Background
Glucagon-like peptide 1 (GLP-1) is an incretin hormone released from enterodocrine L-cells in the gut. GLP-1 analogues and dipeptidyl-peptidase-4 inhibitors are currently used to treat type-2 diabetes. A greater understanding of the mechanisms underlying the release of GLP-1 may facilitate the development of therapeutics to stimulate the release of endogenous GLP-1. Bile acids have been shown to induce GLP-1 release via the G protein-coupled bile acid receptor 1 (GPBAR1/TGR5) and increased cAMP. The apical sodium-dependent bile acid transporter (ASBT) and nuclear farnesoid X receptor (FXR) may also be involved.

Approach
Enterodocrine cells, such as the GLP-1 releasing L-cells, make up less than 1% of intestinal epithelial cells. The study of these specialised cells is facilitated by transgenic mice expressing fluorescent sensors (Epcac2zmps or GCaMP3) specifically in L-cells. GLP-1 release was measured from primary murine intestinal cultures and tissue segments mounted in Ussing chambers using a MesoScale Discovery assay.

Aim
To identify pathways of bile acid-stimulated GLP-1 secretion and whether these are activated from the apical or basolateral direction.

Results

1. Bile acid-induced GLP-1 secretion
GPBAR1 is activated preferentially by TLCA or its specific agonist GPBAR-A (GP-A), however TDCA is a significantly stronger stimulant at 100μM.

2. Intracellular CAMP is increased by bile acids
Measured in intestinal cultures using a FRET-based fluorescent cAMP sensor, Epcac2zmps, expressed specifically in L-cells.

3. Bile acids stimulate influx of Ca2+
Measured in intestinal cultures using a fluorescent calcium sensor, GCaMP3, expressed specifically in L-cells.

4. Bile acid uptake via ASBT
An ASBT-inhibitor (ASBT-i) has no effect upon bile acid induced GLP-1 secretion and intracellular Ca2+ changes in intestinal cultures.

5. Bile acids stimulate GLP-1 secretion from the basolateral side
Basilical stimulation by TDCA is blocked by an ASBT inhibitor.

6. GPBAR1 is essential for bile acid stimulated GLP-1 secretion

Conclusion
Bile acids stimulate GLP-1 secretion primarily via activation of GPBAR1 on the basolateral surface of intestinal L-cells. This suggests the stimulation of gut hormone secretion may include post-absorptive mechanisms. It could impact the design of therapeutics which target GPBAR1 as a means of increasing endogenous gut hormone secretion.