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SIEW NG



03 EMERGING INFECTIOUS DISEASES AND MICROBIOTA

Fecal Microbiota Transplantation

Research Progress Summary

As pioneers in microbiome diagnostics and therapeutics, Siew Ng and her research team focus on translating metagenomic-derived microbiota signatures into novel biomarkers and oral biotherapeutics. This year, the research team has made several cutting-edge discoveries on the role of the gut microbiota with COVID-19 and its vaccine safety and efficacy. They were amongst the first in the world to discover that germs in gut (gut microbiota) modulate human immunity and disease severity in COVID-19. The team discovered that 80% of COVID-19 patients suffered from lingering symptoms known as “long COVID” including memory loss, poor sleep and hair loss after COVID-19 recovery, which was linked to abnormal gut microbiota (dysbiosis). In a recent collaborative research project between Faculty of Medicine in The Chinese University of Hong Kong (CUHK) and The University of Hong Kong (HKU), the team showed that the efficacy of COVID-19 vaccines, especially SinoVac, correlated with a unique probiotic bacterium, *Bifidobacterium adolescentis*, and that people who lacked *Bifidobacterium adolescentis* in their gut had a lower antibody response to

COVID-19 vaccines. This novel finding implies that *Bifidobacterium adolescentis* can serve as a potential therapeutic option to enhance efficacy of COVID-19 vaccines, and is consistent with their earlier clinical findings that a microbiota-based regimen developed by The Chinese University of Hong Kong led to enhanced antibody response among COVID-19 patients. This discovery offers a novel approach to optimise vaccine efficacy and safety through modulation of the gut microbiota. Their data were announced in press conferences which gained widespread media coverage in over 10 countries globally.

Evolving from their work in Fecal Microbiota Transplantation (FMT), the team has identified specific bacteria markers that can predict response to FMT in individuals with obesity, and they are developing personalised microbiota therapeutics for the treatment of obesity and metabolic diseases. Their center will also serve as the sole provider of FMT service to the entire Hospital Authority in Hong Kong covering 13 public hospitals for recurrent *Clostridioides difficile* infections.





Principal Investigator

Siew Ng



Team members

Francis Chan, Paul Chan, Joyce Mak, Lin Zhang, Qin Liu, Zhilu Xu, Jingwan Zhang, CP Cheung, Whitney Tang, Jessica Ching, Fen Zhang, Amy Li, Clinical FMT Team

In the field of microbiome diagnostics, the team has pioneered non-invasive tools for detection and prediction of Autism Spectrum Disorders (ASD). They found that bacteria associated with neurotransmitter activities were substantially reduced in children with ASD and that five unique species of bacteria identified in children with ASD were not typically found in the guts of children without the condition. Using a machine learning analysis, their proprietary algorithm of these bacteria markers achieved a sensitivity of over 80% in distinguishing children with ASD from typically developing children. Their work published in *Gut* (Impact Factor 23.06) was selected for press release by the *British Medical Journal Group* leading to significant recognition

locally and internationally whereby over 100 media outlets, including web, newspapers, trade periodicals and bloggers worldwide picked up the news with an estimated target audience of 12 million. Siew received interviews from *Reuters Health* and *Wall Street Journal*. These promising discoveries have since attracted a research donation of HK\$48 million from The D. H. Chen Foundation for the establishment of the Hub of Advanced Technology for Child Health (HATCH) to further develop novel non-invasive markers to predict ASD in early life.

With their leading-edge discoveries in microbiome medicine and the establishment of the Microbiota I-Centre (MagIC) at the Hong

Kong Science and Technology Park, Siew and her team were selected for a visit by the Chief Executive of Hong Kong SAR, Mrs. Carrie Lam, to gain insight on the team's innovations of developing novel classes of microbiome diagnostic and live biotherapeutics for common diseases.

In the reporting period, the team has published 31 peer reviewed articles and reviews in international journals, 20 international conference abstracts and filed for 22 patents related to their discovery. Siew was awarded the highly cited Researcher by Clarivate which is the second consecutive year she is receiving this honour.



Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Siew Ng	Higher Education Outstanding Scientific Research Output Awards (Science and Technology) 2020 – First-class award in Natural Sciences – Integrative Research on Epidemiology, Pathogenesis and Therapeutics in IBD	Ministry of Education
	Highly Cited Researchers 2021	Clarivate
	Meritorious Research Award	Lo Ying Shek Chi Wai Foundation
	Women of Power 2021	Prestige Hong Kong
	Outstanding Project Team on COVID-19 Research Award	Food and Health Bureau, HKSAR
	Scientific Award	8 th World Congress on Targeting Microbiota, International Society of Microbiota
	Most Read Articles 2021	Gut Journal
	GUT Best Papers 2021	Gut Journal
Winnie Lin	Distinguished Investigator Awards	9 th Annual Meeting of Asian Organization for Crohn's and Colitis 2021

Fellowships

Member's Name	Details	
	Fellowship	Organisation
Raphael Lau	Hong Kong PhD Fellowship	Research Grants Council of Hong Kong
Zhi Lu Xu	Faculty Postdoctoral Fellowship	The Chinese University of Hong Kong

Academic Editorship

Member's Name	Details	
	Fellowship	Journal
Siew Ng	Associate Editor	Gut
		BMC Gastroenterology
	Editorial Board Member	Journal of Gastroenterology and Hepatology
		Gastroenterology
		World Journal of Gastroenterology
		Inflammatory Intestinal Disease
		Journal of Crohn's and Colitis
		Alimentary Pharmacology & Therapeutics
Review Editor	Frontiers in Gastroenterology	
International Editorial Board Member	Indonesian Journal of Gastroenterology	

Reviewer of Journal / Conference

Member's Name	Details		
	Role	Journal / Conference	
Siew Ng	Chair Reviewer	Digestive Disease Week 2022, American Gastroenterological Association (AGA) Institute Council	
	Reviewer	Journal of Hepatology	
		New England Journal of Medicine	
		Nature Medicine	
		Nature Reviews Gastroenterology & Hepatology	
		Gastroenterology	
		Gut	
		American Journal of Gastroenterology	
		Clinical Gastroenterology and Hepatology	
		Journal of Crohn's and Colitis	
		Alimentary Pharmacology and Therapeutics	
		Gastrointestinal Endoscopy	
		Journal of Gastroenterology	
		Inflammatory Bowel Disease	
		Journal of Gastroenterology and Hepatology	
		World Journal of Gastroenterology	
		Digestive Diseases and Sciences	
		BMC Gastroenterology	
		European Journal of Gastroenterology & Hepatology	
		Judge	Asian Pacific Association of Gastroenterology / JGH Foundation Clinician-Scientist Training Fellowship 2021

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK\$)
Siew Ng	Establishment of the Hub of Advanced Technology for Child Health (HATCH)	D.H. Chen Foundation	10/2021	09/2024	48,240,000
	Novel Strategies to Facilitate Early Detection, Prevention and Intervention for Long-term Health Problems Related to COVID-19 (NovITor-COVID study)	Food and Health Bureau – Health and Medical Research Fund	04/2021	05/2026	45,991,725
	Modulation of Gut Microbiota to Enhance Health and Immunity in Vulnerable Individuals during COVID-19 Pandemic	Food and Health Bureau – Health and Medical Research Fund	04/2021	05/2024	9,980,840
	Midstream Research Programme: A Microbiome-based Noninvasive Diagnostic Test for Early Colorectal Cancers	Innovation and Technology Commission	01/2021	12/2024	4,600,000
	HKSTP-KingMed Co-Incubation Scheme	Hong Kong Science and Technology Parks Corporation	01/2021	12/2024	4,000,000
	ICARUS –IBD: International Study of COVID-19 Antibody Response Under Sustained Immune Suppression in Inflammatory Bowel Disease	The Chancellor Masters and Scholars of the University of Oxford	11/2020	04/2022	102,960
	IBD GIVES-21: Global IBD Visualization of Epidemiology Studies (GIVES) in the 21st Century	The Leona M. & Harry B. Helmsley Charitable Trust	09/2020	08/2023	15,564,946
	Recurrence Rates in High-risk Subjects with Baseline Advanced Colorectal Adenomas Followed up at Different Surveillance Intervals: A Multi-center Randomised Controlled Trial in Four Chinese Cities	Food and Health Bureau – Health and Medical Research Fund	09/2020	09/2023	1,460,388

