RGC Ref.: N_HKUST606/17 NSFC Ref. : 81761168038
(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

Gene fusion study in tumor evolution and precision oncology of glioma
腦膠質瘤進化與精准醫療中的融合基因研究

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

	Hong Kong Team	Mainland Team
Name of Principal Investigator *(with title)*	Prof. Jiguang Wang	Prof. Tao Jiang
Post	Associate Professor	Professor
Unit / Department / Institution	Division of Life Science and Department of Chemical and Biological Engineering, HKUST	Beijing Neurosurgical Institute
Contact Information	jgwang@ust.hk	jiangtao_369@163.com
Co-investigator(s) *(with title and institution)*	Prof. Raul Rabadan, Department of Systems Biology and Biomedical Informatics, Columbia University	Dr. Xing Liu, Mr. Zheng Wang, Dr. Zheng Zhao, Dr. Huimin Hu, Dr. Jing Chen, Beijing Neurosurgical Institute

3. Project Duration

	Original	Revised	Date of RGC/ Institution Approval *(must be quoted)*
Project Start date	2018.01.01		
Project Completion date	2021.12.31		
Duration *(in month)*	48		
Deadline for Submission of Completion Report	2022.12.31		

Part B: The Completion Report

5. Project Objectives

5.1 Objectives as per original application

1. To identify novel gene fusions that drive glioma progression.
2. To explore the role of gene fusions in glioma evolution.
3. To apply our discoveries to a precision treatment model of brain tumors.

5.2 Revised Objectives

NA

Date of approval from the RGC: _____

Reasons for the change: _____

_____

1.
2.
3. ....

6. Research Outcome

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

A. **An improved Chinese Glioma Genome Atlas (CGGA) database.** We updated the newly collected data into the database, and now it contains clinical and multi-omics data of over 2,000 Chinese gliomas, covering both low grade and high grade, primary and recurrent, and different histological groups (Zhao et al, 2021). This database included both molecular profiles of both DNA (n=328) and RNA sequencing (n = 1018) data. Moreover, we have also collected comprehensive clinical information of the patients, including age, gender, chemo- and radiotherapy as well as the follow-up information. The data is then deidentified and provided freely accessible via www.cgga.org.cn. To help explore the data we also provide online data visualization tools.

B. **A novel functional gene fusion identification algorithm and the landscape of functional gene fusions in about 2,000 gliomas.** We have developed the GUERRERO algorithm to prioritizes functional gene fusions and predicts structures of the fusion proteins. Applied to RNA-seq data of about 2,000 gliomas, GUERRERO discovered new functional gene fusions including FGFR3-CGNL1, ERAS fusions and MET enhancer fusions (Mu et al, under submission). FGFR3-CGNL1 shared high structural similarity with the FGFR3-TACC3 fusion, and both fusions can activate the TNFα pathway. ERAS fusions lead to exceptionally high ERAS expression, while MET enhancer fusions lead to MET overexpression. We further revealed the landscape of functional gene fusions in glioma, finding that FGFR3 and EGFR fusions are the most frequent gene fusions and are significantly enriched in IDHwt gliomas, while MET fusions are most frequent and significantly enriched in IDH-mutant-non-codel gliomas. Together with NTRK, BRAF, ERAS and RET fusions, about 6.5% (128/1974) adult diffuse gliomas contain druggable gene fusions.

C. **Detection and functional validation of MGMT fusions that contribute to temozolomide resistance in glioma.** We discovered eight recurrent gliomas harboring gene fusions involving the MGMT gene (Oldrini et al, 2020). These fusions are associated with elevated MGMT expression, detected in all subtypes of glioma but are absent in primary gliomas. Reconstruction of the fusion transcripts revealed that in all these gene fusions preserved the functional domains of MGMT, indicating the fusion proteins have similar functions with MGMT which contribute to TMZ resistance. Experiments validated this hypothesis and further demonstrated that MGMT fusions are detectable in exosomes, thus could serve as biomarkers for TMZ resistance.

D. **Identification and elucidation of MET alterations in secondary glioblastoma (sGBM) progression and evolution.** Multiple MET alterations including MET amplification, PTPRZ1-MET fusion and MET exon 14 skipping (*MET*ex14) were identified in a collection of 188 sGBM (Hu et al, 2018). Survival analysis suggested that patients with METex14 marks worse prognosis. Functionally, we found that *MET*ex14 leads to the deletion of the Y1004 ubiquitination site and thus aborted degradation of the protein, causing continuous activating of the MET-STAT3 signaling pathway. Analysis of published drug-screening data revealed that both METex14 and ZM fusion leads to significantly improved sensitivity to MET inhibitors. We validated the efficacy of inhibiting cell growth in in vitro cell line models. However, current MET inhibitors have poor blood brain barrier (BBB) penetrability which limits their application for glioma treatment. Our collaborators found a BBB penetrable MET-specific inhibitor named PLB-1001. Experiments in both subcutaneous and intracranial experiments demonstrated the efficacy of the drug for inhibiting the growth of MET-altered tumor cells.

