

Preclinical modeling of drug resistant acute lymphoblastic leukemia

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CRPP Human Hemato-Lymphatic Diseases



University of
Zurich^{UZH}



UNIVERSITY
CHILDREN'S HOSPITAL
ZURICH

**The hospital of the
Eleonore Foundation**



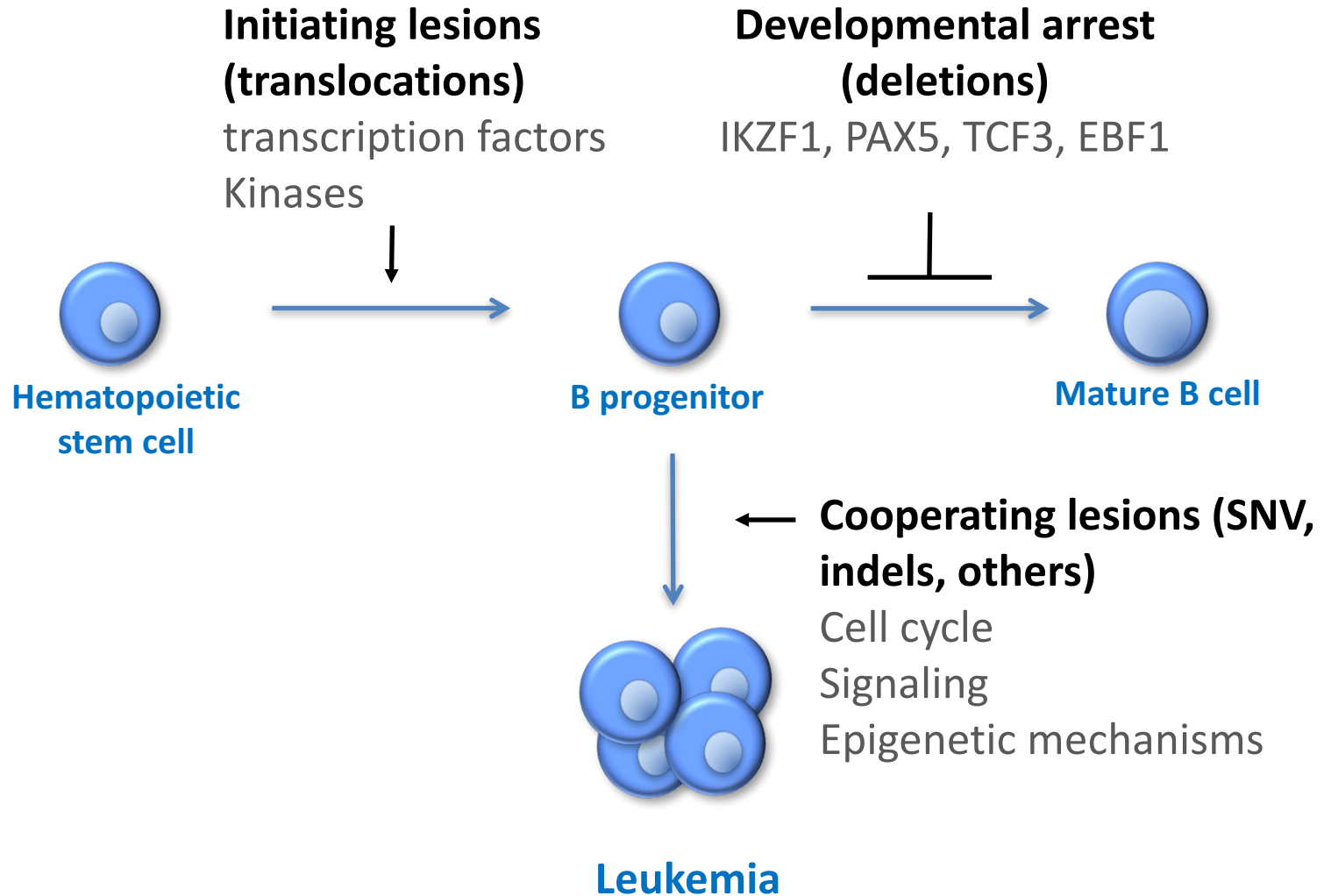
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Acute lymphoblastic leukemia - clinical context

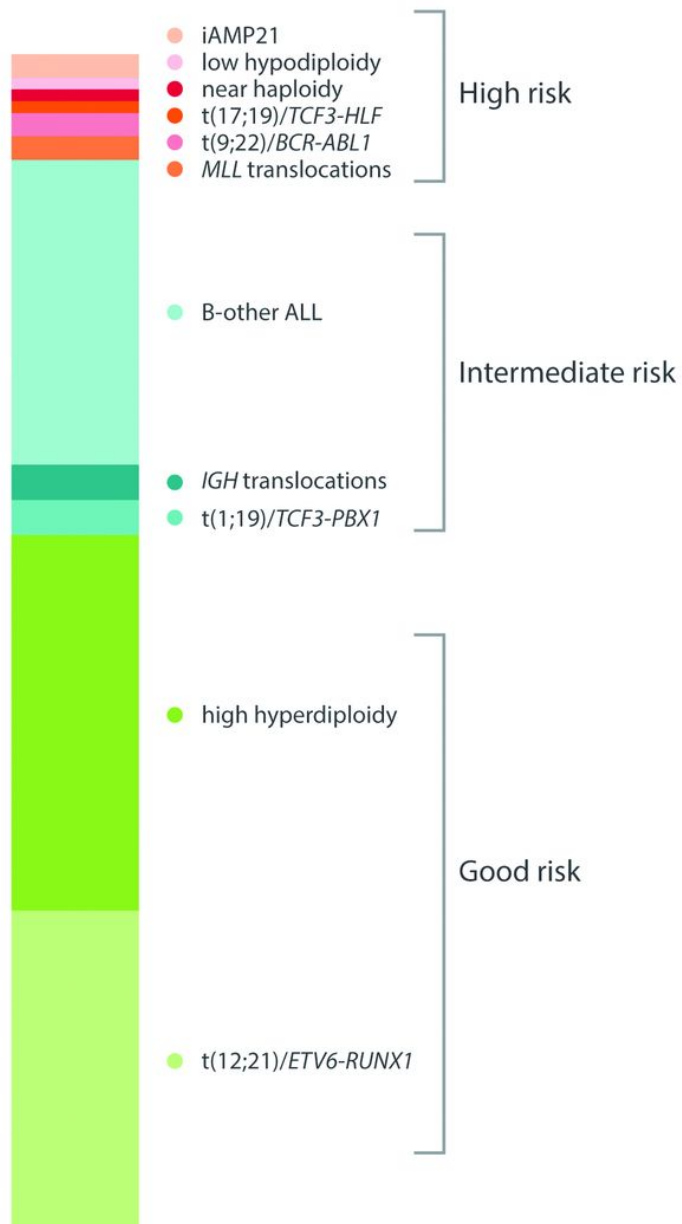
Resistance

		Needs	Research
First diagnosis	15%	Predictive markers Molecular classification Functional understanding Functional classification	Integration of Multi-Omics Functional Profiling
Relapse	55%		Model empiry Model defined molecular types
Refractory	100%	Mechanisms Adaptive treatments	Drug development Exp. Therapy Innovative concepts e.g, basket' trials

