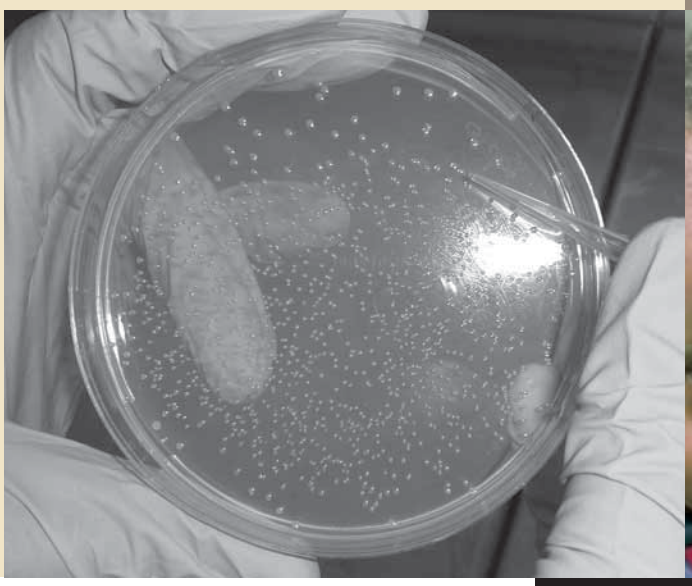

FIND
FOUNDATION FOR INNOVATIVE NEW DIAGNOSTICS

# Annual Report 2006

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# Message from the CEO and Chairman of the Board

*2006 has been a year marked by tremendous development activities and expansion for FIND.*

*We enlarged our business and diagnostics model with the addition of malaria to our existing tuberculosis (TB) and human African trypanosomiasis (HAT) business units.*

*As part of our TB activities, FIND, together with the Special Program for Tropical Disease Research and Training (WHO/TDR), published and launched the first global market analysis report,* Diagnostics for Tuberculosis: Global Demand and Market Potential. *This unique report is considered to be the most comprehensive review of the TB diagnostics market to date. Findings demonstrated that the market for TB diagnostic tools is quite vast and that there exists a significant and largely untapped global market for improved and affordable TB diagnostics in low and middle income countries, where most TB cases occur today. Although roughly US$ 1 billion is being spent each year on TB tests and evaluations, the study pointed out that millions of cases in developing countries still go undiagnosed. The report is available via the FIND and TDR websites.*

*In response to the WHO's urgent call for action to address the emergence of multidrug (MDR) and extensively drug resistant (XDR) TB in the South African region and other parts of the world, FIND accelerated a demonstration study in South Africa, with an enrollment of 40'000 patients, for the evaluation of the Genotype® MTBDRplus and* FASTPlaque Response™ *tests. In addition, the BD MGIT system for rapid liquid culture and drug susceptibility testing (DST) was assessed in four FIND demonstration projects in Russia, Uzbekistan, Nepal and the Philippines. Throughout the year, FIND also advanced the LAMP (Loop-mediated Isothermal Amplification) technology platform being developed together with our Japanese partner, Eiken Chemical Co., a manufacturer of clinical diagnostics. This molecular amplification method reduces the number of steps needed to perform manual nucleic acid amplification, making the test user-friendly even for laboratory personnel with minimal training working in developing countries. LAMP is not only very promising for use in TB but also for HAT diagnosis at point of care level.*

**During 2006, we enlarged our business and diagnostics model with the addition of malaria to our existing tuberculosis (TB) and human African trypanosomiasis (HAT) business units.**

*Several new agreements with various partners were established during the course of the year. FIND initiated collaboration with Cepheid, a broad-based molecular diagnostics company based in the US. The joint project will focus on the development of a new, rapid molecular diagnostic test to detect TB mycobacteria in sputum and simultaneously determine whether the organisms are drug resistant. The test will be designed to run on Cepheid's GeneXpert® System, which is the only closed, self-contained, fully-integrated and automated method for molecular testing commercially available today. We also collaborated with ImmPORT Therapeutics Inc., a California-based company with a leading technology platform for antigen discovery, as well as with the Public Health Research Institute, a not-for-profit research corporation in Newark, New Jersey, to identify TB antigens.*

*Consistent with our commitment to increase and facilitate laboratory preparedness for the introduction of new technologies, FIND and the Government of Uganda signed an agreement during the Clinton Global Initiative in September to support laboratory strengthening and to investigate the opportunity of creating an innovative, sustainable model of laboratory social franchising. In Lesotho, FIND committed to supporting the complete refurbishment of the country's national TB reference laboratory.*

*Regarding FIND's strong functional support, several new staff members were recruited and added to the organization. Dr. Vinand Nantulya was hired in the*

*role of Senior Policy and Implementation Officer to lead FIND's resources mobilization and policy efforts. To consolidate and support FIND's communication and advocacy activities, FIND recruited Beatrice Gordis, Communications Officer, and Jewel Thomas, Communications and Advocacy Coordinator. Dr. C.N. Paramasivan joined FIND in April as Head of TB Laboratory Support. He is also supporting WHO's laboratory strengthening sub-group on a 30% basis. In mid-year, FIND hired Dr. Gerd Michel, formerly a Consultant to FIND, in a full-time role of Senior Technology Officer to oversee research and development of immunodiagnostics across FIND's disease portfolio. The Foundation's ongoing commitment to quality assurance and project management brought on board Dr. Bärbel Porstmann, who came on board as Head of Project Management and Regulatory Affairs. She was also asked to pursue and carry out FIND's application for ISO certification next year. Dr. Joseph Ndung'u, Head of the HAT Diagnostics Programme, joined in May, along with Hanna Yirga, Scientific Team Administrator for HAT. At the end of 2006, Audrey Albertini joined FIND as Scientific Assistant for Malaria Diagnostics. Her responsibilities include assisting the team in all malaria-related tasks. Dr. Madhukar Pai, Assistant Professor of Epidemiology at McGill University, also joined FIND as a consultant for diagnostics for latent TB infection. Please see the section on Human Resources at the end of this report for mention of Dr. Callisto Madavo, who joined the FIND Board of Directors in March.*

*In financial terms, activities for the year ended 31 December 2006 resulted in an excess of income over expenditure for the year of almost $650,000. This surplus was added to the General Reserve of $1.22 million at 31 December 2005, to give a total of just on $1.87 million at the end of 2006.*

*Expenditure incurred throughout 2006 totalled $10,776,000 of which over $9 million (83%) was for analytical and project work (2005 - $3.25 million, or 76%). Expenditure for infrastructure and support was thus reduced from 24% of the total in 2005 to 17% in 2006. Of the $9 million spent on analytical and project work in 2006 almost $5.5 million was for payments to project partners, to whom contract commitments at the end of 2006 amounted to a further $5.6 million.*

*Accounting standards prescribed for the recognition of revenue provide that contributions received from donors are recognised over the grant period set out in grant agreements. In 2006, revenue amounted to $11,423,000 (2005 - $5,109,000), of which almost $3.5 million resulted from shortening the residual grant period of an agreement because of accelerated progress on the development of new diagnostic products.*

*To pursue and accelerate its current projects, FIND received additional funding from the Dutch government, who awarded the foundation a grant of 7.9 million Euros to finance gaps in existing plans and programs for TB, HIV and malaria. FIND's application to the Bill & Melinda Gates Foundation to expand its portfolio to include malaria met with success in the form of a $9.8 million grant to evaluate the performance of existing rapid diagnostic tests for malaria and identify improvements needed in malaria diagnostics.*

*Next year, we look forward to pursuing our efforts to obtain ISO certification for our quality and project management systems. Recognition in this area would be the coronation of more than one year of dedicated efforts. We are also looking forward to submitting our first product data for MGIT and Capilia assays and to further consolidating our technology platforms. Finally, as we renew our efforts with all our partners to accelerate the development of new diagnostic tests for these infectious diseases, we will be paying particular attention to making these technologies accessible to the greatest number of patients at all levels of the health system, but particularly at point of care, where new and affordable diagnostics are most urgently needed.*

Dr Giorgio Roscigno, FIND CEO and Dr. Gerald Moeller, Chairman of the Board





# Major Product Development Activities

## Tuberculosis Programme

### Development of antigen detection tests

In FIND's strategic approach to *M. tuberculosis (M.tb)* antigen assay development, the following key issues were addressed in collaboration with partner companies and public institutions during the year.

#### Chemogen

FIND provided support to the University of Munich (LMU) to conduct a feasibility study on urinary antigen ELISA for the diagnosis of TB developed by Chemogen, a small start-up company in Portland, Maine, USA. The assay is based on an affinity purified, polyclonal rabbit anti-IgG antibody set directed against lipoarabinomannan (LAM) antigen. For the Chemogen prototype, a urine LAM ELISA assay, promising preliminary data showed a sensitivity of 84% in smear positive, 76% in smear negative, culture positive TB patients (HIV positivity in these groups >70%) and a specificity of 99% in 103 healthy Tanzanian controls (Boehme et al. 2005).

By the end of June, 2006, FIND received the final study report on the feasibility study:

- 873 TB suspected individuals and 226 healthy individuals were enrolled at the Mbeya Medical Research Programme (MMRP) in South Western Tanzania between June and November 2005 and followed up between 2 weeks and 5 months, depending on the study group. The sensitivity of the urine LAM ELISA was 62% in smear- and culture- positive patients. The sensitivity of the LAM ELISA in HIV positive smear and culture positive TB patients (79%) was higher than in HIV negative smear and culture positive TB patients (39%). In smear negative, culture positive patients the assay sensitivity was 28% counting positive cultures of typical morphology.
- LAM ELISA specificity was 93% in the non-TB group, consisting of 258 TB suspects with stable recovery without TB treatment and no further suspicion of TB during bacteriological and clinical follow up. In 224 healthy controls the specificity was 99%.
- The feedback from the field site was positive, describing the advantages of being able to use urine as a sample matrix (convenient for patients and lab technicians, good potential in pediatric and extra-pulmonary TB), but sensitivity and specificity results did not meet feasibility target specifications and customer requirements. A further loss in sensitivity has to be expected during reagent transformation into the final lateral flow format.