E. **Targeting MET alterations using a novel inhibitor PLB-1001 in pre-clinical models and a clinical trial.** Based on the results in pre-clinical models, a Phase I clinical trial was conducted to test the potential of PLB-1001 for MET-altered glioma treatment (Hu et al, 2018). In this trial we enrolled 18 MET-altered chemo-resistant glioma patients. Among the 15 patients who stayed in the trial, none experience significant side effects. Meanwhile, two of them achieved partial response and seven achieved stable disease according to the RANO criteria. The phase I trial data indicated safety and efficacy of this treatment, so now a phase II/III clinical trial is on-going.

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

Overall, this project collected sequencing data of thousands of glioma samples, developed a useful functional gene fusion detection tool, and discovered several novel functional gene fusions in gliomas. We showcased the application of MGMT fusions as biomarkers of TMZ resistance and MET fusions as drug targets for glioma treatment. For further development, the joint research team between HKUST and Beijing Tiantan Hospital will continue the collaboration in the following directions:

1) *In vitro* elucidate biological function of these newly identified cancer drivers such as FGFR3-CGNL1 translocation and ERAS gene fusions. Some of these drivers might reveal new mechnisms of cancer initialization and chemo-resistance. More importantly, characterization of the function might lead to the development of new treatment.
2) Further develop MET-targeted therapy via translational studies in more patients. Early phase clinical studies have been encouraging but as shown in our data, most patients will develop additional mutations that might contribute to PLB-1001 drug resistance. Motitoring and overcoming drug resistance are becoming critically important in the next-phase studies.
3) Profile glioma proteomics and develop a multi-omics data platform for discovering novel biomarkers that might improve glioma diagnosis and reveal novel therapies. Although genomics and transcriptomics profiles provided rich information for understanding gliomas, they are far from enough. Technologies of generating data on proteomics and metabolics are maturing, providing a wonderful opportunity to reveal the molecular mechnisms of many phenomenons that are currently unaddressable.
4) Develop multi-omic data integration methods based on deep learning and systems biology. Multi-omics data provides additional dimensions characterizing the same biological phenomenon, and hence it might lead to a better understanding and potential discoveries of new biological mechasnims, yet integrating data of various types from different sources is challenging due to data heterogeneity and batch effect. We shall develop novel deep learning tools and systems biology strategies to overcome these issues.

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)

Diffuse gliomas are the most common and extremely aggeresive brain tumors in adults. Current standard treatment constitutes surgery plus chemo- and radio- therapies that enlongates patient life but are often unable to cure the disease due to tumor recurrence. Gene fusions are mutations found in cancer rather than normal cells that create new proteins by fusing existing ones to promote tumor growth while providing actionable targets for precision oncology. This project focuses on the identification and elucidation of gene fusions in glioma patients. Particularly, we have collected transctiptomic data on a large number of clinical samples from adult diffuse gliomas, and developed a computational tool, named GUERRERO, to identify, priotitize, characterize and elucidate functional gene fusions. Among our main findings, we demonstrated the critical role of MGMT gene fusions in driving chemoresistance of glioma pateints under the temozolomide treatment. We also found that MET altertioans, especially PTPRZ1-MET and METex14, are actionable targets that can be treated by a tyrosin kinase inhibor, named PLB-1001. A phase I clinical trial carried out by our mainland partner has achieved partial response in at least two advanced glioma 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.)

*Please fill in the following table for **each** publication.*

I. **The Latest Status of Publication**	**Published**	**Accepted but not yet published^**	**Under Review^**	**Under Preparation^** (optional)
	✓			
^ For not-yet-published publication, items (vi) to (xxvi) can be left blank if information is not yet available.				
II. **Author(s)** *(denote the corresponding author with an asterisk*)*	Huimin Hu, Quanhua Mu, Zhaoshi Bao, Yiyun Chen, Yanwei Liu, Jing Chen, Kuanyu Wang, Zheng Wang, Yoonhee Nam, Biaobin Jiang, Jason K. Sa, Hee-Jin Cho, Nam-Gu Her, Chuanbao Zhang, Zheng Zhao, Ying Zhang, Fan Zeng, Fan Wu, Xun Kang, Yuqing Liu, Zenghui Qian, Zhiliang Wang, Ruoyu Huang, Qiangwei Wang, Wei Zhang, Xiaoguang Qiu, Wenbin Li, Do-Hyun Nam, Xiaolong Fan*, Jiguang Wang*, Tao Jiang*			
III. **Contact information of the corresponding author(s)**	Name	ORCID (if any)	Email	
	Jiguang Wang	0000-0002-6923-4097	jgwang@ust.hk	
	Tao Jiang	0000-0002-7008-6351	taojiang1964@163.com	
	Xiaolong Fan		xfan@bnu.edu.cn	
IV. **Title (in published language)**	Mutational Landscape of Secondary Glioblastoma Guides MET-Targeted Trial in Brain Tumor			
V. **Title in other language (if any)**				
VI. **Full name of journal/book**	Cell			
VII. **Volume**	175			
VIII. **Issue number**	6			
IX. **Pages**	1665-1678			
X. **Article Number**	N/A			
XI. **Other necessary publishing details (if any)**				
XII. **Year of publication / Year of acceptance**	2018			
XIII. **Original language of the publication**	English			
XIV. **Publisher or equivalent**	Elsevier Inc.			
XV. **Digital object identifier (DOI)**	10.1016/j.cell.2018.09.038			

