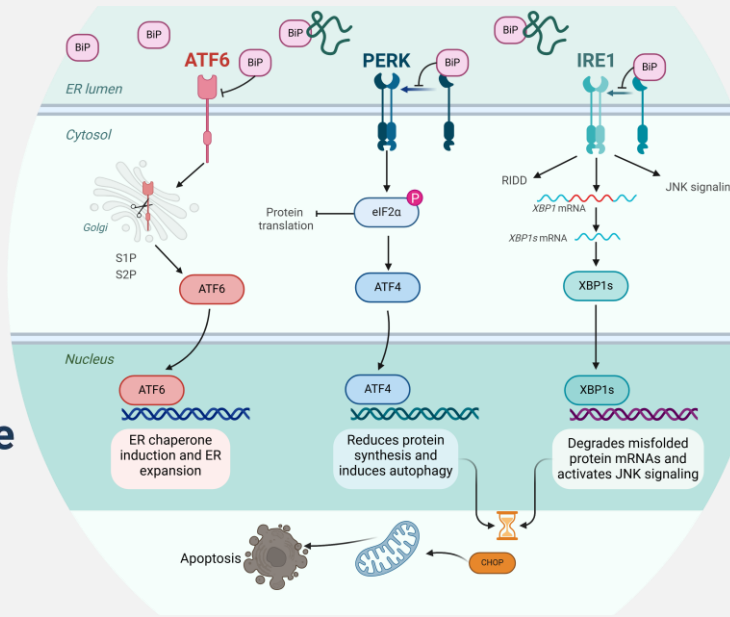
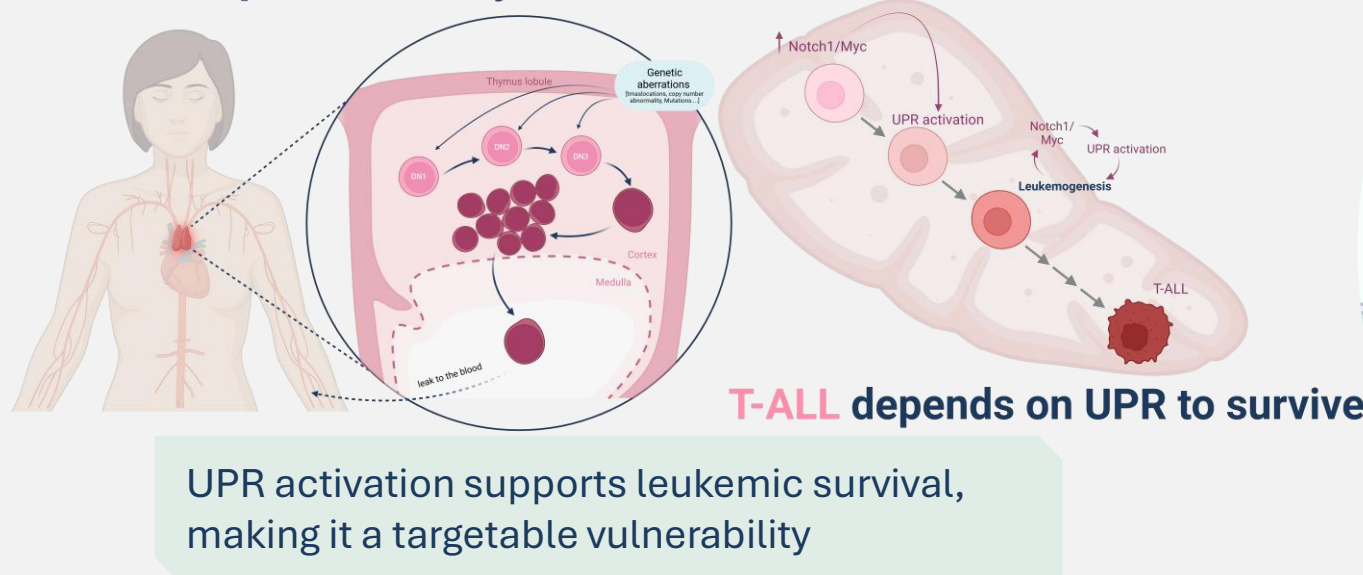




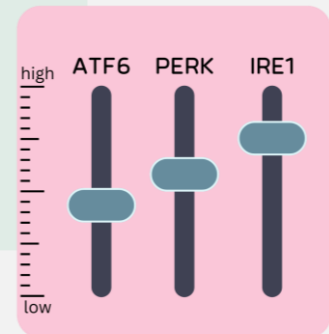
T-ALL's Achilles' Heel: Disrupting the UPR for Therapeutic Gain

