PROJECT TITLE

Humanized mouse models for validation of therapeutic oncolytic virus and biomarker validation

PRINCIPAL INVESTIGATOR
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SCIENTIFIC SUMMARY

Oncolytic viruses (OVs) are gaining traction as effective cancer immunotherapy tools given their ability to selectively target tumor cells and induce effective anti-tumor immune responses without the off-target side effects common with traditional cancer therapies. We have developed Bovine herpesvirus type 1 (BHV-1) as a novel OV based on its unique properties and ability to target multiple cancer indications, including hard-to-treat cancers bearing lesions in KRAS, including pancreatic, lung and colorectal cancers. Our partner Novatio Ventures has spun out the Ontario-based company 3io Therapeutics which has licensed our technology and related IP, which was converted to a PCT filing and is at the national phase with entry into several countries. Working with 3io Therapeutics, we have a four-stage path to clinical testing, including (1) selection of the lead candidate, (2) pre-clinical studies, (3) manufacturing and (4) formal (GLP) toxicity studies. Our previous work has identified our lead clinical candidate, BHV-1dgEmUL49.5. The focus of this proposal is pre-clinical studies to validate cancer indication(s), dosing schedule, route of administration and use of BHV-1dgEmUL49.5 as a single agent or in combination with checkpoint immunotherapy antibodies.

As development of pre-clinical models that translate to human immunity has been identified as the #1 key challenge for cancer immunotherapy, we have initiated studies to evaluate our lead candidate in HLA-matched humanized mouse models. Using this approach, we have preliminary data of single agent efficacy in HLA-A2.1 expressing CFPAC-1 (KRASG12V) pancreatic tumors in transgenic NRG-A2 mice that express HLA-A2.1. One major limitation to our studies is availability of humanized NRG-A2 mice that are generated in house. To enable translation into the clinic, we propose purchasing humanized NCG mice expressing HLA-A2.1 (NCG-HLA-A2.1) from Charles River to complete the following studies:

Aim 1:
Develop additional KRAS-mutated cancer models in HLA-A2 matched humanized mice
Here we will evaluate engraftment and growth of HLA-A2.1 expressing CFPAC-1 (KRASG12V) pancreatic, HCT-116 (KRASG13D) colorectal and NCI-H1355 (KRASG13C) & NCI-H1792 (KRASG12C) lung cancer cells in NCG-HLA-A2.1 mice.

Aim 2:
Establish optimal dosing schedule of our lead OV
In this Aim we will evaluate the therapeutic efficacy of BHV-1dgEmUL49.5 in tumor models optimized in Aim 1. Moreover, we will determine optimal dosing and route of administration parameters.

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SCIENTIFIC SUMMARY (CONTINUED)

Aim 3:
Establish biomarkers to predict therapeutic efficacy of our lead OV in patients
In this aim, we will study blood samples harvested from experiments in Aim 2 to determine serum biomarkers from responders versus non-responders. We will monitor circulating immune cells, perform proteomic analyses on serum and test for viral sequences in clotted blood.

Collectively, these studies will enable the clinical translation of oncolytic BHV-1 to provide new therapy approaches for patients with hard-to-treat cancers, namely pancreatic, lung and colorectal cancers bearing KRAS lesions. Information will serve to inform clinical trial design and mechanisms to monitor efficacy.