Delivering on the promise

Five years of progress towards more effective diagnostic tests for poverty-related diseases

2003
Partnering for better diagnosis for all

2008
Our vision is of a world where everyone will have equitable access to high quality diagnosis.

Our mission is to drive the development and implementation of accurate and affordable diagnostic tests that are appropriate to patient care in low-resource settings.
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This is the story of FIND as it celebrates five years of discovery and development of new diagnostic tools and their application to diseases in ways that will make a real difference for millions of afflicted individuals.

The pioneering people who are involved with FIND – its founders, partners, financial supporters, management and staff – are proud to be at the leading edge of this new frontier. We have not only raised the level of awareness of the critical role that diagnostics play in the effort to deliver better healthcare to communities affected by these diseases, but have also helped to further progress in diagnostic technology and move important products closer to patients.

As you read through these pages, I hope you will come to share my own view that the achievements of this young public-private partnership are quite remarkable from a purely scientific viewpoint and that it has well and truly performed its role as a catalyst accelerating the process of innovation and discovery among its many partners.

None of this would have been possible without the very special team of totally committed people who drive forward the work of FIND, whether this be full time or in another capacity.

What makes them, in my view, so special?

First, we are fortunate to have a top management team that knows how to manage, motivate and show enthusiasm for the job.

Second, everyone rigorously performs to the highest professional standards both in terms of organization and scientific methodology.

Third, they get the best out of individual initiative whilst making sure that this contributes to a strong overall team effort.

Lastly and most significantly, they all have a passionate commitment to FIND which gives me the confidence to say that we are well on the way to fulfilling our mission.

I would like to dedicate this publication to the team that “makes it happen” and to all our partners who together allow our CEO to say with confidence that FIND is delivering on its promise.
Delivering on the promise  Preface

FIND grew out of the realization that if the increasing worldwide prevalence of tuberculosis were to be stemmed, it would require more than just new drugs. The existing diagnostic tools were not up to the job and new discovery and development were urgently needed. In 2002, at the 33rd Conference of the International Union Against Tuberculosis and Lung Disease (IUATLD) in Montreal, Peter Small, Mark Perkins and I discussed how diagnostics could make a greater impact on the treatment and control of tuberculosis. We came to the conclusion that only through a concerted effort involving the research community, private companies and the public sector would it be possible to generate the necessary momentum for rapid progress. And so in May 2003, with the full support of the WHO and the strong backing of the Bill & Melinda Gates Foundation, we set down our first milestone. In those early days there were just four of us setting out on what has become for all of us a most fulfilling professional and challenging journey.

Our initial strategy was to prioritize problems, such as the diagnostic needs for TB based on epidemiological indicators. So we looked for companies whose portfolios included promising candidates for case detection, drug susceptibility and detection of latent TB infection. Today we have evolved from a disease epidemiology towards a patient centred approach which caters to all levels where healthcare is delivered. This has enabled us to work on the basis of “technology platforms” which allow solutions to be applied to more than one disease.

As we move forward, we will continue to focus on the current portfolio covering TB, African sleeping sickness and malaria and to move our projects further down the pipeline. However, we remain convinced that the development of point of care platforms will provide us with the potential to extend our scope into diseases such as leishmaniasis, HIV and others.

FIND operates as a catalyst, not as an implementer. We work hard at building local partnerships and ensuring that our contribution retains maximum relevance to local conditions. We have signed agreements with the governments of India, Lesotho, Ethiopia and Uganda covering both the policy level as well as the strengthening of technical capacity. Through this presence at country level we are able to learn lessons and ensure the continued relevance and value of our contribution.

The ability to be flexible in our response to changing circumstances and to adapt our strategic thinking as a consequence will, I believe, continue to be one of FIND’s strong points.

This publication covers our major achievements in our first five years – achievements of which we can rightly be proud such as the recognition of the quality of our operations which are now certified according to ISO 9001 and ISO 13485.
Our project pipeline is particularly strong in TB, where we put our first efforts, but there are now promising developments in African sleeping sickness and in malaria. All this is set out in more detail on later pages.

I am fortunate to be working with a very talented team who have the right cluster of skills – in research and technology, in business and negotiation, in public health policy, in setting goals and creating the right management structure to achieve them. This team includes 35 full time employees and again as many consultants. Sixty percent of the staff are women and 33 percent come from disease endemic countries, so we keep our feet firmly on the ground and close to reality. We already have offices in India and Uganda with more soon to come.

As our partners are discovering, our approach is delivering results, and together we enjoy the satisfaction of watching the fruits of our collaborations begin to find their way onto the front lines of the battle against infectious diseases. The first wave of faster, simpler and cost-effective diagnostic tools is already making an impact in the developing world and exciting new products are in the late stage of development. This is an inspiration for all of us to continue our commitment to our mission.

At this point I can pledge FIND's ongoing and relentless pursuit of more and better diagnostic solutions and their incorporation into the global effort to make the world a better place.

This publication is not an activity report in the usual sense, but more a review of our scientific achievements and also an informal portrait of the team which I feel so privileged to work with and together with whom we are delivering on the promise we made at the outset.

On that note, I am confident in stating that even in the wake of the tremendous progress and success that FIND has enjoyed over the past five years, the best is truly yet to come.
2003

The Foundation for Innovative New Diagnostics is launched at the World Health Assembly in Geneva, Switzerland, with an initial grant of $30 million from the Bill & Melinda Gates Foundation and a mission to promote the health of people affected by poverty-related diseases by developing safe, affordable and easy-to-use diagnostics.

2004

Addressing one of the most urgent health needs of the developing world, FIND and BD (Becton, Dickinson and Company), a medical technology company, announce an international collaboration aimed at improving diagnosis of pulmonary tuberculosis in HIV-infected patients. The first phase of the agreement is to show via demonstration projects the effectiveness of more rapid and accurate TB diagnosis in low-income settings, while the second phase focuses on sustainable implementation of this new diagnostic technology in the public health sector. TB is the leading cause of death in AIDS patients in high-burden countries, mainly in sub-Saharan Africa.

Building its organizational structure and operational procedures, FIND adopts a business plan and appoints its first Board of Directors.

2005

Expanding its activities to advance new TB diagnostics for remote settings, FIND completes collaboration agreements with several development partners, including Eiken Chemical Co. Ltd, a Japan-based manufacturer of clinical diagnostics, whose loop-mediated isothermal amplification (LAMP) method is designed to visually detect DNA directly from clinical samples in less than two hours with minimal instrumentation.

The pursuit of this technology was in response to the need to look beyond sputum microscopy, which is not sensitive or specific enough in many cases.

2006

A new endowment from the Bill & Melinda Gates Foundation permits FIND to launch its human African trypanosomiasis (HAT) diagnostics programme in February. Sleeping sickness is a fatal disease with disastrous consequences for the community, for which as few as 10 percent of patients are accurately diagnosed. In collaboration with the WHO and partners in research, industry and government, FIND begins the development and evaluation of novel diagnostic tests for this disease.
Progress in the development pipeline gives clear indication that healthcare providers will soon obtain quick and accurate results using the GeneXpert System from Cepheid, the only self-contained, fully-integrated and automated method for molecular testing.

In the third quarter, the Clinton Global Initiative highlights a commitment on the part of FIND and the Government of Uganda to create an innovative and sustainable model of laboratory social franchising with a view to improve diagnostic services in developing countries.

At the end of the year, FIND receives a further grant to evaluate the performance of existing rapid diagnostic tests for malaria and to identify improvements needed for new and improved malaria tests.

2007

FIND responds to the rise of multi and extensively drug-resistant tuberculosis by consolidating an agreement with Hain Lifescience GmbH to fast-track the “GeneType® MTBDRplus” molecular test in large-scale demonstration studies. In an expanded collaboration with BD, they agree to reduce prices on liquid TB culture assays. These tests provide results in just a few hours compared with the weeks it takes with standard culture tests.

An agreement is negotiated with a Japanese company, TAUNS, to provide the Capilia® – TB test for rapid low cost species identification that is required when liquid cultures are used.

A major highlight of the year is the endorsement and approval of both these tests by the WHO Strategic and Technical Advisory Group (STAG) for use in developing country settings.

FIND also enters into agreements with the Government of South Africa regarding the roll-out of the two new tests for the rapid diagnosis of multidrug-resistant tuberculosis (MDR TB), and with the Government of Lesotho to strengthen that country’s national reference laboratory services to improve testing for TB.

The feasibility of developing a molecular diagnostic test for human African trypanosomiasis, based on LAMP technology, is proven.

2008

Three tools for use in developing countries enter into final clinical evaluations. These technologies, including a high quality but low cost battery powered microscope with dual fluorescence capability (Zeiss), a simple molecular case detection test based on LAMP, and a fully automated, 90 minute test for TB and drug resistance (Cepheid), all are targeted for use in laboratories currently performing only routine microscopy.

Again, STAG endorsement of the line probe assay for MDR TB screening in high-burden countries results in WHO recommendations of this test.

To improve the quality of malaria diagnosis, FIND and WHO initiate large-scale testing of the available malaria rapid tests manufactured under quality systems, in collaboration with the US Centers for Disease Control and the Hospital of Tropical Diseases in London.
How it all started

The main health care directives of the 2000 Millennium Development Goals (MDGs) could not be more straightforward. Reduce child mortality; improve maternal health; halt and reverse the spread of HIV/AIDS, malaria and other diseases. And all of this by 2015.

The framers of the MDGs recognized that good health is essential to breaking the cycle of poverty that afflicts hundreds of millions of people across the planet. Yet their ambitious targets brought attention to the fact that the obstacles to treating disease in the world’s least developed countries are present long before we begin to contemplate the medicines to treat them – they are, in fact, part and parcel of our ability to identify and diagnose them.

Yet the tools available in the developing world for diagnosing tuberculosis or malaria and other poverty-related diseases are largely out-dated and ineffective, while those now available in wealthier societies are either too expensive or not adapted for use in the specific conditions prevailing in the developing world.

The inability to diagnose disease properly frustrates care providers, reduces patients’ faith in the healthcare system and results in inappropriate care with sometimes counterfeit or ineffective medicines, resulting in a massive waste of scarce resources.

Accordingly, in the wake of the MDGs’ creation, the focus shifted to the urgent and unmet need in the developing world for better and more suitable diagnostic technologies – particularly those that would improve simplicity, speed and accuracy – and to nurture methods to quickly transfer them to everyday use in countries ravaged by disease.

What was needed was an organization to stand at the intersection of the interests of all who were working to improve diagnostic services in developing countries – academic researchers, private sector companies, public health officials, specialized agencies and civil society organizations – and draw the participants into collaborative, productive arrangements to achieve attainable goals.

And that’s how and why the Foundation for Innovative New Diagnostics was born.
Opening a new door

FIND was created five years ago to bring diagnostic solutions to the very societies where treatable diseases are rampant and where poverty and poor health are closely intertwined.

Launched at a meeting of the World Health Assembly with an initial five-year grant from the Bill & Melinda Gates Foundation, FIND set out to develop – in partnership with academia, public and private research institutes and industry – diagnostic approaches that have been proven in principle and to transform them into effective products for identifying TB in its various ramifications. Additional funding has since been received from the Government of the Netherlands and the European Union. Further effort is being made to expand the funding base.

Focusing initially on tuberculosis, the scope of our activities has since been expanded to include efforts to improve diagnosis of malaria and human African trypanosomiasis (HAT), otherwise known as sleeping sickness.

FIND’s approach is to promote collaboration and cultivate relationships that advance the transformation of proven biological principles into effective products with demonstrated impact on disease control. Research by the World Health Organization has shown that although poverty-related diseases have not always received the attention they deserve from the larger diagnostics companies, there is considerable work going on in smaller biotechnology companies and academic research groups. However, even when diagnostics are developed for infectious diseases, they are often tailored to needs in industrialized countries, or to the private sector.

