The prognosis of latent tuberculosis: can disease be predicted?

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In humans, Mycobacterium tuberculosis persists for long periods in a clinically latent state, creating a huge reservoir of ‘silent’ tuberculosis (TB) (roughly one-third of the global population) from which new cases continually arise. A prognostic marker for active TB would enable targeted treatment of the small fraction of infected individuals who are most at risk of developing contagious TB, contributing greatly to TB control efforts. Here, we propose that TB-specific interferon-γ release assays might be useful for identifying individuals with progressive infections who are likely to develop the disease. This might provide an unprecedented advantage for TB control, namely targeted preventive therapy for individuals who are most at risk of developing active contagious TB.

The global challenge of latent tuberculosis

Tuberculosis (TB) is responsible for 2–3 million deaths every year and, probably, 30 times as many infections [1]. This creates a huge reservoir of untreated latent TB infection (LTBI), which can reactivate later in life, and represents a major source of disease [1]. Despite the existence of effective treatment regimens, control of TB is complicated by the chronic nature of the infection. The fact that only 5–10% of recently exposed individuals develop clinically active TB in the first two years after exposure, together with the often casual nature of exposure, makes diagnosis of LTBI among recently exposed and potentially infected individuals extremely difficult. For many decades, different versions of the tuberculin skin test (TST) have been used, despite widespread recognition of its low specificity for TB and its inability to distinguish reliably individuals infected with Mycobacterium tuberculosis from those vaccinated with Bacillus Calmette-Guerin (BCG). Only recently, specific tests have emerged that replace the TST for the diagnosis of LTBI.

Recent data suggest that the molecules that are encoded by M. tuberculosis infection, immune responses and diagnosis

The study of the immune response to TB is an active research area; it is not within the scope of this article to review the extensive literature on this rapidly growing field (for a review, see [6]). However, it is important to understand which component(s) of the immune response can be used to diagnose the different stages of TB infection and disease. MTB is an intracellular pathogen that resides mainly within macrophages and is able to survive for many years in an intracellular habitat in a slowly-replicating or non-replicating state that is induced by host immune responses and fibrotic encapsulation. Recently, there has been a breakthrough in the understanding of the adaptation of MTB to the hostile intracellular environment of the immune host [7]. MTB responds to the host immune system with dynamic transcriptional changes of a subset of its 4000 genes. Mimicking growth conditions in vivo by O₂ depletion, nutrient starvation or nitric oxide (NO) addition has led to the identification of several MTB genes, the expression of which is rapidly altered to enable intracellular survival [e.g. the dormancy (DosR) regulon, which consists of 48 genes] [8].

It has long been recognized that cell-mediated immune (CMI) responses predominate in TB infection; specifically, a type-1 T-cell response that is characterized by production of IFN-γ and interleukin-2. During the initial phase of infection, when mycobacteria are present almost exclusively within macrophages, little if any free unprocessed antigen leaves the macrophage and is available to stimulate a humoral immune response. Antigens that are secreted by the replicating mycobacteria are clearly presented by infected antigen-presenting cells, as indicated by the rapid induction of a strong CMI response [9]. However, recent data suggest that the molecules that are encoded by...
A latent infection can be defined as one which is ‘subclinical’ – that is, an infection without noticeable symptoms. However, for the prognosis of *M. tuberculosis* infection, it is important to distinguish between a recent infection, where symptoms have not yet developed, a long-term latent infection, where the host successfully contains the pathogen, and an advanced stage of infection (here defined as incipient disease) that leads to clinical disease.

Consequently, measurement of CMI rather than antibody responses provides a sensitive way to detect early TB infection (Figure 1). However, if an individual develops active TB and the bacterial and antigenic load increases, a robust antibody response [12,13] and measurable levels of free antigen (e.g. in sputum or urine) can be detected [14,15]. Therefore, the most successful approach so far in the development of an effective new diagnostic test for TB infection has been the measurement of *M. tuberculosis*-specific type-1 T-cell responses, for which IFN-γ is an appropriate marker.

