于君

JUN YU

01 DIGESTIVE DISEASES

Gut microbiota in Colorectal Cancer:

Dietary fat intake is associated with increased risk of colorectal cancer (CRC). In this study, the team led by Jun Yu examined the role of high-fat diet (HFD) in driving CRC through modulating gut microbiota and metabolites. They found that HFD promotes colorectal carcinogenesis in CRC mice models, an effect that was attenuated by antibiotics treatment, suggesting that the microbiota underlies HFD-induced CRC. Next, metagenome sequencing revealed that HFD triggered a significant shift in the microbiome composition in HFD-fed mice. Pathogenic bacteria *Alistipes sp. Marseille-P5997* and *Alistipes sp. 5CPEGH6* were increased while the levels of probiotic *Parabacteroides distasonis* was depleted. Moreover, microbial dysbiosis was associated with compromised gut barrier function in HFD fed mice. Faecal microbiota transplantation of HFD-fed mice stool to germ-free mice was found to accelerated chemically-induced CRC, confirming the functional role of dysbiosis in HFD-induced CRC development. Finally, metabolomic analysis demonstrated that the gut metabolite lysophosphatidic acid was elevated with HFD fed mice. Lysophosphatidic acid was found to promote CRC growth and impair gut barrier function. In summary, their work showed that gut dysbiosis as a crucial link to diet-induced CRC. *(Gastroenterology, 2021)*

Gut microbial dysbiosis has pivotal involvement in CRC. The team is the first to report a comprehensive mapping of the intratumoural gut microbiome heterogeneity in CRC patients. To this end, they collected multiple biopsies (N=436) from patients with CRC (N=36) or adenomas (N=32), with 2-6 samples from each tumour plus 2-5 biopsies from adjacent normal tissues for each patient. They then performed microbial genome sequencing on these samples, and discovered that there are substantial differences in intratumoural microbial communities even within the same tumour. In particular, abundances of some CRC-associated pathobionts (eg, *Fusobacterium*, *Bacteroides*, *Parvimonas*, and *Prevotella*) were found to be highly varied within a single neoplasia. Moreover, they found that the intra-neoplasia variation in abundance of individual microbes changed along the adenoma-carcinoma sequence. They also observed that tumour intrinsic factors KRAS mutation and microsatellite instability were correlated with of intratumoural microbial heterogeneity. Their work thus shed light on the impact of microbial heterogeneity on CRC development. *(Gastroenterology, 2021)*

Recently, there is a great interest in utilising beneficial microbes for the prevention of cancer. Using faecal shotgun metagenomic sequencing, they identified *Lactobacillus gallinarum* as a commensal bacterium that is the most depleted in the stool of CRC patients as compared to healthy subjects. They thus hypothesise that it might be preventive against CRC. Indeed, the oral gavage of *L. gallinarum* was found to suppress CRC in $Apc^{Min/+}$ and AOM-induced CRC mice models. *In vitro* studies revealed that the *L. gallinarum* culture-supernatant (5%, 10% and 20%) concentration-dependently suppressed cell proliferation and colony formation of CRC cell lines, but had no effect on colon normal cells. Consistently, *L. gallinarum* culture-supernatant significantly promoted apoptosis in CRC cells and patient-derived CRC organoids, but not in normal colon epithelial cells. Using LC-MS/MS, they further identified that indole-3-lactic acid (ILA) as an active component of *L. gallinarum* culture-supernatant that was also enriched in the gut of *L. gallinarum*-treated mice. ILA displayed anti-CRC growth *in vitro* and inhibited intestinal tumourigenesis *in vivo*. Their study therefore identified a novel chemopreventive probiotic *L. gallinarum* that produces the antitumour metabolite ILA to prevent CRC. Sugimura N, Li Q, Chu ESH, et al. *Lactobacillus gallinarum* modulates the gut microbiota and produces anti-cancer metabolites to protect against colorectal tumourigenesis. *(Gut, 2021)*

Research Progress Summary

Principal Investigator
Jun Yu

Team Members
Vincent Wong, Dennis Wong, Jennifer Zhang, Huarong Chen

Molecular Mechanisms of Colorectal Cancer:

RNA N^6-methyladenosine (m^6A) is the most abundant RNA modification in the human and emerging studies have suggested that it plays a critical role in tumourigenesis. They therefore investigated that role of YTHDF1, a m^6A reader, in colorectal tumourigenesis. In multiple patient cohorts, YTHDF1 DNA copy number gain is a frequent event in CRC and contributes to its overexpression, and the overexpression of YTHDF1 is significantly associated with metastatic gene signature in patient tumours. YTHDF1 knockout in mice dampened CRC development, whereas YTHDF1 overexpression promotes cell growth in CRC cells and primary organoids, and lung and liver metastasis *in vivo*, thereby confirming the oncogenic role of YTHDF1 in CRC. Integrative multiomics analysis identified RhoA activator ARHGEF2 as a downstream target of YTHDF1. YTHDF1 binds to m^6A modified ARHGEF2 mRNA resulting in enhanced mRNA translation. ARHGEF2 activated RhoA signalling, cell growth and metastatic ability. Finally, ARHGEF2 siRNA delivered by LNP significantly suppressed tumour growth and metastasis *in vivo*. They thus identified a novel epitranscriptome YTHDF1-m6A-ARHGEF2 axis that drives CRC, and validated the therapeutic potential of targeting this axis in CRC. *(Gastroenterology, 2021)*

Cancer stem cells (CSCs) comprise a tiny portion of the growing tumour, but they are highly tumourigenic cells essential for tumour maintenance and a root cause of therapy resistance and tumour relapse. Targeting of CSCs might therefore an attractive approach to eradicate tumours and prevent tumour metastasis. Here, the team performed CRISPR/Cas9-based dropout screening (Epi-Drug sgRNA library) to identify genes that are specifically essential in CSCs. Using two CSCs models, they revealed 44 essential genes for CSC growth, including genes involved in cholesterol biosynthesis (HMGCR, FDPS, and GGPS1). Accordingly, genetic or pharmacological inhibition of cholesterol biosynthesis genes HMGCR or FDPS impaired self-renewal capacity and tumourigenic potential of spheroid models *in vitro* and *in vivo*. Effect of HMGCR or FDPS inhibition was rescued by cholesterol and geranylgeranyl diphosphate (GGPP), suggesting that cholesterol related metabolites contribute to CSCs survival and growth. Finally, they showed that the combination of cholesterol biosynthesis blockade and chemotherapy were synergistic in suppressing CSCs *in vitro* and *in vivo*. their data suggest that cholesterol biosynthesis as a potential target for CSCs-based therapy. *(Oncogene, 2021)*

Using whole genome sequencing, the team have previously identified the amplification of Ring finger protein 6 (RNF6), a RING-domain E3 ubiquitin ligase, CRC. In this study, they further generated a colon-specific RNF6 transgenic mice, and demonstrated that the colon-specific overexpression of RNF6 promotes the development of chemically-induced CRC in mice. To elucidate the molecular mechanism of RNF6 as a transcription factor, they next performed integrated chromatin immunoprecipitation (ChIP)-sequencing and RNA-sequencing to identify SF3B2 as the target

of RNF6. Knockout of SF3B2 abrogated the effect of RNF6 overexpression on CRC cell growth and migration/invasion, verifying SF3B2 as a functional target of RNF6. Targeting of the RNF6-SF3B2 axis with pladienolide B (SF3B2 inhibitor) suppressed the growth of RNF6-overexpressing CRC cells and potentiated the effect of 5-fluorouracil, leading to tumour regression in xenograft models. Their findings suggest RNF6-SF3B2 axis as an actionable target in CRC. *(Oncogene, 2021)*

Molecular Mechanisms of Liver Diseases:

Metabolites play an important role in the etiology of liver diseases, including hepatocellular carcinoma (HCC). To investigate this, the team has analysed two independent patients with 102 HCC patients and 100 healthy controls. Portal/central vein serum, liver tissues, and stools samples from these subjects were subjected to global metabolomic profiling analysis. Detailed metabolomic evaluation showed distinct clusters of metabolites that differentiate HCC and control individuals ($p<0.001$). HCC patients had higher levels of portal vein serum and HCC metabolites of DL-3-phenyllactic acid, L-tryptophan, glycocholic acid and 1-methylnicotinamide than healthy controls, which were associated with impaired liver function and poor survival. On the other hand, HCC patients had lower levels of linoleic acid and phenol in portal vein and stool samples than healthy controls. Linoleic acid and phenol significantly inhibited HCC cell proliferation, inferring their anti-HCC function. They thus identified key metabolites could be involved in hepatocarcinogenesis in humans. *(Gut, 2021)*

