can be given to all age groups and can address latent and DR-*Mtb* infection is necessary.

Objective 3.4: Discover, develop, and improve interventions that interfere with TB transmission

The factors that drive pathogen infectivity and underlie host susceptibility to infection and disease are poorly understood, and gaps also exist in our understanding of the population dynamics of TB. Key scientific opportunities include determining the factors that drive transmission, methods to measure TB transmission, and novel strategies to prevent transmission. The variable success of preventative therapy combined with growing evidence that TB is transmitted both within family units and in community settings underscore the inadequacy of current tools and approaches used to interrupt transmission.

Further research to characterize TB transmission within high-burden settings is needed, including studies to elucidate the infectious aerosol microenvironment and environmental factors that enable transmission. New methods and studies to measure transmission in high-risk environments should also address underlying pathogen and host factors that affect transmission, including host genetic, epigenetic, or immune cell functions. Other important factors to consider are how HIV infection and ART may affect *Mtb* burden and the likelihood of transmission. Advanced geographical and real-time mapping of clusters of infection and predictive modelling would be valuable to better understand transmission dynamics and could be used as a tool to inform novel approaches for preventing further TB transmission.

Strategic Priority 4: Support Research to Advance and Shorten Treatment of TB

The development of highly effective and short-duration treatments for latent and active DS- and DR-TB will greatly facilitate the care of patients and contribute to ending the TB pandemic. Improved treatments suitable for use in adults and children that are also compatible with ART are under investigation in parallel or in combination with therapies to limit the pathological effects and frequent life-long disabilities resulting from active TB disease.

Interventions that interfere with the development and extent of disease [that is, host-directed therapies (HDTs)] will complement microbially directed treatments. This requires the development of a new generation of safe and effective drugs and drug regimens, as well as new approaches and strategies to accelerate their clinical evaluation and eventual use as therapeutic or preventive modalities. The current TB drug development pipeline contains promising candidates that have the potential to improve and simplify treatment.

Despite the discovery of increasing numbers of *Mtb* drug targets and antimicrobial compounds directed against these targets, the ability to clinically evaluate and bring new interventions to the market is limited because of inadequate clinical capacity and funding, as well as the need for better coordination across the product development pipeline. As a result, many promising TB drug candidates in early phases of development do not yet have a clear pathway to further evaluation as part of combination regimens or in Phase 3 clinical trials.

A critical priority will be to improve our understanding of the pharmacokinetic and pharmacodynamic properties of these drugs to optimize their use, individually and when combined in potential new regimens. It is important to understand and characterize drug penetration into infected tissue and whether a drug can sterilize the infected site. Additionally, because many existing drugs are associated with serious toxicities, focused efforts must be directed at overcoming these limitations and identifying new agents and/or new formulations with improved toxicity profiles.

Optimized strategies for TB treatment remain a top research priority for controlling the TB pandemic and achieving the global elimination of TB. NIAID will continue to advance the discovery of new agents that are directed against the pathogen and/or to the host, as well as to repurpose existing drugs to determine the shortest and most effective therapeutic regimens for latent and active TB. The objectives delineated here support research that will contribute to optimal, shortened, and well-tolerated treatment regimens for pulmonary, disseminated, and latent TB that are also suitable for PLWH, infants, and young children.

Box 5. Strategic Priority 4 Focus Areas
• *Develop new treatment regimens suitable for all populations* • *Develop easier-to-take, effective, shorter, and safer treatment regimens for pulmonary TB, disseminated TB, and latent TB infection* • *Expand understanding of the mechanisms of action and of adverse effects of drugs and candidate therapeutics*

Objective 4.1: Discover, develop, and evaluate new and improved therapeutic interventions and regimens

Efforts to support the discovery of TB drugs based on molecular scaffolds, pathways, and drug targets using novel drug screening assays are ongoing and will be accelerated. A concerted, collaborative effort among TB drug researchers will be needed to identify the best new drug candidates and understand their pharmacokinetic and microbiological characteristics singly and in combination with other drugs. Improvements in clinical trial design, endpoint selection and analysis, and the predictive potential of animal models and early human studies need to be further explored. It is also important to continue complementary studies to explore the repurposing of drugs licensed for other indications for their possible use in the treatment of all forms of TB. Several classes of drugs used to treat other conditions have already been repurposed for the treatment of MDR-TB and XDR-TB.