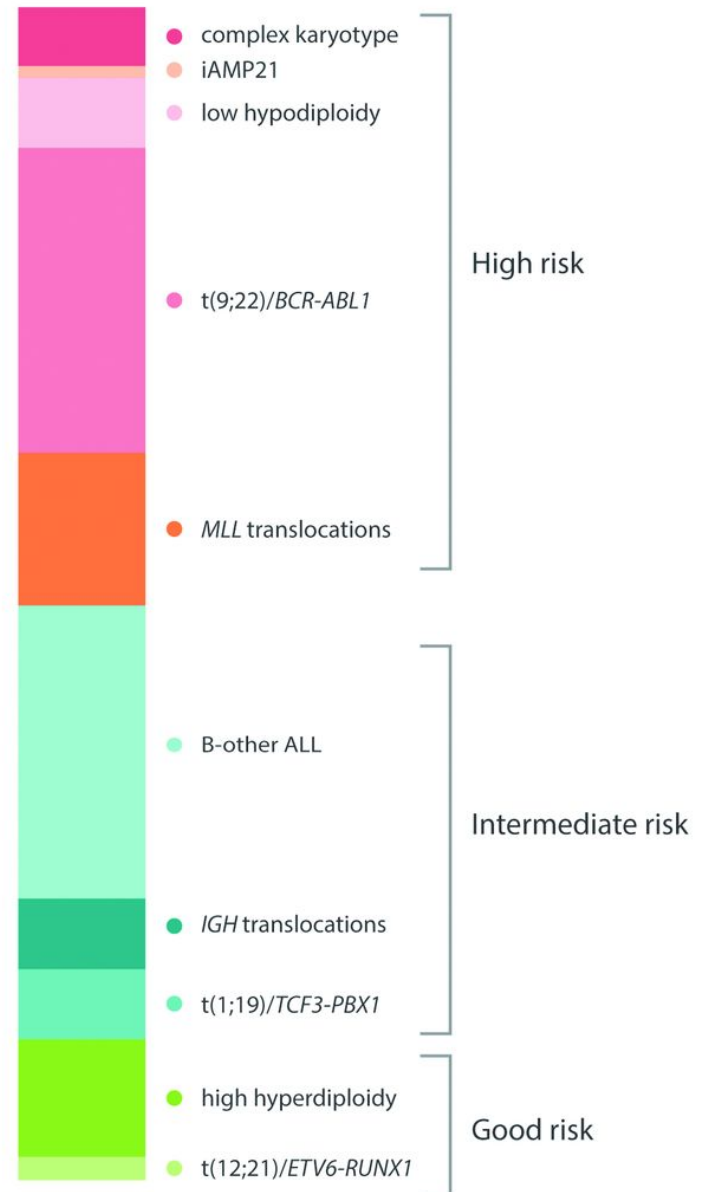
Genetic landscape of ALL



Children & adolescents

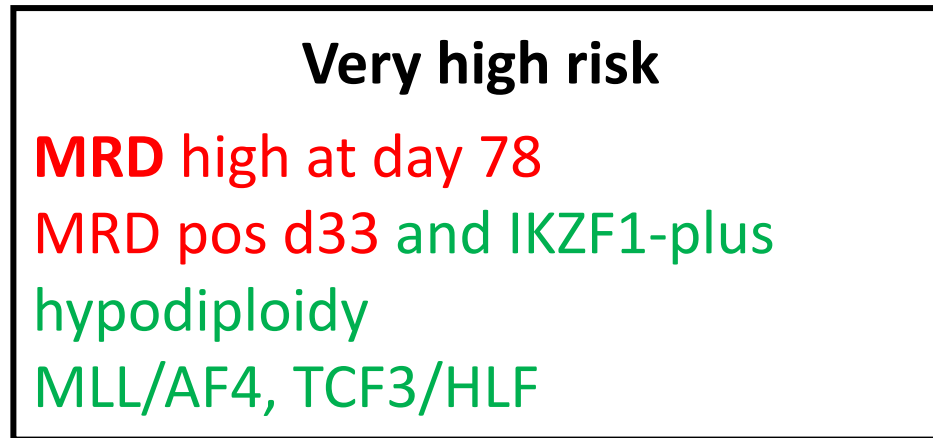
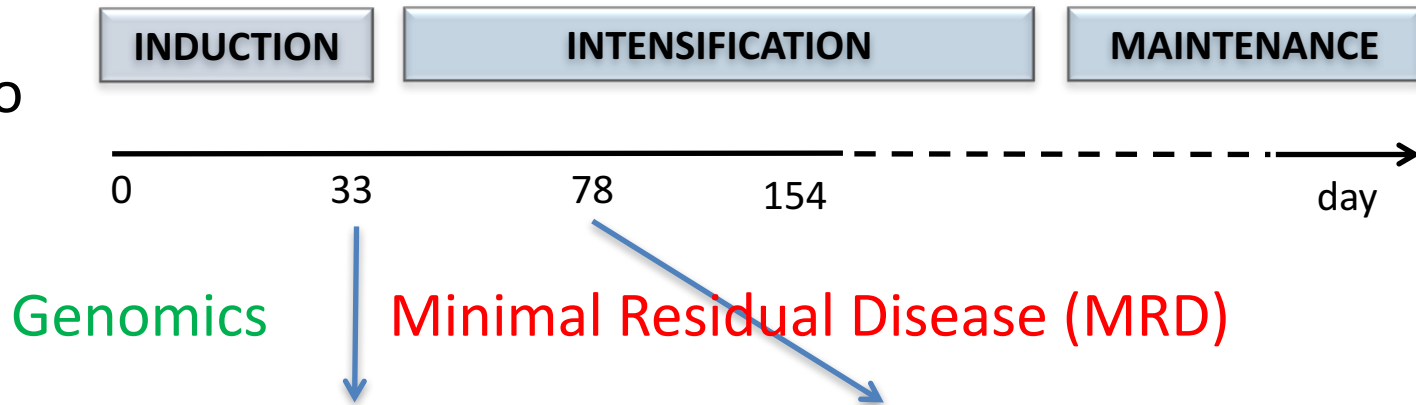