Shani Mistriel Zerbib, Nira Twaik, Leonor Daniel and Michael Berger

T-ALL Development in Thymus



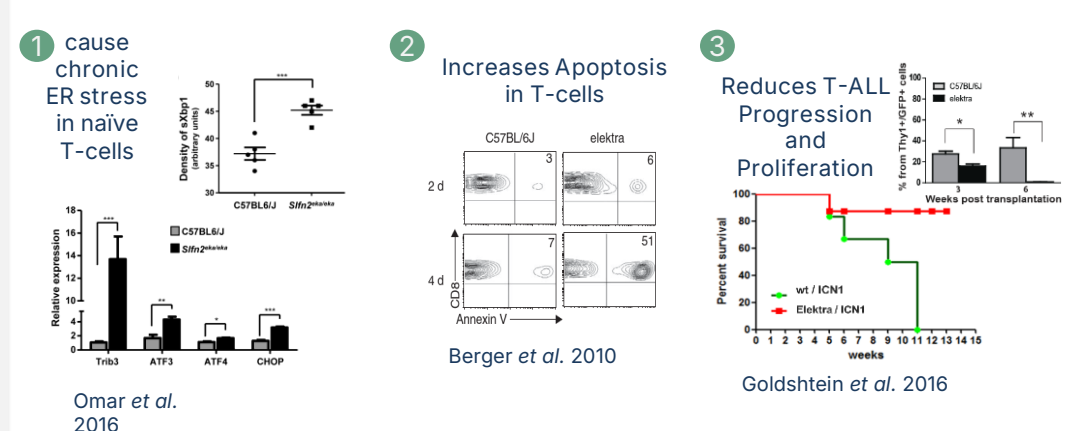
T-ALL relies on an active UPR: IRE1 supports survival, PERK aids stress response, and ATF6 fine-tunes proliferation



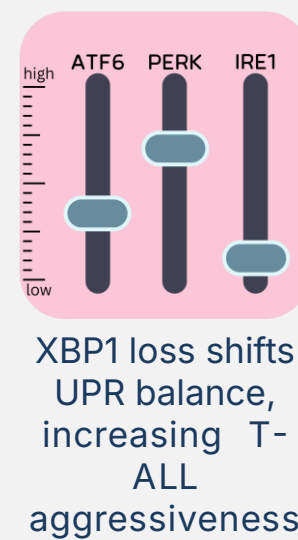
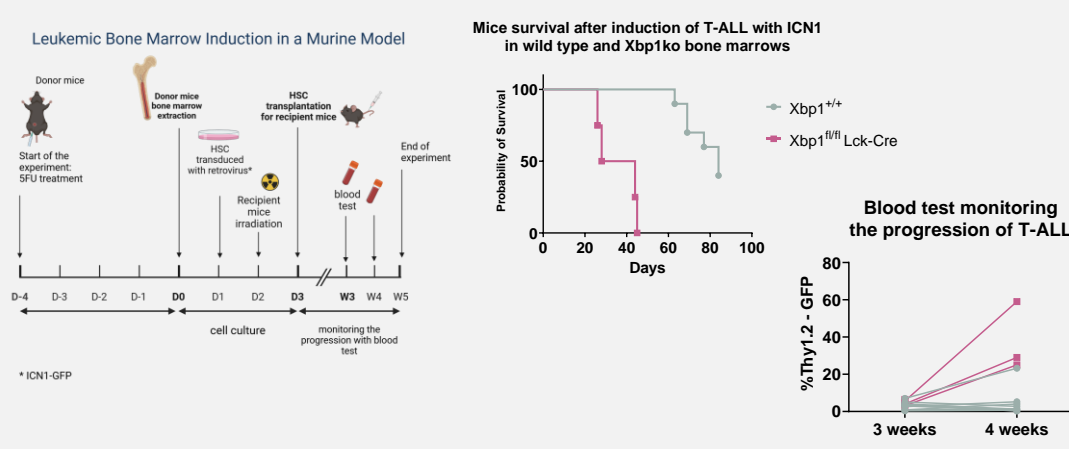
Is UPR Disruption a Therapeutic Strategy for T-ALL?

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

Sfn2 loss of function...

