CRF 8G (Revised Sep 15)

RGC Reference HKU1/CRF/11G
please insert ref. above

The Research Grants Council of Hong Kong
Collaborative Research Fund Group Research Projects
Completion Report

(*for completed projects only*)

Part A: The Project and Investigator(s)

1. Project Title

Molecular mechanisms of innate antiviral response

2. Investigator(s) and Academic Department/Units Involved *(please highlight approved changes in the composition of the project team and quote the date when RGC granted approval of such changes)*

Research Team	Name/Post	Unit/Department/Institution	Average number of hours per week spent on this project in the current reporting period
Project Coordinator	Jin, Dong-Yan Professor	School of Biomedical Sciences, The University of Hong Kong	12
Co-Principal investigator	Au, Shannon Wing Ngor Associate Professor	School of Life Sciences, Chinese University of Hong Kong	8
	Kok, Kin-Hang Assistant Professor	Department of Microbiology, The University of Hong Kong	12
	Lau, Allan Sik-Yin Professor (deceased)	Department of Pediatrics and Adolescent Medicine, The University of Hong Kong	0
	Qi, Robert Z. Professor	Division of Life Science, Hong Kong University of Science and Technology	2
	Sham, Mai Har Professor	School of Biomedical Sciences, The University of Hong Kong	4
	Yuen, Kwok Yung Chair Professor	Department of Microbiology, The University of Hong Kong	4
	Zheng, Bo-Jian Professor	Department of Microbiology, The University of Hong Kong	4

Collaborator	Chan, Chi-Ping Research Assistant Professor	School of Biomedical Sciences, The University of Hong Kong	
Collaborator	Li, James Chun-bong Assistant Professor	Department of Pediatrics and Adolescent Medicine, The University of Hong Kong	
Collaborator	Yeung, Man-Lung Research Assistant Professor	Department of Microbiology, The University of Hong Kong	
Collaborator	Zhou, Jie Research Assistant Professor	Department of Microbiology, The University of Hong Kong	

3. Project Duration

	Original	Revised	Date of RGC Approval *(must be quoted*)
Project Start Date	June 1, 2012		
Project Completion Date	May 31, 2015		
Duration (*in month*)	36		
Deadline for Submission of Completion Report	May 31, 2016		

Part B: The Final Report

5. Project Objectives

5.1 Objectives as per original application

1) We will determine the crystal structures of PACT, RIG-I and PACT-RIG-I complexes, define the interface, stoichiometry and kinetics of PACT-RIG-I interaction, and characterize the conformational changes of RIG-I induced by PACT binding.
2) We will use gene targeting technology to create conditional *Pact*-knockout mice, thereby clarifying the physiological roles of PACT in different cells, tissues and organs *in vivo*.
3) We will shed light on the mechanisms by which PACT activates RIG-I and MDA5. The roles of PACT in viral RNA detection, the regulation of PACT by phosphorylation and the formation of multiple PACT-containing complexes in virus-infected cells will be investigated in cultured cells and mouse models.
4) We will characterize the function of PACT in the context of influenza A virus infection. The mechanisms by which influenza A virus counteracts PACT function will be delineated.

5.2 Revised objectives

Date of approval from the RGC: _____

Reasons for the change: _____
_____

1.
2.
3. ....

