**Animal models of ocular tuberculosis: implications for diagnosis and treatment**

**Authors:** Soumyava Basu, MS1; Narsing Rao, MD2; Paul Elkington, FRCP, PhD3

**Affiliations:**

1. Retina and Uveitis services, L V Prasad Eye Institute (MTC Campus), Bhubaneswar, India
2. Department of Ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
3. NIHR Biomedical Research Centre, School of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, UK

**Address for correspondence**:

Soumyava Basu, MS

L V Prasad Eye Institute (MTC Campus), Patia, Bhubaneswar - 751024, India

Phone: +91-674-2653001; Email: eyetalk@gmail.com

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**Abstract**

The pathogenesis of ocular tuberculosis (TB) has remained unclear due to the challenges of performing mechanistic studies on clinical samples. Animal models have the potential to bridge these gaps by providing information about ocular dissemination and localisation of mycobacteria, innate and adaptive immune response, and granuloma formation in the eye. Here, we critically review various animal models of ocular from the early 20th century to date and derive novel insights into pathogenesis of ocular TB that have direct implications on the diagnosis and treatment of this disease. Future directions on experimental approaches to understanding pathogenesis of ocular TB are also discussed.

**Keywords:** tuberculosis, ocular, uveitis, pathogenesis, animal model

**Introduction**

Tuberculosis (TB) of the eye is characterised by a wide range of clinical manifestations affecting nearly every ocular tissue.1 The clinical signs, diagnostic criteria and treatment of ocular TB are being increasingly reported from both TB-endemic and non-endemic countries.2-5 These reports have provided convincing evidence regarding intraocular inflammation related to *Mycobacterium tuberculosis* (*Mtb*) infection that responds to anti-tubercular therapy (ATT), either through resolution or non-recurrence of inflammation. The *Mtb* infection however, is rarely localised to the eye, and is mostly identified based on surrogate evidence of exposure such as tuberculin skin test, interferon gamma release assays or chest radiography. Histological evidence of acid-fast bacilli or of granulomatous inflammation is rarely found in ocular samples, not only because of limited access to the actual site of infection, but also due to the extremely paucibacillary nature of disease.6 As a result, while our knowledge of the clinical aspects of the disease have increased exponentially, especially in past two decades, the advances in the underlying pathogenesis of the disease have been relatively few.

Animal models of ocular TB have the potential to fill the gap in our knowledge regarding the pathogenesis of the disease. As in the case of pulmonary TB, different animal models can highlight different aspects of ocular TB pathogenesis such as dissemination to the eye, the role of innate and adaptive immune responses, granuloma formation, and efficacy of ATT in the eye.7-8 Indeed, a significant body of work on animal models of ocular TB can be found in literature from the early part of the 20th century. These studies provide surprising insights into pathogenesis that can be directly corelated to clinical observations in patients. Here, we critically review historical literature from the previous century as well as recent observations in diverse animal models of ocular TB. In addition, we also review the inferences that we can draw from existing models of experimental autoimmune uveitis (EAU) and from reports on veterinary ocular TB.

**Early models**

Experimental research on ocular TB generated wide interest in the early part of the 20th century, owing to the high prevalence of TB in the general population. Despite their antiquity, studies from that era contain valuable data that need to be analyzed in the context of current understanding of the disease. In general, early researchers attempted to replicate human ocular TB lesions in two ways: (1) by direct inoculation of live or dead mycobacteria into animal eyes (conjunctiva, anterior chamber, ciliary body, vitreous), or (2) by injecting live or dead bacilli into the systemic circulation.

