

## CELL DEATH AND LEUKEMIA

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**KEYWORDS** — Childhood leukemia, drug resistance, cell death pathways, signal transduction, apoptosis, necroptosis

### SUMMARY & MISSION STATEMENT

The focus of our work is to understand the molecular mechanisms that drive drug resistance in childhood leukemia, and to develop new treatment approaches to eradicate resistant disease.

### OVERVIEW

One hallmark of drug resistance in cancer cells is their failure to undergo apoptosis upon chemotherapy. An attractive idea to reactivate apoptotic programs is the inclusion of new agents into current treatment regimens. For instance, inhibitors of the anti-apoptotic BCL2 proteins are promising candidates to lower the apoptotic threshold. We could show impressive activity of the BCL2-specific BH3 mimetic venetoclax in distinct subgroups of resistant primary ALL. The activation of other, non-apoptotic cell death programs represents an alternative strategy. We have discovered that an alternative non-apoptotic cell death pathway named programmed necrosis or necroptosis specifically killed drug resistant leukemia cells. Using a comprehensive xenograft model of pediatric ALL, we have developed specific CRISPR/Cas9-based tools to identify the molecular players that control necroptosis, apoptosis and also further cell death modalities. We now aim to understand the signals that regulate different cell death pathways including necroptosis, and to develop strategies to establish predictive biomarkers that allow selection of patients for efficient clinical translation of such approaches.

## SELECTED CANCER RELATED PUBLICATIONS

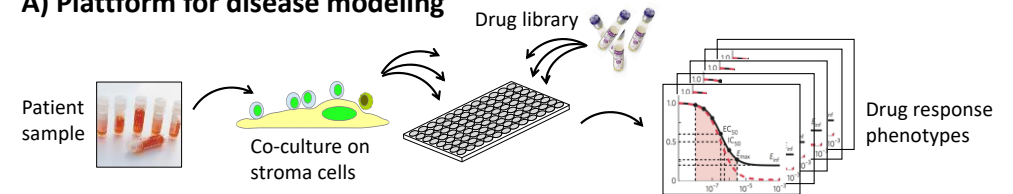
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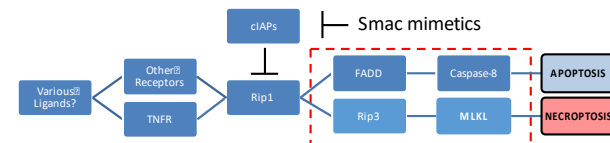
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### A) Plattform for disease modeling



### B) Necroptosis for anti-cancer therapy



- A) Plattform that we have developed to identify drug response patterns in individual leukemia patients
- B) Necroptosis represents an alternative cell death mechanism that could be exploited in drug resistant disease.