6. Research Outcome

6.1 Major findings and research outcome
(maximum 1 page; please make reference to Part C where necessary)

Requirement of PACT for innate antiviral response

We found that the induction of type I interferons (IFNs) and IFN-stimulated genes (ISGs) by herpes simplex virus type 1 (HSV-1), Middle East respiratory syndrome coronavirus (MERS-CoV), Sendai virus and measles virus was abrogated or severely compromised in PACT$^{-/-}$ mice and cells (Kew et al., J. Virol., 2013; Siu et al., J. Virol., 2014; Ho et al., J. Virol., 2016). Particularly, these viruses or their viral RNA could not induce IFN-β and other ISGs in the absence of PACT. A side-by-side comparison with RIG-I$^{-/-}$ and MDA5$^{-/-}$ cells was also made. In addition, the role of PACT in innate antiviral response to a retrovirus has also been implicated (Yuen et al., J. Virol., 2016). Similar findings were obtained from PACT$^{-/-}$ general knockouts from at least three difference sources, with different viruses including Ebola virus and influenza A virus, and also by different groups (Luthra et al., Cell Host Microbe, 2013; Tawaratsumida et al., J. Virol., 2014). Collectively, these findings overturned a previous report by a leading group in the field (Marques et al., J. Interferon Cytokine Res., 2008; Peters et al., PNAS, 2009) and established that PACT is physiologically required for initiation and maintenance of innate antiviral response. This new concept has received more and more recognition by others in the field.

Identification and characterization of a viral RNA agonist of PACT and RIG-I

In search of viral RNA ligands of PACT and RIG-I, we identified and characterized a defective-interfering (DI) RNA specifically expressed by the Hu-191 attenuated vaccine strain of measles virus this strain, capable of inducing IFN-β much more potently than the Edmonston strain. This DI RNA of the copy-back type was predicted to fold into a hairpin structure with a long double-stranded stem region of 206 bp and it potently induced the expression of IFN-β. Its IFN-β-inducing activity was further enhanced when both cytoplasmic RNA sensor RIG-I and its partner PACT were overexpressed. On the contrary, this activity was abrogated in cells deficient of PACT or RIG-I. The DI RNA was found to be associated with PACT in infected cells. In addition, both the 5′-di/triphosphate end and the double-stranded stem region on the DI RNA were essential for its activation of PACT and RIG-I. The Hu-191 vaccine has been used safely in millions of people for many years. Viral RNA similar to the DI RNA of Hu-191, which binds with and activates PACT and RIG-I, might retain the immunostimulatory property of measles vaccines but would not induce adaptive immunity. They are potentially useful as chemically defined vaccine adjuvants, antivirals and immunostimulatory agents (Ho et al., J. Virol., 2016).

PACT targeting as a common viral strategy for innate immune evasion

We and others have found a group of viral IFN-antagonizing proteins that target PACT function to evade innate antiviral response. Two viral proteins in this group that we reported are HSV-1 Us11 (Kew et al., J. Virol., 2013) and MERS-CoV 4a (Siu et al., J. Virol., 2014). Other members reported by others include Ebola virus VP35 (Luthra et al., Cell Host Microbe, 2013) and influenza A virus NS1 (Tawaratsumida et al., J. Virol., 2014). These proteins have dsRNA-binding property. They can also bind to PACT in RNA-independent manner. Their binding to PACT prevented PACT from interacting with and activating RIG-I and MDA5. At least in some cases PACT might also antagonize their function in

viral replication. In other words, PACT exerts dual antiviral activity through two mechanisms. Our work reveals that different viruses including DNA viruses, RNA viruses and retroviruses might use a common strategy to evade innate antiviral response by targeting PACT.

6.2 Potential for further development of the research and the proposed course of action *(maximum half a page)*

Renewal funding has been awarded (C7011-15R) so that we can continue our study of PACT-dependent innate antiviral response. We aim high and target the best journals for publication of our new findings. Particularly, in the renewal project we will delineate the mechanism by which PACT activates MDA5 and publish our findings in a well-respected international journal. In addition, we will shed light on how PACT exerts its dual antiviral activity in the context of influenza A virus and hepatitis B virus infection. Our findings will help to corroborate a model in which PACT facilitates RIG-I and MDA5 to activate innate antiviral response on one hand, but targets viral RNA or ribonucleoprotein (RNP) to suppress viral replication on the other hand. In addition, we will endeavor to identify partners and collaborators who have experience in R&D to push some of the lead compounds we discovered to translational research and drug development. Particularly, the Hu-191 vaccine is highly immunogenic and its combined use with other vaccines is also efficacious. Modelled on DI RNA of Hu-191, we can design RNA molecules that interact with and activate PACT and RIG-I. These agents are highly immunostimulatory but would not induce adaptive immunity. Therefore they are promising and chemically defined agents with good potential to be developed as vaccine adjuvants, antivirals and immunostimulatory agents.