In effect, therefore, FIND bridges the gap by providing a coordinated mechanism to support new and innovative efforts and to develop and optimize tests that meet public needs in disease-endemic countries, to evaluate the tests that emerge and to demonstrate their value in disease control. By fostering cooperation between private industry, the international health community, and the governments of affected nations we are generating the kind of public-private partnership that is needed in the control of some of the most serious diseases afflicting the developing world.

Better diagnostics. Better health. And, in turn, more opportunities for economic and social progress in the world’s least developed countries. That’s how FIND is making a difference by opening a new door for prompt and correct treatment of diseases that affect the world’s poor.
**What FIND does**

**Strategy and partnership building**
Creates links with industry, academic centers, international health agencies, donors and national governments.

**Development**
Partners with industry and academic researchers in order to advance promising reagents and platforms, for which there exists proof of principle, into optimized diagnostic products for the detection of TB cases, mycobacterial drug susceptibility testing and latent infection. Since extended to other diseases.

**Evaluation**
Evaluates the performance characteristics of market-ready tests in regulatory-quality laboratory and field trials and promotes sustainability.

**Demonstration**
Collaborates with public health authorities to demonstrate the feasibility and programmatic impact on patients and disease control programs and thus generate objective evidence for the broader uptake of new diagnostics tests.

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**Cost of poor diagnosis**

<table>
<thead>
<tr>
<th>Individual health</th>
<th>Public health</th>
<th>Overall impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>no treatment</td>
<td>continued illness</td>
<td>growing incidence &amp; prevalence of disease</td>
</tr>
<tr>
<td>lack of diagnosis</td>
<td>continued transmission</td>
<td>increasing burden of disease</td>
</tr>
<tr>
<td>treatment of syndromes</td>
<td>waste of resources</td>
<td>misallocation of resources</td>
</tr>
<tr>
<td></td>
<td>development of drug resistance</td>
<td>increasing difficulty to control disease</td>
</tr>
</tbody>
</table>

Access to diagnostics is critical for individual and for public health. The diagram shows the cost of poor diagnosis at different levels.
What do you see in the promise of better diagnostics?

Over the past 20 years, technology development in diagnostics has moved along very, very quickly – and suddenly there is great hope for addressing one of the key causes of poverty in many countries, that is, the spread of treatable and preventable diseases like TB, malaria and sleeping sickness. At the same time this progress is being made, in technology development, the traditional markets for diagnostics in the industrialized world, centralized tertiary laboratories, are stagnating. The rapid growth markets are in point of care testing and in the developing world. So there is now a growing number of companies developing diagnostic technologies that are focused on the point of care in the developing world. Some benefit from technical advances made through investments in biodefense or other POC testing in established market economies. That is a wonderful thing.

Well, won’t that solve the problem? Why can’t we just let products flow into developing countries to fill the market need?

I wish it were that simple. But the fact is that there is a graveyard of technologies that didn’t make it because there was no market thinking, no understanding of how tests would be manufactured and in what volumes, how and where they would be delivered and exactly who would use them. This is especially true in the developing world, where markets are less defined, and testing infrastructure is shakier. Success in diagnostics development means in ensuring that the right technology, the right financing mechanism, the right manufacturing approach, the right methods for product evaluation and implementation are in place as you work with governments to change national policies and approaches. Also, there is work with laboratories to make sure they have the capacity to use the product effectively. On top of all this, donors and national governments must be engaged to make sure products can be purchased. Imagine a small health technology company, or even a mid-sized one, having to deal with all of this.

So what is FIND’s answer?

Until recently, there has never really been a public sector agency focused solely on driving diagnostics development for disease-endemic countries in a professional manner. Putting best commercial practices for assay development together with a public health mission and a clear understanding of the needs of developing countries makes it possible to pave a pathway from discovery to delivery. We like to think of ourselves as a trusted agent that can bring together all the various entities involved in transferring diagnostic technology to the developing world – public and private – and broker a way forward. Our mission is to be involved in the entire spectrum of the process, play the role of honest broker, and make sure the ball never gets dropped.
Delivering on the promise

Getting down to business

Two unique features inspire FIND’s business model.

First, rather than accept the notion that to be affordable, diagnostics for the developing world should be “low tech,” we operate on the premise that high tech and low cost can go hand in hand. We make use of the latest diagnostic technology to generate robust, simple and highly affordable medical tests that are compatible with field needs in the developing world.

Second, our commercial model motivates some of the very best biotechnology companies to innovate in high tech diagnostics. This is achieved by enabling our partners to retain the rights for use of the developed technologies in the lucrative for-profit sector, while ceding to FIND their use in the public and non-profit private sectors of high endemic countries at a preferential affordable price.

FIND’s operating model is project management centered and this has been a key factor in its ability to grow into new disease areas and extend its research base. Each disease-related unit manages its day-to-day operations supported by several cross-cutting expert functions and general support functions – technology platforms, project management systems, quality assurance and regulation, intellectual property management, contracting and business development, and policy and access.

Prioritizing diagnostic needs

Our initial strategic approach was to prioritize diagnostic needs and to partner with companies who held promising tests in their portfolios for those indications. However, since 2005, FIND has shifted its vision to prioritize diagnostics needs as dictated by the patient and health provider rather than by disease epidemiology. As a result of studies carried out jointly with WHO-TDR, we now have a more sophisticated understanding of how and where diagnostic technologies could be used to have the greatest impact. Given that some 60% or more patients in the case of TB first seek care at the lowest level of the healthcare system, proper diagnosis at this level would significantly increase the impact of treatment. The same holds true for other diseases as well.

However, technologies are still needed at the higher level of the health system, where more complex medical decisions need to be made and where human resources and infrastructure are more widely available, thus allowing the implementation of more sophisticated technologies. FIND’s strategy now aims to introduce incremental improvements to current technological platforms that will integrate the diagnosis of multiple diseases at each level of the health system. We select technology platforms which allow us to match both the complexity of testing and the sophistication of data with the level of the health system at which they would be used. The advantage of this approach is that it allows us to consider how additional disease parameters might be tested on the same platform in the future.

Gerd Michel, Senior Technology Officer

Gerd’s distinguished career in the private sector fits in well with the public-private partnership model to which he brings his experience in the development and launch of a number of diagnostic assays for different laboratory systems, primarily in the fields of infectious diseases, immunology and cardiology.

He appreciates the advantages of the open communication within the relatively small team at FIND, with company politics replaced by frank constructive confrontation, “only when really necessary” he adds.

“Proactive technology scouting” is what he calls his search for new biomarkers for TB. Some of his spare time is devoted to the Wellcome Trust Translational Research Award Committee.
Diagnostic needs at health system levels

<table>
<thead>
<tr>
<th>Test indication/requirement</th>
<th>Health system levels</th>
<th>Percentage of patients seen at a given level</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Surveillance</td>
<td>National ref. lab</td>
<td>5%</td>
</tr>
<tr>
<td>• Reference methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Network supervision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Resolution testing</td>
<td>Referral laboratory</td>
<td>10%</td>
</tr>
<tr>
<td>(screening negative drug resistance)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Case finding</td>
<td>Health centre</td>
<td>25%</td>
</tr>
<tr>
<td>• In-patient care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Primary care level</td>
<td>Peripheral health clinic</td>
<td>60%</td>
</tr>
</tbody>
</table>

Targeting tools to diagnostic needs at different levels of the health system.

Delivering quality

FIND is dedicated to a process of continuous improvement and review of quality management systems and the objectives embodied in them. Senior management defines annual quality objectives and evaluates performance of the organization according to targets attained. Achievement of planned project milestones within the projected timelines is one of the most important performance indicators of high quality project management and is assessed on a regular basis.

This business model has been successful in that it has allowed us to attract and maintain a motivated group of top professionals, validate operating procedures and intellectual property models, identify key existing technologies and include them in a professionally managed portfolio of products. The model also ensures the termination of projects that do not meet performance milestones.

FIND also plays a key role as a catalyst in the efforts of other partners. Between the international funding mechanisms on the one hand and the agencies providing technical assistance for laboratory systems and management strengthening on the other, we intervene as a broker to negotiate with partners to ensure lowest prices, share know-how from the product development process and provide long-term, on-site mentoring for technology transfer.

Bärbel Porstmann, Senior Operating Officer

Bärbel uses her extensive experience in the diagnostic industry to ensure that the products in FIND’s pipeline meet required clinical performance criteria and customer requirements.

“You have to be an all-rounder here,” she says. “I coordinate some 30 projects, monitoring them through a seven stage process, each with its own milestones and forming a kind of circle of verification.”

Bärbel recognizes that FIND’s ISO certification is a distinct advantage, but it also means that all partners in the product development chain must conform to the same performance criteria. “So having broad experience and being adaptable certainly helps me to cope.”
Delivering on the promise

ISO certification

From the beginning, FIND has based its organizational operations on the highest criteria of quality management and strongly emphasized the need for standard operating procedures (SOP). Our quality management systems were audited in 2007 by the Swiss TS/TÜV-Süd authority which confirmed that the procedures implemented throughout the organization were compliant with ISO Standards.

FIND now operates according to ISO 13485:2003 for medical devices, quality management systems and requirements for regulatory purposes and ISO 9001:2000 for quality management systems and requirements.

Protecting Intellectual Property

The advent over the past decade of Public Private Partnerships (PPP) active in the field of neglected diseases or diseases of the poor presents a number of legal and economic challenges when it comes to intellectual property (IP). The relation between the research, discovery, development and final marketing of a product and IP protection through patents is not usually an area of focus in the case of a PPP. The number and the diversity of the partners between public and private sectors, as well as the criteria specific to the geographic, cultural and economic contexts in which a PPP operates, adds to the complexity of the IP equation. Furthermore, FIND implements a global access strategy which includes ensuring that any products supported have clear freedom-to-operate with respect to IP rights.

There is no uniform IP formula which FIND applies to ensure that the products we are developing with our partners are accessible or available at prices that countries can afford. Each project has its own requirements, but it can be said that the IP element is generally based on three components: (i) IP rights which exist prior to the relationship; (ii) IP rights which are developed as part of any funded project; and (iii) access to any third party IP rights required to ensure freedom-to-operate. In practice, we generally share IP developed during a project and ask for royalty free access to pre-existing IP needed to ensure affordability for the public sector.

In the case of research which looks as if it could lead to an invention (patentable or not), we negotiate with the partners in each project in advance, to determine how the IP rights generated by the project will be managed in a way that passes benefits to the patients in resource poor settings by way of affordable pricing. IP in this case may include patent, copyright, trade or a service mark, a trade secret, or other intellectual property right related to any inventions.

In general, FIND's focus is to ensure access under the global roll-out requirements for the public sector (i.e. government-funded) and not-for-profit private sector work in high disease-burden countries and to clearly describe this under the terms and conditions of any contract.
**Understanding the needs of developing countries**

FIND devotes a great deal of effort to understanding the needs of individual countries so that its technological solutions match as closely as possible the conditions and resources that are available. In the emerging economies of China, Russia, Brazil or South Africa, where funding is to a large extent available from national budgets, there are fairly strong human resource capacities and often a considerable private sector with which to interact. In such settings implementation of more complex technologies is not difficult. On the other hand, in the low income countries of Asia and Africa, the situation with respect to funding, human resource capacity, laboratory services and the private sector varies from being barely acceptable to very weak. In these settings, considerable assistance for laboratory strengthening is needed prior to the introduction of new technologies.

Accordingly, we target our investments in countries where we believe there are opportunities to collect evidence and then to scale up solutions to share with others.

In Asia, we established an office in India in 2007 to oversee the coordination of evaluation and demonstration studies in collaboration with the Central TB Division, Ministry of Health. Later in the year, Lesotho was selected as FIND’s first pilot country for laboratory strengthening. Working with the World Health Organization and with Partners in Health, the National Reference Laboratory was upgraded into a quality-assured TB culture facility in order to streamline culture and drug susceptibility testing (DST) in the country. Other pilot countries in Africa, where FIND is working with partners to enhance laboratory capacity, are Ethiopia, Côte d’Ivoire and Uganda.

