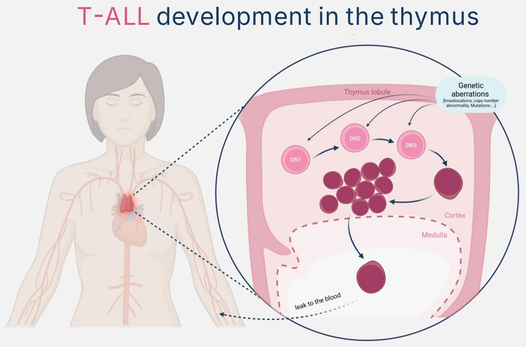
Using BiP inducer X to target the unfolded protein response for T-cell Acute Lymphoblastic Leukaemia treatment

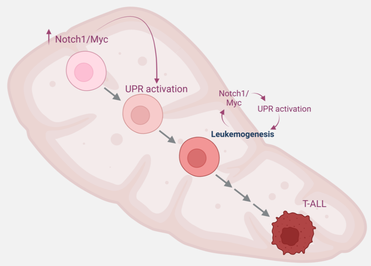
(or: T-ALL's Achilles' Heel- Disrupting the UPR for Therapeutic Gain)

Shani Mistriel Zerbib, Nira Twaik, Leonor Daniel and Michael Berger
The Lautenberg Center for Immunology and Cancer Research, IMRIC, Hebrew University of Jerusalem

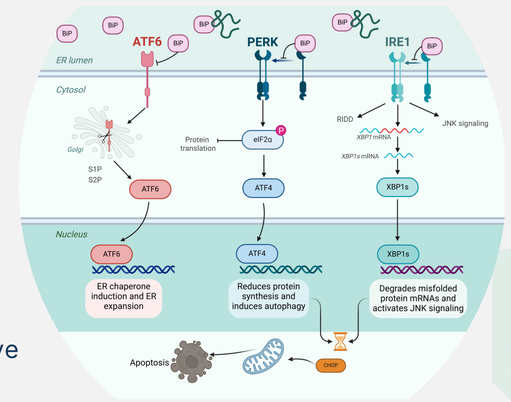
T-ALL development in the thymus

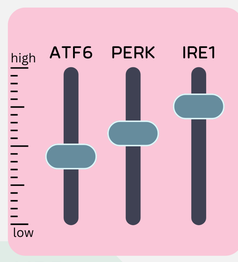


UPR activation supports leukemic survival, making it a targetable vulnerability



T-ALL depends on UPR to survive





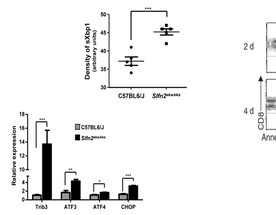
T-ALL relies on an active UPR: IRE1 supports survival, PERK aids stress response, and ATF6 fine-tunes proliferation

Is UPR Disruption a Therapeutic Strategy for T-ALL?

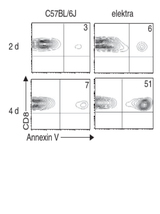
To explore UPR as a therapeutic target, we first examine how T-ALL depends on this pathway for survival

Slfn2 loss of function...

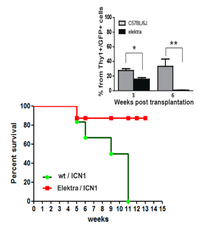
1. cause chronic ER stress in naïve T-cells
2. Increases Apoptosis in T-cells
3. Reduces T-ALL Progression and Proliferation



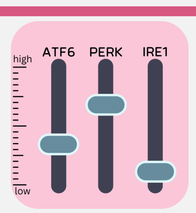
Omar *et al.* 2016



Berger *et al.* 2010

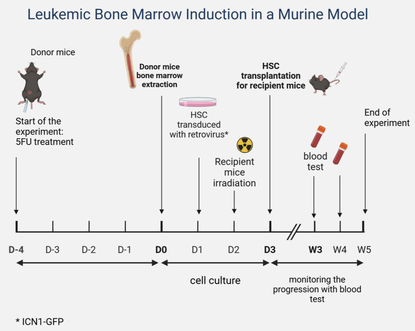


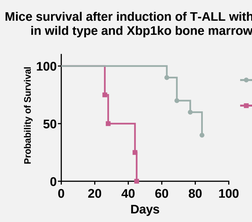
Goldshtein *et al.* 2016

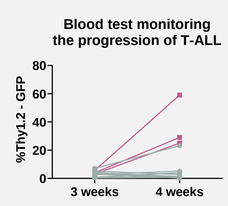


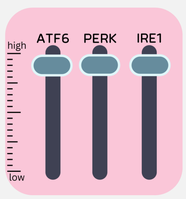
Slfn2 loss drives chronic ER stress, leading to apoptosis and reduced T-ALL progression

