DIGESTIVE DISEASES

01

Principal Investigator

Professor Jun Yu

Team Members

Joseph Sung | Francis Chan | Henry Chan | Vincent Wong | Grace Wong | Dennis Wong | Jennifer Zhang

Research Progress Summary

The Role of Gut Microbiota in the Pathogenesis of GI Cancers

Colorectal Cancer (CRC)

The team led by Professor Jun Yu is the first to profile the Archaea composition of gut microbiota in CRC. Using faecal microbiomes of 2 large cohorts of patients with 585 participants (184 patients with CRC, 197 patients with adenomas, and 204 healthy individuals). They revealed that the Archaea profiles are distinct in faecal samples from CRC, adenomas and healthy individuals, with enrichment of halophilic together with the depletion of methanogenic archaea in CRC. In particular, the halophilic Natrinema sp. J7-2 increased progressively in samples from control individuals, to patients with adenomas, to patients with CRC. With a panel of 9 archaea species, they distinguished CRC patients from healthy controls with high sensitivity and specificity. Collectively, they showed that enteric archaea composition is altered during CRC (*Gastroenterology 2020*).

The team investigated the role of the altered gut microbiome in mediating promoter hypermethylation, a hallmark of cancer, in CRC. Integrative analysis of gut microbiome composition (16S rRNA-seq) and methylation sequencing identified a significant association of gut microbiota with promoter hypermethylation of tumour suppressor genes. In particular, *Fusobacterium nucleatum* and *Hungatella hathewayi* were identified as the top two methylation-regulating bacteria, and their abundance was correlated with CDX2 and MLH1 promoter methylation, respectively. Mechanistically, they demonstrated that *Fusobacterium nucleatum* and *Hungatella hathewayi* up-regulated expression of DNA methyltransferase. Epigenetic dysregulation thus represents a novel mechanism whereby gut microbiota promotes CRC (*Microbiome 2020*).

Gastric Cancer (GC)

Helicobacter pylori is associated with gastric inflammation, pre-cancerous gastric atrophy (GA) and intestinal metaplasia (IM). In this study, the team aimed to identify novel microbes associated with gastric dysplasia one year after *H. pylori* eradication. They analysed 587 *H. pylori*-positive patients treated with *H. pylori* eradication therapy (N=295) or placebo (N=292). Analysis of the microbial sequences revealed that bacterial diversity was increased after *H. pylori* eradication. Moreover, a distinct cluster of oral bacteria comprising *Peptostreptococcus, Streptococcus, Parvimonas, Prevotella, Rothia* and *Granulicatella* were associated with the emergence and persistence of GA and IM. This study thus identified that gastric microbes other than *H. pylori* contribute to gastric carcinogenesis after *H. pylori* eradication (*Gut 2020*).

Non-alcoholic Fatty Liver Disease (NAFLD)-associated Hepatocellular Carcinoma (NAFLD-HCC)

NAFLD-HCC is an emerging malignancy in the developed world. Here, the team established a role of dietary cholesterol driving NAFLD-HCC through modulating gut microbiota and its metabolites. High dietary cholesterol led to the sequential progression of steatosis, steatohepatitis, fibrosis and eventually HCC in mice, concomitant with insulin resistance. Cholesterol-induced NAFLD-HCC formation was associated with gut microbiota dysbiosis, with the enrichment of *Mucispirillum, Desulfovibrio, Anaerotruncus* and *Desulfovibrionaceae*; while *Bifidobacterium* and *Bacteroides* were both depleted in high-fat high cholesterol (HFHC)-fed mice. Gut dysbiosis contributed to metabolic alterations, including increased taurocholic acid and decreased 3-indole propionic acid. The transplantation of stools from HFHC-fed mice into germ-free mice resulted in lipid accumulation, inflammation and cell proliferation. Finally, they showed that statin treatment could reverse gut dysbiosis and prevented NAFLD-HCC development. They, therefore, established a causative role of gut dysbiosis in the development of NAFLD-HCC (*Gut 2020*).