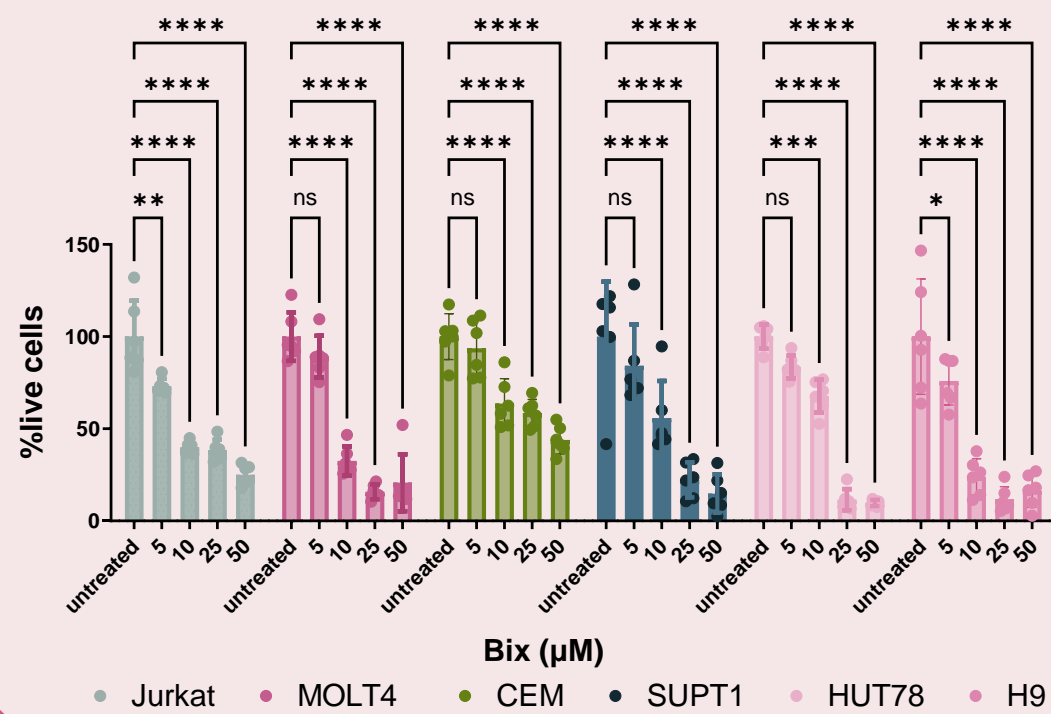


XBP1 loss disrupts UPR balance, making T-ALL more aggressive



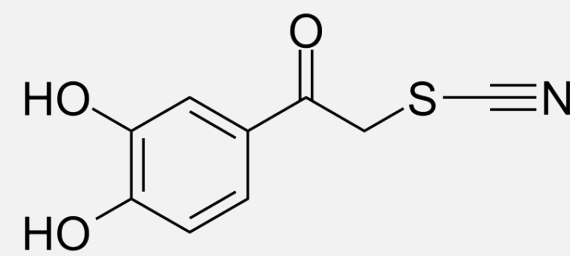
The Disruptor: BIX

Hematopoietic Cancer Cell lines
MTT assay



Targeting UPR homeostasis via ATF6 selectively impairs T-ALL progression, identifying it as a promising therapeutic strategy

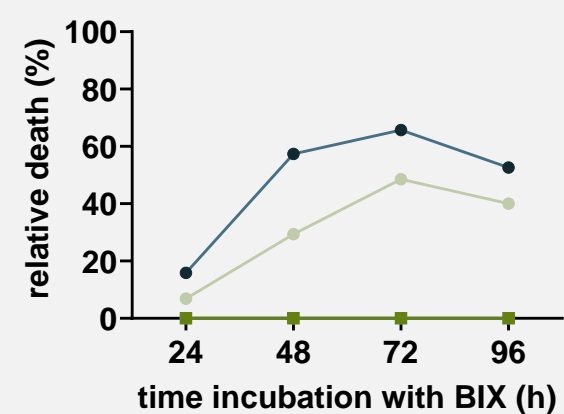
BIX (BiP Inducer X) upregulates BiP/GRP78, reducing ER stress and apoptosis (Hirota et al., 2011)



