#64

TERMINÉ

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Page 2: I. Identification

Q1

PIN Number

23479

Q2

Contact details - Main applicant

Last name, First name(s)	**Shateri Najafabadi, Hamed**
Institution	**McGill University**
Professional position	**Assistant Professor**
Province	**QC**
Email address	**hamed.najafabadi@mcgill.ca**
Telephone number and extension	**(514) 398-5308**

Q3

Report date (date completing this report)

Date **03/04/2022**

Q4

Funding Program

Operating Grants

Q5

Period covered by this report

Start Date **09/01/2018**
End Date **08/31/2021**

Q6

Partnership (if applicable)

Canadian VHL Alliance

Q7

Title of your research project

Modulation of the hypoxia signaling pathway by MBNL2 in clear cell renal cell carcinoma

Q8

Please indicate which research category best applies to your project.

Oncogenes and Tumour Suppressors

Q9

Please indicate the focus of your research project. If your project applies to more than 2 types of cancer, please select only Multiple Cancers

Kidney Cancer

Q10

Check all the boxes that apply to your project.

Metastasis,

Cancer Treatment

Q11

Report typeFinal: at the end of the grantProgress: while the grant is ongoing

Final Report

Q12

Please click here if this is a final report for a project that was granted a no-cost extension.

No-cost extension

Page 3: II. Co-applicants (if applicable)

Q13

Co-applicant 1

Last name, First name(s)	**Riazalhosseini, Yasser**
Institution	**McGill University**
Professional position	**Assistant Professor**

Q14

Co-applicant 2

Le participant a sauté cette question

Q15

Co-Applicant 3

Le participant a sauté cette question

Q16 **Le participant a sauté cette question**

Co-applicant 4

Page 4: III. Your Research Project

Q17

Summarize your research findings or preliminary results in scientific terms.

Clear cell renal cell carcinoma (ccRCC) is the most common form of kidney cancer. In the majority of ccRCC tumours, the von Hippel Lindau (VHL) gene is inactivated, which leads to the constitutive activity of the hypoxia-inducible factors (HIFs) and downstream activation of hypoxia signaling genes. The activation of hypoxia signaling, in turn, triggers a cascade of molecular events that are integral to tumour maintenance and progression. This project aims to systematically identify the genes and pathways involved in the regulation of hypoxia signaling in ccRCC.

Our research findings shed light on three key questions in this regard: (a) What is the genome-wide effect of VHL inactivation and/or hypoxia on gene expression? (b) Is hypoxia signaling uniformly active across all tumour cells? (c) What genes are essential for survival of ccRCC cells in hypoxic condition?

To answer the first question, we have performed RNA-sequencing on VHL-deficient ccRCC cell line models as well as isogenic cell lines that ectopically express VHL, both in normoxic and hypoxic conditions. These experiments have revealed genes that are affected by hypoxia and those that are under the control of VHL, along with their overlaps and differences. Importantly, these experiments have shown that even in cells that lack VHL, hypoxic condition leads to over-activation of hypoxia signalling pathway, pointing to a potential VHL-independent oxygen sensing mechanism in these cell lines.

To answer the second question, we have performed single-cell RNA-seq on several patient-derived xenograft models of ccRCC, which revealed substantial heterogeneity among tumour cells. Interestingly, these data have revealed that, even though the patient-derived models were VHL-deficient, the hypoxia signaling pathway was not uniformly active across the cells, again supporting a VHL-independent mechanism for modulation of hypoxia signaling activity in ccRCC.

Finally to answer the third question, we have performed a genome-wide CRISPR-Cas9 screen in a VHL-deficient ccRCC cell line model, both in normoxic and hypoxic conditions. The data from these screens have revealed the genes that are required by ccRCC cells to survive and their context-dependent functionality.

Together, the data produced by these experiments have revealed which genes respond to hypoxia, their role in tumour cell survival, and their relationship to intra-tumour heterogeneity.

Q18

Did the focus of your project change compared to its initial objectives and timelines? If so, please comment below. If not, please move to the next question.

