Development of a high-throughput screening platform to identify new therapeutic agents for Medulloblastoma Group 3

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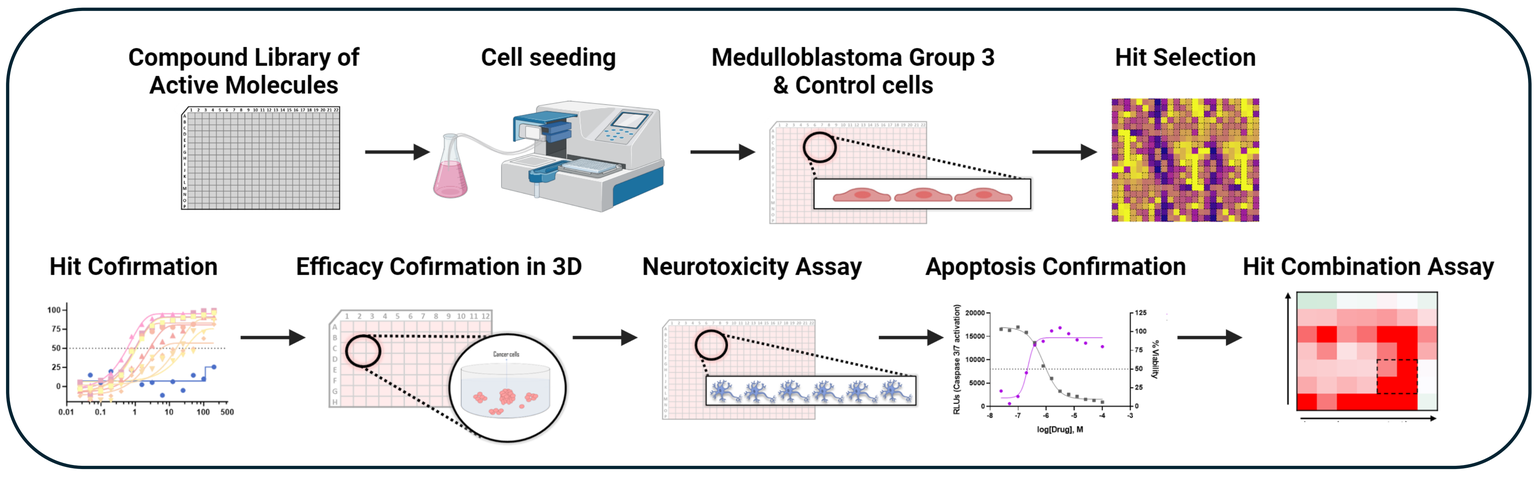
Overview

We have developed a unique screening platform: PBT-SCREEN

PBT-SCREEN is specifically designed to identify new therapies for **Medulloblastoma Group 3** (MB G3).
The platform incorporates optimized and validated 2D and 3D **efficacy** and **toxicity** models, that account for tumor heterogenicity, limited efficacy and unacceptable toxicity from the very early stage of drug discovery.



Introduction

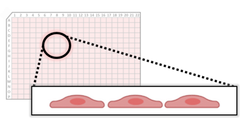
Medulloblastoma Group 3 (MB G3) is the most frequently occurring malignant pediatric brain tumor. Accounts for **20% of all primary brain tumors (PBT)** and almost **10% of all pediatric cancer deaths.**

⚠ NO SPECIFIC TREATMENT ⚠

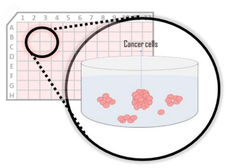
Challenge: difference with adult cancers, highly heterogeneous tumors.

