Research

Epithelial Stem Cells

The availability of robust cell-surface markers for identifying and isolating epithelial stem cells is essential for studying both their normal *in-vivo* function during tissue renewal and for evaluating their contribution to cancer. Such markers are also invaluable for facilitating purification of these stem cell populations for therapeutic applications.

The Wnt target gene Lgr5, an orphan G-protein-coupled receptor, has been shown to mark adult stem cells in a variety of adult organs, including the intestine, skin, stomach, kidney and mammary gland. In the intestine, Lgr5 stem cells are responsible for initiating cancer following mutation. The presence of Lgr5-expressing cells in human cancers of the gastrointestinal tract has also led to speculation that Lgr5 marks a population of cancer stem cells.

Nick Barker's group will employ genetic mouse models and *ex-vivo* organoid culture methods to dissect the role of Lgr5 stem cells in epithelial self-renewal and cancer of various organs, including the stomach and ovary. The ultimate goal is to harness the regenerative capacity of these adult stem cells for therapeutic use, as well as developing ways of blocking the cancer-promoting activities of mutated Lgr5 stem cells.

To achieve this, we will employ the following approaches:

1. *In-vivo* lineage tracing using the Lgr5-EGFP-ires-CreERT2 mouse model in combination with state-of-the-art multi-color reporter mice to assess Lgr5 stem cell function during epithelial renewal.

2. Intra-tumor lineage tracing from candidate Lgr5 cancer stem cell populations in mouse gastric cancer and ovarian cancer models.

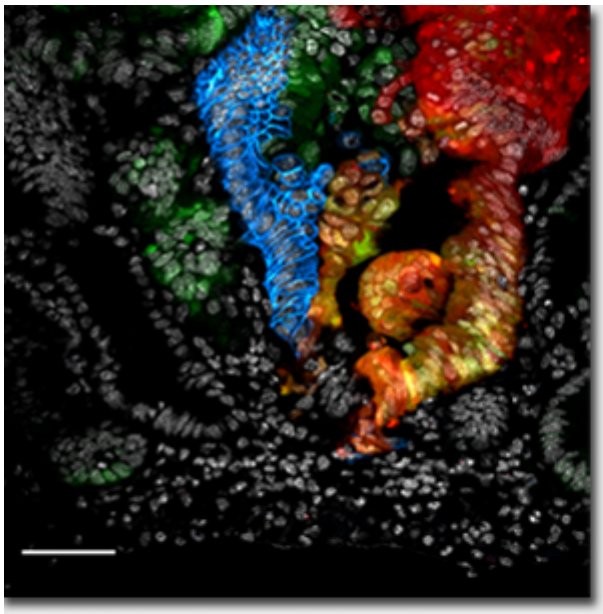
3. Targeted mutation of Lgr5 stem cells in the stomach and ovary using the Lgr5-EGFP-ires-CreERT2 mice in combination with conditional mouse lines to assess the tumor-initiating potential of the Lgr5 stem cells.

4. Gene expression profiling of Lgr5 stem cell populations to reveal novel stem cell markers.

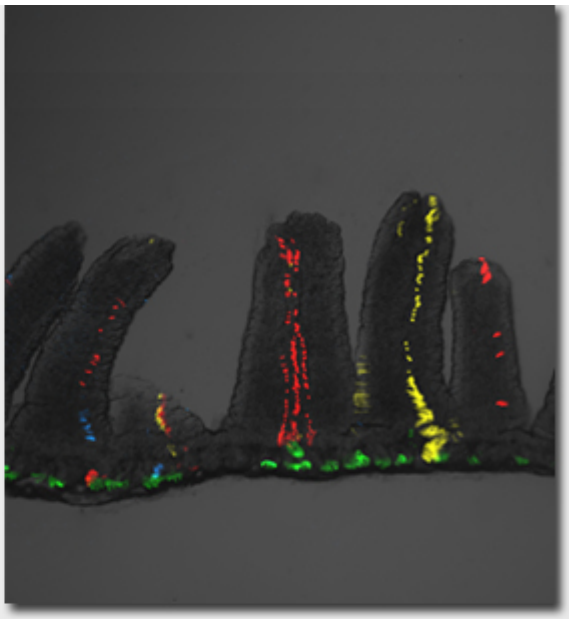
5. Conditional knockdown of Lgr5 on adult stem cells and their cancer counterparts to assess Lgr5 function *in-vivo*.

6. Develop human organoid culture systems for both basic research and potential therapeutic applications.

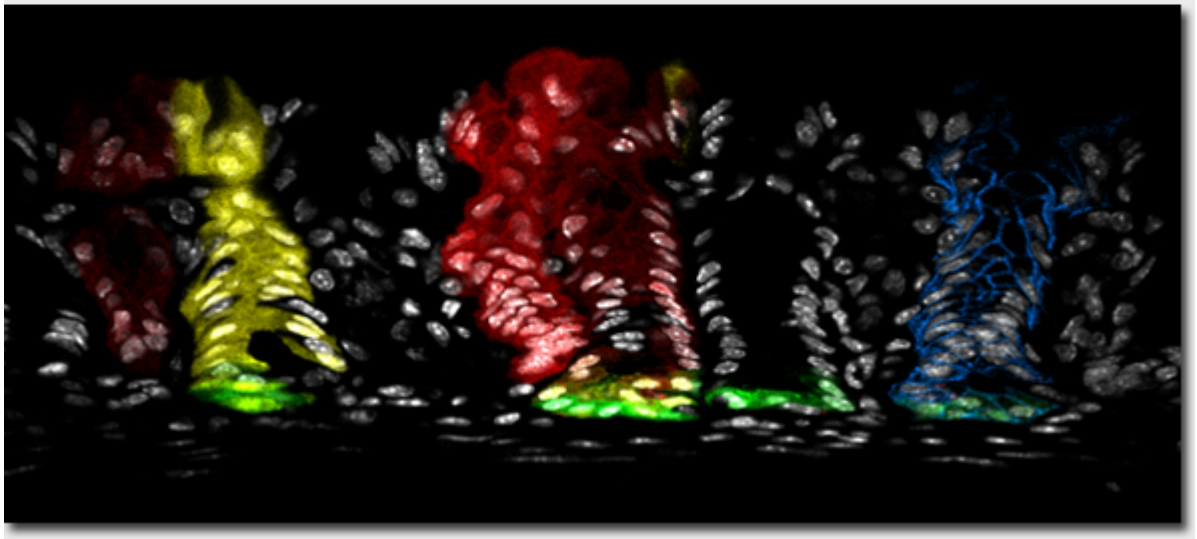
For more information, please contact Nicholas Barker.



Intestinal adenoma induced by targeted mutation of Lgr5-positive intestinal stem cells in an *Lgr5eGFP-Ires-CreERT2/Apcfl/fl/KrasG12D/R26-Confetti* mouse.



Lgr5 stem cell driven 4color lineage tracing in the intestine.



Lgr5 stem cell driven 4color lineage tracing in the pyloric stomach.