XVI. **Abstract (as set out in the journal article)**	Low-grade gliomas almost invariably progress into secondary glioblastoma (sGBM) with limited therapeutic option and poorly understood mechanism. By studying the mutational landscape of 188 sGBMs, we find significant enrichment of TP53 mutations, somatic hypermutation, MET-exon-14-skipping (METex14), PTPRZ1-MET (ZM) fusions, and MET amplification. Strikingly, METex14 frequently co-occurs with ZM fusion and is present in ~14% of cases with significantly worse prognosis. Subsequent studies show that METex14 promotes glioma progression by prolonging MET activity. Furthermore, we describe a MET kinase inhibitor, PLB-1001, that demonstrates remarkable potency in selectively inhibiting MET-altered tumor cells in preclinical models. Importantly, this compound also shows blood-brain barrier permeability and is subsequently applied in a phase I clinical trial that enrolls MET-altered chemo-resistant glioma patients. Encouragingly, PLB-1001 achieves partial response in at least two advanced sGBM patients with rarely significant side effects, underscoring the clinical potential for precisely treating gliomas using this therapy.
XVII. **Open access status** *(Immediate open access / Embargoed open access / Non-open access)*	Immediate open access
XVIII. **Embargo end date (month, year) (if any)**	
XIX. **Accessible from the institutional repository** *(Yes or No)*	Yes
XX. **Hyperlink to the publication (the link to institutional repository if preferred) (if any)**	https://www.sciencedirect.com/science/article/pii/S0092867418312509
XXI. **Other affordable means for access (if any)** *(Individual article purchase offered by the publisher / Access through the university libraries (on membership) / Contacting the corresponding author(s))*	
XXII. **Article Processing Charge (APC) for publishing the article in an open access journal*** *(Required / Not required / Not applicable)*	Required
XXIII. **Total amount of associated APC* (in Hong Kong dollars, if any)**	HK$20,742 ($US2650)
XXIV. **Amount of associated APC paid by university* (or universities, in case it is borne by more than one university) (in Hong Kong dollars, if any)**	N/A

XXV. **Copyright retained by author(s)** *(Yes or No)*	No
XXVI. **Number(s) and jurisdiction(s) of the granted patents associated with the article (if any)**	
XXVII. **Submitted to RGC (indicate the year ending of the relevant progress report)**	2019
XXVIII. **Attached to this report** *(Yes or No)*	Yes
XXIX. **Acknowledged the support of RGC** *(Yes or No)*	Yes

* *This information will be for the Secretariat's reference only and not be disclosed to the public.*

i. **The Latest Status of Publication**	**Published**	**Accepted but not yet published^**	**Under Review^**	**Under Preparation^** (optional)
	✓			
^ For not-yet-published publication, items (vi) to (xxvi) can be left blank if information is not yet available.				
ii. **Author(s)** *(denote the corresponding author with an asterisk*)*	Barbara Oldrini, Nuria Vaquero-Siguero, Quanhua Mu, Paula Kroon, Ying Zhang, Marcos Galán-Ganga, Zhaoshi Bao, Zheng Wang, Hanjie Liu, Jason Sa, Junfei Zhao, Hoon Kim, Sandra Rodriguez-Perales, Do-Hyun Nam, Roel Verhaak, Raul Rabadan, Tao Jiang*, Jiguang Wang*, Massimo Squatrito*			
iii. **Contact information of the corresponding author(s)**	Name	ORCID (if any)	Email	
	Tao Jiang	0000-0002-7008-6351	taojiang1964@163.com	
	Jiguang Wang	0000-0002-6923-4097	jgwang@ust.hk	
	Massimo Squatrito		msquatrito@cnio.es	
iv. **Title (in published language)**	MGMT genomic rearrangements contribute to chemotherapy resistance in gliomas			
v. **Title in other language (if any)**				
vi. **Full name of journal/book**	Nature Communications			
vii. **Volume**	11			
viii. **Issue number**	1			
ix. **Pages**	1-10			
x. **Article Number**	3883			
xi. **Other necessary publishing details (if any)**				
xii. **Year of publication / Year of acceptance**	2020			
xiii. **Original language of the publication**	English			
xiv. **Publisher or equivalent**	Springer			
xv. **Digital object identifier (DOI)**	10.1038/s41467-020-17717-0			