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**Keeping track of the poverty dimension**

Poverty and inequity are the biggest obstacles to good health care. FIND is committed to ensuring that its diagnostic tools are readily accessible and equitable for the underprivileged and the vulnerable. Assessing the impact of products and programmes on the poor is therefore a duty which FIND takes seriously, not just because it is fair but because it makes good scientific sense.

Measuring the equity and societal cost-effectiveness of new diagnostic tests requires developing instruments specially designed for this purpose.

Lesotho, where FIND has together with its partners established a functional central TB reference laboratory, is considered to be the ideal setting for a pilot study. The purpose of the study is to synthesize an approach for assessing the impact of new diagnostic tools and methods upon equity of access to TB and MDR TB diagnosis. By undertaking a poverty profile analysis, FIND will be able to determine whether patients eventually diagnosed belong to a socio-economically selected sector of the population and assess how patient distribution relates to characteristics defined at community level and by geographic area. The study will also look at the cost-effectiveness of diagnosis in Lesotho as measured by the number of patients who are correctly diagnosed with MDR TB and who start treatment.

FIND TB and Poverty Research Officer Delia Boccia is working on this study with strong support from the Liverpool School of Tropical Medicine.
A Postcard from FIND in India

After almost 5 great years spent with FIND in Geneva, it was time for me to move back to the field. This happened to be India, which offered a new challenge for me and my family as well as a new direction for FIND.

Several months have passed since our office became functional. The FIND India team are deeply involved in the support of our field activities, which involve the use of the BD, Hain, TAUNS and Zeiss tests in both regional and national laboratories throughout the country. These tests have been well received by the Central TB Division of the Ministry of Health, and are producing the hoped for results at trial sites and with patients. More than 20 projects all over India are in the pipeline for evaluation and demonstration trials and laboratory preparedness studies. Our aim in India is to assist the trial sites by facilitating their access to new diagnostics.

Compared to my previous position as the HR and Operations Manager of the Geneva office, my new life here in India is remarkable in that I can finally see the direct impact of FIND’s collaborations in the field. Some weeks ago, when for the first time Hain kits were imported to SMS Jaipur for a training session, the excitement amongst the Indian scientists matched the enthusiasm of children at a party. For me this reaction was highly encouraging and heart-warming.

There is a lot that can be achieved in this great country and we aim to play a key role by introducing new and affordable TB diagnostics into the public health system. FIND’s mission in India seems to meet the aspiration of those who are our ultimate concern: The patients.

Jacques Debayle
Partners in the promise

The Public Private Partnership model implies by its very name that it brings together two sectors of the economy who usually sit on opposite sides of the fence. The intractable nature of many of the problems facing society today, from local right up to global levels, requires a different coalition of forces to address appropriate solutions. The model is now well established as the key to addressing the challenges of R&D for diseases afflicting the poor. FIND has made every effort to leverage the advantages of this model by building a comprehensive network of relationships necessary for making reliable, easy-to-use and economically accessible diagnostics available to the populations of countries afflicted by poverty-related diseases.

Each project involves a number of partners ranging from companies, government ministries and development agencies to universities, research institutes and associates at local trial site level. These partners are listed at the end of this report. FIND recognizes that their contribution is an essential ingredient in the formula for success.

Major contributions to FIND

The role of the Bill & Melinda Gates Foundation – BMGF – in establishing FIND has been recognized from the very first pages of this publication. The financial contributions have been several and continue to ensure that we can pursue our mission free from resource constraints and in total independence.

The five year founding grant of US$ 30 million for the establishment of FIND was made in 2003 at which time TB was the only area of investigation. Then in late 2005, the BMGF made a further five year grant of US$ 9.8 million available for the establishment of a new business unit to tackle sleeping sickness.

In November 2006, the Netherlands Ministry of Foreign Affairs provided the first grant from a government to help accelerate work in developing point of care diagnostic tests for TB, HIV and malaria. The value of this grant was EUR7.9 million over a three year period.

The addition of the third disease portfolio for malaria at end 2006 was made possible again by the BMGF with a US$9.8 million five year grant.

In September 2007, FIND received a further five year US$ 62 million grant from the BMGF. This was part of a total of US$ 280 million which the BMGF disbursed for research to speed up the development of TB vaccines, diagnostics and drugs within the Global Plan to Stop TB.

The total value of grants in global health care made by the BMGF since its inception in 1994 is in the region of US$ 9.5 billion. The solid donor base upon which we have been privileged to be able to fast track the development of several of our projects is now set to expand in 2008 with new partners representing governments, development authorities and other agencies.
Delivering on the promise

Five years of progress and what next?

In his preface, Dr. Gerald Mueller, Chairman of the Board clearly indicated that this publication would not be a comprehensive report of everything that has been accomplished since 2003. Formal annual reports perform that function.

To our readers, with various levels of knowledge about FIND, we have endeavored to provide a flavor of what we are working for, how we work and some of the results of these efforts. The following sections reviewing our product portfolio are, in fact, complete and as up to date as we have been able to make them.

Since 2003, FIND has grown and matured without losing its youthful start-up culture and looks set to maintain this healthy balance into the future. So what does the future hold in store?

Probably there will be the addition of new disease areas and certainly continued strong development of the cross-disease technology platforms which have already proven to be so productive. The structure of the organization will continue to expand out from Geneva and increasingly take root in those regions where our tests are applied. A continued focus on point of care will be a priority.

As a partnership, FIND will continue to bring in new contributors whether in science, technology or other forms of support and strengthen its function as a solid bridge between them. This bridge function is in fact symbolized by the new logo for FIND.

At this point in time, the Foundation for New Innovative Diagnostics recognizes that its future and continued relevance as a mechanism for accelerating the delivery of rapid, accurate and affordable diagnostic tests depends on the continued commitment of all its partners to sustain the efforts made so far. This commitment will have to be earned by providing an appropriate environment for results in research and development in close alignment with the needs and realities found at the point of diagnosis delivery. That is the challenge that may be the subject of a similar publication in a few years’ time.

The next section reviews our current product pipeline in the three disease areas of tuberculosis, sleeping sickness and malaria. Measures to strengthen laboratory capacity complete the picture of FIND’s scientific programme.

As President of the European Diagnostic Manufacturers Association and member of the Board of the STOP TB partnership, representing the private sector, I am very pleased to underline the successful public-private partnerships developed by FIND in the field of health.

Jean-François de Lavison
International Affairs and Global Health Corporate Vice President, Mérieux-Alliance
An interview with
Dr. Vinand Nantulya
Senior Policy and Implementation Officer

A focus on the wider environment in which FIND operates

Is there a horizon beyond which you would consider that FIND’s work is done?

Not in the foreseeable future. The need for simple, accurate and affordable tests for many disease conditions in low resource settings is ever increasing. We currently focus on three diseases, but one can foresee the addition of other disease portfolios as success is scored against the initial three. In this regard I view both the communicable diseases like leishmaniasis or Chagas’ disease, and the non-communicable diseases which are making significant inroads into poorer communities. There will certainly be work for FIND in the years to come and I don’t think that the closure horizon will be visible any day soon.

Have you noticed a change in the fund raising climate for PDPs?

Not really, other than that the Product Development Partnerships model has now come to be accepted as a cost-effective means to accelerate the development of health products. We have been very fortunate to start with sizeable and stable support from the Bill & Melinda Gates Foundation. Contrary to what some people may believe, this early dependence on a single donor has not been a handicap in interesting other financial partners. It has provided the confidence to other donors that FIND is a credible partner. We now have funding support from the Government of The Netherlands and the European Union. We expect to diversify further our funding base.

What are you doing to ensure that your solutions don’t stay on the shelf?

This question lies at the core of our vision and mission. From past experiences, we know that new tools can take a long time to be taken up into use especially by the public health sector in low resource settings. FIND is engaging strongly with developing countries, and the global partners – both technical and funding – to craft the way forward in bringing into use the tools we develop. For instance, we maintain close working relationships with WHO, Roll Back Malaria partnership, the Stop TB partnership, the Global Fund to Fight AIDS, TB and Malaria as well as PEPFAR, and UNITAID. All of these and others form part of the same global effort, which will mobilize resources to create conditions in which our diagnostic tools will find their rightful place.

How are you getting your message across to your audience?

My responsibilities at FIND cover advocacy and communications, but all of us are involved in some way or other. I concentrate on providing a policy framework within which various communications initiatives can take place. This can cover relations with the media, speaking platforms at significant events, publications and in general spreading our belief that investing in diagnostics makes good economic sense.
Today, FIND is organized into three main business units, each one targeted at a specific disease – tuberculosis, sleeping sickness and malaria. Projects are managed within these units with the support of a number of cross-cutting functions dealing with technology platforms, project management systems, quality assurance and regulation, intellectual property management, contracting and business development, and policy and access. An additional unit focuses on the development of laboratory capacity, an essential element in the application of many of our diagnostic solutions.

We are now implementing more than 35 projects in our three major disease areas. Our project management system follows best industry practices with each project being structured into phases and milestones which require detailed and documented evidence of the attainment of pre-defined targets. Most projects entail the development and/or validation of in vitro diagnostic (IVD) products. These projects begin with the concept phase and progress through feasibility, evaluation, and demonstration, and end with access and impact in the public health sector.

**Tuberculosis**

**The diagnostic challenge**

TB is one of the greatest threats to health worldwide, with nearly nine million new cases and 1.6 million deaths each year. WHO reports that when left untreated, each person with active TB disease infects an average of 10 to 15 people every year.

To combat the disease, there is an urgent need for a diagnostics technology platform that moves beyond the century-old microscopy-based standard and into a new realm of speed, simplicity and affordability. FIND is rising to that singular challenge.

Manufacturers of diagnostic tools for infectious disease have in general not made significant investments in developing new, affordable and easy-to-use tests for those countries where most of the testing is being done. The market is seen to be too small and too fragmented to warrant investment. A market analysis report published in 2006 by WHO-TDR and FIND, though, revealed that in excess of US$ 1 billion is spent worldwide every year on TB diagnostics alone.

Only about a third of that sum is spent outside of the wealthiest countries, even though that is where three-quarters of diagnostic testing for TB takes
Moving beyond the microscope

Oddly enough, the most common method for diagnosing TB in developing countries is the same one that has been used since the disease was first identified in the 1880s – that is, examining expectorant from a patient’s lungs under a microscope. The test can also take days to complete and requires considerable expertise on the part of the technician – leading to testing conditions that are at times difficult to overcome.

In the case of malaria, although there are many rapid tests that allow malaria detection from a finger-prick blood sample, quality has been variable, and the results are often not trusted or not acted upon. As a result, an estimated 300 million treatments for malaria are given to people who are, in fact, suffering from some other cause of fever.

In the case of human African trypanosomiasis, the problem is that early diagnosis and treatment is critical in avoiding death and preventing its further transmission – and the microscope does not prove effective in identifying the disease at its earliest stages, particularly under remote tropical conditions.

The experiences in addressing these diseases in impoverished countries point directly to the need for better diagnostics, particularly to better tools that bring simple, rapid, affordable and effective means for identifying disease to the communities where people need them most.

Microscopy diagnosis

The slow road to diagnosis of TB when sputum smear microscopy is used
Delivering on the promise  Our product pipeline

“Today’s microscopy-based standard TB detection method was developed over a century ago and is time-consuming and frequently inaccurate. While treatment programs have improved the access of TB patients to effective therapy, diagnostics are now recognized as a primary hurdle in TB control and patient care.”

Dr. Peter Small
Senior Program Officer for Tuberculosis, Bill & Melinda Gates Foundation

TB projects at Referral Level Laboratories

LIQUID CULTURE AND DST – APPROVED BY WHO

In December 2004, FIND negotiated an agreement with Becton Dickinson to greatly reduce the cost of MGIT™ (Mycobacteria Growth Indicator Tube), the leading liquid TB culture system, for the public sector in developing countries. FIND, in turn, initiated a series of demonstration projects to examine the feasibility and impact of implementing MGIT™ culture and DST in high-burden countries.