Adults



Functional application of genomics still limited in the clinic

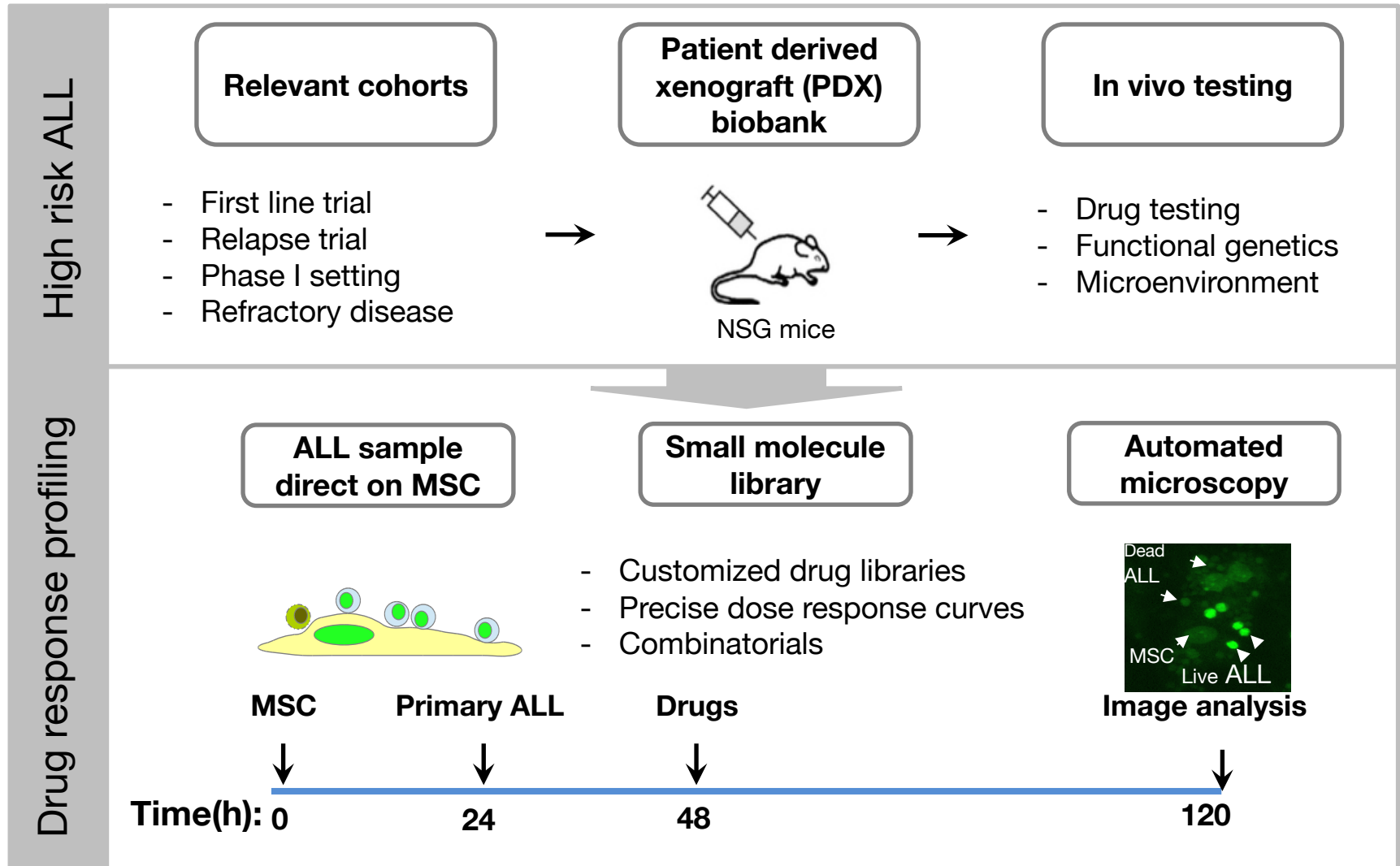
First line
ALL chemo



↓

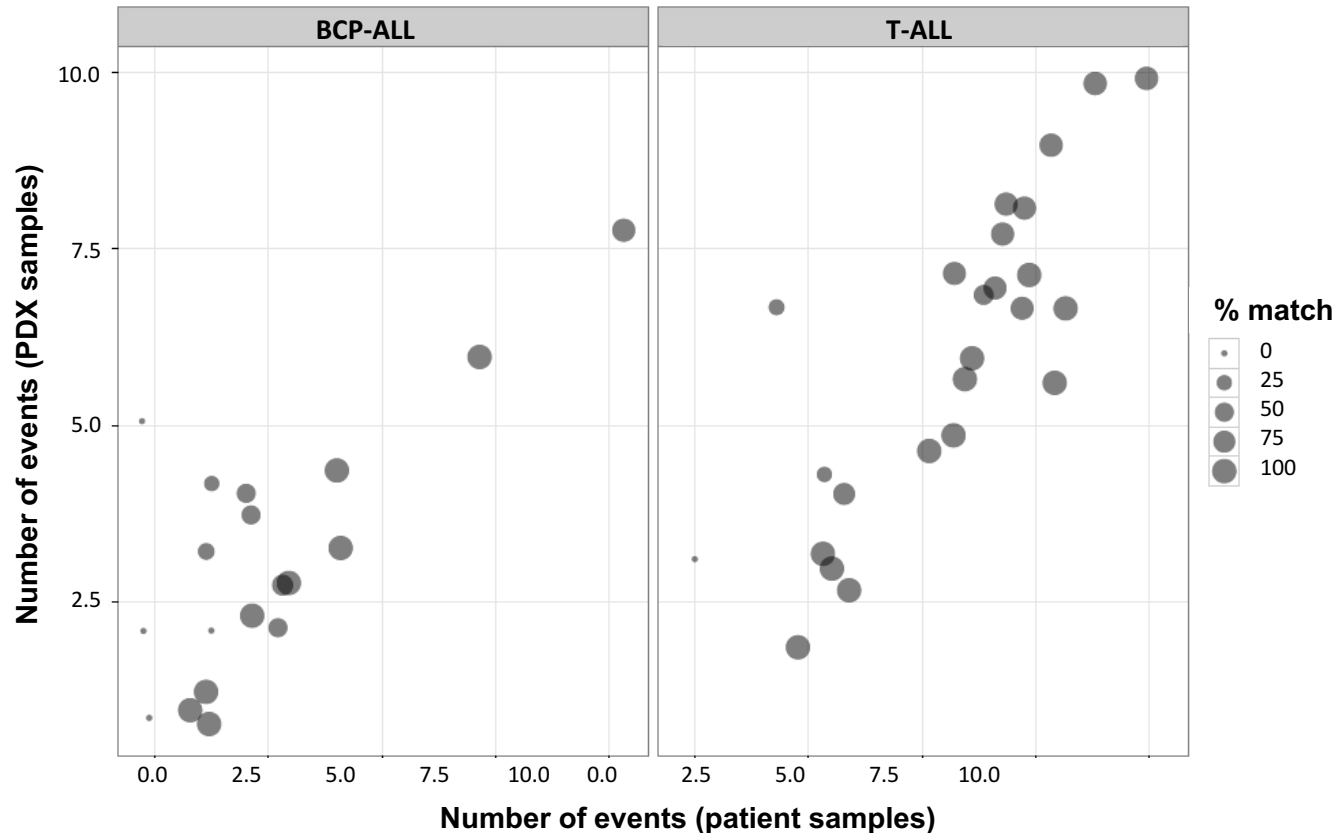
Entities for experimental treatment

Patient-derived models



Leukemia PDX are genetically stable

targeted sequencing 52 genes, SNVs and indels



