ERC Advanced Grant 2019
Research proposal [Part B1]

Targeting cancer vulnerabilities in acute leukemia

ONCODESTROYER

Cover Page:

- Name of the Principal Investigator (PI) Yinon Ben-Neriah
- Name of the PI's host institution for the project The Hebrew University of Jerusalem
- Proposal duration in months 60 months

Background and rationale: Adult acute leukemias pose a great challenge to cancer therapy, with only few advances made in 50 years. As these malignancies are commonly associated with multiple epigenetic aberrations, epigenetic factors represent attractive leukemia drug targets. Nevertheless, most epigenetic-targeting drugs have displayed limited clinical benefit and key leukemia drivers like MYC, ERG and MYB remained mostly undruggable. We have developed a new class of small molecule kinase inhibitors, termed "oncodestroyers" (ODs), single molecules combining supreme p53 activation with selective disruption of multiple leukemia-specific super-enhancers (SEs) that drive oncogenes and dependency/vulnerability factors. These inhibitors demonstrate an unprecedented therapeutic potency in mouse models of human leukemia and are entering now leukemia clinical trials. With this project we wish to study the principles of "oncodestruction", mechanisms of drug action, immune system interface, and preempt drug resistance. Relevant knowledge may be applied to other cancer diseases, sharing vulnerabilities with leukemia. ***Major Goal*:** To expand the therapeutic potential of ODs in leukemia and pre-leukemia by studying their vulnerability basis, mechanisms of drug action and indicators of therapeutic response in individual patients. ***Research plan***: 1) Expand the collection of small molecule kinase inhibitor ODs and develop OD-based PROTACs to gain an optimal spectrum of kinase targets with good therapeutic window in AML; 2) Elucidate the mechanisms of action and what distinguishes an OD, with emphasis on SE disruption, p53 activation and OD-immune-cooperation; 3) Explore the translational aspects of OD treatment by: identifying OD resistance and relapse mechanisms; study clonal evolution in MDS and AML patients undergoing phase 1a/b clinical trial; predict a patient response to ODs and use ODs for ameliorating age-related clonal hematopoiesis, thus possibly averting leukemogenesis.