#### TB-DiaDirect

The group of Professor Ake Svenson at the Swedish Institute for Infectious Diseases Control (SIIDC) in Stockholm, has vast experience with mycobacterial lipopolysaccharides and access to an inventory of anti-LAM producing

*Rapid TB test facility study at UPCH in Peru*

hybridoma cell lines. FIND signed a research agreement with Prof. Svenson on the development of improved monoclonal and polyclonal antibodies against lipoarabinomannan (LAM) that can be used for the detection of TB using urine and/or sputum as sample matrix. The developed reagents will be provided to a manufacturing partner with substantial expertise in lateral flow immunoassay development. So far, the group has grown 9 hybridoma cell lines with high anti-LAM IgG production capacity. 5-10 mg of each of these monoclonal antibodies, as well as of 3 polyclonal anti-LAM IgG antibodies (rabbit polyserum), were purified. The best antibody (AB) candidates will be selected based on affinity/avidity determination by direct immunoassay. Testing of these combinations in well-characterized patient samples will lead to a final identification of the most promising AB binding pairs or cocktails potentially suited for product development.

### Statens Serum Institute (SSI)

SSI have identified a monoclonal antibody, MabTB-3, which in ELISA recognizes 39% of the sputum samples from TB patients, but none in a group of symptomatic non-TB patients. With MabTB-3 as core component SSI will define a panel monoclonal antibodies which in combination give a sensitivity of 70-80%. The planned activities represent a complimentary approach to FIND's collaboration with Proteome Systems. SSI have been known for their existing inventory of more than fifty monoclonal and polyclonal antibodies and purified, partially proprietary M.*tb* antigens, some of which can also be used in FIND's serology projects (see ImmPORT below).

The work is planned to include the following four core activities: antigen discovery, production of antigens, generation of monoclonal antibodies and optimisation of solid phase assay.

### Proteome Systems

In January 2006, FIND signed a research agreement with Proteome Systems, an Australian biotechnology company, aimed at identifying novel protein antigens in vivo (not present in culture filtrate) isolated from sputum samples of patients with active TB. In support of their work, Proteome Systems received sputum samples (1-2 ml each) from FIND/TDR that have been collected from 185 subjects from Uganda, The Gambia, the Republic of South Africa, Brazil and Canada. Matching sera samples (0.5-1 ml each) were also provided for 140 of these subjects. These samples will be used for screening purposes and biomarker/antibody validation. However, there is still a need for additional clinical samples from regions such as China and SE Asia, India, and South America for ongoing test development. FIND will actively pursue sample acquisition at a number of international sites to prevent bottlenecks in this and other projects.

### SBRI-RBC

FIND and the Seattle Biomedical Research Institute (SBRI), in collaboration with Response Biomedical Corporation (RBC), are in the process of finalizing a "Letter of Intent" to provide the basis for an assay development project that makes use of RBC's proprietary RAMP technology for sensitive fluorescent detection in lateral flow assays format. The project aims at rapid point-of-care detection of TB antigens in patient samples. RAMP uses a LFI format with stable, interference-free fluorescent dyes for detection in a small footprint desktop reader currently marketed for cardiology and virology products. FIND's primary goal is to have royalty-free access to this technology and to determine whether this detection system yields the promised benefits of sensitivity and accuracy that would give it an advantage for the detection of antigens or other analytes. The choice of antigens in the current proposal may be substituted for more suitable candidates as they become identified, e.g. from other FIND projects or external sources. Discussions are underway with TAUNS, Godfrey, Svenson, and Wallis on a provision of monoclonals to demonstrate proof of principle for TB antigen detection by RAMP. Alternative quantitative fluorescence (LFI) methods are also under consideration and are currently being pursued.

## Development of antibody detection assays

A recent review by TDR and FIND identified more than two dozen companies marketing rapid serological tests for TB, the great majority of which rely on one or two common antigens. Performance data of these marketed products were very disappointing. When challenged with 300 reference samples collected in controlled studies, none of the 19 products studied showed remotely acceptable performance of the tests with a specificity of more than 90%, none had a sensitivity of over 30% (TDR 2005). The availability of the complete sequence of the M. *tuberculosis* genome led to the identification of approximately 4,000 open reading frames (ORF) coding for the M.*tb* proteome. However, much of the proteome remains unexplored for serodiagnostic potential.

*FIND's mission is to improve global health by developing safe, affordable and easy-to-use diagnostics to fight diseases of the poor at all levels of the health system*

© LHI/TB TB referral lab, Vietnam

*TB referral lab, Vietnam*

The collaboration with ImmPORT is directed towards serological testing of the whole M.*tb* proteome to establish and select a set of antigens for optimal design of a point of care (POC) test.

### ImmPORT

Phil Felgner, in collaboration with the microarray printing unit of UC Irvine, described an empirical approach for identifying diagnostic target antigens and defining immunoreactivity profiles amongst clinically distinct cohorts. This method relies on high throughput amplification of each predicted ORF in the microorganism genome. Protein microarray chips were printed and probed with anti-histidine antibody (against the N-terminal HIS tag) or anti-HA antibody (against the C-terminal HA tag). More than 90% of the proteins were positive for the HIS and HA tags. The unpurified proteins can be printed directly without purification onto microarray chips and the chips used to characterize the humoral immune response profile from infected subjects. A contractual agreement between ImmPORT and FIND was signed in early May 2006 and ImmPORT started expression work to generate the first lot of chips containing approximately 1000 M.*tb* proteins. Training and familiarization work was underway at the serology testing lab in parallel using pre-existing low density arrays. While more than 1200 clinical serum samples have already been collected, the joint ImmPORT-FIND team identified additional needs that being addressed in collaboration with several international collecting sites. It is anticipated that for the whole project, sera from between 2000 and 3000 patients will have to be tested in order to identify subsets of 5-10 antigens for POC product development.

### FIND *M.tb* antigen consortium

FIND resolved that a well-coordinated public sector R&D effort would provide a high probability of:

a) conducting comparative performance experiments of antigens which so far have only been evaluated individually by the discovering investigator;

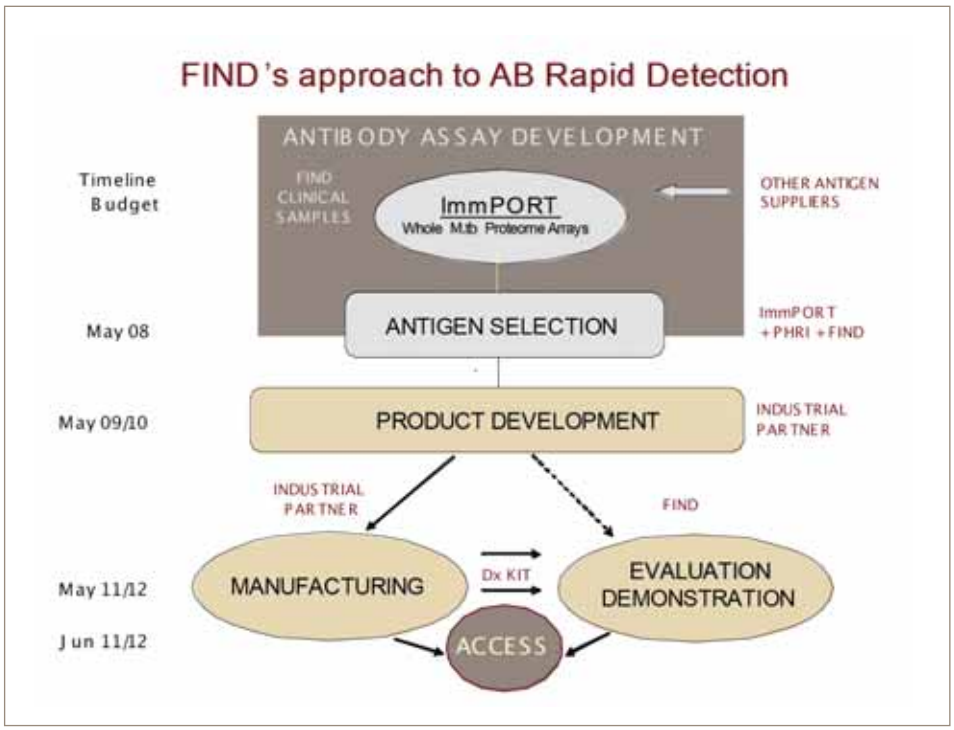
b) determining the best antigens for a POC test; and

c) analyzing and resolving upfront complex intellectual property issues that could jeopardize the successful development and market launch of a multi-antigen test using reagents from various sources.

To achieve these goals, FIND sought to involve scientists and public agencies with experience in this area by creating a consortium with a common platform for shared knowledge and understanding, and exploiting existing intellectual property to maximize both use and impact. These efforts are considered complementary and synergistic to the antigen discovery work conducted at ImmPORT. To initiate the creation of such a consortium, a letter explaining FIND's approach and inviting individual researchers to participate in the consortium was sent out in March 2006. Positive feedback was obtained from Peter Andersen, Maria Laura Gennaro, Suman Laal, Steven Reed, Mahavir Singh and Stefan Kaufmann.

### Carl Zeiss

FIND and Carl Zeiss, one of the leading manufacturers of microscopes, had detailed discussions about developing a low-cost but high quality LED FM. The Zeiss team agreed in principle to the idea of co-developing their existing Primo Star model as a "Zeiss–FIND" brand. Further discussions are taking into careful consideration the IP implications, R&D, manufacturing potentials and customer support, as well as the distribution network with respect to improvements in microscopy production.




*Flow chart of antibody assay development process showing partners, deliverables, time lines and budget. SAC = scientific advisory committee.*



## Development of molecular tools

### Eiken

Under the joint development agreement with FIND, Eiken has modified the LAMP technique and transformed it into a more user-friendly and robust kit format with simplified specimen processing, reaction tubes coated with lyophilized master mix. A small heating unit with 8 reaction wells in an observation chamber has been designed to house the reaction. Clinical feasibility trials started in January 2006 in Bangladesh, Peru and Tanzania. In line with the objective of the study to assess the applicability of LAMP for peripheral laboratories, LAMP was set up in one simple room without laminar flow or hood. Two to three benches served as working areas for sample processing, reaction mix preparation, amplification and detection. Six lab technicians without experience in nucleic acid amplification technologies were trained on LAMP for one week. This was followed by an assessment of the clinical performance of LAMP in 730 sputum specimens from 382 TB suspects (1-2 samples per patient, daily work load 12-24 samples) in comparison with Loewenstein-Jensen (LJ) culture and Ziehl-Neelsen (ZN) microscopy.