The Application of Gut Microbiota in Cancer Diagnosis and Prevention

GI Cancer Diagnosis

There is an urgent need for early detection of CRC at the precancerous-stage adenoma stage. In this study, the team identified a novel faecal *Lachnoclostridium* marker suitable for the diagnosis of adenoma. Using two independent cohorts of 1012 subjects (274 CRC, 353 adenomas and 385 controls), they showed that '*m3*' from a *Lachnoclostridium sp* was enriched in adenoma. Faecal *m3* showed better performance than *F. nucleatum* in distinguishing adenoma from controls, whereas *F. nucleatum* performed better for detection of CRC. *m3* also performed better than FIT in detecting adenoma. Moreover, combining *m3* with FIT improved sensitivity for an advanced adenoma to 56.8%. A combination of *m3* with *F. nucleatum, Clostridium hathewayi, Bacteroides clarus* and FIT performed the best for diagnosing CRC (specificity=81.2% and sensitivity=93.8%). This study thus identifies a novel bacterial marker *m3* for the non-invasive diagnosis of colorectal adenoma (*Gut 2020*).

GI Cancer Prevention

1. Gut microbiota significantly contributes to drug metabolism. In this work, the team studied the impact of gut microbiota in the chemopreventive efficacy of aspirin in mice models of CRC. They utilised both genetic- and chemically-induced CRC models, and revealed aspirin is chemoprevention only in mice treated with antibiotics, but not in mice with intact microbiota. Concordantly, aspirin also prevented CRC in germ-free mice, but not in conventionalised germ-free mice. Mechanistically, they showed that an intact microbiota is associated with decreased plasma levels of aspirin. They further identified *Lysinibacillus sphaericus* as a key bacterium that degrades aspirin. Germ-free mice fed *L. sphaericus* had lower plasma levels of aspirin than germ-free mice that were not fed this bacterium. Increased abundance of *L. sphaericus* also correlated with lack of efficacy of aspirin in CRC models. Thus, they showed that gut microbiota might interfere with the chemopreventive effect of aspirin in CRC (*Gastroenterology 2020*).

2. The team has identified a novel probiotic, *Streptococcus thermophiles*, that is depleted in CRC. Oral gavage of *S. thermophilus* significantly reduced tumour formation in both $Apc^{min/+}$ and chemically-induced CRC in mice. Co-incubation with *S. thermophilus* or its conditioned medium also reduced the proliferation of CRC cells. Mass spectrometry identified β-Galactosidase as a critical protein produced by *S. thermophiles*. β-Galactosidase inhibited cell growth, lowered colony formation, induced cell cycle arrest, and promoted apoptosis of CRC cells. β-Galactosidase mediates its effect via production galactose, which interfered with energy homeostasis to activate oxidative phosphorylation and downregulate the Hippo pathway kinases, which partially mediated the anticancer effects of *S thermophilus*. In conclusion, *S thermophilus* is a novel prophylactic for CRC prevention in mice via secretion of β-galactosidase (*Gastroenterology 2020*).

Investigation of the Genetic and Epigenetic Mechanisms Underlying the Pathogenesis of GI Cancers

Mutant KRAS CRC is resistance to targeted therapy and the development of novel targets is an urgent need. Mutant KRAS promotes glutaminolysis, a process that depends on SLC25A22. Using colon-specific SLC25A22 knockout mice, the team demonstrated that SLC25A22 is essential for colorectal tumourigenesis of $Apc^{Min/+}Kras^{G12D}$ mice. They showed that mutant KRAS cells maintained a low ratio of *α*-ketoglutarate to succinate via SLC25A22, resulting in reduced 5-hydroxymethylcytosine-a marker of DNA demethylation, and hypermethylation at CpG sites. SLC25A22-associated DNA hypermethylation resulted in the silencing of WNT suppressors, which in turn, activate WNT signalling and tumourigenesis. In particular, WNT gene targets related to cancer stemness, including LGR5, is down-regulated upon knockout of SLC25A22 in KRAS-mutant CRC cells, implying that SLC25A22 promotes cancer stemness. Knockout of SLC25A22 in CRC cells that express mutant KRAS increased their sensitivity to 5-fluorouracil, validating this gene as a potential therapeutic target in KRAS-mutant CRC (*Gastroenterology 2020*).

