MHC class II molecules have been recognized as signaling receptors for more than a decade, and recent work has revealed the importance of their signaling for the immune response. Today, we know that the function of MHC class II molecules on antigen-presenting cells (APCs) is not limited to their role as antigen-presenting structures; they are flexible receptors that (Al-Daccak et al., 2004).

Intracellular signals, delivered in professional antigen-presenting cells following the engagement of major histocompatibility complex (MHC) class II molecules, activate a variety of cellular functions that also contribute to efficient antigen presentation. As far as human malignancies, the signaling ability of human leukocyte antigens (HLA) class II molecules is well-characterized in hematological tumors. Among solid malignancies, a significant proportion of human cutaneous melanomas have been shown to express HLA class II molecules, and cutaneous melanoma undoubtedly represents a 'model disease' to investigate tumor immunobiology, to unveil the molecular basis underlying the interactions between neoplastic cells and host's immune system, and ultimately to set up new bio-immunotherapeutic approaches (Altomonte et al., 2003).

SEB binds to MHC-IIα chain and to TCR β chain. Most reports show that this interaction leads to T cell activation, which causes TSS. Fewer reports are there on APCs. In APCs, SEB induces TNFα and activates protein kinase C. It is known that SEB first binds to MHC-II and then is presented to T cells; we wanted to know whether or not inhibition at first step would have any effect on TSS induction. Our data suggests that MHC-II ligation on APCs results in activation of various molecules such as G proteins, TACE, EGFR, p38MAPK and NFκB. We used different inhibitors such as Suramin (G protein inhibitor), TAPI-2 (TACE inhibitor), PD153035 (EGFR inhibitor), SB-203580 (p38MAPK inhibitor) and CAPE (NFκB inhibitor) both in vitro and in vivo to elucidate the effect these inhibitors produced on the course of TSS induction. We observed that only Suramin gives the full protection against TSS. Other inhibitors give resistance to the mice towards TSS induction, which could be because cAMP elevating agents leads to the better presentation of antigen and better effector T cell function. Moreover, cAMP also leads to the increased expression of CD80 and hence helps in increasing the co stimulation, which is the necessary factor in determining the T cell effector function. Other molecules
are downstream of G protein and do not influence cAMP generation and hence do not inhibit CD80 expression.

TACE is implicated in LPS induced shock and inhibition of TACE with hydroxamate based inhibitors leads to the protection against LPS induced shock. We also speculated the similar kind of role, and in our case, we could also get mice protected against TSS. As our earlier data suggests that two peaks of TNFα are generated when peritoneal macrophages are stimulated with SEB, Suramin and TAPI-2 inhibit both these peaks. TNFα is the main cytokine held responsible for the induction of TSS and low amount of TNF can lead proliferation of T cells by increasing CD25 on these T cells. Inhibition of both the peaks will lead to the inhibition of this early TNFα and hence will partly inhibit T cell effector function. These inhibitors also inhibit other factors such as costimulation and antigen presentation.

In APCs, we found that SEB induces activation of p38MAPK, which leads to the translocation of NFκB in nucleus. We have shown that an inhibitor of p38MAPK inhibits activation of p38MAPK in a dose dependent manner and also inhibits NFκB translocation in peritoneal macrophages. Subsequently we observed that p38MAPK inhibition results in inhibition of TNF-α production both at RNA and protein levels as shown by RT-PCR and ELISA respectively.

Since SEB first binds to macrophages and signals in, we checked whether or not inhibition of p38MAPK would lead to any changes in T cell activation by SEB. When purified T cells were co cultured with SB-203580 pretreated macrophages, they produced less IL-2 and were deficient in proliferation. Similar results were observed with NFκB inhibitor. It was further investigated whether SB-203580 can prevent the shock in vivo; it was found that injection of SB-203580 in mice prolonged their survival significantly. Since, p38 MAPK inhibition in macrophages leads to reduced IL-2 production from T cells, this was presumed that it could be an IL-2 dependent phenomenon. In order to check this, IL-2KO mice were injected with D- Gal and were challenged along with IFN-γKO and mortality was recorded.

