Erasmus University Rotterdam CSC PhD 2015

Project Description

School/Faculty:	Dept. of Gastroenterology and Hepatology Erasmus Medical Center (Research school: Erasmus Postgraduate School Molecular Medicine)
Project Title:	**Molecular Mechanisms Controlling Mucus Production in Colorectal Cancer: A Prominent Role for ATOH1**
Abstract:	Worldwide more than 1.2 million colorectal cancer (CRC) cases are diagnosed every year, of which 10-25% present with high mucus levels associated with worse prognosis. Currently, the mechanism responsible for the high mucus production is unknown. ATOH1 is the master regulator of mucinous differentiation in the intestine, which is proteolytically degraded in most CRCs. However, for unknown reasons ATOH1 escapes degradation in mucinous cancers leading to high mucus levels. Therefore, the key to understand the high mucus production is to unravel why ATOH1 remains active in these tumors. We propose that one or more proteins involved in proteolytic regulation of ATOH1 will be altered in functionality. We have identified novel candidate ATOH1 interactors, which will be analyzed for their role in proteolytic regulation of ATOH1 and mucinous differentiation. Moreover, to reveal whether these interactors show altered expression or mutation specifically within mucinous tumors, we will apply immunohistochemistry and mutational analysis on a collection of 120 mucinous tumors. In addition, to facilitate the study of mucinous CRC, we will establish a transgenic model in which ATOH1 is induced in intestinal tumor cells leading to mucinous differentiation. These experiments will increase our understanding of the mechanisms contributing to the strong mucinous differentiation observed in these cancers. This knowledge may be exploited to reduce mucin production in CRC thereby increasing effectiveness of anti-cancer agents, or lead to the identification of targeted therapies.
Requirements of candidate:	Background: Molecular Biology/Cell biology/Medicine Master degree: Yes IELTS Grade: 7.0 (minimal 6.0 per component) or TOEFL: 100 (minimal 20 per component)

Supervisor information:	**Dr. M.J.M. (Ron) Smits** Dept. of Gastroenterology and Hepatology Erasmus MC University Medical Center Rotterdam T: +31 10 7035944 E: m.j.m.smits@erasmusmc.nl Selected publications (from ~ 60 peer-reviewed publications): ▪ Barry ER, Morikawa T, Butler BL, Shrestha K, de la Rosa R, Yan KS, Fuchs CS, Magness ST, **Smits R**, Ogino S, Kuo CJ, Camargo FD (2013). Restriction of intestinal stem cell expansion and the regenerative response by YAP. **Nature** 493**:** 106-110. ***(IF=42.3)*** ▪ Bakker ER, Hoekstra E, Franken PF, Helvensteijn W, van Deurzen CH, van Veelen W, Kuipers EJ, **Smits R** (2013). beta-Catenin signaling dosage dictates tissue-specific tumor predisposition in Apc-driven cancer. **Oncogene** 32**:** 4579-4585. ***(IF=8.6)*** ▪ Bakker ER, Das AM, Helvensteijn W, Franken PF, Swagemakers S, van der Valk MA, ten Hagen TL, Kuipers EJ, van Veelen W, **Smits R** (2013). Wnt5a promotes human colon cancer cell migration and invasion but does not augment intestinal tumorigenesis in Apc1638N mice. **Carcinogenesis** 34**:** 2629-2638. ***(IF=5.3)*** ▪ Raghoebir L, Bakker ER, Mills JC, Swagemakers S, Kempen MB, Munck AB, Driegen S, Meijer D, Grosveld F, Tibboel D, **Smits R***, Rottier RJ* (2012). SOX2 redirects the developmental fate of the intestinal epithelium toward a premature gastric phenotype. **J Mol Cell Biol** 4**:** 377-385. ***(* equal contribution, IF=8.4)*** ▪ Bakker ER, Raghoebir L, Franken PF, Helvensteijn W, van Gurp L, Meijlink F, van der Valk MA, Rottier RJ, Kuipers EJ, van Veelen W, **Smits R** (2012). Induced Wnt5a expression perturbs embryonic outgrowth and intestinal elongation, but is well-tolerated in adult mice. **Dev Biol** 369**:** 91-100. ***(IF=3.6)*** ▪ van Veelen W, Le NH, Helvensteijn W, Blonden L, Theeuwes M, Bakker ER, Franken PF, van Gurp L, Meijlink F, van der Valk MA, Kuipers EJ, Fodde R, **Smits R** (2011). beta-catenin tyrosine 654 phosphorylation increases Wnt signalling and intestinal tumorigenesis. **Gut** 60**:** 1204-1212. ***(IF=13.3)*** ▪ Albuquerque C, Bakker ER, van Veelen W, **Smits R** (2011). Colorectal cancers choosing sides. **Biochim Biophys Acta Rev Cancer** 1816**:** 219-231. ***(IF=7.6)*** ▪ Robanus-Maandag EC, Koelink PJ, Breukel C, Salvatori DC, Jagmohan-Changur SC, Bosch CA, Verspaget HW, Devilee P, Fodde R, **Smits R** (2010). A new conditional Apc-mutant mouse model for colorectal cancer. **Carcinogenesis** 31**:** 946-952. ***(IF=5.3)*** ▪ Gaspar C, Franken P, Molenaar L, Breukel C, van der Valk M, **Smits R**, Fodde R (2009). A targeted constitutive mutation in the APC tumor suppressor gene underlies mammary but not intestinal tumorigenesis. **PLoS Genet** 5**:** e1000547. ***(IF=8.2)*** ▪ Kielman MF, Rindapaa M, Gaspar C, van Poppel N, Breukel C, van Leeuwen S, Taketo MM, Roberts S, **Smits R**, Fodde R (2002). Apc modulates embryonic stem-cell differentiation by controlling the dosage of beta-catenin signaling. **Nat Genet** 32**:** 594-605. ***(IF=29.6)*** ▪ Fodde R, **Smits R** (2002). Cancer biology. A matter of dosage. **Science** 298**:** 761-763. ***(IF=34.5)*** ▪ Fodde R, **Smits R**, Clevers H (2001). *APC*, signal transduction and genetic instability in colorectal cancer. **Nature Reviews Cancer** 1**:** 55-67. ***(IF=37.9)***