RNA N6-methyladenosine (m6A) modification has recently emerged as a novel regulatory mechanism in cancer progression. They aimed to explore the role of m6A regulatory enzyme METTL3 in CRC and its potential as a therapeutic target. METTL3 was overexpressed in 62.2% (79/127) and 88.0% (44/50) of primary CRC from two independent cohorts. High METTL3 expression predicted poor survival in CRC patients. Functionally, silencing METTL3 suppressed tumourigenesis in CRC cells, human-derived primary CRC organoids and Mettl3 knockout mouse models. Mechanistically, METTL3 directly induced m6A-GLUT1-mTORC1 axis as identified by integrated m6A-seq, RNA-seq, Ribosome-seq and functional validation. METTL3 induced GLUT1 translation in m6A-dependent manner, which leads to activation of mTORC1 signalling and CRC development. Inhibition of mTORC1 potentiated the anticancer effect of METTL3 silencing in CRC patient-derived organoids and METTL3 transgenic mice. METTL3 is thus a promising therapeutic target for the treatment of CRC (*Gastroenterology 2020*).

Research and Scholarship

Research Awards and Recognitions

Organisation	Details	
	Award	Organisation
Jun Yu	National Natural Sciences Awards	Ministry of Sciences and Technology, China
Joseph Sung		
Henry Chan		
Vincent Wong		
Joseph Sung	Clarivate Analytics Highly Cited Researchers 2020	Clarivate
Henry Chan		
Vincent Wong		

Fellowships

Member's Name	Details	
	Fellowship	Organisation
Joseph Sung	AGA Fellow	American Gastroenterology Association, USA
Francis Chan	AGA Fellow	American Gastroenterology Association, USA
	Honorary Fellowship	The Royal College of Physicians of Thailand
Jun Yu	Council Member	American Gastroenterology Association Microbiome and Microbial Therapy (MMT) section, USA
		International Cancer Microbiome Consortium, UK
	AGA Fellow	American Gastroenterology Association, USA
	Vice Chairman	China Anti-Cancer Association Committee on Gut Microbiome
		China Medical Women's Association Division of Digestive Disease
		Hong Kong Scientist Association
	Member	International Cancer Genome Consortium (ICGC), USA
		American Association for Cancer Research, USA
Dennis Wong	Member	American Gastroenterology Association, USA
Jennifer Zhang	Member	American Gastroenterology Association, USA

Academic Editorship

Member's Name	Details	
	Role	Journal
Joseph Sung	Chief Editor	Journal of Gastroenterology and Hepatology
Jun Yu	Deputy Chief Editor	Journal of Gastroenterology and Hepatology
	Associate Editor	Oncogene
		Scientific Reports
		The World Journal of Gastroenterology
		Journal of Digestive Disease

Academic Editorship

Member's Name	Details	
	Role	Journal
Jun Yu	Editorial Board Member	Gut
		EBioMedicine
		Journal of Gastroenterology & Hepatology Research
		Scientific Reports
		World Journal of Gastrointestinal Pharmacology and Therapeutics
		Journal of Pathology & Laboratory Medicine
		Journal of Next Generation Sequencing & Applications
		Oncogenesis
		The Open Hepatology Journal
		Pragmatic and Observational Research
		ISRN Gastroenterology
		International Journal of Clinical Medicine
		Insight Knowledge
		The Open Gastroenterology Journal
Francis Chan	Associate Editor	Clinical Gastroenterology and Hepatology
	Editorial Board Member	Precision and Future Medicine
		Digestive Endoscopy

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Jun Yu	Reviewer	American Journal of Gastroenterology
		American Journal of Pathology
		Annals Oncology
		BMC Cancer
		BMC Gastroenterology
		British Journal of Cancer
		Alimentary Pharmacology & Therapeutics
		Cancer
		Cancer Research
		Cancer Letters
		Carcinogenesis
		Cell Death & Disease
		Clinical Cancer Research
		Clinical Gastroenterology and Hepatology
		eBioMed
		Gastroenterology