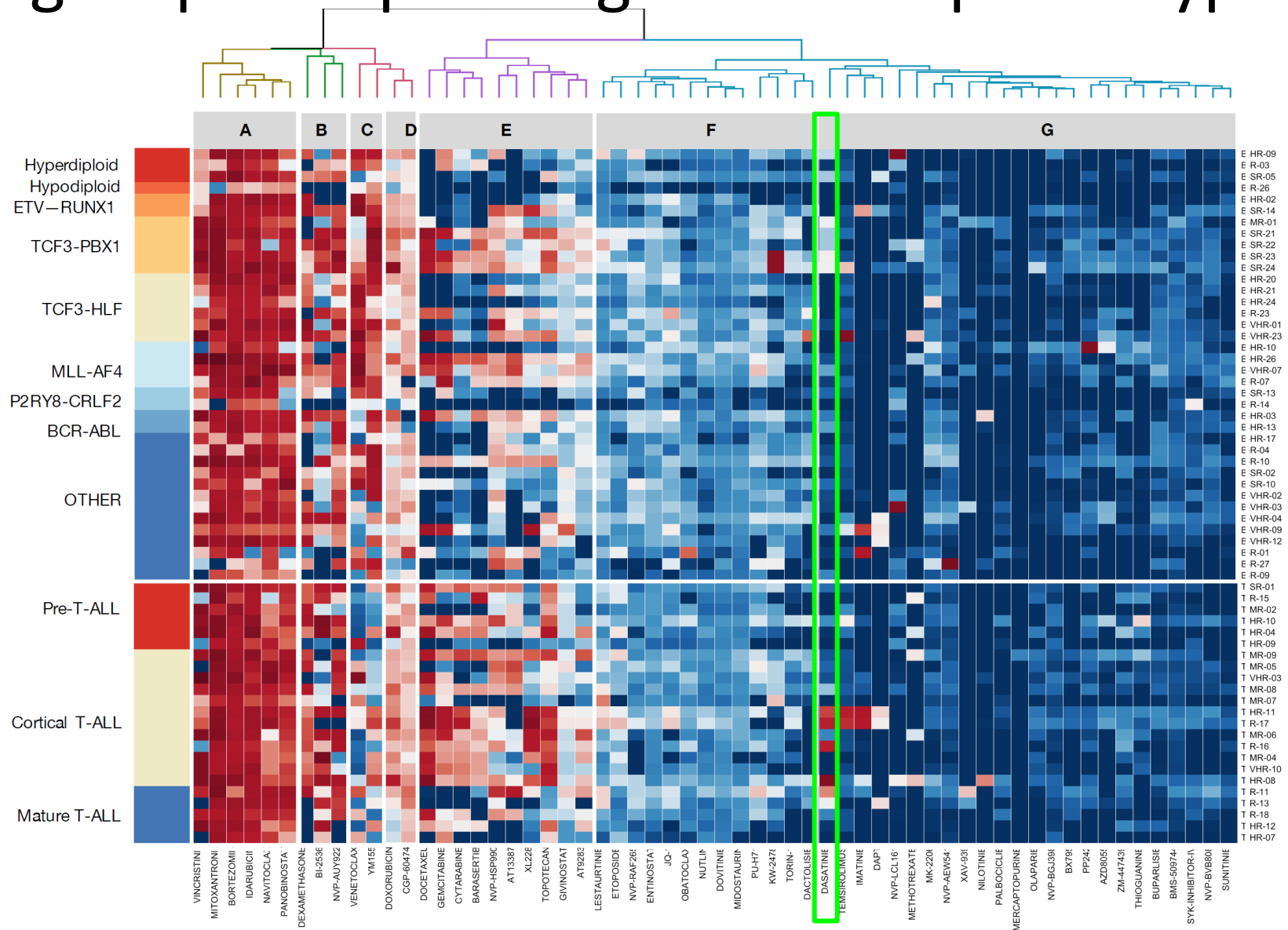
Frismantas et al Blood 2017

Pam Dobay, bioinformatics, IntReALL panel, C. Eckert, A Moorman, J. Irving FP7

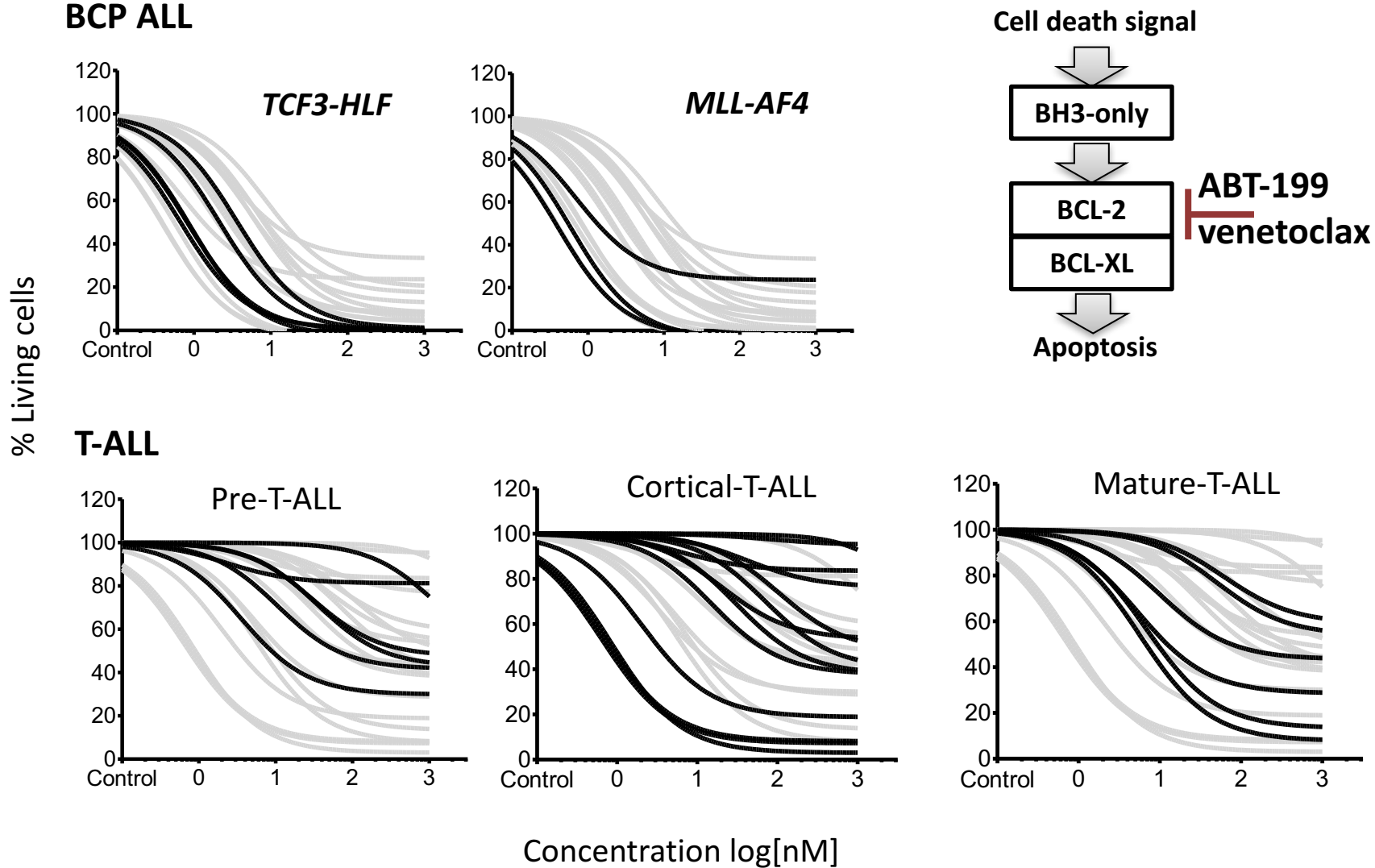
Drug response profiling identifies phenotypes

BCP-ALL

T-ALL

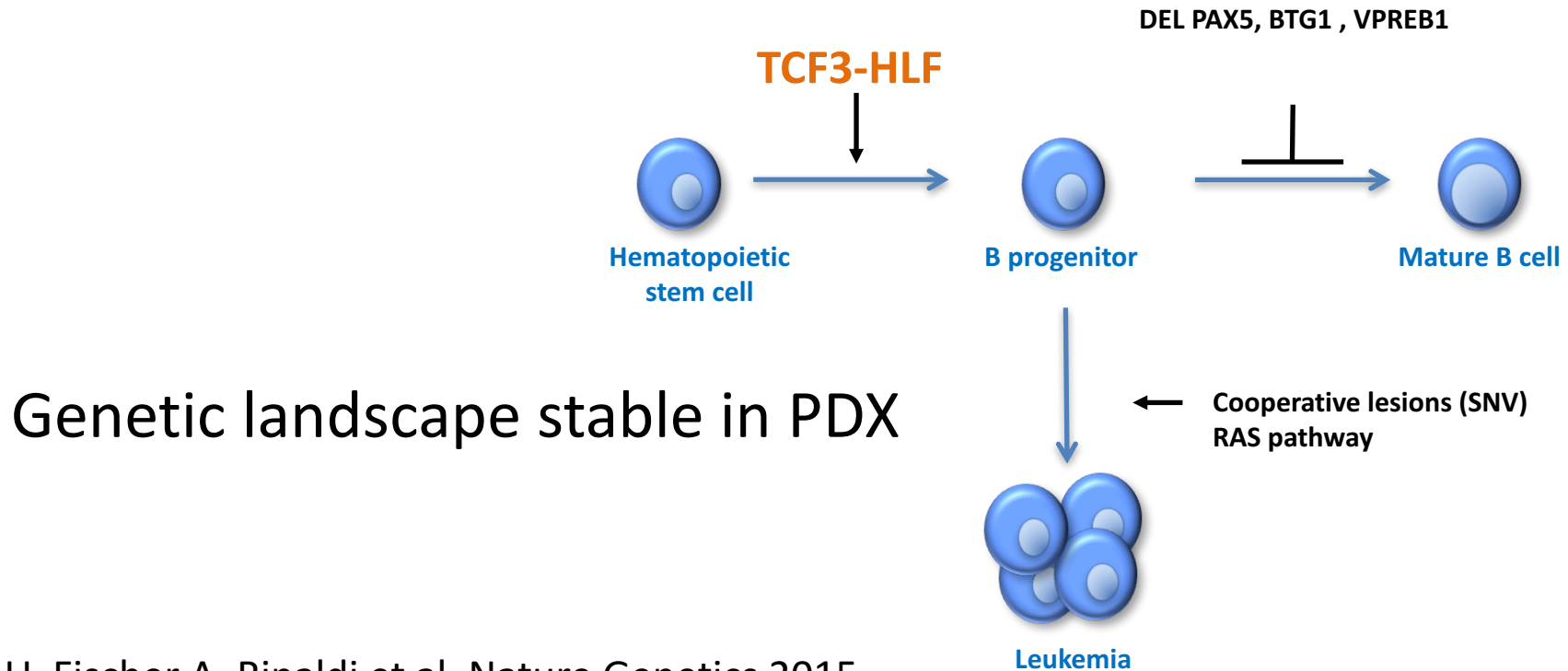
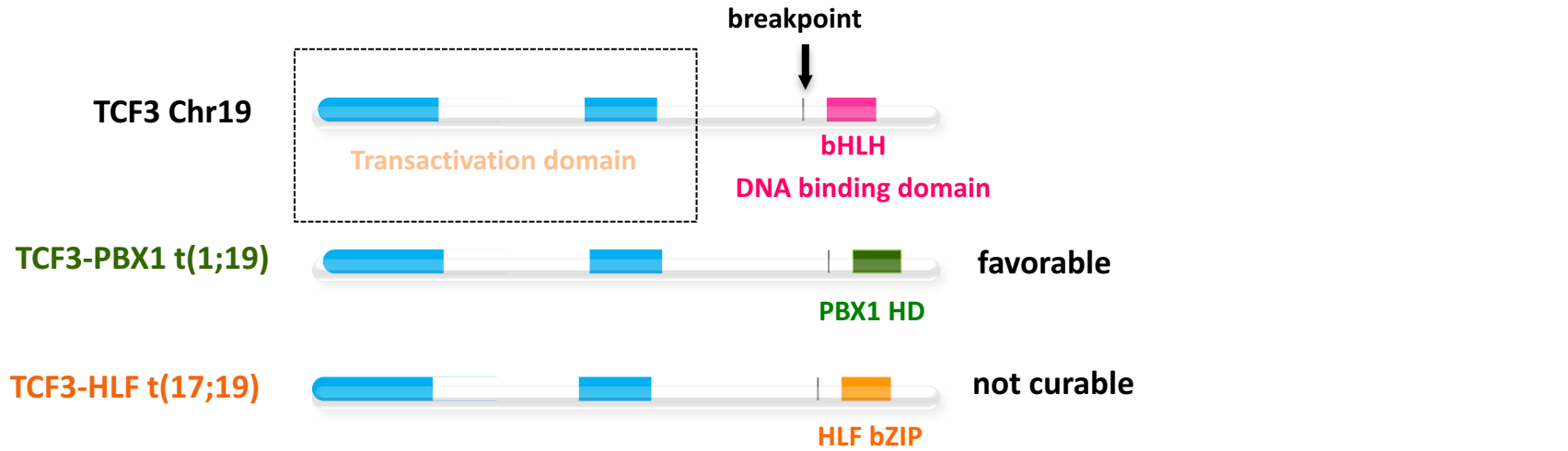


