Introduction
Neoplasms arising from glial cells, called gliomas, are the most common brain tumors, accounting for over 50% of all brain neoplasms. Brain gliomas are characterized by invasive growth and neovascularisation potential. Angiogenesis is a basic mechanism allowing tumor growth, and also contribute to their extremely aggressive behavior by providing oxygenation and nutrition [Lebelt et al., 2008] and removing the metabolic waste from their primary site. Considerable progress has been made in the identification of the pro- and anti-angiogenic factors produced by tumor cells and their neighboring cells. In modern medical science malignant glioma is still posing a difficult challenge due to its unique anatomy and biology. Highly invasive nature, resistance due to blood brain barrier, existence of multi drug resistance family proteins and having more than one kind of cell render the conventional therapies such as surgery, radiotherapy and chemotherapy ineffective against glioma [Maher et al., 2001; Kleihues et al., 2000; McCarthy et al., 2005; Mitchell et al., 2005]. The poor therapeutic index with conventional therapies urged cancer biologist to search for the remedies of glioma through angiogenic therapies. As an angiogenic therapy is based on the selective criteria of the body system, this modality of treatment is very promising to eliminate neoplastic growth more specifically and for that reason considered an important target for tumor treatment.

Initially it was found that sheep red blood cells (SRBC), a nonspecific biological response modifier, had been shown to exert an immunomodulatory and anti-tumor property in experimental animals as well as in human sample [Chaudhuri et al., 1991]. SRBC can form rosette and can activate human lymphocytes upon incubation with lymphocytes [Sarkar et al., 2002]. The active component of SRBC which is responsible for such effects was found to be the cell surface glycoprotein molecule, T11TS. T11-Target Structure (T11TS) is a 42 K SRBC membrane glycoprotein and the classical ligand of the E-receptor (CD2). It was found that T11TS can boost up the dampened immune status of immune suppressed glioma bearing rat model [Begum et al., 2004; Ghosh et al., 2010; Ghosh et al., 2006; kumar et al., 2012]. T11TS can also act as an apoptotic [Bhattacharjee et al., 2008] as well as cell cycle modulatory [Acharya et al., 2010] agent by inducing cytotoxic T lymphocyte mediated immune activation. Preliminary study with T11TS hinted that T11TS inhibit the production of key angiogenic molecule like, vascular endothelial growth factor (VEGF) secreted [Acharya et al., 2009] by tumor cells and it also causes the down regulation of TGFβ-1 in grade I and II glioma sample in human [kumar et al., 2012]. A tight linkage between VEGF and TGF-β secreted by tumor cell during glioma angiogenesis inspired us to delineate whether T11TS exert any significant effect over progression of angiogenesis in glioma. Thus in this backdrop, detailed analysis of angiogenic progression operative within rapidly proliferating glioma associated endothelial cells (ECs) were necessary. During progression of glioma angiogenesis several changes occur including proliferation,
differentiation, migration of EC by degradation of the extracellular matrix by matrix metalloproteinases (MMPs) particularly MMP-2 & MMP-9 [Forsyth et al., 1999], capillary tube formation mediated by various angiogenic factors such as Integrin αvβ3, and CD144[Hynes et al., 1992; Giancotti et al., 1999; Van der Flier et al., 2001]. These factors cause the activation of EC and involves in the expression of angiogenic phenotypic (CD31 & CD34) marker on EC. This expression accelerates the interaction between cell to cell and signaling in the downstream pathway for the proliferation of EC. Simultaneously, CD144/β-catenin constitutes an important pathway regulating the signaling or multiple biological processes such as endothelial cell permeability, migration and assembly of new blood vessels [Breviario et al., 1995; Navarro et al., 1995; Vittet al. 1996]. CD44 is a class I transmembrane glycoproteins, participating in the regulation of a number of diverse processes in normal physiologic condition e.g., leukocyte recruitment, and lymphocyte homing, but in pathologic conditions causes, tumor growth and spread [DeLisse et al., 2009]. The multistep development of cancer is also regulated by inflammatory cells, like monocytes/macrophages, and T lymphocytes which fully participate in the angiogenic process by secreting pro- and anti-inflammatory cytokines that could control endothelial cell (EC) proliferation, their survival and apoptosis, as well as their migration and activation. In recent years, light has been shed on the connection between inflammation-related miRNA as well as tumor angiogenesis [Porta et al., 2009]. Inflammation-induced angiogenesis is accompanied by macrophage infiltration. Interleukin-8 (IL-8), which is released from macrophages as well as EC during a host inflammatory response, also activates ECs through their auto and paracrine function. The progression of angiogenesis is also the result of an intricate balance between proangiogenic and anti-angiogenic soluble factors. In tumor microenvironment low concentration of IL-4 and IL-10 influence the tumor angiogenesis and tumor growth.

In this thesis work an attempt has been made to throw some light over the alternations of growth factor mediated angiogenic signaling through cell to matrix and cell to cell cascades which ultimately culminate into angiogenic control after therapy with T11TS in glioma bearing rats. Growing lines of evidence has indicated that inflammatory associated cytokines control the endothelial cell activation, migration and proliferation. So, simultaneously we undertook the present study to evaluate whether T11TS administration in-vivo glioma model also modulates inflammatory cytokines. This preclinical study in glioma model provides provocative preliminary evidence that warrants further investigation on T11TS as a potential anti-angiogenic therapeutic agent for treating human glioma.