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Jun Yu	Reviewer	Gut
		Hepatology
		Human Molecular Genetics
		Life Sciences
		International Journal of Cancer
		International Journal of Oncology
		Journal of Gastroenterology and Hepatology
		The Journal of Hematology & Oncology
		Journal of Hepatology
		Journal of Molecular Medicine
		Journal of Pathology
		Liver International
		Lancet
		Molecular Cancer Research
		Molecular Cancer Therapeutics
		Molecular Oncology
		Nature Communication
		Nature Reviews Gastroenterology and Hepatology
		New England Journal of Medicine
		Oncogene
		Science Translational Medicine
		Theranostics
		AGA Abstract Review Committee – Oncology
		AGA Abstract Review Committee – Microbiome
Jennifer Zhang	Reviewer	Frontiers in Oncology

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Joseph Sung	Funding to Support State Key Laboratory of Digestive Diseases	Hong Kong Innovation and Technology Commission	2018	Current	10,000,000
	To Implement a Five-year Multi-cancer Education and Prevention Programme for the Prevention of Obesity-related Cancers	The Hong Kong Jockey Club Charities Trust	01/01/2018	03/12/2022	35,360,000
	The Diagnostic Accuracy of Using Faecal-DNA Test (COLOSAFE) for Colorectal Cancer Screening	Creative Biosciences (Guangzhou) Co., Ltd.	01/10/2018	31/03/2021	500,000
	多癌種早期篩查診斷生物標誌物的效用驗證和推廣應用研究	國家重點研發計畫	01/08/2018	31/12/2020	RMB 7,400,000

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Jun Yu	Exploiting Epitranscriptome Dysregulation in Colorectal Carcinogenesis and Metastasis: Mechanisms and Novel Therapeutic Approaches	Research Grants Council – Collaborative Research Fund	01/07/2020	30/06/2023	6,158,384
	Functional Investigation of a Novel Oncogenic Bacterium *Peptostreptococcus anaerobius* in Colorectal Carcinogenesis	Food and Health Bureau – Health and Medical Research Fund	01/08/2018	31/07/2020	1,196,904
	Elucidating a Novel Tumor Promoting Gene Ring Finger Protein 6 in Colorectal Cancer	Research Grants Council – General Research Fund	01/01/2018	30/06/2021	1,229,089
	Study on the Relationship Between Gut Microbe Dysbiosis and Colorectal Cancer	Science and Technology Program Grant, Shenzhen	01/07/2017	30/06/2020	RMB 2,000,000
	Molecular Pathogenesis of Hepatitis B Associated HCC	Guangdong Natural Scientific Funding	01/05/2018	30/04/2023	RMB 3,000,000
	Prospective of Colorectal Cancer Screening Biomarkers and Population Gradient Screening Programs	National Key R&D Program of China	01/09/2018	31/12/2021	RMB 9,000,000
	Translational Cancer Genomic	Gordon Research Conference	01/05/2019	30/04/2021	USD 20,000
	Function of the Immune Receptor Regulator DOK1 in Therapy Response of Gastric Cancer	Germany/Hong Kong Joint Research Scheme 2018/19	01/01/2019	31/12/2021	90,000
	Defining the Role of RNA N6-Methyladenosine Writer Methyltransferase Like 3 (METTL3) in Colorectal Cancer	Research Grants Council – General Research Fund	01/01/ 2020	31/12/2022	1,532,422
	Identification and Characterization of Genes and Microenvironment Factors Driving the Metastasis of Upper Gastrointestinal Tract Cancers	Research Grants Council – Collaborative Research Fund	01/07/2019	30/06/2022	4,416,717
	Exploiting Stemness as a Cancer Cell Vulnerability Using Hepatocellular Carcinoma (HCC) as a Model System	Research Grants Council – Collaborative Research Fund	01/04/2019	31/03/2022	6,990,790
	Fighting Disease Recurrence and Promoting Tissue Repair after Liver Transplantation: Translating Basic Discoveries to Clinical Excellence	Research Grants Council – Theme-based Research Scheme	01/12/2019	30/11/2024	45,000,000
	The Interaction of Key Intestinal Pathogens and Host Factors in Promoting the Development of Colorectal Cancer	National Key R&D Program of China	01/11/2020	30/10/2025	RMB 22,000,000

