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TITLE: New Therapies for Fibrofatty Infiltration

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CONTRACTING ORGANIZATION: UNIVERSITY OF BRITISH COLUMBIA
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14. ABSTRACT The goal of this project is to test three classes of compounds in animal models of muscular dystrophy, and evaluate their therapeutic potential in preventing fibrofatty infiltration. Animals and drugs required for the project have been procured. A change has been made to the kinase inhibitor compound to be tested in animal models of disease, as a more efficacious drug was identified with similar substrate specificity.						
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1) INTRODUCTION: The goal of this project is to test three different classes of compounds, stemming from a screen for molecules capable of inhibiting the fibrogenic differentiation of mesenchymal progenitors, in a mouse model of Duchenne's muscular dystrophy and thus assess their therapeutic efficiency.

2) KEYWORDS: Duchenne's muscular dystrophy, fibrosis, bromodomain inhibitors, kinase inhibitors, NFkB inhibitors.

3) ACCOMPLISHMENTS: This report covers the first year of funding. Based on the Statement of work, the following activities were planned for the first year. Notice they are mostly aimed at getting the animal models ready for the testing, thus most of this year's accomplishment are of a logistic/regulatory nature

What were the major goals of the project?

For the past year, the tasks to be completed according to the SOW were as follow

- a) Sourcing and formulating compounds in fodder. 1-6 months. 80% completed
- b) Obtaining local IRB/IACUC Approval. 3 months. Completed
- c) **Milestone:** Obtaining HRPO/ACURO approval. 6 months. Completed
- d) Import mdx/utx^{+/-} animals and establish a colony. 1-6 months. Completed
- e) Generate animals required for proposed experiments. 1-12 months. Completed

What was accomplished under these goals?

a) Sourcing and formulating compounds in fodder. We have obtained two of the three compounds through MTAs with the manufacturers. Unfortunately, the original academic supplier of the third compound (Bromodomain inhibitor JQ1) has discontinued its production but we have ordered the compound from a commercial source and we expect to receive it soon. An agreement for fodder formulation has been reached with commercial supplier Purina. We have delayed fodder preparation as we were made aware of the expiry date on the fodder would become a problem if we ordered too much in advance of procuring the drugs and having the animals ready for testing. The small delay in completing this activity is not expected to delay progress in the coming year as.

b) Local IRB/IACUC Approval. This has been obtained and is in place.

c) **Milestone:** HRPO/ACURO approval. This has been obtained and is in place.

d) Import mdx/utx^{+/-} animals and establish a colony. These animals have been obtained from Dr. Lisa Hoffman at the Lawson health research institute in London, Ontario. The colony has been expanded and 25 breeders established

e) Generate animals required for proposed experiments. The first batch of 176 animals has been obtained on schedule, however due to the delay in obtaining MTAs mentioned in a) above, we had to sacrifice them as they became too old to be used in the proposed experiments.

What opportunities for training and professional development has the project provided?

ChihKai Chang, our animal surgeon, has now been certified as proficient for osmotic pump implantation by UBC institutional veterinaries.

How were the results disseminated to communities of interest?

The PI has given talks covering the subject of this award at multiple international meetings, including The Gordon Conference on Myogenesis in Barga, Italy, A Parent Project workshop on the role of inflammation in muscular dystrophy in Chicago, and the Ottawa international meeting on neuromuscular disorders.

What do you plan to do during the next reporting period to accomplish the goals?

According to the SOW, we will:

- Establish groups of animals for long-term treatment with medicated fodder, and collect related longitudinal plasma samples.
- Establish groups of animals for short-term treatment through osmotic pump implantation.
- Complete sample processing for the short-term groups, including functional testing (strength testing) as well as histological analysis of harvested tissues.
-

4) IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

This is a first year report and while the research activities are proceeding as planned, they have not yet yielded results that would impact the field. Nothing to report.

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report.

