**Intestinal Stem Cells**

*New concepts and methods*

Toulouse, November 21\textsuperscript{st} 2013

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**Intestinal Stem Cell Culture: A new era for in vitro discovery**

Recent discoveries in biomarker identification and culture methods have fueled a rapid expansion in our understanding of how intestinal stem cells (ISCs) behave in physiology and disease. Our work focuses on describing how the Sox (Sry-Box) family of transcription factors contribute to intestinal stem cell identity and also how these factors influence differentiation and epithelial regeneration. Development of a Sox9EGFP mouse model has enabled the differential isolation of bone fide stem cells that are consistent with 'active' and 'reserve' states. Single 'active' ISCs marked by low levels of Sox9EGFP are able to generate self-sustaining spherical units in long-term 3-dimensional culture conditions. These epithelial structures are termed enteroids (small intestine) or colonoids (colon) and recapitulate the ISC, progenitor and differentiated cellular compartments found in vivo. During post-irradiation regeneration, high-expressing Sox9 cells function as an ISC pool, re-entering cell cycle and adopting ISC-like gene expression and function. Results from these murine studies have also facilitated isolation of human ISCs. A remaining and significant challenge in the field is efficient and quantitative use of culture methods to answer detailed mechanistic questions. In collaboration with biomedical engineers, we have developed novel micro-scale devices to study single ISCs or enteroids/colonoids in long-term culture. These platforms combined with mouse and human intestinal epithelial culture will serve as an in vitro foundation to study a broad range of conditions including cancers, inflammatory bowel disease, congenital birth defects, and ischemic injury.