Cracking the Mechanism

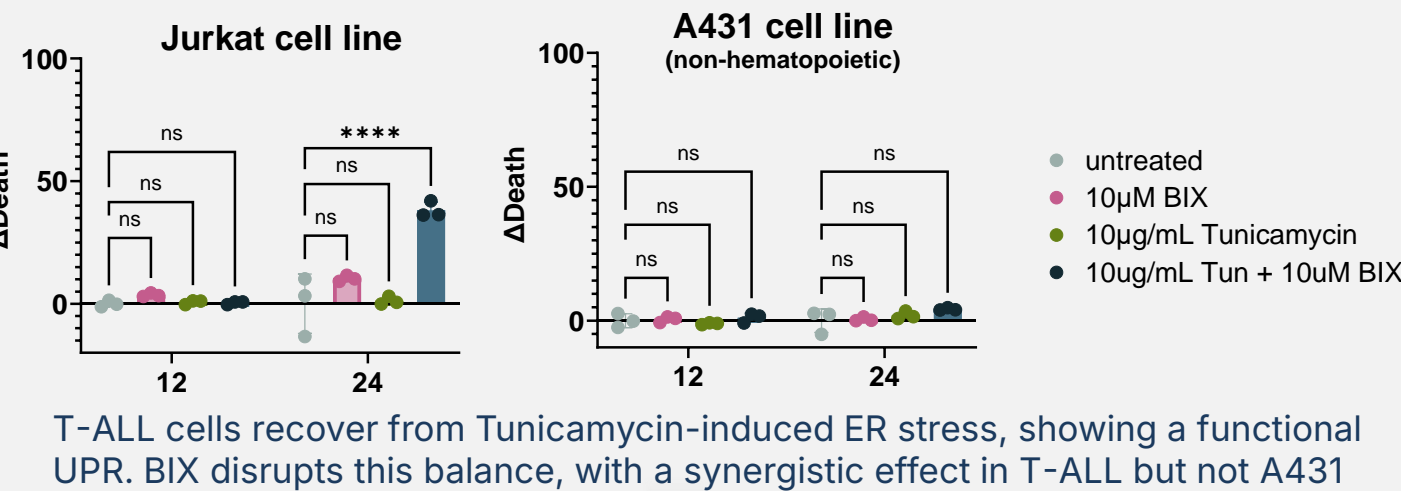
BIX Influences T-ALL Independently of BiP Overexpression

BIX treatment of BiP overexpression induced Jurkat cells

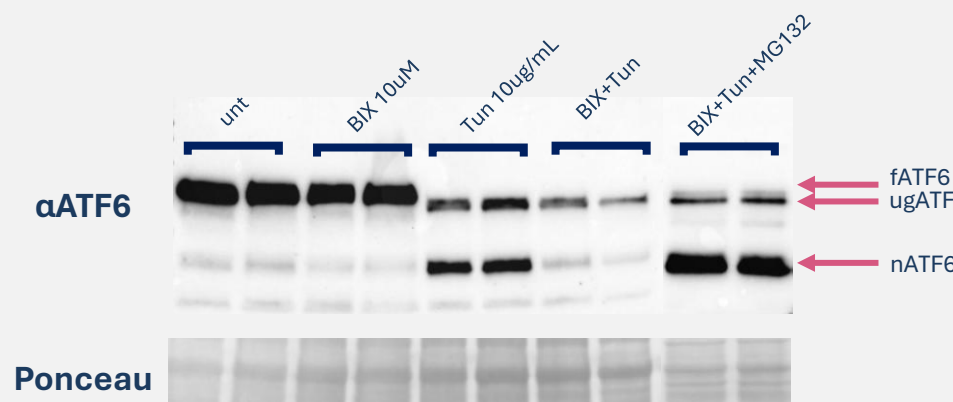


BiP overexpression alone does not trigger apoptosis in T-ALL, suggesting BIX acts via a BiP-independent mechanism

