OSTEOSARCOMA ALLIANCE

FACTOR Fund

Proposal

Guidelines: Proposal must benefit the osteosarcoma patient and be a new (as opposed to ongoing) osteosarcoma initiative. Timeline for completion of initiative must be not greater than 12 months. At the completion of 12 months, results must be made available to share - regardless of succeed or fail outcome. Deadline for submission is May 8, 2017. Email to info@MIBagents.org

Name: Joshua Schiffman, MD

Organization: University of Utah

Email: Joshua.Schiffman@hci.utah.edu **Phone:** (801)-587-4745

Initiative Name: EP53 Nanoparticle Development **Amount Requested:** $100,000

Desired Impact: Introduction of new p53 replacement drug (EP53 protein loaded nanoparticle) for OS.

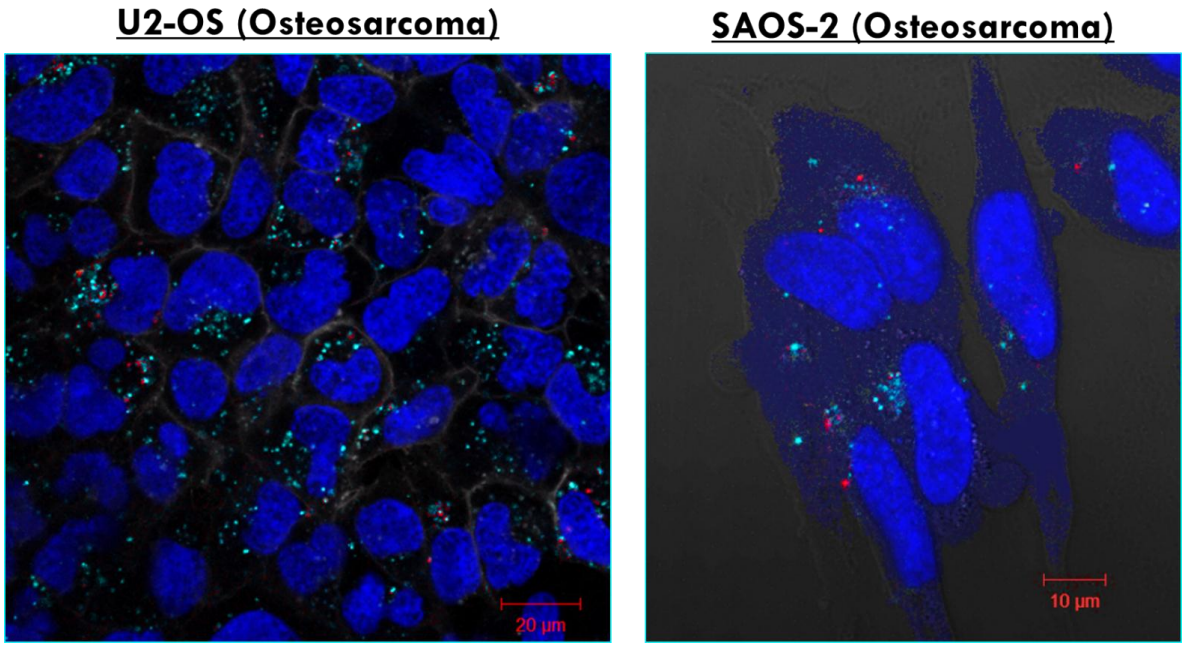
Projected Milestones: 1) Preclinical safety and toxicity, 2) Preclinical ADME, 3) Initial preclinical efficacy

Please use other side if needed

Osteosarcoma is the most common bone tumor in children and adolescents, and has not had a new successful drug introduced for its treatment in over 40 years. Patients with osteosarcoma, especially with metastatic or relapsed tumors, are in desperate clinical need of new therapeutic options. We have learned a lot about the genomics of osteosarcoma over the past decade, including that nearly 100% of osteosarcoma tumors will have disruption of the TP53 gene or its related pathway. The TP53 gene codes for the protein p53 and is known as the "Guardian of the Genome" based on its role in (1) repairing DNA mutations and (2) causing cells to kill themselves if too many DNA mutation develop (a cell death process known as "apoptosis"). Our cancer research laboratory studies the genetic risk for cancer in children and the relationship between inherited mutations in TP53 genes and cancer development like osteosarcoma. As part of our research, we learned that elephants rarely develop cancer due to extra copies of the TP53 gene (JAMA 2015). Cancer resistance in elephants is remarkably surprising given their large number of cells (100x human cells) and increased longevity (up to 70 year lifespan); we believe the extra elephant p53 (EP53) developed to naturally protect elephants from cancer. Our lab group has been studying the 20 different types of EP53 to understand how EP53 proteins protect the increased number of elephant cells that divide decade after decade from accumulating mutations and transforming into cancer. We discovered that EP53 induces even more cell death than human p53 and triggers very robust cell death when transfected into human cancer cells. Osteosarcoma cells in a dish are extremely sensitive to EP53 compared to other cancers, and in fact, osteosarcoma has one of the highest rates of cell death when EP53 protein is expressed. Based on this discovery, we have produced EP53 protein-loaded nanoparticles that can deliver two different types of EP53 as a therapeutic payload to osteosarcoma cells (i.e., EP53-anc and EP53-retro9). This project will provide the critical data necessary to advance this new drug from in vitro studies in a cell dish to preclinical animal studies and then to early human clinical trials to improve the outcome of osteosarcoma. This M.I.B. FACTOR study includes testing the safety and efficacy of the new EP53-based medicine in living animals with osteosarcoma before we can begin trials in human patients.

I agree to Guidelines: Joshua D. Schiffman

The project aims include: MILESTONE #1) Determine the Maximum Tolerated Dose (MTD) of various combinations of EP53-loaded nanoparticles (EP53-anc, EP53-retro9, combination of EP53-anc: retro9). We will expose NRG (NOD-Rag1null IL2rgnull) mice to increasing doses of EP53 nanoparticles and assess the tolerance/toxicity of EP53 nanoparticles in healthy mice. MILESTONE #2) Measure absorption, distribution, metabolism, and excretion (ADME) of EP53-loaded nanoparticles in patient-derived xenograft (PDX) and orthotopic NRG mice with osteosarcoma. We will perform ongoing clinical assessment, tumor measurement, and finally histologically examination of treated mice to determine the ADME of EP53 nanoparticles. MILESTONE #3) Test initial efficacy of EP53 protein-loaded nanoparticles in osteosarcoma xenograft and orthotopic mouse models. We will monitor the clinical response of mice with osteosarcoma when treated with EP53 protein-loaded nanoparticles, and this will include ongoing clinical assessment through physical tumor measurement and radiographic imaging, as well as histological assessment of treated osteosarcoma under the microscope. Based on these results, we will then be able to move forward in the future with preclinical trials in dogs and submit an Investigational New Drug (IND) application to the Food and Drug Administration (FDA) to begin testing in human patients with osteosarcoma. This new medicine to be supported by the M.I.B. FACTOR Fund is based on 55 million years of natural cancer resistance in elephants and may lead to a novel therapeutic approach to osteosarcoma, a deadly bone tumor without any successful new drugs for over 40 years.



EP53 protein-loaded nanoparticles deliver the elephant p53 directly to the inside of two different types of osteosarcoma cells *in vitro* (in a dish). The osteosarcoma cell nucleus is stained blue (Hoechst labeled), the nanoparticle membrane is stained red (Rhodamine labeled), and the EP53 protein is stained cyan (Fluorescently labeled).