Leishmaniasis is a disease complex caused by 17 different species of protozoan parasites belonging to the genus *Leishmania*. The parasites are transmitted between mammalian hosts by phlebotomine sandflies. Leishmaniasis has a worldwide distribution with important foci of infection in Central and South America, southern Europe, North and East Africa, the Middle East, and the Indian subcontinent. Most forms of leishmaniasis are zoonotic, human beings affected only secondarily, but two species of *Leishmania* can maintain arthroponotic, human-human cycle. These are *L. donovani*, the species responsible for VL in the Indian subcontinent and East Africa, and *L. tropica*, which is responsible for CL in the old World.

VL; also known as kala azar is a protozoan systemic infection, which is almost always fatal if left untreated. This illness is endemic in several tropical and subtropical regions and in the Mediterranean basin. The estimated annual global burden of VL is 500,000 new cases and more than 500,000 deaths, of which 90% occur just in five countries—India, Bangladesh, Nepal, Sudan, and Brazil. VL is transmitted through hematophagous sandflies and is caused by *L. donovani* in the Indian subcontinent, Asia, and Africa, *L. infantum* in the Mediterranean basin, and *L. chagasi* in South America. After an incubation period of several months, typical VL manifests with intermittent fever, weight loss, massive hepatosplenomegaly, and progressive deterioration of the host; hemorrhages and edemas may develop late in the course. Leishmaniasis was selected by the World Health Organization for elimination by 2015, along with other neglected tropical diseases. Since there is no antileishmanial vaccine in clinical use, control of VL relies almost exclusively on chemotherapy.

For almost seven decades pentavalent antimonials constituted the standard antileishmanial treatment worldwide, however the last 15 years their clinical value was jeopardized due to the widespread emergence of resistance to these agents in Bihar, India, where half of VL cases occur globally. The last decade novel formulations of conventional antileishmanials as well as new drugs, including the oral agent miltefosine, became available or are under investigation. In practice, however, their wide use in poor countries is hampered mainly due to high costs and also due to concerns of toxicity and emergence of resistance. In response to concerns about preserving the currently available antileishmanials, especially in regions with arthroponotic parasite transmission, there is growing interest on combination regimens. This thesis will focus on the factors that cause variation in response to antileishmanial chemotherapy, evaluate the problems and mechanism associated with clinical resistance, and consider how a system for monitoring and surveillance might be implemented with associated implications for research.

Recent study has suggested that these antimony resistant and sensitive isolate differ markedly in their biophysical and biochemical property and also vary markedly in their genetic constitution. It was quite possible that these wide variations between sensitive and resistant isolates will also be reflected in terms of their interaction with the host cell and thus may result in a different disease outcome. My first chapter deals with this differential modulation of host cell by antimony resistant and sensitive isolates. All previous study has reviled that infection with antimony sensitive LD leads to deactivation of host transcription machinery to evade immune response. In contrast to these previous reports infection with
antimony resistant LD leads to activation of host NF-κB which binds with a specific site of IL-10 promoter resulting in an IL-10 surge. Thus unlike antimony sensitive LD infection, infection with antimony resistant LD modulates host transcription machinery altogether differently for establishing a successful infection.

The first part of my second chapter deals with the critical role of a unique surface glycoconjugate, N-acetyl galactosaminyl residue, significantly upregulated in the surface of antimony resistant isolates and plays a vital role in IL-10 induction in infected host. Infection with Gal T Knock down antimony resistant LD with significantly reduced expression of this sugar resulted in low infectivity and IL-10 induction in host. This observation further support the notion that antimony resistant LD have developed unique genetic variation that provides them a selective advantage over antimony sensitive LD in terms of establish a much more aggressive pathology in host. In the next part we have identified host receptor molecules exploited by antimony resistant LD to evoke this unique signaling cascade. Surface glycoconjugate on surface of antimony resistant LD modulates innate arm of host immune machinery leading to TLR2/TLR6 dimerization and initiates unique downstream signaling cascade that ultimately leads to nuclear translocation and binding of p50/c-Rel with specific site of IL-10 promoter. Reduced infectivity and IL-10 induction in TLR2/-/ mice as compare to wild type C57BL/6 mice further confirmed the critical role of these host receptor during antimony resistant LD infection.

Finally a study on downstream signaling molecules of TLR during antimony resistant LD infection further helped us to understand their disease pathogenesis and mode of interaction with the host. Interestingly, it was observed that deactivation of MyD88 a critical downstream signaling molecule of TLR2 is vital for establishment of successful infection by antimony resistant LD. It was observed during early MyD88 helps to maintain IL-12 level in host. Inhibitory action of IL-12 prevents p50/c-Rel binding and IL-10 promoter activation at early hours of infection. However, in late hours, there was activation of miR-466i within antimony resistant LD infected host. miR-466i binds with 3'UTR of MyD88 leading to its deactivation, which also results in decreased IL-12 level in host. Low IL-12 level leads to recruitment of p50/c-Rel in IL-10 promoter, resulting in an IL-10 surge. It is quite possible that a very early IL-10 surge may kill the host and might not be beneficial for antimony resistant LD in the process of establishing a successful infection. Thus, a gradual deactivation of MyD88 may also be a strategy exploited by this parasite to supports its mode of aggressive infection in host.

Finally we tried to detect the leishmaial antigen in the serum of LD infected patients from Bihar that might serve as the diagnostic tool to identify leishmaniasis. However, we could detect only HIV antigens and fail to detect any leishmanial antigen in serum. Although in this context it should be mentioned that HIV leishmania co-infection is now a days quite frequent, and recent studies have identified a large number of cases with HIV leishmania co-infection.