Plan Overview

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Title: Blocking the long noncoding RNA, INCR1, with an antisense oligonucleotide (ASO) to reverse GBM immuno-evasion"

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Template: NIH-GEN: Generic (Current until 2023)

Project abstract:

Glioblastoma (GBM) has a dismal prognosis, particularly when it recurs after current standard treatments. Based on recent favorable results with other forms of cancer, immunotherapies are increasingly being tested in clinical trials of recurrent GBM (rGBM). However, rGBM is notoriously highly immune-evasive by utilizing a variety of means to escape from therapy. We have discovered a long coding RNA (*INCR1*), whose function enables tumor cells to express multiple immune-evasive signals upon exposure to immunotherapy: immune-activation against tumor cells via CAR-T cells or IL12/IFNg gene expression leads to transcription of the lncRNA, *INCR1*, whose function increases immune checkpoint signaling via *PD-L1* and *JAK2* over-expression. We have discovered that inhibition of *INCR1* renders tumor cells significantly more sensitive to immunotherapy. In fact, *INCR1* inhibition down-regulates multiple immunoevasive pathways utilized by GBM to escape immunotherapy. **Our ultimate objective is to inhibit *INCR1* in a "first-in-human" clinical trial in subjects with rGBM.** We propose to utilize an antisense oligonucleotide (ASO) to do this. We have performed detailed *in silico* and *in vitro* analyses of several putative ASOs against *INCR1* which have yielded one with the most effective blocking *INCR1* action. Our pilot studies show safety of this ASO for endogenous neural cells and retention in mouse CNS when delivered intrathecally. By using this BPN UG3/UH3 mechanism, we will perform IND-enabling studies that will permit the PI to deliver the *INCR1* ASO intraventricularly in a "first-in-human" clinical trial in subjects with recurrent GBM (rGBM). We propose entry at the Discovery phase and then transition to the Development phase. Our aims are **A) UG3 component (Discovery phase): Aim 1-** Finalize the *INCR1* antisense oligonucleotide (ASO) efficacy and toxicity profile against panels of human GBM

cells vs. endogenous human neural cells (year 1). **Aim 2-** Perform exploratory biodistribution and toxicology studies of the *INCR1* ASO in mouse models to determine dosing for aim 3's GLP-grade preclinical biodistribution and toxicology studies (year 2). B) **UH3 component (IND-enabling studies/ Development phase): Aim 3-** Work with BPN team and selected contract research organization to manufacture preclinical and then GMP-grade clinical lots of the *INCR1* ASO (years 3-5) **Aim 4-** Work with BPN team and selected contract research organization to perform IND-enabling mouse toxicology and biodistribution studies (years 3-5) **Aim 5-** Finalize writing of and filing of IND with FDA (year 5) **The impact** of these studies will be to validate *INCR1* inhibition via an ASO as an effective and safe modality in preclinical models of GBM that can be used to increase immunotherapy efficacy.

Start date: 09-01-2023

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Blocking the long noncoding RNA, INCR1, with an antisense oligonucleotide (ASO) to reverse GBM immuno-evasion”