xvi. **Abstract (as set out in the journal article)**	Temozolomide (TMZ) is an oral alkylating agent used for the treatment of glioblastoma and is now becoming a chemotherapeutic option in patients diagnosed with high-risk low-grade gliomas. The O-6-methylguanine-DNA methyltransferase (MGMT) is responsible for the direct repair of the main TMZ-induced toxic DNA adduct, the O6-Methylguanine lesion. MGMT promoter hypermethylation is currently the only known biomarker for TMZ response in glioblastoma patients. Here we show that a subset of recurrent gliomas carries MGMT genomic rearrangements that lead to MGMT overexpression, independently from changes in its promoter methylation. By leveraging the CRISPR/Cas9 technology we generated some of these MGMT rearrangements in glioma cells and demonstrated that the MGMT genomic rearrangements contribute to TMZ resistance both in vitro and in vivo. Lastly, we showed that such fusions can be detected in tumor-derived exosomes and could potentially represent an early detection marker of tumor recurrence in a subset of patients treated with TMZ.
xvii. **Open access status** *(Immediate open access / Embargoed open access / Non-open access)*	Immediate open access
xviii. **Embargo end date (month, year) (if any)**	
xix. **Accessible from the institutional repository** *(Yes or No)*	Yes
xx. **Hyperlink to the publication (the link to institutional repository if preferred) (if any)**	https://www.nature.com/articles/s41467-020-17717-0
xxi. **Other affordable means for access (if any)** *(Individual article purchase offered by the publisher / Access through the university libraries (on membership) / Contacting the corresponding author(s))*	
xxii. **Article Processing Charge (APC) for publishing the article in an open access journal*** *(Required / Not required / Not applicable)*	Required
xxiii. **Total amount of associated APC* (in Hong Kong dollars, if any)**	
xxiv. **Amount of associated APC paid by university* (or universities, in case it is borne by more than one university) (in Hong Kong dollars, if any)**	N/A
xxv. **Copyright retained by author(s)** *(Yes or No)*	No
xxvi. **Number(s) and jurisdiction(s) of the granted patents associated with the article (if any)**	
xxvii. **Submitted to RGC (indicate the year ending of the relevant progress report)**	2021
xxviii. **Attached to this report** *(Yes or No)*	Yes
xxix. **Acknowledged the support of RGC** *(Yes or No)*	Yes

*Please fill in the following table for **each** publication.*

i. **The Latest Status of Publication**	**Published**	**Accepted but not yet published^**	**Under Review^**	**Under Preparation^** (optional)
	✓			
^ For not-yet-published publication, items (vi) to (xxvi) can be left blank if information is not yet available.				
ii. **Author(s)** *(denote the corresponding author with an asterisk*)*	Yongcui Wang*, Yingxi Yang, Shilong Chen, Jiguang Wang*			
iii. **Contact information of the corresponding author(s)**	Name	ORCID (if any)	Email	
	Jiguang Wang	0000-0002-6923-4097	jgwang@ust.hk	
	Yongcui Wang		ycwang@nwipb.cas.cn	
iv. **Title (in published language)**	DeepDRK: a deep learning framework for drug repurposing through kernel-based multi-omics integration			
v. **Title in other language (if any)**				
vi. **Full name of journal/book**	Briefings in Bioinformatics			
vii. **Volume**	22			
viii. **Issue number**	5			
ix. **Pages**	1-10			
x. **Article Number**	N/A			
xi. **Other necessary publishing details (if any)**				
xii. **Year of publication / Year of acceptance**	2021			
xiii. **Original language of the publication**	English			
xiv. **Publisher or equivalent**	Oxford Academic			
xv. **Digital object identifier (DOI)**	10.1093/bib/bbab048			

xvi. **Abstract (as set out in the journal article)**	Recent pharmacogenomic studies that generate sequencing data coupled with pharmacological characteristics for patient-derived cancer cell lines led to large amounts of multi-omics data for precision cancer medicine. Among various obstacles hindering clinical translation, lacking effective methods for multimodal and multisource data integration is becoming a bottleneck. Here we proposed DeepDRK, a machine learning framework for deciphering drug response through kernel-based data integration. To transfer information among different drugs and cancer types, we trained deep neural networks on more than 20 000 pan-cancer cell line-anticancer drug pairs. These pairs were characterized by kernel-based similarity matrices integrating multisource and multi-omics data including genomics, transcriptomics, epigenomics, chemical properties of compounds and known drug-target interactions. Applied to benchmark cancer cell line datasets, our model surpassed previous approaches with higher accuracy and better robustness. Then we applied our model on newly established patient-derived cancer cell lines and achieved satisfactory performance with AUC of 0.84 and AUPRC of 0.77. Moreover, DeepDRK was used to predict clinical response of cancer patients. Notably, the prediction of DeepDRK correlated well with clinical outcome of patients and revealed multiple drug repurposing candidates. In sum, DeepDRK provided a computational method to predict drug response of cancer cells from integrating pharmacogenomic datasets, offering an alternative way to prioritize repurposing drugs in precision cancer treatment. The DeepDRK is freely available via https://github.com/wangyc82/DeepDRK.
xvii. **Open access status** *(Immediate open access / Embargoed open access / Non-open access)*	Immediate open access
xviii. **Embargo end date (month, year) (if any)**	
xix. **Accessible from the institutional repository** *(Yes or No)*	Yes
xx. **Hyperlink to the publication (the link to institutional repository if preferred) (if any)**	https://academic.oup.com/bib/article/22/5/bbab048/6210072
xxi. **Other affordable means for access (if any)** *(Individual article purchase offered by the publisher / Access through the university libraries (on membership) / Contacting the corresponding author(s))*	

xxii. **Article Processing Charge (APC) for publishing the article in an open access journal*** *(Required / Not required / Not applicable)*	Required
xxiii. **Total amount of associated APC* (in Hong Kong dollars, if any)**	HK$ 26,978 (GBP 2,596)
xxiv. **Amount of associated APC paid by university* (or universities, in case it is borne by more than one university) (in Hong Kong dollars, if any)**	HK$ 26,978 (GBP 2,596)
xxv. **Copyright retained by author(s)** *(Yes or No)*	No
xxvi. **Number(s) and jurisdiction(s) of the granted patents associated with the article (if any)**	
xxvii. **Submitted to RGC (indicate the year ending of the relevant progress report)**	2021
xxviii. **Attached to this report** *(Yes or No)*	Yes
xxix. **Acknowledged the support of RGC** *(Yes or No)*	Yes