**The feasibility studies were completed in May and provided very promising results:**

- The LAMP sensitivity in smear and culture positive sputum specimens was 97.7% (173/177 specimens).
- The sensitivity in smear negative, culture positive specimens was 47.5% (19/40 specimens).
- The specificity in culture negative samples was 99% (509/514 specimens).
- Optimal amplification time for the current LAMP version was found to be 40 min. No indeterminate results were reported for this amplification cut-off and the inter-reader variability was only 0.4%.
- Despite the set-up of LAMP in one simple room, no DNA contamination was observed. The high reading-end-point stability and low repeat rate characterized the assay as quite robust.
- The average hands-on-time for 6 samples and 2 controls was 53 min, thus not longer than for smear microscopy. However, it was perceived to be longer due to the complexity and number of steps of LAMP.
- 2 steps in particular caused major problems and delays of up to 30 min per run: a) transfer of viscous sputum samples to Ex2, and more important b) aspiration of viscous supernatants as this led to blocking of microweb tips.
- Feedback from the study teams was generally positive, but revealed the need for further simplification to allow an implementation at the lower levels of their national health systems.
- Significant potential for simplification has been identified.

### Site-specific LAMP sensitivity and specificity data

| LAMP feasibility studies: Clinical performance | | | | |
|---|---|---|---|---|
| | Sensitivity in ss+, LJ+ | Sensitivity in ss-, LJ+ | Overall sensitivity | Specificity in LJ- |
| Lima | 97.7% (75/78) | 51.8% (14/27) | 84.8% (89/105) | 99.3% (152/153) |
| Dhaka | 98.4% (61/62) | 50% (2/4) | 95.5% (63/66) | 97.8% (181/185) |
| Mbeya | 100% (37/37) | 33% (3/9) | 87.0% (40/46) | 100% (176/176) |
| Total | 97.7% (173/177) | 47.5% (19/40)a | 88.5% (192/217) | 99.0% (509/514) |

*ss = ZN smear microscopy* *LJ = Loewenstein Jenssen culture*

*Preparing sputum samples at UPCH in Peru*

## Next steps:

Provided with the study results, Eiken is currently working on an improved version for which the number of steps will be cut down by 1/3 and the number of electrical devices to a single heating block only. Along with these simplifications, the risk of infection and DNA contamination will also drop considerably.

## Urinary DNA detection

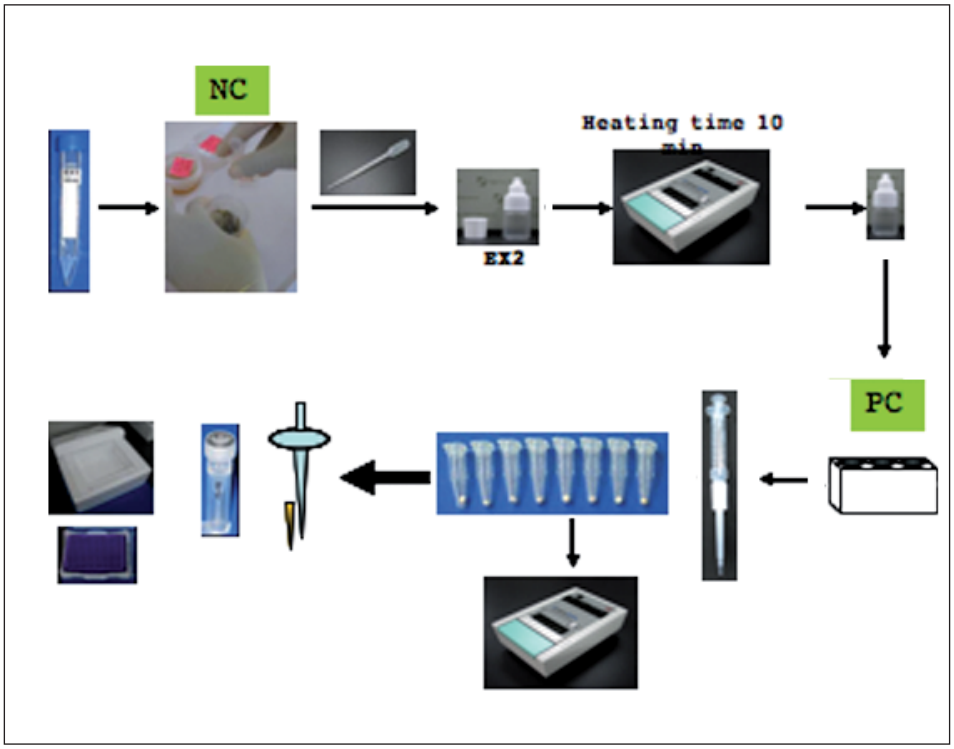
One prong of FIND's molecular detection strategy is to look for methods to detect pathogen DNA in urine. Previous studies of PCR on urine for M.*tb* DNA using conventional primer sets have shown a sensitivity of 30-50%.The finding that DNA from apoptotic human cells was shed in urine in predictable amounts as small (<150bp) fragments suggested that revised targets might increase sensitivity. Proof of principle for this approach has now been established in a limited number of patients.

In February 2006 FIND initiated collaboration with the group of Ali Zumla at University College of London to gather more analytic data on the detection of transrenal DNA fragments of DNA in urine. Under a research agreement ensuring joint ownership of all intellectual property generated, UCL researchers will test the following hypotheses:

a) M.*tb* DNA detected in urine of TB patients is attributable to soluble fragmented DNA.

b) Targeting smaller molecules will improve the detection sensitivity using these samples.

c) Detection of mycobacterial DNA in urine is sufficiently quantifiable to provide a robust diagnostic test.




*Plan for simplified LAMP procedure to be developed by January 2007*

## Cepheid

A fundamental obstacle in the application of molecular methods in developing countries is the complexity of most sample processing protocols. Cepheid, a US microfluidics and microelectronics company, has developed a cartridge-based automated system that holds the promise of fully integrating sample processing, DNA amplification, and target detection.

FIND entered into negotiations with Cepheid in November 2004 based on the strength of GeneXpert technology used in field application of anthrax detection. Preliminary data using this system with molecular beacons as detection molecules for TB and rifampin resistance was developed by Helb, *et al.*[1]

Negotiations between Cepheid and FIND included four face-to-face meetings, four versions of a research and development plan, development of four costing strategies, and multiple conference calls. A final agreement was reached on development of a six-color fluorescent device and real-time PCR assay for TB detection and rifampin resistance determination in May 2006.

The oversight team for the FIND-Cepheid collaboration was composed during a first technical meeting at Cepheid US headquarters in July 2006. A two-year technical workplan for development and beta testing was redrafted at that meeting, including work on the PCR chemistry, on the six-channel instrument, on new in-house proprietary dyes and quenchers, and on an updated software package. Quarterly review meetings are planned.

[1] *Helb D, Jones M, Paul K, Levi M, Eisenach KD, Jones E, McMillan W, Alland D.* Mycobacterium tuberculosis *isolation detection, quantitation, and susceptibility testing in a single hands-free step: Integrating rapid sputum processing with real-time PCR. Poster 2010. Keystone symposium. Tuberculosis: Integrating Host and Pathogen Biology. April 2 - 7, 2005. Whistler, British Columbia*

## Development of assays based on growth detection

### MGIT- MTB

The aim of the MGIT culture case finding projects is to demonstrate the feasibility, scaled-up performance, patient and public health impact, and the cost-effectiveness of using the Mycobacteria Growth Indicator Tube (MGIT) culture system from Becton Dickinson for TB diagnosis of HIV-infected patients in developing countries. Data from these studies will be presented to the WHO Strategic and Technical Advisory Group for TB (STAG-TB) in June 2007 to seek endorsement of rapid liquid culture systems for the diagnosis of TB in low-income settings. The data will also provide ministries of health and other purchasers of TB diagnostics justification to implement these tests in national TB control programs.

In the initial MGIT demonstration projects for case-finding in TB/HIV, FIND partnered with CREATE, the Consortium to Response Effectively to the AIDS/TB Epidemic, a global research and implementation consortium targeting TB control in areas with severe HIV/AIDS epidemics. The purpose of this consortium is to organize, implement and evaluate novel strategies to reduce morbidity and mortality from TB in populations with high rates of HIV and TB co-infection. MGIT technology is being used for improved TB case detection in three CREATE projects in Zambia, South Africa, and Brazil.

The ZAMSTAR study in Zambia and South Africa completed initial screening of approximately 20,000 persons in 24 geographic communities that included MGIT culture. The project then moved to evaluate MGIT culture case-finding among TB suspects in two sites in Zambia. MGIT culture began in early 2006 in the two other CREATE projects, Thibela in South Africa (gold miners) and THRio in Brazil (HIV-infected persons in HIV/AIDS care, see above).

In addition, a MGIT case finding project in Eldoret, Kenya began in mid-2006. This involved the establishment of a new tuberculosis laboratory in a large HIV/AIDS care program (AMPATH) that is following approximately 30,000 HIV-infected persons. This project included an assessment of the new WHO algorithm for the diagnosis of pulmonary tuberculosis in HIV-infected persons. Discussions are continuing with the Tanzania National Tuberculosis and Leprosy Program and the CDC Global AIDS program about a similar project at two Tanzanian sites.

### MGIT- DST

FIND is also assessing MGIT culture and drug susceptibility testing (DST) for the rapid diagnosis of patients with multidrug-resistant TB. Alarming increases in MDR TB, which is not treatable with the currently available first-line anti-tuberculosis drugs, have been found in a number of countries throughout the world. In response to this problem, the WHO Stop TB Department has established the DOTS-Plus strategy and the Green Light Committee (GLC), a mechanism to provide second-line anti-tuberculosis drugs to programs that qualify to undertake MDR TB treatment. However, a major impediment to expansion of MDR TB treatment is lack of DST capability in many programs. To address this problem, FIND is working with WHO and other technical partners to implement MGIT DST demonstration projects in DOTS-Plus sites. The purpose these projects is to assess the implementation of MGIT rapid culture and DST in low-income settings. Specific objectives are:

- To assess the feasibility of implementing MGIT culture and DST for MDR TB diagnosis in low- to moderate-income settings;
- To evaluate the impact of rapid culture and DST on time-to-reporting of results and initiation of proper treatment;
- To assess the impact of MGIT diagnosis on sputum smear and culture conversion times;
- To measure MGIT performance in this context (sensitivity and specificity, and case detection rates) compared to LJ; and
- To evaluate detailed costs associated with MGIT for tuberculosis culture diagnosis and DST in comparison with conventional methods on solid media.

Three projects in Uzbekistan, Nepal, and the Russian Federation were initiated in early 2006 with assistance from MSF-Holland and GENETUP, a German non-governmental organization working in Nepal, and the UK Health Protection Agency. A fourth project at the Tropical Disease Foundation in Manila, the first GLC-approved DOTS-Plus site began in July 2006. Data from these projects will also be presented to STAG-TB in June 2007.

