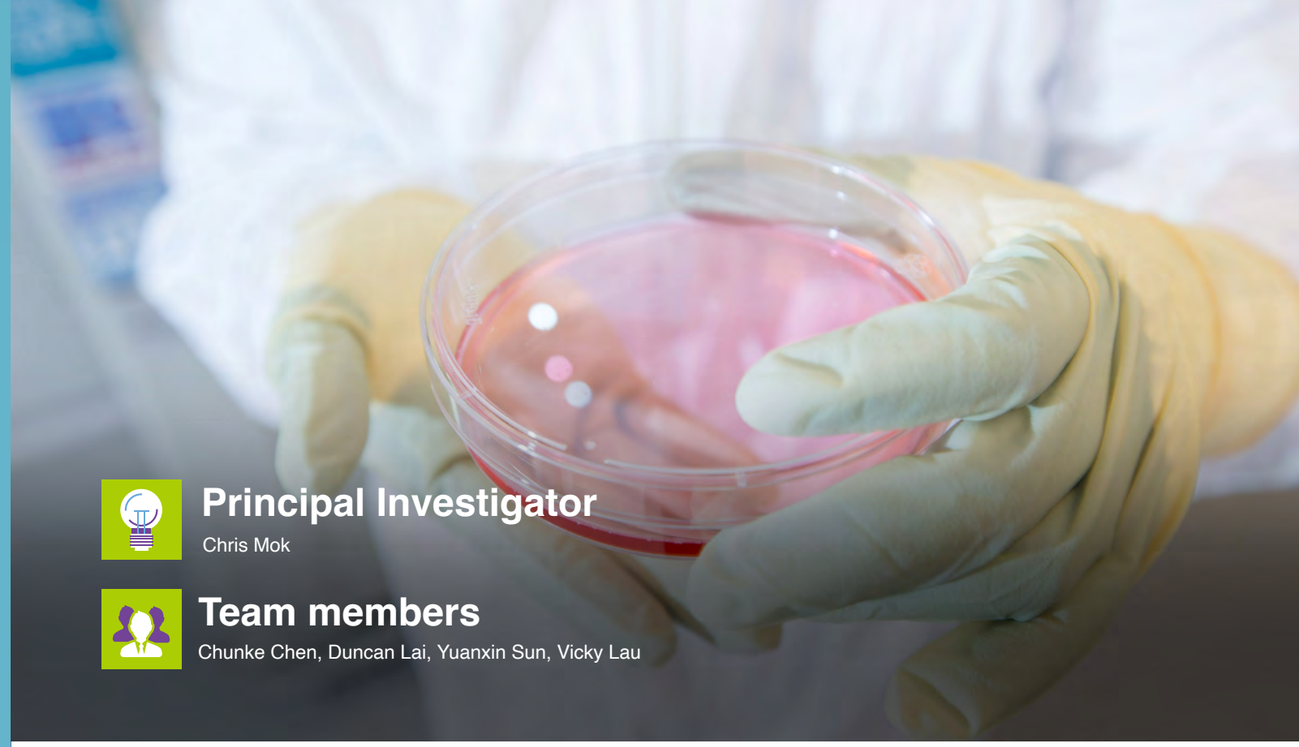
莫家斌

CHRIS MOK

07 INFLAMMATORY DISEASES



Principal Investigator

Chris Mok

Team members

Chunke Chen, Duncan Lai, Yuanxin Sun, Vicky Lau

Research Progress Summary

The research group led by Chris Mok mainly focuses on understanding how the virus infection or vaccination determine the pathogenesis and immunity in host. With the experience of the related topic, they have established very solid platforms for molecular, clinical, virologic as well as immunological studies. In 2021, the team put their effort to investigate the immunological features in humans that are mediated by the stimulation of SARS-CoV-2, the cause of COVID-19 that emerged in late 2019 leading to a devastating pandemic. So far, over 500 million COVID-19 infections including more than 5 million deaths have been reported to the World Health Organization. Many COVID-19 vaccines were rapidly developed, evaluated and deployed with over 4 billion doses of COVID-19 vaccines administered worldwide. These include inactivated whole virus, lipid nanoparticle (LNP)-encapsulated mRNA, adenovirus-vectored and protein sub-unit vaccines. The safety, immunogenicity and efficacy of these vaccines have been evaluated in separate clinical trials but there are few “head-to-head” comparisons of different vaccines. Moreover, the novel SARS-CoV-2 variants have emerged and are rapidly becoming the dominant SARS-CoV-2 virus circulating globally. It is important to define reductions in antibody and T cell response in vaccinated individuals to understand potential loss of protection from vaccination. Addressing these questions together with comparing the similar features in vaccine cohorts will help to justify the performance of different COVID-19 vaccines and is also of use in helping the development of the next generation of COVID-19 vaccines. Chris’s team has set up a longitudinal study cohort to monitor their humoral and cellular immune responses from the participants who received the COVID-19 vaccine. The results provided important implications for understanding the performance of different COVID-19 vaccines and served as references for the policy making of the government.