* **Direct inoculation techniques**: Verhoeff (1913) injected ultraviolet light killed *Mtb* into the anterior chamber of rabbit eyes and the majority of the injected eyes developed scleritis and sclerokeratitis, though other lesions such as iritis and choroiditis were also seen in a few.9 Ohmart injected live *Mtb* into the ciliary body of rabbit eyes that produced granuloma localised mainly to the pars plana but occasionally extending posteriorly to the vitreous and choroid.10 Retinal involvement was rarely seen. In later studies, Woods injected live *Mtb* in different doses, into the anterior chamber of rabbits that were either previously exposed or not exposed to systemic *Mtb* infection.11 He observed that the size of the lesion was directly proportional to the number and virulence of bacilli and to previous immunization, and inversely proportional to the host resistance to infection. While these studies have limited application to understanding human disease due to the unnatural method of infection, they do highlight the ability of killed *Mtb* to incite progressive intraocular inflammation, and of live *Mtb* to survive inside the host eye, while inducing inflammation.
* **Injection into the systemic circulation**: These experiments were first reported in 1903 by Stock who injected live *Mtb* into auricular veins of rabbits to produce chronic ocular inflammation.12 Subsequently, Finnoff (1924) injected live or killed (by boiling for one hour) *M. bovis* into the internal carotid arteries of rabbits. The bacilli were injected as clumps and not as fine emulsion such that they could be trapped in the ocular circulation.13 It was noted that 70% animals developed ocular inflammation following injection with dead bacilli, compared to 100% in those injected with live bacilli. Nonetheless, both live and dead bacilli produced extensive intraocular inflammation, with similar lesions in the iris and choroid, including formation of caseating granuloma. Animals injected with dead bacilli lived long enough for the lesions to heal spontaneously, with associated scarring. Interestingly, retinal vasculitis was not seen in animals in which dead bacilli were injected.

The most useful inference gained from these early studies is regarding the role of mycobacterial viability (live versus dead bacilli) in inducing intraocular inflammation. Dead bacilli were able to produce similar lesions in the eye as live bacilli with the exception of retinal involvement. This challenges the paradigm regarding necessity for live mycobacteria to cause ocular inflammation. The presence of dead organisms is generally perceived as low level of microbial threat by the host and is expected to be accompanied by a muted immune response.14 Our initial instinct was to check the efficacy of mycobacterial inactivation technique used in Finnoff’s study. We found that Finnoff had boiled bacterial suspensions for one hour, which should be considered adequate for heat inactivation and is still routinely used in many laboratories today before extraction of mycobacterial DNA.15 Also, none of the animals injected with dead bacilli died early, such as those injected with live bacilli, indicating that the organisms indeed were inactivated adequately. Thus, there is a need to explore possible mechanisms by which dead bacilli can induce ocular inflammation. One possibility is that dead bacilli, acting as adjuvants (in a manner similar to Complete Freund’s Adjuvant, discussed later) could initiate an innate immune response within the ocular tissues. However, this still does not explain the progression to granuloma formation in the eye. It is interesting that retinal involvement was not seen with dead bacilli, most likely since dead bacilli failed to cross the blood retinal barrier, and therefore could not induce any retinal inflammation or the uveal inflammation was not severe leading to retinal vasculitis or periphlebitis.

**Guinea pig model**

Nearly a century later, there has been renewed interest in the pathogenesis of ocular TB, when ocular manifestations were studied in a guinea pig model, after infection with aerosolised *Mtb*.16 The most significant aspect of this model was the natural route of infection to the host, whereby the dissemination of *Mtb* from the lungs to the eyes also followed the natural route. Two groups were studied. In group 1, six animals were aerosol infected with 103-104 colony forming units (CFU) of *Mtb*, which resulted in infection of 5 of 12 eyes (42%). In group 2, four animals were infected with one log unit higher dose of infection (105 CFU) and also treated with three-drug anti-TB therapy, starting at 14 days after the infection. In this group, none of the eyes developed granulomatous inflammation or showed microbiological evidence of *Mtb* infection, when sacrificed at day 56. However, 4/8 eyes had mild lymphocytic infiltration of the choroid or ciliary body.

