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Vaccine Designing Against Visceral Leishmaniasis: Challenges for Developing Successful Vaccine

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Abstract—*Leishmaniasis is a vector-borne disease caused by different species of protozoan parasites of the genus Leishmania.It is a major health problem yet neglected tropical diseases, with approximately 350 million people worldwide at risk and more than 1.5 million infections occurring each year. Leishmaniasis has different clinical manifestations, including visceral (VL or kala-azar), cutaneous (CL), mucocutaneous (MCL), diffuse cutaneous (DCL) and post kala-azar dermal leishmaniasis (PKDL). Among the three clinical forms of leishmaniasis (cutaneous, mucosal, and visceral), visceral leishmaniasis (VL) accounts for the majority of mortality, as if left untreated VL is almost always fatal. Caused by infection with Leishmania donovani or L. infantum, VL represents a serious public health problem in endemic regions and is rapidly emerging as an opportunistic infection in HIV patients. Currently, the only mean to treat and control leishmaniasis is by rational medications and vector control. However, the number of available drugs is limited and even these are either exorbitantly priced, have toxic side effects or prove ineffective due to the emergence of resistant strains. On the other hand, the vector control methods are not so efficient. Therefore, there is an urgent need for developing a safe, effective, and affordable vaccine for the prevention of leishmaniasis. Although in recent years a large body of researchers has concentrated their efforts on this issue, yet only three vaccine candidates have gone for clinical trial,until date. These are: (i) killed vaccine in Brazil for human immunotherapy; (ii) live attenuated vaccine for humans in Uzbekistan; and (iii) second-generation vaccine for dog prophylaxis in Brazil.In endemic areas, the majority of those infected do not develop clinical symptoms and past infection leads to robust immunity against reinfection.Thus the development of vaccine for Leishmania is a realistic public health goal, and this paper summarizes advances in vaccination strategies and challenges against VL.*

Keywords*: Leishmaniasis, Immune response, Vaccine,Leishmania donovani.*

1. INTRODUCTION

Leishmaniasis is a complex of diseases caused by species of Leishmania. The outcome of Leishmania infection ranges from asymptomatic, self-resolving infection to cutaneous, mucosal, disseminated or visceral disease[1].The World Health Organization estimated in 2000 that there were 12 million cases of all forms of leishmaniasis worldwide, with over 500,000 new cases of visceral disease occurring each year [2]. In the disease, the multiplication of the parasite in the reticulo-endothelial system causes prolonged fever, anaemia, epatosplenomegaly and weight loss. VL is fatal if it is not adequately treated Visceral leishmaniasis can be fatal in 5 to 10% of the cases even with treatment[3], whereas the other forms of leishmaniasis can evolve with high morbidity. People suffering from mucosal leishmaniasis can present with severe disfigurement. There is only a small repertoire of drugs available that are effective in the treatment of leishmaniasis. Pentavalent antimonials have been a mainstay of treatment for decades, but toxicity and increased resistance have led to their decreased use in most areas of the world. Liposomal amphotericin has become accessible in many endemic countries and is approved for visceral leishmaniasis by the United States Food and Drug Administration (FDA), as is miltefosine, the first oral medication for leishmaniasis. However, treatment failures and resistance have been reported with those drugs as well . Failure can also be a consequence of delay in therapy or due to co-morbidities that affect immune responses. A vaccine against leishmaniasis is needed to protect vulnerable populations. While no effective human vaccine against cutaneous, mucosal or visceral human leishmaniasis is available[4]. Although vaccination against VL has received limited attention as compared to cutaneous

leishmaniasis (CL), till date, there is no commercial vaccine against any human parasitic disease including leishmaniasis[5]. Leishmania parasite follow a digenetic life cycle it results in significant antigenic diversity, which ultimately hampered the passage of vaccine development against VL, therefore, the knowledge of such antigenic diversity is of utmost importance [6]. Several approaches utilized for identification of potential antigens, which can be targeted as suitable vaccine candidate (Figure 1).

The profile of an antileishmanial vaccine would need to incorporate several important features, such as safety, ease of production at a low cost in endemic countries, the induction of robust, long-term T cell responses, and both prophylactic and therapeutic efficacy. Ideally, such vaccine would offer cross-species effectiveness against CL and VL. As this might not be

feasible, the development of a VL-specific vaccine remains an important global health priority.

Figure 1: Vaccine Development against Visceral Leishmaniasis

Strategies for Vaccine Development against Visceral Leishmaniasis	
1	Classical Approach Whole Parasite Vaccine Native protein Based vaccine
2	Molecular Approach DNA Vaccine Polyprotein Vaccine Recombinant Vaccine Liposomised Vaccine Salivary Antigen based vaccine
3	Alternative Approach Mutant Vaccine Synthetic Vaccine

2. VARIOUS APPROACHES FOR THE DEVELOPMENT OF VACCINES AGAINST VISCERAL LEISHMANIASIS

2.1 First-Generation Vaccines

The only successful intervention against leishmaniasis is inoculation using virulent parasites, a process known as leishmanization (LZ). This ancient practise involves the administration of cutaneous Leishmania parasites to a discrete skin location, allowing a self-healing lesion to form. Initial immunological exposure then protects the individual from further infection and lesion development. LZ induces a controlled, but full, infection and was successfully used as a prophylaxis throughout the Soviet Union, Asia, and the Middle East, with reported efficacy levels up to 100% [7, 8].Currently only one country, Uzbekistan, employs the use of LZ, where a mixture of live and dead L. major is licensed as a vaccine for high-risk populations. As LZ is the only vaccine strategy against Leishmania with proven efficacy in humans, efforts are being made to improve the safety of this practice.