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK\$)
Siew Ng	Launching of a bacteria-based Non-invasive Diagnostic Test for Early Colorectal Cancer Detection	The Chinese University of Hong Kong Technology and Business Development Fund	09/2020	08/2021	175,211
	Early Detection and Surveillance of COVID-19 Infection by Non-invasive Ophthalmic Evaluations	Food and Health Bureau – Commissioned Research on the Novel Coronavirus Disease (COVID-19)	08/2020	07/2022	4,822,810
	Elucidating Driver Bacteria in Crohn's Disease for Therapeutic Manipulation	Croucher Foundation – Croucher Senior Medical Research Fellowship	08/2020	08/2022	2,877,860
	Role of Gastrointestinal Tract and Gut Microbiota in Pathogenesis of Coronavirus Disease 2019 (COVID-19): A Missing Site for Viral Replication & Transmission	Food and Health Bureau – Commissioned Research on the Novel Coronavirus Disease (COVID-19)	06/2020	05/2021	4,076,580
	Technology Start-up Support Scheme for Universities	Innovation and Technology Commission – Innovation and Technology Fund	04/2020	03/2021	500,000
	Mother-to-Infant Transfer of Bacteriome, Virome, Fungome and Metabolome in Health and Crohn's Disease (Mommy-CD)	The Leona M. & Harry B. Helmsley Charitable Trust	10/2019	09/2022	19,727,952
	A Randomised, Placebo-controlled Study on Fecal Microbiota Transplantation for Patients with Irritable Bowel Syndrome with Fecal and Mucosal Microbiota Assessment	Food and Health Bureau – Health and Medical Research Fund	06/2019	05/2021	1,301,112
	Health@InnoHK: Microbiota I-Center (MagIC)	Innovation and Technology Commission	05/2019	06/2024	350,200,000

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK\$)
Siew Ng	PACIFIC: Prevalence, Characteristics, and Genetics of Adherent-invasive <i>Escherichia coli</i> in Crohn's disease patients: Comparative Study between France and Hong-Kong	The French National Research Agency / Research Grants Council Joint Research Scheme	02/2018	01/2022	2,611,942
	The ENIGMA Studies – Eastern Inflammatory Bowel Disease Gut Microbiota	The Leona M. & Harry B. Helmsley Charitable Trust	03/2017	02/2021	14,259,211

Publications

A. Journal Papers

1. Olivera PA, Zuilvy S, Kotze PG, Regnault V, Al Awadhi S, Bossuyt P, Geary RB, Ghosh S, Kobayashi T, Lacolley P, Louis E, Magro F, Ng SC, Papa A, Raine T, Teixeira FV., Rubin DT, Danese S, Peyrin-Biroulet L. International consensus on the prevention of venous and arterial thrombotic events in patients with inflammatory bowel disease. *Nature Reviews Gastroenterology and Hepatology*. 2021;18(12):857-873. doi:10.1038/s41575-021-00492-8.
2. Shi HY, Zhu X, Li WL, Mak JWY, Wong SH, Zhu ST, Guo SL, Chan FKL, Zhang ST, Ng SC. Modulation of gut microbiota protects against viral respiratory tract infections: A systematic review of animal and clinical studies. *European Journal of Nutrition*. 2021;60(8):4151-4174. doi:10.1007/s00394-021-02519-x. (Review)
3. 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.
4. Yau YK, Mak WYJ, Lui NSR, Ng WYR, Cheung CYK, Li YLA, Ching YLJ, Chin ML, Lau HSL, Chan KLF, Chan KSP, Ng SC. High prevalence of extended-spectrum beta-lactamase organisms and the COVID-19 pandemic impact on donor recruitment for fecal microbiota transplantation in Hong Kong. *United European Gastroenterology Journal*. 2021;9(9):1027-1038. doi:10.1002/ueg2.12160.
5. Zhilu X, Xiangqian D, Keli Y, Caroline C, Jingwan Z, Yu L, Tao Z, Cheung CL, Yang S, Fengrui Z, Ki CF, Jy SJ, Jun Y, Anthony B, Nicolas B, Jean-Frédéric C, Sunny Hei W, Yinglei M, Siew C N. Association of adherent-invasive *Escherichia coli* with severe gut mucosal dysbiosis in Hong Kong Chinese population with Crohn's disease. *Gut Microbes*. 2021;13(1):e1994833. doi:10.1080/19490976.2021.1994833.
6. Rubin DT, Modesto I, Vermeire S, Danese S, Ng SC, Kwok KK, Koram N, Jones TV. Worldwide post-marketing safety surveillance experience with tofacitinib in ulcerative colitis. *Alimentary Pharmacology & Therapeutics*. 2022;55(3):302-310. doi:10.1111/apt.16619. (Epub ahead of print)
7. Yang K, Niu J, Zuo T, Sun Y, Xu Z, Tang W, Liu Q, Zhang J, Ng EKW, Wong SKH, Yeoh YK, Chan PKS, Chan FKL, Miao Y, Ng SC. Alterations in the gut virome in obesity and type 2 diabetes mel-

litus. *Gastroenterology*. 2021;161(4):1257-1269. doi:10.1053/j.gastro.2021.06.056.