Comparison of the Immunogenicity of BNT162b2 and CoronaVac COVID-19 Vaccines in Hong Kong (Mok et al 2021 *Respirology*)

The two types of COVID-19 vaccines which are included in this study use mRNA (Pfizer-BioNTec, BNT162b2), and whole virion inactivation (Sinovac, CoronaVac) as their approaches respectively. All these vaccines are so far only evaluated at their own designated population and countries and there is still lack of prospective study to "side-by-side" compare the immunogenicity and kinetic of different vaccines. In particular, the differences on the long-term responses of either humoral (B cell) or cellular (T cell) immune responses between these vaccines are not yet clear. In this study, the team showed that BNT162b2 elicited significantly higher $PRNT_{50}$, $PRNT_{90}$, sVNT, spike receptor binding, spike N terminal domain binding, spike S2 domain binding, spike FcR binding and antibody avidity levels than CoronaVac one month after the second dose of vaccine. Both vaccines induced SARS-CoV-2 specific $CD4^+$ and $CD8^+$ T cell responses at 1-month post-vaccination but CoronaVac elicited significantly higher structural protein-specific $CD4^+$ and $CD8^+$ T cell responses.

A Randomised Control Trial using CoronaVac or BNT162b2 vaccine as a third dose in adults vaccinated with two doses of CoronaVac (Mok et al 2021 *AJRCCM*)

CoronaVac is one of the WHO approved inactivated virus vaccines and over 750 million doses have been administered in more than 40 countries. However, breakthrough infections, some leading to severe disease and death have been reported in CoronaVac vaccinated adults have raised concern. Given the results suggesting a less than optimal protection afforded by the CoronaVac vaccine, it becomes relevant to consider the rationale for providing a booster dose with either an additional dose of CoronaVac or BionTech to those with low neutralising antibody titers after the two dose CoronaVac schedule. However, there is so far no scientific evidence to inform such a policy decision. They thus conducted a Randomised Clinical Trial (RCT) study to compare the immunogenicity of using BNT162b2 and CoronaVac as a third dose for adults with low antibody response to two doses of CoronaVac. It showed that both CoronaVac and BNT162b2 vaccines boosted antibody responses in CoronaVac immunised individuals but BNT162b2 was markedly superior in immunogenicity. BNT162b2 not only elicited a higher level of SARS-CoV-2 specific antibodies but also led to higher levels of cross-neutralising antibody levels to different variants of concern. The adverse reactions were mild and short-lived.

Altered ISGylation drives aberrant macrophage-dependent immune responses during SARS-CoV-2 infection (Munnur et al 2021 *Nature Immunology*)