**The tuberculin skin test**

Until recently, the TST, which is an interdermal injection of purified protein derivative (PPD), was the only tool for detecting LTBI. The TST measures a delayed-type hypersensitivity reaction based on immunological recognition of mycobacterial antigens in exposed individuals, and is a simple and inexpensive test. However, as PPD contains a poorly defined mixture of mycobacterial antigens, many factors other than TB infection influence the outcome of the test, including BCG vaccination and prior exposure of the subject to non-tuberculous mycobacteria [16,17]. In countries in which BCG is widely used, as many as 60% to 90% of people with low risk of MTB infection can be identified as false positive by the TST [18,19], although this might not be true in all settings, such as in Gambian children [20]. Different TST cut-off values and different tuberculin PPD preparations and concentrations have been used to improve the specificity of the test, taking into consideration BCG-vaccination status, exposure to environmental mycobacteria and likelihood of infection [21,22]. Although the TST has its shortcomings, it is clinically useful and a positive TST remains the most important criteria for triggering preventive therapy among contacts. Interestingly, recent studies performed in Malaysia and Hong Kong demonstrated that, even in a region with widespread TST positivity due to high BCG coverage and latent TB, there is a clear correlation between the size of the TST-induced induration and subsequent development of active TB [23,24].

**Discovery and characteristics of *M. tuberculosis*-specific antigens**

The major breakthrough in the search for novel specific diagnostic reagents came with the identification of the genetic differences between the *Mycobacterium bovis* BCG vaccine strain, virulent *M. bovis* and *M. tuberculosis* [25,26]. During the attenuation process leading to the various BCG strains used worldwide, several genetic segments are lost (the so-called regions of difference, RDs) from the original virulent *M. bovis* strain. The identification and use of antigens encoded by these RDs for diagnosis of TB infection has previously been reviewed [27]. The two that are most well-characterized, ESAT-6 and CFP-10, are encoded by the RD1 region of the *M. tuberculosis* genome, which is deleted in all BCG vaccine strains. The genes encoding ESAT-6 and CFP-10 are also absent in most non-tuberculous mycobacteria, with the exception of the opportunistic pathogens *Mycobacterium szulgai*, *Mycobacterium marinum* and *Mycobacterium kansasii*. Importantly, both ESAT-6 and CFP-10 are secreted from replicating bacteria *in vitro* [28] and *in vivo* [29], and the secretion of these molecules correlate with the virulence of different genetically modified strains of *M. tuberculosis* [30].

**The novel specific tests – upgrading diagnosis of TB from induration to IFN-γ**

With the identification of the antigens ESAT-6 and CFP-10, the way was paved for the development of specific *in vitro* diagnostic tests, and several test formats that measure IFN-γ production have been evaluated over recent years [2,31]. Two standardized diagnostic kits that contain the ESAT-6 and CFP-10 antigens are now on the market: the Quantiferon-TB GOLD (QFT) test (Cellestis Limited, Carnegie, Victoria, Australia) and the T-SPOT.TB assay (Oxford Immunotec, Oxford, UK). Both assays are useful to detect LTBI. Specificity is very high [32–34] and, as expected, BCG vaccination is not a confounding factor for these tests [35]. Assessment of the sensitivity of these tests for LTBI has been complicated.