Nonalcoholic fatty liver disease (NAFLD) is now the major cause of liver disease and a healthcare burden worldwide. In this study, the team identified a novel gene, Squalene Epoxidase (SQLE) as the driver of NAFLD that is highly up-regulated in human NASH and mouse models of NASH. Using a novel SQLE transgenic mice model, they demonstrated that SQLE overexpression in mice triggered spontaneous insulin resistance, hepatic steatosis, liver injury, and accelerated diet-induced NASH. Mechanistically, SQLE caused hepatic cholesterol accumulation, and triggered inflammatory NF-κB signalling and steatohepatitis. Moreover, SQLE directly binds to CA3, which in turn promotes de novo hepatic lipogenesis by inducing sterol regulatory element-binding protein 1C activation. Combined targeting SQLE (terbinafine) and CA3 (acetazolamide) synergistically ameliorated NASH in mice with better efficacy to either drug alone. Lastly, serum SQLE with CA3 could distinguish patients with NASH from steatosis and healthy controls, thus confirming their clinical relevance. *(Gastroenterology, 2021)*

Non-alcoholic steatohepatitis (NASH) is a severe form of NAFLD associated with inflammation and hepatocyte damage, which could progress to cirrhosis and HCC. The development of NASH is closely related to the hepatic immune microenvironment. Natural Killer (NK) cells are a major immune cell type found in the liver; however, its role in NASH is unknown. In this study, they investigated the contribution of NK cells to NASH using NK-deficient mice ($Nfil3^{-/-}$). Absence of NK cells ameliorated diet-induced NASH models with significantly reduced liver inflammation and damage. Mechanistically, they found that NK cells isolated from NASH liver secreted high levels of pro-inflammatory cytokines to induce hepatic JAK/STAT1/3 signalling, leading to increased oxidative damage and apoptosis. The neutralization of NK cells with PK136 antibody suppressed NASH development in mice model, suggesting that modulation of NK cells provides a potential therapeutic strategy for NASH. *(Cellular and Molecular Gastroenterology and Hepatology, 2021)*

Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Jun Yu Vincent Wong Henry Chan Jennifer Zhang Joseph Sung	National Natural Sciences Awards	Ministry of Sciences and Technology, China
Jun Yu	Five Continents Women Science and Technology Award	China Medical Women's Association
Joseph Sung Vincent Wong	Clarivate Analytics Highly Cited Researchers 2021	Clarivate

Fellowships

Member's Name	Details	
	Fellowship	Organisation
Jun Yu	Council Member	American Gastroenterology Association Microbiome and Microbial Therapy 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, USA
		American Association for Cancer Research, USA
Vincent Wong	Member	American Association for the Study of Liver Diseases
		European Association for the Study of the Liver
	Council Member	Asia-Pacific High Energy Physics Panel
		Hong Kong Association for the Study of Liver Diseases
Chi Chun Wong	Member	American Gastroenterology Association, USA

Member's Name	Details	
	Fellowship	Organisation
Jennifer Zhang	Member	American Gastroenterology Association, USA
		Tumour Microecology of China anti-Cancer Association
		Chronic Disease Management of China Medicinal Biotech Association
		Hong Kong Immunology Association
Huarong Chen	Member	Society For Leukocyte Biology
		China Anti-Cancer Association

Academic Editorship

Member's Name	Details	
	Role	Journal
Jun Yu	Deputy Chief Editor	Journal of Gastroenterology and Hepatology
	Associate Editor	Oncogene
		Oncogenesis
		Scientific Reports
		The World Journal of Gastroenterology
		Journal of Digestive Disease
	International Advisor	Advances in Digestive Medicine
	Advisory Board	EBioMedicine
	Editorial Board Member	Gut
		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
Vincent Wong	Associate Editor	Clinical Gastroenterology and Hepatology
	Editorial Board Member	JHEP Reports
		Hepatology Communications
		Alimentary Pharmacology & Therapeutics