*Please fill in the following table for **each** publication.*

i. **The Latest Status of Publication**	**Published**	**Accepted but not yet published^**	**Under Review^**	**Under Preparation^** (optional)
	✓			
^ For not-yet-published publication, items (vi) to (xxvi) can be left blank if information is not yet available.				
ii. **Author(s)** *(denote the corresponding author with an asterisk*)*	Quanhua Mu, Yiyun Chen, Jiguang Wang*			
iii. **Contact information of the corresponding author(s)**	Name	ORCID (if any)	Email	
	Jiguang Wang	0000-0002-6923-4097	jgwang@ust.hk	
iv. **Title (in published language)**	Deciphering Brain Complexity Using Single-cell Sequencing			
v. **Title in other language (if any)**				
vi. **Full name of journal/book**	Genomics, Proteomics & Bioinformatics			
vii. **Volume**	17			
viii. **Issue number**	4			
ix. **Pages**	344-366			
x. **Article Number**	N/A			
xi. **Other necessary publishing details (if any)**				
xii. **Year of publication / Year of acceptance**	2019			
xiii. **Original language of the publication**	English			
xiv. **Publisher or equivalent**	Elsevier Inc.			
xv. **Digital object identifier (DOI)**	10.1016/j.gpb.2018.07.007			

xvi. **Abstract (as set out in the journal article)**	The human brain contains billions of highly differentiated and interconnected cells that form intricate neural networks and collectively control the physical activities and high-level cognitive functions, such as memory, decision-making, and social behavior. Big data is required to decipher the complexity of cell types, as well as connectivity and functions of the brain. The newly developed single-cell sequencing technology, which provides a comprehensive landscape of brain cell type diversity by profiling the transcriptome, genome, and/or epigenome of individual cells, has contributed substantially to revealing the complexity and dynamics of the brain and providing new insights into brain development and brain-related disorders. In this review, we first introduce the progresses in both experimental and computational methods of single-cell sequencing technology. Applications of single-cell sequencing-based technologies in brain research, including cell type classification, brain development, and brain disease mechanisms, are then elucidated by representative studies. Lastly, we provided our perspectives into the challenges and future developments in the field of single-cell sequencing. In summary, this mini review aims to provide an overview of how big data generated from single-cell sequencing have empowered the advancements in neuroscience and shed light on the complex problems in understanding brain functions and diseases.
xvii. **Open access status** *(Immediate open access / Embargoed open access / Non-open access)*	Immediate open access
xviii. **Embargo end date (month, year) (if any)**	
xix. **Accessible from the institutional repository** *(Yes or No)*	Yes
xx. **Hyperlink to the publication (the link to institutional repository if preferred) (if any)**	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6943771/
xxi. **Other affordable means for access (if any)** *(Individual article purchase offered by the publisher / Access through the university libraries (on membership) / Contacting the corresponding author(s))*	
xxii. **Article Processing Charge (APC) for publishing the article in an open access journal*** *(Required / Not required / Not applicable)*	Required
xxiii. **Total amount of associated APC* (in Hong Kong dollars, if any)**	HK$10,567 (US$1350)
xxiv. **Amount of associated APC paid by university* (or universities, in case it is borne by more than one university) (in Hong Kong dollars, if any)**	HK$10,567 (US$1350)

xxv. **Copyright retained by author(s)** *(Yes or No)*	No
xxvi. **Number(s) and jurisdiction(s) of the granted patents associated with the article (if any)**	
xxvii. **Submitted to RGC (indicate the year ending of the relevant progress report)**	2021
xxviii. **Attached to this report** *(Yes or No)*	Yes
xxix. **Acknowledged the support of RGC** *(Yes or No)*	Yes

*Please fill in the following table for **each** publication.*

i. **The Latest Status of Publication**	**Published**	**Accepted but not yet published^**	**Under Review^**	**Under Preparation^** (optional)
	✓			
^ For not-yet-published publication, items (vi) to (xxvi) can be left blank if information is not yet available.				
ii. **Author(s)** *(denote the corresponding author with an asterisk*)*	LUI Ming-Hong, JIANG Biao-Bin, BAO Zhao-Shi, WANG Jiguang*			
iii. **Contact information of the corresponding author(s)**	Name	ORCID (if any)	Email	
	Jiguang Wang	0000-0002-6923-4097	jgwang@ust.hk	
iv. **Title (in published language)**	A Mini-review on Spatiotemporal Evolution of Glioma Under Treatment			
v. **Title in other language (if any)**	脑胶质瘤治疗相关时空演化机制及其在精准治疗中的应用			
vi. **Full name of journal/book**	Progress in Biochemistry and Biophysics			
vii. **Volume**	46			
viii. **Issue number**	11			
ix. **Pages**	1055-1062			
x. **Article Number**	N/A			
xi. **Other necessary publishing details (if any)**				
xii. **Year of publication / Year of acceptance**	2019			
xiii. **Original language of the publication**	English			
xiv. **Publisher or equivalent**	中国科学院生物物理研究所和中国生物物理学会			
xv. **Digital object identifier (DOI)**	10.16476/j.pibb.2019.0216			