In collaboration with technical partners, FIND established demonstration projects to examine the value of MGIT™ DST in MDR TB treatment programs in Nukus, Uzbekistan (MSF-Holland), Samara Oblast, RF (UK HPA), Kathmandu, Nepal (GENETUP), and Manila, Philippines (TDF). The primary purpose of the projects was to determine the feasibility of programmatic use of the test system, its impact on patient management, and associated costs. FIND also undertook demonstration projects of MGIT™ culture to improve case finding for HIV-infected TB patients in Zambia, South Africa, and Brazil (nested in CREATE TB/HIV prevention projects) and western Kenya (with the HIV/AIDS care provider, AMPATH).

Data from these demonstration projects were summarized in a report submitted to WHO in early 2007. Based on this report, an expert committee of WHO developed recommendations on the use of liquid culture and DST in low and medium-income settings. These recommendations were endorsed by the WHO Strategic and Technical Advisory Group (STAG) for TB during its meeting in June 2007 and subsequently adopted as WHO policy. Following STAG-TB approval, FIND and BD negotiated a new pricing agreement that is now providing MGIT™ culture and DST at a substantially discounted price for the public sector in 39 TB high-burden countries.
RAPID MTB SPECIES IDENTIFICATION – CAPILIA TB – APPROVED BY WHO

In the past, mycobacterial species identification was only possible through slow, laborious, and often inconclusive biochemical testing or through rapid but highly expensive methods such as molecular testing. Performing either of these methods on every culture isolate imposes a large financial (molecular) or workflow (biochemical) burden on laboratories in resource-poor settings. FIND identified a simple immunochromatographic test for species confirmation in positive cultures that was developed by a Japanese company, TAUNS, Laboratories, INC., but which was only available locally. This lateral flow test, known as Capilia TB, detects the TB-specific 24kDa antigen MPB-64. It is extremely simple to perform, can be used to identify growth on both solid or liquid culture, and gives results in less than 15 minutes.

Through agreements with TAUNS, FIND has made this assay available globally, with negotiated pricing for low-income countries. In cooperation with CREATE and other partners, FIND evaluated the Capilia TB test at 20 reference laboratories in a dozen countries (Germany, India, Kenya, Latvia, Lesotho, Peru, Philippines, Swaziland, Thailand, Vietnam, Zambia, Zimbabwe). Nearly 15,000 strains were tested in these studies, with so far high degrees of correlation with standard methods for species identification. Results from these studies were submitted to WHO STAG in 2007 and MPB-64 testing was subsequently endorsed as a standard method for species identification of MTB complex strains in culture. It is expected that these recommendations will pave the way for additional assays of this type that meet the needs of TB laboratories in disease-endemic countries.

RAPID SOLID TB CULTURE SYSTEM

There is an urgent need for more rapid, accurate, inexpensive, technically simple methods for detection of M. tuberculosis in clinical specimens. In many developing/transitional country settings, cultures are either not performed or are performed using the relatively low-cost Lowenstein-Jensen (LJ) solid media that takes up to two months to produce results. Automated liquid culture systems (such as MGIT™ system) are much faster, but until recently, high costs for equipment and supplies have precluded the widespread use of these systems in most high TB burden settings.

TK Medium (Salubris, Inc, Cambridge, MA) is a novel solid medium that supports growth of M. tuberculosis. It has multiple colour dye indicators that enable early detection of mycobacterial growth, as well as the differentiation of mycobacterial growth from bacterial contamination. The colour changes indicating growth of TB or contamination can easily be seen by the naked eye. TK Medium is used in “slant” form similar to LJ, and is inoculated and incubated in the same fashion as LJ, which is attractive in settings with existing facilities equipped for LJ culture and personnel trained in LJ culture methods. It is anticipated that the cost of TK Medium will be relatively low and comparable to LJ.

Because of these features, in 2004 FIND decided to partner with Salubris, Inc, on the further development and assessment of this test. However, work on this test is currently suspended pending a review of inconsistencies in its performance.

To hear Rick talk about his work at FIND with the same enthusiasm he no doubt put into his first work in TB some thirty years ago, explains much about the culture of the organization. Together with Giorgio Roscigno and Mark Perkins he completed the “trio” that composed and started to play the tune at FIND from the very early days.

Rick is keen to highlight the demonstration studies of the liquid culture system and the line probe assay for rapid diagnosis of MDR TB, both now endorsed by WHO. “We have helped WHO to develop a process by where it can consider new TB tools and develop policies and recommendations for their appropriate use in high-burden countries.”
As was stated in a scientific publication, assays for MDR screening in July.

Recommendations for use of line probe assays from these studies were submitted to WHO's Strategic and Technical Advisory Group for Tuberculosis (STAG-TB) in June 2008, and WHO issued policy endorsements by STAG-TB in June and issued as WHO policy in July.

Heidi Albert joined FIND as a consultant in March 2007 to oversee demonstration projects aimed at assessing the feasibility and impact of a new improved rapid molecular test for multidrug-resistant tuberculosis in South Africa.

The project was established in collaboration with the South Africa Medical Research Council, the National Health Laboratory Service, and the national and provincial Departments of Health. Operating in four provinces (Western Cape, KwaZulu-Natal, Northern Cape and Gauteng), the study enrolled 20,000 high risk MDR TB suspects over a one year period with the aims of evaluating the feasibility, impact and cost-effectiveness of rapid MDR screening in the public health sector and informing policy decisions on the use of such assays.

The study showed that the GenoType MTBDR plus test, a line probe assay, can detect approximately 98% of MDR TB cases in 1-2 days. Data from these studies were submitted to WHO's Strategic and Technical Advisory Group for Tuberculosis (STAG-TB) in June 2008, and WHO issued policy recommendations for use of line probe assays for MDR screening in July.

As was stated in a scientific publication of this study, molecular testing has the potential to revolutionize MDR TB diagnosis.

FIND has partnered with Hain Lifescience, GmbH on evaluation and demonstration projects using its line probe assay, the GenoType MTBDR plus test, for the direct detection of MDR TB from smear-positive sputum specimens. This molecular assay uses PCR technology to identify M. tuberculosis complex and chromosomal mutations associated with rifampin and isoniazid drug resistance in less than 24 hours. The test was initially validated and marketed for use with culture isolates.

Prior to the implementation of large-scale demonstration projects of the MTBDR plus test, a laboratory evaluation was conducted at the NHLS laboratory in Cape Town, South Africa. The study found that the line probe assay had performance characteristics that were superior to conventional testing in terms of speed, cost and accuracy. As was concluded in a scientific publication of this study, molecular testing has the potential to revolutionize MDR TB diagnosis.

Demonstration studies to assess the feasibility, cost, scaled-up performance, and patient and public health impact of this new technology have now been completed in South Africa. Similar studies are being implemented in Thailand, Vietnam, Turkey, India, and the Philippines. These projects are intended to provide the evidence that this test can have an important medical and public health impact when implemented in programmatic settings. Preliminary data from these projects were presented to an expert WHO committee in March 2008. This committee developed recommendations on the use of line probe assays for MDR TB screening in high-burden settings. These recommendations were endorsed by STAG-TB in June and issued as WHO policy in July.

MDR SCREENING WITH MANUAL MOLECULAR ASSAY – APPROVED BY WHO

To interrupt the spread of MDR and XDR TB, prompt identification, isolation, and treatment of drug-resistant patients are required. However, the standard method of diagnosing such patients, using culture and drug susceptibility testing on solid culture media, takes two months or more. While patients await diagnosis, their disease progresses with an increased chance of dying from TB, and they continue to transmit drug-resistant TB to others, especially family members.

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MDR SCREENING WITH PHAGE REPLICATION

Another rapid assay for MDR TB detection, the FASTPlaque-Response test, is a phage-based method developed through FIND’s collaboration with Biotec, Ltd. The test does not require any specialized equipment beyond that needed for a TB culture laboratory, and may be used directly on processed smear-positive sputum, providing rifampin resistance results in two days. This assay was recently evaluated by WHO/TDR and FIND in a study in Peru. Based on acceptable performance data in the Peru study, FIND embarked on demonstration studies of the test in South Africa.

The goal of the demonstration projects was to assess the applicability and utility of this test for detecting rifampicin resistance in smear-positive TB patients (as a presumptive diagnosis of MDR TB) in a low-income setting. The demonstration projects in South Africa, coordinated by the South Africa Medical Research Council, began with a two-month period for laboratory training and validation of the assay in two TB laboratories of the National Health Laboratory Service. However, during the validation phase in both laboratories, the test failed to meet required performance targets. As a consequence, FIND decided to discontinue all activities with this assay until improvements or satisfactory alternatives are available.

"My personal satisfaction", says Heidi Albert, "comes from using my skills to make my own small contribution to this effort, and to see these new technologies become accessible to those who need them most in South Africa and elsewhere. This goal is now within reach."
“The fruits of research are moving very quickly from the labs in the North into policy and practice in the South, showing that, by working closely together, we can come up with solutions for TB control. FIND is a model that must inspire all those involved in R&D.”

Dr. Mario Raviglione
Director of the World Health Organization (WHO), Stop TB Department

Liquid culture halves the time for performing TB culture and drug susceptibility testing compared to classic solid culture
Delivering on the promise  Our product pipeline

LATENT INFECTION DETECTION IN HIGH-BURDEN SETTINGS

In industrialized countries, newly available interferon-gamma release assays (IGRAs) are revolutionizing the diagnosis of latent TB infection that, until now, has been dependent on tuberculin skin testing (TST). These laboratory-based in vitro tests are founded on antigens specific to *M. tuberculosis*, and test results are not confounded by BCG vaccination or exposure to non-tuberculous mycobacteria. The role of IGRAs in less developed countries, however, is not clear. A research agenda to address this question was elaborated at a meeting in Geneva in March 2006 organized by FIND on behalf of the Stop TB Partnership Working Group on Diagnostics. During that meeting, FIND and Cellestis, Ltd., the manufacturer of one of the commercially available IGRAs, announced a collaborative agreement to evaluate the QuantiFERON® – Gold In-Tube (QGIT) assay in studies in developing countries in order to answer the most pressing research priorities. Preferential pricing of the QGIT test for the public sector of developing countries was part of this agreement.

The goal of these projects is to evaluate the utility of the QGIT assay for three diagnostic indications in disease-endemic countries: 1) the diagnosis of LTBI in HIV-infected persons, 2) the diagnosis of LTBI in adult and childhood contacts of tuberculosis patients, and 3) supporting the diagnosis of active tuberculosis in young children. QGIT testing is being carried out in large adult cohort studies in Zambia, South Africa and Brazil in collaboration with CREATE investigators. In addition, paediatric studies are being carried out in TB contacts in South Africa. These studies help address the critical question of the predictive value of a positive QGIT test for the future development of TB. Finally, studies of QGIT as an aid for the diagnosis of paediatric TB are being conducted in South Africa and India nested in Aeras TB vaccine cohorts. It is expected that data from these various studies will be available for analysis in 2009-2010.

TB projects at Microscopy Level Laboratories

SIMPLE MANUAL DNA AMPLIFICATION

Nucleic acid amplification tests (NAAT) have the potential to detect *M. tuberculosis* DNA in clinical specimens within minutes to hours, and with sensitivity approaching culture. Existing NAAT products have proven to be more sensitive and specific than microscopy in central laboratory settings and have seen increasing use in industrialized countries. However, to date, the commercial NAAT systems that are available have complex, multi-step specimen processing and DNA extraction procedures, and require expensive and dedicated detection instruments in addition to highly trained staff. None of the currently available commercial NAAT tests for *M. tuberculosis* case detection meet the needs of most of the laboratories in resource-poor settings, and are not accessible to most patients in high-burden countries. Recently, a method for DNA detection called LAMP (loop-mediated isothermal amplification) was developed by scientists at Eiken Chemical Co. Ltd. which has characteristics that could make possible the development of a simple, rapid and sensitive detection test for TB and potentially other diseases.