Member's Name	Details	
	Role	Journal
Dennis Wong	Editorial Board Member	Frontiers in Medicine
	Guest Editorial Member	Cells
Jennifer Zhang	Editorial Board Member	Frontiers in Oncology
		Frontiers in Cell and Developmental Biology
Huarong Chen	Guest Editor	Diagnostics

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Jun Yu	Chair	AGA DDW Abstract Review Committee-Microbiome
		AGA DDW Abstract Review Committee-Oncology
	Reviewer	Gastroenterology
		Gut
		Nature Communication
		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
		eBioMedicine
		Hepatology
		Human Molecular Genetics
		Life Sciences
		International Journal of Cancer
		International Journal of Oncology
		Journal of Gastroenterology & Hepatology
		The Journal of Hematology & Oncology
		Journal of Hepatology

Member's Name	Details	
	Role	Journal
Jun Yu	Reviewer	Journal of Molecular Medicine
		Journal of Pathology
		Liver International
		Lancet
		Molecular Cancer Research
		Molecular Cancer Therapeutics
		Carcinogenesis
		Molecular Oncology
		Nature Reviews Gastroenterology and Hepatology
		New England Journal of Medicine
		Oncogene
		Science Translational Medicine
Vincent Wong	Reviewer	Gastroenterology
		Gut
		Hepatology
		Journal of Hepatology
Dennis Wong	Reviewer	Oncogene
		Pathology
		Pharmacological Research
		Pharmaceutics
		Theranostics
		Expert Opinion on Investigational Drugs
		Journal of Gastroenterology & Hepatology
		Molecules
		Metabolites
Jennifer Zhang	Reviewer	Frontiers in Oncology
		Journal of Gastroenterology & Hepatology
Xiang Zhang	Reviewer	Journal of Leukocyte Biology
		Cancer Letters
Huarong Chen	Reviewer	Molecular Cancer
		Theranostics
		Oncogene
		Frontiers in Immunology
		Cells

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Jun Yu	Funding to Support State Key Laboratory of Digestive Diseases	Innovation and Technology Commission – Innovation and Technology Fund	2018	Current	10,000,000
	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
	Evaluation of SQLE as a Novel Therapeutic Target in Non-alcoholic Fatty Liver Disease	Food and Health Bureau – Health and Medical Research Fund	01/07/2020	30/06/2023	1,498,772
	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
	The Role and Mechanism of Methylation Modification and Its Regulatory Genes in the Development of Colorectal Cancer	National Natural Science Foundation of China	01/01/2020	31/12/2023	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

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Jun Yu	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
	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
	Branched Chain Amino Acids (BCAA) Restriction to Alleviate Colorectal Cancer Metastasis	Health and Medical Research Fund – Research Fellowship Scheme	01/12/2021	30/11/2024	1,499,880
Dennis Wong	SLC25A22 Drives Oncometabolite Succinate to Promote Cancer Stemness in KRAS-mutant Colorectal Cancer	Research Grants Council – Early Career Scheme	01/01/2021	31/12/2023	936,520
	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
	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
Huarong Chen	RNA N6-Methyladenosine Methyltransferase- like 3 (METTL3) is a Potential Therapeutic Target for Immunotherapy in Colorectal Cancer	Health and Medical Research Fund – Research Fellowship Scheme	01/09/2021	31/08/2023	1,475,400

Publications

A. Journal Papers

1. Li Q, Hu W, Liu WX, Zhao LY, Huang D, Liu XD, Chan H, Zhang Y, Zeng JD, Coker OO, Kang W, Ng SSM, Zhang L, Wong SH, Gin T, Chan MTV, Wu JL, Yu J, Wu WKK. *Streptococcus thermophilus* inhibits colorectal tumorigenesis through secreting β-galactosidase. *Gastroenterology*. 2021;160(4):1179-1193.e14. doi:10.1053/j.gastro.2020.09.003.

2. Zhang J, Hoedt EC, Liu Q, Berendsen E, Teh JJ, Hamilton A, O' Brien AW, Ching JYL, Wei H, Yang K, Xu Z, Wong SH, Mak JWY, Sung JJY, Morrison M, Yu J, Kamm MA, Ng SC. Elucidation of *Proteus mirabilis* as a key bacterium in Crohn's disease inflammation. *Gastroenterology*. 2021;160(1):317-330.e11. doi:10.1053/j.gastro.2020.09.036.