XBP1 loss disrupts UPR balance, making T-ALL more aggressive





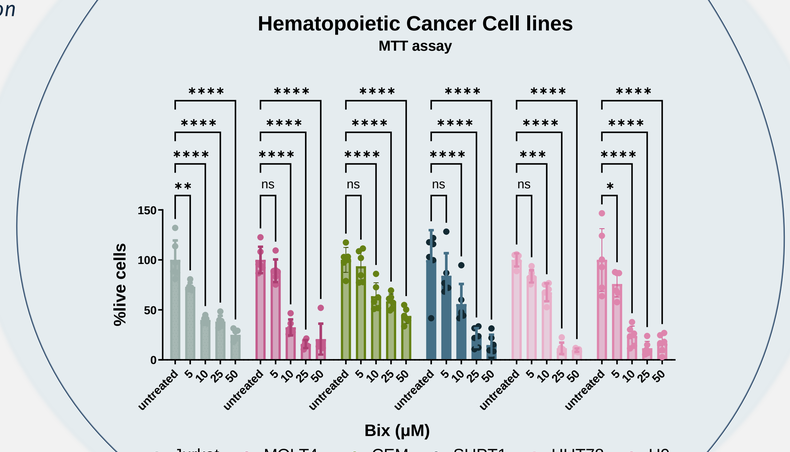


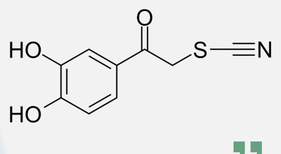


XBP1 loss shifts UPR balance, increasing T-ALL aggressiveness

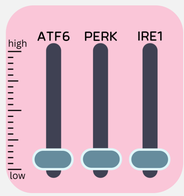
Targeting UPR homeostasis via ATF6 selectively impairs T-ALL progression

The Disruptor: BIX



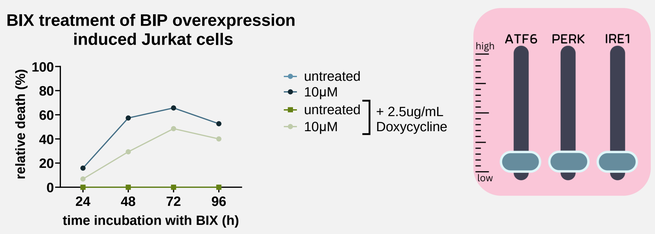


BIX (BiP Inducer X) upregulates BiP/GRP78, reducing ER stress and apoptosis (Hirota et al., 2011)



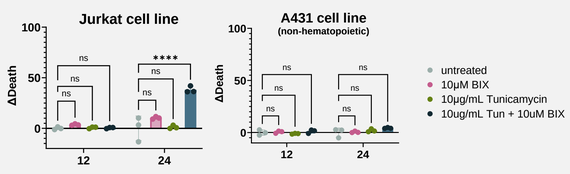
Cracking the Mechanism

BIX Influences T-ALL Independently of BiP Overexpression



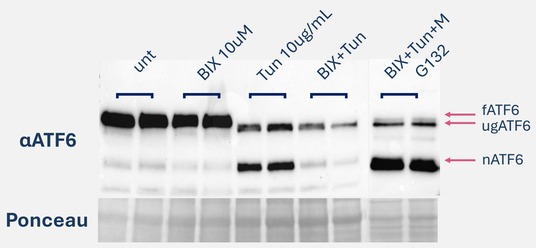
BiP overexpression alone does not trigger apoptosis in T-ALL, suggesting BIX acts via a BiP-independent mechanism

BIX Targets UPR Functionality in T-ALL, Not in A431 Cells



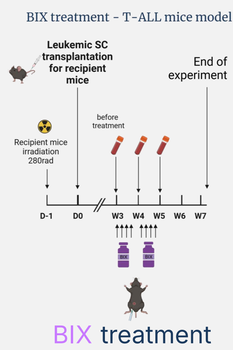
T-ALL cells recover from Tunicamycin-induced ER stress, showing a functional UPR. BIX disrupts this balance, with a synergistic effect in T-ALL but not A431

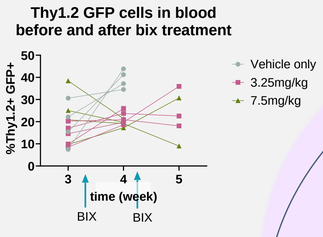
BIX increases nuclear ATF6 degradation, altering UPR signaling

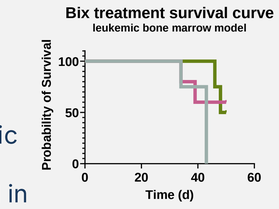


BIX amplifies ATF6 degradation thus impairing T-ALL survival

Preclinical Findings: BIX Disrupts T-ALL Progression



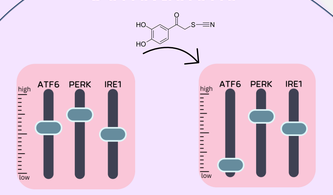




BIX treatment reduced leukemic burden and improved survival in vivo

Think you can disrupt the UPR better than BIX? Prove it!

Conclusions



BIX selectively impairs T-ALL by tipping the UPR balance could be a novel therapeutic strategy