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Jun Yu	Assess Antibiotic Resistome Flows from Pollution Hotspots to Environments and Explore the Control Strategies	Research Grants Council – Theme-based Research Scheme	01/12/2020	31/11/2025	29,000,000
	Regulation and Mechanism of Tumor-intrinsic Oncogene Pathways in Mediating an Immune Suppressed Microenvironment in Hepatocellular Carcinoma	Research Grants Council – Collaborative Research Fund	01/06/2018	30/06/2021	7,544,147
Dennis Wong	A Novel Epigenetic Therapy for KRAS-mutant Colorectal Cancer	Health and Medical Research Fund – Research Fellowship Scheme	30/09/2019	29/09/2022	1,499,371
	Combinatorial Blockade of De Novo Cholesterol Biosynthesis and PCSK9 as a Synergistic Therapy for KRAS-Mutant Colorectal Cancer	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	971,368
	Inhibition of SLC25A22 Synergizes with Chemotherapy to induce KRAS-mutant Colorectal Cancer Cell Death Through Induction of Endoplasmic Reticulum Stress	Research Grants Council – General Research Fund	01/01/2018	31/12/2020	1,203,589
	Mitochondrial Glutamate Transporter (SLC25A22) Promotes the Tumorigenicity of KRAS-mutant Colorectal Cancer Through Regulating DNA and Histone Methylation	National Natural Science Foundation of China	01/01/2018	31/12/2021	RMB 530,000

Publications

A. Journal Papers

1. Wang S, Huang J, Li C, Zhao L, Wong CC, Zhai J, Zhou Y, Deng W, Zeng Y, Gao S, Zhang Y, Wang G, Guan XY, Wei H, Wong SH, He HH, Shay JW, Yu J. MAP9 loss triggers chromosomal instability, initiates colorectal tumorigenesis, and is associated with poor survival of patients with colorectal cancer. *Clinical Cancer Research*. 2020;26(3):746-757. doi:10.1158/1078-0432.CCR-19-1611.

2. Lam SY, Yu J, Peppelenbosch MP. VValue of VAV3 methylation in stool DNA might be restricted to non-thiopurine treated inflammatory bowel disease patients. *Clinical Gastroenterology and Hepatology*. 2020;18(2):520. doi:10.1016/j.cgh.2019.06.020. (Letter)

3. Tao E, Cheng WY, Li W, Yu J, Gao Q. tiRNAs: A novel class of small noncoding RNAs that helps cells respond to stressors and plays roles in cancer progression. *Journal of Cellular Physiology*. 2020;235(2):683-690. doi:10.1002/jcp.29057. (Review)

4. Ho J, Chan H, Liang Y, Liu X, Zhang L, Li Q, Zhang Y, Zeng J, Ugwu FN, Ho IHT, Hu W, Yau JCW, Wong SH, Wong WT, Ling L, Cho CH, Gallo RL, Gin T, Tse G, Yu J, Chan MTV, Leung CCH, Wu WKK. Cathelicidin preserves intestinal barrier function in polymicrobial sepsis. *Critical Care*. 2020;24(1):47. doi:10.1186/s13054-020-2754-5.

5. Kong KY, Kwong TNY, Chan H, Wong K, Wong SSY, Chaparala AP, Chan RCY, Zhang L, Sung JJY, Yu J, Hawkey PM, Ip M, Wu WKK, Wong SH. Biological characteristics associated with virulence in *Clostridioides difficile* ribotype 002 in Hong Kong. *Emerging Microbes & Infections*. 2020;9(1):631-638. doi:10.1080/22221751.2020.1739564.

6. Zhang J, Huang JZ, Zhang YQ, Zhang X, Zhao LY, Li CG, Zhou YF, Wei H, Yu J. Microtubule associated protein 9 inhibits liver tumorigenesis by suppressing ERCC3. *EBioMedicine*. 2020;53:102701. doi:10.1016/j.ebiom.2020.102701.

7. Lau HCH, Kranenburg O, Xiao H, Yu J. Organoid models of gastrointestinal cancers in basic and translational research. *Nature Reviews Gastroenterology & Hepatology*. 2020;17(4):203-222. doi:10.1038/s41575-019-0255-2. (Review)

8. Wong SH, Yu J. Proton-pump inhibitor use before fecal microbiota transplant: A wonder drug, a necessary evil, or a needless prescription? *Journal of Gastroenterology and Hepatology*. 2020;35(6):913-914. doi:10.1111/jgh.15103. (Editorial)

9. Fong W, Li Q, Yu J. Gut microbiota modulation: A novel strategy for prevention and treatment of colorectal cancer. *Oncogene*. 2020;39(26):4925-4943. doi:10.1038/s41388-020-1341-1. (Review)

10. Liang JQ, Li T, Nakatsu G, Chen YX, Yau TO, Chu E, Wong S, Szeto CH, Ng SC, Chan FKL, Fang J-Y, Sung JJY, Yu J. A novel faecal *Lachnoclostridium* marker for the non-invasive diagnosis of colorectal adenoma and cancer. *Gut*. 2020;69(7):1248-1257. doi:10.1136/gutjnl-2019-318532.