![Figure 1. Schematic representation of the immune response of individuals during the course of infection. The shade areas illustrate when it is possible to detect a response using the given test. As early as two weeks after infection with *M. tuberculosis*, a cell-mediated immunity response can be measured. This response is associated with both delayed type hypersensitivity (DTH) responses, as measured by the Mantoux test, and production of type 1 T-cell cytokines, IFN-γ, and often correlates with a temporary arrest or delay of bacterial growth. This response is maintained throughout the course of the infection, but it can wane in individuals who develop very severe TB. Mycobacterial load remains low during the early phase of infection and is therefore not accessible for antigen-detection assays. In individuals who develop acute disease, mycobacterial load and soluble antigen increase. Similarly, *M. tuberculosis*-specific antibody responses are usually undetectable during the early phase of infection, but develop as the infection progresses to active TB.](image-url)
by the lack of a gold standard. However, through screening contacts of active TB cases, in which the association between test results and the level of exposure of contacts to the index case(s) is recorded, the current consensus is that both tests detect individuals affected by LTBI with a sensitivity at least as high as the TST, and the response correlates better with the level of exposure than does the TST [4,19,36–38]. Several recent studies have directly compared the performance of the TST with that of the two novel tests [34,39]. In Europe, USA and Japan, where these tests have entered the market, the value of this approach in contact tracing has rapidly become apparent [36,40]. In the USA, the Centers for Disease Control (CDC) recommends the use of the QFT test instead of the TST for contact investigation, evaluation of recent immigrants and serial testing for infection control [5]. In the UK, the National Institute of Health and Clinical Excellence (NICE) has recommended IFN-γ testing for confirming a positive TST or in individuals for whom the Mantoux test might be less reliable (www.nice.org.uk/page.aspx?o=CG033NICEguideline).

However, to achieve maximum sensitivity for infection, the two test kits have established their optimal cut-off values at the lowest possible level [32,41]. The QFT cut-off value is based on receiver operating characteristic (ROC) curve analyses in which specificity in non-exposed healthy community controls (from a low endemic setting) is compared with sensitivity in patients with active pulmonary TB [18,42]. Indeed, in the study of Mori et al. [18], where community controls have no real exposure to MTB, and therefore have almost no risk for latent infection, the specificity is very high. Essentially, positive results are found only in TB patients. Thus, the cut-off value for what defines a positive test can be set very low. This has resulted in diagnostic tests that are designed to detect the maximum number of individuals with an MTB infection. However, the current versions of the tests do not provide information on which individuals are more likely to develop the disease.

### Correlation between T-cell responses to ESAT-6 and CFP-10, and disease progression in animal models

Although clinical outcome (i.e. development of active disease) is the only feasible read-out in human investigations of the predictive value of ESAT-6, animal studies provide the advantage of direct assessment of disease status and bacterial replication. In animal models, CMI responses to both ESAT-6 and crude culture filtrate correlate closely with bacterial replication in vivo and with the progression of disease. This was first demonstrated by comparing T-cell proliferative responses with culture filtrate antigens and bacterial numbers at different time points post-infection [9], and later by studying the dynamics of T-cell responses that are specific for ESAT-6 in mice infected by MTB [43] or genetically modified strains [30]. It might seem contradictory that a high ESAT-6 response correlates with ongoing bacterial replication, as generating a strong IFN-γ response to ESAT-6 by vaccination leads to efficient control of bacterial replication in a subsequent infection (Box 2). The predictive value of IFN-γ response to ESAT-6 has been recently addressed in a study that monitored the efficacy of novel experimental vaccines in the aerosol mouse model [44]. This study demonstrated a close correlation between ESAT-6-stimulated IFN-γ levels two weeks post-infection and the subsequent bacterial numbers in the lungs when necropsied at week 6 post-infection [44]. Furthermore, in cattle infected with *M. bovis*, high IFN-γ responses to ESAT-6 early in the infection predicted the animals that later developed progressive disease or that were later (at necropsy) positive for *M. bovis* – something that the response to other antigens did not do [45]. Vordermeier et al. [46] later observed a direct correlation between the quantity of IFN-γ secreted in response to ESAT-6 and the degree of pathology in cattle infected with *M. bovis*. The close correlation between ESAT-6 responses and progression of disease has subsequently been confirmed in two more studies in cattle [47,48] and in a recent study in non-human primates [49]. A crucial and often overlooked aspect in all these studies is that it is not the presence of ESAT-6-stimulated IFN-γ that correlates with the outcome: cells from all infected animals produce IFN-γ in response to re-stimulation with ESAT-6. It is the amount of IFN-γ produced (or the number of antigen-specific cells) in response to ESAT-6 that correlates with the ability to restrict bacterial growth.