Methods

DISEASE MODELS



8 MB G3 TUMOR CELL LINES

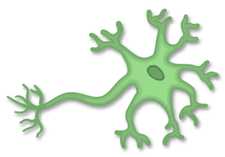


3D CULTURE
REPRESENTATIVE TUMOR CELL LINE

GENERAL TOXICITY

FIBROBLASTS (BJ)

NEUROTOXICITY



NEURONS
DIFFERENTIATED FROM LUHMES

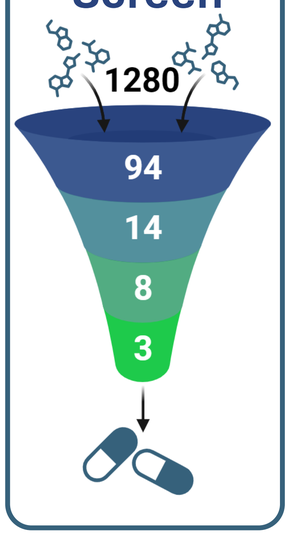
Conclusions

Identified 8 HITS targeting MB reported targets, several approved in clinical trials for PBTs including MB, and 3 SYNERGISTIC COMBINATIONS, 1 of them in clinical trials.

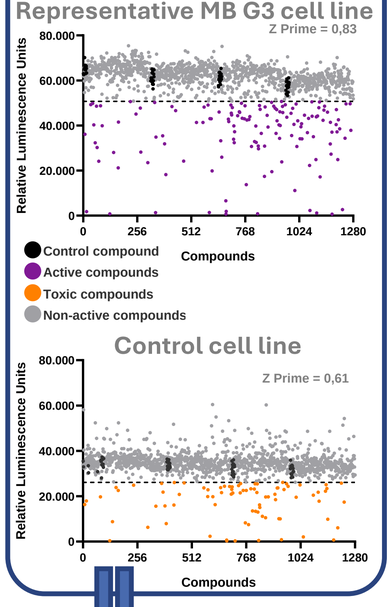
Results

PBT–SCREEN Validation: HTS CAMPAIGN

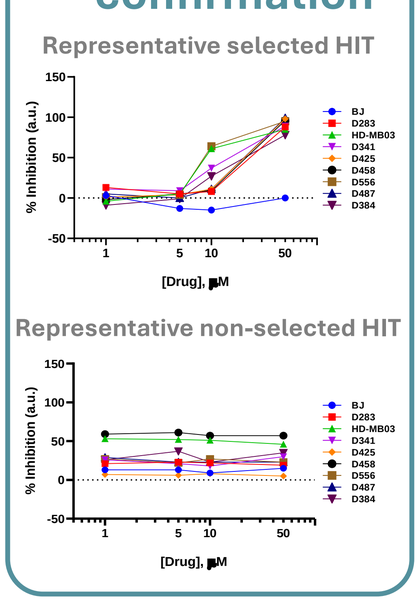
Compound Library Screen



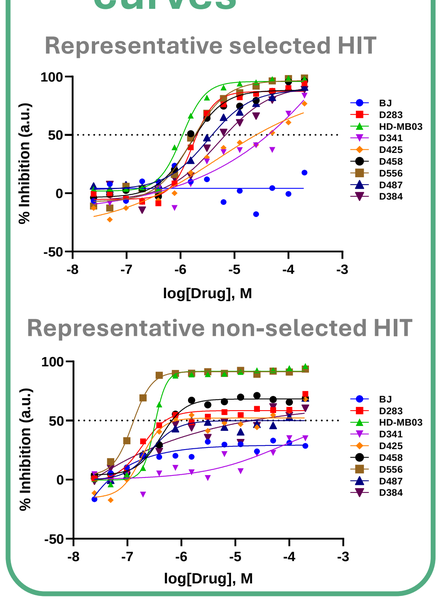