Several interesting inferences can be drawn from these data, besides the obvious dissemination of *Mtb* from the lungs to the eye to induce granulomatous inflammation in the first group. First, there is a lag period of at least two weeks, from the time of alveolar infection to the dissemination to other organs. As noted in the subsequent study, these two weeks are characterized by exponential multiplication of bacilli in the lungs, after which there is a stable population.17 Whether the bacilli are packaged into professional phagocytes during this period, or they are transported as extracellular organisms during dissemination, remains unknown. Also unknown is the impact of development of adaptive immunity against *Mtb* (which also requires at least two weeks) on the extent of dissemination. Second, even if *Mtb* infection in lungs is controlled by anti-TB therapy, bacterial products/antigens may be sufficient to induce inflammation, albeit mild, in the eye (as seen in Group 2). This finding correlates well with earlier studies, where dead bacilli, injected locally or systemically, were able to induce granulomatous inflammation in the eye. An important caveat in this model is that the guinea pig retina is devoid of blood vessels, and therefore retinal vascular inflammation, a common manifestation of ocular TB, could not be studied. It would have been interesting if control eyes of uninfected animals, and other extrapulmonary organs of infected animals (treated and untreated), were also examined in the study.

The guinea pig model was later utilized to further dissect the pathomechanisms of ocular TB.18 In this study, pimonidazole staining was used to demonstrate tissue hypoxia at sites of focal granulomas in the choroid. Additionally, vascular endothelial growth factor (VEGF) staining was noted in the RPE, increasing in intensity from Day 28 to Day 84 of infection. This finding aligned well with observations of tissue hypoxia and increased VEGF expression in TB granulomas in other organs.19-20 The authors proposed that VEGF could be a potential therapeutic target to alter the immune response and minimize tissue damage in human ocular TB. Similar observation has also been made in the zebrafish model where VEGF blockade was found to limit mycobacterial growth and dissemination.21 Notably, in the later guinea pig study,18 the animals were infected with a 100-fold lower inoculum (~200 bacilli) than the earlier study.17 Despite this, 75% eyes (3/4) were found to have microbiologically proven infection at Day 28 (simultaneously with other organs such as brain and spleen), and 100% at Days 56 and 84 (4/4 animals each). No infection was seen in extrapulmonary organs on Days 1 and 14 (0/4 each) at the time of exponential growth in the lungs.

**Zebrafish model**

The early events during *Mtb* infection of the host have significant influence on the final disease outcomes.22 This has been demonstrated from clinical data as well as in multiple animal models. These events may completely eliminate the infection, limit establishment of granuloma or modulate the expansion of such granuloma, influencing bacterial growth and dissemination. The zebrafish model has emerged as an effective tool in dissecting these early host-pathogen interactions in TB.23-24

The advantages include a transparent embryo amenable to live imaging of fluorescent-tagged mycobacteria and host immune cells, easy genetic manipulation and a natural host-pathogen conjugate (since *M.* *marimum* is a natural pathogen of zebrafish). Recently, a zebrafish model of ocular TB was reported, where systemic infection of zebrafish embryos with *M. marinum* led to ocular infection, that subsequently progressed to granuloma formation in the eye.25 The embryos were infected after 3 days post fertilization, since the inner and outer BRBs are formed at that age, rendering the eye into a distinct anatomical compartment. Granulomas were typically located in the proximity of either the inner BRB (hyaloid plexus of vessels) or the outer BRB (RPE and choroid). This matched with the clinical presentation in human ocular TB, where serpiginous-like choroiditis (located at RPE) and retinal vasculitis, are commonly seen. In addition, mycobacteria appeared to be phagocytosed by resident macrophages present in the retina. Thereafter, both resident and circulating macrophages were recruited for granuloma formation. The model is replicated in Figure 1, which shows the progression from infection in the eye at 1-day post injection (dpi), to phagocytosis at 4-dpi and aggregation of macrophages to form early granuloma at 6-dpi. These observations not only help dissect the early host-pathogen interactions in ocular TB but could also provide a model for other infections of the eye.