Clinical investigations of potential treatments for TB patients with other medical conditions, including HIV co-infection and diabetes, are vital. Research efforts will support the development of drug formulations for pediatric populations, from infants to adolescents. Innovative research to evaluate adjunctive HDTs using repurposed drugs and therapeutic vaccines are needed to improve the effectiveness of immune responses to *Mtb* and reduce tissue destruction. The selection of next-generation HDT candidate agents for evaluation must be based on knowledge of host and pathogen factors and their interplay to identify the optimal therapeutic targets. Disseminated TB, especially TB meningitis, continues to exact a substantial toll in morbidity and mortality, and improvements in therapies to treat these conditions are greatly needed. Promising evidence suggests that HDTs specific for TB meningitis can improve survival.

The inability of many patients to complete therapy negatively impacts TB cure rates and contributes to the development of drug resistance. Therefore, in parallel with the development of HDTs, it will be necessary to study new ways to mitigate the risk of drug-related adverse events and promote adherence, including new drug delivery technologies.

Objective 4.2: Better understand and characterize existing TB drugs to extend their treatment utility

Many of the current drugs used to treat DS- and DR-TB were developed decades ago and their mechanisms of action, pharmacological properties, and optimal dosing regimens were not fully determined. Studies that characterize the pharmacokinetic and pharmacodynamic parameters of these

drugs, including their ability to penetrate tissues, are critical to achieve optimal therapeutic effects and limit toxicity. The development of quantitative measures of *Mtb* burden in adults, pregnant women, and children, as well as microbiologic studies to characterize the sterilizing activity of existing drugs would contribute to the rapid advancement of candidate drugs through the development pipeline.

Objective 4.3: Identify strategies to rapidly assess and prevent permanent disability due to drug-related adverse events

Many TB drugs are associated with significant toxicities that can worsen during the long treatment period (9 to 24 months or longer) necessary for MDR- and XDR-TB. Certain injectable agents, namely aminoglycosides, which are part of the current MDR- and XDR-TB treatment regimens, are known to cause hearing loss and kidney damage when given for extended periods of time. The development of new, safer agents with fewer adverse effects is a key priority. In the short-term, research is needed to develop improved methods to quickly detect drug toxicities and to determine the mechanisms of toxicity for TB drugs. Regimens of existing drugs also need to be optimized to reduce adverse events.

Strategic Priority 5: Develop Tools and Resources to Advance Research in Fundamental Knowledge, Prevention, Diagnosis, and Treatment of TB

The strategic priorities described above will require continued expansion and *de novo* development of tools and resources. It is critical to ensure that investigators involved in TB research and product development have access to Biosafety Level 3 (BSL3) facilities, including facilities that have capacity for non-human primate (NHP) research.

To assure that research resources are adequate to meet research objectives, NIAID will facilitate the improvement and expansion of existing resources, particularly to facilitate the analysis of large and diverse datasets derived from global human cohorts and relevant animal models using systems biology and omics approaches. In addition, NIAID will make an effort to standardize and harmonize preclinical and clinical protocols in order to simplify data integration, thus enabling studies to provide a more thorough understanding of TB variability and its impact on the efficacy of drugs and vaccines. This knowledge will help refine animal and other model systems that reflect this complexity and aid in the selection of drug, vaccine, and diagnostic candidates that have the best chances of success in late-stage clinical studies.

Box 6. Strategic Priority 5 Focus Areas

- *Improve and develop tools and resources, animal models, repositories, and observational cohorts*
- *Facilitate the standardization of research protocols and reagents*
- *Stimulate cross-disciplinary training to foster the next generation of TB scientists*
- *Promote collaborative, open sharing of data and resources to advance the field of TB research*

Objective 5.1: Optimize and/or develop animal models that reflect the human disease state to support fundamental research and product development

No animal model perfectly recapitulates all the complex aspects of human *Mtb* infection and disease. Small animal models have been useful for the analysis of fundamental immunological studies and are invaluable tools to assess immune responses and changes in bacterial burden in response to vaccination or treatment. However, differing immune dynamics within current small animal models limit their utility beyond basic mechanistic and feasibility studies.