A subset of ALL responds to BCL2 inhibition with venetoclax

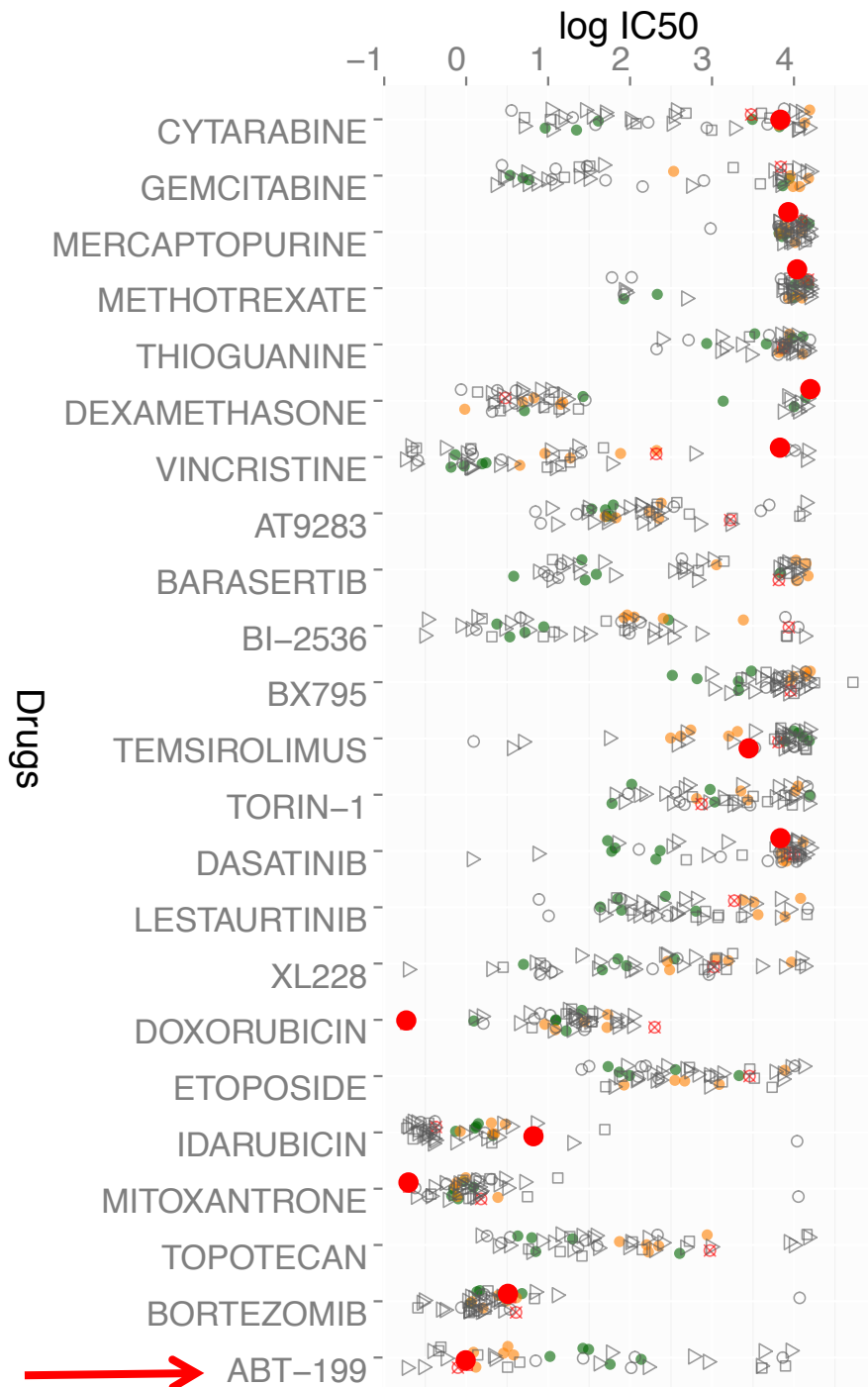


ABBVIE Pediatric Phase I study, Protocol + PIP in 2017 single agent and combination

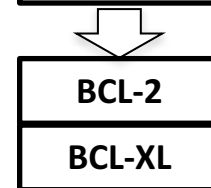
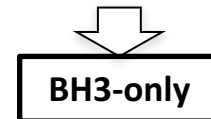
TCF3-HLF: a paradigm of resistant disease