### Correlation between T-cell responses to ESAT-6 and CFP-10, and clinical outcome

Because of a carefully established cut-off value for ESAT-6- and CFP-10-stimulated IFN-γ responses, the IGRAs are becoming an established standard for the diagnosis of MTB infection. It is therefore relevant to re-address some of the intriguing first reported observations made when measuring ESAT-6 immune responses in TB-endemic regions. The first evaluation of ESAT-6 recognition in close contacts such as household contacts to a sputum-positive TB patient in a TB-endemic region showed that most contacts (and many of the community controls) were positive in agreement with the cut-off value established for the commercially available IGRAs (~18 pg/ml). However, within this positive group, subjects can roughly be divided into three distinct subgroups (i.e. low, moderate and high responses) with markedly different

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**Box 2. The role of IFN-γ**

It might seem paradoxical that IFN-γ, an essential T-cell helper 1 (Th1) cytokine for host defense against mycobacteria, can serve as a marker for failing immunity. However, the symptoms in TB are immunopathological, and the same inflammatory cytokines that can eliminate the bacteria are also essential for its transmission; without tissue destruction and cavitation, the bacteria cannot reach the lumen of the bronchioles to be spread in the sputum. In most cases, immune activation (characterized by IFN-γ production) leads to the suppression of infection and the subsequent downregulation of the immune response. In some individuals, however, the bacteria survive by manipulating the host’s immune response [62]. In this case, the immune response, which is directly stimulated by the bacteria, increases in magnitude as the bacteria increase in numbers and, eventually, it might become pathological rather than protective. Similarly, in animal models a certain level of vaccine that promotes an IFN-γ response to ESAT-6 can be protective, whereas in non-vaccinated animals that do not control the early stages of infection the magnitude of the ESAT-6 response after infection correlates with bacterial replication.
ESAT-6 response levels [50]. Recently, grouping of response levels has been further substantiated by studies of ESAT-6- and CFP-10-stimulated IFN-γ responses in Ethiopia [51,52] (Figure 2). An overall assessment of the data suggests that ~30% of the contacts had low IFN-γ responses in the range 0–100 pg/ml (100 pg/ml was the cutoff value for a positive response for the assay system used in this study), whereas ~10% had exceedingly high levels of IFN-γ (>1000 pg/ml). In between these two populations lie ~60% of the contacts, covering a large range of test positive responses (Figure 2). These different ESAT-6 response levels predicted a different outcome of infection as suggested by a study that, although based on small numbers, showed that very strong ESAT-6 responses shortly after exposure to MTB correlated with subsequent development of disease [51]. In these recently exposed, healthy contacts, high levels of IFN-γ in response to ESAT-6 (in this study, >5000 pg/ml) were associated with a tenfold increased risk of subsequently developing clinical TB in the 1–2 years immediately after exposure compared with those healthy contacts from the same households with a low IFN-γ response to ESAT-6. The overall correlation of ESAT-6-specific IFN-γ levels and stage of infection is strongly supported by recent epidemiological investigations, indicating a correlation between the infectious dose to which contacts have been exposed and the magnitude of their response to PPD and ESAT-6 in vitro, although the latter was only a trend (p=0.08) [53].

Recent longitudinal studies from TB endemic countries provide further support to our hypothesis. In a study conducted in India, Pai et al. [54] showed that highly exposed healthcare workers (HCWs) who had TST conversions in India had massive increases in IFN-γ responses to ESAT-6 and CFP-10 (measured using the QFT assay). The QFT assay successfully detected all cases of TST conversion, and every HCW who had a large increase in TST induration had a huge increase in IFN-γ response, which was significantly higher than the diagnostic cut-off point of 0.35 IU/ml. There were similar findings (using ELISPOT) in recent longitudinal studies of nursing students from Zimbabwe [55] and household contacts from Uganda [56]. Thus, it is plausible that individuals with recent exposure to TB have vigorous increases in T-cell responses, probably due to active bacterial replication. Because it is well documented that individuals with recent TST conversions have a high probability to develop the active disease [57], it is plausible that strong increases in IFN-γ responses after recent exposure might predict progression towards active disease.