FIND and Eiken are working jointly to develop a TB detection assay that pairs simple manual specimen processing steps with LAMP, an isothermal
amplification system that generates large amounts of target DNA in real time and results in a visible readout, with no need for instrumentation, probing, or opening the reaction tube to determine the result. The FIND/Eiken team has made considerable progress in developing a specimen processing protocol that minimizes the number of steps and equipment needed, and has developed an amplification protocol with high sensitivity and with priming at multiple sites to ensure specificity.

Preliminary data on a multi-center evaluation of a first version of this assay were published in 2007, and showed the feasibility of performing the assay without sophisticated equipment or training. In that study, LAMP significantly outperformed microscopy. Further improvement and simplification of the assay is underway. The current version of the test requires no equipment other than a heat block, has no moving parts, and utilizes reagent formulations that are stable without a cold chain. A novel sample treatment method has been developed that dramatically simplifies pre-NAAT specimen processing.

The assay is intended to provide a qualitative, Yes/No answer for case detection in a format that can be performed at microscopy level laboratories. The test should be robust and as simple to perform as microscopy, but should be capable of detecting many more patients, including the majority classified as smear-negative. Clinical evaluation of the LAMP TB test is expected to begin in late 2008.

AUTOMATED MDR DETECTION

Molecular testing, with PCR or similar nucleic acid amplification tests, is the only proven alternative to microscopy and culture to detect *M. tuberculosis* in clinical specimens. Moreover, NAAT holds the promise of being rapid and sensitive, providing the possibility of point of care testing during a patient visit. Existing commercial NAAT systems, however, have largely failed to meet this promise, being too expensive and too reliant on highly skilled labor for routine use. Of the 90 million people evaluated annually for tuberculosis worldwide, fewer than 3% are tested using NAAT.

Much of the complexity of existing NAAT systems for TB is related to the need for three separate steps for 1) specimen processing and nucleic acid extraction, 2) DNA amplification, and 3) amplicon detection. These steps may require different skill sets, and even different rooms. Conventional PCR for TB is an overnight assay, and must be performed in a laboratory, usually some distance from the clinic, and thus cannot be used for point of care testing.

FIND sought to identify a NAAT approach that resolved all of these problems by combining the three steps of conventional NAAT mentioned above into a single, automated process. Additional requirements were that the testing be rapid enough to be performed while the patient waits, safe enough to be used outside a biosafety cabinet, simple enough to be operated without molecular training, and that it start from raw sputum rather than from a treated pellet. Lastly, we sought to integrate testing for rifampin resistance-associated mutations into the same assay to allow for MDR screening at the time of diagnosis.

In 2008, in the fourth year of the Eiken-FIND collaboration, the LAMP technology has entered its final clinical evaluations, and is holding enormous promise as an affordable and simple platform to diagnose TB and possibly other infectious diseases further down the line.
Delivering on the promise  Our product pipeline

specimen processing, amplification, and detection can all be carried out. A very simple processing method, it kills mycobacteria while liquefying sputum in a single step. The assay is designed to detect M. tuberculosis in both smear-positive and smear-negative sputum samples in less than 90 minutes. It will also simultaneously detect mutations of the rpoB gene, which are predictive of rifampin resistance and, by extension, MDR TB. The GeneXpert cartridge has all necessary reagents preloaded in a stable configuration for room-temperature storage. The cartridge can be simply placed into the device and used at the push of a button.

Feasibility studies carried out earlier this year in Peru and Latvia have confirmed the ease of use of the assay and its utility for desktop detection of MDR TB. Full clinical trials are being carried out in 2008.

LED FLUORESCENCE MICROSCOPY

Diagnosis of TB by light microscopy (LM) is hampered by both its poor sensitivity and by its heavy workload requirement. Fluorescence microscopy (FM) offers a number of advantages. It saves technician time by allowing a greater viewing field, obviates the need to heat slides in order to fix the stains, and detects an average of 10% more cases than LM. This sensitivity benefit may be even greater in populations, such as those co-infected with HIV, who have paucibacillary disease.

However, the high capital costs for fluorescent microscopes, the use of sensitive and expensive high-pressure lamps with limited bulb life, and the usual requirement for a dark room have dramatically limited the use of fluorescence microscopy in TB-endemic countries. To address this, FIND has partnered with Carl Zeiss MicroImaging GmbH, a well-known manufacturer of high-quality microscopes, to develop an inexpensive FM for routine use in high-burden countries that exploits low-cost, ultra-bright light-emitting diodes (LEDs). During 2007, prototypes were developed and feasibility studies and beta-tests carried out in several conditions. In the last quarter of 2007, evaluation studies of final prototypes were implemented in four different trial sites in Germany, Thailand, Peru, and the Gambia. Large-scale evaluation and demonstration studies with the final product are being carried out in 2008.

TB projects in Primary Care Settings

ANTIGEN DETECTION

In collaboration with several groups, including for the Statens Serum Institute in Denmark and Proteome Systems in Australia, FIND has been supporting a discovery program aimed at identifying novel diagnostic protein antigens from sputum and other clinical samples obtained from TB patients. Targets identified in these projects will lead directly to the development of a prototype assay, or be combined with other FIND-sponsored programs to develop an optimized approach for a point of care immunoassay. On a parallel track, FIND has carried out feasibility studies with a test detecting lipoarabinomannan (LAM), a glycolipid antigen made by Chemogen (Maine, US), while also developing enhanced LAM-detection reagents in collaboration with the Swedish Institute for Infectious Diseases. The goal of this work is to develop POC diagnostics that can be used at the lowest level of the health system to provide simple, rapid and accurate TB case detection.
One important obstacle to the detection of TB antigens is the likelihood that they will be present in clinical specimens in concentrations too low to detect with dipstick-like lateral flow tests. FIND is investigating the development of novel POC technology platforms that are capable of detecting diagnostic antigens at very low concentrations. In a partnership with the Seattle Biomedical Research Institute and a number of other collaborators, FIND is examining innovative labeling chemistry and other immunoassay enhancements to allow highly sensitive detection of tuberculosis antigens in a handheld format.

**DIAGNOSTIC ANTIBODY RESPONSES TO TB**

Many successful diagnostic tests for infectious diseases are based on the detection of antibody responses, but despite years of work in this area, no test for TB using this approach has yet proven accurate enough for routine use. In a structured approach towards identifying a broader panel of diagnostically useful antigens for TB serology, FIND has partnered with Antigen Discovery, Inc. and the Public Health Research Institute in Newark to investigate the diagnostic value of the entire *M. tuberculosis* proteome. Using a high-throughput cloning and expression system, 98% of the nearly 4000 proteins in the *M. tuberculosis* proteome have been cloned, expressed, and individually printed onto microarray chips. To identify the antibody profile characteristic of disease and to define a limited set of antigens that can distinguish latent infection from active disease in a variety of patient populations, the chips will be probed with sera from a large number of well-characterized patients with and without tuberculosis.

Patient cohorts involved in the proteome screening will include those with latent tuberculosis infection, those with and without HIV infection, and, importantly, control patients with symptoms of tuberculosis who are shown not to have TB through longitudinal follow-up and careful and repeated mycobacteriologic examination. Clearly, the quality and size of the serum set being tested is the single most important factor in determining the value of the data from this project. For this reason, FIND and partners, including WHO/TDR, have worked for several years to assemble the appropriate reference materials through standardized prospective studies in over a dozen countries.

This project differs from traditional approaches because the size of the patient cohorts included, and because the entire *M. tuberculosis* proteome will be probed, allowing every protein encoded by the organism to be individually evaluated for its ability to contribute to an accurate test. It is likely that no single antigen will prove capable of distinguishing TB from other causes of illness in the various patient cohorts and that a number of antigens will need to be combined in a multiplex immunochromatographic assay. The final goal is the development of a simple POC test for detection of specific anti-TB antibodies in whole blood with performance adequate for use in screening or definitive diagnosis at the lowest level of the health system.

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*Julie Vercruysse, TB Team Scientific Administrator*

Julie is both the youngest person on FIND’s staff and the longest serving member of its administrative team. Her involvement in event organization and travel logistics often keeps her at the center of the action, especially while so many key staff are on the road.

“Because FIND is driven by a patient-centered approach, the only way we can be truly effective is to be close to the field,” she says. “I am pleased to know that I help facilitate this connection.”

Julie Vercruysse, TB Team Scientific Administrator
Delivering on the promise  Our product pipeline

Human African Trypanosomiasis (HAT)

Since its launch in early 2006, FIND’s HAT diagnostics programme, implemented jointly with the WHO, has established linkages with industry, academic and research institutions in developed and endemic countries as well as with the Pan African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC) office of the African Union (AU). Projects that will enable the development of user-friendly diagnostic tests have been progressing well, and advocacy activities are being undertaken as part of the access strategy for HAT diagnostics. Four categories of diagnostic tests are being researched, including methods of parasite separation from blood and cerebrospinal fluid (CSF), serological assays, molecular tests and markers for staging. To support these activities, and to guarantee availability of biological materials for use in evaluation of the tests, the WHO has established a specific bank and initiated collection of samples from patients in Africa.

The diagnostic challenge

Control of HAT depends primarily on a combination of active and passive case detection and curative treatment to reduce or remove human reservoirs of infection from the population. Diagnosis of sleeping sickness remains a major and neglected problem. At present, diagnosis and subsequent treatment cannot be properly applied because existing tools are difficult to implement in remote, impoverished settings where the impact of the disease is greatest. In addition, most of the drugs used to treat sleeping sickness are not only toxic but also difficult to administer. To address this challenge, better drugs, including possible oral regimens, are urgently needed.

There are two stages to sleeping sickness. During the first stage, when treatment has the greatest chance of success, infection produces few specific symptoms and is rarely detected. Drugs to treat the first stage are relatively safe and effective in interrupting the parasite’s transmission cycle. The second stage, which starts when parasites invade the central nervous system (CNS), is difficult to treat and the drugs used are highly toxic, with 2% to 10% mortality during or shortly after treatment.

EARLY RECOGNITION OF SYMPTOMS

Since early-stage sleeping sickness is difficult to recognize clinically, and late-stage disease often leads to the death of patients, the strategy recommended by the WHO on its control relies on systematic screening of at-risk populations using the card agglutination test for trypanosomiasis (CATT), and confirmation of the presence of parasites by microscopy. CATT is used in the detection of specific antibodies against \( T.b. \) gambiense, which causes a chronic form of the disease found mostly in west and central Africa, and although quite effective, has some problems of sensitivity and specificity. No similar test is available for \( T.b. \) rhodesiense, the cause of acute HAT common to Africa’s east and central African regions. Since microscopy is both laborious and insensitive, many patients go undiagnosed. In addition, the molecular-based tests that are available today are impractical and difficult to maintain in the endemic rural areas due to absence of a developed infrastructure.
Individuals in whom infection is detected must go on to have their cerebrospinal fluid (CSF) examined to determine whether specific treatment for late stage disease is required. This can only be done by means of a lumbar puncture, which is an additional complication because it is invasive, very painful and requires considerable skill. Actual tests on CSF also suffer from limited sensitivity and specificity, resulting in inadequate treatment of some patients.

Better diagnostic tests that are simple, accurate and robust will revolutionize HAT control, and FIND is determined to find ways to facilitate their use in large screening programmes in remote, rural areas.

The role of raising awareness

How do you wage the battle against a neglected disease – neglected because it has long been associated with some of the least-visited, most underdeveloped rural areas in the world’s poorest countries?

If you’re talking about trypanosomiasis – or sleeping sickness – then you use public awareness-raising to facilitate the delivery of new diagnostic tools to the affected areas.

Accordingly, FIND has entered into a three-year agreement with the African Union Commission, under which the two institutions will work collaboratively to increase responsiveness to the need to eradicate the disease as well as disseminate new diagnostic tools under development by FIND and its other partners.

