**Discovery of Neuroprotective Small Molecules Against Chemotherapy-Induced Peripheral Neuropathy**

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PUBLIC ABSTRACT

This project is submitted as a Discovery Award in translational research in response to the Funding Opportunity W81XWH-21-PRMRP-DA. The proposed research project is directed toward identifying small-molecule neuroprotective agents for the treatment of chemotherapy-induced peripheral neuropathy (CIPN) and, as such, specifically focuses on the FY21 PRMRP Topic Areas Peripheral Neuropathy.

Chemotherapy is a powerful strategy in the treatment of the different cancers. However, while such drugs often have dramatic beneficial effects on tumors in cancer patients, they often have serious side effects on many organs including the nerves of these organs. A striking example of this is the clinical use of the drug Bortezomib (BTZ), which has remarkable antitumor effects but, at the same time, induces remarkable pain, tingling and numbness in the hands and feet of about 50% of the treated patients due to nerve damage in the arms and legs. This syndrome is called BTZ-induced peripheral neuropathy or BIPN and can be so intense and disabling that BTZ must be discontinued, with disastrous consequences on the treatment of the multiple myeloma. BIPN is not only a serious challenge for the civilian population, but is also relevant to health in the military, since, for example, the type of cancers treated with BTZ can be caused by environmental toxins such as herbicides including Agent Orange. Thus, should this notion be confirmed, it may have significant implications not only on the number of cases of multiple myeloma, but also on the number of cases of BIPN among Service personnel and Veterans since they may have been or may be exposed to these toxicants during active duty.

Unfortunately, thus far, there are not effective ways of controlling the often unbearable side effects of BTZ, in part, because of the lack of understanding of why and how BIPN arises. In this project, it is thought to exploit one of the hallmarks of BIPN, damage to the long fibers of nerve cells (called axons) that transport sensory information from the skin to the nervous system, to search for molecules that can be used for the treatment of BIPN. To allow this original and powerful approach to BIPN, first a mouse model of BIPN in a dish that mimics the BTZ-induced axon damage seen in treated patients was developed. Thus, it is proposed here, to test in this model of BIPN, 3,500 small molecules that are well-characterized in terms of their structures and mode of actions and, even more important, that about 75% of which have already been approved by the U.S. Food and Drug Administration (FDA) for human use. Accordingly, a set of highly feasible experiments aimed at not only identifying potential neuroprotective compounds but also at confirming that they pass the necessary quality controls such as reproducibility and dose-dependency of their neuroprotective effects has been designed. These are essential properties for any sound therapy. At the end of the first phase, it is expected to be able to

identify about 32 candidates that would be eligible to move to the second phase of testing. This second phase will consist of identifying which, among these 32 expected candidates, not only protects the axons of sensory nerve cells, but also does not prevent BTZ anticancer activity. Every compound that impairs BTZ anticancer activity will evidently be disqualified for further consideration as it is sought to identify potential treatment for BIPN that can be used in cancer patients without reducing the effect of BTZ on the tumor. The pilot data suggest that about one-third of the compounds identified in phase one will be dropped because of their interference with BTZ anticancer activity while two-thirds will be kept thanks to their lack of interference with BTZ anticancer activity, which will correspond to about 21 compounds. Of these 21 compounds, the most promising ones will be selected by identifying a subset for which there are compelling safety and efficacy data in humans and available methods to monitor their activity in humans once administrated. It is expected that this prioritization process will enable the ability to identify about 10 highly promising compounds for future use in clinic, and with these, it will be confirmed that the protective effects observed in the mouse model is preserved in a similar model made of human sensory nerve cells. Note that, because the human cells are scarcer, it had to be proposed to first use a mouse model for the large screening and reserve the human cells to confirm the most salient results.

By the end of the three phases of this 2-year Discovery Award, it is expected to have in hand about four solid compounds, which, given their FDA status, could readily move through a pipeline of regulatory investigations needed prior being used in clinic to fight BIPN.