

## Intestinal tumor development in Lynch Syndrome: a role for the microbiota?

W. Pieters<sup>1\*</sup>, K. Wojciechowicz<sup>1</sup>, E. Cantelli<sup>1</sup>, E. Delzenne-Goette<sup>1</sup>, H. te Riele<sup>1</sup>

\*(lead presenter) w.pieters@nki.nl

<sup>1</sup> The Netherlands Cancer Institute, Department of Tumor Biology & Immunology, The Netherlands

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Lynch syndrome (LS) is an hereditary cancer predisposition syndrome that is mostly caused by defects in the DNA mismatch repair (MMR) genes MLH1 and MSH2. LS patients have an increased lifetime risk of developing a range of neoplasms including colorectal cancer.

Our research group has developed an inducible mouse model that closely mimics the clinical situation in the intestine of LS patients carrying a defective MSH2 allele (Wojciechowicz et al., 2014). After administration of tamoxifen, Lgr5-CreERT2;Msh2flox/- (Msh2-Lynch) mice have been shown to carry about 5% MSH2-deficient intestinal crypts. Since the cells of these crypts lack functional MMR, they have an increased mutational burden and may develop into intestinal tumors. Exposure of Msh2-Lynch mice to the methylating agent temozolomide (TMZ) led to expansion of the MSH2-deficient cell compartment and accelerated tumor development (Wojciechowicz et al., 2014). Strikingly, a change in the housing conditions (conventional housing to SPF) almost fully ablated intestinal tumor development. Having excluded genetic events as the underlying cause of the phenotype, we explored the composition of the gut microbiome between the two facilities. Using 16S rDNA sequencing and principal component analyses (PCoA), we demonstrated that the microbial composition of mice housed in SPF conditions is distinct from that of conventionally housed mice. Furthermore, we have identified microbiomes that are comparable to that of mice from the conventional facility. RNA sequencing and whole exome sequencing of intestinal (tumor) tissue from mice housed in either of the two facilities allowed us to elucidate the effects of a different micro-environment on intestinal (immune) homeostasis. We are currently trying to dissect the interplay of components of the microbiota, inflammation and the immune system on intestinal tumor development in Msh2-Lynch mice. We utilize chemical colitis models as well as microbial transplantation studies in order to divulge distinct factors that modulate cancer risk in LS.