Genetic landscape stable in PDX



Cell death signal



ABT-199
venetoclax

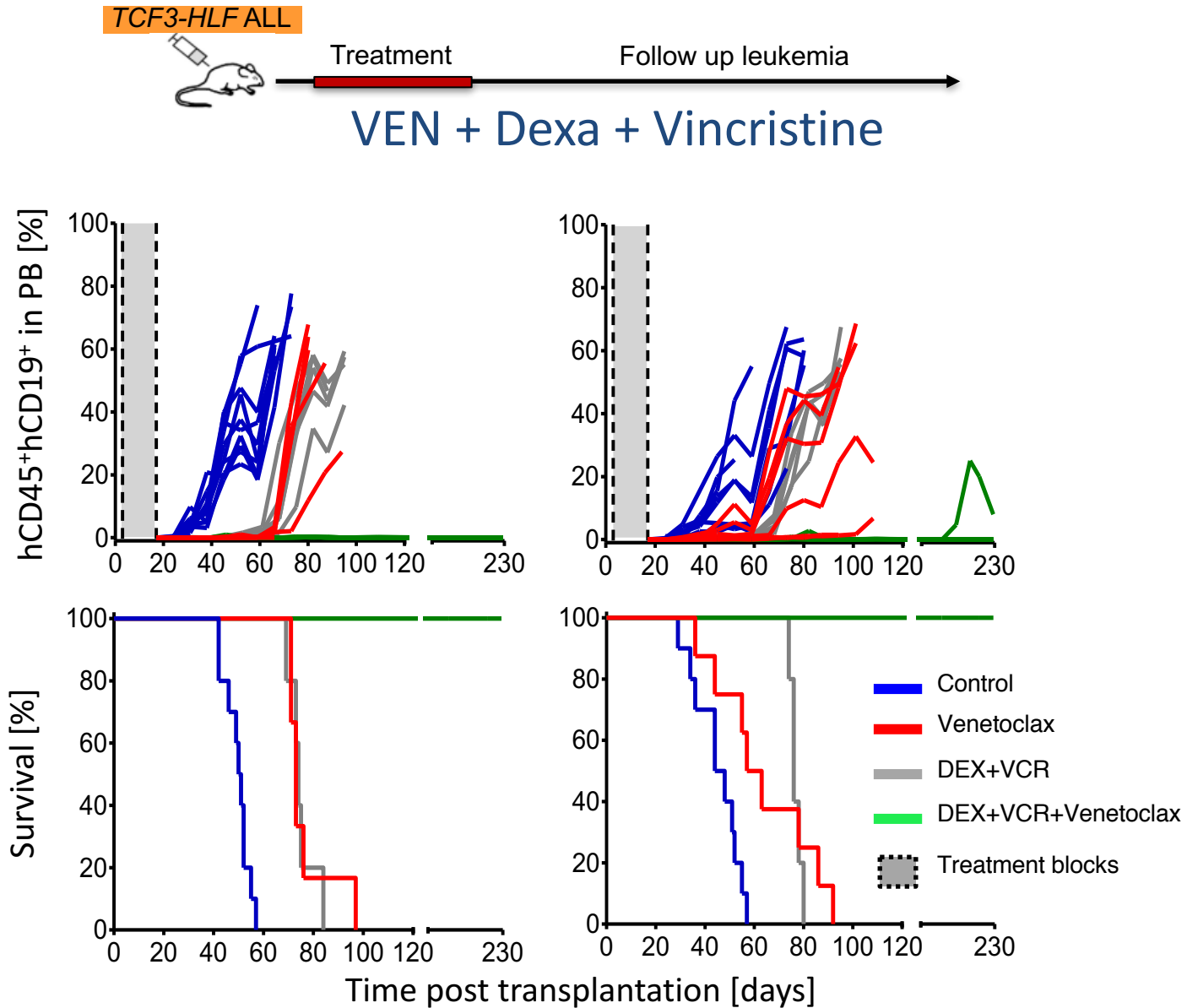
Apoptosis

● ZH96 TCF3-HLF
primary refractory ALL

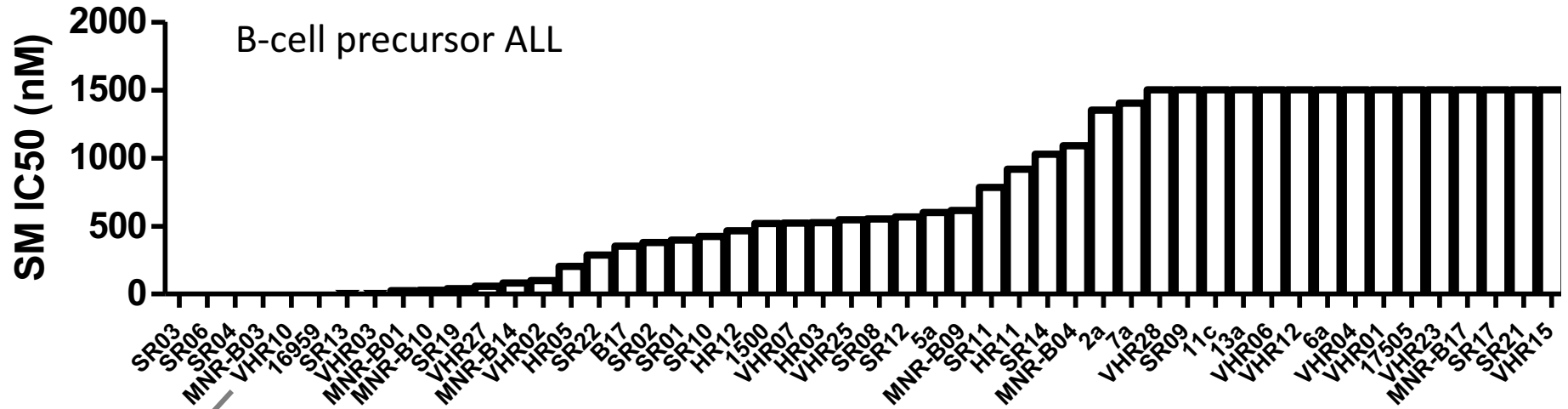
● TCF3-PBX1

● TCF3-HLF

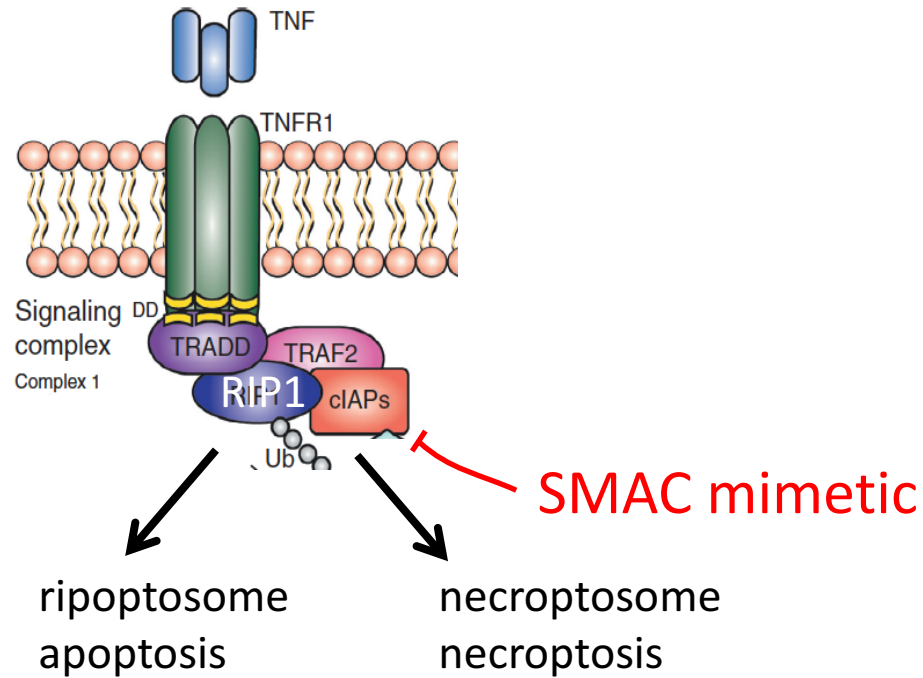
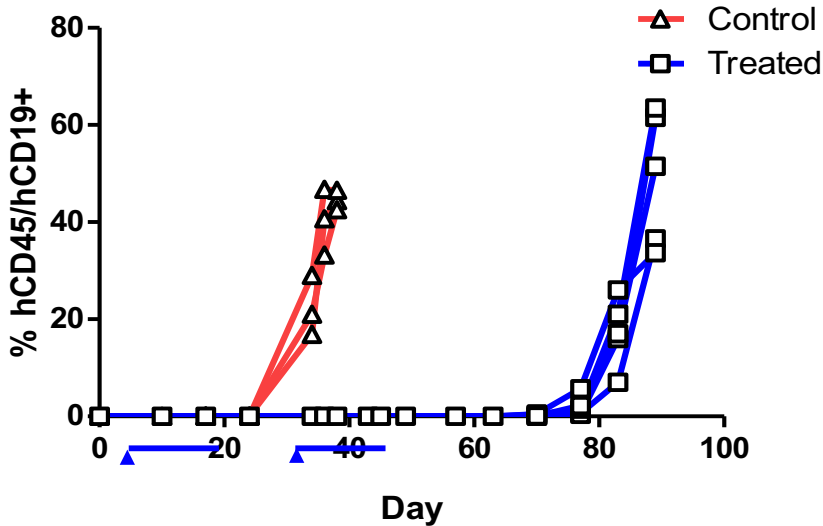
3 Drug mini induction + VEN controls TCF3-HLF ALL