We expect to be sharing data from this project using our own auspices by sharing requested data with requests from the outside utilizing our institutional secure Website, based on Dropbox. Requested files related to transcriptomic, immunologic, imaging or other data related to the experiments described in this proposal are routinely posted in our laboratory's institutional laboratory server with files transferrable into a dropbox folder. Usage of data that has not been
published yet will be governed by requesters having to fill out a data user agreement provided by our institution. Sharing of data, protocols, and resources generated by this project is an essential part of our proposed activities and will be carried out in several differentways. We wish to make our results, protocols and resources available both to the community of scientists and physicians interested in GBM, cancer immunology and immunotherapy. Conversely, we would welcome collaboration with others who could make use of the protocols, data and resources developed by this project. Following the characterization and peer-reviewed publication of DNA constructs and other reagents, they will be freely distributed to investigators at academic institutions wanting our reagents for non-commercial research. The Project Leader Dr. Chiocca will ensure that research and clinical
data, protocols, and resources developed within the Project are made readily available in a timely fashion to the research community for further research and application. Following the characterization and peer-reviewed publication of DNA constructs, cell lines, and other reagents, they will be freely distributed to investigators at academic institutions wanting our reagents for non-commercial research. All models generated by this project will be distributed freely or
deposited into a repository/stock center making them available to the broader research community, either before or immediately after publication. Following the characterization and peer-reviewed publication, any model generated will be freely distributed to investigators at academic institutions for non-commercial research to the extent third-party patent rights and contract obligations permit. The recipient investigators will be asked to provide written assurance that the models will be used solely for research and in accord with their local IACUC review for animals. “Other Research Resources” generated with funds from this grant would also be freely distributed upon request to qualified academic investigators for non-commercial research, to the extent third-party patent rights and agreements permit and subject to availability. We will make several levels of data are made available during the course of this project, and pursue rapid and aggressive data release to the greatest extent possible. These include raw single-cell transcriptome and bulk transcriptome data. The exact nature of the data release (NCBI GEO, NIAID Immport, dbGAP) and the regulations regarding access (that is, which level of data is available on what timeline) will be developed based on the NIH genomic data sharing guidelines (http://gds.nih.gov/03policy2.html). Our institution and we will adhere to the NIH grants policy on sharing of unique research resources including the "Sharing of unique biomedical research resources: principles and guidelines for recipients of NIH grants and contracts". Specifically, material transfers to non-profit researchers would be made with no more restrictive terms than in the Simple Letter Agreement or the UBMTA and without reach through requirements to the extent permitted by any third-party patent of contract obligations. Should any intellectual property arise that our institution decides to patent, we would ensure that the technology remains widely available to the non-profit research community in accordance with the NIH Principles and Guidelines.

Access to unpublished data will be made available if requested after filing a data user agreement provided by our institution. Following the characterization and peer-reviewed publication of DNA constructs, models and other reagents, they will be freely distributed to investigators at academic institutions wanting our reagents for non-commercial research to the extent third-party patent rights and contract obligations permit. The recipient investigators will be asked to provide written assurance that the models will be used solely for research and in accord with their local IACUC review for animals

We currently employ an institutional web-based data repository

For unpublished data, a dat user agreement is provided by our institution to the requester

Data provided is accompanied by documentation related to the aim of the experiment, experimental methods and reagents utilized to perform the experiment, randomization procedures, collection methods and analyses of results, statistical methods used to analyze the results, number of replicate experiments, graphs, and/or tables generated by analyses, and the names of individuals who performed each of the steps above. The above would be for any set of data/ metadata that has completed an experimental cycle. It is also possible that some experiments and data may not have been finalized to the extent described above. In these cases, if there is a request for such data, the PI and requestor will discuss the limitations related to the provisions of limited and incomplete datasets

File formats utilized in the laboratory are in a variety of sources from word documents, to excel files, to various adobe, powerpoint, sharepoint programs

For data sharing we do not expect that the files used will require transformations. Data will be preserved for the length of the funded project and beyond, as required by institutional and NIH policies

We do not expect to, since these activities are currently funded by the PI's Departments

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Planned Research Outputs

Dataset - "Experiments related to aim 1"

Aim 1- Finalize the *INCR1* antisense oligonucleotide (ASO) efficacy and toxicity profile against panels of human GBM cells vs. endogenous human neural cells (year 1).

Dataset - "Experiments related to aim 2"

Aim 2- Perform exploratory biodistribution and toxicology studies of the *INCR1* ASO in mouse models to determine dosing for aim 3's GLP-grade preclinical biodistribution and toxicology studies (year 2).

Dataset - "Experiments related to aims 3-5"

Aim 3- Work with BPN team and selected contract research organization to manufacture preclinical and then GMP-grade clinical lots of the *INCR1* ASO (years 3-5)

Aim 4- Work with BPN team and selected contract research organization to perform IND-enabling mouse toxicology and biodistribution studies (years 3-5)

Aim 5- Finalize writing of and filing of IND with FDA (year 5)

Planned research output details

Title	Type	Anticipated release date	Initial access level	Intended repository(ies)	Anticipated file size	License	Metadata standard(s)	May contain sensitive data?	May contain PII?
Experiments related to aim 1	Dataset	2028-08-31	Open	None specified		None specified	None specified	No	No
Experiments related to aim 2	Dataset	2028-01-08	Open	None specified		None specified	None specified	No	No
Experiments related to aims 3-5	Dataset	2028-01-08	Open	None specified		None specified	None specified	No	No