OSTEOSARCOMA ALLIANCE

MIB AGENTS OutSmarting OSTEOSARCOMA
Funding Meaningful Osteosarcoma Research Together

Guidelines: Proposal must benefit the osteosarcoma patient and be a new project or distinct portion of an ongoing larger project for which results can be expected in 12 months. At the completion of 12 months, results must be made available to share - regardless of succeed or fail outcome. The recipient must be available to present work underway and completed at the FACTOR conference in 2019. Fund may not be used for the formation of new organization or used for planning stages of research or other initiative. Presentation of check and tour of facility by MIB Agents is requested.

Please fill out the form below, proposals will be submitted as a layman's summary and are limited to front and back of this page. Completed RFP will be available for the public to view on MIB Website and social media so the public can vote. Deadline for submission is April 20, 2018. Email to info@MIBagents.org

Name: Rosandra Kaplan, MD

Organization: National Cancer Institute, National Institutes of Health

Email: Redacted Phone: Redacted

Initiative Name: Targeting tumor microenvironment in OS Amount Requested: 60,000

Desired Impact: Develop new therapies to limit metastatic progression in patients with OS

Projected Milestones: Generate preclinical studies to support clinical trial development for patients with OS

I agree to Guidelines: Yes

Osteosarcoma is a rare but too often deadly bone cancer that occurs in people of any age but mostly commonly in children and young adults. This cancer is the most common cancer to occur in bone. Further, Osteosarcoma is particularly challenging because it makes bone matrix. This matrix hardens and makes treatment to shrink once mineralized with calcium a particular challenge. Many patients with osteosarcoma have large bulky tumors by the time they are diagnosed and the main stay of treatment is to remove them and give chemotherapy before and after surgery to prevent/limit metastatic progression. When Osteosarcoma spreads it makes a milieu with bone matrix no matter the organ it grows in. This unique characteristic makes it critical to develop strategies that prevent metastatic tumor growth or treat these disseminated tumor cells before they develop a calcified osteoid matrix.

Our laboratory is interested in osteosarcoma metastasis and in particular the process of pre- and early metastatic niche formation which is a multi-step process that occurs first with a growing primary tumor secreting growth factors and exosomes (small subcellular microparticles) systemically that act on distant tissue sites and results in activation of hematopoietic stem and progenitor cells that proliferate in the bone marrow, enter circulation and home to distant metastatic sites or future metastatic sites and differentiate into immune suppressive myeloid cells. These monocytes can inhibit T cell proliferation and inhibit effective anti-tumor T cell mediated immunity. The hematopoietic cells home to particular sites of pre- and early metastatic microenvironments based on localized areas of up-regulated fibronectin production. Stromal cells and in particular vascular smooth muscle cells and pericytes normally reside adjacent to endothelium and provide survival and instructive cues to the endothelium. When activated by tumor secreted factors or inflammation or injury they can develop an altered phenotype marked by loss of usual perivascular cell markers, activation of specific markers such as PDGFRa, proliferation, motility and enhanced extracellular matrix production including increased fibronectin. This altered matrix promotes recruitment of the monocytes discussed above. Together this process creates a unique environment that supports disseminated tumor cells that are seeding in the lung. We have developed strategies to inhibit this process by targeting stromal cell plasticity or immune suppressive cells. One approach that we propose to develop is investigating ROCK1 inhibitor in treatment/prevent of metastatic disease. ROCK1 is a Rho GTPase that works to mediate cell shape, motility, extracellular matrix secretion and proliferation in vascular and perivascular cells as well as in certain tumors including Osteosarcoma. ROCK1 as a target was discovered after a network analysis performed by Theresa Beach after examining over 150 tumors from osteosarcoma patients. We also propose that not only will ROCK1 inhibition be potentially effective in targeting the tumor cells specifically but also the stromal cell plasticity that promotes the growth and survival of the disseminated tumor cells that lead to metastatic progression. We plan to investigate ROCK1 inhibitors in murine models with low and high metastatic potential and determine the impact and mechanism of this agent within the tumor cells and within the tumor microenvironment. We plan to examine tumor cells and alterations in both immune cells and stromal cells in tumor bearing treated and tumor bearing untreated controls. These preclinical studies if promising can inform development of a clinical trial in children and young adult patients with osteosarcoma.

We also plan to continue our investigations with immunotherapy in osteosarcoma. We currently completed a Phase I trial of PLX3397, a tyrosine kinase inhibitor that inhibitors CSF1R that is expressed on immune suppressive myeloid cells that we have identified as a key component of a conducive microenvironment for disseminated metastatic tumor cells as well as a Phase I trial of GD2 CAR T cell therapy. We plan to preform combination studies targeting immune suppressive myeloid cells and macrophages with different immune therapy and stromal cell and tumor cell plasticity with ROCK1. We also plan to perform combination studies with other chemotherapies, targeted therapies and immunotherapies to determine the most effective strategy to move forward into a Phase II clinical trial. Currently we have some preliminary data to suggest that ROCK1 effectively targets a gene transcription factor protein KLF4, that is known to regulate stromal cell plasticity and metastatic progression. In vitro studies show some early efficacy against Osteosarcoma.

We plan to use the funds to support a post bac fellow interested in a career in pediatric oncology to dedicate a year before further graduate or medical school training to perform these pre-clinical studies under my direction in the laboratory.