NHPs may offer additional insights into complex biological questions that are not accessible in small animals. They have great utility for modeling complex aspects of human immunity; however, it is still being determined how well the dynamics of host-pathogen interactions and pathology, and responses to vaccines and therapeutics align with humans. Small and large animal models will have to be refined and improved in parallel and iteratively with human clinical studies to validate hypotheses and endpoints. To facilitate this effort, appropriate reagents will also need to be developed. More predictive animal models to inform drug efficacy and vaccine studies in humans will be critical to selecting the most promising product candidates and ensuring that clinical resources are efficiently and effectively utilized.

Objective 5.2: Develop, standardize, and share tools to facilitate product testing and resource and data/sample sharing

The development of TB diagnostics, vaccines, and therapeutics is conducted in diverse organizations, from academia to industry, each contributing expertise and resources to defined steps along the product development pathway. More rapid translation of biomedical research findings into relevant TB product candidates and maximized use of available resources will require the further development of tissue repositories, as well as development of standardized nomenclatures, protocols, and reagents that facilitate the sharing of samples and datasets. Effective use of data repositories requires standardized nomenclatures and ontologies and the development of sophisticated data analysis and visualization tools. Existing NIAID databases (Appendix 1) can be leveraged to foster collaborations and data sharing.

Objective 5.3: Develop tools to assess low bacillary burden in humans

One of the limiting factors in studying the dynamic nature of TB infection and disease is our inability to quantitate and localize the pathogen in the body and correlate its presence with host responses. To study aspects of TB that precede active pulmonary disease or reflect persistence after therapy has been completed (paucibacillary stages of TB), it is necessary to develop sampling technologies and biomarkers of microbial or host responses to improve diagnostics and other clinical tools. Development of these tools requires generation of imaging probes that can locate bacilli in live animals and production of *Mtb* strains suitable for imaging technologies and *in vivo* studies, including tracking the presence, growth, and distribution of *Mtb* following infection and through disease progression.

Objective 5.4: Leverage and expand current clinical capacity of NIAID resources to test new therapeutic candidates and drug regimens, diagnostics, and vaccine candidates

NIAID will build on its existing investments in clinical research infrastructure and resources in the U.S. and locations where TB is endemic. In addition, leveraging NIAID resources (Appendix 1) in settings where HIV and TB are both endemic will facilitate the development of products for TB, as well as products for people co-infected with HIV.

Objective 5.5: Promote cross-disciplinary research and support early investigators to expand the cadre of innovative TB researchers

To accomplish the ambitious research agenda outlined in the strategic priorities above, it will be critical to recruit experienced, as well as new investigators to the field of TB research and increase collaborative, multidisciplinary research efforts. NIAID will draw on expertise from diverse disciplines, including immunology, data science, genetics, and epidemiology, to drive the research that will increase fundamental knowledge and the development of new diagnostics, preventive measures, and

treatments. NIAID will also support research opportunities for early career investigators to establish themselves as the next generation of TB researchers to ensure continuity within and to bring fresh perspective to the field.

Conclusion

The aspirational goal of ending the TB pandemic by 2035 will require collaborative, accelerated global efforts among governmental, non-governmental, and community-based organizations. The *NIAID Strategic Plan for Tuberculosis Research* builds on the momentum generated from high-profile, international reports and meetings, including the WHO End TB Strategy, the 1st WHO Global Ministerial Conference on TB, and the UN General Assembly High-Level Meeting on Ending TB. The *NIAID Strategic Plan for Tuberculosis Researc*h aligns with the global goals and supports the objectives delineated in the U.S. Government Global TB Strategy and the National Action Plan for Combating Multidrug-Resistant Tuberculosis. These reports and meetings highlight the importance of biomedical research as a critical component of a global strategy to end TB and underscore the need to continue efforts to improve knowledge and tools to prevent, diagnose, and treat TB. NIAID aims to address these critical needs through a comprehensive scientific agenda and infrastructure expansion that are geared towards strengthening TB research.

NIAID will leverage its existing portfolio of resources and investments in biomedical research to expand and modernize its TB research program. These efforts are expected to reinvigorate TB research and accelerate the development and evaluation of new methods to diagnose, prevent, and treat TB. By advancing fundamental TB research, resource development, and training of the next generation of TB researchers, NIAID will expand the knowledge base and expertise critical for accelerating the development of a comprehensive toolkit to end TB.