“Humankind has developed the technically feasible means to eliminate the scourge of trypanosomiasis,” said Dr. Ahmadu Babagana, the Director for Rural Economy and Agriculture at the AUC, who spoke at the signing ceremony for the Memorandum of Understanding with FIND. “We need to make people aware that this can be done and what we must do to make it happen. And thanks to financial and technical support from FIND, we can pave the way for these tools to get to the rural communities where they can be effective in eradicating this awful disease.”
HAT projects

PARASITE DETECTION

The most sensitive method for detecting trypanosomes in blood is the mini Anion Exchange Centrifugation Technique (mAECT). However, this method, which still requires some improvements, is expensive, time consuming, not easy to standardize, and can not be used in field situations where electricity is lacking.

Although several attempts to produce the mAECT kit in Africa have been made, they have always been met with problems of sustainability. We have been working with the Institute of Tropical Medicine (ITM) in Antwerp, Belgium to improve the mAECT technology and ensure its availability to screening programmes. A mAECT production unit at the Institut National de Recherche Biomédicale (INRB) in Kinshasa, Democratic Republic of Congo, has been upgraded and staff trained to produce and market the kit in disease-endemic countries. The upgrading included training, implementation of a rigorous quality control system and in-depth analysis of costs to guarantee sustainability of production. A second generation version of mAECT is undergoing evaluation, and will soon be introduced into the production unit at the INRB.

Meanwhile, we continue to work with our partners in the search for another test to replace mAECT – one that will be more sensitive and simpler to perform – including filtration of test samples through membranes, and fluorescence microscopy. The same iLED fluorescence microscope being developed jointly by FIND and Carl Zeiss for TB detection is currently under evaluation for trypanosomiasis. Other options that are being considered include using other gels, separation in an electric field, biosensors and fluorimetry.

SERODIAGNOSIS

Antibody detection test

Identifying cases of sleeping sickness currently depends on microscopic demonstration of trypanosomes in blood, CSF or lymph node aspirates. This approach is not practical in screening programs that require testing large numbers of people in the shortest amount of time in remote, rural settings. Development of serological tests for the disease has been hindered by the ability of the parasite to keep changing its surface antigenic coat, which allows it to evade the host's defence mechanisms.

We are working with partners to determine the feasibility of developing a serological method that is simple, more sensitive and more specific than CATT by using purified, recombinant or synthetic antigens, rather than whole organisms, that will be recognized by parasite-specific antibodies in the serum. The strategy taken is to select candidate antigens amongst those that are currently available, rather than investing in discovery of new ones. Scientists and laboratories with such antigens are collaborating with FIND in screening them for their potential for diagnosis of both *T. b. gambiense* and *T. b. rhodesiense*. The first 32 antigens have undergone initial screening at Microcoat in Germany, resulting in a selection of 18 that are going through a second, more intensive round, with the hope of identifying the best to be used in developing the test.
Antigen detection test

A test that would detect the presence of trypanosome antigens in body fluids would be more preferable than one that only detects host antibodies against the parasites. Together with the Institute of Tropical Medicine (ITM) in Antwerp we are working with the Institute of Biotechnology at the University of Brussels, Belgium, to determine the feasibility of using camel heavy-chain antibodies (nanobodies), and with the Department of Genetics at Darmstadt University of Technology in Germany, to explore the use of RNA aptamers in tests to detect parasite antigens.

Further work is being carried out with the Seattle Biomedical Research Institute (SBRI) to apply the single chain variable fragment (scFv) antibody engineering technology in development of optimized antibody probes for trypanosome antigens in blood. Using a technology called yeast display, high-affinity antibody fragments for a number of *T. brucei* proteins are being generated, and the ones that are best in binding parasite antigens identified. The sensitivity and stability of the probes for the chosen antigens will be further enhanced by antibody engineering methods. The outcome will be a set of antibody probes with characteristics of sensitivity, stability, and manufacturability that are superior to probes generated by traditional methods.

MOLECULAR TOOLS FOR DIAGNOSIS

The parasitologic tests in use for diagnosis of HAT have low sensitivity, and serological ones have inadequate specificity. Detection of trypanosomal DNA sequences from a patient’s blood, urine or saliva could be a significant improvement on parasitological examination. Loop-mediated isothermal amplification of DNA is a promising new molecular technique that has high sensitivity and specificity, which involves the amplification of target DNA under isothermal conditions. This implies that the test can be carried out with minimal equipment, can also be used for the simultaneous analysis of large numbers of samples, and can be performed by staff with minimal experience in molecular biology. The test may also be useful for confirming cure during follow-up after treatment.

FIND has been working with Murdoch (Australia) and Obihiro (Japan) Universities, and research institutes in endemic countries, to develop and evaluate the potential for HAT diagnostics based on LAMP technology. Sets of primers that are specific to the subgenus *Trypanozoon*, *T. b. rhodesiense* and *T. b. gambiense* have been designed and tests optimized using DNA from various members of *Trypanozoon*. The most sensitive and specific primer sets are under validation using samples from HAT patients. Reproducibility of the tests in endemic country laboratories has already been verified. This work has given sufficiently promising results to support adaptation of the LAMP technique for diagnosis of HAT.

In 2005, FIND partnered with Eiken Chemical Company Ltd, to work together in developing and supplying a diagnostic test for *Mycobacterium tuberculosis* for the developing world. Eiken has already developed and marketed LAMP tests for other infectious diseases, including assays for detection of *Salmonella*, various *E. coli*, *Listeria monocytogenes* and *Campylobacter*, and we are working closely with them in exploring opportunities to use LAMP in HAT and other infectious diseases.
DEVELOPING TOOLS FOR DISEASE STAGING

To distinguish the early and late stages of sleeping sickness, a lumbar puncture is performed and the cerebrospinal fluid (CSF) examined for presence of parasites and elevated number of white cells. These parameters suffer from insufficient sensitivity and, in the case of white cell count, of specificity as well. Moreover, the two diagnostic approaches are hampered by technical problems, and there is controversy over what the cut-off values should be. Due to shortcomings such as the invasive nature of a lumbar puncture and toxicity of drugs used to treat the late stage, there is an urgent need for improved markers for staging the disease.

After treatment is completed, patients are followed for a period of 24 months to confirm that they have been cured. Since relapses are mainly of central nervous system origin, and parasites are often difficult to find in blood, follow-up relies mainly on lumbar puncture and CSF examination.

We are supporting a number of projects to determine the feasibility of developing new tests for staging of sleeping sickness with improved accuracy to guide treatment and to determine treatment success. Special attention is being given to speed, simplicity, cost, and reliability of the new tests, as well as reduced invasiveness. In connection with this, scientists at the University of Geneva have identified a number of molecules which, when used alone or in combination, appear to be by far the most promising in discriminating between the two forms of the disease. On this strength, and in line with our strategy of guaranteeing access to diagnostic tests, FIND has filed a patent application to protect the invention.

THE SPECIMEN BANK

Some critical obstacles in the development of improved assays for sleeping sickness include access to quality diagnostic and clinical data, and to carefully collected and stored reference materials. Sustained field programs that have the capacity and facilities for long-term follow-up constitute another important challenge. Although a number of small, independent specimen collections from HAT patients already exist, most of them may have been collected under uncertain ethical conditions, taken from poorly characterized subjects, or stored in unstable conditions.

FIND and the Department of Neglected Tropical Diseases (NTD) of the World Health Organization are addressing these problems and have established a HAT specimen bank belonging to the WHO. The Pasteur Institute in Paris, France has been contracted by WHO to manage the receipt of specimens from collection sites, as well as their storage and distribution to end-users. This is guaranteeing more efficient use of limited resources, reducing the need for field trials, promoting product comparisons and facilitating quality control.

Specimen collection is being carried out by a network of collaborating diagnostic centers in Africa, following internationally accepted guidelines regarding the collection, transport, storage and use of clinical specimens, including control of confidential information such as patient data. Geographic variability and differences in patient subgroups are being considered when choosing collection sites. Linkages are also continuously being established with ongoing clinical trials and control programmes to donate sample materials for the bank.

We recognize the invaluable contribution of FIND in developing critically needed diagnostics that are a key element in providing adequate treatment for the poorest. In particular, by choosing sleeping sickness, FIND is showing a strong commitment towards controlling this debilitating disease in rural Africa.

Dr. Bernard Pécoul
Executive Director, Drugs for Neglected Diseases initiative, DNDi
ADVOCACY FOR HAT

In a partnership that could lead to accelerated elimination of African trypanosomiasis, we are supporting the African Union Commission’s efforts to establish enduring mechanisms through which countries are building up support for the eradication of tsetse and trypanosomiasis. Under the auspices of the Pan African Tsetse and Trypanosomiasis Eradication Campaign office of the AUC, advocacy activities are being intensified (a) to encourage governments of endemic countries to prioritize HAT surveillance and control by ensuring adequate budgetary allocation (b) to create the environment necessary for sustainable introduction of new diagnostic tests in the public sectors of endemic countries, and (c) to increase community awareness of the disease.

Of note is that probably for the first time, African countries have most of the ingredients required to mount effective interventions against trypanosomiasis: they have the determination; a strategic plan for advocacy; and the fellowship needed to effectively and successfully implement the campaign. Since the countries have shown their commitment to this objective, it is expected that implementation of the strategic plan on advocacy for African trypanosomiasis will result in improved health infrastructure, diagnosis and surveillance of HAT; synchronization of current information on HAT and its control; enhanced awareness and ownership of the HAT problem at local, regional and national levels; a greater index of suspicion for HAT among health workers; and a guide for national policies on HAT in disease endemic countries.

This collaboration will generate critical data that will allow us together with our partners to develop a robust access plan for HAT diagnostics, designed to ensure their sustainability in the public health sector.

Hanna Yirga, HAT Scientific Team Administrator

Hanna appreciates the multicultural atmosphere at FIND.

“There are 15 nationalities represented here,” she says. “Yet, despite the cultural and national diversity on this team, I have found there are always a number of common threads among all cultures – team work and tolerance being chief among them”.

“I have felt comfortable working here and adapting myself to an environment where we work hard to get things done on time and efficiently,” says Hanna. “And the reward is to feel I am making a personal contribution towards better health in my country, where both TB and malaria are the biggest killers; and sleeping sickness (HAT) is still a neglected disease.”
Delivering on the promise  Our product pipeline

Malaria

The diagnostic challenge

Today malaria is one of the greatest global threats to public health, causing over 300 million cases of acute illness worldwide. There are over one million deaths a year from the disease, of which some 80 to 90% are in sub-Saharan Africa. Billions of dollars are lost each year in low productivity due to malaria and in some countries the malady may account for as much as 40% of public health expenditure.

Accurate and early diagnosis is critical to malaria control and for targeting the often expensive therapy towards the right patients. This is especially relevant with respect to ACT, the new artemisinin combination therapy. Without confirmation of a cause, over diagnosis and mistreatment are common. This not only wastes scarce resources, but fuels drug resistance and results in much morbidity from undertreatment of the true cause of the illness in many a patient.

Microscopy for malaria is technically demanding, and extending high-quality microscopy services to the community level has been difficult to achieve. Thus, the advent of rapid diagnostic tests (RDTs) that can detect malaria antigens in a fingerprick blood sample has been an important advance. Their appropriate use will be critical in implementing WHO recommendations to confirm parasitemia in all patients over 5 being treated with ACT. From a single manufacturer 15 years ago, the field has grown to include more than 50 manufacturers of such tests. This profusion of choice, and the variable quality of products reaching patients in developing countries, has made it difficult for national malaria control programs to determine which tests to purchase, and has left users uncertain whether they can always rely on the test result. The degradation of these tests on exposure to heat during shipping and storage compounds this problem. Mechanisms are urgently needed which can 1) indicate which RDTs are manufactured with the quality and performance needed by public health programs, 2) determine whether lots of RDTs are performing up to expectations after being shipped to countries but before dissemination to remote field sites, and 3) provide clinic technicians and health workers with a means to verify that the RDTs they are using are still of acceptable quality.

Once accuracy of these tests is assured, other issues of RDT usage can be properly addressed and the full impact of malaria RDTs, a potential revolution for the management of febrile disease in malaria-endemic regions, can be realized.
Malaria projects

FIND is working with WHO to implement an accelerated three-stage solution to ensure the quality of malaria RDTs used in national disease control programs.

