THEME-BASED RESEARCH SCHEME
PUBLIC SYMPOSIUM 2024
主題研究計劃研討會

Fighting Disease Recurrence and Promoting Tissue Repair after Liver Transplantation: Translating Basic Discoveries to Clinical Excellence

Project number: T12-703/19-R

Aim of study

To improve the long-term outcomes of liver transplantation (LT) by tackling two major recurring diseases including hepatocellular carcinoma (HCC) recurrence and hepatitis B virus (HBV) reactivation through exploring underlying mechanisms, identifying efficacious biomarkers, and developing potential treatments by integrating basic, translational and clinical research.

Goal: Predict smart! Treat right! Live longer!

Research Team

Advisory Committee

Clinical oriented study design

Clinical issues in liver transplantation

Liver Diseases
- Hepatitis B (HBV), Cirrhosis
- Hepatocellular carcinoma (HCC)

Living donor liver transplantation
- Fatty liver
- Small-for-size

Post-transplantation
- HCC & HBV Recurrence
- Graft fibrosis, NASH

Research themes

Theme I: HCC recurrence

Delineation of regional specialization of immune system in HCC recurrence after liver transplantation

Theme II: HBV recurrence

Development of novel non-invasive strategies for overcoming HBV reactivation after liver transplantation

Theme III: Tissue repair

Novel therapeutics to overcome graft injury by engineered cells for tissue repair and liver regeneration

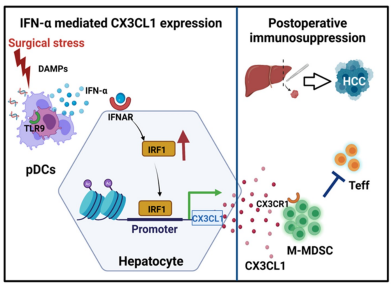
Key findings of Theme I: Cancer recurrence

(Outputs: 19 International publications; 24 Awards; 16 invited lectures; 39 Conference abstracts)

1. *Novel Mechanisms of regional immune regulation*

Dendritic Cells

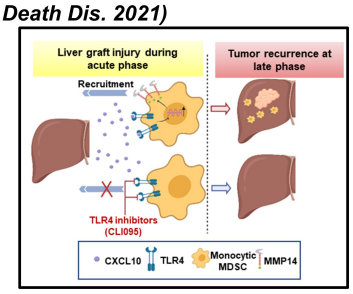
Postoperative plasmacytoid dendritic cells (pDCs) drive HCC recurrence. ***(Cancer Letters 2021) (Cancer Research 2022) (Rising Star Award 2021) (Young Investigator Awards 2023)***



pDCs promote HCC recurrence (*Cancer Research* 2022)

MDSCs

- MDSCs-induced activation of NLRP3 inflammasome promotes HCC recurrence after steatotic graft liver transplantation. ***(JHEP Report 2023)***
- Monocytic MDSCs mobilization promotes tumor recurrence. ***(Cell Death Dis. 2021)***



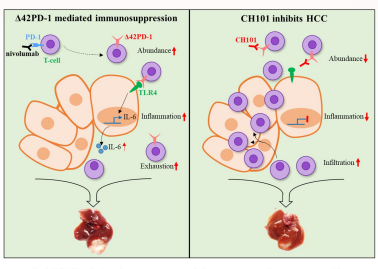
Monocytic MDSCs promote HCC recurrence (*Cell Death Dis.* 2021)

NK Cells & T Cells

- Post-transplant TLR4-induced NKG2A+ natural killer (NK) cells promote HCC recurrence after LT. ***(Young Investigator Award 2024)***
- CXCR6+CD69+ liver-resident memory CD8 T cells reduce HCC recurrence after LDLT. ***(Young Investigator Award 2024)***
- Tumor-derived iron loaded-exosomes impair CD8+ T anti-tumor ability via ferroptosis in HCC. ***(Young Investigator Award 2022 & 2024)***

2. *Novel Therapies for HCC*

- Δ42PD-1 is a novel immunotherapeutic target of HCC. ***(Gut 2023) (Faculty Outstanding Research Output Award 2023)***
- Implemented precise in situ delivery of a photo-enhanceable inflammasome-activating nanovaccine to activate anti-cancer immunity. ***(Cancer Res 2024)***
- Clinically implemented stereotactic body radiation for the treatment of HCC on waitlist for liver transplant. ***(Hepatology. 2021)***



Δ42PD-1 to be a novel immunotherapeutic target of HCC (*Gut 2023*)

3. *Novel Prediction Models*

- Established P3C-UCSF-AFP score in predicting HCC recurrence after LT. ***(Hepatol Int 2023)***
- Synergized multi-disciplinary collaboration in using machine learning to develop prognostic models for liver transplantation and liver diseases ***(ITC-MRP 2022)***

TRS THEME-BASED RESEARCH SCHEME
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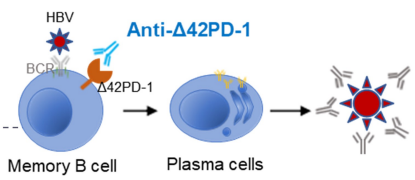
Key findings of Theme II: HBV Recurrence