### *FASTPlaque*TB Test

After two years of rigorous development work, problems of inadequate sensitivity, excess sample-to-sample variability and complex processing remained important obstacles to

meeting targets for a phage-based case detection test. In December 2005 the decision was made to halt further development activities for the case detection assay. Support continued in 2006 to fund an ongoing trial in Khayelitsha, South Africa to evaluate the clinical sensitivity of the final modification in the methodology supported by FIND. After data from a total of 181 specimens were reviewed in an interim analysis, the trial was suspended due to concerns relating to the specificity of the revised test method. The specificity of the test was only 85%, versus 98% with the previous version. Given the difficulty addressing the major developmental problems, and the high risk of ongoing investment, FIND removed the case detection test from its active portfolio.

### *FASTPlaque-Response* Test

The *FASTPlaque* assay from Biotec Ltd. is a phage replication assay that permits the diagnosis of rifampin-resistance (as a surrogate for MDR-TB) within 48 hours. A FASTPlaque study – "Phase III Trial Comparing Four Alternative Methods for Drug Susceptibility Testing of M.*tb* with Gold Standard in Patients with Smear-Positive Pulmonary Tuberculosis" – was conducted by investigators from the Instituto de Medicina Tropical "Alexander von Humboldt" at the Universidad Peruana Cayetano Heredia and the Instituto Nacional de Salud in Lima, Peru.

### Capilia TB

An easy, faster and more robust solution to the traditional phenotypic method of identifying M.*tb* has become available in the form of Capilia TB, an assay which detects MPB 64 antigen that is specifically present only in the organisms belonging to M.*tb* complex strains grown either in liquid or solid media is a simple and rapid immunochromatographic lateral flow method. This test requires neither a sample processing procedure nor any instrumentation. The sensitivity and specificity of this test has been reported to be similar to nucleic acid probe-based methods with a turn-around time of less than 15 minutes. Capilia TB is produced by the Japanese company Tauns Laboratories, Inc. and has, so far, only been available at a high price for the Japanese market.

FIND is currently in the process of negotiations with the company and plans to promote Capilia as a simple, rapid and inexpensive M.*tb* confirmation assay in combination with the MGIT culture system for case detection and drug susceptibility testing. Capilia's operational and clinical performance still needs to be evaluated in more strains from Africa, Asia and South America, in developing country settings and in view of the customer requirements. Laboratory comparison of Capilia TB performance with routine speciation methods within the framework of MGIT demonstration trials at CREATE sites is ongoing. Evaluations of this test in three high volume laboratory settings in Asia have been planned. The TB Reference Laboratory in Borstel, Germany, is evaluating Capilia in collaboration with FIND on >100 strains from different geographical settings.

### TK Medium

TK Medium (Salubris, Inc, Cambridge, MA) is a novel, solid mycobacterial growth media that supports rapid growth of M.*tb*. Initial evaluations of the TK Medium in Turkey indicated that the culture system is as sensitive as the Lowenstein-Jensen (LJ) medium; the most widely used solid culture system in the world, and has a much more rapid time to detection, approaching that of liquid culture systems that are the standard for TB diagnosis in industrialized countries. Based on reported results by Salubris using clinical specimens at a chest disease hospital in Turkey, FIND decided to proceed to "clinical" studies in Rio de Janeiro and Cape Town being coordinated by investigators from Johns Hopkins University with USAID funding. However, based on results of a small pilot study in Cape Town in January 2006 and data from Turkey (not shared with FIND), Salubris concluded that it was unable to produce a quality product in a consistent way and that moving to the clinical studies was destined to failure. Thus, plans for the Johns Hopkins studies were canceled and FIND's plans for similar assessments at three mycobacteriology laboratories in North America were put on hold indefinitely. FIND concluded that unless Salubris is able to identify a suitable manufacturing partner, aditional support for this project is not advisable.

## Detection of latent TB infection

An estimated one third of the world's population is infected with *Mycobacterium tuberculosis*. This enormous pool of individuals with latent tuberculosis infection (LTBI) poses a major hurdle for the elimination of TB. Treatment of persons with LTBI, including those with HIV coinfection, effectively reduces the risk of progression from LTBI to active disease, but there is currently no accurate tool to predict which latently infected individuals are at greatest risk of disease progression. For nearly a century, the tuberculin skin test (TST) was the only tool available for the detection of LTBI. Although the TST has proven to be useful in clinical practice, it has known limitations in accuracy and reliability.

A major breakthrough in recent years has been the development of *in vitro* assays that measure T-cell release of interferon- (IFN- ) in response to stimulation with highly M.*tb*-specific antigens. In contrast, the TST is based on the cellular immune response to purified protein derivative (PPD), a crude mixture of proteins from heat-killed M.*tb*. Within a short span of time, two IFN- release assays (IGRAs) have become commercially available: the QuantiFERON-TB Gold® assay (Cellestis Ltd, Carnegie, Australia) and the TSPOT.TB® test (Oxford Immunotec, Oxford, UK).

With the availability of standardized IGRAs, there is great interest in using these assays in variety of settings. Current evidence suggests IGRAs have higher specificity than the TST, better correlation with surrogate markers of exposure to M.*tb* in low incidence settings, and less cross-reactivity due to BCG vaccination and sensitization by non-tuberculous mycobacteria (NTM) than the TST. IGRAs also appear to be at least as sensitive as the TST for active tuberculosis (used as a surrogate for LTBI). In the absence of a gold standard for LTBI diagnosis, sensitivity and specificity for LTBI cannot be directly estimated. Besides high specificity, other potential advantages of IGRAs include logistical convenience, need for fewer patient visits to complete testing, avoidance of unreliable, and somewhat subjective, measurements such as skin induration, and the ability to perform serial testing without inducing the boosting phenomenon. Overall, because of its high specificity and other potential advantages, IGRAs are likely to replace the TST in low-incidence, high income settings where crossreactivity due to BCG might adversely impact the interpretation and utility of the TST.

The body of literature supporting the use of IGRAs has rapidly expanded. However, despite a growing evidence base, several unresolved and unexplained issues remain. These include unexplained discordance between the TST and IGRAs results, ill-defined correlation between bacterial burden and T cell responses, unknown predictive value of IGRAs for the development of active TB, insufficient data on test performance in high-risk populations such as children and individuals with HIV infection, inadequate information on IGRA performance in serial testing, and lack of evidence on the utility of IGRAs in epidemiologic studies. Scientific knowledge gaps are matched by the paucity of data pertaining to the feasibility, applicability, cost effectiveness, and potential utility of these assays in high incidence and resource limited settings.

An international effort is required to address knowledge gaps efficiently, and, to this end, an expert group was assembled in Geneva (March 2006) by the Stop TB Working Group on New Diagnostics. The meeting was organized by FIND and the World Health Organization (WHO). The group was charged with reviewing the research evidence supporting the use of IGRAs, their clinical utility, their limitations, and directions for future research, with a specific focus on resource-limited settings. The overarching goal was to move the field forward by identifying critical areas for research and implementation.

Based on two days of presentations and discussions, a comprehensive research agenda was generated, which is intended to stimulate focused, high-impact research and encourage the investment of resources needed to tackle priority research questions, especially in resource-limited settings. The research agenda included key questions grouped under seven headings:

1) Biologic issues and assay development
2) Test performance in high risk populations and poorly studied groups
3) Risk prediction and modeling
4) Reproducibility and serial testing
5) T cell responses during treatment and role in treatment monitoring
6) Epidemiologic and field applications
7) Health systems, operational and economic research.

A comprehensive report based on the research agenda has been submitted for publication. Once published, this document will be widely disseminated.

During the meeting on LTBI Diagnostics, FIND and Cellestis, Ltd. announced that they had signed a Letter of Intent to jointly undertake work to evaluate the QuantiFERON-TB Gold® (QFT-G) assay in public health settings in high burden countries. FIND stated that it would work with national Ministries of Health and TB control programs on projects in which the impact and cost-effectiveness of this test are to be assessed. The initial studies are likely to involve the evaluation of the test in people with HIV, or who are living in a household or community with active TB patients, since they are at high risk of developing active tuberculosis through exposure.

Cellestis Ltd. agreed to grant FIND rights to make the QFT-G test available at an affordable price in the public health sector of developing countries. In return, FIND will aim to provide these products at the lowest possible price. The partnership with FIND will provide the critical support to speed up evaluation and demonstration of the QFT-G diagnostic, including clinical materials and assistance with field trials, in high burden developing countries.

Subsequent to this announcement, FIND received unsolicited proposals from two CREATE projects, ZAMSTAR and THRio that are sites for FIND-supported MGIT culture demonstration studies (see below). The proposals address research priorities identified during the March LTBI meeting and take advantage of established research infrastructure and population groups that have been enrolled into CREATE TB/HIV intervention studies.

ZAMSTAR is a large community-randomized trial that is evaluating


Photo courtesy of Dr. Madhukar Pai

*Screening of household childhood contacts for TB infection in a village in India (blood being drawn for QuantiFERON-TB Gold In Tube)*

different approaches to reduce the transmission of TB in communities and households. One of the outcome measures is to follow prospectively the household members of TB patients in 150 households in each of the 24 study communities. These "secondary outcome cohorts" (SOCS) consist of about 10,000 individuals who will be followed for three years. The aim of the ZAMSTAR QFT-G study is to use the SOCS cohort to compare the utility, feasibility and costs of QFT-G and TST tests in resource poor settings. The specific study objectives are to:

- Compare the cumulative incidence of TB for the two-three years following exposure in individuals with positive and negative QFT-G and TST tests, stratified by HIV status and sputum smear microscopy of the index case and HIV status of the contact;
- Compare the age specific prevalence of QFT-G and TST test results in HIV positive and negative tuberculosis patients and their contacts;
- Measure conversion and reversion rates of QFT-G and TST over a three year follow-up period;
- Determine the reliability and reproducibility and the proportion of indeterminate and "failed" QFT-G tests when applied on a large scale in a resource poor setting; and
- Determine the health system costs of applying QFT-G on a large scale and comparing these to the costs of using tuberculin skin tests.

The THRio study is a cluster-randomized trial to determine if the routine detection and treatment of LTBI in HIV infected patients receiving routine care, including antiretrovirals, in HIV clinics in Rio de Janeiro, Brazil, will reduce TB incidence in that population. The intervention consists of implementing a comprehensive



policy of screening for and treating LTBI with isoniazid in all HIV-infected patients. Operationally, all eligible patients receive a TST at baseline, and those with a negative TST are retested annually. Those with a positive result are offered isoniazid preventive therapy. The trial is taking a phased-implementation approach to ensure that all participating clinics will eventually have full coverage. The THRio study will phase in 29 HIV clinics over a 29-month period (2 clinics every 2 months) to begin implementing the TST/isoniazid preventive therapy policy.