Therefore, on the basis of these studies, we hypothesize that high and/or rising levels of IFN-γ produced in response to ESAT-6 by T cells from recently TB-infected individuals signal incipient disease and, thus, might serve as a prognostic marker for subsequent development of overt disease (Figure 3). This hypothesis is in agreement with the observation that ESAT-6-stimulated IFN-γ response levels decline significantly during successful therapy (when both bacterial load and risk of disease also decline) [58–60].

The potential use of IFN-γ assay as a prognostic test

Most TB cases are concentrated in resource-poor countries where the incidence of active TB represents the tip of the iceberg compared with the immense pool of LTBI. At present, most TB control efforts in these countries are devoted to the identification and chemotherapy of patients with active TB. This makes sense in a resource-poor setting, because these cases are already infectious and, thus, the major source of new cases. However, even in these settings, treating LTBI before the development of active disease also makes sense both economically and in terms of public health, especially in high-risk groups. Unfortunately, the immense numbers of LTBI-infected individuals makes identification and treatment almost impossible using existing approaches and resources. Nevertheless, what might be possible in these countries is a better targeted approach that aims to identify and treat those individuals with incipient disease. As suggested above, these would most likely be identified via their exceedingly high and/or rising levels of ESAT-6-specific IFN-γ (Figure 3). Similar to the TST, in which a 5 mm result is considered positive in individuals without confounding factors (such as vaccination) in many developed countries, but considered negligible in African and most Asian countries, cut-off values can be meaningfully discussed only in a specific context (Box 3). The major practical problem is setting appropriate cut-off values and the challenge is not to identify positive responses per se, but to establish a cut-off point within the positive category that predicts subsequent development of active TB. Furthermore, a high IFN-γ response measured 10–30 years after exposure in healthy individuals might not pose the same risk as a high IFN-γ response measured 2–3 months after exposure. Therefore, in addition to identifying an absolute cut-off level for incipient disease, a certain increase in the IFN-γ response among recently exposed individuals (conversion) might be a strong indicator of bacterial replication and, therefore, a predictor of progression to active disease [54]. Prognosis based on conversion will be most helpful in situations in which serial testing is usually done (e.g. annual screening of HCWs as part of TB-infection control programs). A completely separate issue is the utility of this test in individuals co-infected with HIV. Depending on the
severity of the HIV infection, they might have reduced ability to produce IFN-γ and it is therefore possible that another cut-off value should be applied for this group of patients. Few data on this are available, although what has been done indicates that IGRAs retain their utility unless CD4-positive T-cell numbers are greatly decreased[61].

Further studies have recently been launched to address these issues (Table 1). Although the study populations are different, the basic methodology is similar: screening of at-risk, but healthy, populations for their level of responsiveness to ESAT-6 and CFP-10 or the TST (after excluding active TB) and then following their clinical status over time, so that those who develop clinical disease can be identified. In all cases, TB is defined by a combination of sputum culture and/or smear, X-ray and clinical examination. Because TB can be self-limiting, active follow-up is planned for these studies to find those who develop active TB, without becoming so seriously ill that they seek hospitalization, otherwise the true disease rate is likely to be underestimated[51]. Although the studies have a basic common approach, they are also designed to answer slightly different questions.

The first five studies listed in Table 1 are all contact studies designed to estimate positive predictive values. By looking at close contacts of sputum-positive TB cases, who are at high risk of developing disease, the ratio of individuals expected to develop TB increases markedly, enabling accurate estimation of the positive predictive value of IGRA. The third study listed in Table 1 differs from the other contact studies in several important points. It focuses on immigrants to the Netherlands with prior TB exposure, which is a group with a traditionally high TB incidence (www.iphcr.res.in/html/RESEARCH-infectious.htm). However, because they are now resident in a region with very low TB incidence, acute re-infection can be ruled out as a significant factor. To the best of our knowledge, this is

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**Box 3. Outstanding questions**

There are data indicating that a high response to ESAT-6 and CFP-10 reflects a serious infection. However, what constitutes a 'high' response is, to some extent, context-dependant and might differ from TB endemic to TB non-endemic regions and from HIV-infected to HIV-infected individuals. Furthermore, recent infection, long-term latent infection contained by host immunity and incipient disease are not characterized by identical immune responses.