Appendices

Appendix 1. NIAID-Supported Clinical and Basic Research Resources

Resources	
Name	**Description**
AIDS Reagent Program	Acquires, develops, and produces state-of-the-art reagents and provides these reagents at no cost to qualified investigators throughout the world
BEI Resources Repository	Central repository that supplies organisms and reagents to the broad community of microbiology and infectious diseases researchers
Bioinformatics Resource Centers	Collect, archive, update, and integrate research data with user friendly interfaces and computational analysis tools
Cooperative Centers on Human Immunology	Translate immunology research into clinical applications in infectious disease
Genomic Centers for Infectious Disease Resources	Provide innovative application of genomic technologies and rapid, cost-efficient production of high-quality genome sequences for pathogens, hosts, etc.
HIV/AIDS Clinical Trials Networks	Group of clinical trials networks addressing HIV scientific priorities, including therapeutics for co-infections
HIV, Opportunistic Infection and TB Therapeutics Database (ChemDB)	Extracts from the scientific literature structure/activity information on compounds tested against HIV, opportunistic infections, and TB
Human Immunology Project Consortium	Uses modern tools to examine the human immune system before/after infection, vaccination, or adjuvant treatment
ImmPort	Platform to share bioinformatic immunology data
Immune Epitope Database and Analysis Resource	Contains detailed information for more than 100,000 unique immune epitopes related to infectious and immune-mediated diseases
ImmuneSpace	Powerful data management and analysis engine that enables integrative modeling of human immunological data
IMPAc-TB	Targeted to increase knowledge of immune mechanisms and the predictive value of animal models to advance novel TB vaccine strategies
International Epidemiology Databases to Evaluate AIDS Cohort Consortium	Generates large, harmonized HIV/AIDS data sets from seven international regional data centers to help address high priority research questions
International Clinical Sciences Support Center	Provides support services, including consultation and protocol development, site assessment, and data management for clinical investigators supported by DMID[1]
In-Vitro Assessment for Antimicrobial Activity Program	Tests for antimicrobial activity of products against microbial pathogens and vectors; strains and panels include those derived from clinical specimens
NIH Tetramer Core Facility	Produces and distributes major histocompatibility complex (MHC) tetramers and related reagents to the research community
PATRIC (Bacterial Bioinformatics Resource Center)	Information system that integrates bacterial pathogen information with rich data and analysis tools to support work on infectious diseases
Phase I Clinical Trial Units for Therapeutics	Support design, development, implementation, and conduct of Phase I clinical trials
Preclinical Models of Infectious Disease Program	Provides development, screening, and efficacy testing in pre-clinical infectious diseases models, including traditional lab species, NHPs, and non-traditional models
Structural Genomics Centers for Infectious Diseases Resources	Applies state-of-the-art technologies/methodologies to characterize 3-D atomic structures of molecules to support infectious disease research
TB Portals	Web-based, open-access repository of drug-resistant TB patient data with linked physical samples and advanced analytical tools

[1] Division of Microbiology and Infectious Diseases, NIAID

Appendix 1, Continued. NIAID-Supported Clinical and Basic Research Resources

Resources	
Name	**Description**
Therapeutic Development Services: Biopharmaceutical Development Services	Offers services for biotechnology products, such as planning, product characterization, process development, formulation, GMP manufacturing and CMC documentation
Therapeutic Development Services: Interventional Agent Development Services	Facilitates development of therapeutics including lead identification and development, chemistry and manufacturing, toxicology and pharmacokinetics
Tuberculosis Research Units Network	Integrates scientific and clinical research disciplines to study aspects of human TB in endemic countries, including TB latency and persistence
Vaccine Adjuvant Development Program	Aims to advance novel vaccine adjuvants toward licensure for human use
Vaccine Adjuvant Discovery Program	Identifies novel adjuvant candidates that may augment vaccine efficacy
Vaccine and Treatment Evaluation Units	Support efforts to develop new and improved vaccines and therapies against infectious diseases
Vaccine Development Services: Vaccine Manufacturing Services	Provide services including product development plans, process development, release and potency assays, pilot and cGMP manufacturing, audits, regulatory support
Vaccine Development Services: Vaccine Testing Services	Support assay development, immunogenicity and efficacy studies, clinical and non-clinical sample testing, and safety/toxicity testing