6.3 Research collaboration achieved *(please give details on the achievement and its relevant impact)*

Through this project we have significantly strengthened our collaboration with structural biologists (Dr. Shannon Au and Prof. Robert Qi), clinical virologists (Prof. KY Yuen and Prof. BJ Zheng), immunologist (Dr. James Li) and mouse genetist (Prof. MH Sham). A combination of these expertise has become the new strength of our group. In addition, we have also trained several young scientists, two of whom (Dr. KH Kok and Dr. James Li) have moved up to tenured-track faculty positions during this period. With the addition of a few energetic young scientists (Dr. CP Chan, Dr. ML Yeung and Dr. Jie Zhou), the same group has started to work on the renewal project. Most Co-PIs have been co-authors in the papers that we published.

Dr. Au has been working together with us to use many new methods in protein biochemistry and structural biology to tackle critical issues in the study of how PACT activates RIG-I and MDA5. This adds a new dimension to our project and we will continue to strengthen our collaboration so that we can achieve new heights.

Without Prof. Yuen's support, we would be unable to identify and characterize a PACT-targeting viral protein in MERS-CoV. We have learned a lot about emerging infectious diseases from him. Our collaborative work has already developed into a major part in another joint project under the Theme-based Research Scheme. We have

complementary expertise and resources, our joint effort will enable us to be even more successful in the study of new viruses such as MERS-CoV and Zika virus.

With the support from Prof. MH Sham, we obtained, created and used the first gene knockout mouse in our group. This adds new strength to our team which is strong in molecular virology. We will continue and expand our collaboration to other areas in the broad field of innate antiviral response.

7. The Layman's Summary

(describe in layman's language the nature, significance and value of the research project, in no more than 200 words)

Innate antiviral response is the host's front-line barrier to viral infection. To activate this response, signature molecules of the virus have to be recognized by highly specialized sensor proteins of the host. One major sensor called RIG-I is responsible for the sensing of viral RNA. We demonstrated that RIG-I does not sense viral RNA on its own but fulfills this task together with another host protein named PACT, which is capable of binding directly to viral RNA. To clarify whether PACT is essential in virus sensing, we showed that mouse cells in which PACT gene is completely deleted are unable to mobilize antiviral response. We next determined what type of viral RNA is recognized by PACT and RIG-I using the vaccine strain of measles virus. We found that PACT and RIG-I recognize a special type of viral RNA, which can be made to stimulate antiviral response just like the adjuvant in a vaccine. Finally, we found that different pathogenic human viruses including herpes simplex virus and Middle East respiratory syndrome coronavirus use their viral proteins to cripple PACT in virus sensing. Our work provides not only new knowledge but also new strategies for developing vaccines, adjuvants and antivirals.

CRF 8G (Revised Sep 15)

Part C: Research Output

8. Peer-reviewed journal publication(s) arising directly from this research project

(Please attach a copy of the publication and/or the letter of acceptance if not yet submitted in the previous progress report(s). All listed publications must acknowledge RGC's funding support by quoting the specific grant reference.)