The central component to the success of THRio study is the reliability of the TST for detection of LTBI. The study offers a unique opportunity to compare the sensitivities of TST and QFT-G for detection of LTBI among HIV-infected individuals, and thereby to contribute to a better understanding of optimal strategies for TB prevention among high-risk populations. A priori estimates based on the literature from the Brazilian surveys indicated that 35% of HIV-infected patients would be TST positive. As of April 2006, six of 29 clinics have begun the TST intervention and only 15% of the population has had positive TST results. Thus, as high as 20% of patients receiving TSTs may actually have false-negative TST results.

The primary objective of the THRio QFT-G study is to determine and compare the cumulative incidence, over a two-year follow-up, of active tuberculosis among TST-negative/QFT-G-positive persons versus TST-negative/QFT-G-negative persons. Secondary objectives are to:

- Determine the utility, feasibility and cost effectiveness of QFT-G in an HIV- infected population undergoing routine screening in the context of a public health system;
- Determine the proportion of concordant and discordant test results when TST and QFT-G are used together to assess for LTBI. Results will be stratified by CD4 count;
- Estimate the impact of HAART on qualitative and quantitative QFT-G results, and
- Estimate the predictive value, for active TB, of QFT-G quantitative results or the change over time in QFT-G quantitative results.

In addition to the these two QFT-G studies, FIND discussed with the Aeras Global TB Vaccine Foundation possible support for an assessment of the QFT-G test as a diagnostic aid in evaluating between 1200-1600 young children for active TB. This study would be nested in two vaccine studies in South Africa and India that will enroll and follow for two years large cohorts of BCG-vaccinated infants. Including QFT-G testing in this group of subjects presents a unique opportunity to evaluate the test as a diagnostic for pediatric tuberculosis.

## Human African trypanosomiasis programme (HAT)

### Addressing the diagnostic challenge

Since its launch in early 2006, FIND's human African trypanosomiasis (HAT) or sleeping sickness diagnostics programme, implemented jointly with the World Health Organization (WHO), has established linkages with industry, academic and research institutions in both developed and endemic countries. Projects have been initiated to enable the development of more user-friendly and accurate point-of-care (POC) diagnostic tests.

*Launch of the HAT diagnostics project in February 2006*

### Activities

Several projects were launched in 2006 that are expected to significantly facilitate the development of better and affordable diagnostic tests for HAT. These are progressing well and four areas of emphasis have been identified: improvement in *parasite separation from blood and cerebrospinal fluid* (CSF), *serological assays, molecular tests, and staging biomarkers*. The partnership with the World Health Organization (WHO) will lead to the collection of biological materials from sleeping sickness patients, and strengthening of field clinical trial sites, both crucial elements in the development and evaluation of diagnostic tests.

*HAT Project Management Meeting, November 2006*

### Parasite detection

FIND is working with the Institute of Tropical Medicine (ITM) in Antwerp, Belgium, and a number of other companies to improve some of the components of the most sensitive method for detection of trypanosomes in blood known as the mini Anion Exchange Centrifugation Technique (mAECT). Although several attempts to produce the mAECT kit in Africa have been made, they have always been met with problems of sustainability. A mAECT production unit at the Institut National de Recherche Biomédicale (INRB) in Kinshasa, Democratic Republic of Congo, will be upgraded and local staff trained to produce and market the kit in disease endemic countries. The upgrading will include training, implementation of a rigorous quality control system, and in-depth analysis of costs to guarantee sustainability of production.

The mAECT* kit is problematic for use in low income countries and in many field conditions. To address this limitation, FIND is working closely with several of its partners to determine the feasibility of developing an alternative technique to disclose parasites that will be more sensitive and simpler to perform than mAECT. Some of the options under consideration include the use of other gels, separation in an electric or magnetic field, membrane filtration, density separation, biosensors and fluorimetry, among others.

### Serodiagnosis

FIND is working to determine the feasibility of developing another serological method that is simpler, more sensitive and more specific by using purified, recombinant or synthetic antigens rather than whole organisms. The project involves selecting candidate antigens amongst those that are currently available, rather than investing in a discovery phase. Scientists and laboratories with such antigens are collaborating with FIND in screening recombinant and synthetic peptides for their potential for diagnosis of *T.b. gambiense* and *T.b. rhodesiense*, the two forms of African sleeping sickness. FIND is also exploring the feasibility of using camel heavy-chain antibodies (nanobodies) (in collaboration with the Institute of Biotechnology at the University of Brussels, Belgium) or RNA aptamers (with the Department of Genetics at Darmstadt University of Technology in Germany) in tests to detect parasite antigens.

* The *mini Anion Exchange Centrifugation Technique* (mAECT) is the most sensitive method for detection of trypanosomes in blood. This method involves separating trypanosomes from venous blood by anion exchange chromatography and concentrating them at the bottom of a sealed glass tube by low speed centrifugation (3000 rpm).

## Molecular tests for diagnosis

FIND entered an additional collaboration with Murdoch University in Australia, as well as 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* are being designed while tests are being optimized using DNA from various members of the sub-genus *Trypanozoon*. The most sensitive and specific primer sets will be validated using samples from HAT patients. Determination of the reproducibility of the tests in laboratories based in the endemic regions will be carried out. This work is anticipated to give sufficiently promising results to support adaptation of the LAMP technique for diagnosis of HAT.

## Developing tools for disease staging

FIND started a project to examine the feasibility of developing new tests for staging disease staging, and for treatment follow-up. Special attention is being given to speed, simplicity, cost, and reliability of the new tests, as well as reduced invasiveness. In 2006, FIND commissioned a review of the current status of development of staging methods, and the prospects for their improvement. This was followed with a meeting of experts, which recommended a request for applications to explore new staging techniques from our academic partners. Results and a review of responses will be published in 2007. This will be advertised in early 2007.

## Specimen bank

Some critical obstacles in the development of improved assays for HAT, or sleeping sickness, include access not only to quality diagnostic and clinical data, but also 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 WHO Department of Neglected Tropical Diseases (NTD) are now addressing these problems by establishing a HAT specimen bank, which will be owned by the WHO. This will guarantee more efficient use of limited resources, reduce the need for field trials, promote product comparisons and facilitate quality control.

The specimen bank is to include samples from:

- People who are asymptomatic but at risk of infection (screened populations in a HAT focus);
- HAT suspects who have not been confirmed parasitologically (positive screening test results but no evidence of parasites);
- Patients in whom disease has been confirmed; and
- Control subjects (negative screening test results and no evidence of parasites).

Photo courtesy of Veerle Lejon

*Technicians performing the card agglutination test for trypanosomiasis (CATT) on human blood*

## Malaria programme

Today, malaria is one of the greatest global threats to public health, causing over 300 million cases of acute illness worldwide. The disease results in over a million deaths each year, with 80-90 percent of these in sub-Saharan Africa. Billions of dollars are lost each year in low productivity due to malaria. In countries with a heavy malaria burden, the disease may account for as much as 40% of public health expenditure, and up to half of outpatient visits and inpatient admissions.

In 2006, FIND received a US$ 9,840,000 grant for a 5-year period from the Bill and Melinda Gates Foundation to establish standard protocols and methods to evaluate commercially available rapid diagnostic tests (RDTs), along with a network of laboratories and reference materials for testing RDTs. Devices for monitoring the quality and performance of RDTs in the field (positive control wells) are also being developed. Work on development of new point-of-care diagnostics for malaria is underway, along with research on RDT use to develop a business plan for improvements in quality and accessibility of RDTs.

*A rapid diagnostic test showing positive result for malaria in a blood sample*

### Projects in the Malaria Programme

#### Project 1: Extending LAMP Molecular Diagnosis platform to Malaria

The LAMP technology is a novel platform being developed for a relatively wide number of pathogens of all classes. Development of an optimized product, however, will require a more considered understanding of optimal target sequences, minimization of sample handling steps, and optimization of reagents to take manufacturing issues into consideration. FIND is engaged with the Hospital for Tropical Disease (HDT) in London to design and select appropriate amplification targets for all four species of malaria, develop optimized sets of species-specific primer sets, demonstrate proof of performance, optimize sample preparation, and validate data against existing assays to provide limits of detection, species specificity, and reaction time cut-offs. Year 1 spending was slowed because it turned out that sequencing work was required in order to allow primer design.

However, lysis experiments will be carried out in parallel to the sequencing work. Once the activities described above are accomplished, completion of assay development will require field testing at several sites (South America, Africa, and Asia), which is planned for year 2.

#### Project 2: Improving Antigen – Dipstick for Malaria

Many currently available RDTs have reasonable sensitivity in patients with parasite burdens of over 100-200 parasites/µl, but with lower levels of parasitemia their sensitivity decreases. Other drawbacks to current tests, particularly those detecting HRP2, include persistence of the target antigen, and restricted reactivity of capture or detection reagents due to geographic variability in target antigen epitopes. Lastly, and perhaps most importantly, many of the currently available tests are not stable at temperatures higher than 25-30 degrees C. Thermo-instability is a critical issue leading to variable performance in field settings.

FIND is working with the Royal Dutch Tropical Institute (KIT) 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. As this work stream continues, FIND will also begin collaboration with the Queensland Institute of Medical Research by year 2 to further determine the range of sequence variability in particular Histidine Rich Protein II (HRP2) and to propose alternative similar or duplicate targets to decrease the diagnostic impact of this variability.

## Challenges

**Technical obstacles:**
The technical obstacles to TB detection mentioned in the 2005 report are still being addressed. Some of the technology challenges (need for exquisite analytic sensitivity and to combine ease of use with sophisticated chemistry, large dynamic range, and low manufacturing costs) are being met by the emergence of novel methodologies and technologies.

**Sample processing:**
Several technologies in the FIND portfolio have strong proof of principle using experimental materials but become insensitive or difficult to use when applied to raw clinical material, especially sputum. Sputum processing remains a formidable challenge and one that FIND expects to address in a project renewal proposal to be submitted to the BMGF in 2007.

**Fundamental knowledge gaps:**
Missing biologic information significantly complicates test design. The types of missing information include such data as: What bacterial products are shed into blood and/or urine in TB disease, and in what quantity? How does state of disease or co-infection with HIV affect the shedding of such products? What variables (geographic, racial, strain variability or exposure to BCG or environmental mycobacteria) are relevant to diagnostic antibody responses to TB disease?

**Relative weakness of small partners:**
This was mentioned in the 2005 report, and is being addressed through work to link smaller companies with larger corporate partners.

**Specimen bank:**
Access to reliable reference materials is fundamental to many of the projects in FIND's pipeline. The decision by TDR to dissolve the Specimen Bank Steering Committee on which FIND sat and to increase the cost of specimen aliquots 18-fold from $5 to $90 illustrates the impracticality of continuing to rely on TDR as a source of materials. FIND has resolved to develop its own collection of reference materials to drive test development and validation.

