XIX CONGRESSO NAZIONALE SIES 2026

SR59230A Targets Fatty Acid Oxidation to Trigger Ferroptotic Vulnerabilities in Pediatric T-ALL

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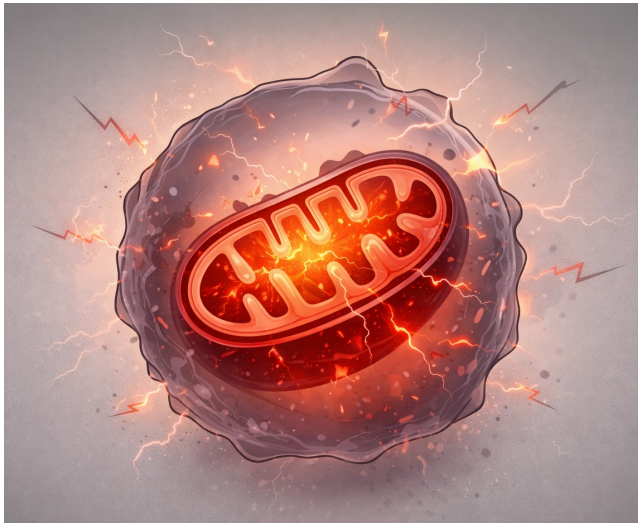
Palazzo degli Affari

Disclosures of Cristina Banella

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

Metabolic Plasticity as a Driver of Therapy Resistance in T-ALL

- Relapsed T-ALL is associated with poor overall survival and limited therapeutic options
- Leukemic cells rewire mitochondrial metabolism under stress
- T-ALL shows high mitochondrial dependency
- OXPHOS drives stress adaptation and survival
- Metabolic vulnerabilities remain largely unexplored
- Targeting metabolism could represents a new therapeutic option



Dissecting the Metabolic Role of SR59230A: β3-Adrenergic Receptors as Novel Targets for Metabolic Reprogramming

Physiological Functions

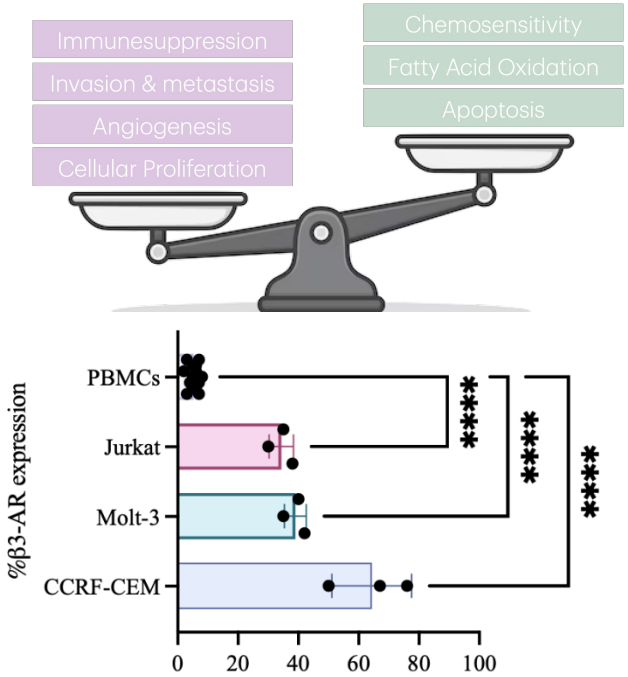
- Regulates adipose lipolysis and thermogenesis (**UCP1-mediated**)
- Contributes to bladder relaxation and anti-stress effects in CNS

Role in Cancer

- Upregulated in melanoma, neuroblastoma, colon, breast → promotes proliferation
- Stimulates angiogenesis and supports pro-tumor microenvironment (MDSC, M2 macrophages, invasiveness)

Therapeutic Potential

- Antagonists (e.g., **SR59230A**) reduce tumor growth and induce apoptosis
- Potential adjuvant target in melanoma and neuroblastoma