The Latest Status of Publications				Author(s) *(denote the corresponding author with an asterisk*)*	Title and Journal/Book *(with the volume, pages and other necessary publishing details specified)*	Submitted to RGC *(indicate the year ending of the relevant progress report)*	Attached to this report *(Yes or No)*	Acknowledged the support of RGC *(Yes or No)*	Accessible from the institutional repository *(Yes or No)*
Year of publication	Year of Acceptance (For paper accepted but not yet published)	Under Review	Under Preparation (optional)						
2016				Yeung ML, Yao Y, Jia L, Chan J, Chan KH, Cheung KF, Chen H, Poon V, Tsang A, To K, Yiu MK, Teng J, Chu H, Zhou J, Zhang Q, Deng W, Lau S, Lau J, Woo P, Chan TM, Yung S, Zheng BJ, Jin DY, Mathieson P, Qin C, Yuen*KY.	MERS coronavirus induces apoptosis in kidney and lung by upregulating Smad7 and FGF2. *Nat. Microbiol.*, 1:16004	2016	Yes	Yes	Yes
2016				Lui PY., Wong LYR, Fung CL, Siu KL, Yeung ML, Yuen KS, Chan CP, Woo PCY, Yuen KY, Jin* DY.	MERS coronavirus M protein suppresses type I interferon expression through inhibition of TBK1-dependent phosphorylation of IRF3. *Emerg. Microbes Infect.*, 5:e39	2016	Yes	Yes	No
2016				Wong LYR, Lui PY, Jin* DY.	A molecular arms race between host innate antiviral response and emerging human coronaviruses. *Virologica Sinica*, 31:12-23	2016	Yes	Yes	Yes
2016				Yuen CK, Chan CP, Fung SY, Wang PH, Tang HMV, Yuen KS, Chan CP, Jin* DY, Kok* KH.	Suppression of type I interferon production by HTLV-1 oncoprotein Tax through inhibition of IRF3 phosphorylation. *J. Virol.*, 90:3902-12	2016	Yes	Yes	Yes

2016				Ho TH, Kew C, Lui PY, Chan CP, Satoh T, Akira S, Jin* DY, Kok* KH.	PACT- and RIG-I-dependent activation of type I interferon production by a defective-interfering RNA in measles virus vaccine. *J. Virol.*, 90:1557-68	2016	Yes	Yes	Yes
2016				Zhao H, Zhou J, Zhang K, Chu H, Liu D, Poon VK, Chan CC, Leung HC, Fai N, Lin YP, Zhang AJ, Jin DY, Yuen KY, Zheng* BJ	A novel peptide with potent and broad-spectrum antiviral activities against multiple respiratory viruses. *Sci. Rep.*, 6:22008	2016	Yes	Yes	Yes
2016				Chu H, Zhou J, Wong BH, Li C, Chan JF, Cheng ZS, Yang D, Wang D, Lee AC, Li C, Yeung ML, Cai JP, Chan IH, Ho WK, To KK, Zheng BJ, Yao Y, Qin C, Yuen* KY	Middle East respiratory syndrome coronavirus efficiently infects human primary T lymphocytes and activates the extrinsic and intrinsic apoptosis pathways. *J. Infect. Dis.*, 213:904-14	2016	Yes	Yes	Yes
2016				Zhang XM, Zhang Q, Wu H, Lau TC, Liu X, Chu H, Zhang K, Zhou J, Chen ZW, Jin DY, Zheng* BJ.	Novel mutations L228I and Y232H cause nonnucleoside reverse transcriptase inhibitor resistance in combinational pattern. AIDS Res. Hum. Retroviruses., doi: 10.1089/aid. 2015.0359	2016	Yes	Yes	No
2015				Chaudhary V, Zhang S, Yuen KS, Li C, Lui PY, Fung SY, Wang PS, Chan CP, Li D, Kok KH, Liang* M, Jin* DY.	Suppression of type I/III interferon signalling by NSs protein of SFTSV through inhibition of STAT1 phosphorylation and activation. *J. Gen. Virol.*, 96:3204-11	2016	Yes	Yes	Yes
2015				Tang HMV, Gao WW, Chan CP, Cheng Y, Deng JJ, Yuen KS, Iha H, Jin* DY.	SIRT1 suppresses human T-cell leukemia virus type 1 transcription. *J. Virol.*, 89:8623-31	2016	Yes	Yes	Yes