3. 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 n6-methyladenosine methyltransferase METTL3 facilitates colorectal cancer by activating the m6A-GLUT1-mTORC1 axis and is a therapeutic target. *Gastroenterology*. 2021;160(4):1284-1300.e16. doi:10.1053/j.gastro.2020.11.013.

4. 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*. 2021;70(4):761-774. doi:10.1136/gutjnl-2019-319664.

5. Liang JQ, Wong SH, Szeto CH, Chu ESH, Lau HC, Chen Y, Fang J, Yu J, Sung JJY. Fecal microbial DNA markers serve for screening colorectal neoplasm in asymptomatic subjects. *Journal of Gastroenterology and Hepatology*. 2021;36(4):1035-1043. doi:10.1111/jgh.15171.

6. Chen Y, Cheng WY, Shi H, Huang S, Chen H, Liu D, Xu W, Yu J, Wang J. Classifying gastric cancer using FLORA reveals clinically relevant molecular subtypes and highlights LINC01614 as a biomarker for patient prognosis. *Oncogene*. 2021;40(16):2898-2909. doi:10.1038/s41388-021-01743-3.

7. Kang X, Li W, Liu W, Liang H, Deng J, Wong CC, Zhao S, Kang W, To KF, Chiu PWY, Wang G, Yu J, Ng EKW. LIMK1 promotes peritoneal metastasis of gastric cancer and is a therapeutic target. *Oncogene*. 2021;40(19):3422-3433. doi:10.1038/s41388-021-01656-1.

8. Liu W, Zhang X, Xu H, Li S, Lau HCH, Chen Q, Zhang B, Zhao L, Chen H, Sung JJY, Yu J. Microbial community heterogeneity within colorectal neoplasia and its correlation with colorectal carcinogenesis. *Gastroenterology*. 2021;160(7):2395-2408. doi:10.1053/j.gastro.2021.02.020.

9. Rahaman S, Li X, Yu J, Wong K-C. CancerEMC: Frontline non-invasive cancer screening from circulating protein biomarkers and mutations in cell-free DNA. *Bioinformatics*. 2021;37(19):3319-3327. doi:10.1093/bioinformatics/btab044.

10. Liu D, Wong CC, Zhou Y, Li C, Chen H, Ji F, Go MYY, Wang F, Su H, Wei H, Cai Z, Wong N, Wong VWS, Yu J. Squalene epoxidase induces nonalcoholic steatohepatitis via binding to carbonic anhydrase III and is a therapeutic target. *Gastroenterology*. 2021;160(7):2467-2482.e3. doi:10.1053/j.gastro.2021.02.051.

11. Teh JJ, Berendsen EM, Hoedt EC, Kang S, Zhang J, Zhang F, Liu Q, Hamilton AL, Wilson-O'Brien A, Ching J, Sung JJY, Yu J, Ng SC, Kamm MA, Morrison M. Novel strain-level resolution of Crohn's disease mucosa-associated microbiota via an *ex vivo* combination of microbe culture and metagenomic sequencing. *ISME Journal*. 2021;15(11):3326-3338. doi:10.1038/s41396-021-00991-1.

12. Chen H, Liu W, Wang Y, Liu D, Zhao L, Yu J. SARS-CoV-2 activates lung epithelial cell proinflammatory signaling and leads to immune dysregulation in COVID-19 patients. *EBioMedicine*. 2021;70:103500. doi:10.1016/j.ebiom.2021.103500.

13. Liu J, Geng W, Sun H, Liu C, Huang F, Cao J, Xia L, Zhao H, Zhai J, Li Q, Zhang X, Kuang M, Shen S, Xia Q, Wong VWS, Yu J. Integrative metabolomic characterisation identifies altered portal vein serum metabolome contributing to human hepatocellular carcinoma. *Gut*. Published online 2021. doi:10.1136/GUTJNL-2021-325189.

14. Liu Y, Ling L, Wong SH, Wang MH, Fitzgerald JR, Zou X, Fang S, Liu X, Wang X, Hu W, Chan H, Wang Y, Huang D, Li Q, Wong WT, Choi G, Zou H, Hui DS, Yu J, Tse G, Gin T, Wu WK, Chan MT, Zhang L. Outcomes of respiratory viral-bacterial co-infection in adult hospitalized patients. *EClinicalMedicine*. 2021;37. doi:10.1016/j.eclinm.2021.100955.