**Positioning FIND products for global access:**
FIND aims to ensure that new diagnostic technologies achieve wide distribution to under-privileged patients in the public health sector as well as the non-profit private sector, including civil society organizations. These two sectors are the main TB service providers in developing countries.

To assure global access, FIND engages developers and national TB control programs throughout the different phases of the product value chain: development, evaluation, demonstration, policy and access.

The first three phases cover the work carried out by FIND in collaboration with developers to produce diagnostic tests that meet the criteria of certifying authorities. For each project, the first three phases are typically covered by a contract between FIND and its partner, and include an intellectual property strategy. This protection takes the form of a fully paid-up, royalty-free, irrevocable, and exclusive license for access to the product at an affordable price in the public, as well as locally-registered and recognized non-profit, health sector in developing countries. The project partner takes the distribution rights to all other markets. In addition, FIND reserves the right to use a toll manufacturer if necessary to ensure an affordable product.

Apart from securing an affordable product, FIND will ensure the tests will be made readily available to reach the greatest number of patients at the most remote level of the public health systems. For this reason, FIND aims to develop POC technical solutions that are not only simple and accessible but will most easily bridge the gap between patients and the health system itself by bringing technologies to the patient rather than patient to technologies.

Policy is based on global-level guidelines formulation aimed at ensuring that the product achieves the widest possible recognition through approval by validating agencies. For this purpose, FIND involves the WHO and similar licensing authorities, as well as national organizations in developing countries, in broad partnerships throughout the course of demonstration so that the product meets quality criteria and can be included in WHO guidelines and recommendations. Access is achieved when distribution of the test to the public sector is made possible through public health tenders. This is accomplished by working with national health programs and civil society in the public health sector, and is sustained by general advocacy with donors and the community at large.

Adoption of new tools, however, depends ultimately on the preparedness and willingness of countries to use the tools. To this end, FIND's strategy includes the engagement with national

programs and civil society throughout the four phases. At the development phase, national TB programs and civil society participate in the development of customer requirement documents to ensure relevance of tools to the needs of national programs and user groups. This document forms the basis for choice of technological platforms for the different levels of the health system.

At demonstration phase, communication with Ministries of Health and national programs, patient advocacy groups, and other key partners at global and national levels about product pipeline and progress is critical for accelerating adoption of tools as they become available. Forums to share results at country level to inform the stakeholders about progress and to obtain their input and support is critical both for success of demonstration trials and for preparing the ground for uptake of new tools when they become available. To foster stakeholder participation, FIND has established policy that requires demonstration projects to involve local stakeholders through formation of local Project Advisory Committees.

At the global policy level, the global partners need continuous update on tools in the pipeline, and progress towards introduction of new tools into disease control programs. The full dossier on the results of evaluation and demonstration needs to be shared with the Stop TB Taskforce for "Retooling" and WHO for consideration to include new tools in policy guidelines.

## Advocacy, communications and resource mobilization

### Progress and Achievements:

The Bill and Melinda Gates Foundation contracted Ogilvy Public Relations Worldwide to work with its grantees to strengthen their capacity to be effective advocates for their own work. As a first step, Ogilvy conducted a communications audit of each grantee, including FIND. All recommendations were implemented throughout the year.

### Communications:

Some key developments in 2006 included the:

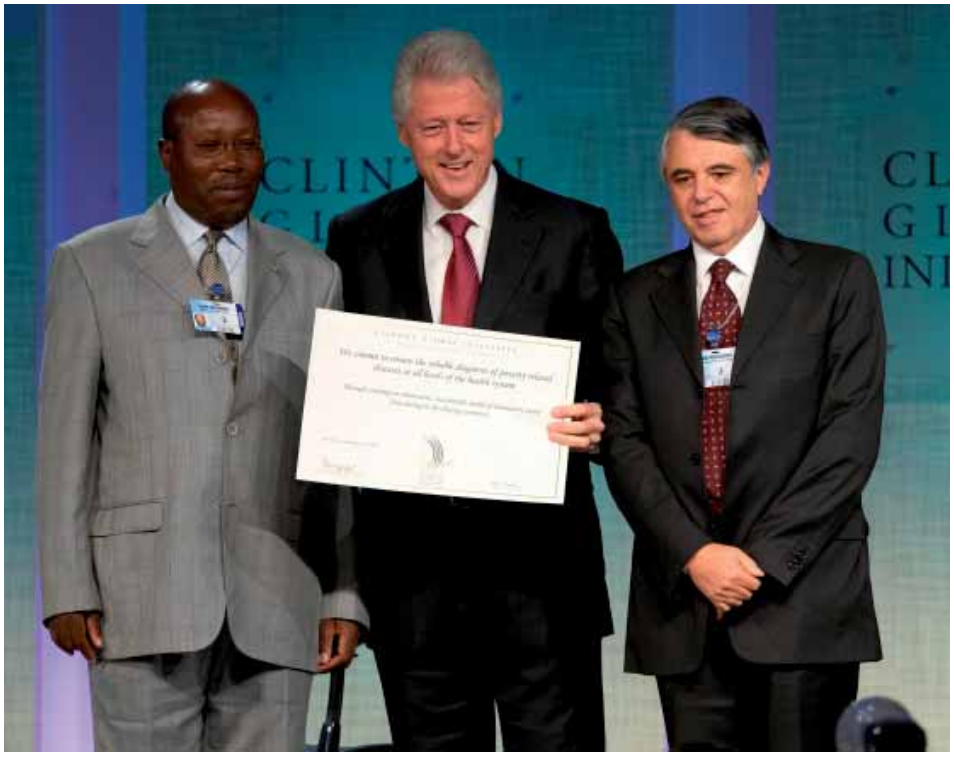
- Development of FIND's communication strategy.
- Re-design and continuous improvement of the FIND website.
- Development of a crisis communication manual. FIND staff also benefited from a special workshop organized by Ogilvy.
- Publication of two FIND newsletters *(policy is to make it a quarterly)* and 14 press releases issued. These are available on the FIND web site.
- Design and production of a FIND leaflet for distribution at various conferences.
- The report *Diagnostics for Tuberculosis: Global Demand and Market Potential*, a joint effort between WHO's Special Programme for Tropical Disease Research and Training (WHO/TDR) and FIND, was published in October 2006. Prior to its launch, FIND organized special partner and media calls.
- Organization of a FIND booth, advocacy and scientific presentations, at the Geneva Global Health Forum in August 2006, as well as during the annual conference of the International Union against TB and Lung Disease in October 2006 in Paris, France.

*Dr. Giorgio Roscigno and Dr. Vinand Nantulya answering questions from reporters after the XDR-TB press conference at the Centre d'Accueil de la Presse Etrangère in Paris*

*Dr. C.N. Paramasivan (FIND Head of TB Laboratory Support), Dr. Madhukar Pai (Assistant Professor, Department of Epidemiology, Biostatistics & Occupational Health at McGill University) and Dr. Antonino Catanzaro (Professor of Medicine at University of California San Diego Medical Center)*

*STOP TB Working Group on New Diagnostics annual meeting, Paris, 1 November 2006*

**Partnership building:**
FIND is continuing to build partnerships, and participating in various events and conferences to promote and advocate for the need for increased investments in diagnostic technologies. The foundation's efforts in this area have included collaborating on a regular basis with other product-development partnerships such as MMV, DNDi, Aeras, the TB Alliance and the STOP TB Partnership. FIND continues its efforts on positioning its products for inclusion in global policy guidelines as they become available, through strategic partnerships with civil society, WHO/STOP TB, The Global Fund, national control programs, governmental and private donors (bilateral and multilateral).



*Former President Bill Clinton flanked by Dr. Sam Zaramba, Director of Health Services at the Ministry of Health of Uganda and Dr. Giorgio Roscigno at the Clinton Global Initiative 2006 Annual Meeting in NYC*

**Resource mobilization activities and fundraising initiatives included:**

- Several meetings and briefings in the United Kingdom, held with DFID ministers, Principal Private Secretary of the UK Prime Minister, shadow cabinet members, Members of House of Lords and House of Commons, senior staff at Wellcome Trust, and Medical Research Council. FIND expects substantial funding from the UK Government during the year 2007.
- Fundraising efforts with the Dutch Government were successful. FIND was awarded 7.9 million by the Dutch Government to develop improved diagnostics for TB, HIV and malaria.
- The funding by USAID of one full-time position (shared between FIND and WHO) to work on laboratory strengthening activities.
- An award of 200,000 from the European Union.
- Concerted efforts are under way targeting Irish AID and Canadian CIDA.
- Evaluation of FIND's profile was made with support from a Google grant.
- Through the Clinton Global Health Initiative, resources were raised to test a social franchising model for laboratory accreditation.

**Media Relations:**
To increase the awareness of its work and the need for new tools globally, FIND has successfully strengthened its media relations, particularly in Geneva, Switzerland, where it was featured for the first time in two Geneva papers, l'AGEFI and the Tribune de Genève. News about FIND's recent malaria grant was broadcast on World Radio Geneva, the main English radio station. FIND is continuing to build its media relations, both locally and internationally.To accelerate the move from policy to access, FIND uses a Public Health Advisory Committee which provides advice on customer requirements throughout the project cycle as technologies move from development and evaluation to access. As part of the Public Health Focus Area Commitments, FIND's and the Ugandan Government's Commitment to improve diagnostic services in developing countries through the creation of an innovative and sustainable model of laboratory social franchising was highlighted at the Clinton Global Initiative 2006 Annual Meeting in New York.