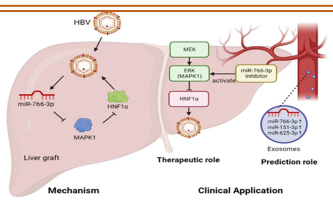
1. Novel mechanisms and therapeutic intervention of Δ42PD-1 B cells in HBV reactivation after liver transplantation

- Rapid up-regulation of Δ42PD-1 on B cells contributes to HBV reactivation after liver transplantation. The Δ42PD-1-SHP1 axis causes memory B cell exhaustion.
- Δ42PD-1-specific monoclonal antibody is an effective therapeutic intervention for B cells responses and HBV therapy. ***(GRF 2022, APCMV Congress 2024)***



2. Novel circulating biomarker for HBV reactivation after liver transplantation

- Upregulation of exosomal miR766-3p significantly associates with HBV reactivation after liver transplantation. Inhibition of miR766-3p functionally suppresses HBV infection. ***(ILTS Annual Congress 2021, IDDF 2022)***

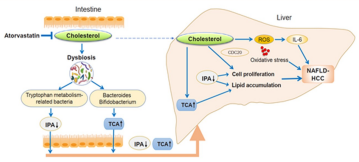


Key findings of Theme III: Tissue Repair & NASH/NAFLD-HCC

(Outputs: 36 International publications; 19 Awards; 37 invited lectures; 27 Conference abstracts)

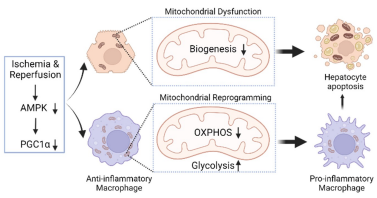
1. Novel mechanisms of steatotic graft injury and NASH

- Revealed the mechanisms of dietary cholesterol in driving gut microbiota-associated fatty liver-associated liver cancer. ***(Gut. 2021)***



Mechanism and therapeutic target of cholesterol-induced NAFLD–HCC development *(Gut. 2021)*

- Deciphered the role of mitochondrial metabolic reprogramming in steatotic graft injury after LT. ***(Ann Surg 2022)*** ***(Cell Mol Gastroenterol Hepatol 2023)***



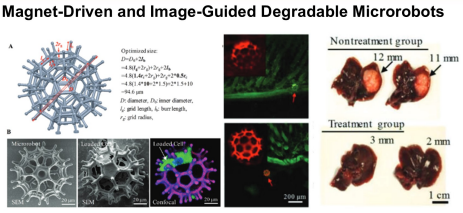
AMPK-PGC1α axis regulates mitochondrial homeostasis in steatotic graft *(Ann Surg 2022)*

- Uncovered the distinct role of beta-catenin mutation in NAFLD-associated liver cancer. ***(J Hepatol 2022)***
- Identified the mechanism of altered portal vein serum metabolome in contributing to human HCC. ***(Gut. 2022)***
- Delineated the mechanism of Squalene epoxidase in inducing NASH. ***(Gastroenterology 2021)***
- Unveiled the mechanism of METTL3 in driving the development of NAFLD-related HCC. ***(Cell Rep Med 2023)***

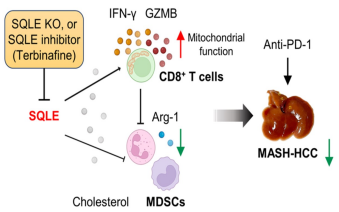
2. Novel therapies for graft injury and NASH/NAFLD-HCC

- Developed magnetic-driven microrobot-assisted cell therapy and embolization for the treatment of HCC. ***(Small 2021)***

Magnet-Driven and Image-Guided Degradable Microrobots



- Targeted SQLE to restore anti-PD-1 efficacy in metabolic dysfunction-associated steatohepatitis-induced HCC. ***(Gut. 2024)***



Targeting SQLE promote anti-PD-1 therapy response in MASH-HCC *(Gut. 2024)*

- Utilized *P.distasonis* with dietary inulin to suppress NASH ***(Nat Microbiol 2023)***
- Identified TUBB4B as a novel therapeutic target in NAFLD-HCC. ***(J Pathol 2023)***

Achievements and Impacts

Clinical Impacts

- Translated the anti-Δ42PD-1 immunotherapy into clinical trial for the treatment of HCC

Faculty Outstanding Research Output Award 2023 for the jointed publication in *Gut 2023*

- Conducted the first prospective trial using the combination of immunotherapy and locoregional treatment as conversion therapy for advanced HCC

Innovative Invention & Translations

- A patented bionic liver-in-cube for precision oncology & a spin-off biotech company (CRF, ITC-MHKJFS, ITC-TSSSU, HKSTP Incubio)

- China Association of Inventions Award & Gold Medal at 49th Geneva Inventions 2024

International Recognitions

- ILTS Basic Science Established Investigator Award 2022 – Kwan Man

- ILTS Rising Star Award & Young Investigator Award 2022 – Tao Ding & Zhe Wang

- ILTS Vanguard-Basic Science Award 2023 – Jiang Liu & Li Pang

Organized Conferences

- The Annual Congress of HKSI 2023/24

- HKSA Submit on Life Science Technology, Innovation and Translation 2023

- The 18th Congress of Asia Society of Transplantation 2023

Sustainable Collaborations

- Joint Beijing Key Laboratory of LT and Bionic Manufacturing
- New Laboratory at HKU Materials Innovation Institute for Life Sciences and Energy

- Medical-Engineering collaborations with CityU