15. Yang J, Wei H, Zhou Y, Szeto CH, Li C, Lin Y, Coker OO, Lau HCH, Chan AWH, Sung JJY, Yu J. High-fat diet promotes colorectal tumorigenesis through modulating gut microbiota and metabolites. *Gastroenterology*. 2022;162(1):135-149.e2. doi:10.1053/j.gastro.2021.08.041. (Epub ahead of print)

16. Wang F, Zhang X, Liu W, Zhou Y, Wei W, Liu D, Wong CC, Sung JJY, Yu J. Activated natural killer cell promotes nonalcoholic steatohepatitis through mediating jak/stat pathway. *Cellular and Molecular Gastroenterology and Hepatology*. 2022;13(1):257-274. doi:10.1016/j.jcmgh.2021.08.019. (Epub ahead of print)

17. Xu H, Wong CC, Li W, Zhou Y, Li Y, Wang L, Liu L, Yu J. RING-finger protein 6 promotes colorectal tumorigenesis by transcriptionally activating SF3B2. *Oncogene*. 2021;40(47):6513-6526. doi:10.1038/s41388-021-01872-9.

18. Wang S, Wong CC, Zhang Y, Huang J, Li C, Zhai J, Wang G, Wei H, Zhang X, He HH, Yu J. ZNF545 loss promotes ribosome biogenesis and protein translation to initiate colorectal tumorigenesis in mice. *Oncogene*. 2021;40(48):6590-6600. doi:10.1038/s41388-021-01938-8.

19. Gao S, Soares F, Wang S, Wong CC, Chen H, Yang Z, Liu W, Go MYY, Ahmed M, Zeng Y, O'Brien CA, Sung JJY, He HH, Yu J. CRISPR screens identify cholesterol biosynthesis as a therapeutic target on stemness and drug resistance of colon cancer. *Oncogene*. 2021;40(48):6601-6613. doi:10.1038/S41388-0c21-01882-7.

20. Zhang J, Zhai J, Wong CC, Chen H, Wang X, Ji J, Yu J. A novel amplification gene PCI domain containing 2 (PCID2) promotes colorectal cancer through directly degrading a tumor suppressor promyelocytic leukemia (PML). *Oncogene*. 2021;40(49):6641-6652. doi:10.1038/s41388-021-01941-z.

21. Liu W, Gou H, Wang X, Li X, Hu X, Su H, Li S, Yu J. TTPAL promotes gastric tumorigenesis by directly targeting NNMT to activate PI3K/AKT signaling. *Oncogene*. 2021;40(49):6666-6679. doi:10.1038/s41388-021-01838-x.

22. Li R, Ong Q, Wong CC, Chu ESH, Sung JJY, Yang X, Yu J. O-GlcNAcylation inhibits hepatic stellate cell activation. *Journal of Gastroenterology and Hepatology*. 2021;36(12):3477-3486. doi:10.1111/jgh.15690.

23. Jiang B, Mu Q, Qiu F, Li X, Xu W, Yu J, Fu W, Cao Y, Wang J. Machine learning of genomic features in organotropic metastases stratifies progression risk of primary tumors. *Nature Communications*. 2021;12(1):1-15. doi:10.1038/s41467-021-27017-w.

24. Wang S, Gao S, Zeng Y, Zhu L, Mo Y, Wong CC, Bao Y, Su P, Zhai J, Wang L, Soares F, Xu X, Chen H, Hezaveh K, Ci X, He A, McGaha T, O'Brien C, Rottapel R, Kang W, Wu J, Zheng G, Cai Z, Yu J, He HH. N6-methyladenosine reader YTHDF1 promotes ARHGEF2 translation and RhoA signaling in colorectal cancer. *Gastroenterology*. Published online December 28, 2021. doi:10.1053/j.gastro.2021.12.269. (In press)

25. Sugimura N, Li Q, Siu E, Chu H, Cheuk H, Lau H, Fong W, Liu W, Liang C, Nakatsu G, Chin A, Su Y, Coker OO, Ka W, Wu K, Ka F, Chan L, Yu J, Leung FK. Lactobacillus gallinarum modulates the gut microbiota and produces anti-cancer metabolites to protect against colorectal tumourigenesis. *Gut*. 2021;0:gutjnl-2020-323951. doi:10.1136/gutjnl-2020-323951.