**Lessons from models of experimental uveitis**

Research on animal models of autoimmune uveitis, especially in the past three decades, have been far more extensive than those for ocular TB. Experimental autoimmune uveoretinitis (EAU) is a T-cell mediated autoimmune disease of the neural retina and surrounding tissues, induced by immunization with retinal antigens. The details of various models of autoimmune uveitis have been summarized elsewhere.26-28 Broadly, these are divided into: induced models of uveitis (in which the retinal antigen is typically combined with Complete Freunds Adjuvant [CFA]), and ‘spontaneous’ models, where mice expressing transgenic T-cell receptor for retinal antigen, interphotoreceptor binding protein (IRBP), can develop uveitis without the need for immunization or adjuvants. Interestingly, CFA contains heat-killed *Mtb*, which provide the innate signals essential to polarize retinal-antigen specific T-cells towards proinflammatory phenotype. This phenomenon can be extrapolated to a similar role in human uveitis, of mycobacterial antigens (from live or dead *Mtb*) located either in the eye or other organs. Mycobacterial products may also have a role in activating T-cells in the peripheral circulation (remote immune priming), which is essential for these cells to cross the BRB.29

*Primed mycobacterial uveitis* in rats (also called experimental mycobacterial uveitis in rabbits) is another animal model of uveitis that can offer interesting insights into the pathogenesis of at least some forms of ocular TB.30-31 The model is of value, as it was used in the preclinical studies for the only two local treatments currently available for uveitis: implantable fluocinolone acetonide and sustained release dexamethasone implants. In this model, systemic priming of the animal is performed by subcutaneous injection of *Mtb* H37Ra antigen, followed 7 days later by an intravitreal injection of the same antigen. This induces an acute inflammation in the vitreous and anterior chamber (with sparing of retina and choroid) that resolves spontaneously in two weeks but can be made chronic by repeated intraocular injections. Histologically, non-caseating granulomatous inflammation is seen in the iris, with predominance of macrophages and T-lymphocytes. In general, the inflammation is milder compared to EAU, though the cytokine secretion pattern is similar in both models. This model, although not specific to TBU, may recapitulate at least some forms of anterior (granulomatous and non-granulomatous) and intermediate uveitis, seen in patients with immunological (and/or radiological) evidence of past *Mtb* infection.

**Developing cellular models of ocular TB**

Ultimately, *Mtb* is an obligate of humans, and host and pathogen have undergone prolonged co-evolution. Therefore, all model systems make assumptions that altering the host-pathogen pairing will still accurately reflect biology in patients infected with TB. An alternative approach would be to develop an *in vitro* cellular model of ocular TB, and development of such systems has been the subject of growing interest recently. The complexity of the eye clearly presents multiple challenges in optimizing a model system, but conversely the benefits would permit mechanistic dissection of events within a human system that are impossible from study of clinical specimens or animal models. Ocular models have been developed to study other eye conditions , and this is a rapidly developing field. The combination of stem cell technology and lab-on-a-chip platforms permit the possibility of replicating complex multicellular processes within a controlled environment, within which different immune and infectious stimuli can be delivered . For example, such as system could be developed to study whether *ex vivo* proliferated Mtb-responsive T cell lines are auto-reactive to an *in vitro* retinal model generated from induced pluripotent stem cells from the same donor, or whether exogenous Mtb antigens are required to precipitate an inflammatory response. Evidently, significant investment in time and resources will be required to develop and validate such systems, but they will reduce the reliance on animal experimentation and also may act as a translational bridge to test novel treatment approaches in a fully humanized system with virulent Mtb .

**BCG-induced uveitis: a ‘human’ model of ocular TB?**

Bacille Calmette-Guérin (BCG), a live attenuated strain of *M. bovis* used to vaccinate infants against TB, is also commonly used as an intravesical infusion for treatment of superficial bladder carcinoma. At least 5% of these patients develop systemic complications such as hepatitis or pneumonitis and/or ocular complications such as anterior uveitis (common), chorioretinitis or endophthalmitis (rare).32-33 The latter two conditions have also yielded *M. bovis* on culture, which points towards dissemination of mycobacteria from the bladder to the eye in this condition. However, in a patient with BCG-induced anterior uveitis, the authors found that peptides derived from retinal proteins that induced highest T-cell responses, “shared highly similar or even identical regions of between 5-11 amino acids”.34 Based on these data, they suggested that these epitopes could be responsible for cross-reactivity between retinal antigens and BCG-specific T-cells. We recently observed a case, wherein a patient developed recurrent episodes of bilateral granulomatous anterior uveitis, following intravesical injections (monthly) of BCG, from the third injection onwards. PCR of the aqueous tap of the patient was positive for the *M. bovis* sequence. However, the uveitis resolved with topical corticosteroid therapy, without any specific anti-mycobacterial therapy. We collected peripheral blood T-cells from this patient and found that these were neither responsive to *Mtb*-specific antigen ESAT-6 nor retina specific antigens (Figure 2). Together, our findings suggested that BCG-induced anterior uveitis is due to hematogenous dissemination of mycobacteria to the eye, and not due to molecular mimicry between mycobacterial and retinal antigens, as suggested by the earlier study.34

