

Defining the Cellular Origin and Mechanistic Basis for Therapy Resistant B-cell Lymphomas

Principal Investigator:

- Ari Melnick, MD - Weill Cornell Medicine

Co-Principal Investigators:

- Gabriel Victora, PhD - The Rockefeller University
- Olivier Elemento, PhD - Weill Cornell Medicine

Abstract: This project will address the critical unmet need of defining the biology and developing targeted therapy for therapy resistant diffuse large B-cell lymphomas (DLBCLs). The project harnesses the serendipitous convergence of basic immunology and lymphomagenesis discoveries by experts in these respective fields. They discovered **a**) a novel T-cell dependent phase of the germinal center (GC) reaction where B-cells undergo massive mTORC1-dependent anabolic growth without cell division, and **b**) that somatic BTG1 hotspot mutations in DLBCL are strongly linked to poor outcome and confer a gain of function effect that may induce this same GC “recycling cell” phenotype. They hypothesize that BTG1 mutations define a new type of “GC recycling” DLBCL. They propose that mutant BTG1 causes these lymphomas by inducing the GC recycling mTORC/MYC phenotype independent of the need for T-cell help, resulting in lymphomas enriched for highly metabolically fit and relatively quiescent cells that cannot be eradicated by chemotherapy. Using a suite of novel and highly sophisticated experimental methods unique to this program, they will i) Determine whether BTG1 mutation uncouples GC recycling from T-cell help and affinity maturation, ii) Determine whether and how BTG1 controls GC recycling cell metabolism and anabolic pathways and iii) Determine whether mutant BTG1 drives formation of a novel class of chemo-resistant GC recycling cell lymphomas susceptible to specific targeted therapies. This project will provide fundamental insights into the functioning of the immune system, define a novel type of lymphoma with unique molecular features, and develop novel targeted therapy regimens to benefit these patients.