26. Peng Y, Wong CC, Yu J. The paradox of immunotherapy in NASH-HCC. *Signal Transduction and Targeted Therapy*. 2021;6(1):1-2. doi:10.1038/s41392-021-00654-9. (Editorial)

27. She J, Wong CC, Yu J. Targeted prebiotics alter the obese gut microbiome in humans. *Signal Transduction and Targeted Therapy*. 2021;6(1):1-2. doi:10.1038/s41392-021-00758-2. (Editorial)

28. Kang X, Zhang R, Kwong TN, Lui RN, Wu WK, Sung JJ, Yu J, Wong SH. Serrated neoplasia in the colorectum: Gut microbiota and molecular pathways. *Gut Microbes*. 2021;13(1):1-12. doi:10.1080/19490976.2020.1863135. (Review)

29. Lau HCH, Sung JJY, Yu J. Gut microbiota: Impacts on gastrointestinal cancer immunotherapy. *Gut Microbes*. 2021;13(1):1-21. doi:10.1080/19490976.2020.1869504. (Review)

30. Wang F, Lau JKC, Yu J. The role of natural killer cell in gastrointestinal cancer: Killer or helper. *Oncogene*.2021;40(4):717-730. doi:10.1038/s41388-020-01561-z. (Review)

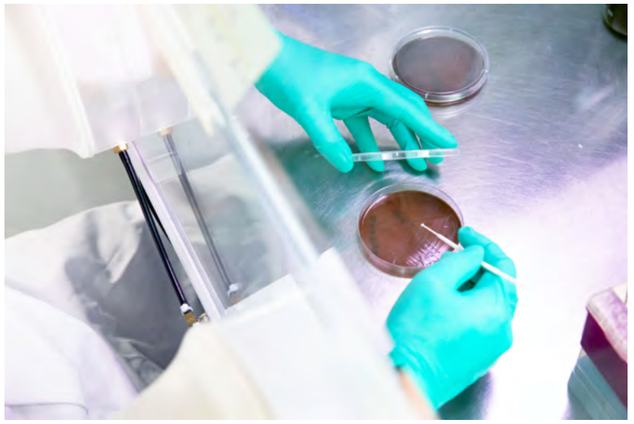
31. Xu H, Liu L, Li W, Zou D, Yu J, Wang L, Wong CC. Transcription factors in colorectal cancer: Molecular mechanism and therapeutic implications. *Oncogene.* 2021;40(9):1555-1569. doi:10.1038/s41388-020-01587-3. (Review)

32. Wen J, Lau HCH, Peppelenbosch M, Yu J. Gastric microbiota beyond H. pylori: An emerging critical character in gastric carcinogenesis. *Biomedicines*. 2021;9(11):1680. doi:10.3390/biomedicines9111680. (Review)

33. Peng Y, Nie Y, Yu J, Wong CC. Microbial metabolites in colorectal cancer: *Basic and clinical implications*. *Metabolites*. 2021;11(3):159. doi:10.3390/metabo11030159. (Review)

34. Lin Y, Wang G, Yu J, Sung JJY. Artificial intelligence and metagenomics in intestinal diseases. *Journal of Gastroenterology and Hepatology*. 2021;36(4):841-847. doi:10.1111/jgh.15501. (Review)

35. Cheung H, Yu J. Machine learning on microbiome research in gastrointestinal cancer. *Journal of Gastroenterology and Hepatology*. 2021;36(4):817-822. doi:10.1111/jgh.15502. (Editorial)



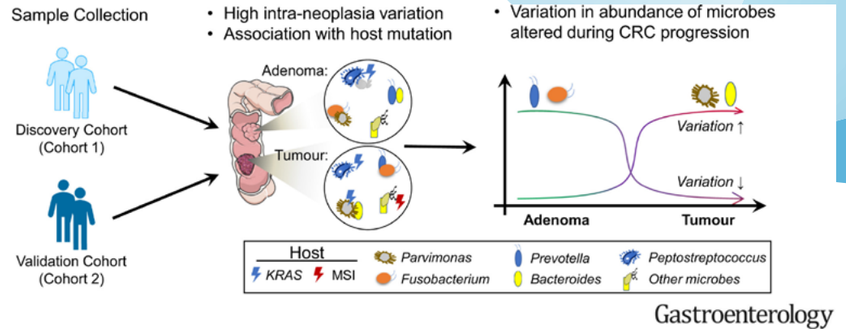
Patents

1. US Patent:
   - Inventors: Ka Kei Wu, Jun Yu
   - Title: Use of Streptococcus Thermophilus for Treatment and Prevention of Colorectal Cancer
   - Patent Application No. 62/799,162