1.- HTS



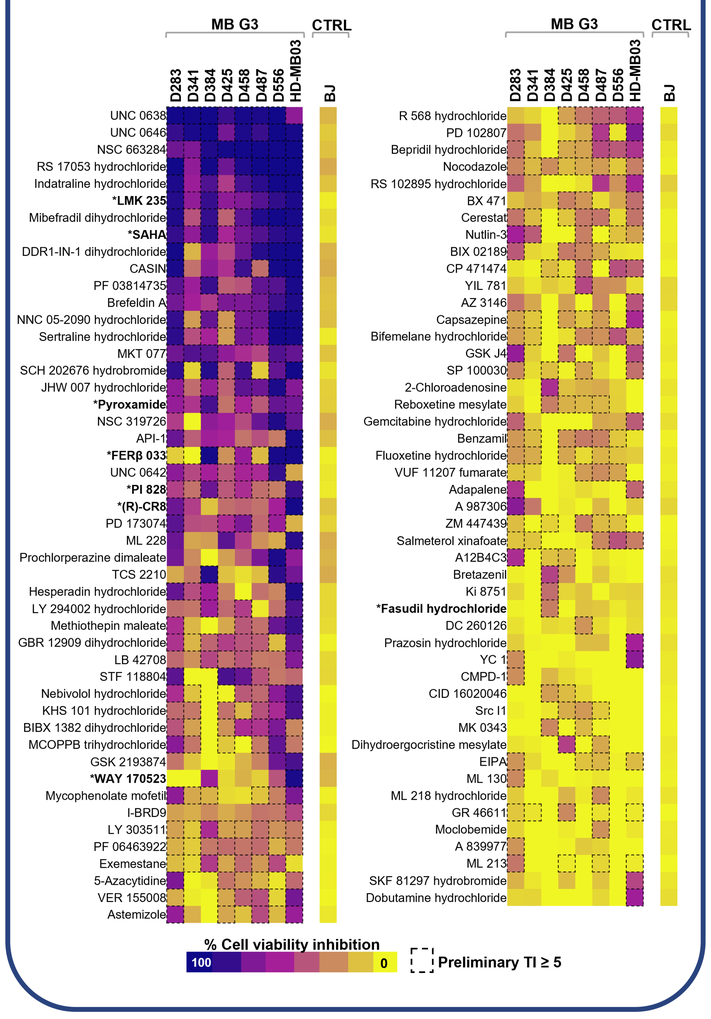
2.- Hit confirmation



3.- Dose-response curves

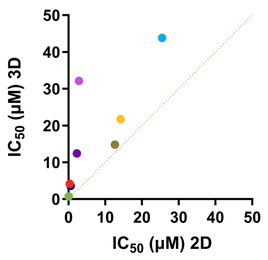


Hit Identification:



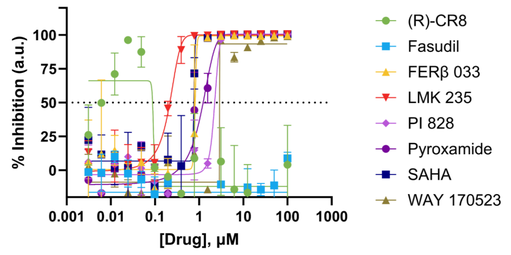
4.- Confirmation Assays

3D Efficacy:

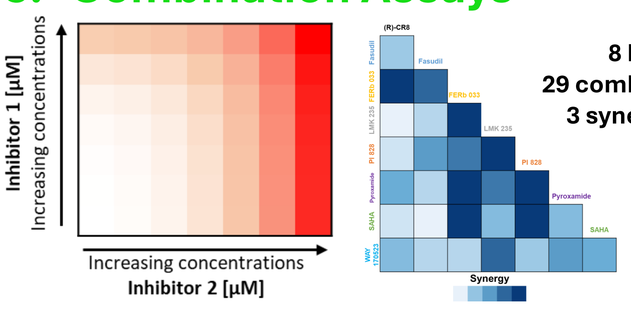


	3D IC_{50} (µM)	2D IC_{50} (µM)
(R)-CR8	0.71	0.05
Fasudil	43.82	25.45
FERb 033	21.72	14.20
LMK 235	4.2	0.36
PI 828	32.12	2.84
Pyroxamide	12.41	2.26
SAHA	3.61	0.61
WAY 170523	14.8	12.65

Neurotoxicity:



5.- Combination Assays



8 hits
29 combinations
3 synergistic

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