Appendix 2. NIAID Tuberculosis Research Strategic Plan Working Group Members

Last Name	First Name	Position	Division
Boggiano	**Cesar**	Program Officer, Vaccine Clinical Research Branch	DAIDS[2]
Church	**Elizabeth**	Deputy Director, Therapeutics Research Program	DAIDS
Dieffenbach	**Carl**	Director	DAIDS
Hafner	**Richard**	Chief, Tuberculosis Clinical Research Branch	DAIDS
Jayashankar	**Lakshmi**	Scientific Officer, Tuberculosis Clinical Research Branch	DAIDS
Jean-Philippe	**Patrick**	Chief, Maternal, Adolescent, and Pediatric Research Branch	DAIDS
Kim	**Peter**	Director, Therapeutics Research Program	DAIDS
Palmer	**Robert**	Health Specialist	DAIDS
Read	**Sarah**	Deputy Director	DAIDS
Rustomjee	**Roxana**	Medical Officer, Tuberculosis Clinical Research Branch	DAIDS
Augustine	**Alison**	Chief, Basic Immunology Branch	DAIT[3]
Hackett	**Charles**	Deputy Director	DAIT
Hauguel	**Travis**	Health Specialist	DAIT
Leitner	**Wolfgang**	Chief, Innate Immunity Section	DAIT
Ramachandra	**Lakshmi**	Program Officer, Immunoregulation Section	DAIT
Schneider	**Johanna**	Director, Office of Program Planning, Operations, and Scientific Information	DAIT
Grace	**Beth**	Senior Operations Officer	DCR[4]
McNay	**Laura**	Director, Office of Planning and Operations Support	DCR
Shaffer	**Meredith**	Assistant Director for Policy and Communications	DIR[5]
Boyce	**Jim**	Program Officer, TLMDS[6]	DMID
Eichelberg	**Katrin**	Program Officer, TLMDS	DMID
Embry	**Alan**	Chief, Respiratory Diseases Branch	DMID
Erbelding	**Emily**	Director	DMID
Glowinski	**Irene**	Deputy Director	DMID
Lacourciere	**Karen**	Program Officer, TLMDS	DMID
Laughon	**Barbara**	Senior Scientist, Respiratory Diseases Branch	DMID
Leyva	**Francisco**	Medical Officer, TLMDS	DMID
Makhene	**Mamodikoe**	Medical Officer, TLMDS	DMID
Miers	**Sarah**	Program Analyst, OSCPO[7]	DMID[8]
Mulach	**Barbara**	Director, OSCPO	DMID
Schuster	**Claire**	Health Specialist, OSCPO	DMID
Sizemore	**Christine**	Chief, TLMDS[9]	DMID
Caviston	**Juliane**	Health Science Policy Analyst, SPEB[10]	OD[11]
Eisinger	**Robert**	Special Assistant for Scientific Projects	OD
Folkers	**Gregory**	Chief of Staff, Immediate Office of the Director	OD
Parker	**Marie**	Acting Director, Office of Strategic Planning, Initiative Development, and Analysis	OD
Robinson	**Daphne**	Policy Analyst, SPEB	OD
Schwetz	**Tara**	Chief, SPEB	OD
Taylor	**Brandie**	Chief, Evaluation Section, SPEB	OD
Walsh	**Elizabeth**	Health Science Analyst, SPEB	OD
Daucher	**Marybeth**	Associate Director of Management and Operations	VRC[12]

[2] Division of AIDS
[3] Division of Allergy, Immunology, and Transplantation
[4] Division of Clinical Research
[5] Division of Intramural Research
[6] Tuberculosis, Leprosy, and Other Mycobacterial Diseases Section, Respiratory Diseases Branch
[7] Office of Scientific Coordination and Program Operations
[8] Division of Microbiology and Infectious Diseases
[9] Director, Division of International Relations, Fogarty International Center as of September 2018
[10] Strategic Planning and Evaluation Branch
[11] NIAID Office of the Director
[12] Vaccine Research Center

Appendix 3. Portfolio Analysis Results

As an essential first step in the strategic planning process, NIAID staff conducted a critical analysis of the current NIAID TB research portfolio. These data, summarized below, provide an overview of the NIAID research portfolio and establish a foundation for NIAID TB experts to develop a new strategic research agenda by identifying opportunities for innovation and areas where more focused research efforts may be needed.

Globally, more than 50 governments fund TB research. NIAID, the largest funder of TB research in the world, accounted for nearly 30 percent of all TB research support in 2016. Other funders in 2016 included philanthropic organizations (19 percent—with 90 percent from the Bill & Melinda Gates Foundation), and the private sector (23% from pharmaceutical and biotechnology companies, and international multilateral organizations, such as Unitaid, that mostly fund drug development efforts).