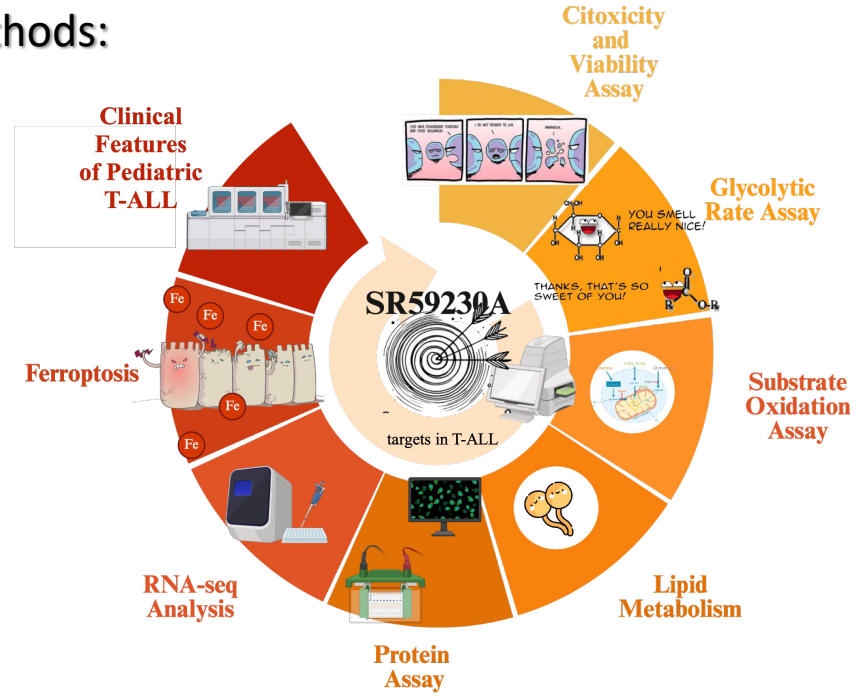


Aims & Methods

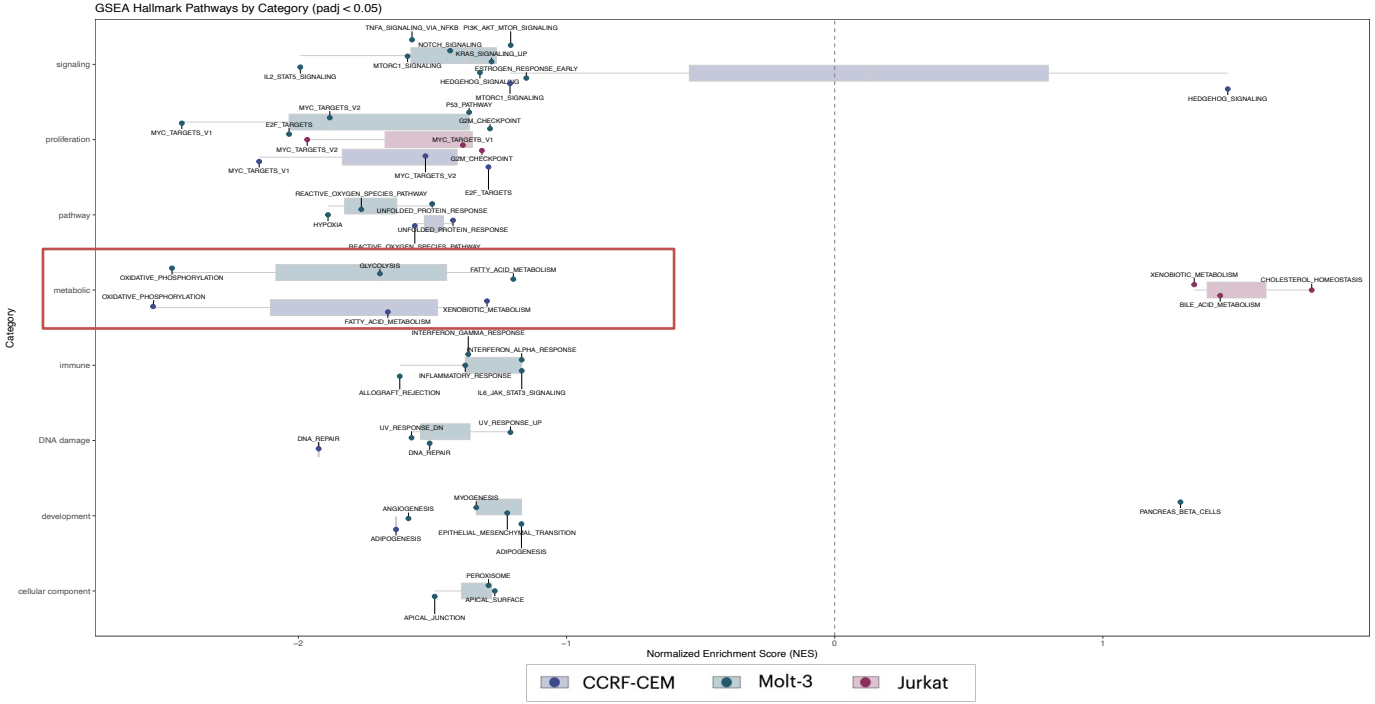
Aims:

- Dissection the potential antileukemic mechanism of SR59230A in pediatric T-ALL
- Exploiting mitochondrial metabolism, FAO, and ferroptosis as therapeutic vulnerabilities in pediatric T-ALL

