KPCRTF State Funded Projects Reporting Template

University of Louisville
Role of the Immunosuppressive Tumor Microenvironment in Therapeutic Resistance in Pediatric Central Nervous System Cancers
Program Director: Dr. Michael Huang

Reporting Period: April 1, 2021 to June 30, 2021

Below please provide a brief summary of the status of the Project listed as well as for each Objective listed below. Include any barriers, how and if they were overcome, and successes achieved.

Please provide a short overall summary of the status of your project here.

The COVID-19 pandemic, alongside a drawn out process of research integration between Norton Children's Hospital and the University of Louisville School of Medicine has resulted in significant delays in local IRB and contracts approval. The protocol has been approved by both UofL and CHFS IRBs and has received final approval from Norton Healthcare to start the project. We have 2 brain tumor patients that we will be enrolling before they start chemoradiation in the upcoming weeks.

Please provide a brief summary of the status of this objective here as well as the other objectives below.

The below listed secondary objectives are in actuality the primary objectives for this study. I request the modifications to the template as noted below.

Primary Objective**s**:
~~#1 – Determine the role of MDSCs in therapeutic resistance in pediatric Central Nervous System tumors and consequently the role of the tumor microenvironment (TME) in MDSC-mediated immune suppression.~~

~~Secondary Objectives:~~

1. Investigate the correlation between immunosuppressive cells and cancer phenotype/therapeutic resistance in pediatric CNS cancers.
    a. Determine associations between circulating MDSCs and cancer phenotype as well as therapeutic response in pediatric with CNS tumors receiving chemo- and immunotherapies.
    b. Immune profiling of circulating and tumor-infiltrating biomarkers to identify predictors of therapeutic response.

    Although we have thus been unable to formally start this project, we do have preliminary data that relates to this objective from the precursor study involving detecting MDSCs in all pediatric solid tumors. In that study, where we had 5 CNS tumors, we have shown that MDSCs were present at high levels only in metastatic and high risk tumors (2 of the 5 CNS tumors).

2. Investigate the role of CD200-CD200R signaling in MDSC-mediated immune suppression in pediatric CNS cancers.
    a. Correlate CD200R*M-MDSCs and CD8* T effector phenotypes to therapeutic responses and disease severity in pediatric patients with CNS tumors receiving therapies.
    b. Effect of abrogation of CD200-CD200R signaling on suppressive function of MDSCs isolated from pediatric patients with CNS tumors.
    c. Effect of blocking CD200-CD200R signaling on in vitro tumor cell line-induced M-MDSC suppressive function.
    d. Characterize the functional contributions of hypothesized CD200-CD200R-dependent pathway in murine brain tumors.
    e. Effect of ablation of CD200-CD200R signaling on the peripheral MDSC frequency, T cell function and anti-tumor effects in vitro.

3. Elucidate the precise signaling pathways in cancer stem cells associated with cancer phenotype and therapeutic resistance in pediatric CNS cancers.
    a. Correlation of CSC markers to therapeutic response and disease severity in pediatric CNS cancer patients receiving immune- and chemotherapies.
    b. Effect of CSC's on tumor-mediated immune response.
    c. Identification of the precise signaling pathways in pediatric brain tumor CSCs.

The deliverables listed below must be used to coordinate with what is listed in the contract. If you want to include other deliverables under each that is listed here, that is okay with me. Either way, please check the appropriate spot when each deliverable is completed.

The listed deliverables below are not the appropriate deliverables stipulated in the project. Below this table, please find the correct deliverables. I request that that table be used.

~~**Deliverables (check when completed)**~~	~~**Month 1-3**~~	~~**Month 4-6**~~	~~**Month 7-9**~~	~~**Month 10-12**~~	~~**Month 13-15**~~	~~**Month 16-18**~~	~~**Month 19-21**~~	~~**Month 22-24**~~	~~**√**~~
~~Investigate the correlation between immunosuppressive cells and cancer phenotype/therapeutic resistance in pediatric CNS cancers~~ ~~Determine associations between circulating MDSCs and cancer phenotype as well as therapeutic response to in pediatric with CNS tumors receiving chemo- and immunotherapies~~ ~~Immune profiling of circulating and tumor-infiltrating biomarkers to identify predictors of therapeutic response~~									

~~Investigate the role of CD200-CD200R signaling in MDSC-mediated immune suppression in pediatric CNS cancers.~~ ~~Correlate CD200R*M-MDSCs and CD8* T effector phenotypes to therapeutic responses and disease severity in pediatric patients with CNS tumors receiving therapies.~~ ~~Effect of abrogation of CD200-CD200R signaling on suppressive function of MDSCs isolated from pediatric patients with CNS tumors.~~ ~~Effect of blocking CD200-CD200R signaling on in vitro tumor cell line-induced M-MDSC suppressive function.~~ ~~Characterize the functional contributions of hypothesized CD200-CD200R-dependent pathway in murine brain tumors.~~ ~~Effect of ablation of CD200-CD200R signaling on the peripheral MDSC frequency, T cell function and anti-tumor effects in vitro.~~ ~~Elucidate the precise signaling pathways in cancer stem cells associated with cancer phenotype and therapeutic resistance in pediatric CNS cancers.~~ ~~Correlation of CSC markers to therapeutic response and disease severity in pediatric CNS cancer patients receiving immune- and chemotherapies.~~ ~~Effect of CSC's on tumor-mediated immune response.~~									

~~Identification of the precise signaling pathways in pediatric brain tumor CSCs.~~									

Deliverables (check when completed)	**Month 1-3**	**Month 4-6**	**Month 7-9**	**Month 10-12**	**Month 13-15**	**Month 16-18**	**Month 19-21**	**Month 22-24**	**√**
To determine whether circulating MDSCs inversely correlate to CD8+ T cell activation and treatment response and directly correlate with tumor burden and disease severity. To determine whether soluble CD200 levels correlate with tumor burden and therapeutic response in pediatric patients with CNS tumors. To determine whether blocking CD200 signaling in MDSCs reduces their immunosuppressive activity and increases anti-tumor T cell responses in vitro. To determine whether blocking CD200 signaling in MDSCs reduces their immunosuppressive activity and increases anti-tumor T cell responses in vivo. To determine cancer stem cell (CSC) markers that correlate with disease burden and therapeutic response.									

Quarterly Reports are due:

- July 15, 2021
- October 15, 2021
- January 15, 2022
- April 15, 2022
- July 15, 2022

Reports should be returned to:
Pediatric Cancer Program Manager
CHFS/DPH/Chronic Disease Prevention Branch

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