2015				Zhang XM, Wu H, Zhang Q, Lau TCK, Chu H, Chen Z, Jin DY, Zheng* BJ.	A novel mutation D404N in the connection subdomain of reverse transcriptase of HIV-1 CRF08_BC subtype confers cross-resistance to NNRTIs. *J. Antimicrob. Chemother.*, 70:1381-90	2016	Yes	Yes	Yes
2015				Yuen KS, Chan CP, Wong NHM, Ho CH, Ho TH, Lei T, Deng W, Tsao SW, Chen H, Kok KH, Jin* DY.	CRISPR/Cas9-mediated genome editing of Epstein-Barr virus in human cells. *J. Gen. Virol.*, 96:626-36	2016	Yes	Yes	Yes
2014				Siu KL, Yeung ML, Kok KH, Yuen KS, Kew C, Lui PY, Chan CP, Tse H, Woo PCY, Yuen KY, Jin* DY.	Middle East respiratory syndrome coronavirus 4a protein is a double-stranded RNA-binding protein that suppresses PACT-induced activation of RIG-I and MDA5 in innate antiviral response. *J. Virol.*, 88:4866-76	2015	No	Yes	Yes
2013				Kew C, Lui PY, Chan CP, Liu X, Au SWN, Mohr I, Jin* DY, Kok* KH.	Suppression of PACT-induced type I interferon production by herpes simplex virus type 1 Us11 protein. *J. Virol.*, 87: 13141-9	2015	No	Yes	Yes
2013				Kok KH, Jin* DY.	Balance of power in host-virus arms races. *Cell Host Microbe,* 14:5-6	2013	No	Yes	Yes
2013				Lau SKP, Lau CCY, Chan, KH, Li CPY, Chen H, Jin DY, Chan JFW, Woo PCY, Yuen* KY.	Delayed induction of proinflammatory cytokines and suppression of innate antiviral response by the novel Middle East respiratory syndrome coronavirus: implications for pathogenesis and treatment. *J. Gen. Virol.*, 94:2679-90.	2013	No	Yes	Yes

2014				Zhou J, Chu H, Li C, Wong BH, Cheng ZS, Poon VK, Sun T, Lau CC, Wong KK, Chan JY, Chan JF, To KK, Chan KH, Zheng BJ, Yuen* KY.	Active replication of Middle East respiratory syndrome coronavirus replication and aberrant induction of inflammatory cytokines and chemokines in human macrophages: Implications for pathogenesis. *J. Inf. Dis.*, 209:1331-42.	2015	No	Yes	Yes
2014				Chu H, Zhou J, Wong BH, Li C, Cheng ZS, Lin X, Poon VK, Sun T, Lau CC, Chan JF, To KK, Chan KH, Lu L, Zheng BJ, Yuen* KY.	Productive replication of Middle East respiratory syndrome coronavirus in monocyte-derived dendritic cells modulates innate immune response. *Virology*, 454-455:197-205.	2015	No	Yes	Yes
2013				Chan JFW, To KKW, Tse H, Jin DY, Yuen* KY.	Interspecies transmission and emergence of novel viruses: lessons from bats and birds. *Trends Microbiol.*, 21:544-55.	2013	No	Yes	Yes
2014				Siu KL, Chan CP, Kok KH, Woo PCY, Jin* DY.	Suppression of innate antiviral response by severe acute respiratory syndrome coronavirus M protein is mediated through the first transmembrane domain. *Cell. Mol. Immunol.*, 11:141-9.	2015	No	Yes	Yes
2014				Siu KL, Chan CP, Woo PCY, Jin* DY.	Comparative analysis of the activation of unfolded protein response by spike proteins of severe acute respiratory syndrome coronavirus and human coronavirus HKU1. *Cell Biosci.*, 4:3.	2015	No	Yes	Yes

2014				Lee, S.M.Y., Kok, K.-H., Jaume, M., Cheung, T.K. W., Yip, T.F., Lai, J.C.C., Guan, Y., Webster*, R.G., Jin, D.-Y., Peiris*, J.S.M.	Toll-like receptor 10 is involved in induction of innate immune responses to influenza virus infection. *Proc. Natl. Acad. Sci. USA*, 111:3793-8.	2015	No	Yes	Yes
2014				Tang, H.-M. V., Gao, W.- W., Chan, C.- P., Cheng, Y., Chaudhary, V., Deng, J.-J., Yuen, K.-S., Wong, C.-M., Ng, I.O.-L., Kok, K.-H., Zhou, J., Jin*, D.-Y.	Requirement of CRTC1 coactivator for hepatitis B virus transcription. *Nucl. Acids Res.*, 42:12455-68.	2015	No	Yes	Yes
2014				Wen, X., Huang, X., Mok, B.W. -Y., Chen, Y., Zheng, M., Lau, S.-Y., Wang, P., Song, W., Jin, D.-Y., Yuen, K.-Y., Chen*, H.	NF90 exerts antiviral activity through regulation of PKR phosphorylation and stress granules in infected cells. *J. Immunol.*, 192:3753-64	2015	No	Yes	Yes