Methods:



SR59230A triggers convergent mitochondrial suppression and metabolic rewiring in T-ALL



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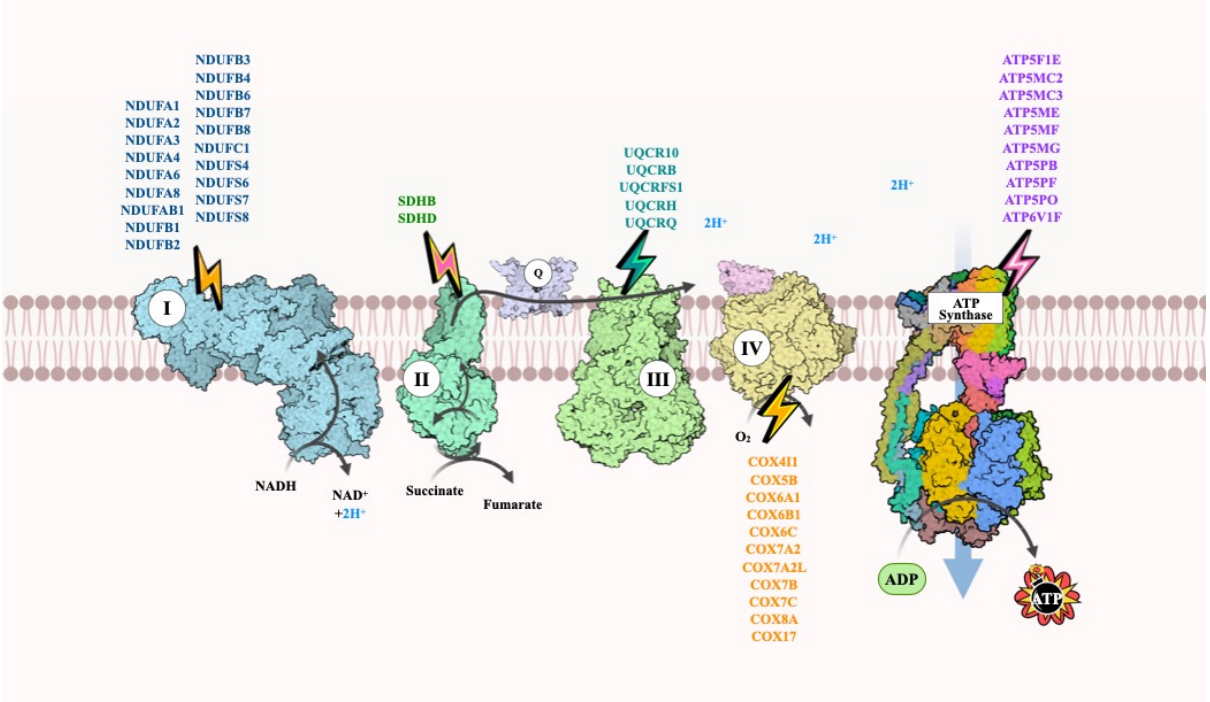
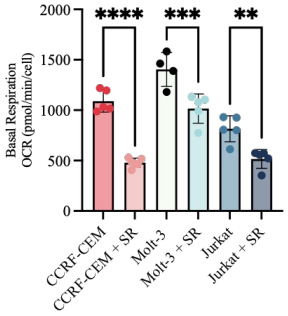
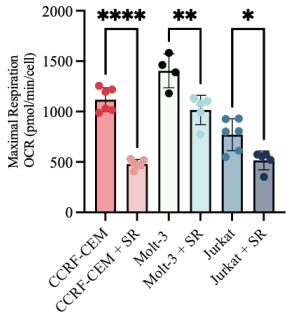
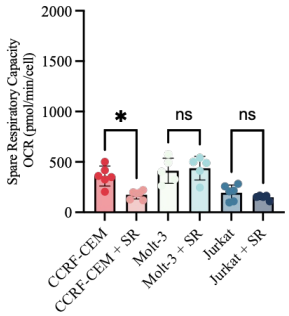
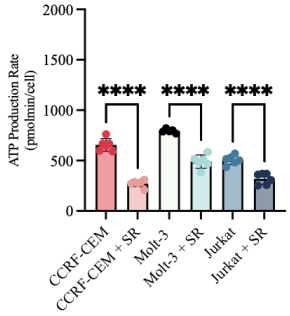


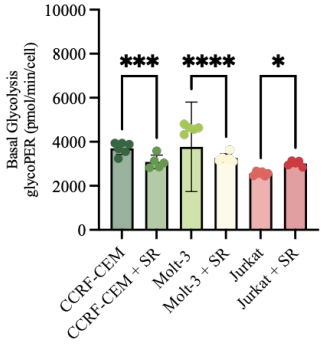
SR59230A selectively impairs mitochondrial and glycolytic metabolism in T-ALL cell models

