**Bombesin 3 receptor: a novel target for the deadliest cancer**

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**Introduction.** Despite significant treatment advances, lung cancer remains one of the biggest killers of Australians. Highly innovative strategies are urgently needed to target lung cancer with a limited side effect profile. Early evidence suggests that the orphan G protein-coupled receptor, bombesin 3 (BB3), may be overexpressed in cancer and functionally absent in healthy tissue, presenting a unique opportunity for a biologically selective target for cancer.

**Aims**. First, to characterise expression of BB3 and determine the extent of its biological selectivity in cancer. Then, to validate recently described synthetic ligands and the pharmacological properties of BB3 that have otherwise been poorly characterised. Finally, to develop a highly disease-relevant model to measure the impact of BB3 activity in cancer.

**Methods**. Gene expression data was mined from RNA-sequencing databases and extracted as transcripts per million RNA reads (TPM) for BB3 and control genes. To measure constitutive and synthetic agonist activity at BB3, HEK293 cells were co-transfected with BB3 and luciferase reporter plasmids with and without agonist stimulation. A high-throughput GCaMPassay was used to measure increases in Ca2+ following BB3 agonism. Human lung cancer organoids expressing BB3 were incubated with BB3 agonists and changes to disease phenotype and cell viability were measured.

**Results.** BB3 mRNA was found exclusively in lung adenocarcinoma (LUAC), and not in adjacent healthy lung, other cancers and other healthy human tissue. BB3 expression in LUAC was more prevalent (83%) than any other LUAC marker (<44%). BB3 signals in the absence of ligand via the Gαq/11, Gα12/13, and Gαs pathways, and agonism increases Ca2+. Lung cancer organoids expressing BB3 were assessed for morphological and molecular characteristics of cancer in the absence and presence of BB3 ligands.

**Discussion.** The exclusive expression of BB3 in LUAC offers the possibility of selective and targeted treatment in a disease with high resistance to chemotherapy and other clinically used drugs. Barriers to BB3’s development as a LUAC target have been overcome with our characterisation of the receptor’s pharmacology and development of a disease-specific model. This study awards us the opportunity to engineer targeted therapies that exploit BB3’s unique pharmacology in lung cancer.