

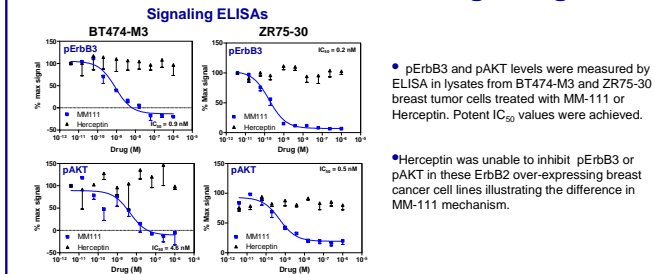
MM-111: a novel bispecific antibody targeting ErbB3 with potent antitumor activity in ErbB2 over-expressing malignancies

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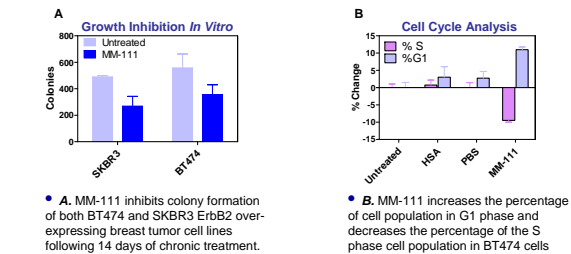
Abstract

ErbB3 has been identified as a preferred dimerization partner of ErbB2, critical for driving the proliferation of ErbB2 over-expressing breast tumors. We have designed a bispecific antibody, MM-111, which inhibits ligand-induced phosphorylation of ErbB3 with sub-nanomolar potency by exploiting the abundant expression of its dimerization partner, ErbB2, for specific targeting to cancer cells that express both receptors. We employed computational physicochemical modeling to guide the kinetic optimization of the monovalent binding affinities to the ErbB2 and ErbB3 receptors to increase the potency and specificity of MM-111 for tumor cells. We have demonstrated that MM-111 inhibits activation of the phosphatidylinositol 3-kinase pathway *in vitro* and *in vivo*, resulting in attenuation of tumor proliferation. Inhibition of growth by MM-111 has been observed in several murine xenograft models including BT474 and MDA-MB-361 breast tumors. While the antitumor activity of MM-111 is positively correlated with ErbB2 expression levels, MM-111's potent inhibition of ErbB3 phosphorylation and signaling downstream from this receptor differs markedly from currently available therapies targeting ErbB2 over-expressing breast tumors and thus provides a novel approach to treatment for these malignancies. In conclusion, our data demonstrate that the combination of computational biology with antibody engineering has resulted in the development of a promising, novel therapeutic, MM-111, that has potent antitumor activity in malignancies driven by the ErbB2/3 oncogenic unit.

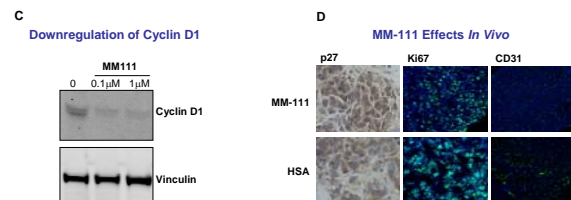
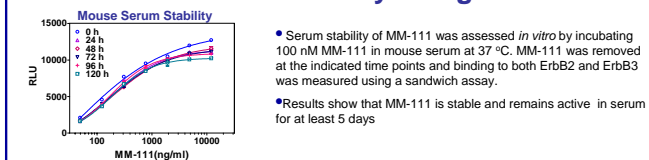
MM-111 Inhibits ErbB3 Signaling



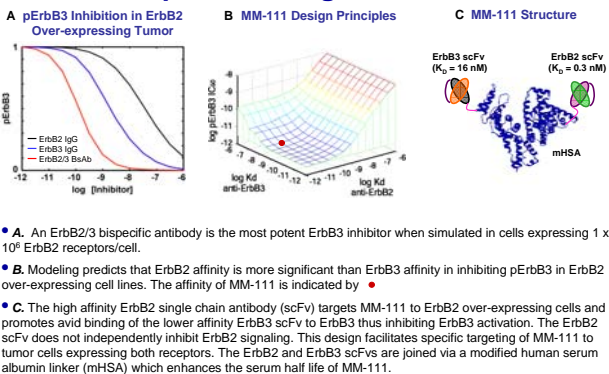
MM-111 Inhibits Tumor Proliferation



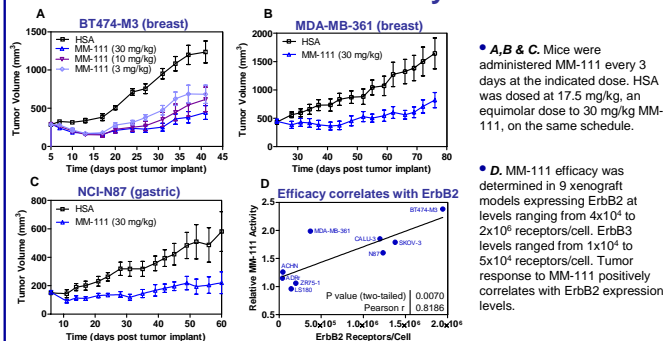
MM-111 is Stable under Physiological Conditions



Bispecific Design of MM-111



In Vivo Antitumor Activity of MM-111



Summary

- ErbB3 signaling is increasingly reported as a resistance mechanism in ErbB2 +ve breast tumors treated with currently approved tyrosine kinase inhibitors.
- A combination of computational biology and protein engineering has been utilized to generate an optimal bispecific antibody, MM-111, for inhibition of ErbB3 signaling in ErbB2 over-expressing tumors.
- In vivo* xenograft studies show that the anti-proliferative activity of MM-111 results in a potent antitumor response which positively correlates with ErbB2 expression levels.
- MM-111 is a promising, novel therapy for the treatment of ErbB2 +ve breast cancers that may offer an alternative approach in tumors that are resistant to Herceptin or Tykerb.