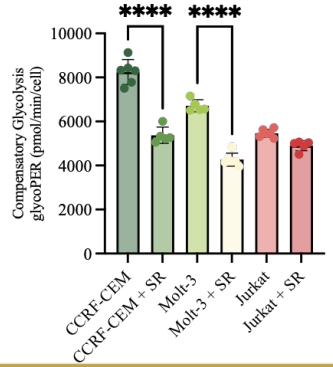












Mitochondrial Metabolism

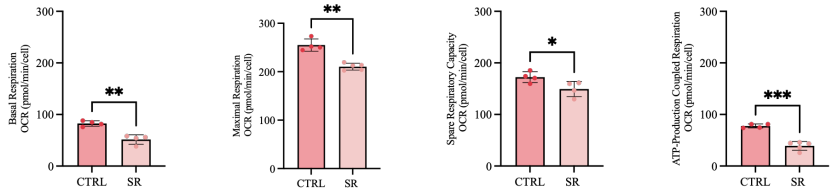
- **Complex I inhibition → decreased OXPHOS**
- ↓ Complex I activity
- ↓ Oxygen consumption rate (OCR)
- ↓ ATP production
- Mitochondrial energetic deficiency

Glycolytic Metabolism

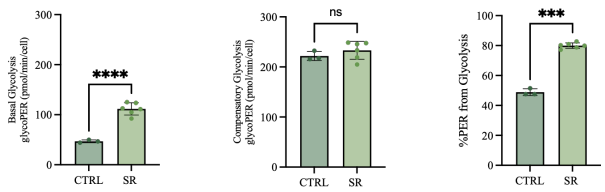
- **Decreased glycolysis**
- ↓ Basal glycolysis
- ↓ Compensatory glycolysis (after mitochondrial inhibition)
- Reduced glycolytic ATP production

SR59230A disrupts mitochondrial bioenergetics in primary T-ALL blasts

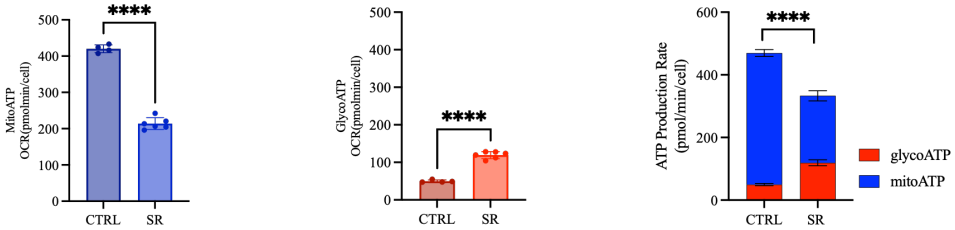
Mito Stress Test



Glycolytic Rate Assay



ATP Rate Assay



Mitochondrial metabolism (OXPHOS)

