2015 DRUG DISCOVERY INITIATIVE Awardees:

CTF awarded five Drug Discovery Initiative (DDI) awards in its first of two calls for applications in 2015. Two of the awards will target novel therapies for NF1-related tumors, specifically malignant peripheral nerve sheath tumors (MPNSTs), and three for NF2-related tumor therapies. We are enthused to be able to fund these exciting projects!

*Alexander Schulz, MD, PhD, of Leibniz Institute for Age Research, Germany, received an $85,000 *in vivo* award for his proposed study, “Establishing a protein replacement therapy for the treatment of Schwann cell-derived nerve sheath tumors.” This proposal aims to establish an innovative approach using recombinant proteins to prevent schwannoma development by altering the interaction of Schwann cells and axons (long nerve cell protrusions).

*Andrea McClatchey, PhD, of Massachusetts General Hospital/Harvard University, received a $40,000 award allowing her to continue to work on her 2014 project, “Expanded testing of centrosome-unclustering drugs in NF2-mutant tumors.” Centrosomes are so-called cellular organelles that are essential for normal cell division, and their overduplication is a feature in tumor cells. The goal in this expanded study is to investigate the sensitivity of other NF2-mutant tumor cells, particularly meningioma, to centrosome targeting drugs and to test an expanded panel of these drugs that act in different ways on all NF2 tumor types.

*Lei Xu, MD, PhD, of Massachusetts General Hospital, received an $85,000 award for her proposed study “Combining immunotherapy and antiangiogenic therapy in an NF2 schwannoma model.” The use of bevacizumab, a so-called antiangiogenic drug, in the treatment of NF2 vestibular schwannomas has shown an ability to improve hearing in some patients. The proposed study will combine the use of bevacizumab with immunotherapy, and if the results are superior to either treatment alone, Dr. Scott Plotkin of MGH will use the results to design a clinical trial for NF2 patients.

*Jeffrey Field, PhD, of University of Pennsylvania, received a $40,000 *in vitro* award for his proposal “MPNST profiling and screening: an experiment in research-based education.” This project will create the first ever college course in drug screening, and will specifically screen for drugs for NF1 MPNSTs. Students will screen drugs, both known and novel, against NF tumor cell models, primarily cancer models. The known drugs will serve as a starting point for comparison with other screening efforts.

*Steven Lewis Carroll, MD, PhD, of the Medical University of South Carolina, received an $85,000 *in vivo* award for his proposed study “Combinatorial therapy with receptor tyrosine kinase inhibitors for MPNST.” This study will identify three drugs (all currently in clinical use or clinical trials for other cancer types) that effectively inhibit MPNST proliferation. These drugs will be tested in various combinations in hopes of generating sufficient data to attract follow-on funding from the NIH or DOD to expand testing of RTK therapies for the difficult-to-treat MPNSTs.
A. THOMAS LOOK, MD, of the Dana-Farber Cancer Institute, was granted an in vivo DDI Award for his proposal, “Drug discovery for NF1-associated malignant peripheral nerve sheath tumors using the zebrafish model.”

NF1-related MPNSTs are very aggressive tumors with poor prognoses for the patients who are diagnosed with it. Surgery to remove MPNSTs is not effective because they often recur and metastasize. Chemotherapy regimens are not only ineffective, but toxic to the patient. Dr. Look and his team have developed a zebrafish model, through which they will rapidly screen drugs that are already in use in humans, obviating the need to perform expensive and time-consuming toxicology studies. They predict that they will be able to identify one or more already-FDA-approved drugs, which have been developed for other diseases, that will show activity against MPNSTs. These drugs could potentially be “repurposed” to more effectively treat this small subset of NF1 patients.

JOSEPH KISSIL, PhD, of the Scripps Research Institute, was granted an in vivo DDI Award for his project, “Assessing the anti-tumor activity of crizotinib in NF2-deficient meningioma.”

Dr. Kissil and his team have identified an already-FDA-approved drug, known as crizotinib, as having anti-tumor activity against NF2-related schwannomas. This drug is already in use in patients with lung cancer and has demonstrated few side effects, and is therefore safe. A clinical trial is currently being initiated to test crizotinib against schwannoma in NF2 patients. The group will now assess whether crizotinib can also be useful against another NF2-related tumor, meningioma, by testing this drug in cell and animal models. Should this show a desirable effect, it would indicate that the trial being initiated should be expanded to include meningioma in addition to schwannoma.

NANCY RATNER, PhD, of Cincinnati Children’s Hospital, was granted an in vitro DDI Award for her study, “Mechanisms of resistance to MEK inhibition in neurofibroma.”

This study aims to find drugs that reduce neurofibroma size and are potentially curative. We already know that drugs that target MEK proteins shrink most neurofibromas. In patients with NF1, the mutated gene, neurofibromin, can no longer do its proper function of turning off a protein called Ras. When Ras is on, downstream pathways (that include MEK) are also active, contributing to neurofibroma formation. By using a drug to inhibit MEK, the over-active pathway is turned off, which can shrink neurofibromas. However, both in humans and in preclinical trials in mice, inhibiting MEK doesn’t always work and some neurofibromas show resistance to MEK inhibition. Dr. Ratner and her team will work to determine what else is being turned on during MEK inhibition so that it can also be targeted, prevent drug resistance, and identify an increasingly successful treatment for patients with NF1.