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Therapy for Tuberculosis: *M. vaccae*
Inclusion into Routine Treatment

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1. Introduction

Tuberculosis (TB) – an infectious airborne disease – is a re-emerging major global health problem. Each year, there are around nine million new cases of TB, and close to two million deaths among 14 million persons with active clinical disease. All countries are affected, but 85% of cases occur in Africa (30%) and Asia (55%), of which India and China alone represent 35% (World Health Organization, 2011).

Control and cure of tuberculosis has become a very serious problem in recent years because of its association with the Acquired Immune Deficiency Syndrome (AIDS) of the Human Immunodeficiency Virus (HIV) infection and its increasing resistance to generally used antituberculosis drugs (DOTS) (Ferreira Gonçalves, M. J.; Ponce de Leon, A. C. & Fernandez Penna, M. L., 2009).

The HIV epidemic has led to an increase in the incidence of tuberculosis globally, with an important increase in the mortality rate.

Despite this, TB is in most instances, a curable disease with 85% to 90% of people with newly diagnosed drug-susceptible TB cured in six months using combinations of first-line drugs (Nunn, P.; Williams, B.; Floyd, K.; Dye, C.; Elzinga, G. & Raviglione, M., 2005).

Treatment of multidrug-resistant TB (MDR-TB), of which there are around 0.5 million cases each year, is more exigent and the use of newer therapies is required. Cure rates for MDR-TB are lower, typically ranging from around 50% to 70% (World Health Organization, 2011). Extensively drug-resistant TB has been reported in 45 countries, including countries with limited resources and a high TB burden (Mitnick, C. D.; Shin, S. S.; Seung, K. J.; et. al., 2008). When tuberculosis patients (TBP) are co-infected with HIV, have drug-resistant or relapsed TB, the commonly indicated drugs are less effective. It takes between 12-24 months to cure such patients. In these cases second line drugs are required. This involves a significant increase in the cost of therapy, particularly important in poor countries (Arjanova, O. V.; Prihoda, N. D.; Yurchenko, L. V.; Sokolenko, N. I.; Frolov, V. M.; Tarakanovskaya, M. G.; Batdelger, D.; Jirathitikal, V. & Bourinbaiair, A. S., 2011).
Considerable labors are aimed at finding new drugs and vaccines against TB and several immune-based interventions have been proposed as adjunct immunotherapy to conventional treatment.

Thus, TB is considered a re-emerging global public disease, particularly in developing countries, where its incidence has reached alarming proportions. BCG, the only vaccine available for prevention in humans has been inefficient when tested in several field trials. It is therefore an urgent need for new vaccines against tuberculosis to be developed. A better understanding of the immune response induced during infection with *Mycobacterium tuberculosis* (*M. tuberculosis*, *Mtb*) could help in a relatively short time to obtain the desired vaccine against this organism (García, M. A.; Sarmiento, M. E. & Acosta, A., 2009).

TB accounted for one in four deaths among HIV-positive people. Coinfection with HIV leads to difficulties in both the diagnosis and treatment of tuberculosis. Because of the poor performance of sputum smear microscopy in HIV-infected patients, more sensitive tests—such as liquid culture systems, nucleic acid amplification assays, and detection of mycobacterial products in various body fluids—are being investigated. The treatment of coinfected patients requires a combined therapy of antituberculosis and antiretroviral drugs administered concomitantly. Difficulties include pill burden and patient conformity, drug interactions, extending beyond the toxic effects, and immune reconstitution syndrome. Both multidrug-resistant and extensively drug-resistant tuberculosis can spread rapidly among an immunocompromised population, with resulting high mortality rates. Current guidelines recommend starting antiretroviral treatment within a few weeks of antituberculosis therapy for patients with CD4 cell counts <350 cells/µL. However, important problems concerning the drug regimens and timing of antiretroviral therapy still remain unresolved. Ongoing trials may answer many of these questions (Swaminathan. S.; Padmapriyadarsini, C. & Narendran, G., 2010).

The risk of developing tuberculosis is estimated to be between 20-37 times greater in people living with HIV than among those without HIV infection. In 2009 there were 9.4 million new cases of TB, of which 1.2 (13%) million were among people living with HIV and of the 1.7 million people who died from TB 400,000 (24%) were living with HIV. With 13% of new TB cases and 24% of TB deaths being HIV associated, TB is a leading cause of morbidity and mortality among people living with HIV and as such TB remains a serious health risk for people living with HIV. The AIDS and Rights Alliance for Southern Africa (ARASA), in collaboration with WHO hosted a workshop to develop an advocacy toolkit on the *Three I*s for HIV/TB based on WHO policy for healthcare workers, HIV/TB advocates (World Health Organization, 2011). Several factors including previous therapeutic failure, duration of antiretroviral therapy, low CD4+ T-cell count at the initiation of HAART, severe manifestations of disease, low adherence to HAART, and previous treatment interruption are contributory of defective immune reconstitution. It was not definitively demonstrated that age, viral strain/clade, or host genetic factors play a role in these different responses to HAART (Aiuti, F. & Mezzaroma, I., 2006).

The roles of different T-cell subsets which participate in the protector mechanisms against *M. tuberculosis*, thymic function, and cytokines involved in immune response against the bacilli have been investigated. The increased T-cell activation or apoptosis has been associated with a deficiency of effective immunologic response. The continuous virologic
replication in lymphoid tissues, regardless of the undetectable plasma viral load, has been proposed as the fundamental mechanism of cellular activation. This incoherent response probably can be associated with other procedures. Insufficient CD4+ T-cell repopulation of lymphoid tissues may be due to a thymus failure or a defect in bone marrow function. Permanent infection, the toxic effect of antiviral drugs on T- and B-cell precursors, the severity of disease, and the low number of CD4+ T-cells before HAART could also prime for thymus exhaustion and deficient T-cell renewal. Finally, an imbalance in the production of cytokines such as TNF-α, IL-2 and IL-7 may also be crucial for the induction of immune system failure. In patients in which CD4+ T-cells are not increased by HAART, therapeutic tactics aimed at increasing these cells and reducing the risk of infections are needed. IL-2 and/or other cytokines may be of benefit in this scene. Some antiviral drugs may be better than others in immunologic reconstitution. Protease inhibitors may have additional, independent positive effects on the immune system.