- ↓ Basal respiration
- ↓ Maximal respiration
- ↓↓ Mito-ATP production

→ *Mitochondrial ATP production decreased*

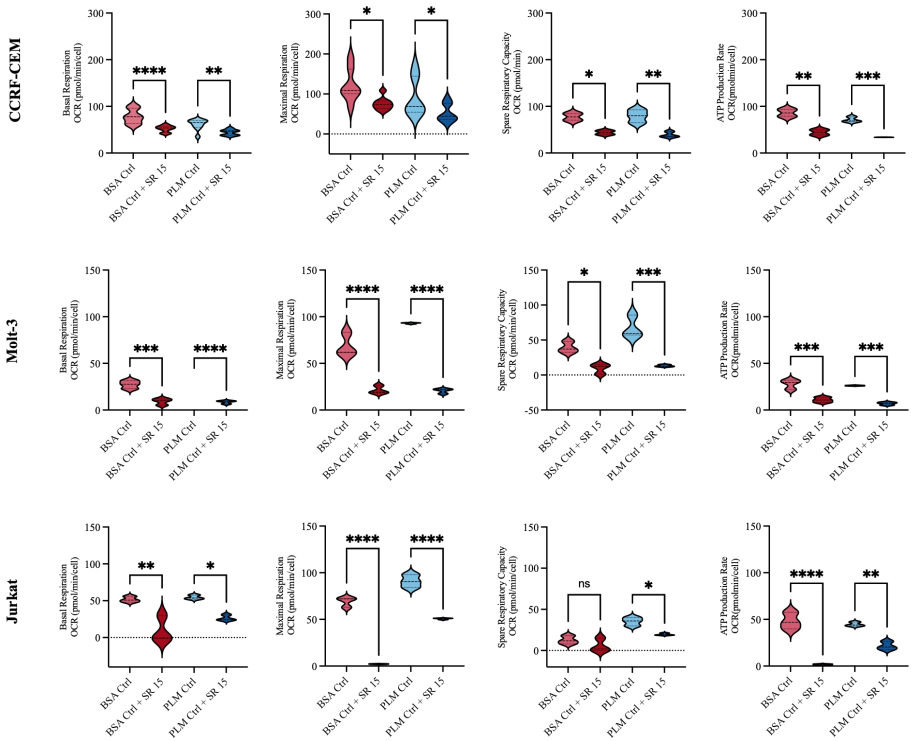
Glycolytic metabolism

- ↑ Basal glycolysis
- ↑ %PER from glycolysis

→ *Glycolytic ATP production increased*

Total ATP production decreased despite glycolytic compensation

SR59230A disrupts FAO and exposes T-ALL to metabolic vulnerability

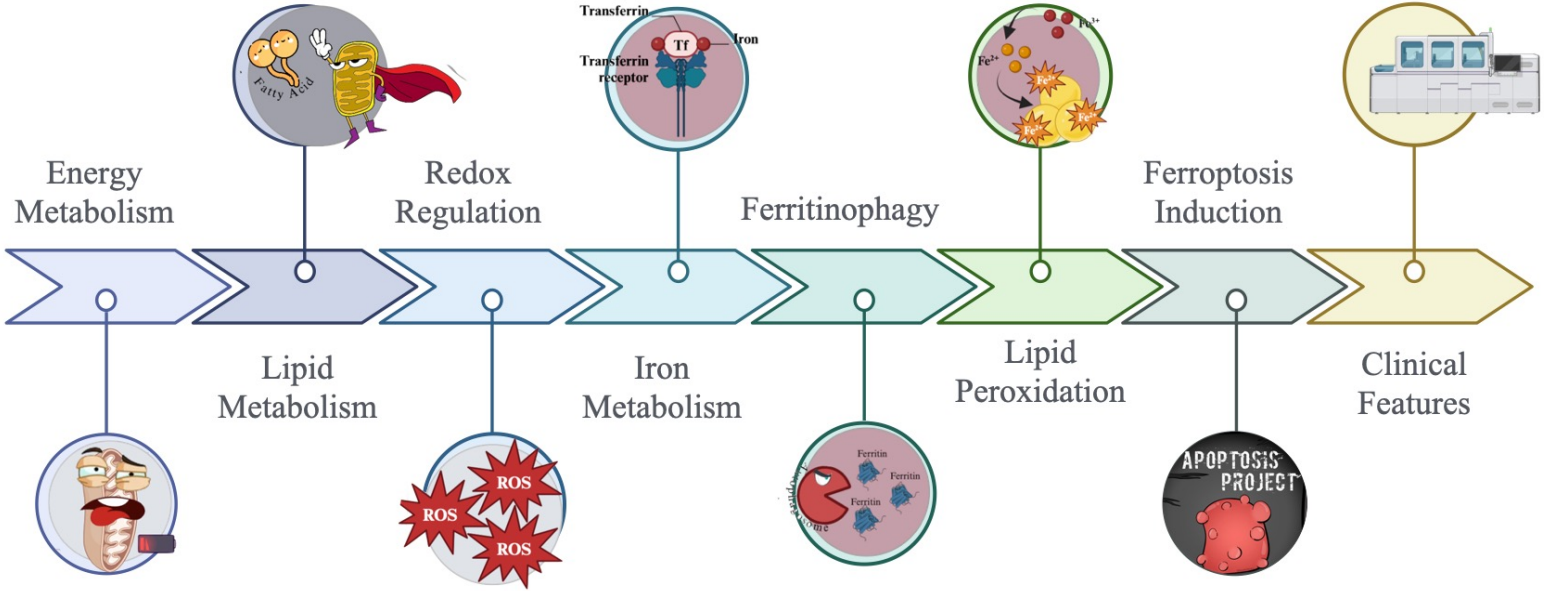


- **Endogenous (BSA control) and Exogenous (Palmitate-BSA) FAO**

