Lgr5 stem cells in epithelial self-renewal and cancer of the stomach

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The availability of robust cell-surface markers for identifying and isolating adult stem cells is essential for studying both their normal in-vivo function during tissue renewal and for evaluating their contribution to cancer. The Wnt target gene Lgr5 is expressed at the base of prospective corpus and pyloric glands in the neonatal stomach, whereas expression in the adult is predominantly restricted to the base of mature pyloric glands. Lineage tracing reveals these $Lgr5^{+ve}$ cells to be self-renewing, multipotent stem cells responsible for the long-term renewal of the gastric epithelium. Using a novel *in-vitro* culture system, single $Lgr5^{+ve}$ cells efficiently generate long-lived organoids resembling mature pyloric epithelium. Selectively deletion of the APC tumor suppressor gene in the gastric stem cells rapidly initiates adenoma formation, supporting a role for aberrant Wnt pathway activation in the gastric stem cells as a route to gastric cancer.

Tumor-resident $Lgr5^{+ve}$ cells in colorectal cancers are considered to be potential cancer stem cell populations. Here, we demonstrate using both Wnt-driven gastric cancer mouse models and primary human biopsies that a subset of human gastric cancers also harbor populations of $Lgr5^{+ve}$ cells. We aim to isolate these tumor-resident $Lgr5^{+ve}$ cells for in-depth expression profiling to reveal novel biomarkers and for evaluating their cancer stem cell properties in our in-vitro culture system and xenograft assays. Our current progress will be presented here.

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EDUCATIONS/TRAINING

1988-1992	Heriot-Watt University, Riccarton, Edinburgh
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POSITIONS AND HONORS

1995-2001	Postdoctoral Fellow, University Medical Center Utrecht, the Netherlands
2001-2005	Senior Research Scientist, Semaia Pharmaceuticals BV, the Netherlands
2006-2010	Staff Scientist, Hubrecht Institute, Utrecht, the Netherlands
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2010-present	Visiting Professor at Center for Regenerative Medicine (CRM), Edinburgh

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1. Muñoz J, Stange DE, Schepers AG, van de Wetering M, Koo BK, Itzkovitz S, Volckmann R, Kung KS, Koster J, Radulescu S, Myant K, Versteeg R, Sansom OJ, van Es JH, Barker N, van Oudenaarden A, Mohammed S, Heck AJ, Clevers H (2012). The Lgr5 intestinal stem cell signature: robust expression of proposed quiescent '+4' cell markers. ***EMBO J.*** Jun 12. [Epub ahead of print]
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