**Diagnostic platforms:**
The broad vision of the TB programme has remained unchanged. FIND has continued to refine its strategic approach

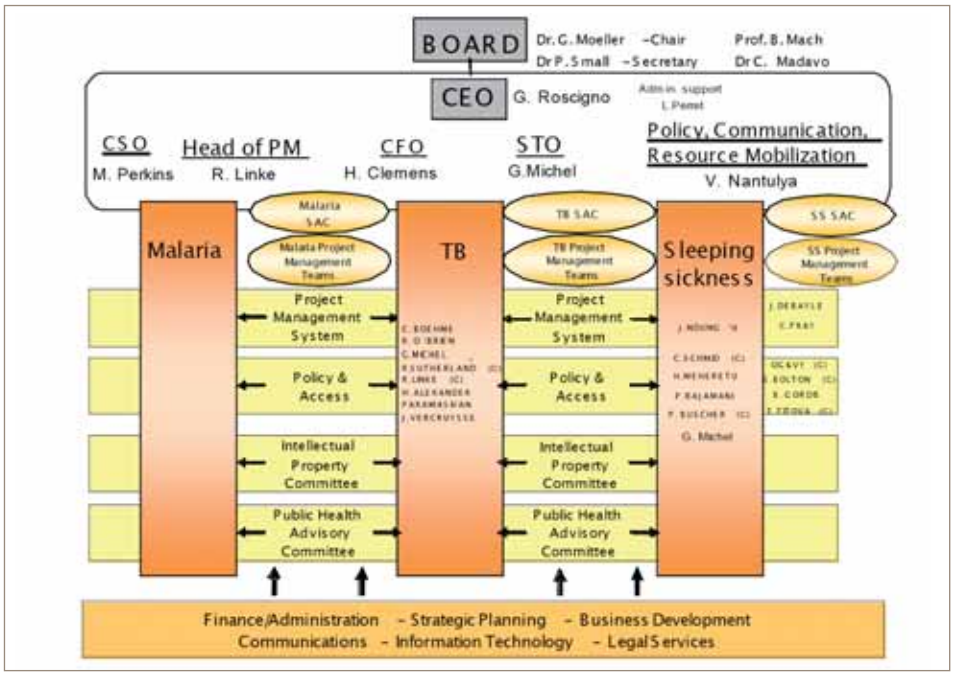
to the development of TB diagnostics along the line of patients' and health-care providers' needs at different levels of the health system. FIND is therefore consolidating its focus on two levels of the health system: the health center level where, at present, sputum smear microscopy is the mainstay of TB diagnosis, and the lowest or health post level of the public sector health system, where TB diagnosis is based on symptoms and clinical signs. These two levels account for up to 85% of TB patients who seek service in the public health sector.

For these reasons, FIND has selected two diagnostic platforms for development of TB diagnostics. The first platform is the point-of-care lateral flow technology (dipstick immunoassays) for use at the lowest level of the health system where two million patients go undiagnosed each year. The assays for this level are qualitative and are based on antigen or antibody detection.

For the health center level, where microscopy is currently positioned, FIND aims to develop molecular technology-based assays. The two platforms also have potential application to other diseases in FIND's portfolio.

Another important development during this reporting period was the grant from BMGF to develop POC and disease staging tools for human African trypanosomiasis (HAT) or sleeping sickness.

The addition of new programmes to FIND's disease portfolio means that FIND must fine-tune and reinforce its business model on an ongoing basis. Each disease portfolio is managed as an independent business unit with clear targets and milestones, and is supported by a disease-specific team guided by FIND's project management system, policy and access, and intellectual property strategies. Each disease team has its own scientific advisory committee.



*FIND operating model*

FIND must ensure that the tools being developed are relevant to the needs of both the patients and health service providers at the different levels of the health system. For this purpose, FIND established a Public Health Advisory Committee made up of senior policymakers with extensive knowledge of developing country health systems, socio-political environments, civil society and National TB Control Programs to serve as representatives of the end-users of FIND-supported diagnostic tools. The Committee met at the end of September 2006 to review and provide input into FIND's customer requirement documents and product profiles; to provide advice on the selection of evaluation and demonstration study sites; to review results from evaluation and demonstration studies; and to advise on and promote uptake of well-performing tools into global and national policy and promote strategy for access to quality assured laboratory services.

**Human resources:**

In March 2006, Dr. Callisto Madavo accepted the nomination to join FIND's Board of Directors. Dr. Madavo has held numerous senior level positions during his thirty-four years at the World Bank and was most recently the World Bank Vice-President for Africa. He brings to the Board a wide range of country program experience in Asia, Africa, Latin America and the Caribbean. He has supported a number of key initiatives at the World Bank, including the HIV/AIDS initiative, capacity development and infrastructure.

In July 2006, FIND recruited a full time Senior Technology Officer for immunodiagnostics, Dr. Gerd Michel.


Gerd worked with FIND as a consultant in product development since October 2005. In this new position, Gerd is responsible for bringing his extensive technical and industry skills to bear on the development of antigen and antibody-based POC diagnostic tests across the entire FIND disease portfolio.

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## Publications and Data Sharing

FIND staff have submitted or published the following scientific articles and chapters since the last report.

### Manuscripts

1. Steingart KR, Henry M, Ng V, Hopewell PC, Ramsay A, Cunningham J, Urbanczik R, Perkins M, Aziz MA, Pai M. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis. (submitted)
2. Perkins MD, Small PM. Admitting defeat. Int J Tuberc Lung Dis 2006;10(1):1-1
3. Ramsay A, Squire SB, Siddiqi K, Cunningham J, Perkins MD. The bleach microscopy method and case detection for tuberculosis control. Int J Tuberc Lung Dis 2006;10(3):256–258
4. Perkins MD, Roscigno G, Zumla A. Progress towards improved tuberculosis diagnostics for developing countries. Lancet. 2006;367:942-3.
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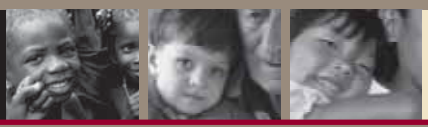



# *Financial Information*

## *Foundation for Innovative New Diagnostics (FIND)*

*Geneva*

*Financial Statements for the Year ended 31 December 2006 and Auditors' Report*

Deloitte.

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## REPORT OF THE STATUTORY AUDITORS

To the Board of the
**Foundation for Innovative New Diagnostics (FIND),** Geneva

As statutory auditors, we have audited the accounting records and the financial statements of the Foundation for Innovative New Diagnostics (FIND) for the year ended December 31, 2006.

These financial statements are the responsibility of the Board of the Foundation. Our responsibility is to express an opinion on these financial statements based on our audit. We confirm that we meet the legal requirements concerning professional qualification and independence.

Our audit was conducted in accordance with Swiss Auditing Standards and with the International Standards on Auditing (ISA), which require that an audit be planned and performed to obtain reasonable assurance about whether the financial statements are free of material misstatement. We have examined on a test basis evidence supporting the amounts and disclosures in the financial statements. We have also assessed the accounting principles used, significant estimates made and the overall financial statements presentation. We believe that our audit provides a reasonable basis for our opinion.

In our opinion, the accounting records and the financial statements comply with Swiss law and the By-laws of the Foundation.

We recommend that the financial statements submitted to you be approved.

DELOITTE SA

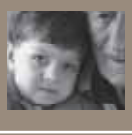
Peter Quigley
*Auditor in charge*

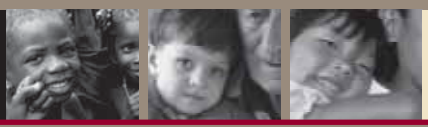
Céline Burnichon

October 29, 2007

Attached : Financial statements (balance sheet, statement of income and expenditure, cash flow statement and notes)

Member of
Deloitte Touche Tohmatsu



## FOUNDATION FOR INNOVATIVE NEW DIAGNOSTICS (FIND)

**Geneva, Switzerland**

### BALANCE SHEET AS AT 31 DECEMBER 2006

(all amounts in US dollars)

| | 2006 | 2005 |
|---|---|---|
| ASSETS | | |
| **Current assets** | | |
| Cash on hand | 3 797 | 426 |
| UBS Current accounts | 444 445 | 52 657 |
| UBS Short-term Deposits | 13 497 488 | 2 350 000 |
| UBS Rental Guarantee Deposit | 67 121 | 44 439 |
| Accounts receivable | 156 176 | 39 051 |
| Prepayments | 82 889 | - |
| | 14 251 916 | 2 486 573 |
| **Fixed assets** | | |
| Office furniture & fittings | 49 808 | 26 276 |
| Computers & printers | 40 268 | 19 485 |
| Electrical installations | 25 706 | 23 103 |
| Fax machine & telephones | 5 639 | 7 617 |
| | 121 421 | 76 481 |
| **Patents** | 46 242 | 53 949 |
| **Total assets** | 14 419 579 | 2 617 003 |
| LIABILITIES AND CAPITAL | | |
| **Current liabilities** | | |
| Accounts payable | 1 204 357 | 764 493 |
| Accrued expenses | 144 814 | 47 296 |
| Contributions received in advance | 11 162 460 | 544 221 |
| | 12 511 631 | 1 356 010 |
| **Capital and reserves** | | |
| Capital | 40 430 | 40 430 |
| General reserve | 1 867 518 | 1 220 563 |
| **Total liabilities and capital** | 14 419 579 | 2 617 003 |

The accompanying notes are an integral part of these financial statements.

## FOUNDATION FOR INNOVATIVE NEW DIAGNOSTICS (FIND)

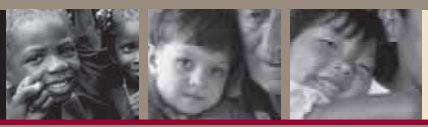
Geneva, Switzerland

### STATEMENT OF INCOME AND EXPENDITURE FOR THE YEAR ENDED 31 DECEMBER 2006

(all amounts in US dollars)

| | 2006 | 2005 |
|---|---|---|
| **INCOME** | | |
| Contributions income | 11 152 692 | 4 980 532 |
| Interest income | 258 591 | 42 005 |
| Sundry income | 12 292 | 48 914 |
| Exchange gains, net | - | 37 858 |
| **Total income** | 11 423 575 | 5 109 309 |
| **EXPENDITURE** | | |
| **Analytical & Project Work** | | |
| Project activities | 7 505 153 | 2 193 605 |
| Partnership building | 525 307 | 391 858 |
| Promotion & external relationships | 361 069 | 279 619 |
| Strategic planning & operations | 359 203 | 239 839 |
| Regulatory activities | 98 664 | 24 196 |
| Technical meetings | 154 979 | 126 938 |
| | 9 004 375 | 3 256 055 |
| **Information & Communication** | | |
| Donor relations & communications | 192 517 | - |
| Publications production | 69 811 | 14 572 |
| Website | 8 500 | 5 793 |
| | 270 828 | 20 365 |
| **Governing & Advisory Bodies** | | |
| Staff costs allocated | 55 003 | 46 010 |
| Advisory Committees | 2 856 | 2 403 |
| Foundation Board | 27 098 | 17 408 |
| | 84 957 | 65 821 |
| **General Administration** | | |
| Staff costs and travel | 544 758 | 349 783 |
| IT expenses | 93 482 | 97 568 |
| Photocopies, stationery, printing & sundries | 106 307 | 43 386 |
| Rent of premises | 248 129 | 212 448 |
| Repairs & maintenance | 29 803 | 17 585 |
| Telecommunications | 81 133 | 62 741 |
| | 1 103 612 | 783 511 |
| **Finance & Service Expenses** | | |
| Auditing & accounting | 21 983 | 21 762 |
| Bank charges | 5 730 | 3 012 |
| Exchange losses, net | 34 191 | - |
| Legal fees | 98 887 | 57 745 |
| Insurance | 100 931 | 64 180 |
| | 261 722 | 146 699 |
| **Depreciation** | 51 126 | 33 932 |
| **Total expenses** | 10 776 620 | 4 306 383 |
| **Excess of income over expenditure for year** | 646 955 | 802 926 |
| **Surplus at 31 December 2005 brought forward** | 1 220 563 | 417 637 |
| **Surplus carried forward in General Reserve** | 1 867 518 | 1 220 563 |

The accompanying notes form an integral part of these financial statements.