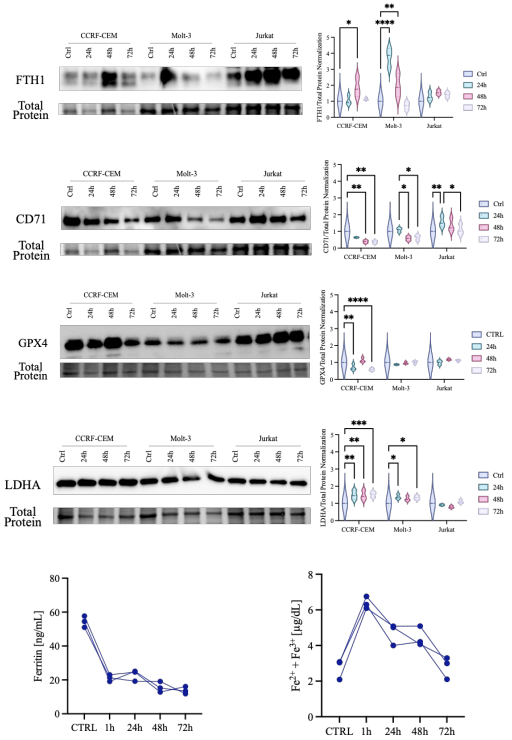
- ↓ Basal respiration
- ↓ Maximal respiration
- ↓ Spare respiratory capacity
- ↓ ATP production rate

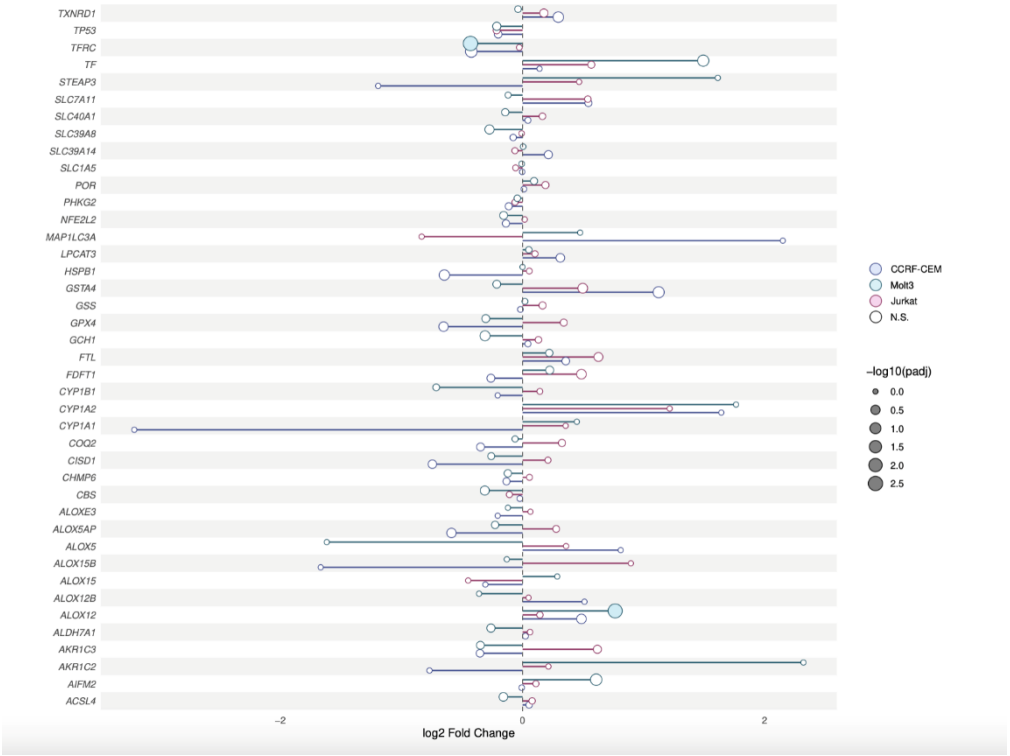
→ **Mitochondrial ATP from endogenous and exogenous FAO decreased**

Linking SR59230A-Induced Metabolic Deficiency to Ferroptosis in T-ALL



SR59230A Couples FAO Blockade to Ferroptotic cell death in T-ALL





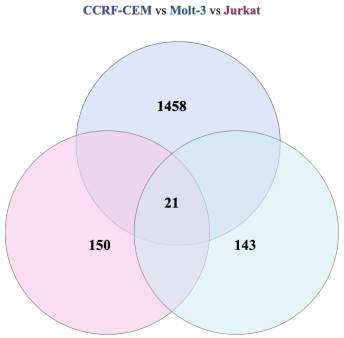
- **Decreased ferroptosis-protective genes:** GPX4, FSP1, NRF2