9. Recognized international conference(s) in which paper(s) related to this research project was/were delivered *(Please attach a copy of each conference abstract)*

Month/Year/ Place	Title	Conference Name	Submitted to RGC *(indicate the year ending of the relevant progress report)*	Attached to this report *(Yes or No)*	Acknowledged the support of RGC *(Yes or No)*	Accessible from the institutional repository *(Yes or No)*
December 2012, Hefei, Anhui, China	Immunostimulatory function of measles virus defective interfering RNA	The 3rd Cross Straight Immunology Conference and the 3rd CMI Symposium on Immunology	2013	No	Yes	Yes
May 2013, New York	Immunostimulatory function of the defective interfering RNA of measles virus	78th Cold Spring Harbor Symposium on Quantitative Biology: Immunity and Tolerance	2013	No	Yes	Yes
May 2013, New York	Herpes simplex virus type 1 Us11 suppresses innate antiviral immune response by preventing PACT-induced activation of RIG-I	78th Cold Spring Harbor Symposium on Quantitative Biology: Immunity and Tolerance	2013	No	Yes	Yes

June 2013, Montreal, Canada	Suppression of type I interferon production by human T-cell leukemia virus type 1 Tax oncoprotein	16th International Conference on Human Retrovirology: HTLV and Related Viruses	2013	No	Yes	Yes
July 2013, Xi'an, China	Differential roles of RNA-binding proteins TRBP and PACT in RNA silencing and sensing	The 14th Society of Chinese Bioscientists in America International Symposium	2013	No	Yes	Yes
July 2013, Xi'an, China	Influenza A virus NS1 protein suppresses innate antiviral immune response by preventing PACT-induced activation of RIG-I	The 14th Society of Chinese Bioscientists in America International Symposium	2013	No	Yes	Yes
September 2013, Amsterdam	Herpes simplex virus type 1 Us11 inhibits type I interferon production by suppressing PACT-mediated RIG-I activity	The EMBO Meeting 2013	2013	No	Yes	Yes
October – November 2014, Lorne, Australia	Viral suppression of type I interferon production through PACT targeting.	The Yin & Yang of the Interferon System. International Cytokine and Interferon Society Satellite Symposium 2014	2015	No	Yes	Yes
June 2014, Quebec City, Canada	Interplays between RNA-binding proteins determine viral infection outcome.	RNA 2014: The 19th Annual Meeting of the RNA Society	2015	No	Yes	Yes
June 2014, Fort Collins, Colorado, USA	The double-stranded RNA-binding protein PACT activates cytoplasmic viral sensor MDA5 by promoting its oligomerization.	The American Society for Virology 33rd Annual Meeting 2014	2015	No	Yes	Yes
July 2014, Brisbane, Queensland, Australia	Modulation of innate antiviral response by a single Epstein-Barr virus-encoded microRNA.	16th International Symposium on EBV and Associated Diseases, organized by the EBV Association	2016	Yes	Yes	Yes
July 2014, Brisbane, Queensland, Australia	Roles of Epstein-Barr virus-encoded BART microRNAs in viral persistence and nasopharyngeal carcinogenesis.	16th International Symposium on EBV and Associated Diseases, organized by the EBV Association	2016	Yes	Yes	Yes
November 2014, Guangzhou, China	The CRISPR/Cas9-mediated genome editing of Epstein-Barr virus: a new platform for genetic study.	International Forum for Herpesvirus, Associated Diseases and Antiviral Development 2014	2016	Yes	Yes	Yes

