

## Department of Internal Medicine

### Division of Gastroenterology and Hepatology

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#### Research Activities

##### *Alimentary Tract*

1. Examination of new biomarkers to assess disease activity in inflammatory bowel disease

1) Prostaglandin E-Major Urinary Metabolite as a Reliable Surrogate Marker for Mucosal Inflammation in Ulcerative Colitis

We evaluated whether prostaglandin E-major urinary metabolite (PGE-MUM) can be used as a biomarker for Ulcerative colitis. Areas under the receiver operating characteristic curves of simple clinical colitis activity index, Mayo endoscopic scoring, and Matts' grading (Histologic Activity) for PEG-MUM were each higher than for CRP.

The main advantage of PGE-MUM appears to be differentiation of colonoscopic or histologic remission from active disease in UC. On the other hand, this maker of UC patients in remission was lower compared to healthy volunteers. By comparison to CRP level, PGE-MUM level demonstrated better sensitivity for reflecting UC activity, especially in cases of histologic inflammation, and thus seems to be a better evaluator of mucosal healing.

According to this result, we have conducted a comparison trial to detect a most reliable marker for detecting endoscopic mucosal healing in UC patients among immunochemical fecal occult blood test, fecal calprotectin, and PGE-MUM.

2) The clinical benefit of serum and tissue IL-6 to assess disease activity and severity in inflammatory bowel disease

Levels of serum IL-6 are relevant to UC and CD as well as systemic inflammatory responses. Herein, we hypothesized the serum and tissue IL-6 level might be helpful to predict the treatment efficacy in UC and CD especially for the evaluation of anti-TNF-alpha antibody treatment.

2. The development of molecular-specific cancer theranostics

We have developed a method for molecular-specific phototherapy based on near-infrared fluorescence molecular imaging.

3. Nutrition treatment for inflammatory bowel disease

The intake of n-3 PUFA and the subsequent associated efficacy for the maintenance of

remission may be achieved by understanding the importance of n-3 diet therapy.

#### 4. The study of fatty acids in CD

In CD patients, various fatty acids were specifically altered in both plasma and erythrocytes, and p-PA and p-CDFAI are potentially useful as new serological markers for CD.

#### *Liver*

##### 1. The development of targeting therapy for cancer stem cells in liver cancers

The only curative treatments for primary liver cancers are surgical resection for early-stage patients. However, most patients are diagnosed at advanced stages by which time extant therapies are ineffective. Therefore, the identification of novel molecules that can become targets for future therapies is urgently needed. We have reported that 1) SALL4 regulates cell fate decision in hepatic stem/progenitor cells during normal liver development 2) SALL4 is indicative of aggressiveness and poor prognosis and maintains the stemness of cancer stem cells in liver cancers. Further analyses on cancer stem cell-mediated mechanisms may provide a novel future therapeutic strategy against liver cancers.

##### 2. Pathogenesis, mRNA and miRNA expression profiling of primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH)

The pathogenesis is unknown in autoimmune liver disease. To investigate the pathogenesis and identify novel therapeutic targets, we analyzed mRNA and miRNA expression in CD4+ T cells derived from 14 PBC patients using microarray analyses. We found that decreased expression of four miRNAs (miR-425, -181a, -181b, -374b) which dysregulate TCR signaling in PBC-CD4 T+ cells. Especially, the decreased miR-425 expression strongly induced inflammatory cytokines via N-Ras upregulation in the TCR signaling pathway, suggesting that the restoration of decreased mir-425 or the suppression of N-Ras may be a promising immunotherapeutic strategy against PBC.

##### 3. The relationship between nutritional condition and neuropsychological test results in liver cirrhosis patients

Liver cirrhosis (LC) cases complicate minimum hepatic encephalopathy (MHE) and have caused some traffic accidents and communication problems. Neuropsychological disturbance is typical of MHE. However, the diagnostic criteria for MHE have not yet been clarified. We studied the pathophysiological findings of MHE using a neuropsychological test (NPT) and food frequency questionnaire (FFQg). 17% of LC patients were Digit Symbol Test (DST)-abnormal. DST-abnormal was related to Child-Pugh score, serum albumin, Branched chain amino acid & Tyrosine Ratio, nutrient intake as usual energy intake, and fat energy ratio. Thus, NS using the FFQg may be a useful method to prevent MHE.

##### 4. The investigation of Frailty index in elderly digestive disease patients

We evaluate whether simplified Frailty Scores are associated with clinical outcomes or adverse outcomes after treatments in elderly patients over 80 years old with digestive disease.