STAGE 1: PRODUCT TESTING

Reference materials against which to test RDTs have so far not been available, and even manufacturers themselves are sometimes unsure of the performance of the tests that they release for sale. Geographic variability in the parasites themselves also means that these tests may underperform in some regions. Lastly, many of the RDTs are susceptible to degradation at temperatures commonly found in malaria-endemic countries.

Over the past two years, a globally-representative reference collection of blood from individuals infected with malaria has been established, and blood dilutions have been carefully made to standardize the concentration of malaria parasites in each sample. These materials have been characterized by PCR to establish parasite species and by ELISA to determine the concentration of parasite antigen in the dilutions. Nucleic acid sequencing of the relevant variable genes has been carried out. These blood samples form a stable reference panel that can be used to reproducibly evaluate RDTs.

The product testing exercise is the result of extensive collaboration between WHO, FIND and agencies from all over the world.

STAGE 2: LOT TESTING

The good performance of an RDT in a controlled product testing scheme is no guarantee that other lots of this product, once shipped to the country of intended use, will perform as well as expected. Not infrequently, countries unknowingly purchase lots that are poorly performing, or that have been heat-damaged during transit. For this reason, mechanisms are needed for local or regional testing of purchased RDT lots before they are distributed for use. Health Ministries need rapid access to information on the quality of the tests they are buying.

Together with WHO, we are establishing four regional lot-testing sites that have the capacity to carry out rapid and high-quality performance evaluations of RDTs sent from anywhere in the world. These centers also provide a secondary service of storing and retesting the RDTs over time to ensure that they still function up to the time of their expiry date. All this information is rapidly transmitted to the submitting country so that decisions on the acceptability of purchased RDTs can be made. Lot-testing is currently successfully under way in the Philippines and Cambodia and an additional site has been established in Ethiopia.

STAGE 3: POSITIVE CONTROL WELLS

It is vital that RDT quality can be checked and assured at the level of their use, often in remote clinics or in the hands of village volunteers. Ensuring accuracy saves lives by guiding correct treatment, and demonstrating accuracy itself gives both health workers and patients the assurance necessary for effective treatment. Lack of confidence in results is a major impediment to current RDT-based programmes.
Delivering on the promise

Our product pipeline

LED fluorescence microscopy – a multiple disease platform
Some days Audrey misses her former job with the hands-on side of lab work, but the wide framework at FIND gives her satisfaction in knowing her work will make a difference in the lives of so many people.

Responsible for ensuring the flow of information between FIND’s partners – including WHO/TDR, the Hospital for Tropical Diseases in London, and KIT in Amsterdam – Audrey coordinates inputs and makes sure deadlines are met.

“What I really like about FIND is facilitating the marriage between the public and private sectors to produce diagnostic solutions that neither could do on their own. It’s a real value we add to the equation.”

Again with WHO, we are working with partners, including the National Bioproducts Institute in South Africa and the Hospital for Tropical Diseases in the UK to develop stable wells containing the major target antigens of commercially-available RDTs. When available, these will provide a simple, low-cost method to test RDTs and ensure quality can be monitored from manufacture to the end-user, vital elements for a diagnostic programme focused on a high mortality disease. Transfer of this technology to a manufacturer is planned, and large-scale field trials of a prototype are anticipated from the end of 2008.

EXTENDING LAMP TO MALARIA

The LAMP molecular diagnosis platform is a novel platform being developed for a relatively wide number of pathogens of all classes (see HAT and TB above). Together with the Hospital for Tropical Diseases in London, we are designing and selecting appropriate amplification targets for all major species of malaria.

IMPROVING ANTIGEN-DIPSTICK FOR MALARIA

The Royal Dutch Tropical Institute, the Queensland Institute for Medical Research and FIND are working to identify novel antigens that can be used for test development and to research the potential for improving the stability of the various separate test components and RDT devices as a whole.
Delivering on the promise

Our product pipeline

Laboratory Preparedness

Stronger labs for new tools

Local laboratories are a key component of ensuring that the next generation of fast, simple and cost-effective diagnostic tools can be successfully used in countries where disease is rampant.

One of our strategies is to ensure that these new tools are developed in such a way that local laboratories will be able to use them effectively. Equally important, however, is upgrading the capacity of the laboratories – where oftentimes there are irregular electricity supplies, deficient equipment and a lack of trained staff – and ensuring they are able to deliver on their role as a cornerstone of successful diagnostic program implementation.

In the context of a global response to MDR and XDR TB, the WHO Stop TB Department and Partners in Health (PIH) asked FIND in November 2006 to assess the National TB Laboratory in Lesotho in order to evaluate the operational feasibility of establishing an automated liquid culture system as a rapid DST detection tool. Part of our evaluation was to determine which laboratory upgrades needed to be undertaken before demonstration of this test could begin.

In collaboration with the Head of the Central Laboratory, the National TB Program, WHO, PIH and the Clinton Foundation, we wrote a proposal on how to rapidly reinforce the Central TB Laboratory and introduce a modern liquid culture system for TB drug susceptibility testing.

Our interest in Lesotho was to monitor, within the framework of a demonstration project, the process of implementing a modern and rapid technology for TB drug-susceptibility testing in a laboratory that up until now suffered from major quality constraints.

In a very short period of time during 2007, we supervised the upgrading of Lesotho’s National Reference Laboratory into a quality-assured TB culture facility with the aim to streamline culture and DST facilities in the country. Under the leadership of Lesotho’s Health Ministry and WHO guidance, we prepared detailed technical and resource requirements and PIH provided the necessary human and financial support.

One of the most urgent needs for countries in sub-Saharan Africa, where TB is compounded by the HIV-AIDS epidemic, is to establish quality-assured, aerosol-free, safe laboratory facilities for tuberculosis culture and DST. Among these countries, the Kingdom of Lesotho, with a population of 1.88 million, ranks among the worst affected.

At the end of this two-year project, the Kingdom of Lesotho will have a state-of-the-art mycobacteriology laboratory – one capable of addressing the challenges posed by the multi- and extensively drug-resistant TB crisis and comparable to any laboratory in the developed world.
New York, 21 September 2006: the Clinton Global Initiative highlights FIND’s and the Ugandan Government’s laboratory strengthening commitment proposal. From left to right: Director of Health Services, Ministry of Health of Uganda, Dr. Sam Zaramba, Former President Bill Clinton and FIND CEO, Dr. Giorgio Roscigno.
Delivering on the promise  The partners of FIND

2003 - 2008

THE PARTNERS OF FIND

Non-commercial research partners

Tuberculosis

- Johns Hopkins University, Baltimore, USA
- Ludwig Maximilians University, Munich, Germany
- University College London, UK
- London School of Hygiene and Tropical Medicine (LSHTM), UK
- Aurum Institute for Health Research, Johannesburg, South Africa
- Queen Mary College, London, UK
- Medical Research Council, Pretoria, South Africa
- Columbia Earth Institute, New York, USA
- Health Concept International, Bangkok, Thailand
- Seattle Biomedical Research Institute (SBRI), USA
- University of Medicine and Dentistry of New Jersey (UMDNJ), USA
- University of San Francisco, USA
- Universidad Peruana Cayetano Heredia (UPCH), Lima, Peru
- Center for Health and Population Research, Dhaka, Bangladesh
- Mbeya Medical Research Program (MMRP), Tanzania
- MSF-Holland DOTS-Plus Laboratory, Nukus, Uzbekistan
- Samara Oblast Reference Laboratory, Samara, Russian Federation
- GENETUP Laboratory, Katmandu, Nepal
- TDF (Tropical Disease Foundation) Laboratory, Manila, Philippines
- CDL (Chest Disease Laboratory), Lusaka, Zambia
- Stellenbosch University, Tygerberg, South Africa
- National Health Laboratory Services, Braamfontein, South Africa
- Fundação Oswaldo Cruz, Rio de Janeiro, Brazil
- AMPATH Laboratory, Eldoret, Kenya
- National TB Reference Laboratory, Bangkok, Thailand
- Pham Ngoc Thach Hospital for Tuberculosis and Lung Diseases, Ho Chi Minh City, Vietnam
- Mycobacterial Reference Laboratory, Borstel, Germany
- Geneva University Hospital, Switzerland
- National JALMA Institute for Leprosy & Other Mycobacterial Diseases, Agra, India
- All India Institute of Medical Sciences (AIIMS), New Delhi, India
- Dutch Royal Tropical Institute (KIT), Amsterdam, Netherlands
- SMS Medical College, Jaipur, India
- National Health Laboratory Services, Greenpoint TB Laboratory, Cape Town, South Africa
- National Health Laboratory Services, Kimberley Hospital, South Africa
- Biomedical Research and Training Institute, Harare, Zimbabwe
- National Health Laboratory Services, TB Laboratory Inkosi Albert Luthuli Central Hospital, Durban, South Africa
- Lesotho National TB Reference Laboratory, Maseru, Lesotho
• State Agency for TB and Lung Diseases, Bacteriological Laboratory, Latvia, Riga
• Christian Medical College, Vellore, India
• Medical Research Council, Banjul, The Gambia
• Saint John’s Research Institute, Bangalore, India
• Perinatal HIV Research Unit, University of the Witwatersrand, Diepkoof, South Africa
• Centre for Infectious Disease Research in Zambia, Lusaka, Zambia
• National Referral Laboratory, Mbabane, Swaziland
• Institut für Mikrobiologie und Laboratoriumsdiagnostik, Gauting, Germany
• Bangkok City TB Laboratory, Thailand
• Unit for Clinical and Biomedical TB Research, Medical Research Council, Durban, South Africa
• Turkish National TB Reference Laboratory, Ankara, Turkey
• Hinduja Laboratory, Mumbai, India
• L.R.S. Institute of Tuberculosis and Respiratory Diseases, New Dehli, India
• Ethiopian Health & Nutrition Research Institute, Addis Ababa, Ethiopia
• State TB Demonstration Centre (STDC), Gujarath, India
• State TB Demonstration Centre (STDC), Andhra Pradesh, India
• Main Medical Department, Ministry of Justice, Azerbaijan
• Mycobacteriology Laboratory of the University Hospital Clementino Fraga Filho/Thorax Disease Institute (HUCFF/IDT), Rio de Janeiro, Brazil
• New Delhi Tuberculosis Centre, India
• General Hospital Thoracic Medicine, Thambaram, India
• Thoracic Research Centre, Chennai, India
• Cho Ray Hospital, Ho Chi Minh City, Vietnam
• National Centre for TB and Leprosy Control (CENAT), Kingdom of Cambodia

Human African Trypanosomiasis

• Bristol University, UK
• Cambridge University, UK
• Centre International de Recherche-Développement sur l’Elevage en zone Subhumide (CIRDES), Burkina Faso
• Christian de Duve Institute of Cellular Pathology (ICP-TROP), Belgium
• Drugs for Neglected Diseases initiative (DNDi), Switzerland
• Free University of Brussels, Belgium
• Institut National de Recherche Biomédicale (INRB), DRC
• Institute of Tropical Medicine (ITM), Belgium
• International Livestock Research Institute (ILRI), Kenya
• Laboratoire Vétérinaire de Kinshasa (LVK), DRC
• Leicester University, UK
• Makerere University, Uganda
• Murdoch University, Australia
• National Institute of Medical Research (NIMR), Tanzania
• National Livestock Resources Research Institute (NALIRRI), Uganda
• Obihiro University, Japan
• Royal Tropical Institute, Department of Biomedical Research (KIT), Netherlands
• Seattle Biomedical Research Institute (SBRI), USA
• St. George’s University of London, UK
• Swiss Tropical Institute (STI), Switzerland
• Trypanosomiasis Research Centre-Kenya Agricultural Research Institute, Kenya
• University of Aberdeen, UK
• University of Bordeaux, France
Delivering on the promise