Box 7. TB Portfolio Analysis Summary

- *NIAID is the largest funder of TB research (~30% of global funding)*
- *NIAID TB research funding increased nearly 50% from FY 2013 to FY 2017*
- *Basic, epidemiology, and therapeutics research received largest NIAID TB funding increases from FY 2013 to FY 2017*
- *Nearly 50% FY 2017 NIAID TB research projects included human subjects*

The FY 2013–FY 2017 NIAID TB research portfolio included basic science and epidemiology studies as well as efforts for the discovery and development of diagnostics, prevention strategies, and therapeutics. NIAID funding for TB research increased nearly 50 percent during that time, up to $299 million in FY 2017. Basic, epidemiology, and therapeutics topics received the largest proportional increases in support, reflecting NIAID's renewed commitment to accelerate improved TB treatments and fundamental understanding of TB that may inform future advances in diagnosis, prevention, and treatment. In FY 2017, the majority (70 percent) of the research portfolio focused on basic research and therapeutics.

Projects involving human subjects represented nearly half of the NIAID TB research portfolio in FY 2017, and more than half of these projects focused on basic and therapeutics research. From FY 2013 to FY 2017, NIAID funded 47 TB clinical studies listed in clinicaltrials.gov. Other NIH institutes supported 12 additional clinical studies and the FDA funded two. Therapeutics studies made up the largest proportion of clinical trials, whereas the other studies focused on natural history, prevention and diagnostics. Phases 1 and 2 clinical trials for TB products dominated the development pipeline, with fewer studies in Phases 3 and 4.

Analysis of the NIAID TB research portfolio examined projects related to immunology, latency, biomarkers, antimicrobial resistance (AMR), and bioinformatics and functional genomics. Funding for immunology increased from FY 2013 to FY 2017 and represented more than one quarter of the total TB portfolio budget in FY 2017. Most immunology projects were basic research projects, with a strong emphasis on innate immunity projects. A significant proportion of immunology projects linked to prevention and vaccine development.

Additional NIAID funding increases from FY 2013 to FY 2017 supported TB biomarker identification (ten-fold increase), TB latency (nearly four-fold increase), antimicrobial resistance (AMR, greater than two-fold increase), and bioinformatics and functional genomics projects (two-fold increase). The dramatic increase in research on TB biomarkers reflected NIAID's effort to capitalize on existing studies by adding TB research to ongoing clinical research activities in other areas, such as projects within the Human Immunology Project Consortium. The increase in funding for TB latency projects correlated with increased support for basic and therapeutics research, including projects that incorporated people living with HIV (PLWH). Some TB AMR clinical projects examined treatment and prevention of TB in PLWH, whereas others focused on AMR mechanisms, epidemiology, transmission, and diagnosis. Although NIAID initiatives for clinical trial networks, research centers, or omics research supported many bioinformatics and functional genomics projects, the portfolio also contained several investigator-initiated projects. These data and the extensive knowledge of NIAID TB experts informed the development of a strategic plan to strengthen TB research and better address this urgent global health problem.

Appendix 4. Abbreviations

Abbreviation	Definition
ART	Antiretroviral therapy
BCG	Bacillus Calmette–Guérin vaccine
BSL3	Biosafety level 3
DR	Drug-resistant
DS	Drug-sensitive
HDT	Host-directed therapy
HHS	Department of Health and Human Services
HIV/AIDS	Human immunodeficiency virus/Acquired immunodeficiency syndrome
HIV-CTN	HIV/AIDS Clinical Trials Networks
IMPac-TB	Immune Mechanisms of Protection Against *Mycobacterium Tuberculosis* Center
INH	Isoniazid
MDR-TB	Multidrug-resistant TB
Mtb	*Mycobacterium tuberculosis*
NGS	Next-generation sequencing
NIAID	National Institute of Allergy and Infectious Diseases
NTM	Nontuberculous mycobacteria
PET/CT	Positron emission tomography/computed tomography
PLWH	Persons living with HIV
RePORT	Regional Prospective Observational Research in Tuberculosis
RIF	Rifampin
TB	Tuberculosis
U.S.	United States
VRC	Vaccine Research Center
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis