Tuberculosis: Experimental Models, Innovations, and Challenges

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Abstract

Tuberculosis (TB) is among the top ten killer diseases and remains the number one cause of death due to infection. A major bottleneck in TB research remains the availability of suitable animal models to understand the disease pathogenesis and progression, immune responses elicited by the pathogen, new molecule and vaccine testing, development and validation of diagnostics, and genetics of the pathogen about these myriad aspects of the infection. Although a broad range of organisms has been employed in TB research, most of the studies have been performed in mice due to cost-effectiveness, ease of handling, availability of immune reagents, and genetically-modified strains as well as ease of availability of strains with a relatively uniform genetic background. The commonly used mouse strains do not mimic human disease progression characteristics. More relevant models like guinea pig and macaque are not frequently employed due to high costs and/or lack of availability of immune reagents. Several models involving alternate, non-pathogenic mycobacteria have been evaluated in mammals and non-mammalian species like fish, frogs, nematodes, and protists. In vitro models such as macrophage infection and co-culture systems provide insights into drug activity and host cell-mycobacterial interactions. An even more straightforward approach relies on using mycobacterial cultures to evaluate drug sensitivity and drug activity. However, the in vitro models suffer from a

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shortcoming that compounds which require metabolic activation by enzymes, such as prodrugs and drug conjugates, could be falsely rejected as being inactive. This is because the cells/tissues employed for in vitro assays may not express the activating enzymes.

Keywords

Experimental models · In vitro · In vivo · Latent tuberculosis · Tuberculosis

28.1 Introduction

Tuberculosis (TB) continues to inflict mankind since time immemorial and has assumed even more significance in recent decades. TB is the number one killer in the world due to a bacterial infection. TB is a deadly disease that has killed more people than any other infectious disease. According to the World Health Organization (WHO), nearly 10 million people were infected and 1.5 million died in the year 2018 alone making TB one of the top 10 causes of death globally. Clinically, pulmonary TB caused by *Mycobacterium tuberculosis* is the most prevalent among non-HIV-positive patients, while *M. tuberculosis* and *M. avium* complex infection occurs in HIV-positive patients (Iacobino et al. 2020).

Despite efforts from various resources, the dream of TB elimination remains a distant reality. To accomplish it, sustainable and affordable programs are needed with anti-TB measures. To accomplish this task, three areas, vaccination, diagnosis, and treatment, need to be explored. Advancing these areas requires a deeper knowledge of host-pathogen interactions and better experimental models are needed. Animal models of TB are important tools for the assessment of the efficacy of vaccines and potential drug candidates as well as the identification and validation of disease biomarkers (Cardona and Williams 2017; Zhan et al. 2017; Bucsan et al. 2019; Gong et al. 2020).

Treatment of TB is compounded by the long duration of treatment (6 months to 2 years) and the side effects of anti-TB drugs. Both factors contribute to low patient compliance resulting in the re-emergence of infection after an initial recession as well as the emergence of multidrug-resistant strains. Therefore, the focus of new drug development has been to develop drugs that reduce treatment duration, have lesser side effects, and are active against multidrug-resistant strains. The long treatment duration is considered largely due to the continuous backflow of latent TB bacilli; hence, drugs active against latent TB bacilli are desirable (Defraine et al. 2018; Cohen et al. 2019). After a lull of over half a century, two new anti-TB drugs were approved—bedaquiline (2012) and delamanid (2013) followed by proteomanid (2019). Additionally, investigational molecules like diarylquinolines, fluoroquinolones, nitroimidazoles, and oxazolidinone are in clinical development with a large proportion being that of oxazolidinone (AZD5847, contezolid/MRX-1, sutezolid, delpazolid). Drug repurposing is yet another approach that has resulted in the identification of linezolid and auranofin as treatments for TB. Pretomanid is a novel compound developed by TB Alliance which has been granted authorization

(Khare et al. 2019). The activity of anti-TB drugs has been shown to depend on the immune status of the host which results in lower drug efficacy in immune-compromised patients. Hence, another approach for treatment has been to stimulate the host immune system for bacterial clearance, either as a standalone therapy or in combination with anti-mycobacterial agents (Ahmad et al. 2010, 2011; Gupta et al. 2012; Zhang et al. 2020). These approaches include immunotherapy with small molecules (Mourik et al. 2017; Bryk et al. 2020; Rao Muvva et al. 2021) or microbes and microbial products (Chaturvedi et al. 1999; Hernandez-Pando et al. 2008; Rodrigues et al. 2015). Drug repurposing of existing drugs is yet another viable alternative for the discovery of immune modulator compounds for TB (Mishra et al. 2018). We have found that low doses of morphine can protect infected mice from TB, the protection being comparable to standard anti-TB drugs (Singh et al. 2008). Bacillus Calmette-Guerin (BCG), the only approved TB vaccine, can prevent childhood TB but is ineffective in adults. Over a dozen vaccine candidates are in various stages of clinical trials but are years away from commercialization (Kaur et al. 2019; Li et al. 2020). Other targets of anti-TB drugs have focused on inducing autophagy in macrophages (Pelaez Coyotl et al. 2020; Rao Muvva et al. 2021), disruption of mycobacterial biofilms (Wang et al. 2019), and use of efflux pump inhibitors to overcome drug resistance (Grossman et al. 2015; Pieterman et al. 2018; Xu et al. 2018).

The mouse has been predominantly used as an experimental model of active and latent TB following intravenous inoculation or inhalation exposure to the mycobacterium. Guinea pig is considered a better model for pulmonary TB but is not frequently used due to the risk of aerosol transmission to persons handling these animals. Monkeys remain the most relevant models as they mimic several aspects of pulmonary and extrapulmonary TB which are not observed in other models. However, their high cost of maintenance, high inter-group variability, and limited availability of immune reagents are major obstacles to their application (Cardona and Williams 2017; Bucsan et al. 2019; Gong et al. 2020).

Despite the health impact of TB, research in TB has remained slow. This sluggish pace can be attributed to two factors: the pathogenicity of the organism and the slow growth rate of the organism. *Mycobacterium tuberculosis* (Mtb) infects macrophages (primarily alveolar macrophages) and adapts to the hostile intracellular milieu due to a variety of defense mechanisms. TB is primarily a disease of the respiratory system and the cycle of TB infection commences with the release of Mtb-carrying aerosols. A dose of 1–10 Mtb dispersed in the air is likely to cause a risk of transmission. Following their entry into the lung, Mtb are phagocytized by alveolar macrophage cells where they may either be completely cleared by the immune reactions or may reside and proliferate in macrophages. Under suitable conditions, Mtb may divide and invade the epithelial cells as well. Experimental studies in TB require biosafety level 3 laboratories, which are costly to develop and maintain making these unaffordable to most microbiology laboratories (Bucsan et al. 2019; Gong et al. 2020). The slow growth of *M. tuberculosis* makes it extremely difficult to perform studies since chances of microbial contamination are increased during the 1–2 months long incubation period required to observe colonies on agar

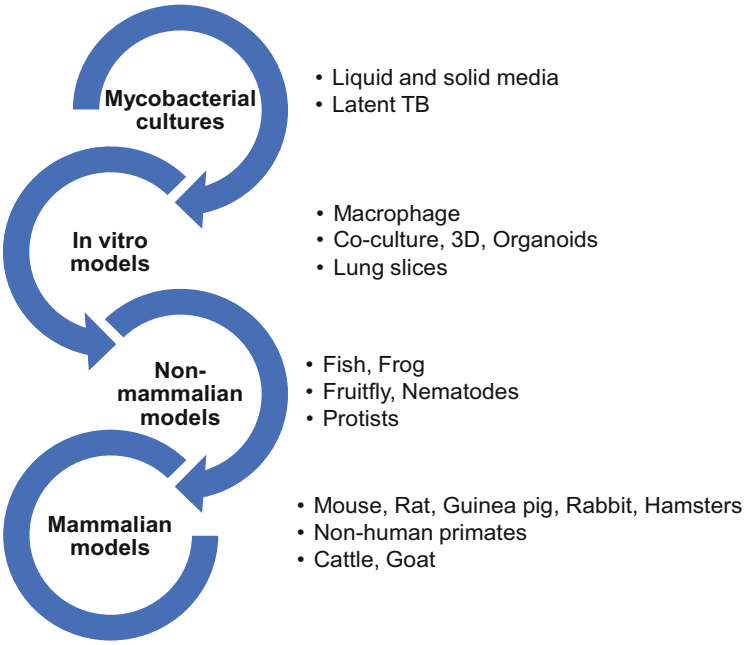

Fig. 28.1 Schematic diagram showing the different experimental models used currently in tuberculosis research

plates. In recent years, models using non-pathogenic and/or fast-growing alternates such as *M. smegmatis* (Jhamb and Singh 2009; Singh et al. 2009; Altaf et al. 2010; Costa et al. 2016; Arthur et al. 2019), *M. fortuitum* (Alim et al. 2017), *M. bovis* BCG (Altaf et al. 2010), *M. aurum* (Gupta et al. 2009; Gupta and Bhakta 2012), and *M. marinum* (Lienard and Carlsson 2017) have been developed to circumvent these issues. The models commonly employed in the laboratory are summarized in Fig. 28.1. Additionally, luminescence- and fluorescence-based methods employing genetically-engineered bacteria expressing luciferase (Zhang et al. 2012; Andreu et al. 2013) or fluorescent proteins (Zelmer et al. 2012; MacGilvary et al. 2019), as well as the use of fluorescent dyes (Amin et al. 2009), have hastened the screening process not only in experimental studies (Durkee et al. 2019) but also antimicrobial sensitivity of clinical isolates for drug therapy decisions (Amin et al. 2009; Cui et al. 2013). Additionally, polymerase chain reaction-based methods have also been evaluated as faster alternates compared to traditional methods based on the colony-forming unit (CFU) counts (Pathak et al. 2012; da Silva et al. 2017; de Knegt et al. 2017).

28.2 In Vivo Models of TB

28.2.1 Mouse Model

The mouse has remained a model of choice to study disseminated and pulmonary TB. Nearly a century ago, murine TB was experimentally induced in mice using bovine strains or BCG (Lewis and Margot 1914; Murphy and Ellis 1914; Grumbach et al. 1967; Collins et al. 1975; Forget et al. 1981), whereas Mtb infection models in mice appeared much later (Youmans and Mc 1945; Martin 1946; Mc et al. 1946; Youmans and Williston 1946). Several inbred strains of mice have been investigated resulting in their classification as susceptible (Balb/c, C57BL/6, B10.A, I/St, SWR) and resistant (C3H/HeCr, A/J, DBA/2, A/Sn) (Pierce et al. 1947; Kelley and Collins 1999; Nikonenko et al. 2000; Turner et al. 2003b); nevertheless, contrasting classification of mouse strains (C3H/HeJ as sensitive and C57BL/6 as resistant) has also appeared in the literature (Chackerian et al. 2001) highlighting the importance of Mtb strain, inoculum size, and route of administration on susceptibility to infection (Actor et al. 1999; Chackerian and Behar 2003). Apart from the inbred strains, outbred strains such as Swiss (Lynch et al. 1965; Lecoeur et al. 1989) and ICR mice (Shkurupy et al. 2020) have also been used which have not been equivocally classified as being susceptible or resistant. The dissemination model requires intravenous injection of millions of CFUs which results in a significant bacterial load in the lungs, liver, and spleen with a small number of bacilli also detectable in other organs and blood. The treatment with test compounds is typically initiated either on the day of inoculation or 24 h post-inoculation and CFU counts in target organs are determined after 1 month of treatment/inoculation (Singh et al. 2008). This model, although convenient for experimental screening of compounds, does not represent the actual pathology of the disease in humans since pulmonary TB is the major manifestation in humans (Cardona et al. 1999). Alternatively, a low-dose aerosol model has been employed which requires exposure of mice to a relatively lower number of bacteria (typically, 50 CFUs) via the inhalation route. The aerosol droplets, owing to their small size, deliver the bacilli in alveoli. After treatment with test compounds, lung CFU counts are determined after 3 or 4 weeks (Kelly et al. 1996; De Groote et al. 2011). A similar approach relies on intratracheal instillation of about a million CFUs in mice which results in the development of aspirating pneumonia but the pathology does not mimic pulmonary TB (Dormans et al. 2004; Eruslanov et al. 2004). Mouse model of pulmonary M. tuberculosis infection exhibits immune responses similar to that observed in humans but the disease characteristics differ significantly. Several pathological hallmarks of TB infection in humans such as caseous necrosis, granulomas, and lung cavitations are not observed in mouse strains (Bucsan et al. 2019). The pathogens traffic intracellularly in murine lungs of commonly used BALB/c and C57BL/6 strains in contrast to observations in DBA/2 and 129/Sv mice. This difference translates into differences in pathological outcomes whereby inflammation ensues in murine models but without development of necrotic lesions (Medina and North 1998; Guirado et al. 2006). On the other hand, the disease is progressive in nature in humans and other

experimental models along with development of necrotic lesions with extracellular bacteria. The susceptibility of mice to infection is also impacted by the strain implying a role of genotype. For example, C57BL/6 mice are resistant compared to BALB/c mice, while C3HeB/FeJ mice exhibit development of necrotic granulomas similar to those observed in humans (Driver et al. 2012; Harper et al. 2012; Lee et al. 2018; Moreira-Teixeira et al. 2020). B6.C3H^{sst1} mice exhibit hypoxic lesions (Kramnik 2008), while CBA/J IL-10 knockout mice develop mature fibrotic granulomas (Cyktor et al. 2013; Bucsan et al. 2019). In recent years, humanized mice have been developed which not only mimic human pathology but also enable study of HIV/TB co-infection as well as anti-mycobacterial drug screening in mice (Calderon et al. 2013; Heuts et al. 2013; Nusbaum et al. 2016; Grover et al. 2017; Arrey et al. 2019; Corleis et al. 2019; Gong et al. 2020; Huante et al. 2020). Mouse strains also differ in their response to BCG and consequent protection from TB. Balb/C mice exhibit higher degree of immune response compared to C57BL/6 mice but afforded comparable protection from Mtb infection (Garcia-Pelayo et al. 2015). In another study, the effect of prior BCG vaccination on protection from Mtb aerosol infection has also been compared in susceptible (C3Heb/FeJ) and resistant (C3H/HeOuJ) mouse strains (Henao-Tamayo et al. 2015).

The commonly used mouse strains have been criticized in recent years as an oversimplification of human pathology since the effects of allelic variations on disease pathology as well as treatment and vaccination effects could not be studied. Recently, collaborative cross (CC) and diversity outbred (DO) models have been developed which could be used to study the effects of allelic variations on TB. CC model is a panel of recombinant inbred mouse strains derived from an eight-way cross. Five parental strains included two used in mouse genetics (C57BL/6J and 129S1/SvImJ) and three models of common diseases (A/J, NOD/ShiLtJ, and NZO/HiLtJ), while three founder strains included wild-inbred strains (CAST/EiJ, PWK/PhJand WSB/EiJ) (Churchill et al. 2004; Noll et al. 2019). CC mice have been shown to be susceptible to Mtb infection (Smith et al. 2016, 2019). The diversity outbred (DO) model was obtained from the same eight strains used to obtain the CC model. However, in contrast to the funnel breeding used in the CC model, the DO model was obtained by extensive inbreeding in these strains resulting in outbred DO strains (Churchill et al. 2012). DO model developed at Jackson Laboratories was obtained by using 160 CC mice as founder strains. Pulmonary infection of DO mice with Mtb resulted in super-susceptible, susceptible, and resistant phenotypes (Niazi et al. 2015; Tavolara et al. 2020). BCG vaccination of DO mice followed by aerosol exposure to Mtb also exhibited different intensities of TB infection (Kurtz et al. 2020).

Models of extrapulmonary TB have also been developed in mice representing brain infection. These models typically employ intravenous injection or intratracheal delivery of Mtb strains in Balb/C mice which disseminate to the brain and other organs (van Well et al. 2007; Be et al. 2008; Hernandez Pando et al. 2010; Gupta et al. 2016; Husain et al. 2017). These studies have revealed that Mtb dissemination to the brain is Mtb strain/genotype-dependent. Another model of TB meningitis relies on the intracerebral injection of Mtb which offers two advantages over other

models of central nervous system (CNS) infection. First, the infection is localized to the brain unlike in other models where the infection is disseminated to other organs. Second, the Mtb strains which do not cause meningitis in other models can cause brain infection; thus, a very broad range of Mtb strains could be evaluated (van Well et al. 2007). The dissemination model has also been employed to model intraocular (Abhishek et al. 2019; Basu et al. 2020) and musculoskeletal TB in mice (Kager et al. 2014). Another model employs $NOS_2-/-$ mice where intradermal injection of one thousand CFUs in the ear dermis resulted in hypoxia and granuloma formation in the lungs along with significant bacillary load in the spleen (Reece et al. 2010; Kupz et al. 2016).

Latent TB is yet another challenging area that suffers from a lack of suitable models. A mouse model of latent TB called the Cornell mouse model is the most commonly employed model. The original model required infection of mice with Mtb (by intravenous administration) followed by antimicrobial chemotherapy with two drugs for 12 weeks and a rest period of 90 days to obtain detectable CFUs in organs. Several modifications of this model have appeared in literature which vary in the inoculum size of infection, duration between inoculation of mice and commencement of treatment, dose of anti-TB drugs, duration of treatment, and duration of rest period (Scanga et al. 1999). Another model of latent TB requires low-dose aerosol infection in mice followed by a rest period of up to 3 months (Scanga et al. 1999). More recently, a model based on NOS2−/− mice has also been reported (Kupz et al. 2016). Studies in mice have revealed important insights into the persistence of TB suggesting that the microbe can persist in adipose tissue even after clearance from the lungs (Agarwal et al. 2014, 2016; Ayyappan et al. 2019) which is also corroborated by findings in humans (Neyrolles et al. 2006) and rabbits (Ayyappan et al. 2018). Mesenchymal stem cells have also been identified as a home to dormant Mtb in mice (Das et al. 2013; Beamer et al. 2014; Garhyan et al. 2015; Tornack et al. 2017; Fatima et al. 2020; Jain et al. 2020) as well as in humans (Garhyan et al. 2015; Tornack et al. 2017).

Apart from Mtb, several other species of mycobacteria have been used for infection in mice. These studies aimed at either developing short-term models of human TB to decrease the time required for screening of anti-TB compounds or using non-pathogenic strains/species for adoption in non-BSL3 facilities. *M. smegmatis* has been proposed for the screening of antimycobacterial agents in a mouse model (Jhamb and Singh 2009; Singh et al. 2009). *M. smegmatis* has also been employed to understand molecular mechanisms of Mtb pathogenesis (Sha et al. 2017, 2021; Sun et al. 2017; Yang et al. 2017; Li et al. 2019; Guo et al. 2021) as well as expression of proteins for vaccination purposes (Junqueira-Kipnis et al. 2013; Liu et al. 2015a; Kannan et al. 2020; Safar et al. 2020).

Mouse infection models have also been developed to mimic avian (Fujita et al. 2010; Haug et al. 2013; Andrejak et al. 2015; Cha et al. 2015; Bruffaerts et al. 2017; Dong et al. 2017; Babrak and Bermudez 2018) and bovine TB (Logan et al. 2008; Waters et al. 2014; Garcia-Pelayo et al. 2016; Garcia et al. 2020). Mouse models have also provided insights into the role of co-morbidities such as diabetes (Martens et al. 2007; Alim et al. 2017, 2019, 2020) and co-infections such as malaria (Mueller

et al. 2012, 2014; Blank et al. 2016a, b), influenza (Florido et al. 2013; Redford et al. 2014; Ring et al. 2019), herpes (Miller et al. 2019), HIV (Nusbaum et al. 2016), and helminth infections (Monin et al. 2015; Rafi et al. 2015; McFarlane et al. 2017) on the progression of TB.

28.2.2 Guinea Pig Model

Guinea pigs were the preferred model for understanding TB pathogenesis and diagnosis as well as drug and vaccine screening (Negre and Bretey 1945; Steenken Jr. and Wagley 1945; Dessau et al. 1949; Steenken Jr. and Pratt 1949; Soltys and Jennings 1950; Wasz-Hockert and Backman 1954; Lithander 1957; Collymore et al. 2018; Williams et al. 2020). Their use in diagnosis has ceased since the introduction of culture medium and other diagnostic tests (Mitchison et al. 1973; Saxena and Sharma 1982; Martin et al. 1989; Smith et al. 1991). Nevertheless, guinea pigs are the second most employed model after mice for drug and vaccine efficacy studies and in understanding disease pathology (Morton 1916; Goyal 1938; Gharpure 1945; Kerr 1946). Guinea pigs exhibit several characteristic features of human TB pathology as observed in humans such as the development of granulomas, caseous necrosis, and secondary lesions after systemic dissemination (Wilkinson and White 1966; Narayanan et al. 1981; Shakila et al. 1999; McMurray 2003; Turner et al. 2003a; Basaraba et al. 2006; Ordway et al. 2007; Via et al. 2008). Although guinea pigs have been addressed as being highly susceptible to TB infection, high CFU counts need to be administered compared to mice. Guinea pigs also do not show any significant observable signs and symptoms of the disease even weeks after the Mtb challenge making this species unsuitable for studies where the death of the animal is a study parameter (Smith et al. 1991; Shakila et al. 1999; Williams et al. 2005). BCG vaccine has been shown to be more protective in guinea pigs compared to mice thereby raising concern that guinea pigs may not be a suitable model to screen vaccines better than BCG (Sugawara et al. 2007; Ly et al. 2008; Cardona and Williams 2017; Gong et al. 2020). Further, the lack of immunological reagents is also an impediment to employing guinea pigs in vaccine screening. Guinea pigs have also been employed to study non-pulmonary TB such as pleuritis (Phalen and McMurray 1993), ocular TB (Rao et al. 2009; Thayil et al. 2011), and central nervous system dissemination (Be et al. 2011) as well as TB in co-morbid conditions (Podell et al. 2014). Although highly virulent strains of Mtb such as H37Rv and Erdman strains (Palanisamy et al. 2008; Li et al. 2010) as well as clinical isolates (Shanley et al. 2013; Aiyaz et al. 2014; Pardieu et al. 2015) have been used, experimental models of *M. bovis* and BCG infection have also been reported in guinea pigs (Aygun et al. 2000; Chambers et al. 2001). Guinea pig model of latent TB has also been reported (Kashino et al. 2008; Klinkenberg et al. 2008; Rifat et al. 2009; Sugawara et al. 2009; Patel et al. 2011) and found to be suitable for study of latent TB.

28.2.3 Non-human Primates

Non-human primates are known to be susceptible to TB and reports have emerged showing the spontaneous spread of infection in wild and captive animals (Schroeder 1938). These include rhesus macaques (Lindsey and Melby Jr. 1966), stump-tailed macaques (Wolf et al. 1967; Indzhiia et al. 1977), squirrel monkeys (Chrisp et al. 1968; Hessler and Moreland 1968; da Silva et al. 2017), spider monkeys (Rocha et al. 2011), cebus monkeys or capuchins (Leathers and Hamm Jr. 1976; Broncyk and Kalter 1980; Ehlers et al. 2020), owl monkeys (Bone and Soave 1970; Snyder et al. 1970), pig-tailed monkeys (Sedgwick et al. 1970; Lau et al. 1972; Stockinger et al. 2011; Engel et al. 2012), lemur (Knezevic and McNulty 1967), langurs (Plesker et al. 2010), baboons (Heywood et al. 1970; Broncyk and Kalter 1980; Fourie and Odendaal 1983; Martino et al. 2007; Wolf et al. 2016), chimpanzees (Chaparas et al. 1970; Broncyk and Kalter 1980; Coscolla et al. 2013; Wolf et al. 2016), mandrills (Amado et al. 2006), grivet (Broncyk and Kalter 1980), marmosets (Broncyk and Kalter 1980; Via et al. 2013), and several species of New World monkeys (Alfonso et al. 2004; Rosenbaum et al. 2015). Non-human primates genetically resemble humans due to evolutionary proximity and hence, exhibit characteristic hallmarks of human TB. These characteristics include the development of caseous necrosis, granulomas, and dissemination of pulmonary TB to other organs (Via et al. 2008; Mattila et al. 2013, 2017; Pacheco et al. 2013; Dutta et al. 2014b; Marino et al. 2015; Esaulova et al. 2020; Wessler et al. 2020). Apart from the characteristic pulmonary pathology, several non-human primates have also been found to exhibit non-pulmonary manifestations of TB such as hepatic (Stockinger et al. 2011), spinal (Martin et al. 1968; Fox et al. 1974), cerebral (Machotka et al. 1975), cutaneous (Bellinger and Bullock 1988) and ocular (West et al. 1981) as well as infection by other species of mycobacteria, including non-tuberculous mycobacteria (Smith et al. 1973; Renner and Bartholomew 1974; Latt 1975; Sesline et al. 1975; Sapolsky and Else 1987; Brammer et al. 1995; Alfonso et al. 2004; Henrich et al. 2007; Chege et al. 2008; Parsons et al. 2010; Wachtman et al. 2011; Via et al. 2013; Rahim et al. 2017; Min et al. 2018). Further, immunological reagents targeted towards human proteins show reactivity with NHP proteins, and vice versa, due to the high degree of sequence and structural homology. Additionally, co-infection with simian immunodeficiency virus also mimics HIV/TB co-infection (Kuroda et al. 2018) and has been employed to study the effect of antiretroviral therapy on active and latent TB progression (Ganatra et al. 2020; Sterling and Lin 2020). However, the high cost of procurement and maintenance along with stringent ethical protocols restrict the use of NHPs to very few laboratories (Gong et al. 2020). Several species of NHP have been investigated as models for screening of anti-TB compounds as well as vaccines but the major species include cynomolgus macaques (*Macaca fascicularis*) (Marino et al. 2004; Dutta et al. 2014b; Tsujimura et al. 2020; Winchell et al. 2020) and rhesus macaques (*Macaca mulatta*) (Fremming et al. 1957; Pacheco et al. 2013; Rayner et al. 2013; Gong et al. 2020; Sterling and Lin 2020). Significant differences between the two species have been reported with regard to TB susceptibility and response to vaccination. Rhesus macaques have been found to be more susceptible to

the development of active TB but BCG vaccination showed poor protection in this species compared to cynomolgus macaques (Langermans et al. 2001). The higher susceptibility of rhesus macaques to develop active TB, compared to cynomolgus macaques, has been attributed to differences in innate immune responses (Maiello et al. 2018; Dijkman et al. 2019) and monocyte: lymphocyte ratios in the two species (Sibley et al. 2019). Further, mutations in the natural resistance-associated macrophage protein 1 (NRAMP1) gene have been linked to differences in intraspecies susceptibility to TB in rhesus macaques (Deinard et al. 2002). The role of the route of administration on disease pathology has also been demonstrated: a uniform disease was obtained following aerosol exposure, while bronchoscopic instillation resulted in disease localized at the instillation site (Sibley et al. 2016). In contrast to rhesus macaques which develop active TB, cynomolgus macaques have been found to develop latent TB following low-dose pulmonary delivery of Mtb. These macaques remain asymptomatic, with no clinical manifestations in chest radiography, but show positive tuberculin tests after at least 6 months of Mtb administration (Walsh et al. 1996; Capuano et al. 2003; Lin et al. 2006; Flynn et al. 2015; Gideon et al. 2015; Sharpe et al. 2016). Nevertheless, a model of asymptomatic TB has also been described in rhesus macaques (Gormus et al. 2004; Lin et al. 2009). The macaque model has also been used to study the reactivation of latent TB in SIV-TB co-infection models (Diedrich et al. 2020; Ganatra et al. 2020) as well as identify biochemical and cellular markers in latent TB (Esaulova et al. 2020). More recent studies using PET-CT (Coleman et al. 2014a, b; Lin et al. 2016; Stammes et al. 2021), serial intravascular staining (Potter et al. 2021), in silico/mathematical models (Marino et al. 2016; Marino and Kirschner 2016; Pienaar et al. 2016; Sershen et al. 2016; Evans et al. 2020), omics studies (Mehra et al. 2010; Kunnath-Velayudhan et al. 2012; Luo et al. 2014; Gideon et al. 2016; Javed et al. 2016; Pienaar et al. 2016; Hudock et al. 2017; Martin et al. 2017; Thompson et al. 2018; Duffy et al. 2019; Ault et al. 2020), and other methods have been found to be useful in the study of TB pathogenesis in macaques (Lewinsohn et al. 2006; Lerche et al. 2008; Sharpe et al. 2009; Hudock et al. 2014; Pena and Ho 2016).

28.2.4 Other Mammalian Models

Rabbits have been employed in TB for a long time. The severity and nature of the infection have been attributed to the strain of the infecting organism as well as the rabbit strain employed (Dorman et al. 2004; Subbian et al. 2013a; Tsenova et al. 2020). Following aerosol challenge with *M. bovis*, rabbits exhibit several characteristics of human disease such as cavitation and granuloma formation (Via et al. 2008; Subbian et al. 2013b; Gong et al. 2020) as well as extrapulmonary dissemination (Nedeltchev et al. 2009). Notably, most of the rabbit strains are not susceptible to common human virulent strains (Gong et al. 2020); however, these strains could produce pulmonary lesions (Bishai et al. 1999; Manabe et al. 2003). The rabbit model has also been modified to study extrapulmonary TB such as meningitis (Tsenova et al. 2005, 2007; Tucker et al. 2016; O'Brien et al. 2020),

spinal TB (Geng et al. 2015; Liu et al. 2015b) and bladder TB (Liu et al. 2015b). Imaging studies have demonstrated localization of administered drugs in pulmonary necrotic lesions thus providing a pharmacokinetic basis for the comparison of drug activity (Kjellsson et al. 2012; Via et al. 2012; Pienaar et al. 2017; Blanc et al. 2018a, b; Rifat et al. 2018; Tucker et al. 2018; Sarathy et al. 2019). A skin infection model has recently been reported in rabbits to assess the virulence of mycobacterial strains and liquefaction potential (Zhang et al. 2010; Sun et al. 2012). The rabbit model has also been investigated for the study of latent TB but the model has not been extensively studied (Manabe et al. 2008; Kesavan et al. 2009; Subbian et al. 2012, 2013b).

The earliest report on a study of TB in rats is over a century old (Bodkin 1918); however, their use in the assessment of drug effects on the course of TB was studied several years later (Smith et al. 1946a, b; Scheid and Mendheim 1949; Michael Jr. et al. 1950; Cummings et al. 1952; Grumbach 1960). Despite their early applications, rats were not extensively investigated as a model of TB. In recent years, several strains and species of rat have been employed such as Fischer rats (Sugawara et al. 2004a), Lewis rats (Sugawara et al. 2004b), Sprague-Dawley rats (Li et al. 1998), Wistar rats (Gaonkar et al. 2010; Singhal et al. 2011a, b), cotton rats (Daigeler 1952; Elwood et al. 2007; McFarland et al. 2010), vole rats (Jespersen 1974) and others (Sugawara et al. 2004c, 2006; Clarke et al. 2007; Sugawara and Mizuno 2008). Nevertheless, preliminary studies have demonstrated the formation of granulomas and pulmonary lesions in rats (McFarland et al. 2010; Heng et al. 2011). The application of rats in studying the effects of vaccines has been a recent development with preliminary studies indicating their utility in screening vaccines (McFarland et al. 2010; Singhal et al. 2011b; Cardona and Williams 2017; Gong et al. 2020). Rats offer additional advantages compared to mice such as the ability to collect multiple blood samples which makes them an attractive alternative to mice for pharmacokinetic studies (Kumar et al. 2014).

Apart from studying the effect of drugs and vaccines, rats have also been investigated for understanding the role of co-morbidities in TB such as diabetes (Sugawara and Mizuno 2008) and silicosis (Dong et al. 2014). Rats have also been investigated in the diagnosis of TB such as cotton rats (*Sigmodon hispidus hispidus*) (Daigeler 1952). African pouched rats have been studied for the olfactory detection of TB in clinical samples. Pouched rats were found to be more sensitive than smear microscopy in the detection of Mtb (Mahoney et al. 2012; Mgode et al. 2012; Ellis et al. 2017; Mulder et al. 2017; Webb et al. 2020).

Hamsters have also been investigated as a model for the study of human and bovine TB pathology (Steenken Jr. and Wagley 1945; Glover 1946; Dennis and Gaboe 1949; Rozenberg and Pisarenko 1965). Pulmonary infection of hamsters has been shown to exhibit tubercle formation and the pathological outcome was dependent on a diet (Ratcliffe and Palladino 1953; Merrick and Ratcliffe 1957). The cheek pouch has also been used as an inoculation site that exhibits granulomatous lesions (de Arruda and Montenegro 1995). Hamsters have also been used to study the antimycobacterial effects of compounds (Rozenberg and Pisarenko 1965; Gupta and Mathur 1969; Righi et al. 1999; Ugaz et al. 1999; Domingues-Junior et al.

2000; Palermo-Neto et al. 2001) as well as the effect of BCG on TB progression (Viallier and Cayre 1955; Rozenberg and Pisarenko 1965). Hamsters, like guinea pigs, have also been investigated in the diagnosis of TB but are not extensively used (Hussel 1951; Eskuchen 1952; Starck and Viehmann 1955). Minipigs have also been investigated as a model of pulmonary Mtb infection which exhibits characteristics of human pulmonary lesions such as granuloma formation (Gil et al. 2010; Ramos et al. 2017).

Several other mammalian models have been developed to model TB in wild animals and cattle (Palmer et al. 2012; Reis et al. 2020). These models typically rely on the induction of *M. bovis* infection in animals such as badgers, boars, deer, and possums (Palmer et al. 2012; Reis et al. 2020). These animals act as reservoirs of TB in the wild and play a key role in the spread of TB in wild animals and domesticated cattle (Fulford et al. 2002; Corner et al. 2003; Green et al. 2008; Fenwick 2012; Donnelly and Nouvellet 2013; Nugent et al. 2015; Sichewo et al. 2020). Experimental models of *M. bovis* infections have been developed in badger (Lesellier et al. 2008; Gormley and Corner 2017; Queiros and Vicente 2018), boar (Naranjo et al. 2006; Ballesteros et al. 2009; Gasso et al. 2016; Lopez et al. 2016), deer (Palmer et al. 1999; Mackintosh et al. 2000; Waters et al. 2003; Stringer et al. 2011) and possum (Dennis and Gaboe 1949; Skinner et al. 2002; Cooke et al. 2003; Nugent et al. 2013a, b; Rouco et al. 2016) which have provided insights into disease pathology progression, transmission as well as effects of vaccination on disease control. A model of aerosol infection has also been described in ferrets as a replacement for the badger model (McCallan et al. 2011). Apart from these reservoirs of infection, models of *M. bovis* infection have also been reported in goats (Schinkothe et al. 2016a, b), buffalo (De Klerk et al. 2006) and cattle (Kao et al. 1997, 2007; Joardar et al. 2002; Palmer et al. 2002; Griffin et al. 2006; Rodgers et al. 2007). Additionally, the *M. caprae* infection model has also been reported in goats (Bezos et al. 2010; de Val Perez et al. 2011). Cattle have been reported to be resistant to Mtb (Whelan et al. 2010) but *M. bovis* infection in cattle has been proposed as an alternate model for human TB for evaluating the effect of drugs and vaccines (Dean et al. 2008; Van Rhijn et al. 2008; Waters et al. 2014).

28.2.5 Fish and Other Models

Zebrafish infection with *M. marinum* has been a subject of considerable interest in recent years. *M. marinum* induces granuloma formation in zebrafish which resembles lung granulomas in humans (Prouty et al. 2003; Swaim et al. 2006; Davis and Ramakrishnan 2009; Carvalho et al. 2011; Cheng et al. 2020). The investigation of mechanisms of granuloma formation in zebrafish has provided important insights into the mechanisms operable in humans, including mechanisms operable in presence of co-morbidities (Benard et al. 2016; Kenyon et al. 2017; Bouz and Al Hasawi 2018; Johansen et al. 2018; Luukinen et al. 2018; Harjula et al. 2020; Oehlers et al. 2020; Hosseini et al. 2021). The optically transparent adult zebrafish and embryos allow easy visualization of disease progression while also allowing

studies with large sample sizes due to the low cost of maintenance as well as the ability to conduct studies in BSL2 facilities (Myllymaki et al. 2016; Sommer and Cole 2019; Cheng et al. 2020; Gong et al. 2020; Hogset et al. 2020). The zebrafish model has been employed for the screening of anti-TB compounds and candidate vaccines (Oksanen et al. 2013; Lopez et al. 2018; Risalde et al. 2018; Sommer and Cole 2019; Commandeur et al. 2020; Nie et al. 2020; Saralahti et al. 2020; van Wijk et al. 2020). Genetically engineered zebrafish, expressing drug-metabolizing enzymes, has also been employed for studying the activity of anti-TB prodrugs (Ho et al. 2021). The zebrafish model has also been extended to study ocular (Takaki et al. 2018) and latent TB (Parikka et al. 2012) as well as tuberculous meningitis (van Leeuwen et al. 2014; Chen et al. 2018). In vivo models of *M. marinum* infection have also been described in goldfish (Ruley et al. 2002; Hodgkinson et al. 2012) and medaka (Broussard and Ennis 2007; Broussard et al. 2009) as well as in vitro models employing a carp cell line (El-Etr et al. 2001).

M. marinum infection model has also been proposed in frogs which results in granuloma formation (Ramakrishnan and Falkow 1994; Ramakrishnan et al. 1997; Cosma et al. 2006; Rhoo et al. 2019). Frog tadpoles are resistant to infection compared with adults (Rhoo et al. 2019) but tadpoles exhibit immune responses against mycobacteria similar to those observed in mammals (Hyoe and Robert 2019). In vitro studies using frog macrophages have demonstrated contrasting roles of cytokines in susceptibility to *M. marinum* infection (Popovic et al. 2019). Additionally, *M. marinum* infection model has also been described in the fruit fly (Dionne et al. 2003; Oh et al. 2013; Pushkaran et al. 2019), silkworm (Yagi et al. 2017, 2021), nematodes (Lopez Hernandez et al. 2015; Galbadage et al. 2016), and protists (Solomon et al. 2003; Andersson et al. 2006; Hagedorn and Soldati 2007; Arafah et al. 2013; Kolonko et al. 2014; Sanchez-Hidalgo et al. 2017; Trofimov et al. 2018). *Galleria mellonella* larvae have also been reported to be susceptible to a wide range of mycobacteria, including Mtb, (Asai et al. 2019b, 2020; Budell et al. 2020) and have been employed for screening antimycobacterial compounds (Entwistle and Coote 2018; Asai et al. 2019a). Models of avian TB have also been described in chick and quail (Chaudhuri et al. 1980; Tell et al. 2003).

28.3 In Vitro Models

Mycobacteria reside in macrophages and dendritic cells; hence, Mtb-infected macrophages have been frequently used as in vitro models to study drug activity and molecular aspects of pathology (Chingwaru et al. 2016; Keiser and Purdy 2017; Pi et al. 2019). Alveolar macrophages are the primary target for pulmonary TB (Cardona et al. 2003; Cohen et al. 2018) while hepatic and splenic macrophages are targets for systemic infection (Ozeki et al. 2006; Sivangala Thandi et al. 2020). Although primary macrophages obtained from the lungs, liver, and spleen appear to be obvious choices for in vitro studies, their application (particularly, alveolar and hepatic macrophages) is thwarted by low abundance and difficulty in the isolation of pure cell types. Splenic macrophages can be obtained in large quantities but exhibit

much lower phagocytic activity compared to alveolar or hepatic macrophages (Guirado et al. 2013). These problems have resulted in a search for more convenient and representative sources of macrophages. Bone-marrow-derived macrophages have found particular interest in this regard as the precursor cells can be obtained in large amounts and can be differentiated into desired cell types using cytokines or conditioned culture media (Keiser and Purdy 2017). However, the high cost of cytokines could be a limiting factor. Peritoneal macrophages are yet another model which has been frequently employed for decades. The naïve/unelicited macrophages are obtained in relatively lower amounts but their numbers can be increased by eliciting the mice with chemicals. The yield of elicited macrophages is several folds higher compared to unelicited macrophages thereby reducing the number of animals required for experimentation. In recent years, several cell lines of murine alveolar macrophage origin have been developed. The cell lines offer several advantages over primary cells such as a virtually unlimited supply of cells with uniformity in genetic, biochemical, and physiological characteristics. Primary macrophages, as well as cell lines derived from a variety of cell lineages from mice (Chingwaru et al. 2016; Andreu et al. 2017), rat (Weikert et al. 2000; Hino et al. 2005; Markova et al. 2005; Hirota et al. 2010) and other animals, have been investigated as in vitro models for the study of Mtb-cell interactions (El-Etr et al. 2001; Hino et al. 2005; Keiser and Purdy 2017).

Human alveolar, hepatic and splenic macrophages are difficult to obtain due to ethical reasons; however, in recent years, these have become commercially available but their cost remains a major stumbling block (Henao et al. 2007). Human peripheral blood mononuclear cells (PBMCs) are relatively much easier to obtain, technically as well as ethically, and have also been widely used. These cells are differentiated into macrophages using cytokines or human serum and can then be used for infection with mycobacteria (Duque et al. 2014; Zhang et al. 2018). Several cell lines of human origin have also been used—the THP-1 monocytic cell line is the most frequently used. This cell line can be differentiated into macrophages by treatment with phorbol myristate acetate and then used for Mtb infection (Bai et al. 2010; Mendoza-Coronel and Castanon-Arreola 2016).

Under physiological conditions, macrophages phagocytose the mycobacteria while cytokines released by macrophages and T-cells contribute to macrophage activation and subsequent killing of the intracellular bacteria. The macrophage infection model is considered relevant for in vitro screening of anti-TB activity of test compounds since the ability of the test compound to cross biological membranes (plasma and phagosomal membranes of host and mycobacterial cell membrane) and exert activity in a biological relevant milieu can be determined (Clemens et al. 2019). However, this model is an oversimplification of the immune response and macrophage-T-cell co-cultures have been used to decipher the molecular basis of crosstalk between these cell types (Skinner et al. 1997; Lyadova et al. 1998; Gautam et al. 2018). As an alternative, Mtb has been incubated in whole blood to determine immune responses as well as study drug effects (Al-Attiyah et al. 2006; Newton et al. 2011; Raposo-Garcia et al. 2017; Cross et al. 2019; Kwan et al. 2020).

Three-dimensional culture and organoids have attracted immense interest in recent years since these methods are more closely related to in vivo conditions and have been successfully employed for drug and vaccine screening. A 3D model employing human PBMCs in an extracellular matrix has been shown to mimic human granulomas and found relevant as a model of latent TB (Crouser et al. 2017). Similar 3D models have been employed which either contain a single cell type or co-culture of macrophages with other cell types to mimic lung tissue or granuloma (Braian et al. 2015; Benmerzoug and Quesniaux 2017; Tezera et al. 2017a, b; Palucci et al. 2019; Thacker et al. 2020; Walter et al. 2020). Additionally, precision-cut lung slices and other models have also been reported to study disease pathology and drug effects (Carranza-Rosales et al. 2017; Carius et al. 2020). The hollow fiber system was developed over a decade ago and approved by European Medicines Agency to study as an in vitro model for pharmacokinetic/pharmacodynamic studies (Cavaleri and Manolis 2015). This method has been successfully employed for pharmacokinetic/pharmacodynamic studies involving single-drug or multi-drug regimens (Gumbo et al. 2015a, b; Pasipanodya et al. 2015; Srivastava et al. 2016; Kloprogge et al. 2019; Pieterman et al. 2021) including the ability to extend the results to children (Srivastava et al. 2020). Additionally, microfluidic systems have also been developed to study environmental milieu and signaling in granulomas as well as a study of drug resistance (Bielecka et al. 2017; Berry et al. 2020).

28.4 Mycobacterial Cultures

The field of mycobacterial culture has witnessed a steady improvement in terms of the development of culture media and detection methods. These methods are useful in detecting direct-acing anti-TB compounds but are irrelevant for indirect-acting compounds (such as immunomodulators) or those requiring metabolic activation (such as prodrugs) as well as vaccines.

In the case of compounds that act both directly and indirectly, the anti-TB activity determined by these methods is expected to be much lower compared to that observed under in vivo conditions. Currently, Middlebrook 7H9 broth is the liquid medium of choice while Middlebrook 7H10 medium and Middlebrook 7H11 medium are commonly employed solid media for experimental purposes. On the other hand, the Lowenstein-Jensen medium is the preferred solid medium for isolating Mtb from clinical samples. Mtb is a slow-growing bacterium with a doubling time of approximately 20 h which requires 1–2 months of incubation for CFU determination. Therefore, broth media are commonly employed to study the anti-TB activity of test compounds whereby mycobacterial growth is determined using turbidimetry or optical absorbance (Franzblau et al. 2012; Parish 2020). These methods, although widely used traditionally, suffer from low reliability in quantifying live bacteria due to possible interference by cell debris and have hence been superseded by dye-based methods. Colorimetric dyes such as Alamar blue or MTT are converted to fluorescent or colored products by viable bacteria. The

metabolic conversion of dye, and resulting fluorescence/color intensity, is proportional to the number of viable bacteria (Amin et al. 2009; Cui et al. 2013). This provides the advantage that these methods could be adopted to high throughput formats, requires extremely small amounts of test compounds, and decreases operator exposure to pathogenic strains due to automation.

Commercially available radiometric systems such as BACTEC were employed which provided results relatively faster but have been replaced with fluorescence detection systems like MGIT in recent years due to concerns arising out of the use of radioactive media components (Franzblau et al. 2012; Jhamb et al. 2014). Additionally, luminescent methods based on the assay of ATP or luciferase-expressing Mtb have also been employed (Idh et al. 2017; Parish 2020).

A total of 80 amide derivatives had been tested for their anti-TB activity against metabolically active M. tuberculosis H37Rv. Out of this 34 compounds were found active at 6.25 μg/mL concentration and 11 of them were further tested for MIC determination. MIC values of these compounds ranged between ≤0.39 μg/mL and 6.25 μg/mL (unpublished data). Daily percent growth inhibitions values of all the compounds were evaluated in comparison to standard anti-TB drugs INH and rifampin. Further, 19 more compounds for MIC determination against Mycobacterium tuberculosis H37Rv were tested. All of these were tested at five different concentrations (0.39, 0.78, 1.56, 3.125, and 6.25 μg/mL) for MIC determination. Out of these, six compounds showed MIC values of ≤0.39 μg/mL (unpublished data). The rest of the compounds exhibited MIC values between 0.39 and 6.25 μg/mL. Day-wise percent growth inhibition by compounds was also studied to know the possible mode of action. MGIT 960 TB system was also established in our lab for anti-TB drug susceptibility testing. A total of 15 active compounds were tested at a concentration of 6.25 μg/mL by the MGIT- 960 method (unpublished data). All the 15 compounds were found to be active by MGIT as well as BACTEC 460 methods at a concentration of 6.25 μg/ml and the results correlated well with both the methods. A total of 16 Indian isolates were collected from different institutions in India. The isolates were tested by the BACTEC method against standard anti-TB drugs INH, rifampin, streptomycin, and ethambutol at critical drug concentrations of 0.1, 2.0, 2.0, and 2.5 μg/mL, respectively. All the isolates were sensitive to rifampin whereas some isolates were resistant to INH which is one of the two critical first-line anti-TB drugs. A total of 15 compounds were tested at 6.25 μg/mL concentration against one of the isolates which were resistant to INH. Interestingly three compounds were found to be inactive against this isolate whereas 12 compounds were active against this isolate which was resistant to INH. Intra-macrophage anti-TB activity determination against *M. tuberculosis* (in mouse non-activated peritoneal macrophages) was also established and MIC of standard anti-TB drugs was determined using this assay (our unpublished data).

In vitro mycobacterial cultures have also been investigated for the study of latent TB phenotypes. These models aim at mimicking the conditions observed in granulomas such as hypoxia (Aly et al. 2006; Harper et al. 2012; Dutta et al. 2014a) and nutrient starvation (Sarathy et al. 2018; Yuan and Sampson 2018) to induce a latent phenotype in Mtb (Via et al. 2008). The Wayne model was one of the

earliest models described whereby bacteria are cultured in sealed containers. Cessation of aeration in the culture results in a decrease in dissolved oxygen concentration resulting in a shift towards hypoxia. After an extended duration of growth arrest, the bacteria could re-enter logarithmic growth if the cultures are aerated. The dormant stage under hypoxic conditions has been termed non-replicating persistence (NRP) and two distinct stages of NRP have been identified. NRP stage I, also described as microaerophilic, is reached when oxygen saturation decreases to 1% and is characterized by growth arrest, steady ATP levels, and increased glycine dehydrogenase production. As oxygen falls below 0.06% saturation, the bacteria enter anaerobic conditions, termed NRP stage II, which is characterized by a decrease in glycine dehydrogenase (Wayne and Hayes 1996; Wayne 2001). NRP stage II exhibits a reversal in the antimicrobial activity of metronidazole whereby the drug shows bactericidal activity in NRP stage II bacilli but is ineffective in aerobically growing bacilli. Based on the Wayne model, hypoxic resazurin reduction assay, as well as MTT assay, has been developed which enables high throughput screening of drugs against latent TB (Martin et al. 2006; Meinzen et al. 2016). A luciferase reporter has also been used to monitor bacterial growth using a protocol similar to the Wayne model. In this method, termed low oxygen recovery assay, the luminescence readout has been used to study the activity of drugs. A red fluorescent protein-expressing Mtb has also been used whereby the reporter protein expression could be monitored to determine the stage of bacterial growth (Sohaskey and Voskuil 2015; Gibson et al. 2018). In order to hasten and improve readout, the BACTEC method has also been employed to determine persisters (Kharatmal et al. 2009). Models based on hypoxia-induced dormancy have been most frequently employed; however, others in vitro models such as nutrient deprivation and selective carbon sources have also attracted attention in recent years (Patel et al. 2011; Gibson et al. 2018; Parish 2020). Additionally, nitric oxide and streptomycin have also been used as stressors to induce NRP-like conditions under in vitro conditions. A multi-stress model employing low oxygen and low pH has also been reported (Patel et al. 2011; Gibson et al. 2018; Parish 2020).

We evaluated the in vitro efficacy of satranidazole, a novel nitroimidazole-based bioreductive prodrug, against non-replicating persistent latent *M. tuberculosis* under oxygen depletion and nutrient starvation models/conditions. It exhibited a concentration-dependent effect (2–50 μg/mL) in both models; however, the maximum effect was observed at 50 μg/mL. Moreover, it showed statistically significant activity as compared to metronidazole. However, at lower concentrations (<10μg/mL), no significant difference was observed between satranidazole and metronidazole. In conclusion, the noteworthy activity of satranidazole against latent *M. tuberculosis* makes it an attractive drug candidate to target latent tuberculosis. Nevertheless, further detailed investigations, along these lines, using suitable animal models of latent tuberculosis are warranted.

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