INTRODUCTION
Organisms in nature compete with each other for the survival of the fittest. This competition occurs at many levels. There is always a tussle between parasite and host. Bacteria have restriction-modification system for DNA to check the organisms, such as bacteriophages infecting them. Higher animals possess an immune system to check and eliminate parasites. Immune system responds both specifically (acquired immunity) and non-specifically (innate immunity) in terms of its specificity towards the parasite/antigen encountered by it. Innate immune system responds very fast, thus it prevents and limits the pathogen before the acquired immune system takes over. B and T lymphocytes are involved in acquired immunity and recognize pathogen/antigen by clonal antigenic receptor, the B cell receptor (BCR) and the T cell receptor (TCR) respectively expressed on their surfaces. The BCR (membrane bound immunoglobulin) directly recognizes the antigen. Many pathogens can escape binding to immunoglobulin specific to them by hiding inside host cells. This problem is overcome by utilizing T cells as they recognize the peptide fragments of antigen/pathogen bound to major histocomptability complex (MHC) molecules on the surface of the antigen presenting cells (APCs) [Yague et al., 1985]. The APCs either capture the antigen from extracellular pathogens or express them intracellularly as in the case of intracellular parasites, and process it into smaller peptide fragments, to facilitate its binding to MHC molecules [Germain et al., 1993]. This whole MHC-peptide complex is recognized by T lymphocytes. Each MHC molecule bound to a given peptide (MHC-peptide complex) can be recognized by specific T cell/s. So MHC molecules are the major factor deciding which peptide will be presented to which T lymphocyte.

MHC molecules are heterodimeric, integral membrane glycoproteins. Based on their structure and function, they are divided into three major categories, the MHC class II molecules, MHC class I and the nonclassical
MHC molecules. In MHC class I and MHC class II molecules, the extracellular portions of the MHC molecule have a highly polymorphic peptide binding groove, which provides a basis for how allelic variation influences peptide binding and its recognition [Germain et al., 1993]. On the other hand nonclassical MHC molecules are monomorphic to oligomorphic [Stroynowski et al., 1990]. The peptide binding groove in MHC class I and nonclassical MHC molecules are made up of single chain, while in MHC class II molecule it is made up by two chains. MHC molecules on APCs are recognized by both TCR as well as a coreceptor expressed on T cells [Dialynas et al., 1983; Sarmiento et al., 1980]. T cells normally express either of the two coreceptor the CD4 or CD8.

MHC class I molecules are expressed on all nucleated cells and nonclassical MHC molecules are expressed in a tissue specific fashion [Stroynowski et al., 1990]. The expression of many nonclassical MHC molecules can be induced on constitutively non-expressing cells by various cytokine treatments [Wang et al., 1993; Porcelli, 1992]. MHC class I molecules and most of the nonclassical MHC molecules usually bind to peptides/antigens present in endoplasmic reticulum or cytosol [Germain et al., 1993], Lindahl et al., 1993]. MHC class I molecules binds to CD8 coreceptor expressed on a subset of T cells and thus they present antigens primarily to CD8 T cells [Sarmiento 1980]. There are few examples of T cell recognition of peptides presented by nonclassical MHC molecules and so, it would be interesting to know what kinds peptides are presented by nonclassical molecules and which immune cells recognize them, which will throw some light on their biological significance.

The CD4 coreceptor expressed on T cells binds to MHC class II molecule [Dialynas et al., 1983]. Normally B lymphocytes and cells of monocyte/macrophage and dendritic lineage express MHC class II molecules on their surface and hence are the major APCs for CD4 T cells. A successful
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T cell activation occurs only when a relevant MHC-peptide complex (the 'first' signal) is presented to an appropriate T cell along with other antigen-nonspecific accessory signals (the 'second' or costimulatory signal) from the microenvironment such as costimulatory molecules expressed by APCs, cytokines present in extracellular milieu [Lafferty et al., 1975]. Different APCs differ in their ability to deliver second signals to CD4 T cells. Presentation of MHC-peptide complexes by B cells have been shown to silence the T cells [Eynon, et al., 1992; Ephraim et al., 1992], while dendritic cells have been shown to be important for priming of CD4 T cells [Inaba et al., 1992; Levin et al., 1993]. Previous studies have demonstrated that targeting antigens to macrophages in vivo leads to generation of IgG isotype antibodies against the immunizing antigen [Chu et al., 1994] but the role of macrophages in T cell priming has not been studied in detail.