Originally, we had planned to only focus on the role of ~200 genes in the context of hypoxia signaling (which were selected based on their association with the RNA-binding protein MBNL2). However, with the increasing availability of genome-wide approaches, we expanded our studies beyond these ~200 genes. Our genome-wide strategy enabled us to identify a large number of genes involved in regulation of hypoxia signaling and/or cell survival in hypoxic conditions. We also expanded our methodology, from the originally proposed CRISPR screening and functional experiments, to also include single-cell analysis of patient-derived models to understand the role of hypoxia signaling pathway in driving intra-tumour heterogeneity.

Q19

Please indicate the total number of items as a result of the awarded grant during this reporting period.

	Number
Scientific publications-submitted	**0**
Scientific publications-accepted	**0**
Oral presentations	**3**
Poster Presentations	**2**
Book chapters	**0**
Patents	**0**

Q20

Please attach a list of references, for all the above-mentioned work, indicating the year of publication (including expected publication date).

Presentation_List.pdf (73KB)

Q21 **Le participant a sauté cette question**

Attach all accepted publications as a result of this grant.First publication:

Q22 **Le participant a sauté cette question**

Second publication:

Q23 **Le participant a sauté cette question**

Third publication:

Q24 **Le participant a sauté cette question**

Fourth publication:

Q25 **Le participant a sauté cette question**

Fifth publication:(If more than 5, please send them by email grants@src-crs.ca)

Q26

Training of students, post-doctoral fellows and research staff associated with this funded project

1. Name and Role	**Ariel Madrigal, PhD student**
2. Name and Role	**Zohreh Mehrjoo, PhD student**
3. Name and Role	**Rick Farouni, Postdoctoral Fellow**

Page 5: IV. Description of your Project for the General Public

Q27

Describe the most significant accomplishment made possible because of this grant. What have you learned so far?

The VHL gene is key to the normal function of the cell. This gene, which is mutated in the most common form of kidney cancer as well as the Von Hippel-Lindau syndrome, allows the cells to sense and adapt to the amount of oxygen that is available. We have found that hypoxia signaling forms a key axis of heterogeneity across cancer cells, even though all our cancer models are VHL-deficient. This observation challenges the conventional view that all VHL-deficient kidney cancer cells have a similar pseudohypoxic status, underlining a potential VHL-independent oxygen sensing mechanism.

Q28

What's next? How do you intend to follow-up on the results you achieved through this grant?

The questions that we will address next will include (a) the upstream molecular and gene regulatory factors that are responsible for VHL-independent modulation of hypoxia signaling pathway and (b) the role of these pathways in kidney cancer metastasis.

Q29

What do you see as the potential impact of your work on patient outcomes?

Treatments that target angiogenesis, which in turn is activated through the oxygen-sensing mechanism of the cells, are frontline agents in metastatic kidney cancer. However, responses to these agents are transient, variable and unpredictable. Our study provides targets for development of new therapeutics by revealing alternative genes and pathways that contribute to oxygen-sensing.

Q30

If you had an opportunity to thank the Cancer Research Society donors and its partners, what would you say?

The funds provided by CVHLA and the Cancer Research Society have been critical in our efforts to understand oxygen-sensing mechanisms in VHL-deficient tumour cells. These funds have supported outstanding trainees who will be future scientific leaders, and have provided the resources to expand our knowledge of tumour cell function and behaviour in kidney cancer. We are grateful for this support, and will continue our efforts toward a better understanding of the functions of VHL and other oxygen-sensing mechanisms in kidney tumours.

Page 6: V. Other grants obtained thanks to the support of your project

Q31

Grant 1

Organization and nature of funding	**New Frontiers in Research Fund - Exploration (Research Grant)**
Title of the project	**Understanding the driving forces behind cellular heterogeneity in cancer**
Name of researcher	**Hamed S. Najafabadi**
Annual amount	**125000**
Funding period (yyyy-yyyy)	**2020-2022**

Q32 **Le participant a sauté cette question**

Grant 2

Q33 **Le participant a sauté cette question**

Grant 3

Q34 **Le participant a sauté cette question**

Would you have suggestions for improving our grant programs?