Crazy 8 Initiative
Crazy 8 Award Progress Report
Principal Investigator: Yael P. Mosse, MD
Institution Name: The Children's Hospital of Philadelphia
Reporting on Grant Year 3
Project Title: Drugging MYCN

Lay Summary & Impact:

Childhood cancers are caused by genetic mutations that lead to changes in proteins that are essential for normal human development. The human MYC gene is the founding member of a highly conserved gene family that includes MYCN. The protein MYCN is the cause of many of the most aggressive pediatric cancers, including high-risk neuroblastoma and medulloblastoma. One of the holy grails of pediatric cancer drug development is finding a way to directly target MYCN in patient tumors, but this has been elusive. To address this major unmet need, Dr. Yael Mosse and an international team of scientists, with complementary expertise, are working to attack this problem with innovative new technologies. In this project, they plan to "drug the undruggable" by developing hybrid molecules that can specifically attach to MYCN and then trick the cancer cells own internal machinery to dissolve MYCN, which will lead to cancer cell death.

They have made substantial progress over the last year of funding, both in the development and testing of MYCN-Aurora CTMs (chimeric targeting molecules) in vivo and in their discovery efforts to identify integral MYCN binding partners for potential therapeutic targeting. They have also established that MYCN binds to RNA and that this stable complex can be purified in sufficient amounts for input into a DEL (DNA-Encoded chemical Library) screen. Their key collaboration with Nurix Therapeutics, and their innovative drug development platform, is highly collaborative and productivity this year has been far greater than anticipated. In the third year of funding, Nurix has developed hundreds of candidate CTMs as potential MYCN degraders that are being screened through the team's pipeline. They are now refining the drug-like properties of these CTMs and entering a DEL screen with purified MYCN bound to RNA. They are also making new discoveries about candidate MYCN interacting proteins.

The goal is to develop such a MYCN-direct drug in four years, prove that it is effective against the most lethal pediatric cancers in their collaborative laboratories, and be ready to launch a clinical trial shortly after the grant is completed. Successful completion of this project as planned will lead to curative new drugs for children with currently incurable cancers.