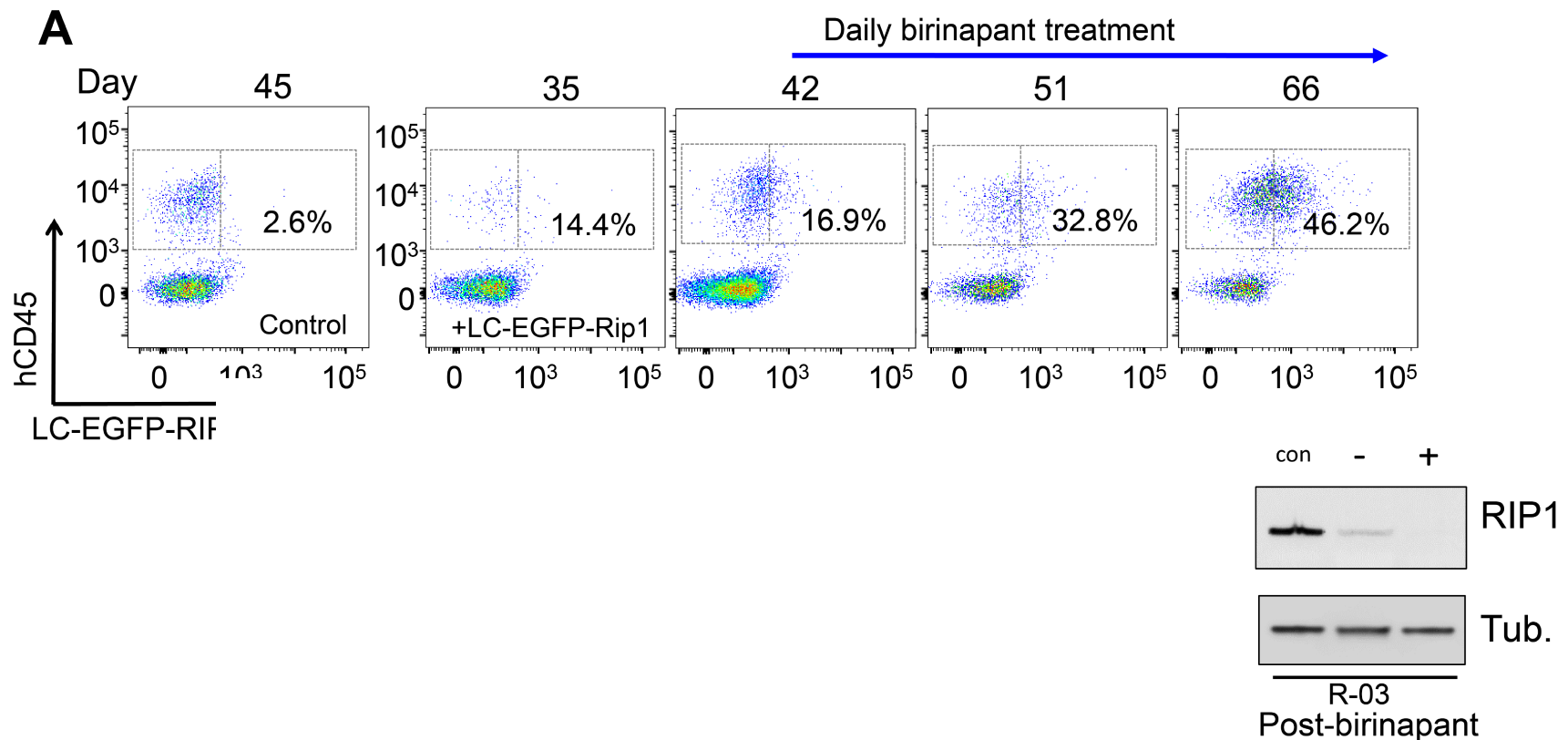
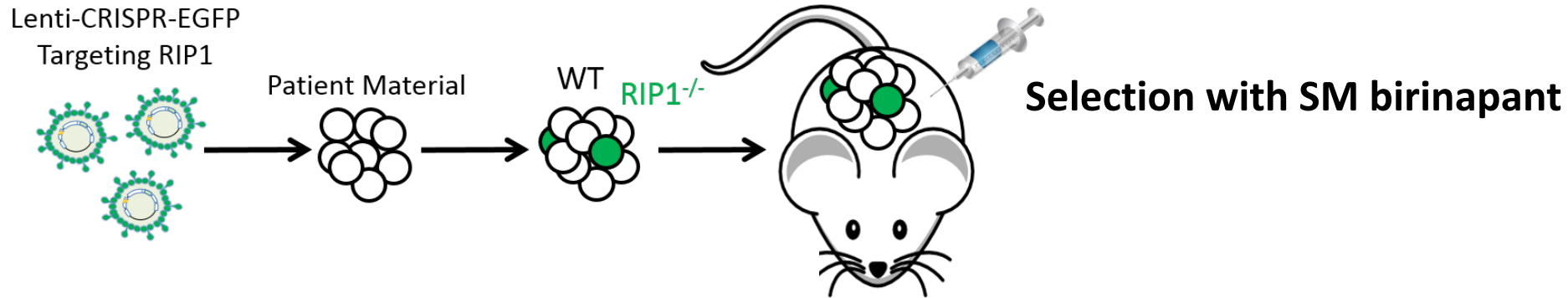
Selective activity of the SMAC mimetic birinapant