xvi. **Abstract (as set out in the journal article)**	Glioblastoma is the most malignant form of brain tumors in adults. Therapeutic development has been stagnant for decades until recent years. With the advent of precision medicine and next generation sequencing, it is crucial to examine the complex mechanisms underlying this deadly disease for accurate prognostic prediction. Secondary or recurrent glioblastomas with matched initial tumors are invaluable cases to study, as they allow us to understand glioma progression over time and space with resistance to treatment. Here we review the complexities within glioblastomas, including a wide array of driver alterations, spatial heterogeneity and diverging evolutionary trajectories over time, and how these knowledge can facilitate prognostic prediction and therapeutic translation.
xvii. **Open access status** *(Immediate open access / Embargoed open access / Non-open access)*	Non-open access
xviii. **Embargo end date (month, year) (if any)**	
xix. **Accessible from the institutional repository** *(Yes or No)*	Yes
xx. **Hyperlink to the publication (the link to institutional repository if preferred) (if any)**	https://repository.ust.hk/ir/Record/1783.1-101792
xxi. **Other affordable means for access (if any)** *(Individual article purchase offered by the publisher / Access through the university libraries (on membership) / Contacting the corresponding author(s))*	Access through the university libraries (on membership) / Contacting the corresponding author(s)
xxii. **Article Processing Charge (APC) for publishing the article in an open access journal*** *(Required / Not required / Not applicable)*	Not applicable
xxiii. **Total amount of associated APC* (in Hong Kong dollars, if any)**	
xxiv. **Amount of associated APC paid by university* (or universities, in case it is borne by more than one university) (in Hong Kong dollars, if any)**	
xxv. **Copyright retained by author(s)** *(Yes or No)*	No
xxvi. **Number(s) and jurisdiction(s) of the granted patents associated with the article (if any)**	
xxvii. **Submitted to RGC (indicate the year ending of the relevant progress report)**	2019
xxviii. **Attached to this report** *(Yes or No)*	Yes
xxix. **Acknowledged the support of RGC** *(Yes or No)*	Yes

*Please fill in the following table for **each** publication.*

i. **The Latest Status of Publication**	**Published**	**Accepted but not yet published^**	**Under Review^**	**Under Preparation^** (optional)
	✓			
^ For not-yet-published publication, items (vi) to (xxvi) can be left blank if information is not yet available.				
ii. **Author(s)** *(denote the corresponding author with an asterisk*)*	Bao, Zhaoshi; Wang, Yongzhi; Wang, Qiangwei; Fang, Shengyu; Shan, Xia; Wang, Jiguang; Jiang, Tao*			
iii. **Contact information of the corresponding author(s)**	Name	ORCID (if any)	Email	
	Tao Jiang	0000-0002-7008-6351	taojiang1964@163.com	
iv. **Title (in published language)**	Intratumor heterogeneity, microenvironment, and mechanisms of drug resistance in glioma recurrence and evolution			
v. **Title in other language (if any)**				
vi. **Full name of journal/book**	Frontiers of Medicine			
vii. **Volume**	15			
viii. **Issue number**	4			
ix. **Pages**	551-561			
x. **Article Number**	N/A			
xi. **Other necessary publishing details (if any)**				
xii. **Year of publication / Year of acceptance**	2021			
xiii. **Original language of the publication**	English			
xiv. **Publisher or equivalent**	Springer Nature			
xv. **Digital object identifier (DOI)**	10.1007/s11684-020-0760-2			

