RGC Ref.: N_HKU709/13 NSFC Ref. : 31361163002
(please insert ref. above)

The Research Grants Council of Hong Kong
NSFC/RGC Joint Research Scheme
Joint Completion Report

(Please attach a copy of the completion report submitted to the NSFC by the Mainland researcher)

Part A: The Project and Investigator(s)

1. Project Title

Study Role of PCNA-binding protein TRAIP in Replicative Stress Responses and Tumor Suppression

與PCNA結合的蛋白TRAIP在複製應急反應和腫瘤抑制中的作用機理研究

2. Investigator(s) and Academic Department/Units Involved

	Hong Kong Team	Mainland Team
Name of Principal Investigator *(with title)*	Dr. Michael Shing-Yan Huen 禤承恩博士	Prof. Jianye Zang 臧建業教授
Post	Associate Professor	Professor and Associate Dean
Unit / Department / Institution	School of Biomedical Sciences, The University of Hong Kong	School of Life Science, University of Science and Technology of China
Contact Information	huen.michael@hku.hk	zangjy@ustc.edu.cn
Co-investigator(s) *(with title and institution)*	Dr. Wanjuan Feng, School of Biomedical Sciences, The University of Hong Kong	

3. Project Duration

	Original	Revised	Date of RGC/ Institution Approval *(must be quoted)*
Project Start date	Jan 1, 2014		
Project Completion date	Dec 31, 2017		
Duration *(in month)*	48		
Deadline for Submission of Completion Report			

Part B: The Completion Report

5. Project Objectives

5.1 Objectives as per original application

1. *Define Interaction of TRAIP with Replication Factor PCNA*
2. *Study Molecular Regulation of TRAIP in Replicative Stress Responses*
3. *Explore Functional Roles of TRAIP in Maintenance of Genome Stability*

5.2 Revised Objectives

6. Research Outcome

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

As elaborated in Section 5.3 (Realisation of The Objectives), we have provided several lines of evidence that TRAIP promotes genome stability maintenance, and that this requires its interaction with the DNA replication factor PCNA. Because TRAIP is mutated in patients with primordial dwarfism (Nat Genetics 2016), our results highlight the link between faithful DNA replication and repair and human development.

Findings to the work have been published in Cell Discovery (2016), a newly established sister journal of Cell Research (IF: 15.606). The work was also presented in a number of major international meetings, including an oral presentation at the Keystone Symposia in 2015. We have therefore successfully completed our project.

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

During the preparation of our manuscript, TRAIP was reported to be mutated in patients with primordial dwarfism (Nat Genetics 2016). With an interest to characterise the patient-derived TRAIP mutations (i.e. TRAIP R18C and TRAIP R185X) in the context of genome integrity protection, we have cloned these TRAIP mutants and have analysed their sub-cellular localization. Interestingly, in stark contrast to wildtype TRAIP which resides predominantly in the nucleoli, we found that the TRAIP R18C mutation phenocopied TRAIP RING mutants (i.e. RING domain deletion or a point mutation on its conserved cysteine - C7A), and was mislocalised in the cell nuclei. On the otherhand, TRAIP R185X localized in the cytoplasm. These data indicate that the patient-derived TRAIP mutations do not properly localise in the nucleoli, and suggest that this may underlie their loss of function in the protection of genome integrity. We are currently continuing to functionally characterize these patient-derived TRAIP mutations, and are exploring whether TRAIP may also be important in promoting rDNA transcription, a key process that takes place in the nucleoli.

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)

DNA replication is pivotal to cell proliferation and animal development. We have identified TRAIP as a key factor that ensures faithful duplication of the genetic material, and that inactivation of TRAIP compromised genome stability. Our work suggests that TRAIP mutations may lead to genome instability-associated human diseases, and will

provide mechanistic insight for the development and management of TRAIP-associated human syndromes.

Part C: Research Output

8. Peer-reviewed journal publication(s) arising directly from this research project
(Please attach a copy of each 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) *(bold the authors belonging to the project teams and 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 this Joint Research Scheme *(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				**Wanjuan Feng, Yingying Guo,** Jun Huang, Yiqun Deng, **Jianye Zang, Michael S.Y. Huen***	TRAIP regulates replication fork recovery and progression via PCNA / Cell Discovery	No	Yes	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 delivered paper. All listed papers must acknowledge RGC's funding support by quoting the specific grant reference.)*

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 this Joint Research Scheme *(Yes or No)*	Accessible from the institutional repository *(Yes or No)*

2013	*Role of PCNA-binding protein TRAIP in replicative stress responses and genome stability maintenance*	The 14th SCBA International Symposium, Xi'an	Yes	No	Yes	
2014	*Role of PCNA-binding protein TRAIP in replicative stress responses and genome stability maintenance*	Maintenance of Genome Stability, Abcam, St. Kitts	Yes	No	Yes	
2014	*Role of PCNA-binding protein TRAIP in replicative stress responses and genome stability maintenance*	Gordon Research Conference, Genomic Instability: Mechanisms that Cause DNA Damage and Related Diseases, Hong Kong	Yes	No	Yes	
2015	*A PCNA clamp unloader at stressed replication forks*	Keystone Symposia - Genomic Instability and DNA Repair, Whistler, Canada	Yes	No	Yes	
2015	*A PCNA clamp unloader at stressed replication forks.*	Zing Conferences: Genomic Integrity, Cairns, Australia	Yes	No	Yes	

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
Yingying Guo	PhD	2012	2016

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

N/A