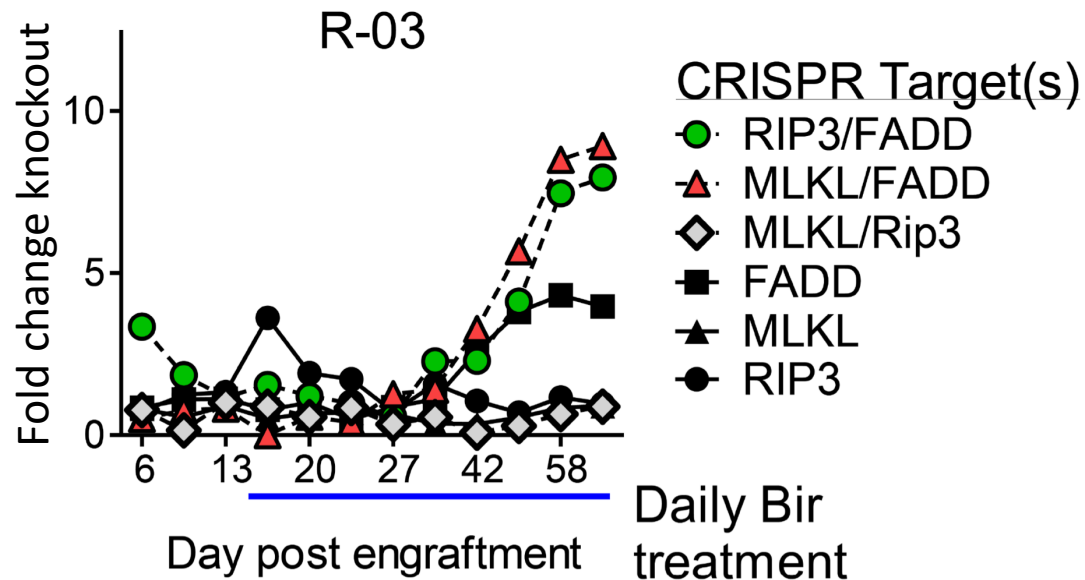
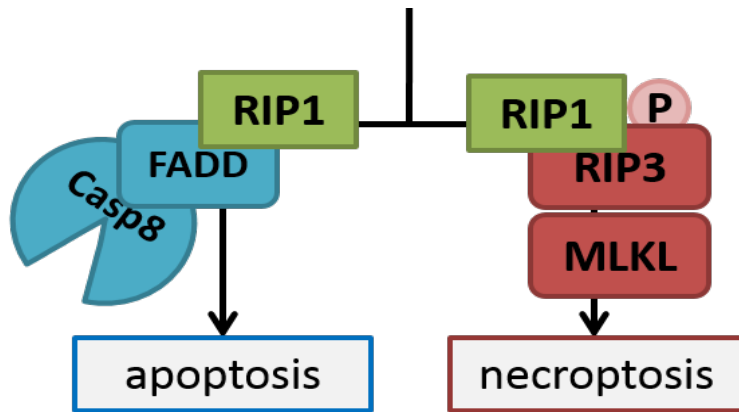
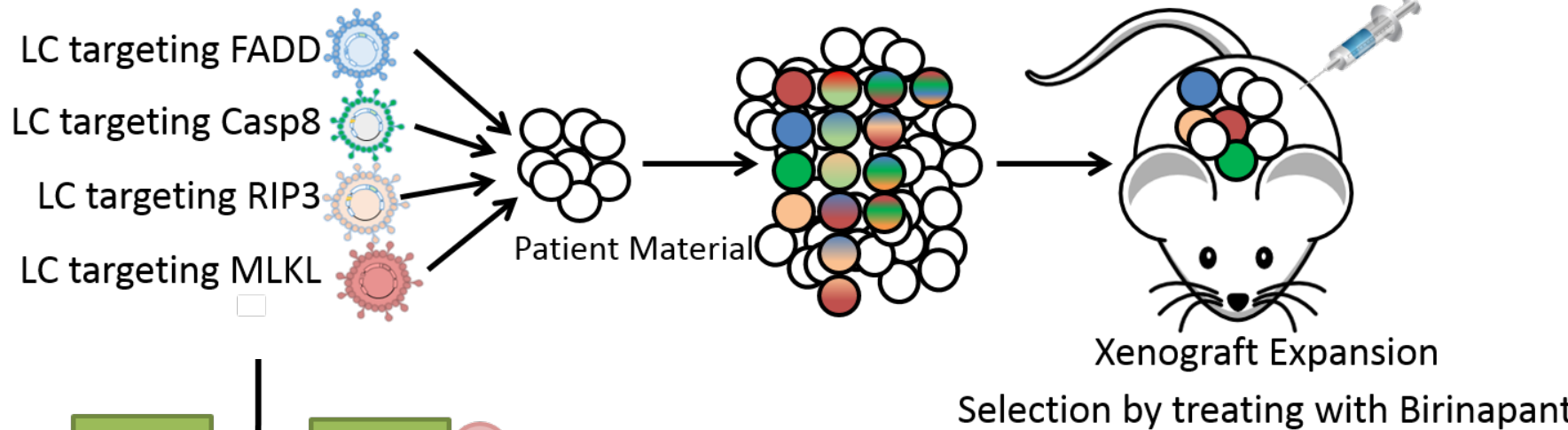
De novo resistant (high MRD load)



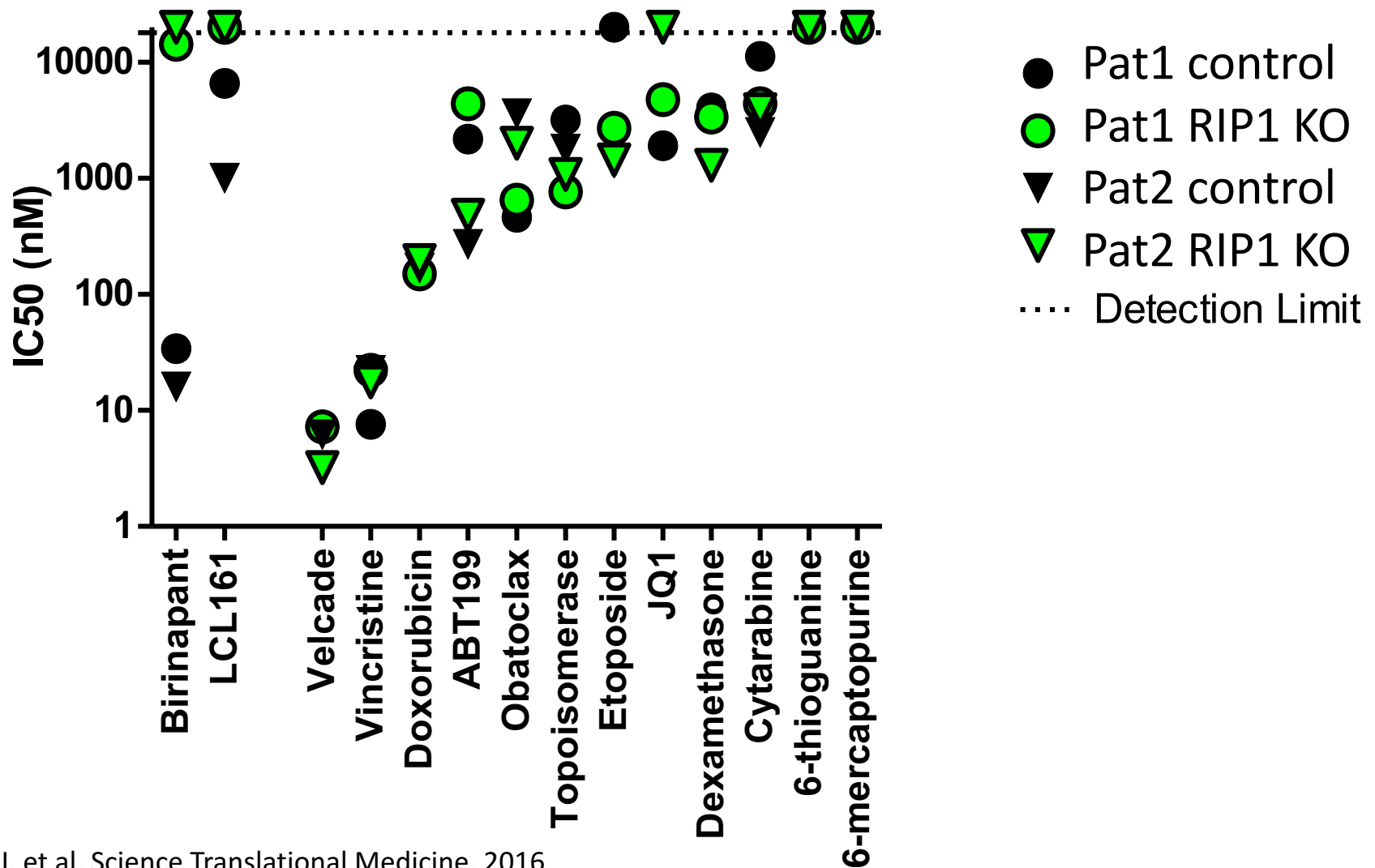
Functional genomics: lentiviral CRISPR to target RIP1



SM: simultaneous apoptosis and necroptosis



RIP1 dependent death is not exploited by current chemotherapeutic agents



Preclinical modeling with PDX:

- Modeling and definition of clinically relevant cohorts
- Mechanistic studies in the real cellular context
- Ex vivo screening, drug activity profiling, functional omics
- Proof of concept for new combination in vivo
- Correlation with clinical activity of new agents



Leukemia Research Group

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