2. China Patent:
   - Inventors: Ka Kei Wu, Jun Yu
   - Title: 結腸直腸癌的治療性和預防性處理
   - Application No. 202010077512.3

3. US Patent:
   - Inventors: Jun Yu, Ka Kei Wu, Qing Li
   - Title: Probiotic composition for treating and preventing colorectal cancer
   - Application No. 63/229,933

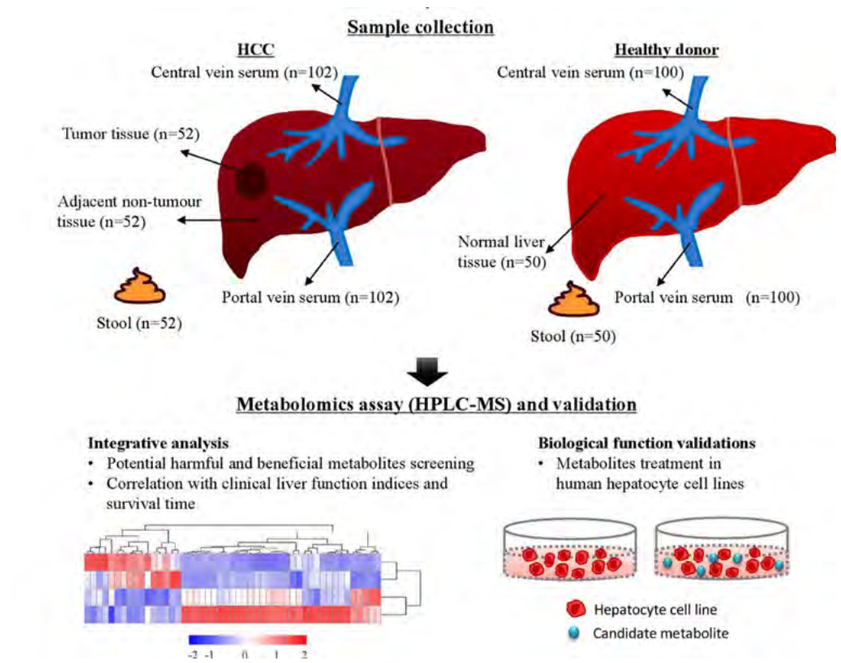
4. China Patent:
   - Inventors: Jun Yu, Ka Kei Wu, Qing Li
   - Title: 用於預防和治療結直腸直腸癌的益生菌組合物
   - Application No. 202111411744.9



Gastroenterology

The microbial community within a colorectal tumour or precancerous adenoma is heterogeneous, and such heterogeneity is significantly correlated with adenoma-carcinoma sequence and CRC-associated genetic alterations (KRAS mutation and microsatellite instability). The findings have provided new insight for the contribution of gut microbiota heterogeneity in CRC progression.

Source: Liu W, Zhang X, Xu H, Li S, Lau HCH, Chen Q, Zhang B, Zhao L, Chen H, Sung JJY, Yu J. Microbial community heterogeneity within colorectal neoplasia and its correlation with colorectal carcinogenesis. Gastroenterology. 2021;160(7):2395-2408. doi:10.1053/j.gastro.2021.02.020.



Hepatocellular carcinoma (HCC) patients had distinct clusters of metabolites in portal and central vein serum, liver tissue and stool samples. In portal vein, Jun Yu and her team identified elevated and depleted metabolites signifying that they might play a role in HCC development.

Source: Liu J, Geng W, Sun H, Liu C, Huang F, Cao J, Xia L, Zhao H, Zhai J, Li Q, Zhang X, Kuang M, Shen S, Xia Q, Wong VWS, Yu J. Integrative metabolomic characterisation identifies altered portal vein serum metabolome contributing to human hepatocellular carcinoma. Gut. Published online 2021. doi:10.1136/gutjnl-2021-325189.