March 2015, Hinxton, Cambridge, UK	Influenza A virus NS1 protein targets double-stranded RNA binding protein PACT to suppress innate antiviral response.	Innate Immune Memory: A Wellcome Trust Scientific Conference	2016	Yes	Yes	Yes
June 2015, Trois Ilets, Martinique, French West Indies	Suppression of HTLV-1 transcription by SIRT1 deacetylase. An abstract has been published: *Retrovirology* 12(Suppl 1):P53, 2015	17th International Conference on Human Retrovirology: HTLV & Related Viruses (HTLV 2015)	2016	Yes	Yes	Yes
June 2015, Academic Sinica, Taipei	Retroviral oncoprotein Tax-induced activation of LKB1-SIK and SIRT1 signaling in the regulation of HTLV-1 transcription.	The 15th International Symposium of the Society of Chinese Bioscientists in America	2016	Yes	Yes	Yes
June 2015, Academic Sinica, Taipei	Suppression of innate interferon production and signaling by NSs protein of SFTS virus.	The 15th International Symposium of the Society of Chinese Bioscientists in America	2016	Yes	Yes	Yes
July 2015, London, Ontario, Canada	Activation of cGAS/cGAMP signaling by Sindbis virus.	The American Society for Virology 34th Annual Meeting	2016	Yes	Yes	Yes
July 2015, London, Ontario, Canada	Activation of NLRP3 inflammasomes by severe acute respiratory syndrome coronavirus 3a protein.	The American Society for Virology 34th Annual Meeting	2016	Yes	Yes	Yes
July 2015, London, Ontario, Canada	A vaccine strain of Measles virus produces a copy-back type defective-interfering RNA that potently activates innate antiviral response through RIG-I and PACT	The American Society for Virology 34th Annual Meeting	2016	Yes	Yes	Yes
July 2015, London, Ontario, Canada	A novel transcript isoform of STING that suppresses innate antiviral response	The American Society for Virology 34th Annual Meeting	2016	Yes	Yes	Yes
July 2015, London, Ontario, Canada	Targeted genome editing of Epstein-Barr virus by CRISPR/Cas9 technology in human cells	The American Society for Virology 34th Annual Meeting	2016	Yes	Yes	Yes
October 2015, Taipei	Influenza A virus NS1 protein targets double stranded RNA-binding protein PACT to suppress innate antiviral response.	10th Asia-Pacific Congress of Medical Virology 2015	2016	Yes	Yes	Yes
October 2015, Taipei	Activation of hepatitis B virus transcription by CRTC1 coactivator and PRMT5 protein arginine methyltransferase.	10th Asia-Pacific Congress of Medical Virology 2015	2016	Yes	Yes	Yes

January 2016 Basal, Switzerland	Inhibition of interferon production and signaling by severe fever with thrombocytopenia syndrome virus NSs protein.	Viruses 2016: At the forefront of virus-host interactions	2016	Yes	Yes	Yes
January 2016 Basal, Switzerland	Severe acute respiratory syndrome coronavirus 3a protein activates NLRP3 inflammasomes by promoting ASC ubiquitination.	Viruses 2016: At the forefront of virus-host interactions	2016	Yes	Yes	Yes
May 2016 Seattle, Washington, USA	Antagonising roles between PACT and influenza A virus polymerase subunits in viral replication and innate immune response.	The American Association of Immunologists Annual Meeting 2016	2016	Yes	Yes	No
June 2016, Blacksburg, Virginia, USA	Suppression of the dual antiviral activity of PACT against influenza A virus by NS1.	The American Society for Virology 35th Annual Meeting	2016	Yes	Yes	No
June 2016, Blacksburg, Virginia, USA	Human T-cell leukemia virus type 1 Tax protein suppresses both RIG-I/PACT-dependent RNA sensing and cGAS/STING-dependent DNA sensing pathways.	The American Society for Virology 35th Annual Meeting	2016	Yes	Yes	No
June 2016, Blacksburg, Virginia, USA	Middle-East respiratory syndrome coronavirus M protein is a type I IFN antagonist that impedes TRAF3-TBK1complex formation.	The American Society for Virology 35th Annual Meeting	2016	Yes	Yes	No
June 2016, Blacksburg, Virginia, USA	PRMT5 protein arginine methyltransferase activates hepatitis B virus transcription.	The American Society for Virology 35th Annual Meeting	2016	Yes	Yes	No
June 2016, Blacksburg, Virginia, USA	Loss of immunostimulatory property of Sendai virus-derived defective-interfering RNA by adenosine-to-inosine editing	The American Society for Virology 35th Annual Meeting	2016	Yes	Yes	No
June 2016, Blacksburg, Virginia, USA	Mutual antagonism between PACT and influenza A virus polymerase subunits regulates viral replication and interferon production.	The American Society for Virology 35th Annual Meeting	2016	Yes	Yes	No