There may be little justification for using immunosuppressive agents such as cyclosporine or hydroxyurea in this subgroup of immunologic non responder patients, as these molecules may increase T-cell decline and/or favor susceptibility to infections.

Different mechanisms are involved in the control of the tuberculosis dissemination such as granuloma.

Granulomas, the hallmark of the host response to mycobacterial infection, represent a strategy to physically contain infections that cannot otherwise be eradicated by host defenses. The successive recruitment of cells to the site of *M. tuberculosis* infection forms a physical barrier to mycobacterial propagation and creates a hostile microenvironment in which oxygen tension, pH, and micronutrient supply may all be reduced. In this environment, mycobacteria go through profound alterations in metabolism, biosynthesis, and replication.

This adaptation creates the basis of clinical latency in tuberculosis. Although these sequestered, semidormant bacilli have been much investigated, their paucity makes direct studies in vivo problematic, and multiple researches on this question have been performed such as in vitro oxygen deprivation or intracellular growth in macrophages (Wallis, R. S., 2005).

*M. tuberculosis* is an atypical member of its genus (Stanford, J. L.; Bahr, G. M.; Rook, G. A. W.; Shaaban, M. A.; Chugh, T.D.; Gabriel, M.; Al-Shimali, B.; Siddiqui, Z.; Ghardanis, F.; Shahin, A. & Behbehani, K., 1990). Apparently the capacity of *M. tuberculosis* to cause illness is due not only to the severity of the damage it causes to the host tissue but also to its aptitude to alter the immune response, to one that is inappropriate. It is evident that new alternative and improved treatment options are needed. In consequence, more efficient resources were considered crucial to improve the employed chemotherapy. Significant efforts have been directed at finding new drugs and vaccines against TB. (Small, P. M., 2009). Thus, the immunomodulatory effects of a heat killed *Mycobacterium vaccae* (*Mv*) preparation have been investigated by Stanford, J. et. al. during the 1970’s.

It has been stated that the variation of disease expressions and severity was entirely inherent in the host and his surroundings, disease depending on human genetic control of the immunological response in interaction with environmental factors rather than to bacterial
features. In the environment a free-living mycobacterium, the potentially beneficial *M. vaccae* was recognized as an important source for influencing the human immune response (Stanford, J.L. & Paul, R. C., 1973; Stanford, J. L. & Rook, G. A.W., 1983).

Several studies using an optional new therapy, which involved the addition of a preparation of inactivated *M. vaccae*, were carried out over the last twenty-five years with successful results. In those investigations it has been shown that the killed bacterium or its components are enhancers of the immune responses in opposition to different infectious agents. A number of pre-clinical studies of tuberculosis, bronchospasm, *Trypanosoma cruzi* infection, Leishmaniasis, autoimmune conditions and cancer have been also carried out in mice, demonstrating protection induced by this treatment. (Hernandez-Pando, R.; Pavon, L.; Arriaga, K.; Orozco, H.; Madrid-Marina, V. & Rook, G., 1997; Zuany-Amorim, C.; Sawicka, E.; Manlius, C.; Le Moine, A.; Brunet, L. R.; Kemeny, D. M.; Bowen, G.; Rook, G. & Walker, C., 2002; Valian, H. K.; Kenedy, L.K.A.; Rostami, M.N.; Mohammadi, A. M. & Khamesipour, A., 2008).


2. Clinical trials of adjunctive immunotherapy

The concept of immunotherapy in tuberculosis is not new and many immune based interventions have been investigated as adjuncts to conventional chemotherapy. It is evident that the modulation of immune reactivity can be of great therapeutic value.

**IFN-γ**: As IFN-γ is central to antimycobacterial host defenses; it has been used in several clinical trials of adjunctive immunotherapy. In mice, IFN-γ enhances the mycobactericidal capacity of macrophages by increasing the production of reactive nitrogen intermediates, such as nitric oxide. Condos et al. reported in 1997 the first study of therapeutic IFN-γ in patients with tuberculosis without evident defects on IFN-γ production or responsiveness. In this investigation 500 µg of IFN-γ was administered 3 times per week by aerosol to 5 patients with MDR tuberculosis together with their previous therapy. The study found that sputum smear results became negative and the number of colony-forming units (CFU) tended to fall. Three similar successive studies performed by other investigators showed that differed in IFN-γ type, dose, and route of administration were not successful in inducing any hopeful results. The only randomized, placebo-controlled, multicenter trial of inhaled adjunctive IFN-γ for MDR tuberculosis was done by InterMune in 2000, and the trial was stopped because of a lack of efficacy and the data obtained have never been published. Subsequent investigations have indicated that IFN-γ-induced genes, such as *IP-10* and *iNOS*, are already upregulated in the lung in patients with tuberculosis and that therapeutic aerosol IFN-γ has a relatively minor additional effect. These findings indicate that the fairly
small mycobactericidal capacity of lung macrophages cannot effectively be increased by therapeutic IFN-\(\gamma\) (Wallis, R. S., 2005).

**IL-2** Considering that IL-2 is able to induce T cell replication and is essential for cellular immune function and granuloma formation, a small, unblinded study of 2 low-dose IL-2 regimens (daily or in 5-day “pulses”) in patients with MDR tuberculosis demonstrated that the daily treatment produce a decrease of sputum counts of acid-fast bacilli (Johnson, B. J.; Bekker, L. G.; Rickman, R.; Brown, S.; Lesser, M.; Res, S.; Willcox, P.; Steyn, L. & Kaplan, G., 1997; Wallis, R. S., 2005).

Taking into account this observation, a randomized, double-blind, placebo-controlled study of the effect of IL-2 on conversion of sputum culture was conducted by the Case Western Reserve University Tuberculosis Research Unit (Cleveland, OH) with 110 Ugandan, HIV-uninfected patients with drug-susceptible tuberculosis (Johnson, J. L.; Ssekasanvu, E.; Okwera, A.; Mayanja, H.; Hirsch, C. S.; Nakibali, J. G.; Drzayich Jankus, D.; Eisenach, K. D.; Boom, W. H.; Ellner, J. J. & Mugerwa, R. D., 2003; Wallis, R. S., 2005).

IL-2 or placebo was administered twice daily for the first month of standard therapy. Contrary to expectations, the study found significant delays in clearance of viable \(M.\) \textit{tuberculosis} CFU and conversion of sputum culture results in the IL-2 treatment arm. This report suggested a possible antagonism during combined chemotherapy and immunotherapy for tuberculosis.

**TNF-\(\alpha\)** TNF-\(\alpha\), like IFN-\(\gamma\), is crucial for host defenses against tuberculosis. TNF-\(\alpha\) is a potent proinflammatory cytokine, expressed by macrophages and T cells, (Wallis, R.S.; Amir Tahmasseb, M. & Ellner, J. J., 1990; Black, R. A.; Rauch, C.T.; Kozlosky, C.J.; Peschon, J. J.; Slack, J. L.; Wolfson, M. F.; Castner, B.J.; Stocking, K. L.; Reddy, P.; Srinivasan, S.; Nelson, N.; Boiani, N.; Schooley, K. A.; Gerhart, M.; Davis, R.; Fitzner, J. N.; Johnson, R. S.; Paxton, R. J.; March, C. J. & Cerretti, D. P., 1997; Wallis, R. S., 2005). TNF-\(\alpha\) stimulates the release of inflammatory cytokines, endothelial adhesion molecules, and chemokines, and is considered essential for the formation and conservation of granulomas.


The effects of potent immunosuppressive and/or anti-TNF-α therapies on microbiologic outcomes in tuberculosis have been investigated in two controlled clinical trials. Both were conducted with HIV-1-infected patients who had relatively well-preserved tuberculosis immune responses (based on the presence of high CD4 cell sum and cavitary lung disease). The studies shared a single placebo control arm (for tuberculosis therapy only). Their major aim was to examine the role of TNF-α in the HIV disease progression due to tuberculosis; as such, their main end points were CD4 cell count and plasma HIV RNA load. Nevertheless, both studies prospectively accruce clinical and microbiologic data as indicators of safety.

**High-dose methylprednisolone**: In a comparative study was reported (Mayanja-Kizza, H.; Jones-Lopez, E.; Okwera, A.; Wallis, R. S.; Ellner, J. J.; Mugerwa, R. D.; Whalen, C. C. & Uganda-Case Western Research Collaboration, 2005; Wallis, R. S., 2005) in which 189 subjects received either prednisolone (2.75 mg/kg/day) or placebo during the first month of conventional anti-TB therapy. The prednisolone dosage was selected on the basis of a phase I study indicating that it reduced the rate of tuberculosis-stimulated TNF-α production *ex vivo* by one-half. During the second month, the daily dose was reduced to 0 mg/kg; the average subject received a cumulative dose of 16500 mg. Though there is extensive experience with the use of corticosteroids to diminish tuberculosis symptoms, no previous studies have examined the microbiologic effects of doses of this magnitude. Unexpectedly, one-half of prednisolone-treated subjects had conversion of sputum culture results to negative after 1 month of treatment, compared with 10% of subjects in the placebo arm (*P*<0.001). This effect was bigger than that observed in the landmark study in which the addition of rifampin to a 6-month regimen of streptomycin and isoniazid reduced the relapse rate from 29% to 2% and increased the 2-month sputum culture conversion rate from 49% to 69% (East African-British Medical Research Councils, 1974; Wallis, R. S., 2005). The effect of prednisolone therapy was not due to reduced sputum production, which decreased similarly during treatment in both study arms. There were no serious opportunistic infections. However, prednisolone-treated subjects were more likely to experience other early serious adverse events, including edema, hyperglycemia, electrolyte disturbances, and severe hypertension.

Two other prospective, randomized trials of adjunctive corticosteroids administered at lower doses have observed similar, albeit smaller, effects on the kinetics of conversion of sputum culture results (Bilaceroglu, S.; Perim, K.; Buyuksehir, M. & Celikten, E., 1999; Wallis, Horne, N.W., 1960; R. S., 2005), but a third trial found no effect (Tripathy, S.P.;

There have been no reports of deleterious effects of corticosteroids on microbiologic outcomes in patients with TB.

Early studies of immunotherapy for TB were those of Robert Koch who used injections of “old tuberculin” during the last 10 years of the 19th century (Koch, R., (a) 1890; Koch, R., (b) 1890).

In the early 20th century, Charles Stevens developed “Stevens cure” based on a root called Umckaloabo from South Africa (Sechehaye, A., 1920), recently shown to have potent antimycobacterial activity (Seidel, V. & Taylor, P. W., 2004; Kim, C. E.; Griffiths, W. J. & Taylor, P. W., 2009) and particularly to act as a TNF-α antagonist. In 1904 Friedrich Friedmann developed a turtle tubercle suspension of live Mycobacterium chelonae, which he later called “Anningzochin” which was available until recently from Laves-Arzneimittel GmbH, Barbarastr. 14, A-30952, Ronnenberg, Germany (Friedmann, F., 1904; Hart, C. A.; Beeching, N. J. & Duerden, B. I., 1996; Rosenau, M. J. & Anderson, J., 1915). Although Friedman investigated this mycobacterium species and showed that it was able of confer immunity against tuberculosis, he never considered that it might cause a limited tuberculous process. In the 1920s and 30s, Henry Spahlinger developed a serum from horses immunized with various extracts of tubercle bacilli (Spahlinger, H.; Macassey, L. & Saleeby, C. W., 1934). Even though many investigations supported the success of these different preparations in the treatment of tuberculosis, until very recently immunotherapy has not contributed significantly to its treatment (Sechehaye, A., 1920).

2.1 Immunomodulatory therapy in tuberculosis

Two problems confronted the early attempts of immunotherapy for tuberculosis. First, in the absence of drugs, the immunotherapy was directed towards the total destruction of the tubercle bacillus in the host. Secondly it was then thought that the triggering of immune reactivity in tuberculosis was synonymous with protection. The concept of immune reactivity in mycobacterial infections embraces both protective immunity and also tissue destruction. Distinguishing between them has been a controversial topic for many years (Stanford, J. L. & Rook, G. A.W., 1983). During the last decades it was resolved by the demonstration of two functional subpopulations of helper T cells - TH1 and TH2 (Flynn, J. L. & Ernst, J. D., 2000).

Immunotherapy, is directed to replace an inadequate immune reaction by an appropriate one. The keys to reaching success for immunotherapy arise from the evidence of the considerable variation in the efficacy of vaccination with BCG from one country to another. This is due to prior contact with environmental mycobacteria, which, depending on species, could provide some degree of protection or the antagonistic reaction of tissue necrosis.

Although the search for new vaccines and immunotherapies should continue, investigation of those already available to us is important and is the purpose of our investigations.

For many years it has been accepted that variation in clinical presentation and severity entirely rested in the host and his environment, disease depending on an interaction...
between human genetic control of the immunological response influenced by environmental factors. In the environment are the free-living mycobacteria and it was from amongst them that the potentially beneficial *M. vaccae* and the deleterious *M. scrofulaceum* were identified as important factors influencing the human immune response (Stanford, J. L. & Paul, R. C., 1973; Stanford, J. L. & Rook, G. A.W., 1983). It is now established that genetic diversity within *Mtb*, expressing significant phenotypic differences between clinical isolates, may also be important (Flynn, J. L. & Ernst, J. D., 2000).

BCG is commonly referred to as a vaccine but its effects are very different from those of other vaccines and it is better designated as an immune modulator influencing susceptibility to leprosy (Truoc, L. V.; Ly, H. M.; Thuy, N. K.; Trach, D. D.; Stanford, C. A. & Stanford, J. L., 2001) and malignant melanoma (Grange, J. M.; Stanford, J. L.; Stanford, C. A. & Kölmel, K. F., 2003) as well as tuberculosis. Indeed the concept of a vaccine in its commonly used sense against tuberculosis is a difficult one as illustrated by the difficulty in interpreting the Tuberculin test. A positive Tuberculin test can signify protection, susceptibility and the presence of disease (Stanford, J. L. & Lemma, E., 1983), thus attempting to vaccinate using the species-specific, group iv antigens of *Mtb* (Stanford, J.; Stanford, C.; Stansby, G.; Bottasso, O.; Bahr, G. & Grange, J., 2009) is unlikely to be successful.

3. Immunotherapy with *Mycobacterium vaccae* in the treatment of respiratory disease

3.1 *Mycobacterium vaccae* - a part of our environment

The idea of using a saprophytic mycobacterium that causes no harm, has few side effects and is unable to induce adverse reactions in patients, as a potential immunotherapeutic or vaccine has only been considered during the last few years. *Mycobacterium vaccae* (NCTC 11,659), is a rapidly growing scotocromogenic organism.

First isolated in Germany from the surroundings of cattle, the potential and the importance of the species was first appreciated from field studies in Uganda. A killed suspension of this strain was first added to BCG and investigated as a combined vaccine. Later it was recognized as an immunotherapeutic agent. Immunotherapy with *M. vaccae* improves immune recognition of common mycobacterial antigens and also regulates immune reactions away from necrotic processes. The re-introduction of cellular responsivness to common mycobacterial antigens indicates that *M. vaccae* should induce protective immunity and suppress antagonistic responses. Looked at in the opposite way, failure to make a response to common mycobacterial antigens is an attribute of diseases that should be responsive to treatment with heat-killed *M. vaccae*.

3.2 *M. vaccae*, its adjuvants

The cell walls of all mycobacteria possess potent adjuvant activity attributed to structural lipids and glyco-lipids.

The actions of these adjuvants vary between species. Thus BCG and most species of mycobacteria enhance the type of immune response for which the recipient is already primed, whereas *M. vaccae* and probably a small number of other Actinomycetales enhance the most beneficial cellular immune responses.
3.3 *M. vaccae*, its antigens

*M. vaccae* possesses the group I antigens shared by all mycobacteria and most other aerobic genera of the Actinomycetales.

Some of these antigens are partially cross-reactive with those expressed by mitochondria, when stressed, in animal tissues.

*M. vaccae* lacks the groups II and III antigens, and the group IV antigens of pathogenic mycobacterial species.

All the information obtained from several studies performed in countries around the world, from minor investigations to those made using a placebo control and a properly randomized trial, show that increased cure rates in newly diagnosed TB patients receiving *M. vaccae* is only associated with minimal side effects. Studies of immunotherapy with *M. vaccae* in drug-resistant, relapsed and chronic TB patients have shown that it is also favorable under these conditions. The effects are more readily seen when specific chemotherapy is difficult to establish or ineffective because of low patient compliance, or resistance to multiple drugs.

Progress was suggested from the early work with irradiation-killed organisms in leprosy to the study in London of modulation of tuberculin skin-test responses, and the first comparative trials in The Gambia and Kuwait. In these successive investigations the dose of $10^9$ heat-killed organisms, equivalent to 1 mg wet-weight of bacilli, has been used as a standard dose. A series of small trials in Argentina, India, Nigeria, Romania, South Africa, Uganda and Vietnam have shown that the method can be effective across wide-ranging geographic variability, with South Africa as the only country where almost no effects were recorded (Dlugovitzky, D.; Stanford, C. & Stanford, J., 2011).

Despite this wide geographical efficacy, it is likely that the schedule of treatment with *M. vaccae* should change with different environments. Thus single doses were effective in the Gambia, Nigeria, Kuwait, Romania and the UK, but further South in Africa the environment may necessitate multiple doses, just as some diseases such as cancer require repeated doses to overcome the drive towards Th2 exerted by the tumour.

Numerous studies have shown that certain patterns of cellular immunity are associated with active disease and others are associated with health and recovery from disease. Modulating the immune response from the one to the other is now possible with *M. vaccae* and this chapter records its successful achievement (Ottenhoff, T.H.; Verreck, F. A. & Lichtenauer-Kaligis, E. G., 2002; Dlugovitzky, D.; Torres-Morales, A.; Rateni, L.; Farroni, M.A.; Largacha, C.; Molteni, O. & Bottasso, O.A., 1997).

3.4 Our initial studies on immune response against *M. tuberculosis*

The purpose of the early series of studies that we have carried out to investigate the immune response of patients with pulmonary tuberculosis has been to make steps towards immunotherapy as an effective addition to standard short-course chemotherapy and to identify proper *in vitro* alternative markers of successful treatment for its evaluation. A good deal of the immunological work on TB has been done on murine models – animals that have...
short lives and do not normally suffer from this disease. And in consequence we wanted to make use of appropriate methods for and related to human patients. Initial studies in our laboratory in Rosario, Argentina, have shown that the changes in cellular immune response in pulmonary tuberculosis patients are related to the severity of disease and to the administration of tuberculosis chemotherapy. We showed that increased levels of IL-8 in the pleural exudates of patients with pulmonary tuberculosis, in comparison with those patients with pneumonia-associated pleural effusions, was associated with different levels of expression of CD3, CD4, CD19, CD25 and CD68 markers on their cells (Dlugovitzky, D.; Rateni, L.; Torres-Morales, A.; Ruiz-Silva, J.; Piñésky, R.; Canosa, B.; Molteni, O. & Bottasso, O., 1997; Caruso, A. M.; Serbina, N.; Klein, E.; Triebold, K.; Bloom, B. R. & Flynn, J. L., 1999). This data suggested that increased IL-8 levels in pleural effusions plays a key role in initiation and maintenance of inflammatory reactions.

Patients with moderate to severe pulmonary tuberculosis showed a marked and significant decrease in their circulating levels of cells bearing these phenotypes when compared with those of healthy persons, with patients with pneumonia-associated pleural effusions or with patients with mild pulmonary tuberculosis. Differences between the levels of these cell markers on pleural and peripheral T-cells from pulmonary tuberculosis patients may be the consequence of an incursion of T-lymphocytes from the circulatory system to the pleural cavity, probably linked to the presence of chemokines within the pleural fluid including IL-8 (Fulton, S. A.; Reba, S. M.; Martin, T. D. & Boom, W. H., 2002).

In other assays in pulmonary tuberculosis, circulating immune complexes and the main peripheral blood T-cell subsets were evaluated (Dlugovitzky, D.; Luchesi, S.; Torres-Morales, A.; Ruiz-Silva, J.; Canosa, B.; Valentini, E. & Bottasso, O., 1995). This showed that immune complex levels in cases with severe disease are significantly higher, and expression of CD4 on T lymphocytes significantly lower than in cases of mild disease (Fiorenza, G.; Farroni, M. A.; Bogué, C.; Selenscig, D.; Martín Lamas, D. & Dlugovitzky, D., 2007). Diverse studies of our group helped to explain the effective cellular immune response detected in less severe tuberculosis cases and simultaneously, the impaired cell-mediated immune response in severe cases. Several immune mechanisms within cell-mediated immunity generate a multifaceted response involving activated macrophages, T cells, and cytokines directed to manage mycobacterial infection. Other cell populations also take part in the immune response against mycobacteria and may be important in the development of the disease (Dlugovitzky, D.; Torres-Morales, A.; Rateni, L.; Farroni, M. A.; Largacha, C.; Molteni, O. & Bottasso, O. A., 1999; Dlugovitzky, D.; Bay, M. L.; Rateni, L.; Urizar, L.; Rondelli, C. F.; Largacha, C.; Farroni, M. A.; Molteni, O. & Bottasso, O. A., 1999; Dlugovitzky, D.; Bay, M. L.; Rateni, L.; Fiorenza, G.; Vietti, L.; Farroni, M. A.; Bottasso, O. A., 2000).

Polymorphonuclear neutrophils (PMN) are the professional phagocytes first at the site of bacterial invasion and are set to play a protective role in opposition to M. tuberculosis in the early phase of infection controlled by T lymphocytes. Although recruitment of neutrophils to bronchoalveolar spaces has been described during active human tuberculosis and associated with local chemokine expression, it has not been clarified whether neutrophils have direct bactericidal or immunologic functions. In vitro studies suggest that human neutrophils are mycobactericidal and are activated by soluble mycobacterial antigens (Fiorenza, G.; Bottasso, O. A.; Rateni, L.; Farroni, M. A. & Dlugovitzky, D., 2003).
Several mechanisms including phagocytosis of bacteria and the subsequent generation of reactive oxygen intermediates during oxidative bursts are considered important instruments for destruction of mycobacteria (Jones, G. S.; Amirault, H. J. & Andersen, B. R., 1990). Several findings demonstrated a significant alteration in PMN functions in pulmonary tuberculosis. Production of reactive oxygen intermediates was reduced in severe disease and was significantly increased by antituberculosis chemotherapy (Denis, M. J., 1991). Recognition of \textit{Mtb} by phagocytic cells leads to cell activation and production of cytokines, which in itself leads to further activation and cytokine production in a complex process of regulation and cross-regulation (Denis, M. J., 1991). Thus phagocytic cells are thought to contribute to the control of infection through the production of chemokines (Appelberg, R.; Castro, A. G.; Gomes, S.; Pedrosa, J. & Silva, M. T., 1995), the induction of granuloma formation (Riedel, D. D. & Kaufmann, S. H., 1997) and the transference of their own microbialic molecules to infected macrophages (Ehlers, S., 2003). Levels of circulating cytokines correlate significantly with the severity of the disease, antibody concentration and the reduction of Th1 activities. We evaluated plasma cytokines of type-1 and type-2 in relation to humoral and cell-mediated responses in patients with different amounts of lung damage and with different clinical symptoms of tuberculosis. We found that patients with pulmonary tuberculosis of different levels of severity have higher serum levels of IFN-\gamma, IL-2, IL-4 and IL-10 when compared with those of healthy controls. Mean titers of IFN-\gamma, and IL-2, in mild and moderate patients were found to be greater than in those with severe disease, whereas moderate and advanced patients showed higher levels of IL-4 in comparison with mild cases. Raised levels of interleukin-10 were more prevalent in advanced disease, and statistically different from those in patients with mild disease. This cytokine pattern would explain the effective cellular immune responses found in patients with less severe tuberculosis in comparison with those of patients with advanced disease in whom cellular immunity is seriously damaged (Dlugovitzky, D.; Luchesi, S.; Torres-Morales, A.; Ruiz-Silva, J.; Canosa, B.; Valentini, E. & Bottasso, O., 1995).

We investigated the relationship between the competence of lymphocytes to proliferate and induce cytokine synthesis in vitro, in response to stimulation with antigens, and the amount of pulmonary involvement in tuberculosis patients. Higher levels of IFN-\gamma compared with IL-4 in culture supernatants of Peripheral Blood Mononuclear Cells (PBMC) stimulated with \textit{Mtb} antigens were observed in patients with mild tuberculosis (Bay, M. L.; Dlugovitzky, D.; Urizar, L., 1997). To amplify these results we assessed in vitro the synthesis of the cytokines - transforming growth factor beta (TGF-\beta) and IL-1\beta. Reduced concentrations of IFN-\gamma and IL-4 and an increased synthesis of TGF-\beta were observed in patients with moderate tuberculosis in comparison with those with mild disease.

In patients with severe disease, PBMC synthesize the highest levels of IL-4 and TGF-\beta, with low levels of IFN-\gamma synthesis, suggesting that in these cases an expressed Th2-type response suppresses the Th1 reaction in vitro (Dlugovitzky, D.; Bay, M. L.; Rateni, L.; Urizar, L.; Rondelli, C. F.; Largacha, C.; Farroni, M. A.; Molteni, O. & Bottasso, O. A., 1999).

Rook \textit{et al} confirmed this type of response and demonstrated strong links between IL-4 and TGF-\beta. In their studies PBMC from patients with the most advanced TB showed the highest release of both IL-4 and TGF-\beta (Rook, G. A. W.; Lowrie, D. B. & Hernandez-Pando, R., 2007; Hernández-Pando, R.; Aguilar, D.; Orozco, H.; Cortez, Y.; Brunet, L. R. & Rook, G. A., 2008).
The immune system generally responds in a regulated way to microbes and eliminates them, but it does not respond to self-antigens unless regulatory mechanisms are impaired and unresponsiveness or tolerance to self-antigens is not maintained (Van Parijs, L. & Abbas, A. K., 1998). Such a disharmonic immune response may result in several autoimmune diseases. The altered Th1 and Th2 expression found in severe tuberculosis patients may lay them open to such diseases. To investigate this we inquired into the incidence of arthritic manifestations (Poncet’s disease) in such patients. The kinds and distribution of T cell subsets in these cases and the presence of several auto-antibodies were also investigated. In the detected arthritic cases an augmented number of CD4+ T cells was observed in comparison with CD8+ T cells and autoantibodies were detected. However, we could not rule out the presence of unknown factors that might be partly responsible for the reactive arthritis. (Dlugovitzky, D.; Torres, A.; Hourquescos, M. C.; Svetaz, M. J.; Quagliato, N.; Valentini, E.; Amigot, B.; Molteni, O. & Bottasso, O., 1995; Kroot, E. J.; Hazes, J. M.; Colin, E. M. & Dolhain, R. J., 2006)

In addition to these results it has been demonstrated that CD8+ cells also synthesize IL-4, and this cytokine profile correlates with cavitation (van Crevel, R.; Karyadi, E.; Preyers, F.; Leenders, M.; Kullberg, B. J.; Nelwan, R. H. & van der Meer, J. W., 2000).

Several studies have established that continuous IL-12 production is necessary for maintenance of the pulmonary Th1 cells required for host control of persistent Mtb infection and suggest that breakdown of this mechanism could be a contributing factor in the reactivation of disease (Feng, C. G.; Jankovic, D.; Kullberg, M.; Cheever, A.; Scanga, C. A.; Hieny, S.; Caspar, P.; Yap, G. S. & Sher, A., 2005).

The capacity of IL-12 to induce the differentiation of naive CD4+ T cells into Th1 cells and stimulate production of IFN-γ was investigated by studying the capacity of PBMNC from patients with different severities of tuberculosis to produce IFN-γ, IL-4 and IL-12. The production of IFN-γ is increased in patients with less severe tuberculosis rather than in those with severe disease (Dlugovitzky, D.; Bay, M. L.; Rateni, L.; Fiorenza, G.; Vietti, L.; Farroni, M. A. & Bottasso, O. A., 2000). In this study we also demonstrated that Tumour Necrosis Factor-alpha (TNF-α) production is increased in moderate and advanced tuberculosis patients and nitrite levels are augmented in severe tuberculosis cases, significantly different from those of healthy controls (Feng, C. G.; Jankovic, D.; Kullberg, M.; Cheever, A.; Scanga, C. A.; Hieny, S.; Caspar, P.; Yap, G. S. & Sher, A., 2005; Trinchieri, G., 2003; Casanova, J. L. & Abel, L., 2002; Fieschi, C. & Casanova, J. L., 2003). Several mycobactericidal and immunoregulatory mechanisms are developed by host cells including the production of NO and inflammatory cytokines, through extra- and intra-cellular mediated cytotoxicity, or cytostatic activity, which restrain a variety of pathogens including Mtb (Vouldoukis, I.; Riveros-Moreno, V.; Dugas, B.; Ouaz, F.; Bécherel, P.; Debré, P.; Moncada, S. & Mossalayi, M. D., 1995; Kitabatake, A; Sakuma, I., 1999).

Our results suggest that the synthesis of nitric oxide by the host is not always associated with a favourable evolution since higher levels are synthesized in cases with severe tuberculosis. Other authors propose that this event may be related to the interaction of several cytokines and/or eicosanoids through disease related induction of immune reactions (Tunçtan, B.; Okur, H.; Çalışır, C. H.; Abacioglu, H.; Cakıcı, I.; Kanzik, I. & Abacioglu, N., 1998). It has also been shown that an inverse correlation exists between TNF-
α, TGF-β and NO concentrations in serum, behavior that could be a predominantly TGF-β effect (Fiorenza, G.; Rateni, L.; Farroni, M A.; Bogué, C. & Dlugovitzky, D. G., 2005).

The production of NO, TNF-α and IL-12 by the peripheral blood monocytes of patients suffering from MDR-TB has been investigated by others and NO production was found to be significantly depressed. A sub-cellular fraction of Mtbo whole cell lysate, culture filtrate protein or lipoarabinomannan induced higher concentrations of NO to be released by peripheral blood monocytes from newly diagnosed tuberculosis patients in comparison with those from MDR-TB patients (Sharma, S.; Sharma, M.; Roy, S.; Kumar, P. & Bose, M., 2004).

**Respiratory diseases treated with M. vaccae to date have been:** Pulmonary tuberculosis, Bronchial aspects of hay-fever, Bronchial asthma, Lung cancer

**Related conditions under investigation** Chronic obstructive pulmonary disease (COPD) in man and recurrent airway obstruction (RAO) in horses.

- Arterial disease.
- Myocarditis.

(These are being investigated with related bacterial immuno-modulators)

**4. Salient results of immunotherapy studies in treatment of tuberculosis**

In a preliminary study conducted some years ago in Carrasco Hospital, 14 pulmonary tuberculosis patients receiving heat-killed, borate-buffered *M. vaccae* (SRL172) had a better outcome than did 7 patients who received placebo (Vacirca, A.; Dominino, J. C.; Valentini, E; Bottasso, O. & Stanford, J., 1993. Subsequently we have carried out three small studies of this immunotherapy. All were performed in newly diagnosed, moderate to severe, pulmonary tuberculosis patients. In the first of these, the effects of a single dose given by intradermal injection was monitored to evaluate the potential of the approach and assess the value of the selected investigations. Levels of IFN-γ rose and TNF-α fell, with decreases also in levels of IL-4, IL-10 and anti-hsp 70 kDa (Dlugovitzky, D.; Bottasso, O.; Dominino, J. C.; Valentini, E.; Hartopp, R.; Singh, M.; Stanford, C. & Stanford, J., 1999) (Table 1). From subsequent researches performed by our group, we concluded that immunotherapy with *M. vaccae* promotes changes in the immune response and improves patient recovery.

![Plasma levels of IL-4](https://www.intechopen.com)

**Fig. 1.** Plasma levels of interleukin-4 for patients treated with placebo, intradermal or oral *Mycobacterium vaccae*. id: Intradermal, o: oral.
## Table 1. Result of ELISA absorption measurements. ± SE of IgG antibodies to heat shock proteins 65 kD and 70 kD and of the serum cytokines interleukin-4 (IL-4), interleukin-10 (IL-10), interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) in pg/ml

<table>
<thead>
<tr>
<th></th>
<th>Immunotherapy</th>
<th>Placebo</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hsp 65 kD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission</td>
<td>0.30±0.03</td>
<td>0.23±0.04</td>
<td>0.20±0.04⁣⁺</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.001</td>
<td>P&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>After 1 month</td>
<td>0.19±0.02</td>
<td>0.2±0.02</td>
<td></td>
</tr>
<tr>
<td>% decrease</td>
<td>32±5.5</td>
<td>P&lt;0.05</td>
<td>15.6±5.4</td>
</tr>
<tr>
<td><strong>Hsp 70 kD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission</td>
<td>0.59±0.05</td>
<td>0.62±0.06</td>
<td>0.25±0.06⁣⁺</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.001</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>After 1 month</td>
<td>0.31±0.03</td>
<td>P&lt;0.001</td>
<td>0.53±0.06</td>
</tr>
<tr>
<td>% decrease</td>
<td>48±3.6</td>
<td>P&lt;0.0001</td>
<td>17±2.6</td>
</tr>
<tr>
<td><strong>IL-4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission</td>
<td>685±77</td>
<td>586±58</td>
<td>69±9</td>
</tr>
<tr>
<td>After 1 month</td>
<td>342±36</td>
<td>P&lt;0.02</td>
<td>495±58</td>
</tr>
<tr>
<td>% decrease</td>
<td>47±4.7</td>
<td>P&lt;0.001</td>
<td>15±4.9</td>
</tr>
<tr>
<td><strong>IL-10</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission</td>
<td>3800±302</td>
<td>3863±270</td>
<td>35±6</td>
</tr>
<tr>
<td>After 1 month</td>
<td>2292±187</td>
<td>P&lt;0.002</td>
<td>3663±286</td>
</tr>
<tr>
<td>% decrease</td>
<td>38±5.3</td>
<td>P&lt;0.007</td>
<td>16.5±5.8</td>
</tr>
<tr>
<td><strong>IFN-γ</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission</td>
<td>524±76</td>
<td>553±57</td>
<td>157±7</td>
</tr>
<tr>
<td>After 1 month</td>
<td>1172±173</td>
<td>P&lt;0.05</td>
<td>700±99</td>
</tr>
<tr>
<td>% increase</td>
<td>124±21</td>
<td>P&lt;0.005</td>
<td>41±20</td>
</tr>
<tr>
<td><strong>TNF-α</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>On admission</td>
<td>86±6</td>
<td>85.5±3.3</td>
<td>None detectable⁣⁺</td>
</tr>
<tr>
<td>After 1 month</td>
<td>52±5</td>
<td>P&lt;0.001</td>
<td>74±3.7</td>
</tr>
<tr>
<td>% decrease</td>
<td>38±3.6</td>
<td>P&lt;0.01</td>
<td>14±4.1</td>
</tr>
</tbody>
</table>

* Different form immunotherapy group. P<0.02
⁺ Different from immunotherapy and placebo groups. P<0.001 n.s., not significant

Table 1. Result of ELISA absorption measurements. ± SE of IgG antibodies to heat shock proteins 65 kD and 70 kD and of the serum cytokines interleukin-4 (IL-4), interleukin-10 (IL-10), interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) in pg/ml.

Salient results of serology and cell culture supernatant immunology of data drawn from all three studies of *M. vaccae*, injected or oral are shown. With the rise in serum IFN-γ and fall in serum IL-4 (Fig. 1), is seen a reduction in production of IgG antibodies to stress proteins and a reduction in circulating TNF-α (Fig. 2). Culture supernatants of both PBMC and PMN cells showed steady increases with time of IFN-γ and IL-2, and as the disease regressed production of TNF-α fell steeply.

In addition to these results it has been demonstrated that CD8+ cells also synthesize IL-4, and this cytokine profile correlates with cavitation (van Crevel, R.; Karyadi, E.; Preyers, F.; Leenders, M.; Kullberg, B. J.; Nelwan, R. H. & van der Meer, J. W., 2000).
Respiratory Burst expression (Fig. 3) increased in the successives samples of intradermal and oral *M. vaccae* treated TBP, and it was higher in those patients receiving oral *M. vaccae* than in those receiving intradermal *Mv* in relation to placebo recipients.

IFN-γ (Fig. 4), TNF-α (Fig. 5), IL-6 and IL-10 (Fig. 6) levels in PBMC and PMN culture supernatants. and IL-6, IL-10 (Fig. 7) and TNF-α values in plasma (Fig. 2) also increased more in those receiving oral *M. vaccae* than in intradermal *M. vaccae* recipients. The immunomodulatory effect of both oral *M. vaccae* and intradermal *M. vaccae* treatments was shown both by Respiratory Burst expression and cytokine increase in culture supernatants and plasma, with oral therapy the more effective.

Fig. 2. Plasma TNF-α values for patients treated with placebo, intradermal or oral *Mycobacterium vaccae*. id: Intradermal, o: oral.

Fig. 3. Respiratory index for polymorphonuclear cells and for mononuclear cells, calculated by dividing the mean fluorescence value for H37Rv-stimulated cells by the mean fluorescence value for unstimulated cells.
Fig. 4. IFN-γ levels in the supernatants of cultured cells
Fig. 5. TNF-α levels in the supernatants of cultured cells
Fig. 6. IL-10 levels in the supernatants of cultured cells.

The data obtained with all 3 immunotherapy regimens produced significantly better results than those achieved with chemotherapy alone.

The data show that the addition of oral capsules of *M. vaccae* to a DOTS program in the treatment of drug-sensitive tuberculosis would have the clinical advantages of hastening sputum negativity and recovery from the disease. Such a strategy would reduce new infections, both among contacts and in the community at large and might allow shortening of the treatment period.

Fig. 7. Plasma IL-10 values for patients treated with placebo, intradermal or oral *Mycobacterium vaccae*. id: Intradermal, o: oral.
The mechanism of action of injected *M. vaccae* is thought to be via immunomodulating adjuvant activities of the mycobacterial cell envelope. The short amino acid-chain lengths of common mycobacterial antigens and sugars preserved by the borate buffer on dermal dendritic cells (Stanford, J. L. & Grange, J. M., 1974; Stanford, J.; Stanford, C.; Stanisby, G.; Bottasso, O.; Bahr, G. & Grange, J., 2009; Hernández-Pando, R.; Aguilar, D.; Orozco, H.; Cortez, Y.; Brunet, L. R. & Rook, G. A., 2008) act to direct the modulated response to the sites of expression of host-cell stress proteins (Matzinger, P., 1994). This may be especially to those stress proteins of mitochondrial origin showing homologies with the common antigens of mycobacteria (Cohen, I. R. & Young, D. B., 1991) and the bacteriometric sugars expressed by rapidly replicating cells. The results reported in animals (Stainsby, K. J., 1989; Zuany-Amorim, C.; Sawicka, E.; Manlius, C.; Le Moine, A.; Brunet, L. R.; Kemeny, D. M.; Bowen, G.; Rook, G. & Walker, C., 2002; Hernandez-Pando, R.; Pavon, L.; Arriaga, K.; Orozco, H.; Madrid-Marina, V. & Rook, G., 1997) and our observations in man suggest that the same, or similar, beneficial immunomodulation can be stimulated via the mucosal immune system, where the multifold (M) cells (Gebert, A.; Rothkotter, H. J. & Pabst, R., 1996) of the intestine play a part analogous to that of the dermal dendritic cells in the skin.

In addition to the reported immunological results, the bacteriological findings indicated that the conversion to negative of both sputum smear and culture was significantly enhanced by injected or oral immunotherapy with *M. vaccae* above that achieved by chemotherapy alone.

Although this study deals with drug-sensitive tuberculosis, the reported immunological changes, which are paralleled in both injected and oral studies, allow confidence that the oral formulation will prove of similar efficacy in patients infected with drug-resistant bacilli (Stanford, J. L.; Stanford, C. A.; Grange, J. M.; Lan, N. N. & Etemadi, A., 2001). This would accord with our earlier experience of intradermal injection of *M. vaccae* in patients with a variety of drug resistance (Farid, R.; Etemadi, A.; Mehvar, M.; Stanford, J. L.; Dowlati, Y. & Velayati, A. A., 1994; Corlan, E.; Marica, C.; Macavei, C.; Stanford, J. L. & Stanford, C. A., 1997) in many countries (Stanford, J. L.; Stanford, C. A.; Grange, J. M.; Lan, N. N. & Etemadi, A., 2001), where excellent clinical results have already been obtained in the treatment of MDR-TB. As the immunological data obtained in the oral study, albeit with a more intensive schedule, paralleled that of the intradermal study it is logical to suppose that MDR-TB could also be treated successfully with oral *M. vaccae*. The properly functioning immune system recognizes and regulates the appropriate response to disease and would be capable of destroying both drug-sensitive and drug-resistant organisms quite impartially.

This approach to treatment at the outset would allow initial resistance to be treated early and at the same time discourage secondary resistance due to treatment inadequacy. As an example, at the chest hospital in Ho Chi Minh City, Vietnam, 12 patients accepted for immigration into the USA were subsequently found to be infected with highly drug-resistant organisms. They failed to be cured with the latest drugs provided from the USA, but following up to twelve injections of *M. vaccae* (administered on the initiative of the staff of the Chest Hospital) all were cured and allowed into the USA. Similar results have been obtained in several countries (Stanford, J. L.; Stanford, C. A.; Grange, J. M.; Lan, N. N. & Etemadi, A., 2001).
5. Conclusions of the 3 studies

The inclusion of immunotherapy with SRL-172 improved the results of DOTS chemotherapy and it led us to the conclusion that this therapy might allow a reduced period of chemotherapy without loss of efficacy and help to prevent the development of multi-drug-resistance. The three small studies of immunotherapy with heat-killed, borate-buffered, M. vaccae for drug-susceptible pulmonary TB developed in the department in Medicine Faculty of Rosario have produced successful results. It was demonstrated that the transformation of a Th2 response, towards Th1, is accompanied by clinical, bacteriological and radiological improvement in the immunotherapy recipients.

The results showed that three injected doses of M. vaccae were more effective than a single dose, and that ten oral doses scattered throughout the period of chemotherapy, were as effective, or more so, than was the injected preparation. The reagent deserves formal field trials, particularly in patients infected with highly drug-resistant strains of tubercle bacilli.

In conclusion, we have found that immunotherapy with M. vaccae in TB, whether by injection or by the oral route, hastens recovery, bacteriologically, clinically and radiologically, as well as returning immune responses towards those of healthy persons.

6. References


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Mycobacterium tuberculosis in an attempt to understand the extent to which the bacilli has adapted itself to the host and to its final target. On the other hand, there is a section in which other specialists discuss how to manipulate this immune response to obtain innovative prophylactic and therapeutic approaches to truncate the intimal co-evolution between Mycobacterium tuberculosis and the Homo sapiens.

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