Summary

This thesis describes the results of pharmacogenetic studies for the association of germline genetic polymorphisms with drug effects of capecitabine and oxaliplatin in patients with advanced colorectal cancer (ACC) from the CAIRO and CAIRO2 study.

The first section of the thesis focuses on general pharmacogenetic considerations.

Chapter 2 gives an overview of information from pharmacogenetic publications available until the time when the research leading up to this thesis was initiated. In addition to pharmacogenetic considerations for capecitabine and oxaliplatin, irinotecan and the targeted drugs bevacizumab and cetuximab are also addressed.

In the analyses described in **chapter 3**, we compared genotyping results in DNA samples extracted from peripheral blood derived leukocytes, with results in DNA extracted from archived colorectal tumor samples in the same patients. We found an almost complete concordance between both sample types for the selected polymorphisms, with only 1.4% of sample pairs showing unequal genotypes. Conflicting results were shown to result from logistic errors, rather than somatic mutations or loss of heterozygosity in at least half of all discordant sample pairs.

In the second section of this thesis, four candidate-gene studies are described. Capecitabine pharmacogenetics is addressed first, followed by two studies focusing on the pharmacogenetics of oxaliplatin.

In **chapter 4**, we investigated the effect of two common polymorphisms in the gene encoding for methylene tetrahydrofolate reductase (*MTHFR* 677C>T and *MTHFR* 1298 A>C) on capecitabine-induced adverse events. We found that neither polymorphism was associated with the incidence of severe (grade 3 or higher) toxicity, regardless whether expressed as overall toxicity, or specific adverse events, including hand-foot syndrome, diarrhea and febrile neutropenia. Also, no effect of these polymorphisms on patient survival upon capecitabine treatment for ACC was found.

Chapter 5 describes a study for the effect of eight germline polymorphisms on efficacy of capecitabine in ACC patients. Four single nucleotide polymorphisms were selected based on their location in the methionine synthase reductase (*MTRR*) gene, and another four markers were included because of their significance in a recently published *in vitro* genome wide association study (GWAS). Our results showed, however, that none of the selected markers are useful predictors of capecitabine efficacy in ACC.

In **chapter 6**, results are presented for our study investigating the association of variation in the genes encoding for organic cation transporter 1 (OCT1, *SLC22A1*), OCT2 (*SLC22A2*) and the human multidrug and compound extrusion protein 1 (hMATE1, *SLC47A1*) on the incidence and severity of oxaliplatin-induced neurotoxicity. We found that homozygote carriers of the rare allele of *SLC22A1* Arg61Cys had a reduced risk of severe neurotoxicity,

regardless of the cumulative dose of oxaliplatin. None of the other selected polymorphisms were associated with oxaliplatin-induced neurotoxicity.

Chapter 7 focuses on the effect of the common, synonymous SNP *ERCC1* C118T on DNA repair capacity after administration of oxaliplatin. Using *in vitro* transfection experiments, we showed that this SNP does not affect cellular DNA repair, or cell survival upon oxaliplatin administration. In addition, our clinical association analysis in ACC patients found no effect of *ERCC1* C118T genotype on patient survival upon second-line or third-line treatment with oxaliplatin.

After the pathway-based analyses in the previous chapters, the last section of this thesis describes a study applying a genome wide association approach.

Chapter 8 describes a GWAS searching for germline genetic markers for the prediction of progression free survival (PFS) of ACC patients treated with either capecitabine-oxaliplatin-bevacizumab (CAPOX-B), or CAPOX-B plus cetuximab. We found that a cluster of SNPs on chromosome 8 that was associated with PFS, with almost genome wide significance. More importantly, a marker on chromosome 2 showed a significant effect on PFS, that was opposite in both treatment arms. The minor allele was associated with increased PFS in patients receiving CAPOX-B plus cetuximab, but a reduced PFS in patients treated only with CAPOX-B.