11. Xia X, Wu WKK, Wong SH, Liu D, Kwong TNY, Nakatsu G, Yan PS, Chuang YM, Chan MW, Coker OO, Chen Z, Yeoh YK, Zhao L, Wang X, Cheng WY, Chan MTV, Chan PKS, Sung JJY, Wang MH, Yu J. Bacteria pathogens drive host colonic epithelial cell promoter hypermethylation of tumor suppressor genes in colorectal cancer. *Microbiome*. 2020;8(1):108. doi:10.1186/s40168-020-00847-4.

12. Zhao R, Coker OO, Wu J, Zhou Y, Zhao L, Nakatsu G, Bian X, Wei H, Chan AWH, Sung JJY, Chan FKL, El-Omar E, Yu J. Aspirin reduces colorectal tumor development in mice and gut microbes reduce its bioavailability and chemopreventive effects. *Gastroenterology*. 2020;159(3):969-983.e4. doi:10.1053/j.gastro.2020.05.004.

13. Cheng WY, Wu CY, Yu J. The role of gut microbiota in cancer treatment: Friend or foe? *Gut*. 2020;69(10):1867-1876. doi:10.1136/gutjnl-2020-321153. (Editorial)

14. Coker OO, Wu WKK, Wong SH, Sung JJY, Yu J. Altered gut archaea composition and interaction with bacteria are associated with colorectal cancer. *Gastroenterology*. 2020;159(4):1459-1470.e5. doi:10.1053/j.gastro.2020.06.042.

15. Liang JQ, Wong SH, Szeto CH, Chu ES, Lau HC, Chen Y, Fang J, Yu J, Sung JJ. Fecal microbial DNA markers serve for screening colorectal neoplasm in asymptomatic subjects. *Journal of Gastroenterology and Hepatology*. Published online July 15, 2020:jgh.15171. doi:10.1111/jgh.15171. (Epub ahead of print)

16. Zhang X, Coker OO, Chu ESH, Fu K, Lau HCH, Wang YX, Chan AWH, Wei H, Yang X, Sung JJY, Yu J. Dietary cholesterol drives fatty liver-associated liver cancer by modulating gut microbiota and metabolites. *Gut*. 2020;0:1-14. doi:10.1136/gutjnl-2019-319664.

17. Wang K, Li E, Busuttil RA, Kong JC, Pattison S, Sung JJY, Yu J, El-Omar EM, Simpson JA, Boussioutas A. A cohort study and meta-analysis of the evidence for consideration of lauren subtype when prescribing adjuvant or palliative chemotherapy for gastric cancer. *Therapeutic Advances in Medical Oncology*. 2020;12:175883592093035. doi:10.1177/1758835920930359.

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19. Wei Q, Qian Y, Yu J, Wong CC. Metabolic rewiring in the promotion of cancer metastasis: Mechanisms and therapeutic implications. *Oncogene*. 2020;39(39):6139-6156. doi:10.1038/s41388-020-01432-7. (Review)

20. Li Q, Hu W, Liu WX, Zhao LY, Huang D, Liu XD, Chan H, Zhang Y, Zeng JD, Coker OO, Kang W, Man Ng SS, Zhang L, Wong SH, Gin T, Vai Chan MT, Wu JL, Yu J, Wu WK. Streptococcus thermophilus inhibits colorectal tumorigenesis through secreting ß-galactosidase. *Gastroenterology*. 2020 Sep 10:S0016-5085(20)35129-5. (Meeting Abstract)

21. Li X, Lau HCH, Yu J. Microbiota-mediated phytate metabolism activates hdac3 to contribute intestinal homeostasis. *Signal Transduction and Targeted Therapy*. 2020;5(1):211. doi:10.1038/s41392-020-00321-5. (Commentary)