The partners of FIND

• University of Bristol, UK
• University of California San Francisco, USA
• University of Dundee, UK
• University of Geneva, Switzerland
• University of Glasgow, UK
• University of Limoges, France
• University of Texas Southwestern Medical Center at Dallas, USA
• University of Wisconsin, USA
• Centre Neuro-Psycho-Pathologique (CNPP), Democratic Republic of the Congo
  • Hôpital du Roi Baudouin, Kinshasa, Democratic Republic of the Congo
• Centre de traitement de la Trypanosomiase de Maluku, Kinshasa, Democratic Republic of the Congo
  • Unité Mobile de Miabi, Kasai Oriental, Democratic Republic of the Congo
  • Unité Mobile de Tshilenge, Kasai Oriental, Democratic Republic of the Congo
  • Centre de traitement de la Trypanosomiase de Katanda, Kasai Oriental, Democratic Republic of the Congo
  • Centre de traitement de la Trypanosomiase de Dipumba, Kasai Oriental, Democratic Republic of the Congo
• Centro de referencia e Investigação (CRIV) de Vianna, Angola
  • Kalia Health Centre, Urambo District, Tanzania
• National Institute of Medical Research (NIMR) Tabora, Tanzania
• Forecariah (IRD mobile team), Guinea
• Makerere University, Uganda
• National Livestock resources Research Institute (NALIRRI), Uganda
• Institute Nationale Recherche Biomédicale (INRB), Democratic Republic of the Congo
• Kinshasa University, Kampala, Democratic Republic of the Congo

Malaria

• Malaria Consortium, UK
• National Bioproduct Institute (NBI), South Africa
• Queensland Institute for Medical Research (QIMR), Australia
• Royal Tropical Institute (KIT), The Netherlands
• The Hospital for Tropical Diseases (HTD), UK
• University College London Hospital (UCLH), UK
• Centro Internacional de Entrenamiento y Investigaciones Medicas (CIDEIM), Colombia
• Universidad Peruana Cayetano Heredia (UPCH), Lima, Peru
• Kenya Medical Research Institute (KEMRI), Kenya
• Research Institute for Tropical Medicine (RITM), Philippines
• Institut Pasteur de Madagascar
• University of Lagos, Nigeria
• Fakara Health Research and Development Centre, Tanzania
• Institut Pasteur du Cambodge, Cambodia
• Institut Pasteur de Bangui, Central African Republic
• Department of Medical Research, Myanmar
• Ethiopian Health and Nutrition Research Institute (EHNRI), Ethiopia
Commercial or development partners

- Becton, Dickinson and Company (BD), USA
- BioMérieux, France
- Cellestis Ltd, Australia
- Cepheid, USA
- Cibitost GmbH, Germany
- Eiken Chemical Co. Ltd, Japan
- Genovac GmbH, Germany
- Hain Lifescience, GmbH, Germany
- Antigen Discovery, Inc., USA
- LRE Medical GmbH, Germany
- Microcoat GmbH, Germany
- Oxyphen, Switzerland
- Reametrix, India
- TAUNS, Laboratories, INC., Japan
- TBDiaDirect, Sweden
- Zeiss, Germany
- priTest, USA
- Deutsches Krebsforschungszentrum (DKFZ), Germany

Governmental partners and international organizations with whom FIND has signed Memoranda of Understanding

- Ministry of Health of Samara Oblast, Russia
- Ministry of Health of the Kingdom of Lesotho
- Ministry of Health and Social Welfare, Tanzania
- Ministry of Health, Government of the Republic of Uganda
- Ministry of Health, Ethiopia
- Ministry of Health, Kingdom of Cambodia
- Central TB Division, Ministry of Health, Government of India
- African Union Commission, Ethiopia
- Pan African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC)
- Centers for Disease Control and Prevention (CDC), USA
- International Organization for Migration, Switzerland
- World Health Organization, Department of Neglected Tropical Diseases (NTD), Switzerland
- World Health Organization, Regional Office for the Western Pacific (WHO-WPRO), Philippines
- Special Programme for Research and Training in Tropical Diseases (TDR), Switzerland
The Chairman of the FIND Board of Management is Dr. Gerald H. Moeller whose career in healthcare spans some 25 years, a significant part of it in the diagnostics industry. He has been CEO of Boehringer Mannheim Therapeutics and later a member of the Executive Committee of Roche. Today he holds several directorships in biotech companies and healthcare venture capital firms.

Dr. Jan Gheuens is the Senior Program Officer for the Tuberculosis program at the Bill & Melinda Gates Foundation. He was previously with Amgen where he was responsible for clinical trials in more than 35 countries and prior to that with Johnson & Johnson where he spent a decade in product and clinical development.

Professor Bernard Mach is the inventor of cDNA cloning and is specialized in the molecular biology of immune response genes. From Geneva, where he has a long teaching career, Professor Mach is a special member of the Swiss Academy of Medical Sciences and of the French Academy of sciences. He sits on the boards of Serono and Lonza and acts as scientific advisor to a number of institutes and companies.

Dr. Callisto Madavo brings to FIND his long experience with the World Bank where he was most recently Vice-President for Africa. His work has focused on economic growth, poverty reduction and good governance covering country programme experience on all continents. Serving as special advisor to the President of the World Bank he supported key agendas such as the HIV/AIDS initiative.

Dr. Giorgio Roscigno, FIND CEO is an ex officio member of the Board to which he brings his extensive experience in both the pharmaceutical industry and field work and research in tropical diseases. He was one of the founding members of the Global Alliance for TB Drug Development and has been in his current position since FIND was launched in 2003.

During the first five years of FIND, Dr. Peter Small served on the Board. As a global expert in several aspects of TB epidemiology, biology and control, as well as Senior Program Officer for Tuberculosis at the Bill & Melinda Gates Foundation, for the past 5 years Dr. Small has been responsible for developing and implementing the Foundation’s tuberculosis activities. He currently serves as a member of the WHO Stop TB Coordinating Board, and is on the Board of the Global Alliance for TB Drug Development and the Aeras Global TB Vaccine Foundation.
Chief Executive Officer: Giorgio Roscigno

In alphabetical order
Eric Adam: Project Manager and Regulatory Affairs
Audrey Albertini: Scientific Assistant, Malaria Programme
David Bell*: Scientific Officer, Malaria Programme
Sylvain Biéler: Project Manager
Delia Boccia: TB & Poverty Policy Research Officer
Catharina Boehme: Medical Officer, TB Programme
Nora Champouillon: Logistics Officer
Louisa Chaubert: Accounting Manager
Diana Choa: Personal Assistant to CEO
Herbert Clemens: Chief Financial Officer
Rossana Gambin: Human Resources Manager
Iveth J. Gonzalez: Scientific Officer, Malaria Programme
Beatrice Gordis: Communications Officer – HAT & Malaria
Julian Gordon*: Medical Diagnostic Technologies & IP
Solomon Haile Mariam*: Advocacy Officer, HAT Programme
Linda Hinni: Accounting Assistant
Peter Koller*: Quality Manager
Heather Alexander Konopka*: Health Scientist, TB Programme
G. Kubendiran*: TB Control Programme, Lesotho
Evan Lee: Senior Medical Officer
Gerd Michel: Senior Technology Officer
Pamela Nabeta: Associate Medical Officer, TB Programme
Vinand Nantulya: Senior Policy and Implementation Officer
Joseph Ndung'u: Head of HAT Programme
Richard O'Brien: Head of Product Evaluation and Demonstration
Madhukar Pai*: Consultant for latent TB infection
C.N. Paramasivan: Head of TB Laboratory Support
Mark Perkins: Chief Scientific Officer
Antoine Pierson: Senior Manager, Laboratory Support
Bärbel Porstmann: Senior Operating Officer
Magdalena Radwanska: Scientific Officer, HAT Programme
Sharon Saacks: Document Controller
Hojoon Sohn*: LCAT for TB tests
John Sudduth*: IT Support
Ranald Sutherland*: Technology and Business Development
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Jewel Thomas: Communications Officer – TB
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Diego Zallocco*: TM-REST and TB PAN-NET
Delivering on the promise  The FIND team

FIND INDIA

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* Consultants

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ACT</td>
<td>Artemisinin combination therapy</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired immunodeficiency syndrome</td>
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<tr>
<td>AUC</td>
<td>African Union Commission</td>
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<tr>
<td>BCG</td>
<td>Bacille Calmette-Guerin</td>
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<tr>
<td>BMGF</td>
<td>Bill &amp; Melinda Gates Foundation</td>
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<tr>
<td>CATT</td>
<td>Card agglutination test for trypanosomiasis</td>
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<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>CREATE</td>
<td>Consortium to Respond Effectively to the AIDS &amp; Tuberculosis Epidemics</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<tr>
<td>DEC</td>
<td>Disease endemic country</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>DOTS</td>
<td>Directly Observed Treatment Short-course</td>
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<tr>
<td>DST</td>
<td>Drug susceptibility testing</td>
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<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
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<tr>
<td>FM</td>
<td>Fluorescence microscopy</td>
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<tr>
<td>GENETUP</td>
<td>German Nepal Tuberculosis Project</td>
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<tr>
<td>GFATM</td>
<td>Global Fund to Fight AIDS, Tuberculosis and Malaria</td>
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<tr>
<td>GDF</td>
<td>Global TB Drug Facility</td>
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<tr>
<td>GLI</td>
<td>Global Laboratory Initiative</td>
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<tr>
<td>HAT</td>
<td>Human African Trypanosomiasis</td>
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<tr>
<td>HBC</td>
<td>High burden country</td>
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<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>IGRA</td>
<td>Interferon-gamma release assay</td>
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<tr>
<td>INRB</td>
<td>Institut National de Recherche Biomédicale</td>
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<tr>
<td>IVD</td>
<td>In vitro diagnostics</td>
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<tr>
<td>IPT</td>
<td>Ionized preventive therapy</td>
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<tr>
<td>LAMP</td>
<td>Loop-mediated isothermal amplification</td>
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<tr>
<td>LED</td>
<td>Light-emitting diodes</td>
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<tr>
<td>LM</td>
<td>Light microscopy</td>
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<tr>
<td>LTBI</td>
<td>Latent TB infection</td>
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<tr>
<td>mAECT</td>
<td>mini Anion Exchange Centrifugation Technique</td>
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<tr>
<td>MDGs</td>
<td>United Nations Millennium Development Goals</td>
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<tr>
<td>MDR TB</td>
<td>Multidrug-resistant TB</td>
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<tr>
<td>MGIT</td>
<td>Mycobacteria Growth Indicator Tube</td>
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<tr>
<td>MOH</td>
<td>Ministry of health</td>
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<tr>
<td>MTB</td>
<td>Mycobacterium tuberculosis</td>
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<tr>
<td>NAT</td>
<td>Nucleic acid testing</td>
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<tr>
<td>NAAT</td>
<td>Nucleic acid amplification test</td>
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<tr>
<td>NGO</td>
<td>Nongovernmental organization</td>
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<tr>
<td>NHLS</td>
<td>National Health Laboratory Service</td>
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<td>NRL</td>
<td>National Reference Laboratory</td>
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<td>NTM</td>
<td>Non tuberculous Mycobacteria</td>
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<td>PATTEC</td>
<td>Pan African Tsetse and Trypanosomiasis Eradiation Campaign</td>
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<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
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<tr>
<td>PEPFAR</td>
<td>President’s Emergency Plan for AIDS Relief</td>
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<tr>
<td>PDP</td>
<td>Product development partnership</td>
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<td>PPP</td>
<td>Public private partnership</td>
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<tr>
<td>POC</td>
<td>Point of care</td>
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<tr>
<td>RDT</td>
<td>Rapid diagnostic test</td>
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<tr>
<td>ROW</td>
<td>Rest of the world</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
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<tr>
<td>TDR</td>
<td>UNICEF/UNDP/World Bank/WHO Special Programme for Research &amp; Training in Tropical Diseases</td>
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<tr>
<td>TST</td>
<td>Tuberculin skin testing</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>XDR-TB</td>
<td>Extensively drug-resistant TB</td>
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Partnering for better diagnosis for all