Abstract
In order for a cell to interact and adapt to its environment, the cell needs receptors to recognize and respond to external signals. These signals tell a cell to migrate, proliferate, or specialize. Without receptors, a cell would be unable to function within its environment. One group of receptors that enable a cell to interact with its environment are the integrins. There are several families of integrins, one of which is the β3 family, Cyr61, a protein associated with breast cancer, wound healing, and vascular diseases such as atherosclerosis and restenosis, is an activation-dependent ligand of the β3 integrin family. This group of adhesive receptors mediates cell-cell and cell-extracellular matrix interactions. One of the two family members is αβ3, an integrin expressed on the surfaces of endothelial cells, smooth muscle cells, monocytes, platelets, and osteoclasts. Binding of Cyr61 to αβ3 stimulates angiogenesis, the creation of blood vessels, and migration of tumor cells.

αβ3 integrin commonly binds to the amino acid sequence RGD (arginine, glycine, and aspartic acid) on many extracellular molecules such as vitronectin and fibronectin, however, Cyr61 binds to αβ3 via a unique sequence. When a ligand binds to αβ3 integrin, a conformational change in αβ3 initiates a signaling cascade that results in increased cell migration. Over-expression of αβ3 can lead to life-threatening cancers such as breast cancer, melanoma, and colon cancer. Understanding and finding a way to restrict the expression and activation of αβ3 integrin may lead to a new treatment of tumors with decreased side effects compared to conventional chemotherapy.

Introduction
Conventional chemotherapy is a common treatment for cancer, but it still has many flaws and side-effects. Chemotherapy is designed to destroy fast-growing cancer cells, but unfortunately, the drug also attacks other rapidly-growing cells such as hair and blood cells. In addition, some cancer cells grow slowly; therefore, the drug may not detect the cancer. One potential treatment that scientists are working on is blocking the binding of an angiogenesis-inducing protein, Cyr61, to an integrin, αβ3. αβ3 is expressed in blood vessel cells, and plays a role in angiogenesis (the growth of blood vessels). When the two proteins (Cyr61 and αβ3) bind, it causes a cascade of signals to create more blood vessels, which enhances tumor growth. Blocking the binding of these two proteins could potentially be an alternative to conventional chemotherapy.

The connection between RGD & Cyr61
RGD (arginine, glycine, and aspartic acid)
- RGD is the binding site of αβ3
Cyr61
- Plays a role in regulating cell survival or apoptosis
- A 20-residue sequence in domain II of Cyr61 binds to αβ3
- Pro-angiogenic
- Plays a role in wound healing and cancer cell migration

Cyr61 mutated at D125 in the VWF domain is hindered in binding to αβ3

Cyr61 (CCN1) and synthetic peptides V1-V4 which correspond to domains 1-4 of Cyr61 were used to coat tissue culture plates (see graph above). BSA (Bovine Serum Albumin) is used as a control. Human umbilical vascular endothelial cells (HUVECs) were added to the culture wells and allowed to adhere for 30 minutes. The degree of adhesion was measured by methylene blue staining. The cells bound to Cyr61 (CCN1) and V2. This is because V2 supports binding to αβ3 (as shown in Figure A). In Figure B, where BSA does not bind to the synthetic peptides, there is not a reaction (V1, V3, and V4). We can use this data to create a potential cancer preventing drug.

Conclusion
Creating an artificial peptide sequence or small molecular inhibitor to prevent the binding of Cyr61 to αβ3 is potentially beneficial to treating cancerous tumors. The artificial peptide sequence would bind to αβ3 and block the process of angiogenesis, cutting off the tumor’s ‘food’ supply causing the tumor to disintegrate. This could lead to a potential treatment with less side effects compared to conventional chemotherapy.

Citations
Chen, N et al. Identification of a novel integrin αβ3 binding site in CCN1 (Cyr61) critical for pro-angiogenic activities in vascular endothelial cells. Journal of Biological Chemistry. (279) 44166-44176. 2004