Debouganin (deB) is a de-immunized form of bouganin, a Ribosome Inactivating Protein (RIP) that when internalized blocks protein synthesis. DeBouganin conjugated to trastuzumab (T-deB) and T-DM1, a variant of bouganin, has been created through the genetic linking of small molecule payloads. Not only was a greater potency for deBouganin demonstrated that demonstrates potent antitumor activity when delivered in the absence of antibodies, Trastuzumab and C6.5 diabody armed with deBouganin overcome drug resistance to ADCs comprised of anti-microtubule agents Taxol and C225, ribosome inactivating protein - Shigella dysenteriae (T-deB) or the gemtuzumab-odotaxil (MMAE) conjugate of antiherb-C20 which contains a payload of a single cell internalization mechanism.

**RESULTS**

- **No significant proliferation is measured with any of the deB-C6.5 diabody treated cell lines**
- **HCC1419 cells surviving T-DM1 or T-MMAE treatment continue to grow while BT-474 surviving cells remain viable and show minimal growth.**

**Mechanisms of resistance in T-DM1 and T-MMAE Treated Cells**

- Potency of both doxorubicin and trastuzumab is completely or partially restored in the presence of MDR1, MRP1 or BCRP inhibitors.
- Co-treatment with inhibitors is largely ineffective at restoring T-DM1 or T-MMAE cytotoxicity.

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**Growth Profile of Treated Cell Lines**

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