Chapter 2

Scope and Aim

SCOPE

Fibrosis is a pathological process, associated with the majority of chronic diseases, which causes the accumulation of extracellular matrix (ECM) proteins. Fibrosis is the endpoint of, among others, an inflammatory process and results in the replacement of normal tissue with ECM. Fibrosis can occur in various organs, including kidney, liver, intestine and lung. Among these, intestinal fibrosis (IF) is a major complication in inflammatory bowel disease, especially in Crohn's disease. IF greatly hampers normal physiological functioning of the bowel and the only therapeutic option currently available is surgery. In **chapter 1** the background, basic mechanisms and available markers of IF are introduced. Additionally, the available *in vivo* and *in vitro* models for IF are described, illustrating that it is difficult to unravel the mechanisms underlying IF due to a lack of appropriate models. Moreover, the potential of using precision-cut tissue slices as a novel *ex vivo* model for IF is delineated.

Chapter 3 details the application of precision-cut intestinal slices (PCIS) as a novel model for IF. In this chapter, the early onset of IF was studied in both human and rodent PCIS. Furthermore, since current drug therapies for IF are lacking, the slices were used to evaluate the antifibrotic effect of various inhibitors related to the TGFβ or PDGF pathway (**chapter 4**).

The search for a potential antifibrotic compound was further explored in **chapter 5**. Here, organ- and species-specific antifibrotic effects of rosmarinic acid were investigated using precision-cut intestinal and liver slices prepared from rodent and human tissue.

Renal fibrosis is an integral part of chronic kidney disease, and similar to IF, effective therapeutic modalities are lacking due to the absence of suitable disease models (**chapter 1**). In **chapter 6**, kidney-specific antifibrotic effects were studied in more detail using precision-cut kidney slices. The slices were used to elucidate the impact of TGFβ1 on the development of renal fibrosis and to evaluate the potential antifibrotic effects of IFNγ and PPB-PEG-IFNγ.

Finally, the outcome of all studies and future perspectives are discussed in **chapter 7**.

AIM

The aims of this thesis are to investigate whether the *ex vivo* model of precision-cut tissue slices, prepared from intestine and kidney, can be utilized as a novel model to investigate the pathophysiological mechanisms of fibrosis. Moreover, determine whether the *ex vivo* model is a potential tool that can used to assess the antifibrotic effects of various compounds.