Future studies therefore need to address the following issues:

- Can an incipient disease cut-off value for IGRAs be established so that a single measurement of the IFN-γ response to ESAT-6 and CFP-10 can simplify the clinician decision to treat an M. tuberculosis-infected but asymptomatic individual? Or alternatively, is it only on the basis of conversion (i.e. increasing levels of IFN-γ responses in two consecutive readings) that a decision can be made?
- Does the specificity and/or cytokine profile of the immune response to the pathogen change over time to include latency antigens? Can responses that are characteristic of the different stages of infection be identified?
Table 1. Summary of human studies examining the correlation between levels of ESAT-6- and CFP-10-induced IFN-γ response and subsequent progress to disease

<table>
<thead>
<tr>
<th>Aim</th>
<th>Study location (principal investigator)</th>
<th>Readout</th>
<th>Refs</th>
<th>Study description</th>
<th>Number of participants</th>
<th>Start–end date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive predictive value</td>
<td>Hollis and Butajira, Ethiopia (T Mark Doherty)</td>
<td>TST, in house ESAT-6-CFP-10 ELISA*</td>
<td><a href="http://www.iphcr.res.in/html/RESEARCH-infectious.htm">www.iphcr.res.in/html/RESEARCH-infectious.htm</a></td>
<td>A prospective household contact study of asymptomatic contacts from households with an active TB case, plus community controls with no known TB contact, recruited locally. Two-year active follow-up at yearly intervals. Households identified through local TB clinics.</td>
<td>500</td>
<td>2003-2006</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>The Netherlands (Martin Borgdorff)</td>
<td>TST, QFT, T-SPOT.TB</td>
<td><a href="http://www.iphcr.res.in/html/RESEARCH-infectious.htm">www.iphcr.res.in/html/RESEARCH-infectious.htm</a></td>
<td>A prospective contact study of asymptomatic immigrant TB contacts, with one-year active follow-up. Participants identified through municipal health services.</td>
<td>800</td>
<td>2005-2008</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>Zambia and South Africa (ZAMSTAR) (Peter Godfrey-Faussett, Helen Ayles and Nulda Beyers)</td>
<td>TST, QFT in tube</td>
<td><a href="http://www.tbhiv-create.org/ZAMSTAR.htm">www.tbhiv-create.org/ZAMSTAR.htm</a></td>
<td>A prospective household contact study in which adult and child contacts of newly diagnosed TB patients will be enrolled and followed for the development of TB over a three-year period.</td>
<td>8000</td>
<td>2007-2010</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>Palamaner Taluk, India (Mario Vaz)</td>
<td>TST, QFT, ESAT-6-based skin test</td>
<td><a href="http://www.iphcr.res.in/html/RESEARCH-infectious.htm">www.iphcr.res.in/html/RESEARCH-infectious.htm</a></td>
<td>A prospective household contact study of asymptomatic contacts from households with an active TB case, with two-year active follow-up at six monthly intervals. Households identified through local TB clinics.</td>
<td>400</td>
<td>2007-2010</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>Worcester, South Africa (William Hanekom)</td>
<td>TST, QFT</td>
<td><a href="http://www.satvi.uct.ac.za/research.htm">www.satvi.uct.ac.za/research.htm</a></td>
<td>A prospective cohort study of adolescents attending local high schools, with two-year follow-up. Cohort split equally between active (three monthly visits) and passive (entry and closeout visits only) arms for follow-up.</td>
<td>8000</td>
<td>2005-2008</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>Palamaner Taluk, India (Mario Vaz)</td>
<td>TST, QFT, ESAT-6-based skin test</td>
<td><a href="http://www.iphcr.res.in/html/RESEARCH-infectious.htm">www.iphcr.res.in/html/RESEARCH-infectious.htm</a></td>
<td>A prospective cohort study of adolescents attending local high schools, with two-year active follow-up. Cohort split equally between active (three monthly visits) and passive (entry and closeout visits only) arms for follow-up.</td>
<td>7500</td>
<td>2007-2010</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>Palamaner Taluk, India (Mario Vaz)</td>
<td>TST, QFT, ESAT-6-based skin test</td>
<td><a href="http://www.iphcr.res.in/html/RESEARCH-infectious.htm">www.iphcr.res.in/html/RESEARCH-infectious.htm</a></td>
<td>A prospective cohort study of all newborns recruited through the pregnancy registration system and followed actively by household visits and TB clinic surveillance for two years after birth.</td>
<td>4800</td>
<td>2007-2010</td>
</tr>
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*ELISA, enzyme-linked immunosorbent assay.

