Research Proposal

Title: Modelling of Chagas Disease.

Introduction: Chagas disease, caused by infection with the parasite Trypanosoma cruzi, remains a significant cause of morbidity and mortality in Central and South America. Also known as American trypanosomiasis, Chagas disease was discovered in 1909 by Dr. Carlos Chagas and is characterized by chronic cardiac and gastrointestinal manifestations. Human infection with T. cruzi most often occurs via a bite from the insect vector of the parasite, the triatomine bug, which lives in traditional human dwellings in endemic countries. In addition, there exist large numbers of people chronically infected with T. cruzi who can transmit the infection by blood donation, organ donation, or congenitally from mother to child. In 2009, the World Health Organization reported 11,000 deaths due to T. cruzi infection, and estimated that eight million infected people remain worldwide. In 2002, in Latin America, the WHO estimated the burden of Chagas disease to be as high as 2.7 times the combined burden of malaria, schistosomiasis, leishmaniasis and leprosy. Though traditionally a disease endemic to Central and South America, due to human migration, there are now significant numbers of people infected with T. cruzi in the USA (>300,000), Canada (>5,500), Europe and the Western Pacific (>80,000), Japan (>3,000), and Australia (>1,500). T. cruzi infection persists throughout the lifetime of the host, if left untreated. Because of extensive sylvatic reservoirs of T. cruzi in triatomine bugs and wild mammalian hosts, eradication of the parasite in its natural habitat is unlikely. Control efforts to date have focused on large-scale release of pesticides in and around dwellings in endemic areas to prevent infestation with infected triatomines. Though eradication programs have been remarkably successful in some endemic areas, recent surveillance data suggests resurgence of human infections. Acute Chagas disease in endemic countries often occurs in children younger than 10 years old and may be asymptomatic or mild and self-limited. Approximately 10–30% of patients with acute T. cruzi infection will be symptomatic, with those ages 1–5 years at highest risk. Survivors of acute Chagas disease progress to an asymptomatic "indeterminate" stage, which can last for decades. Acute Chagas disease is treatable with appropriate and timely antiparasitic medication. Anti- parasite treatment of chronic disease is of questionable clinical benefit. Large-scale governmental programs in endemic countries aimed at preventing transmission require extensive time and money to implement and maintain. A vaccine-elicited immune response may be capable of reducing parasite burdens to a level at which host tissue injury and immune dysregulation could be minimized. Traditionally, concern for worsening of suspected autoimmune components of human response to infection has hampered vaccine development as well. Due to lack of effective and well-tolerated antiparasitic treatments, and problems plaguing vaccine development, in recent years a novel approach to reducing vector-borne transmission of T. cruzi, known as paratransgenic modification, has been developed. This technique entails genetic transformation of bacterial symbionts, which are cohabitants with T. cruzi in the gut of the triatomine bug. Symbionts are transformed to express antimicrobial peptides in the gut of the triatomine bug, which kill T. cruzi, thus preventing transmission of the parasite to humans. Proof of concept of the paratransgenic strategy for control of vectorial transmission of T. cruzi has been achieved under laboratory conditions. Field

application of this approach is still a distant prospect and would involve release of foreign genetic material into populations of triatomine bugs via engineered symbiotic bacteria. Therefore, a rigorous and comprehensive risk assessment is mandated prior to consideration of field release. An important part of this assessment involves estimating probability of transgene horizontal transfer (HGT) to environmental organisms. Since HGT plays a vital role in bacterial evolution in many natural settings, the potential for foreign genes to migrate to non target bacterial reservoirs poses a risk and should be critically evaluated. Since HGT events are, in general, of low probability, predictive models can play a valuable role as a first step in assessing environmental risk of paratransgenesis.

Targets of Proposed Research:

1. Construction of mathematical models, both deterministic and statistical, to represent the dynamics of the disease. To represent the methods of eradication, vaccination, treatment through medication both for acute and chronic stages of disease, paratransgenesis- in the models.

2. Analysis of the model to understand the dynamics of the spread of the disease and to develop techniques to counter the disease.

3. Draw inferences from the analysis so that (i) the model actually represents the disease dynamics and to (ii) provide appropriate solutions for the control of the disease at least theoretically.

4. Application of the techniques developed at field level.