5) CHANGES/PROBLEMS:

Changes in approach and reasons for change

We have changed the kinase inhibitor originally selected for testing in vivo. Instead of using Sorafenib, which was designed for cancer therapy and has significant side effects that may preclude its use in a chronic setting, we have identified a new drug, Masitinib, as having overlapping specificity and better efficacy but less side effects. In vitro testing using assays described in the original application indicated that Masitinib is superior to Sorafenib in suppressing the fibrogenic differentiation of fibro/adipogenic progenitors. Masitinib is also being tested in human trials in Amyotrophic lateral sclerosis, another neuromuscular disease, for its ability to delay neuronal loss. With the work performed under this funding, we hope to expand the range of the use of masitinib to muscular dystrophy and to prove it has a direct antifibrotic activity. We have an MTA in place with AB Sciences, the company that is developing masitinib, and we have already procured enough drug for our studies. This change has been approved by our local IACUC.

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to report.

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

The local IACUC approval has been renewed for the coming year, now expiring in Sept 2018.

Significant changes in use or care of human subjects.

Nothing to report.

Significant changes in use or care of vertebrate animals.

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6) PRODUCTS:

Publications, conference papers, and presentations

Journal publications. No publication resulted from this work yet. *Nothing to report*

- **Books or other non-periodical, one-time publications.** Nothing to report

Other publications, conference papers, and presentations.

The PI presented our progress as an invited speaker at the following international conferences:

- Gordon conference on myogenesis, June 2017, Barga, Italy.
- Parent Project Muscular Dystrophy meeting on Inflammation and Immunity in Duchenne, June 2018, Chicago.

- The 4th Ottawa meeting on Neuromuscular Diseases, September 2017, Ottawa.

Website(s) or other Internet site(s)

N/A

Technologies or techniques

Nothing to report

Inventions, patent applications, and/or licenses

Nothing to report

Other Products

Nothing to report

7) PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

▪ What individuals have worked on the project?

Name:	<i>Fabio Rossi</i>
Project Role:	<i>Principal Investigator</i>
Researcher Identifier (e.g. ORCID ID):	<i>orcid.org/0000-0002-0368-2620</i>
Nearest person month worked:	<i>2.4</i>
Contribution to Project:	<i>Dr Rossi is the PI on the project</i>
Funding Support:	<i>N/A</i>

Name:	<i>Marcela Low</i>
Project Role:	<i>Postdoctoral fellow</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	<i>9</i>
Contribution to Project:	<i>Dr Low has been working on refining the readout of assays used to test the anti-fibrotic potential of the drugs, which has led to the change, mentioned above, in the kinase inhibitor that will be tested</i>
Funding Support:	

Name:	<i>Elena Groppa</i>
Project Role:	<i>Postdoctoral fellow</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	<i>3</i>
Contribution to	<i>Dr Groppa has replaced Dr Low in coordinating the</i>

Project:	<i>project and optimizing the readout assays during Dr. Low's maternity leave</i>
Funding Support:	

Name:	<i>ChihKai Chang</i>
Project Role:	<i>Research Assistant</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	<i>12</i>
Contribution to Project:	<i>Mr Chang has been working on procuring the animals required for testing, breeding enough of them, and perfecting osmotic pump implantation surgeries</i>
Funding Support:	

■

Name:	<i>Andrew Wu</i>
Project Role:	<i>Graduate Research Assistant</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	<i>4</i>
Contribution to Project:	<i>Mr Wu has been working through the summer in support of Dr Low, performing in vitro assays of antifibrotic activity</i>
Funding Support:	<i>Other PI funds</i>

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last.

No Change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations were involved as partners?

We have now MTAs in place with two commercial entities that provided the drugs to be tested. Specifically, Imstar Therapeutics (withaferin analogue) and AB Sciences (masitinib).

Organization Name: Imstar Therapeutics

Location of Organization: Canada

Partner's contribution to the project: providing a proprietary synthetic withaferin analogue for testing in animal models of muscular dystrophy

Financial support; N/A

In-kind support: Providing drug for testing.

Facilities N/A;

Collaboration N/A;

Personnel exchanges N/A

Other. N/A

Organization Name: AB Sciences

Location of Organization: France

Partner's contribution to the project: providing a proprietary kinase inhibitor (masitinib) for testing in animal models of muscular dystrophy.

Financial support; N/A

In-kind support: Providing drug for testing.

Facilities N/A;

Collaboration N/A;

Personnel exchanges N/A

Other. N/A

8) SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A

QUAD CHARTS: N/A

9) APPENDICES: Nothing to Report