22. Lau HCH, Yu J. Gut microbiome alters functions of mutant p53 to promote tumorigenesis. *Signal Transduction and Targeted Therapy*. 2020;5(1). doi:10.1038/s41392-020-00336-y. (Commentary)

23. Chen H, Gao S, Liu W, Wong CC, Wu J, Wu J, Liu D, Gou H, Kang W, Zhai J, Li C, Su H, Wang S, Soares F, Han J, He HH, Yu J. RNA m6A methyltransferase METTL3 facilitates colorectal cancer by activating m6A-GLUT1-mTORC1 axis and is a therapeutic target. *Gastroenterology*. Published online November 18, 2020. doi:10.1053/j.gastro.2020.11.013. (Epub ahead of print)

24. Chen Z, Wong PY, Ng CWK, Lan L, Fung S, Li JW, Cai L, Lei P, Mou Q, Wong SH, Wu WKK, Li RJ, Meehan K, Lui VWY, Chow C, Lo KW, Chan ABW, Boon SS, Lau EHL, Yeung Z, Chan KCA, Wong EWY, Cheng ASL, Yu J, Chan PKS, Chan JYK. The intersection between oral microbiota, host gene methylation and patient outcomes in head and neck squamous cell carcinoma. *Cancers*. 2020;12(11):3425. doi:10.3390/cancers12113425.

25. Xu H, Liu L, Li W, Zou D, Yu J, Wang L, Wong CC. Transcription factors in colorectal cancer: Molecular mechanism and therapeutic implications. *Oncogene*. Published online December 15, 2020. doi:10.1038/s41388-020-01587-3. (Review) (Epub ahead of print)

26. Pan Y, Chen H, Yu J. Biomarkers in hepatocellular carcinoma: Current status and future perspectives. *Biomedicines*. 2020;8(12):576. doi:10.3390/biomedicines8120576. (Review)

27. Ng YL, Lo MCK, Lee KH, Xie X, Kwong TNY, Ip M, Zhang L, Yu J, Sung JJY, Wu WKK, Wong SH, Kwok KW. Development of an open-access and explainable machine learning prediction system to assess the mortality and recurrence risk factors of *Clostridioides difficile* infection patients. *Advanced Intelligent Systems*. 2021;3(1):2000188. doi:10.1002/aisy.202000188. (Epub ahead of print)

B. Book Chapter

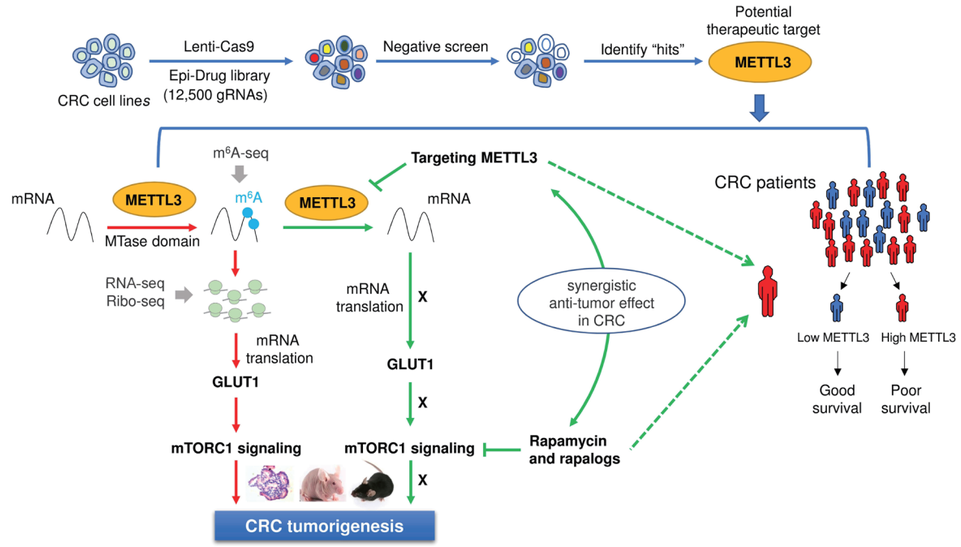
1. Chen H, Yu J. Crosstalk of molecular signaling in hepatocellular carcinoma. "Liver Diseases. A Multidisciplinary Textbook." F. Radu-Ionita et al. (eds.), *Springer Nature Switzerland*. 2020 Aug; chapter 8, pp 85-94.