The inclusion of killed parasites in the inoculum and the use of adjuvants that promote rapid immune responses reduce the severity of primary lesions and accelerate wound healing during LZ [9].

Over the ensuing decades numerous preparations of killed parasites were tested, either alone or in combination with a variety of different adjuvants. Although displaying well-tolerated safety profiles, to date no first-generation vaccine using killed parasites has demonstrated sufficient efficacy as a prophylactic vaccine to be used in widespread control programmes [10]. A major advantage of first-generation vaccines is that they are conceptually simple and relatively easy to produce in Leishmania endemic countries at low cost. However standardization of vaccines derived from cultured parasites is difficult, and this has hindered commercial development efforts. The route of administration, formulation, and adjuvant are also important considerations in the development of whole-parasite vaccines, and optimisation is essential for the induction of protective immune responses. The most recent clinical trials of first-generation vaccines have demonstrated a good safety profile but have not conferred significant levels of protection for use as prophylactic vaccines. However promising results from trials using therapeutic vaccination in combination with chemotherapy warrant further investigation.

2.2 Second-Generation Vaccines

The development of Second-generation vaccines for Leishmania has included recombinant proteins, polyproteins, DNA vaccines, liposomal formulation, and dendritic cell vaccine delivery systems. The natural combination of dogs and L. infantum [11] and L. donovani in golden hamsters [12] reproduces many features of human VL. The canine model is particularly useful in evaluating vaccine candidates since successful vaccination of dogs might control the spread of disease to humans in endemic areas where the dog is the reservoir of the parasite [13]. However, both models suffer from lack of immunological reagents and assays needed for the characterisation of immune responses. Therefore, the mouse model of VL has been widely used to assess vaccine candidates. While experimental VL infection in mice does not fully reproduce the disease observed in humans, mice are competent hosts for both L. donovani and L. infantum and exhibit organ-specific pathology in the liver and spleen. Other major advantages of the mouse model are that it is amenable to genetic manipulation to create mutants with specific deficiencies in the immune system and a wide range of immunological reagents is available. . An optimized version, known as Leish-110f, has recently demonstrated strong immunogenicity and some protective efficacy against L. infantum in mice [14]. The Leish-111f vaccine is moving forward into clinical trials as LeishF1 and is being trialled in combination with the MPLSE adjuvant. This adjuvant consists of monophosphoryl lipid A, a potent TLR4 agonist, formulated with the antigen as a stable emulsion. A recent small-scale clinical trial in a L. donovani endemic area showed Leish-F1-MPL-SE was safe and well tolerated in people with and without prior VL exposure and induced strong antigen-specific T cell responses[15].

2.3 Live Attenuated Vaccines

Historically the most successful vaccines against intracellular pathogens have been based on live attenuated organisms. Vaccination strategies using live attenuated Leishmania parasites are attractive as they closely mimic the natural course of infection and may elicit clinically protective immune responses. A live attenuated vaccine strain would present a full complement of Leishmania antigens to the host immune system along with appropriate pattern-recognition molecules for the parasite. Live vaccines also deliver antigens to the correct cellular and tissue compartments for appropriate

processing and presentation to the host immune system. Together, this enhances the capacity of live attenuated vaccines to promote antigen-specific effector and memory immune responses that confer long-lasting protective immunity. The development of robust in vitro culture systems for growth and differentiation of Leishmania promastigote and amastigote life cycle stages has enabled the production of attenuated vaccine strains. It should be noted that most research in this area has utilized CL strains, such as L. major; however the attenuation techniques are broadly transferrable to VL causing species. It is has been known for some time that long-term in vitro culture of promastigote parasites leads to a loss of virulence in vivo. Studies in experimental mouse models of CL have shown that infection with cloned avirulent lines provides clear protection against a virulent challenge infection [16]. Avirulent strains of the VL species L. donovani and L. infantum have been generated by repeated in vitro subculture of promastigotes in the presence of gentamicin [17]

The major concern regarding these approaches to attenuation is that the underlying genetic mechanisms are not defined. This creates safety concerns as the stability of parasite attenuation is uncertain and parasites could revert to a virulent form. Conversely, a progressive loss of virulence may occur, resulting in parasite lines that are incapable of establishing infection or inducing protective host responses. A loss of parasite virulence due to long-term in vitro culture has been demonstrated in both human patients undergoing leishmanization and experimental mouse models [18]. Thus in the absence of a clear genetic profile, nonspecific parasite attenuation is not acceptable for the development of a human VL vaccine[19].

3. CONCLUSION

Preventive vaccines are recognized as the best and most cost effective protection measure against pathogens and save millions of lives across the globe each year. Leishmania vaccine development has proven to be a difficult and challenging task and is hampered by an inadequate knowledge of disease pathogenesis, the complexity of immune responses needed for protection, and the cost of vaccine development. The burden of VL is concentrated in resource poor nations, and a lack of political will and philanthropic investment further aggravates the situation. However, the rise of biotechnology industries in endemic countries, such as India, may provide an impetus for VL vaccine development and investment. A recent clinical trial in India assessed the safety and immunogenicity of the LEISH-F1+MPL-SE vaccine [20] which is the only Second-generation vaccine currently in clinical development for human Viceral Leishmaniasis[21].

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