It is well established that TNF-α is the shock inducing cytokine, which. We checked the status of TNF-α in IL-2KO mice and found that TNF-α is less in IL-2KO as compared to wild type BALB/c mice. This could be a possible reason for resistance to
shock induced by SEB. We further investigated whether there is IL-2 dependent TNF-production. For this, we reconstituted the splenocytes from IL-2KO with rIL-2 and found that TNF-α production was equivalent to that produced by BALB/c wild type. This study explains a new concept to prevent SEB induced shock.

In this study a detailed signaling pathway is deciphered which MHC class II uses in mediating the immune responses. This study will have broad implications in various autoimmune diseases like rheumatoid arthritis, diabetes and cancer.

Arthritis is a disease that causes pain and loss of movement of the joints you rely on for everyday activities. Arthritis is usually chronic. This means that it can last on and off for a lifetime. Inflammation is a reaction of the body that causes swelling, redness, pain, and loss of motion in an affected area, and is the major physical problem in the most serious forms of arthritis. The HLA-DRB1*0401 MHC class II molecule (DR4) is genetically associated with rheumatoid arthritis. It has been proposed that this MHC class II molecule participates in disease pathogenesis by presenting arthritogenic endogenous or exogenous peptides to CD4+ T cells, leading to their activation and resulting in an inflammatory response within the synovium (Hill et al., 2003, Adarichev et al., 2002, Fugger et al., 1996). In this study it is shown and shown by others earlier, that when any antigen is presented to T cells by MHC class II it activates both the cells and TNF-α is released, which is proinflammatory cytokine. TNF-α has been shown to be the main cytokine in the disease prognosis of arthritis and TSS. This study deals with modulation of TSS at APC and T cell. By inhibiting MHC-II signaling intermediates TSS induction could be modulated in mice similarly we can modulate the course arthritis induction. Arthritis is characterized by high MHC-II expression on APCs.

Insulin-dependent diabetes mellitus (IDDM) is an autoimmune disease in which the target tissue is the endocrine pancreas. Human and murine diseases share a number of similarities. Both are spontaneous, occur at a young age, have a similar genetic makeup, and progress in two steps: insulitis, followed by β cell destruction. In the nonobese diabetic (NOD) mouse, islet infiltration of T cells, B cells, macrophages, and dendritic cells starts at 3–4 wk of age (Lo et al., 1993, Miller et al 1988) and is followed by a progressive destruction of the islets over a period of a few weeks. The susceptibility to IDDM is determined by the conjunction of multiple genetic factors with unknown environmental factors (Tisch et al., 1996). In this respect, like most autoimmune diseases, IDDM develops in two stages: pancreatic injury, followed by an inappropriate
autoimmune response. A striking feature of class II molecules associated with IDDM is the presence of a serine, alanine, or valine residue at position 57 of the $\beta$-chain instead of a conserved aspartic acid in IDDM-resistant haplotypes (Tisch et al., 1996). It is well characterized that MHC class II not only present antigen but also induces signal in the cells expressing it. Inhibiting MHC class II signaling will reduce TNF-$\alpha$ from both macrophages and T cells and hence will prevent destruction of $\beta$ cells.

Increasing evidence from both human and animal studies indicates that CD4+ T cells play a central role in orchestrating the host immune response against cancer and other diseases (Wang et al., 2001). DCs have been used to develop a strategy against cancer; DCs are pulsed with cancer antigens and then injected in organisms to present antigen to T cells so that they start destroying cells, which have these antigens. This study can be used in combination with our study. MHC class II signaling activator can be injected along with these DCs to enhance the immune function, as MHC class signaling is essential for effective presentation of antigen to T cells.