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

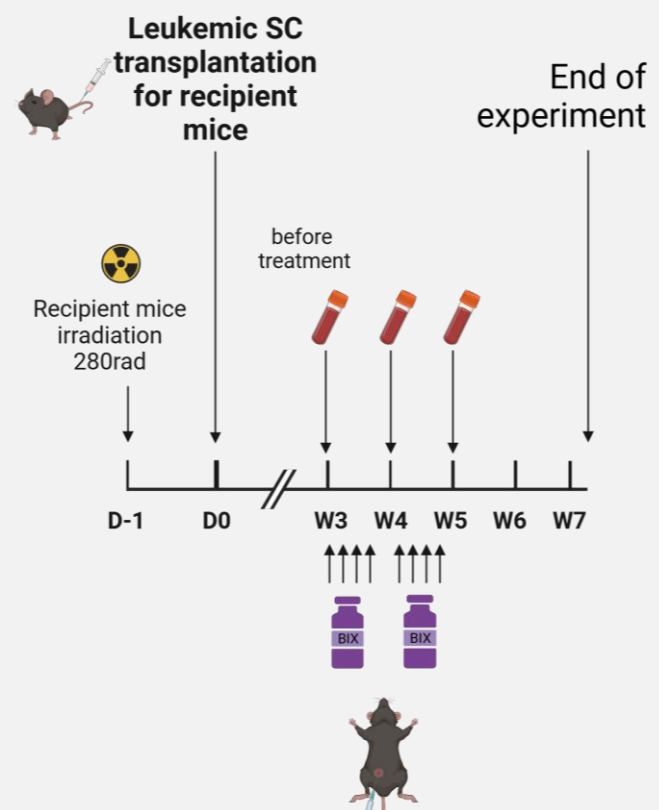


BIX increases nuclear ATF6 degradation, altering UPR signaling

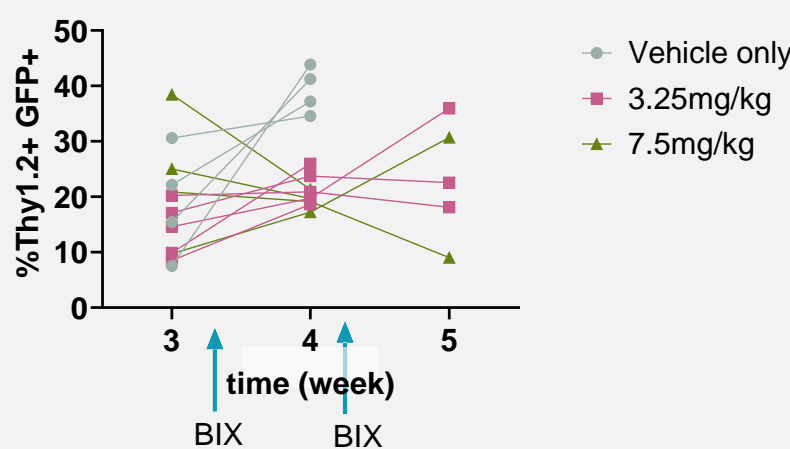


Preclinical Findings: BIX Disrupts T-ALL Progression

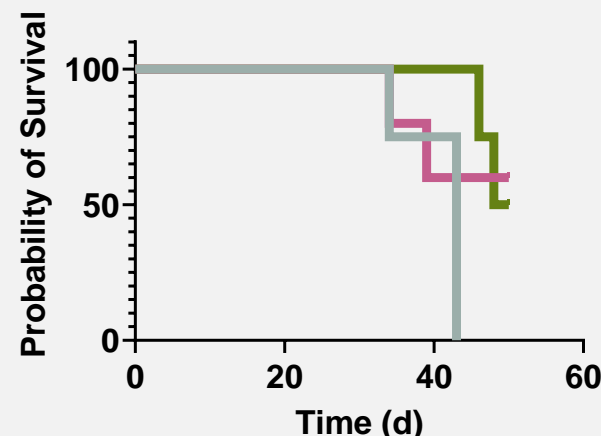
BIX treatment - T-ALL mice model



Thy1.2 GFP cells in blood before and after bix treatment

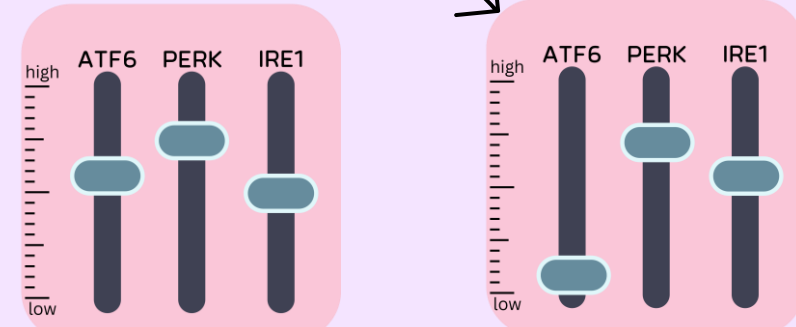
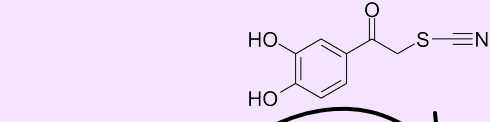


Bix treatment survival curve leukemic bone marrow model



BIX treatment reduced leukemic burden and improved survival in vivo

Conclusions



Targeting UPR homeostasis via ATF6 selectively impairs T-ALL progression, identifying it as a promising therapeutic strategy

This work provides a basis for exploring UPR modulation as a strategy for T-ALL therapy So, Step into my shoes to play with the UPR!