Apart from the antigen induced proliferation, T cell priming also involves the commitment of T cells towards either of the two alternate pathways for cytokine secretion, the 'type-1' (or 'Th1') or 'type-2' (or 'Th2'). Type-1 T cell responses are characterized by secretion of IL-2, IFN-γ and TNF-β, while type-2 T cell responses are associated with secretion of mainly IL-4, IL-5 and IL-10 by the T cells [Kim et al., 1985, Cherwinski et al., 1987]. Apart from these, type-1 T cells mediate delayed type hypersensitivity [DTH] reactions and help B cells for isotype switching to IgG2a [Cher et al., 1987], while type-2 T cells efficiently help B cells for class switching to IgG1 and IgE [Stevens et al., 1988]. There has been a lot of interest in studying the factors that govern the commitment of T cells towards these alternate pathways as they have been associated with either beneficial or harmful effects in many infections or autoimmune diseases [Carter et al., 1996]. A number of possible reasons have been postulated for the differential priming of T cells towards these alternate pathways. It has been proposed that these decisions are made in thymus when T cells get positively selected, or that these two
responses may chronologically follow each other, or that the APC- or microenvironment-based differences determine the choice of pathways. Early presence of IL-12 favors a type-1 based response [Hsieh et al., 1993] while earlier presence of IL-4 favors the type-2 response [Sabin et al., 1995]. However the genetic background of the mouse strain used also affects these outcome as T cells from IL-4 gene disrupted BALB/c mice fail to mount a type-1 response to *Leishmania* in presence of IL-12 [Guler et al., 1996]. There are data also showing that CD80 as a costimulatory signal favors a type-1 T cell response while, CD86 as a costimulatory signal results in type-2 T cell responses [Kuchroo et al., 1995]. B cells as APCs have been shown to prime type-2 T cell responses [Stockinger et al., 1996] while, macrophages and dendritic cells as APCs has been implicated for priming of type-1 T cell responses [Macatonia et al., 1993]. A T cell peptide epitope with higher affinity has been shown to prime type-1 T cells while a mutant variant peptide with lower affinity primes a type-2 T cell response [Pfeiffer et al., 1995]. Based on these data it has been argued that a high number of MHC-peptide complexes generated by high affinity peptides would result in priming a type-1 T cell response, and on the other hand lower numbers of MHC-peptide complexes generated by lower affinity peptides would prime a type-2 T cell response.

With this background, the role of a putative nonclassical MHC molecule in the antigen presentation has been investigated in this study using one experimental system and the regulation of quantitative and qualitative T cell immunogenicity from the point of view of presentation of MHC-peptide complexes has been investigated using a second experimental model.

For the first system a unique T cell hybridoma, 1E3, which was generated from an H-2<sup>k</sup> mouse immunized with I-A<sup>b</sup> transfected L cell fibroblasts (H-2<sup>k</sup>) has been used. Its activation, which has been shown to be
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dependent upon MHC class II in isotype and allele degenerate fashion, but not to be restricted by them or by MHC class I has been analyzed further to show that, it can also be activated by LPS-stimulated spleen cells, macrophages and macrophage cell line from mice with various haplotypes. Generation of stimulatory ligand for this T cell hybridoma has also been explored using genetically defined strains of mice. LPS treated macrophages from I-Aα- deficient mice, β2-M deficient mice or TAP-1 deficient mice can also stimulate this T cell hybridoma. Thus, it is possible that a highly conserved peptide from MHC class II molecule is being presented by a novel nonclassical MHC molecule (expressed by L cells and macrophages) to 1E3 leading to its activation.

In the second study, qualitative and quantitative changes in immune responses by increasing number of the MHC-peptide ligand complexes on macrophages in vivo have been studied using targeted delivery to scavenger receptors. Scavenger receptors are expressed on mature macrophages and to lesser extent on vascular endothelial cells and they have been utilized for targeting protein antigens to macrophages in vivo. This results in increased expression of peptide (putative T cell epitope) derived from targeted protein in context of MHC class II on macrophages. Effect of this increased antigen presentation by macrophages in vivo, on T cell responses has been analyzed in absence of adjuvant. Spleen cells from mice immunized with maleylated-diphtheria-toxoid intraperitoneally, in phosphate-buffered saline (PBS), proliferate better in vitro than those from immunized with native diphtheria-toxoid, irrespective of the recall antigens (native or maleylated) used. T cells from maleylated-diphtheria-toxoid immunized mice comparatively produced more of IFN-γ and less of IL-4 and IL-10 (Type-1 response) as compared to those immunized from native diphtheria-toxoid immunized ones. Ligation of scavenger receptors on macrophages does not seem to change the costimulatory capability of these macrophages in any
functionally critical fashion. However the higher number of appropriate MHC-peptide complexes are generated \textit{in vivo} after injection of maleyl-protein as compared to native protein.

Thus these studies have attempted to discuss the basis of a non-classical antigen recognition in one experimental system, and have investigated the control of type-1/type-2 T cell responses to exogenous antigens in another experimental model.