8. Zhang F, Wan Y, Zuo T, Yeoh YK, Liu Q, Zhang L, Zhan H, Lu W, Xu W, Lui GCY, Li AYL, Cheung CP, Wong CK, Chan PKS, Chan FKL, Ng SC. Prolonged impairment of short-chain fatty acid and L-isoleucine biosynthesis in gut microbiome in patients with COVID-19. *Gastroenterology*. 2022;162(2):548-561. doi:10.1053/j.gastro.2021.10.013. (Epub ahead of print)
9. Lau HCH, NG SC, Yu J. Targeting the gut microbiota in coronavirus disease 2019: Hype or hope? *Gastroenterology*. 2022;162(1):9-16. doi:10.1053/j.gastro.2021.09.009. (Commentary, Epub ahead of print)
10. Sasson AN, Ingram RJM, Zhang Z, Taylor LM, Ananthakrishnan AN, Kaplan GG, Ng SC, Ghosh S, Raman M. The role of precision nutrition in the modulation of microbial composition and function in people with inflammatory bowel disease. *Lancet Gastroenterology & Hepatology*. 2021;6(9):754-769. doi:10.1016/s2468-1253(21)00097-2.
11. Zhang L, Zhan H, Xu W, Yan S, Ng SC. The role of gut mycobiome in health and diseases. *Therapeutic Advances in Gastroenterology*. 2021;14:1-18. doi:10.1177/17562848211047130. (Review)
12. D'Amico F, Solitano V, Aletaha D, Hart A, Magro F, Selmi C, Ng SC, Al Awadhi S, Choy E, Schulze-Koops H, Bossuyt P, Olivera PA, Kotze PG, Ghosh S, Peyrin-Biroulet L, Danese S. Biobetters in patients with immune-mediated inflammatory disorders: An international delphi consensus. *Autoimmunity Reviews*. 2021;20(7):102849. doi:10.1016/j.autrev.2021.102849. (Review)
13. Wan Y, Zuo T, Xu Z, Zhang F, Zhan H, Chan D, Leung TF, Yeoh YK, Chan FKL, Chan R, Ng SC. Underdevelopment of the gut microbiota and bacteria species as non-invasive markers of prediction in children with autism spectrum disorder. *Gut*. 2021;0:1-9. doi:10.1136/gutjnl-2020-324015.
14. Burke KE, D'Amato M, Ng SC, Pardi DS, Ludvigsson JF, Khalili H. Microscopic colitis. *Nature Reviews Disease Primers*. 2021;7(1):1-17. doi:10.1038/s41572-021-00273-2.
15. Xu Z, Chan FKL, Ng SC. Dysbiosis in SARS-CoV-2-infected patients. *Gastroenterology*. 2021;160(6):2195-2196. doi:10.1053/j.gastro.2021.01.198. (Letter)
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17. Ianiro G, Mullish BH, Hvas CL, Segal JP, Kuijper EJ, Costello SP, Kelly CR, Allegretti JR, Fischer M, Iqbal TH, Satokari R, Kao D, van Prehn J, Ng SC, Bibbò S, Baunwall SMD, Quraishi MN, Sokol H, Zhang F, Keller J, Masucci L, Quaranta G, Kassam Z, Sanguinetti M, Tilg H, Gasbarrini A, Cammarota G. SARS-CoV-2 vaccines and donor recruitment for FMT. *Lancet Gastroenterology & Hepatology*. 2021;6(4):264-266. doi:10.1016/s2468-1253(21)00032-7. (Letter)
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19. Ungaro RC, Brenner EJ, Geary RB, Kaplan GG, Kissous-Hunt M, Lewis JD, Ng SC, Rahier JF, Reinisch W, Steinwurz F, Underwood FE, Zhang X, Colombel JF, Kappelman MD. Effect of IBD medications on COVID-19 outcomes: Results from an international registry. *Gut*. 2021;70(4):725-732. doi:10.1136/gutjnl-2020-322539.
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- Kahr WHA, Lemaire M, Genomics England Research Consortium, Lu CY, Siddiqui I, Surette MG, Kotlarz D, Engelhardt KR, Griffin HR, Rottapel R, Decaluwe H, Laxer RM, Proietti M, Hambleton S, Elcombe S, Guo CH, Grimbacher B, Dotan I, Ng SC, Freeman SA, Snapper SB, Klein C, Boztug K, Huang Y, Li D, Uhlig HH, Muise AM. Gain-of-function variants in SYK cause immune dysregulation and systemic inflammation in humans and mice. *Nature Genetics*. 2021;53(4):500-510. doi:10.1038/s41588-021-00803-4.
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27. Zuo T, Liu Q, Zhang F, Lui GCY, Tso EYK, Yeoh YK, Chen Z, Boon SS, Chan FKL, Chan PKS, Ng SC. Depicting SARS-CoV-2 faecal viral activity in association with gut microbiota composition in patients with COVID-19. *Gut*. 2021;70(2):276-284. doi:10.1136/gutjnl-2020-322294.
28. Zhang F, Zuo T, Yeoh YK, Cheng FWT, Liu Q, Tang W, Cheung KCY, Yang K, Cheung CP, Mo CC, Hui M, Chan FKL, Li CK, Chan PKS, Ng SC. Longitudinal dynamics of gut bacteriome, mycobiome and virome after fecal microbiota transplantation in graft-versus-host disease. *Nature Communications*. 2021;12(1):1-11. doi:10.1038/s41467-020-20240-x.
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B. Conference Abstract

