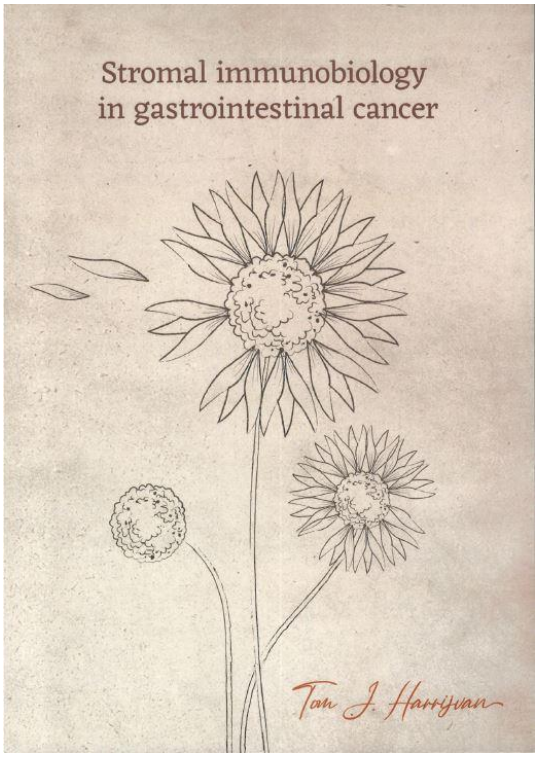

Samenvatting van het proefschrift

T.J. Harrijvan
"Stromal immunobiology in gastrointestional cancer"

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The goal of this thesis was to gain insight into the interactions between cancer-associated fibroblasts (CAFs) and cells of the immune system, together comprising the field of stromal immunobiology, in colorectal carcinoma (CRC) and pancreatic ductal adenocarcinoma (PDAC). The interactions between CAFs, tumor-specific T cells and myeloid cells are studied as well as interventions aimed at alleviating the suppressive effects of CAFs on immune cell function. Emphasis is put on CAF subsets that have immunomodulatory properties, as have been currently identified in several GI cancers. Our research shows a novel mechanism of CAF-mediated, tumor-specific T cell inhibition, through cross-presentation of neoantigens by CAFs that leads to decreased T cell function. Furthermore, we tried to recreate a representative cellular tumor-microenvironment in vitro to further study the role of CAF-immune cell interactions in a multicellular context. This aided in studying the multicellular interactions between CAFs, hepatocytes and neutrophils in promoting CRC-metastasis to the liver. Moreover, we studied the possibility of targeting CAFs by use of oncolytic viruses, with a focus on reovirus. We show that certain CAFs, based on expression of Junctional Adhesion Molecule-A (JAM-A), are susceptible to killing by oncolytic reovirus and that this potentially enhances subsequent

infection of adjacent tumor cells. Finally, we studied factors regulating JAM-A expression in CAFs, and through chemical modulation try to enhance CAF susceptibility to reovirus infection, to try and further broaden the applicability of reovirotherapy in GI cancer treatment. In conclusion, our results further add to the view that a combinatorial approach of targeting both immunoregulatory CAFs while also promoting the anti-tumor response by the immune system can act synergistically and that this might help in further advancing the use of immunotherapy in GI oncology.