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Abstract 2689: Breast cancer inhibition by a novel and potent biguanide, N1-hexyl-N5-benzyl-biguanide

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Metformin is a widely used biguanide diabetes drug that is associated with decreased breast cancer risk and is currently being studied for treatment and prevention of breast cancer. While metformin and biguanides buformin and phenformin exhibit inhibitory activity against breast cancer in vitro and in vivo, they lack potency (IC50=5-20 mM) and their mechanisms of action remain unclear. More potent biguanides may provide insights into biguanide anti-cancer activity and we therefore studied the novel biguanide N1-hexyl-N5-benzyl-biguanide mesylate (HBB), which potently inhibits the MCF-7 and MDA-MB-231 breast cancer lines (IC50=20 uM for both lines). HBB induces AMPK phosphorylation in both lines at 10 uM concentration, whereas similarly dosed metformin, buformin or phenformin exhibits no activity. HBB also inhibits STAT3 phosphorylation at 10 uM concentration, whereas metformin dosed at 10 uM exhibits no activity. HBB reduced the mitochondrial membrane potential of both lines, but the effect was more prominent in the MDA-MB-231 line. HBB also induced ROS within 2.5 hours of exposure in the MCF-7 and MDA-MB-231 lines and caused rapid necrosis, but not apoptosis. N-acetylcysteine provides partial protection from HBB for MDA-231 line, but not the MCF-7 line. HBB provides proof of principle that highly potent biguanides can be synthesized with at least 250-fold greater potency than metformin, which can provide insights into the cancer inhibitory mechanisms of biguanide drugs. R01 CA113570, Randy Shaver Foundation, CTSI University of Minnesota