## FOUNDATION FOR INNOVATIVE NEW DIAGNOSTICS (FIND)

Geneva, Switzerland

### CASH FLOW STATEMENT FOR THE YEAR ENDED 31 DECEMBER 2006

(all amounts in US dollars)

| | 2006 | 2005 |
|---|---|---|
| **Excess of income over expenditure for the year** | 646 955 | 802 926 |
| Add back non-cash charge - depreciation | 51 126 | 33 932 |
| | 698 081 | 836 858 |
| **Cash flows - operating activities** | | |
| Increase/(decrease) in contributions in advance | 10 618 239 | (2 218 782) |
| Increase/(decrease) in accounts payable | 439 864 | 338 525 |
| Increase/(decrease) in accrued expenses | 97 518 | ( 3 250) |
| (Increase)/decrease in accounts receivable | ( 117 125) | ( 16 338) |
| (Increase)/decrease in prepayments | ( 82 889) | 13 899 |
| | 10 955 607 | (1 885 946) |
| **Cash flows - investing activities** | | |
| Additional office furniture & fittings | ( 35 248) | - |
| Additional computers & printers | ( 42 471) | ( 1 779) |
| New electrical installations | ( 10 640) | - |
| Additional telephones | - | ( 4 804) |
| Additional patent costs | - | ( 3 949) |
| (Increase)/decrease in rental guarantee account | ( 22 682) | 6 998 |
| | ( 111 041) | ( 3 534) |
| **Net increase in cash and cash equivalents for year** | 11 542 647 | (1 052 622) |
| **Cash and cash equivalents at start of year** | | |
| Cash on hand | 426 | 2 619 |
| Current accounts & short-term deposits | 2 402 657 | 3 453 086 |
| | 2 403 083 | 3 455 705 |
| **Cash and cash equivalents at end of year** | | |
| Cash on hand | 3 797 | 426 |
| Current accounts & short-term deposits | 13 941 933 | 2 402 657 |
| | 13 945 730 | 2 403 083 |
| **Net increase in cash and cash equivalents for year** | 11 542 647 | (1 052 622) |

The accompanying notes form an integral part of these financial statements.

**FOUNDATION FOR INNOVATIVE NEW DIAGNOSTICS (FIND)**
Geneva, Switzerland

## NOTES TO THE FINANCIAL STATEMENTS FOR THE YEAR ENDED 31 DECEMBER 2006

### 1. General

The Foundation for Innovative New Diagnostics (FIND) is an independent non-profit Foundation created under Article 80 of the Swiss Civil Code, and is registered in the Geneva Register of Commerce under by-laws dated 22 July 2003.

FIND's mission is to support and promote the health of people in developing countries through the development and introduction of new but affordable diagnostics for infectious diseases.

FIND is exempt from federal and cantonal income and capital taxes.

### 2. Significant accounting policies

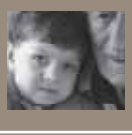
2.1 Basis of presentation - The financial statements are prepared under the historical cost convention.

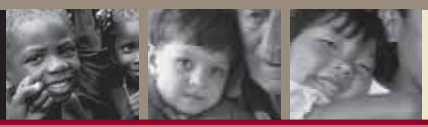
2.2 Fixed assets - Fixed assets are recorded at cost and are depreciated under the straight-line method at 20% annually for office furniture and fittings, electrical installations and fax machine and telephones, and 33.3% annually for computers and printers.

2.3 Patents - The Patents owned at 31 December 2006 were purchased as part of an agreement completed with a project partner early in 2004. A purchase option on the Patents granted to the project partner was not exercised and expired on 8 September 2006. FIND's title thereby became unconditional and the Patents are subject to amortization under the straight-line method over their remaining useful life (seven years).

2.4 Foreign currency - Accounting records are maintained in US dollars. Income and expenditures in other currencies are recorded at accounting rates approximating actual rates in effect at the time of the transaction. Year-end balances for assets and liabilities in other currencies are translated into US dollars at rates of exchange prevailing at balance sheet date. At 31 December 2006 the rate of exchange used for the Swiss franc, the main foreign currency for 2006, was USD/CHF = 1.22 (2005 - 1.32). Exchange gains and losses are included in the determination of net income.

2.5 Recognition of revenue - Contributions received are recorded according to the grant period indicated in donor agreements, with amounts received relating to periods extending beyond balance sheet date recorded as contributions received in advance. Donor agreements in effect at 31 December 2006 provide for a total of USD 21.035 million to be paid to FIND between January 2007 and January 2011.
In 2003, a donor pledged an initial contribution of USD 23.3 million for the years 2003 to 2008. In 2006, the donor anticipated the payment of the contributions and in 2007 pledged additional contributions of USD 62.631 million for the period from August 2007 to August 2012. In 2006, the impact of the recognition of the initial contribution over the shortened grant period was USD 3.489 million.



**FOUNDATION FOR INNOVATIVE NEW DIAGNOSTICS (FIND)**
Geneva, Switzerland

**NOTES TO THE FINANCIAL STATEMENTS**
(continued)

2.6 Accounts payable and accrued expenses - Accounts payable and accrued expenses represent expenditures chargeable in the 2006 financial year, for which invoices were not received for payment before year-end. Settlements are charged to the accruals in the following financial period.

2.7 Rental guarantee deposit - The guarantee relates to the rental of the FIND office premises and is recoverable in accordance with the rental contract upon vacation of the premises.

2.8 Project expenditure - Project expenditure during 2006 under contracts signed up to 31 December 2006 totalled USD 5,492,942. Commitments at 31 December 2006 for future payments under those contracts total USD 5,600,986 (2005 - USD 494,165).

**3. Fixed assets and intellectual property**

3.1 Fixed assets as at 31 December 2006 were as follows:

| | | 2006 | 2005 |
|---|---|---|---|
| Cost price | | | |
| Office furniture & fittings | | 76,523 | 41,275 |
| Computers & printers | | 96,143 | 53,672 |
| Electrical installations | | 45,509 | 34,869 |
| Fax machine & telephones | | 9,891 | 9,891 |
| | | 228,066 | 139,707 |
| Less: Accumulated depreciation | | 106,645 | 63,226 |
| Net book value | USD | 121,421 | 76,481 |

Fire insurance cover as at 31 December 2006 was USD 108,200 (2005 - USD 100,000).

3.2 Intellectual property as at 31 December 2006 was as follows:

| | | 2006 | 2005 |
|---|---|---|---|
| Cost price | | | |
| Patents | | 53,949 | 53,949 |
| | | 53,949 | 53,949 |
| Less: Accumulated depreciation | | 7,707 | - |
| Net book value | USD | 46,242 | 53,949 |

**FOUNDATION FOR INNOVATIVE NEW DIAGNOSTICS (FIND)**
Geneva, Switzerland

## NOTES TO THE FINANCIAL STATEMENTS
(continued)

### 4. Pension Fund liabilities

No amounts were due to the pension fund at 31 December 2006 (2005 - nil).

### 5. Rent commitments

At 31 December 2006 FIND had future rent commitments totalling USD 712,670 up to 31 May 2009 (2005 - USD 603,994).

### 6. Funds

The Endowment Capital of CHF 50,000 is fully subscribed and equates to USD 40,430 at the rate of exchange on the date of payment.

### 7. Events subsequent to 31 December 2006

There were no events occurring subsequent to 31 December 2006 which could have a material impact on the understanding of these financial statements.



# FIND Board of Directors, Management and Staff, Public Health Advisory Committee

*As at 31 December 2006*

## Board of Directors

**Dr. Gerald Moeller,** *Chairman of the Board*
**Dr. Bernard Mach** *Member*
**Dr. Callisto Madavo** *Member*
**Dr. Peter Small,** *Board Secretary*

## FIND Team

**Giorgio Roscigno,** *Chief Executive Officer*
**Audrey Albertini,** *Scientific Assistant for Malaria Diagnostics*
**Catharina Boehme,** *Medical Officer*
**Herbert Clemens,** *Chief Financial Officer*
**Jacques Debayle,** *Human Resources & Operations Manager*
**Beatrice Gordis,** *Communications Officer*
**Heather Alexander*,** *Health Scientist*
**Ralf Linke*,** *Quality Manager*
**Gerd Michel,** *Senior Technology Officer*
**Vinand Nantulya,** *Senior Policy and Implementation Officer*
**Joseph Ndung'u,** *Head of HAT Diagnostics Programme*
**Richard O'Brien,** *Head of Product Evaluation and Demonstration*
**C.N. Paramasivan,** *Head of TB Laboratory Support*
**Mark Perkins,** *Chief Scientific Officer*
**Laurence Perret,** *Administrative assistant to CEO*
**Bärbel Porstmann,** *Head of Project Management & Regulatory Affairs*
**Ranald Sutherland*,** *Technology and Business Development*
**Jewel Thomas,** *Communications and Advocacy Coordinator*
**Julie Vercruysse,** *TB Scientific Team Administrator*
**Hanna Yirga,** *HAT Scientific Team Administrator*
* Consultants

## Public Health Advisory Committee

**Dr. Jaap Broekmans,** *Director, Royal Netherlands Tuberculosis Association (KNVC)*
**Ms. Lucy Chesire,** *Project Leader, TB Action Kenya*
**Dr. Manuel Dayrit,** *Director, Department of Human Resources for Health (WHO)*
**Dr. Saidi Egwaga,** *Program Manager, National Tuberculosis and Leprosy Program, MoH, Tanzania*
**Dr. Anthony Mbewu,** *Executive Director of Research, Medical Research Council of South Africa*
**Dr. Francis Omaswa,** *Executive Secretary, Global Task Force on Human Resources for Health (WHO)*
**Dr. Surrender K. Sharma,** *Chief, Division of Pulmonary & Critical Care Medicine, AIIMS, India*

FIND
FOUNDATION FOR INNOVATIVE NEW DIAGNOSTICS



Edited by: FIND Team

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