RGC Ref.: M-HKU703/13
(please insert ref. above)

The Research Grants Council of Hong Kong
SRFDP & RGC ERG Joint Research Scheme
Completion Report

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

Part A: The Project and Investigator(s)

1. Project Title

In search for critical inflammatory modulator regulated by MT1-MMP

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

	Hong Kong Team	Mainland Team
Name of Principal Investigator *(with title)*	Zhongjun ZHOU	Prof Pengyuan YANG
Post	Professor	Professor and Director
Unit / Department / Institution	School of Biomedical Science, The University of Hong Kong	Institute of Biomedical Science, FUDAN UNIVERSITY
Contact Information		
PhD student(s) (with period of involvement)	Name: Shuo ZHANG Institution:HKU Period from Jan 1st, 2014 to Dec 31st , 2015	

Note: The Hong Kong project team must involve at least one research postgraduate student pursuing a Doctor of Philosophy degree at the UGC-funded university (PhD student) at any time throughout the project period.

3. Project Duration

	Original	Revised	Date of RGC/ Institution Approval *(must be quoted)*
Project Start date	Jan 1st, 2014		
Project Completion date	Dec 31st, 2016		
Duration *(in month)*	36		
Deadline for Submission of Completion Report	Dec 31st, 2017		

Part B: The Completion Report

5. Project Objectives

5.1 Objectives as per original application

1. To test the role of MT1-MMP in pathologic lymphangiogenesis

2. To identify nuclear proteins interacting with nuclear localized MT1-MMP

3. To identify proteins released by MT1-MMP on macrophage cell surface

4. To validate candidates of MT1-MMP targets in corneal lymphangiogenesis

5.2 Revised Objectives

Date of approval from the RGC: _____

Reasons for the change: _____

_____

6. Research Outcome

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

Lymphangiogensis is involved in various pathological conditions, such as arthritis and cancer metastasis. Although many factors have been identified to stimulate lymphatic vessel growth, little is known about lymphangiogenesis inhibitors.

In this project, we found that membrane type 1-matrix metalloproteinase (MT1-MMP) is an endogenous suppressor of lymphatic vessel growth. MT1-MMP-deficient mice exhibit spontaneous corneal lymphangiogenesis without concomitant changes in angiogenesis. Mice

lacking MT1-MMP in macrophages recapitulate corneal lymphangiogenic phenotypes observed in Mmp14$^{-/-}$ mice, suggesting that the spontaneous lymphangiogenesis is macrophage associated. Mechanistically, MT1-MMP directly cleaves LYVE-1 on lymphatic endothelial cells to inhibit LYVE-1-mediated lymphangiogenic responses. Furthermore, We found that macrophage derived MT1-MMP also suppresses the tumor associated lymphangiogenesis and growth. Thus, we identify MT1-MMP as an endogenous inhibitor for both physiological and pathological lymphangiogenesis (Wong et al 2016. Nature Communication).

In addition, we found that MT1-MMP is also involved in pathological lymphangiogenesis particularly in tumor growth and likely metastasis. From our observation, it is conceivable that inhibiting MMP especially MT1-MMP may not necessarily beneficial to patients with cancer as it may promote lymphatic metastasis。

Furthermore, we found that MT1-MMP can translocated to the nucleus and bind to NF-kb complex to inhibit VEGF-C expression.

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

The findings from current study can be further developed. The exact role for MT1-MMP as a transcriptional regulator can be further investigated. The role for MT1-MMP in various tumor metastasis conditions can be delineated in more details with more substantial evidence.

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)

MT1-MMP is n cell surface enzyme that cleave lymphatic endothelial cells receptor LYVE-1. In addition, in macrophage, MT1-MMP can inhibit the production of inflammatory cytokines that stimulate the lymphatic vessel growth. Through these two major mechanisms, MT1-MMP can suppress lymphatic vessel growth in physiological and pathological conditions. Furthermore results from current study provide the first evidence that inhibiting MT1-MMP may not be beneficial to cancer patients.

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)	Title and Journal/ Book	Submitted to RGC	Attached to this report	Acknowledged the support of this Joint Research Scheme	Accessible from the institutional repository
Year of publication	Year of Acceptance *(For paper accepted but not yet published)*	Under Review	Under Preparation *(optional)*	***bold** the authors belonging to the project teams and denote the corresponding author with an asterisk*)*	*(with the volume, pages and other necessary publishing details specified)*	*(indicate the year ending of the relevant progress report)*	*(Yes or No)*	*(Yes or No)*	*(Yes or No)*
2016				**Wong HLX**, Jin GX, **Zhang S,** Cao R, Cao Y, **Zhou Z***	MT1-MMP sheds LYVE-1 on lymphatic endothelial cells and suppresses VEGF-C production to inhibit lymphangiogenesis **Nature Communication.** 2016, Vol.7, pp.10824	Yes (final report)	Yes	yes	yes
2015				**Li, Hong ; Wang, Yi ; Zhang, Lei ; Lu, Haojie ; Zhou, Zhongjun ; Wei, Liming ; Yang, Pengyuan***	Facile synthesis of novel magnetic silica nanoparticles functionalized with layer-by-layer detonation nanodiamonds for secretome study **Analyst**, 2015, Vol.140(23), pp.7886-7895	Yes (final report)	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)*
08/2015 Xi'an	MT1-MMP in development and neurogenesis (Invited Oral Presentation)	International Forum of Stem Cell Research	YES	NO	Yes	Yes
10/2014 Lanzhou	MT1-MMP inhibits lymphangiogenesis through suppressing VEGF-C production. (Invited Oral Presentation)	2nd National Conference on Developmental Biology	YES	NO	Yes	Yes
July/2017 USA	MT1-MMP sheds LYVE-1 on lymphatic endothelial cells and suppresses VEGF-C production to inhibit lymphangiogenesis.	Gordon Conference on MMPs	NO	Yes	Yes	Yes
Nov/2017 Guangzhou	MT1-MMP suppresses corneal lymphangiogenesis	Asian Pacific Vascular biology Organization	NO	Yes	Yes	Yes
Dec/2017	MT1-MMP sheds LYVE-1 on lymphatic endothelial cells and suppresses VEGF-C production to inhibit lymphangiogenesis.	2017 中国转化医学高峰论坛		Yes	Yes	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
Shuo Zhang	PhD	Sep 1 2011	29-Feb-2016

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