*International Journal Of*

**Recent Scientific Research**

**ISSN: 0976-3031**

**Volume: 7(1) January -2016**

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THE OFFICIAL PUBLICATION OF
INTERNATIONAL JOURNAL OF RECENT SCIENTIFIC RESEARCH (IJRSR)
http://www.recentscientific.com/ recentscientific@gmail.com

ISSN: 0976-3031

Available Online at http://www.recentscientific.com

*International Journal of Recent Scientific Research*
*Vol. 7, Issue, 1, pp. 8276-8278, January, 2016*

***International Journal of Recent Scientific Research***

**REVIEW ARTICLE**

# ANIMAL MODELS OF LEISHMANIASIS: A REVIEW

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**ARTICLE INFO**

***Article History:***

Received 16th October, 2015
Received in revised form 24th November, 2015
Accepted 23rd December, 2015
Published online
28st January, 2016

***Key words:***

Animal models, Mouse, Hamster, Visceral leishmaniasis

**ABSTRACT**

Visceral leishmaniasis, also known as kala-azar, black fever, and Dumdum fever, is the most severe form of leishmaniasis. Leishmaniasis is a disease caused by protozoan parasites of the *Leishmania* genus. This disease is the second-largest parasitic killer in the world after malaria. The parasite migrates to the internal organs such as the liver, spleen hence visceral, and bone marrow, and, if left untreated, will almost always result in the death of the host. Signs and symptoms include fever, weight loss, fatigue, anemia, and substantial swelling of the liver and spleen. Of particular concern, according to the World Health Organization (WHO), is the emerging problem of HIV/VL co-infection. Many experimental animal models like rodents, dogs and monkeys have been developed, each with specific features, but none accurately reproduces what happens in humans. This review discusses various animal models of visceral leishmaniasis.



## INTRODUCTION

Leishmaniasis is a disease caused by the protozoan parasites belonging to the genus Leishmania. The disease is included in the list of the world's most neglected diseases, prevalent in developing countries (McCall *et al*., 2013). It ranks the second only to malaria, and the control remains a serious problem with ever increasing cases worldwide (WHO, 2002). *Leishmania* infection continues to have a major impact on public health inducing significant morbidity and mortality mostly in the poorest populations (Badiee *et al*., 2013).The world's leishmaniasis prevalence is between 1.5 to 2.5 million cases each year (Singh *et al*., 2006) and a further, more than 350 million people are living at risk in 98 countries (WHO, 2010). The transmission of leishmaniasis occurs through vectors of genus Phlebotomous in Old World and Lutzomyia in the New World (Weniger *et al*., 2001).

### *A. Mouse model*

Outbred mice are generally resistant to infection with L. donovani (visceral leishmaniasis) but inbred strains of mice are widely used with susceptible, resistant and intermediate strains that share similarities with human visceral leishmanisis. There is a generic basis for susceptibility to infection with L. donovani based on the presence of Slc11a1 gene (Blackwell, 1996; Liew and O'Donnell, 1993). The Slc11a1 gene encodes a protein expressed on the membrane of infected phagosomes that removes Fe2+ Mn2+ ions from the intra-phagosomal compartment restricting intracellular Leishmania multiplication in iron-limited intracellular environments (Huynh and Andrews, 2008; Marquis and Gros, 2007). Genetically resistant mouse strains (e.g., CBA) possess a functional Slc11a1 gene which confers innate resistance to early Leishmania parasite growth. In contrast, susceptible mice strains (e.g., C57BL/6 and BALB/c) possess a non-functional Slc11a1 gene and early parasite growth in the liver cannot be controlled (Kaye *et al*., 2004). However, most susceptible mouse strains, including BALB/c, develop acquired immune mechanisms to control hepatic parasite growth at later stages of infection (Stanley and Engwerda, 2007).