The sequence of events in our patient bears striking resemblance to the PMU model described above. The initial intravesical injections (when no uveitis occurs) probably lead to priming of immune cells to BCG antigens, with hematogenous dissemination during subsequent injections generating granulomatous inflammation in the anterior segment, similar to PMU. Considering that a known dose of a well-characterised mycobacterium is injected into an extraocular site, as an accepted mode of therapy for cancer, leads to a spectrum of ocular inflammatory manifestations that are also seen in TBU, we propose that intravesical BCG injections can serve as a model to further investigate the pathomechanisms of TBU. That majority of patients develop anterior uveitis and not chorioretinitis, which could be accounted for by the low virulence of *M. bovis* BCG, and possibly the small inoculum of bacilli entering the eye in majority of cases.

**Implications for diagnosis and treatment of human ocular TB**

The strengths and weaknesses of each animal model of ocular TB are outlined in Table 1. Broadly, the animal data suggests that there are both direct and indirect effects of mycobacteria on the genesis of intraocular inflammation. The direct role is suggested by multiple models, where mycobacteria entered the bloodstream either by injection into the systemic circulation (rabbits, zebrafish) or through inhalation and passage through the lungs (guinea pigs). In either case, mycobacteria and granulomatous inflammation with or without caseous necrosis could be demonstrated in the ocular tissues. In humans, such a disease process should be investigated for evidence of *Mtb* in ocular fluids (by culture, microscopy or molecular techniques) and the treatment should be based primarily on elimination of *Mtb* from the infected ocular tissue, though adjunctive corticosteroids may be required. Notably, involvement of the retina (including retinal vasculitis) and choroid required either the presence of live bacteria (essential for crossing the blood retinal barrier) or a large inoculum of bacilli (including killed bacilli for a choroidal lesion).13

In contrast, the indirect mechanisms highlight the role of either killed bacilli/ bacterial products present within the eye, or the facilitation of ocular inflammation by remotely located mycobacteria/ bacterial products. The former mechanism is demonstrated when intraocular inflammation was produced in rabbits by heat or ultraviolet light killed *Mtb* injected into the systemic circulation or eye; or in pre-immunised mice/rats, where mycobacterial antigen was injected into the vitreous (PMU). In these cases, the inflammation was relatively low grade (as compared to live *Mtb*) and had a propensity for the anterior segment of the eye. It is possible that such mechanisms have a role in patients with recurrent uveitis (specifically anterior uveitis) that develops after successful completion of ATT. Dead bacilli resulting from ATT could be the source of a persistent antigenic pool that generates intraocular inflammation. The latter indirect mechanism (by remotely located mycobacteria) envisages a role similar to that of CFA in EAU. Notably, retinal antigen specific autoreactive T-cells are known to be present in the peripheral circulation, either by escaping central tolerance mechanisms in the thymus, or being generated by gut microbiota. Peripherally located mycobacteria/products can support priming of these autoreactive T-cells, such that they can cross the BRB, and induce intraocular inflammation.

**Conclusion**

Each model system provides different experimental clues into the pathogenesis of ocular TB. Cross-correlation to events in patients is likely to inform new therapies based on the mechanistic insights, and further development of innovative systems will be required to bridge the translational gap between animal systems and clinical trials. It seems likely that both direct and indirect mechanisms of inflammation act in tandem in different manifestations of human ocular TB. Future studies should dissect the relative predominance of one or other mechanism in each clinical manifestation. This would inform tailored diagnosis and treatment in patients with ocular TB.

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