C. Patents

1. US Patent:
   - Inventors: Jun Yu, Joseph Sung, Qiaoyi Liang
   - Title: Faecal Bacterial Markers for Colorectal Cancer
   - U.S. Provisional Application No. 62/379.635
   - Filed on 25 August 2016
   - Publication No. US-2020-0002769-A1
   - Publication Date: 2 January 2020

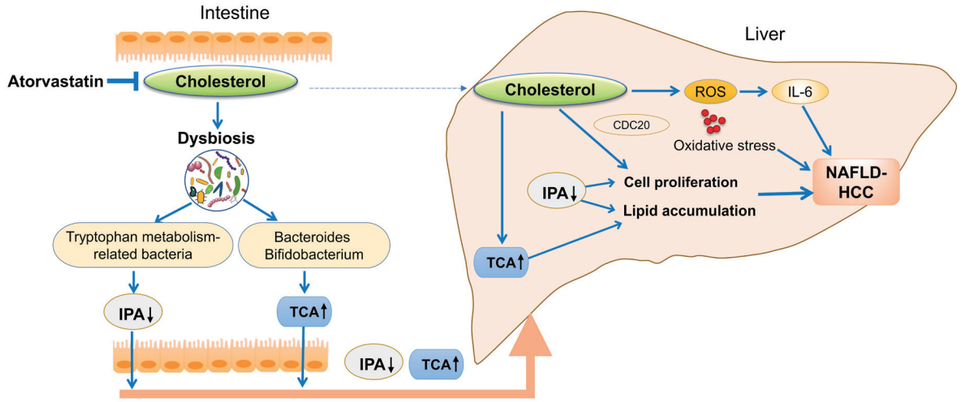
2. US Patent:
   - Inventors: Jun Yu, Joseph Sung, Qiaoyi Liang
   - Title: Tumor suppressor REC8 as a biomarker for gastric cancer
   - US Divisional Application No. 16/443,621
   - Filed on 17 June 2019
   - Publication No. US-2020-0024668-A1
   - Publication Date: 23 January 2020

3. Hong Kong Patent:
   - Inventors: Jun Yu, Joseph Sung, Shiyan Wang
   - Title: Biomarker DACT1 for Gastric cancer 胃癌的生物標誌物 DACT1
   - Patent Application No. 14103063.0
   - Application date: 31 March 2014
   - Patent Granted No: HK1190170
   - Date of Patent: 13 March 2020



METTL3 is an essential m6A regulator enzyme in colorectal carcinogenesis. METTL3 promotes CRC initiation and progression through inducing a novel m6A-GLUT1-mTORC1 axis. High METTL3 expression is associated with poor survival of CRC patients. Co-targeting of METTL3 and mTORC1 synergistically suppressed colorectal carcinogenesis.

Source: Chen H, Gao S, Liu W, Wong C-C, Wu J, Wu J, Liu D, Gou H, Kang W, Zhai J, Li C, Su H, Wang S, Soares F, Han J, He HH, Yu J. RNA m6A methyltransferase METTL3 facilitates colorectal cancer by activating m6A-GLUT1-mTORC1 axis and is a therapeutic target. Gastroenterology. Published online November 18, 2020. doi:10.1053/j.gastro.2020.11.013.



Prolonged high dietary cholesterol induces spontaneous and progressive development of NAFLD-HCC in male mice by modulating the gut microbiota. Cholesterol induces increased TCA and decreased IPA through gut microbiota alteration, thereby promoting lipid accumulation, cell proliferation in the liver, leading to NAFLD-HCC development.

Source: Zhang X, Coker OO, Chu ESH, Fu K, Lau HCH, Wang YX, Chan AWH, Wei H, Yang X, Sung JJY, Yu J. Dietary cholesterol drives fatty liver-associated liver cancer by modulating gut microbiota and metabolites. Gut. 2020;0:1-14. doi:10.1136/gutjnl-2019-319664.