*Gall bladder and Pancreas*

## 1. The mechanistic effects of cigarette smoking for pancreatic cancer development

We have commonly recognized as that cigarette smoking is a major risk factor of human malignancies including pancreatic cancer. In spite of recent remarkable advances in medicine, pancreatic cancer is a malignant tumor which cannot be overcome by any available therapeutic strategies under the circumstances. Therefore, in view of effective prevention for such a refractory disease, we think that the understanding of the specific mechanisms related to the effects of cigarette smoking as a major risk for pancreatic cancer development can be helpful for a reduction in number of the patients. Now we are planning a basic research which demonstrates the underlying mechanisms of cigarette smoking in pancreatic cancer progression through autophagy pathway.

## 2. Clinical trial of a surveillance targeted IPMN patients by using EUS for early detection of pancreatic cancer

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is considered to be a premalignant lesion. The incidence of pancreatic cancer in patients with IPMN is higher than that of the general population. In addition, by the time pancreatic cancer is discovered in patients with IPMN, it has frequently progressed to an unresectable advanced stage. Endoscopic ultrasonography (EUS) is considered the most trusted imaging modality for evaluating pancreatic cystic diseases including IPMN. Thus, we think that an investigation of beneficial surveillance by using EUS for IPMN patients as high risk populations of pancreatic cancer is crucial for the early detection and can lead the patients to curative surgical resection.

## 3. Clinical analysis of long-term management for autoimmune pancreatitis

It is still controversial whether low-dose steroid treatment is indispensable for maintaining remission of autoimmune pancreatitis (AIP) or not. In addition, taking the adverse effects of steroid into consideration, the required dosage and the specific characteristics of the possibilities of the recurrence should be defined in the expected guidelines. By using clinical data of our AIP patients, we will evaluate them comprehensively and will try to suggest the diagnostic criteria for the management of AIP.

## 4. Clinical research about the relationship of gut microbiota and oxidative stress with pancreatic cancer

Gut microbiota has been received substantial attention as a current research topic in various diseases including malignant tumors. Especially, the effects of short-chain fatty acid (SCFA) in several cancers were reported in some previous studies. Oxidative stress which is a risk factor of senescence is also a recent focused theme in cancer research. However, both of the effects of SCFA and oxidative stress in pancreatic cancer growth are still unknown. Therefore, we will assess the clinical usefulness of several SCFA and oxidative stress markers in our pancreatic cancer patients as the potential diagnostic/prognostic marker.

5. The investigation of Wilm's tumor protein 1 (WT1) - pulsed dendritic cell vaccines for the advanced pancreatic cancer patients

WT1 targeted cancer vaccine may be effective in patients with pancreatic ductal adenocarcinoma.

6. The trend of disease of the hepatobiliary system in super-aging society

The opportunities to examine super-elderly patients over 80 years old with digestive disease have significantly increased in our hospital. Thus, we investigate the clinical characteristics and outcomes of super-elderly patients over 80 years old with digestive disease, including chronic hepatitis C, acute cholecystitis, and acute cholangitis. Moreover, we investigate the safety and usefulness of nab-Paclitaxel and Gemcitabine combination therapy in elderly patients with pancreatic cancer over 75 years old and Tolvaptan in elderly patients with cirrhosis over 75 years old.

7. The investigation of the relationship between biliary tract disease and inflammation-based prognostic scores

Inflammation-based prognostic scores have been reported to have prognostic value in patients with various types of cancer. These inflammation-based prognostic scores have also been shown to correlate with outcomes or disease severity in patients with, sepsis, acute heart failure, and Crohn's disease. Therefore, we evaluate whether the inflammation-based prognostic scores are associated with disease severity in patients with acute cholangitis. We demonstrated the relationship between the inflammation-based prognostic scores and disease severity in patients with acute cholecystitis.

## Publications

**Matsuoka K<sup>1</sup>, Kobayashi T<sup>1</sup>, Ueno F<sup>1,2</sup>, Matsui T<sup>1</sup>, Hirai F<sup>1</sup>, Inoue N<sup>1</sup>, Kato J<sup>1</sup>, Kobayashi K<sup>1</sup>, Kobayashi K<sup>1</sup>, Koganei K<sup>1</sup>, Kunisaki R<sup>1</sup>, Motoya S<sup>1</sup>, Nagahori M<sup>1</sup>, Nakase H<sup>1</sup>, Omata F<sup>1</sup>, Saruta M, Watanabe T, Tanaka T<sup>1</sup>, Kanai T, Noguchi Y<sup>1</sup>, Takahashi K<sup>1</sup>, Watanabe K<sup>1</sup>, Hibi T<sup>1</sup>, Suzuki Y<sup>1</sup>, Watanabe M<sup>1</sup>, Sugano K<sup>1</sup>, Shimosegawa T<sup>1</sup> (Japanese Society of Gastroenterology, <sup>2</sup>Ofuna Central Hospital).** Evidence-based clinical practice guidelines for inflammatory bowel disease. *J Gastroenterol.* 2018; **53**: 305-53.

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**Reviews and Books**

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