Interferon stimulated gene 15 (ISG15) is a ubiquitin-like modifier frequently induced during virus infections and involved in versatile host defence mechanisms. Not surprisingly, many viruses including SARS-CoV-2 have evolved de-ISGylating activities to antagonise its effect. In this study, the team compared ISG15-driven macrophage responses upon infection by two (+) RNA viruses, Zika and SARS-CoV-2 as well as by influenza virus. All three viruses triggered induction of ISGylating enzymes; while influenza and Zika viruses induced cellular ISGylation, SARS-CoV-2 triggered hydrolysis of ISG15 modifications instead, to generate free ISG15, which appeared in the extracellular space via a non-classical autophagy-related secretory process. Increased extracellular ISG15 was also reflected in serum samples from COVID-19 patients. The high ratio of free versus conjugated ISG15 in SARS-CoV-2 infected cells correlated directly with macrophage polarisation towards a M1 phenotype, increased secretion of pro-inflammatory cytokines, and attenuated cell surface presentation of MHCI/II. This phenomenon was recapitulated by expressing the wild-type but not the catalytically inactive PLpro de-ISGylating enzyme of SARS-CoV-2. In vitro characterisation of purified wild-type and mutant PLpro revealed its higher de-ISGylating compared to its de-ubiquitylating activity. Quantitative proteomic analyses of PLpro substrates revealed several metabolic enzymes that have been implicated in the biogenesis of secretory granules that transport inflammatory cytokines. Further proteomic analyses of the secretome from SARS-CoV-2 infected macrophages revealed that besides ISG15, they were enriched in non-classical secretory proteins and cytokines. Collectively, the results indicate that increased proportions of free ISG15 dramatically alter macrophage responses and is likely a key feature of cytokine storms triggered by highly pathogenic respiratory viruses such as influenza and SARS-CoV-2.

Research and Scholarship

Academic Editorship

Member's Name	Details	
	Role	Journal
Chris Mok	Associate Editor	Virology Journal
		Frontier of Immunology
	Guest Editor	Viruses

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Chris Mok	Reviewer	Virology Journal
		Emerging Infectious Diseases
		EBiomedicine
		Science immunology
		Nature Communication
		Emerging Microbes & Infections
		Biosensors and Bioelectronics
		Plos Biology

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Chris Mok	Long-term Longitudinal Comparisons of Health Status and Immune Responses in Convalescent COVID-19 and Vaccinated Cohorts in Hong Kong	Food and Health Bureau – Health and Medical Research Fund	01/04/2021	31/05/2025	24,000,000
	Development of Anti-influenza Drugs Based on Anti-flu Herbs Ganlanye and Furongye (Leaves of Canarium Album (Lour.) Raeusch and Folium Hibisci Mutabilis)	Food and Health Bureau – Health and Medical Research Fund	01/05/2021	31/03/2024	1,500,000
	Preclusion of an Antigenically Disruptive Mutation in Egg-based H3N2 Seasonal Influenza Vaccines by Mutational Incompatibility	Food and Health Bureau – Health and Medical Research Fund	01/05/2020	30/04/2022	1,488,520

Publications

A. Journal Papers

1. Mok CKP, Cohen CA, Cheng SMS, Chen C, Kwok KO, Yiu K, Chan TO, Bull M, Ling KC, Dai Z, Ng SS, Lui GCY, Wu C, Amerasinghe GK, Leung DW, Wong SYS, Valkenburg SA, Peiris M, Hui DS. Comparison of the immunogenicity of BNT162b2 and CoronaVac COVID-19 vaccines in Hong Kong. *Respirology*. Published online 2021. doi:10.1111/resp.14191. (Epub ahead of print)