- Xu Z, Mak JWY, Lin Y, Yang K, Liu Q, Zhang F, Lau I, Li A, Cheung K, Tang W, Ching JYL, Chan PK, Chan FKL, Ng SC. Recipient's gut bacteria composition predicts efficacy of fecal microbiota transplantation in inducing weight loss in obese subjects. In: *United European Gastroenterology Week 2021*. Virtual. 2021 October 3-5.
- Hong HS, Leung WK, Ng KMC, Sze ASF, Li M, Leung CM, Lo FH, Lam BCY, Chan KH, Shan EHS, Tsang SWC, Hui AJ, Chow WH, Ng SC, Park SH, Yang SK, Mak JWY, Ye BD. Differences in direct healthcare cost utilization in the first year of IBD diagnosis: A binational study. In: *United European Gastroenterology Week 2021*. Virtual. 2021 October 3-5.
- Sandborn W, D'Haens G, Sands BE, Panaccione R, Ng SC, Lawendy N, Kulisek N, Guo X, Mundayat R, Su C, Panes J. Tofacitinib for the treatment of ulcerative colitis: Up to 7.8 years of safety data from global clinical trials. In: *American College of Gastroenterology Annual Meeting 2021*. Las Vegas, United States. 2021 October 25-27.
- Sandborn W, D'Haens G, Sands BE, Panaccione R, Ng SC, Lawendy N, Kulisek N, Guo X, Mundayat R, Su C, Panes J. Tofacitinib for the treatment of ulcerative colitis: Up to 7.8 years of safety data from global clinical trials. In: *United European Gastroenterology Week 2021*. Virtual. 2021 October 3-5.
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twice daily who were in stable remission and either dose-reduced to tofacitinib 5 mg twice daily or remained on 10 mg twice daily: 6-month data from the double-blind, randomised riveting study. In: *16th Congress of European Crohn's and Colitis Organisation 2021*. Virtual. 2021 July 2-3 & 8-10.

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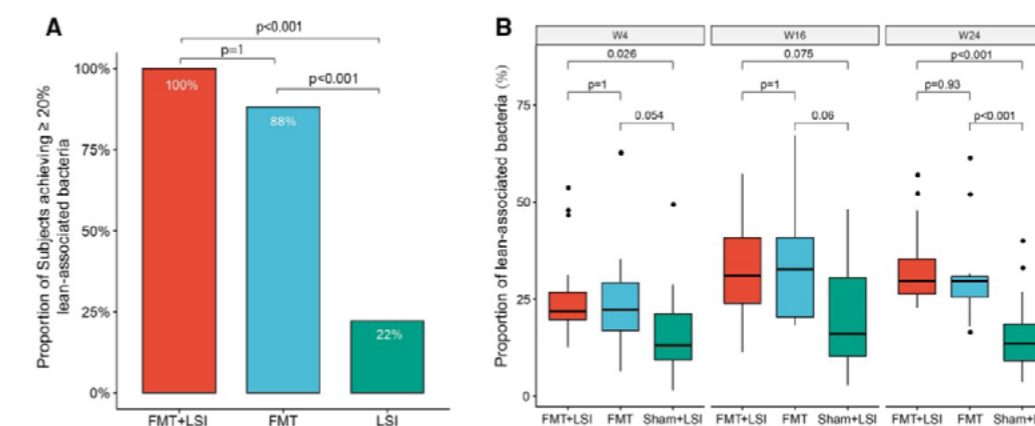
Delayed Gut Microbiome Maturity in Autism

自閉症患者腸道微生物發展遲緩



The study of Siew Ng's team showed for the first time that the gut microbiota of children with autism is abnormally developed and lags that of age-matched peers.