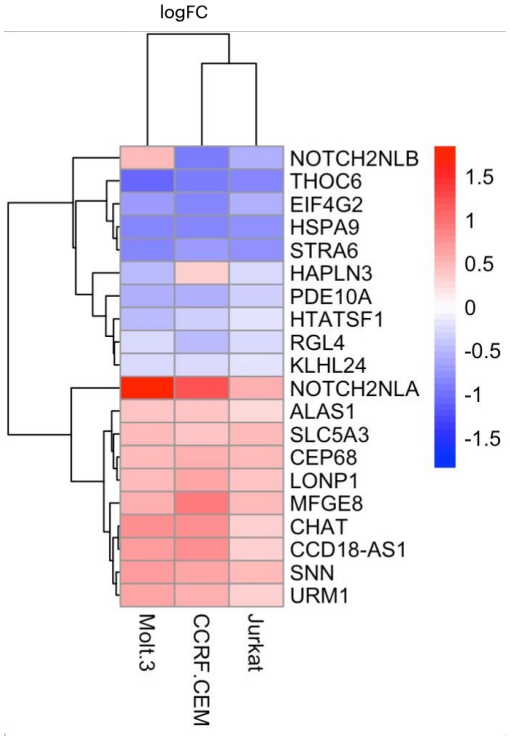
- **Increased lipid peroxidation genes** → promotes ferroptotic stress

- **Altered iron metabolism:** FTH1 ↓, CD71 ↑, labile iron ↑

- **Increased stress marker:** LDHA

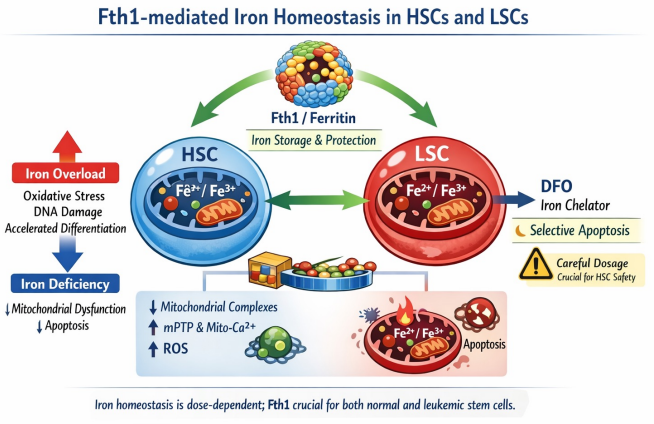
SR59230A Couples FAO Blockade to Ferroptotic cell death in T-ALL



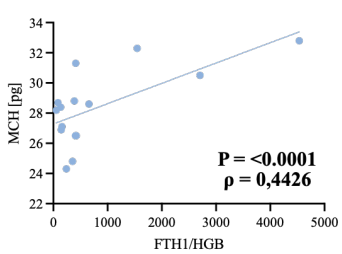


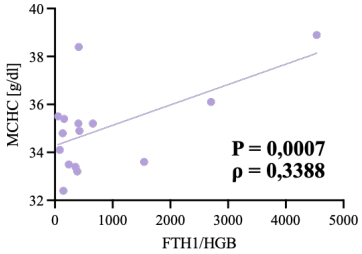
Gene	Function	Notes / Associations
Mitochondrial / Metabolism		
HSPA9	Mitochondrial chaperone	Mitochondrial stress, leukemia, cancer
LONP1	Mitochondrial protease	Mitochondrial stress, metabolism, cancer
ALAS1	Heme biosynthesis enzyme	Mitochondrial metabolism, porphyrias
SLC5A3	Inositol transporter	Osmotic stress response, metabolism
SNN	Stannin, mitochondrial protein	Metal toxicity sensitivity (Cd, As)
MFGE8	Apoptotic cell clearance	Metabolic stress, tissue homeostasis
Transcription / RNA / Signaling		
NOTCH2NLA / NOTCH2NLB	Notch pathway modulators	Neurogenesis, development
THOC6	mRNA nuclear export	Neurodevelopmental disorders
EIF4G2	Cap-independent translation initiation	Stress response, apoptosis
HTATSF1	Transcription & RNA maturation	Cell proliferation
RGL4	Ral GTPase effector	Ras signaling, proliferation, tumor growth
URM1	Ubiquitin-like modifier	Oxidative stress response, tRNA thiolation
CCD18-AS1	lncRNA, transcription regulation	Tumor regulation, epigenetics
Cell Signaling / Surface / Other		
STRA6	Retinol transporter	Development, congenital defects
HAPLN3	ECM component	Tissue-specific, tumor roles
PDE10A	cAMP/cGMP phosphodiesterase	Brain function, neurological disorders
KLHL24	E3 ubiquitin ligase	Protein degradation, skin disorders
CEP68	Centrosome component	Centriole duplication, cell division
CHAT	Choline acetyltransferase	Acetylcholine synthesis, nervous system