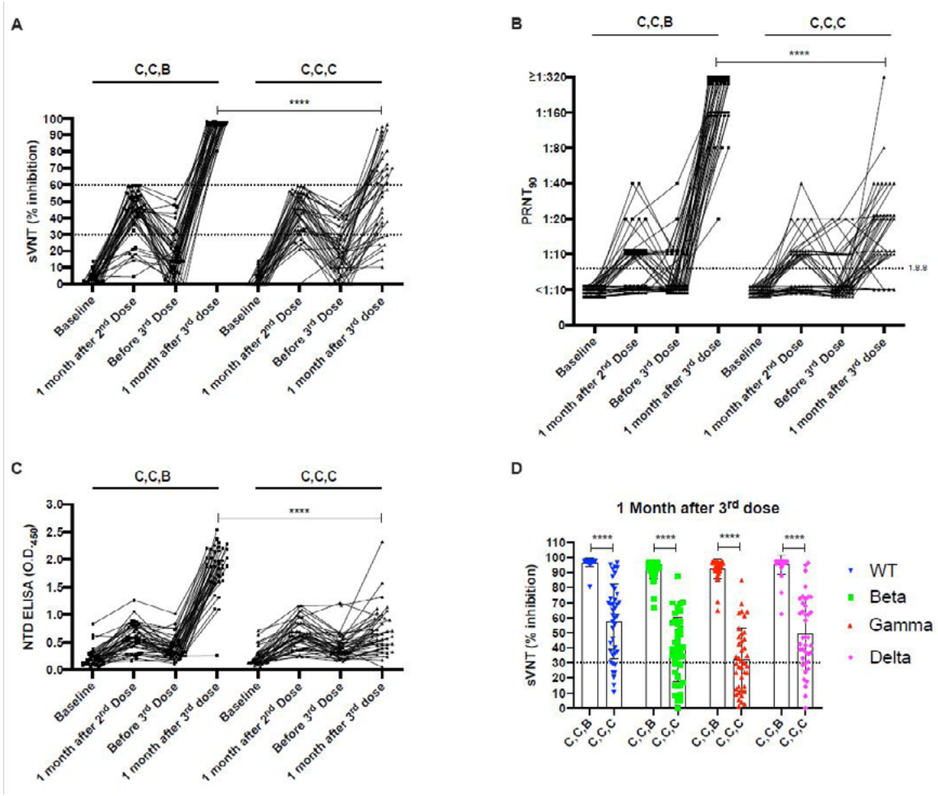
2. Vanhove B, Marot S, So RT, Gaborit B, Evanno G, Malet I, Lafrogne G, Mevel E, Ciron C, Royer P-J, Lheriteau E, Raffi F, Bruzzone R, Mok CKP, Duvaux O, Marcelin A-G, Calvez V. XAV-19, a swine glyco-humanized polyclonal antibody against SARS-CoV-2 spike receptor-binding domain, targets multiple epitopes and broadly neutralizes variants. *Frontiers in Immunology*. 2021;12(11):1-11. doi:10.3389/fimmu.2021.761250.

3. Munnur D, Teo Q, Eggermont D, Lee HHY, Thery F, Ho J, van Leur SW, Ng WWS, Siu LYL, Beling A, Ploegh H, Pinto-Fernandez A, Damianou A, Kessler B, Impens F, Mok CKP, Sanyal S. Altered ISGylation drives aberrant macrophage-dependent immune responses during SARS-CoV-2 infection. *Nature Immunology*. 2021;22(11):1416-1427. doi:10.1038/s41590-021-01035-8.

4. Au KK, Chen C, Chan YM, Wong WWS, Lv H, Mok CKP, Chow CK. Tracking the transcription kinetic of SARS-CoV-2 in human cells by reverse transcription-droplet digital PCR. *Pathogens*. 2021;10(10):1-11. doi:10.3390/pathogens10101274.

5. Montague Z, Lv H, Otwinowski J, DeWitt WS, Isacchini G, Yip GK, Ng WW, Tsang OTY, Yuan M, Liu H, Wilson IA, Peiris JSM, Wu NC, Nourmohammad A, Mok CKP. Dynamics of B cell repertoires and emergence of cross-reactive responses in patients with different severities of COVID-19. *Cell Reports*. 2021;35(8):109173. doi:10.1016/j.celrep.2021.109173.

6. Lv H, Tsang OTY, So RTY, Wang Y, Yuan M, Liu H, Yip GK, Teo QW, Lin Y, Liang W, Wang J, Ng WW, Wilson IA, Peiris JSM, Wu NC, Mok CKP. Homologous and heterologous serological response to the N-terminal domain of SARS-CoV-2 in humans and mice. *European Journal of Immunology*. 2021;51(9):2296-2305. doi:10.1002/eji.202149234.



Antibody responses of individuals before and after the third dose of either BNT162b2 or CoronaVac. The levels of antibodies after the third dose of either BNT162b2 or CoronaVac were detected from the plasma collected from vaccinated adult individuals who had received two doses of CoronaVac. (A) Surrogate virus neutralisation test (sVNT). (B) PRNT90 (C) NTD-specific IgG antibodies (D) The % inhibition against the wild type, beta, gamma and delta variants. C,C,B and C,C,C indicate the vaccines (C: CoronaVac; B: BNT162b2)

Source: Mok CKP, Cheng SMS, Chen C, Yiu K, Chan T-O, Lai KC, Ling KC, Sun Y, Peiris M, Hui DS. A RCT using CoronaVac or BNT162b2 vaccine as a third dose in adults vaccinated with two doses of CoronaVac. https://doi.org/101164/rccm202111-2655LE. Published online January 11, 2022. doi:10.1164/rccm.202111-2655le.