10. ***Student(s) trained*** (please attach a copy of the title page of the thesis)

Name	Degree registered for	Date of registration	Date of thesis submission/ graduation
Zhao, Hanjun	Ph.D.	September 2009	August 2013
Lui, Pak-Yin	Ph.D.	September 2010	August 2014
Yuen, Kit San	Ph.D.	September 2010	August 2014

Ho, Ting-Hin	M. Phil.	September 2011	August 2013
Wang, Pei-Hui	Ph.D.	September 2011	August 2015
Li, Can	Ph.D.	September 2011	August 2015
Zhang, Xiao-Min	Ph.D.	September 2011	August 2015
Kew, Chun	M. Phil.	September 2012	August 2014
Gao, Wei-Wei	Ph.D.	September 2012	August 2016

11. Other impact *(e.g. award of patents or prizes, collaboration with other research institutions, technology transfer, etc.)*

Dr. Dong-Yan Jin was promoted to Full Professor in 2012. Dr. Mai Har Sham was promoted to Full Professor in 2013. Dr. Robert Qi was promoted to Full Professor in 2014. Dr. Dr. Kin-Hang Kok was promoted to a tenure-track Assistant Professor in the Department of Microbiology, The University of Hong Kong in 2014. Dr. James Li was promoted to Assistant Professor in 2015. Prof. Dong-Yan Jin was awarded the Croucher Senior Research Fellowship (the Croucher Award) 2014-2015. Prof. Jin was also awarded an Outstanding Research Student Supervisor Award of the University of Hong Kong in 2014. He was endowed as Clara and Lawrence Fok Professor in Precision Medicine in 2016.

Dr. Chi Ping Chan (Postdoc) won a Best Presentation Award given by the Society of Chinese Bioscientists in America in July 2013. Mr. Pak-Yin Lui (PhD student) won a travel award at the 33rd American Society for Virology Annual Meeting in July 2014. Mr. Vidyanath Chaudhary (PhD student), Mr. Wei-Wei Gao (PhD student) and Dr. Jian-Jun Deng (Postdoc) won a Best Poster Presentation Award at the Society of Chinese Bioscientists in America (SCBA) International Symposium in June 2015. Dr. Sam Yuen (Postdoc), Mr. Jasper Ho (PhD student), Miss Kitty Fung (MPhil student) and Mr. Pei-Hui Wang (PhD student) won an American Society for Virology travel grant to attend its 34th Annual Meeting in July 2015. Dr. Jian-Jun Deng (Postdoc), Mr. Hinson Cheung (PhD student) and Mr. Roy Wong (PhD student) won an American Society for Virology travel grant to attend its 35th Annual Meeting in June 2016.

We have established collaborations with Prof. Haiwei Song from IMCB, Singapore on structural analysis of PACT, RIG-I and MDA5; with Prof. Shizuo Akira from Osaka University, Japan on phenotypic analysis of RIG-I$^{-/-}$ and MDA5$^{-/-}$ cells; with Prof. Ian Mohr from New York University, USA on the study of PACT by herpes simplex virus 1 Us11 protein; and with Dr. Hidekatsu Iha from Oita University, Japan on the study of retroviral subversion of innate immunity.

We have filed a provisional US patent (Application Number: US62/170780) entitled "Diagnosis and treatment of MERS-related renal diseases" in June 2015.

Project Coordinator

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