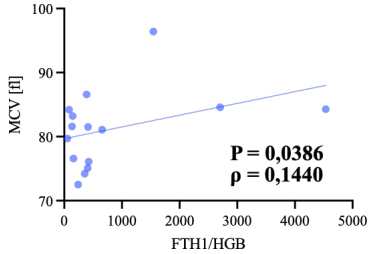
Ferritin-dependent iron homeostasis links metabolic vulnerability to clinical features in Pediatric T-ALL

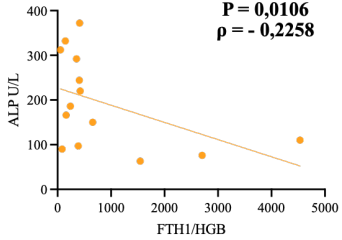


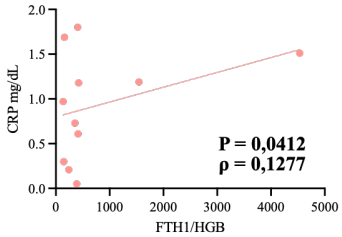
Weiwei Yi, et all. *Leukemia*, 2024

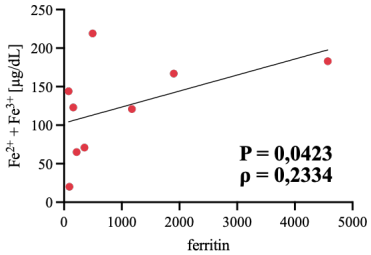




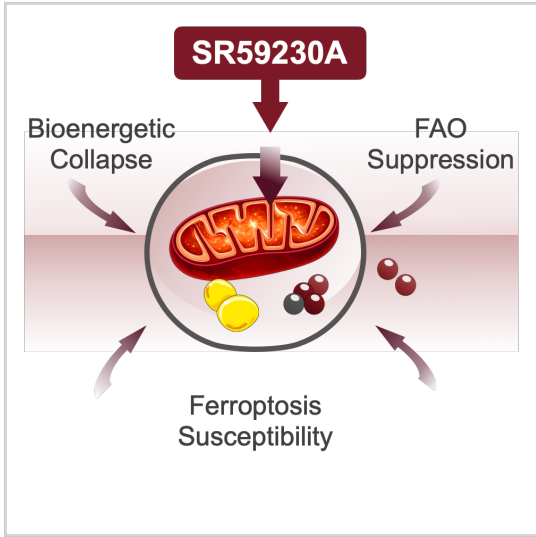


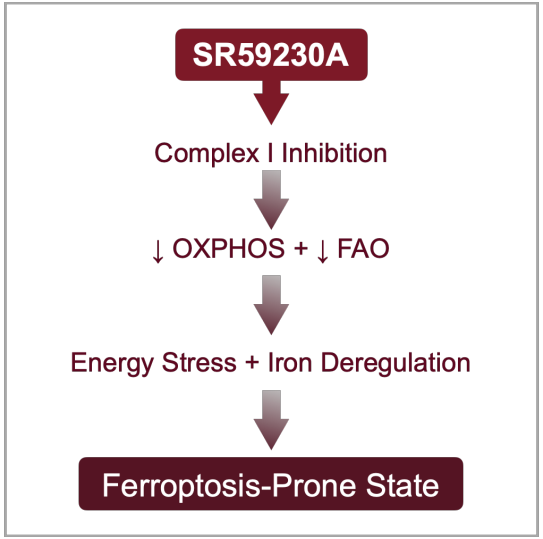


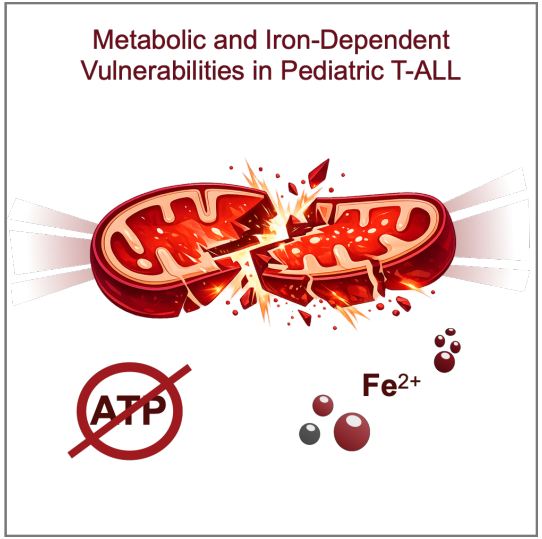




Conclusion







SR59230A disrupts mitochondrial oxidative phosphorylation in pediatric T-ALL, predominantly affecting Complex I and fatty acid oxidation

This metabolic perturbation is associated with altered iron homeostasis and increased susceptibility to ferroptosis

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