Source: Siew Ng

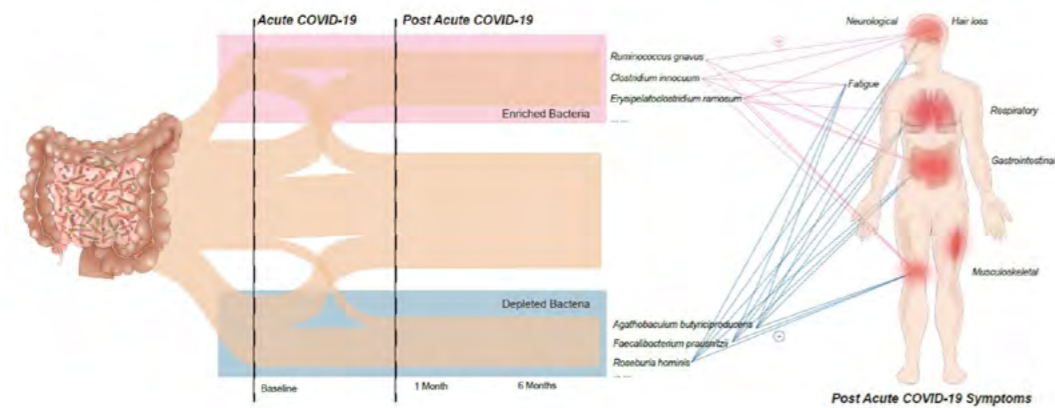


Faecal microbiota analysis showing FMT led to durable engraftment of lean-associated microbiota in obese subjects with type 2 diabetes.

(A) Proportion of subjects with $\geq 20\%$ lean-associated microbiota at W24. (B) Boxplot depicting of the percentage of lean-associated microbiota at W4, W16 and W24. Significance between treatment arms were calculated by Mann-Whitney U test with Bonferroni correction. FMT, faecal microbiota transplantation; LSI, lifestyle intervention.

Source: Ng SC, Xu ZL, Mak JWY, et al. Ng SC, Xu Z, Mak JWY, Yang K, Liu Q, Zuo T, Tang W, Lau L, Lui RN, Wong SH, Tse YK, Li AYL, Cheung K, Ching JYL, Wong VWS, Kong APS, Ma RCW, Chow EYK, Wong SKH, Ho ICH, Chan PKS, Chan FKL. Microbiota engraftment after faecal microbiota transplantation in obese subjects with type 2 diabetes: A 24-week, double-blind, randomised controlled trial. *Gut*. 2021;0:1-8. doi:10.1136/gutjnl-2020-323617.

Gut microbiota composition at admission predicts Long COVID



Schematic summary of associations between gut microbiome and development of post-acute COVID-19 syndrome. The team found overlap of bacteria species such as *R. gnavus*, *C. innocuum*, *Erysipelatous ramosum* remained altered from baseline to follow-up and exhibited association with several PACS symptoms.

Source: Liu Q, Mak JWY, Su Q, Yeoh YK, Lui GCY, Ng SSS, Zhang F, Li AYL, Lu W, Hui DSC, Chan PKS, Chan, FKL, Ng SC. Gut Microbiota Dynamics in a Prospective Cohort of Patients with Post-acute COVID-19 Syndrome. *Gut*. Accepted Manuscript.



Press Conference on 31 March 2021: CU Medicine Study Shows Modulation of Gut Microbiota Helps Enhance Safety and Efficacy of COVID-19 Vaccine

Source: <https://www.cpr.cuhk.edu.hk/en/press/cu-medicine-study-shows-modulation-of-gut-microbiota-helps-enhance-safety-and-efficacy-of-covid-19-vaccine/>



Press Conference on 2 December 2021: Joint CUHK-HKU study discovers efficacy of COVID-19 vaccines correlates with a probiotic bacterium, *Bifidobacterium adolescentis*

Source: <https://www.med.cuhk.edu.hk/press-releases/joint-cuhk-hku-study-discovers-efficacy-of-covid-19-vaccines-correlates-with-a-probiotic-bacterium-bifidobacterium-adolescentis>