### *B. Hamster model*

Although many hamster species are susceptible to L. donovani infection, the Syrian golden hamster (Mesocricetus auratus) establishes a good model for VL and provides a more synchronous infection in liver and spleen that can develop into chronic infection more similar to human VL (Hommel *et al*., 1995). The usual routes of infection in the hamster model of VL are intracardiac and intraperitoneal. However, the administration of parasites by the saphenous vein in order to minimize stress on the hamsters has also been reported (Lei *et*

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*al*., 2010). Experimental studies in L. infantum and L. donovani-infected Syrian hamsters (Mesocricetus auratus) often reveal several clinical signs of progressive VL (hypergammaglobulinemia, hepatosplenomegaly, anemia, cachexia and immunodepression) that closely mimic active canine and human disease (Dea-Ayuela *et al*., 2007).

In this model, surprisingly, there are significant amounts of Th1 cytokines (IFN-γ, IL-2 and TNF-α) in the spleen, but there is little or no IL-4. However, to allow the parasites to multiply, deactivating Th2 cytokines (TGF-beta and IL-10) may act on infected macrophages as well as anti-Leishmanial antibodies (which have no protective role in leishmaniasis) that opsonize amastigotes and induce IL-10 production in macrophages. These high activation and deactivation processes are likely to occur mainly in the spleen and liver (Goto and Prianti, 2009). Interestingly, Syrian hamsters exhibit reduced expression of the gene encoding iNOS in response to IFN-γ, and this is thought to lead to a low NO generation, subsequently defaulting in parasite killing (Goto and Lindoso, 2004). Thus Syrian hamster is a suitable experimental model for the study of the pathological features of active VL, but it is not a suitable model for the evaluation of immunization strategies, as a result of the animal's high innate susceptibility. In Syrian hamsters, manifestations of VL can range from asymptomatic and oligosymptomatic infections to progressive fatal visceral disease (Melby *et al*., 2001). The pathological features reported during VL include hypoplasia of the white pulp in the spleen, hepatic granulomas and the deposition of a secondary amyloid substance both in the spleen and the liver (Rica-Capela *et al*., 2003). Also, other studies of active VL have reported that infected hamsters develop glomerulonephritis associated with deposition of immunoglobulins and parasite antigens (immune complexes) in the kidneys. Finally, the disseminated amyloidosis and glomerulonephritis produce renal failure and nephritic syndrome in infected hamsters (Sartori *et al*., 1992). The visceral infection in hamsters also induces pathological alterations in hepatocytes, mainly in the endomembrane system and the peroxisomal compartment, leading to a disturbance of liver metabolism (Vianna *et al*., 2002).

### *C. Dog model*

Dogs have also been used as experimental models of Leishmania infections and experimental infections have been achieved with Leishmania spp. for which it is not a natural reservoir e.g. L. donovani from India (Chapman *et al*., 1979). German shepherd dogs are reported to give better results than beagles but some workers claim highly successful infection rate with mixed breeds (Abranches *et al*., 1991).

### *D. Non Human primate model*

Monkeys are normally the experimental animals to be used in studies of the efficacy and safety of vaccines and drugs. Earlier studies in establishing VL in New and Old World monkeys demonstrated that *Aotus trivirgatus* (owl monkeys) (Chapman *et al*., 1983) and *Saimiri sciureus* (squirrel monkey) (Chapman and Hanson, 1981) developed an acute and fulminating, but short lived, infection. Old World monkeys such as *Macaca* spp. viz. *M. mulatta*, *M. fascicularis* and *M. nemestrina*, and african vervet monkeys developed low and/or inconsistent infections (Hommel *et al*.,1995). The infected animals presented all the clinicoimmunopathological features as observed in human kala azar (Anuradha *et al*., 1992; Dube *et al*., 1999). The Indian langur has also been used for preclinical evaluation of potential antileishmanial drugs and vaccines (Dube *et al*., 1998; Misra *et al*., 2001).

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**How to cite this article:**

Heena Sachdeva.2016, Animal Models of Leishmaniasis: A Review. *Int J Recent Sci Res.* 7(1), pp. 8276-8278.

TSSN 0976-3031