

## **Colorectal Cancer Research group**

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### **Discipline and Location of laboratory:**

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### **Description of current research interests:**

In colorectal cancer (CRC), a proportion of patients with early stage (TNM stage I or II) disease still die of recurrent or metastatic disease within 5 years of diagnosis despite undergoing "curative" resection. The implication is that tumour cells with metastatic potential had already escaped from the primary tumour, before or at the time of surgery, into the bloodstream or the peritoneal cavity [1]. Currently, adjuvant chemotherapy is only offered to more advanced stage patients but is still only effective in reducing mortality by 40% and recurrence by 33%. Development of resistance to chemotherapy drugs remains a major problem. The benefit of adjuvant chemotherapy in stage II patients has not been clearly established and its toxic side effects are a dose-limiting factor. Due to such problems, chemotherapy is only offered to patients with advanced disease, and is not recommended for early stage patients. Development of a tumour-specific therapy is warranted to overcome the problems of chemo-resistance and the often severe toxicity associated with non-specific cytotoxic drugs.

In the clinic, a novel antibody, cetuximab is available to treat metastatic CRC. Cetuximab targets EGFR by binding to the extracellular binding domain, preventing activation of tyrosine kinase within the cytoplasmic domain and inhibiting autophosphorylation and downstream signalling via several pathways including the Ras/Raf/MAPK pathway and PI3K/Akt pathway. It has been shown recently that response to this treatment is dependent on the presence of wild type *K-ras*. However, there is a proportion of patients with wild-type *K-ras* that are resistant to cetuximab, possibly due to constitutive activation of members of the PI3K/Akt pathway or loss of the *PTEN* tumour suppressor gene function. The aim is to identify biomarkers of tumour resistance to therapies directed at the EGFR.