the only study that was designed to compare directly the predictive value of the two IGRA assays commercially available. The final study in this group includes a novel skin test in which ESAT-6 has replaced PPD, in a way analogous to that used for the in vitro tests (www.iphcr.res.in/html/RESEARCH-infectious.htm).

The contact studies will be supplemented by larger cohort studies to determine negative predictive values (www.satvi.uct.ac.za/research.htm and www.iphcr.res.in/html/RESEARCH-infectious.htm). Study six and seven listed in Table 1 will enroll healthy 12–18 year-olds, thus covering the age range at which cases of pulmonary TB start to increase markedly. On the basis of earlier data, between 50 and 100 cases of TB are expected to develop during the course of these two studies, and this low number of TB cases should enable a precise definition of the negative predictive value of these tests. The adult studies will be supplemented by a study in infants in India (www.iphcr.res.in/html/RESEARCH-infectious.htm). All neonates born during the study period will be enrolled via local birth registers and, if they are found to have an identified TB contact or TB-like symptoms, they will receive a full clinical examination including immunodiagnosis. This is a group with high risk for both infection and serious disease, but one in which disease is often hard to diagnose and for which identifying technologies that could speed up diagnosis and identify incipient disease could be expected to save many lives.

These studies will all monitor the value of the test, not merely report a positive or negative result, and are pow-
erred so that they should produce sufficient data within the next few years to establish the efficacy of IGRAs in predicting incipient TB.

A prognostic test for incipient disease – even if it were only moderately accurate – would change current practice markedly and enable the prioritization of treatment to those at highest risk of developing contagious disease. This would enable the best use of scarce resources and, by treating latently infected individuals before they infect others, offer the possibility of breaking the cycle of transmission. Apart from a new vaccine that is active against latent TB, such an approach offers the best hope of achieving the final goal of controlling this longstanding global health emergency.

Concluding remarks

The development of highly specific IGRAs has enabled the accurate identification of TB infection, but it has not been possible so far to translate this into a better – or earlier – identification of contagious disease. A prognostic marker that enables targeted treatment of populations in high endemic regions that are in the process of developing contagious TB would greatly contribute to the control of this global epidemic. We hypothesize that, instead of using IGRAs only in a binary mode (infected and not infected) based on a cut-off value, the magnitude or conversion of an IGRA response might enable the identification of individuals who, although still asymptomatic, are in the process of developing active TB.

There are still several unresolved issues to address before the hypothesis discussed can have any effect on clinical practice (Box 3). However, these issues involve interpretation of results from existing technologies, not the invention of new tools. Although the observation that IFN-γ produced in response to specific antigens increases with increasing bacterial load seems simple enough to apply, ultimately the utility of this approach can be determined only by testing the hypothesis in large-scale cohort studies. This is the next challenge.

Acknowledgement

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References

cattle vaccinated with Mycobacterium bovis BCG and infected with M. bovis. Infect. Immun. 72, 2462–2467
52 Demissie, A. et al. (2004) Healthy individuals that control a latent infection with Mycobacterium tuberculosis express high levels of Th1 cytokines and the IL-4 antagonist IL-4G. J. Immunol. 172, 6936–6943
60 Aiken, A.M. et al. (2006) Reversion of the ELISPOT test after treatment in Gambian tuberculosis cases. BMC Infect. Dis. 6, 66
61 Dheda, K. et al. (2005) Performance of T-cell-based diagnostic test for tuberculosis infection in HIV-infected individuals is independent of CD4 cell count. AIDS 19, 2038–2041

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