xvi. **Abstract (as set out in the journal article)**	Glioma is the most common lethal tumor of the human brain. The median survival of patients with primary World Health Organization grade IV glioma is only 14.6 months. The World Health Organization classification of tumors of the central nervous system categorized gliomas into lower-grade gliomas and glioblastomas. Unlike primary glioblastoma that usually develop *de novo* in the elderly, secondary glioblastoma enriched with an isocitrate dehydrogenase mutant typically progresses from lower-grade glioma within 5–10 years from the time of diagnosis. Based on various evolutional trajectories brought on by clonal and subclonal alterations, the evolution patterns of glioma vary according to different theories. Some important features distinguish the normal brain from other tissues, e.g., the composition of the microenvironment around the tumor cells, the presence of the blood-brain barrier, and others. The underlying mechanism of glioma recurrence and evolution patterns of glioma are different from those of other types of cancer. Several studies correlated tumor recurrence with tumor heterogeneity and the immune microenvironment. However, the detailed reasons for the progression and recurrence of glioma remain controversial. In this review, we introduce the different mechanisms involved in glioma progression, including tumor heterogeneity, the tumor microenvironment and drug resistance, and their pre-clinical implements in clinical trials. This review aimed to provide new insights into further clinical strategies for the treatment of patients with recurrent and secondary glioma.
xvii. **Open access status** *(Immediate open access / Embargoed open access / Non-open access)*	Immediate open access
xviii. **Embargo end date (month, year) (if any)**	
xix. **Accessible from the institutional repository** *(Yes or No)*	Yes
xx. **Hyperlink to the publication (the link to institutional repository if preferred) (if any)**	https://link.springer.com/article/10.1007/s11684-020-0760-2
xxi. **Other affordable means for access (if any)** *(Individual article purchase offered by the publisher / Access through the university libraries (on membership) / Contacting the corresponding author(s))*	
xxii. **Article Processing Charge (APC) for publishing the article in an open access journal*** *(Required / Not required / Not applicable)*	Not applicable
xxiii. **Total amount of associated APC* (in Hong Kong dollars, if any)**	
xxiv. **Amount of associated APC paid by university* (or universities, in case it is borne by more than one university) (in Hong Kong dollars, if any)**	
xxv. **Copyright retained by author(s)** *(Yes or No)*	No
xxvi. **Number(s) and jurisdiction(s) of the granted patents associated with the article (if any)**	

xxvii. **Submitted to RGC (indicate the year ending of the relevant progress report)**	2021
xxviii. **Attached to this report** *(Yes or No)*	Yes
xxix. **Acknowledged the support of RGC** *(Yes or No)*	Yes

*Please fill in the following table for **each** publication.*

i. **The Latest Status of Publication**	**Published**	**Accepted but not yet published^**	**Under Review^**	**Under Preparation^** (optional)
	✓			
^ For not-yet-published publication, items (vi) to (xxvi) can be left blank if information is not yet available.				
ii. **Author(s)** *(denote the corresponding author with an asterisk*)*	Biaobin Jiang, Dong Song, Quanhua Mu, Jiguang Wang*			
iii. **Contact information of the corresponding author(s)**	Name	ORCID (if any)	Email	
	Jiguang Wang	0000-0002-6923-4097	jgwang@ust.hk	
iv. **Title (in published language)**	CELLO: a longitudinal data analysis toolbox untangling cancer evolution			
v. **Title in other language (if any)**				
vi. **Full name of journal/book**	Quantitative Biology			
vii. **Volume**	8			
viii. **Issue number**	3			
ix. **Pages**	256-266			
x. **Article Number**	N/A			
xi. **Other necessary publishing details (if any)**				
xii. **Year of publication / Year of acceptance**	2020			
xiii. **Original language of the publication**	English			
xiv. **Publisher or equivalent**	Springer Nature			
xv. **Digital object identifier (DOI)**	10.1007/s40484-020-0218-1			
xvi. **Abstract (as set out in the journal article)**	The complex pattern of cancer evolution poses a huge challenge to precision oncology. Longitudinal sequencing of tumor samples allows us to monitor the dynamics of mutations that occurred during this clonal evolution process. Here, we present a versatile toolbox, namely CELLO (Cancer EvoLution for LOngitudinal data), accompanied with a step-by-step tutorial, to exemplify how to profile, analyze and visualize the dynamic change of somatic mutational landscape using longitudinal genomic sequencing data. Moreover, we customize the hypermutation detection module in CELLO to adapt targeted-DNA and whole-transcriptome sequencing data, and verify the extensive applicability of CELLO in published longitudinal datasets from brain, bladder and breast cancers. The entire tutorial and reusable programs in MATLAB, R and docker versions are open access at https://github.com/WangLabHKUST/CELLO.			

xvii. **Open access status** *(Immediate open access / Embargoed open access / Non-open access)*	Immediate open access
xviii. **Embargo end date (month, year) (if any)**	
xix. **Accessible from the institutional repository** *(Yes or No)*	Yes
xx. **Hyperlink to the publication (the link to institutional repository if preferred) (if any)**	https://journal.hep.com.cn/qb/EN/10.1007/s40484-020-0218-1
xxi. **Other affordable means for access (if any)** *(Individual article purchase offered by the publisher / Access through the university libraries (on membership) / Contacting the corresponding author(s))*	
xxii. **Article Processing Charge (APC) for publishing the article in an open access journal*** *(Required / Not required / Not applicable)*	Not applicable
xxiii. **Total amount of associated APC* (in Hong Kong dollars, if any)**	
xxiv. **Amount of associated APC paid by university* (or universities, in case it is borne by more than one university) (in Hong Kong dollars, if any)**	
xxv. **Copyright retained by author(s)** *(Yes or No)*	No
xxvi. **Number(s) and jurisdiction(s) of the granted patents associated with the article (if any)**	
xxvii. **Submitted to RGC (indicate the year ending of the relevant progress report)**	2021
xxviii. **Attached to this report** *(Yes or No)*	Yes
xxix. **Acknowledged the support of RGC** *(Yes or No)*	Yes

*Please fill in the following table for **each** publication.*

i. **The Latest Status of Publication**	**Published**	**Accepted but not yet published^**	**Under Review^**	**Under Preparation^** (optional)
				✓
^ For not-yet-published publication, items (vi) to (xxvi) can be left blank if information is not yet available.				
ii. **Author(s)** *(denote the corresponding author with an asterisk*)*	Quanhua Mu, Dong Song, Jihong Tang, Zheng Zhao, Ruichao Chai, Zhaoshi Bao, Qiangwei Wang, Kuanyu Wang, Junhu Zhou, Tao Jiang*, Jiguang Wang*			
iii. **Contact information of the corresponding author(s)**	Name	ORCID (if any)	Email	
	Jiguang Wang	0000-0002-6923-4097	jgwang@ust.hk	
	Tao Jiang	0000-0002-7008-6351	taojiang1964@163.com	
iv. **Title (in published language)**	A comprehensive landscape of functional gene fusions in adult diffuse glioma			
v. **Title in other language (if any)**				
vi. **Full name of journal/book**				

vii. **Volume**	
viii. **Issue number**	
ix. **Pages**	
x. **Article Number**	
xi. **Other necessary publishing details (if any)**	
xii. **Year of publication / Year of acceptance**	
xiii. **Original language of the publication**	
xiv. **Publisher or equivalent**	
xv. **Digital object identifier (DOI)**	

xvi. **Abstract (as set out in the journal article)**	Background: Multiple gene fusions have been identified in glioma as cancer drivers and therapeutic targets or drug resistance biomarkers, but the overall prevalence and relative importance of functional gene fusions in glioma remain unclear. The aim of this study was to systematically characterize the landscape of functional gene fusions in both primary and recurrent adult diffuse gliomas. Methods: We have developed a functional gene fusion identification pipeline based on machine learning and state-of-the-art protein structure prediction algorithms. The pipeline, named GUERRERO, was applied to analyze RNA sequencing data of about 2,000 adult diffuse gliomas. Results: GUERRERO detected known glioma driver fusions such as FGFR3-TACC3 and PTPRZ1-MET, and additionally discovered new functional gene fusions including FGFR3-CGNL1, ERAS fusions and MET enhancer fusions. Three-dimensional structure modeling demonstrated that FGFR3-CGNL1 shared high structural similarity with the widely studied FGFR3-TACC3 fusion, and both fusions can activate the TNFα pathway. ERAS fusions lead to exceptionally high ERAS expression and PI3K-AKT pathway, while MET enhancer fusions lead to MET overexpression. FGFR3 and EGFR fusions are the most frequent gene fusions and are significantly enriched in IDHwt gliomas, while MET fusions are most frequent and significantly enriched in IDH-mutant-non-codel gliomas. Together with NTRK, BRAF, ERAS and RET fusions, about 6.5% (128/1974) adult diffuse gliomas contain druggable gene fusions. Conclusions: GUERRERO is a useful tool for functional gene fusion identification. With this tool we portrayed the gene fusion landscape of adult diffuse glioma by a comprehensive and unbiased screen of almost 2,000 tumors. The novel functional gene fusions may serve as drug targets for the development of glioma therapy.
xvii. **Open access status** *(Immediate open access / Embargoed open access / Non-open access)*	
xviii. **Embargo end date (month, year) (if any)**	
xix. **Accessible from the institutional repository** *(Yes or No)*	
xx. **Hyperlink to the publication (the link to institutional repository if preferred) (if any)**	

xxi. **Other affordable means for access (if any)** *(Individual article purchase offered by the publisher / Access through the university libraries (on membership) / Contacting the corresponding author(s))*	
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xxv. **Copyright retained by author(s)** *(Yes or No)*	
xxvi. **Number(s) and jurisdiction(s) of the granted patents associated with the article (if any)**	
xxvii. **Submitted to RGC (indicate the year ending of the relevant progress report)**	N/A
xxviii. **Attached to this report** *(Yes or No)*	No
xxix. **Acknowledged the support of RGC** *(Yes or No)*	Yes

7. 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)*
N/A	N/A	N/A	N/A	N/A	N/A	N/A

8. 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
MU Quanhua	PhD in Bioengineering	2017.02	2020.08
HUNAG Shengshuo	Mphil in Life Science	2018.02	2020.07
CHEN Yiyun	PhD in Life Science	2017.02	2021.06
NAM Yoonhee	PhD in Life Science	2017.02	2021.12
HUANG Hanli	Mphil in Bioengineering	2019.09	2021.12

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

Under the support of this grant, the PC has been awarded the following prizes:

2021 Padma Harilela Associate Professor of Life Science
2021 Zhong Nanshan Youth Science and Technology Innovation Award
2021 School of Science, School Research Award, HKUST
2020 AUA Scholar Award, Asian Universities Alliance
2019 Excellent Young Scientist Fund (Hong Kong and Macau), National Natural Science Foundation of China
2019 School of Engineering Young Investigator Research Award, HKUST

10. Statistics on Research Outputs *(Please ensure the summary statistics below are consistent with the information presented in other parts of this report.)*

	Peer-reviewed journal publications	Conference papers	Scholarly books, monographs and chapters	Patents awarded	Other research outputs (Please specify)
No. of outputs arising directly from this research project [or conference]	7	0	0	0	NA