

Application of patient tumors derived Tumor Ecosystem platform for the development of novel HDAC inhibitor in solid cancers

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Abstract

Histone deacetylases (HDAC) are deregulated in many human cancers and a few HDAC inhibitors (HDACi) have been shown to be effective in patients with rare leukemia. However, clinical responses are not very promising for many HDACi in solid cancers. There is an urgent need to develop best in class HDACi with higher therapeutic index in solid cancers.

At present less than 10% of anti-cancer drugs entering phase 1 clinical trials are successful in getting market approval. There are many factors for this poor clinical success for oncology therapeutics, and one of them is the lack of robust preclinical model driving clinical development. Cancer is a very heterogeneous disease and many of the present preclinical models do not represent this heterogeneity. As a result, while a candidate drug may appear good in present preclinical models, they often fail to make the cut in clinical development.

To circumvent this critical problem, we have developed a robust TE (Tumor Ecosystem) platform technology using patient tumors, autologous ligands, and immune compartments from the same patients. Our TE platform preserves patient tumor heterogeneity along with other functional and genomic markers and immunogenic cytokines. Efficacy of drugs exposed to the patient's tumor tissue in our TE platform is assessed by as many as 17 orthogonal assays within a week. The results from these assays are converted into a single predictive score called the "M-Score," and it has been clinically validated using FDA approved drugs in > 1,800 patients across multiple solid and hematological cancers. Our data shows that TE platform predicts treatment outcome of FDA approved drugs in clinical setting with very high sensitivity and specificity.

We have the opportunity to use this platform technology to identify cancer indications and appropriate combinations for MIT-1102, a novel HDACi that exhibited potent histone deacetylase inhibitory activity. Our data further indicates that the anti-tumor efficacy of MIT-1102 is superior to Vorinostat and comparable with Pracinostat (SB-939) while being more tolerable than Pracinostat. Results indicated the superiority of MIT-1102 when combined with SOC in a subset of patients with gastric and pancreatic cancers. We are also using different omics to identify markers associated with response in those tumor types. MIT-1102 has the potential to be more effective in a defined patient population than other molecules in this class. In summary, we have identified a novel, potent HDACi with drug-like properties, and identified the correct cancer indications and most effective combinations using TE platform Technology.

Objectives

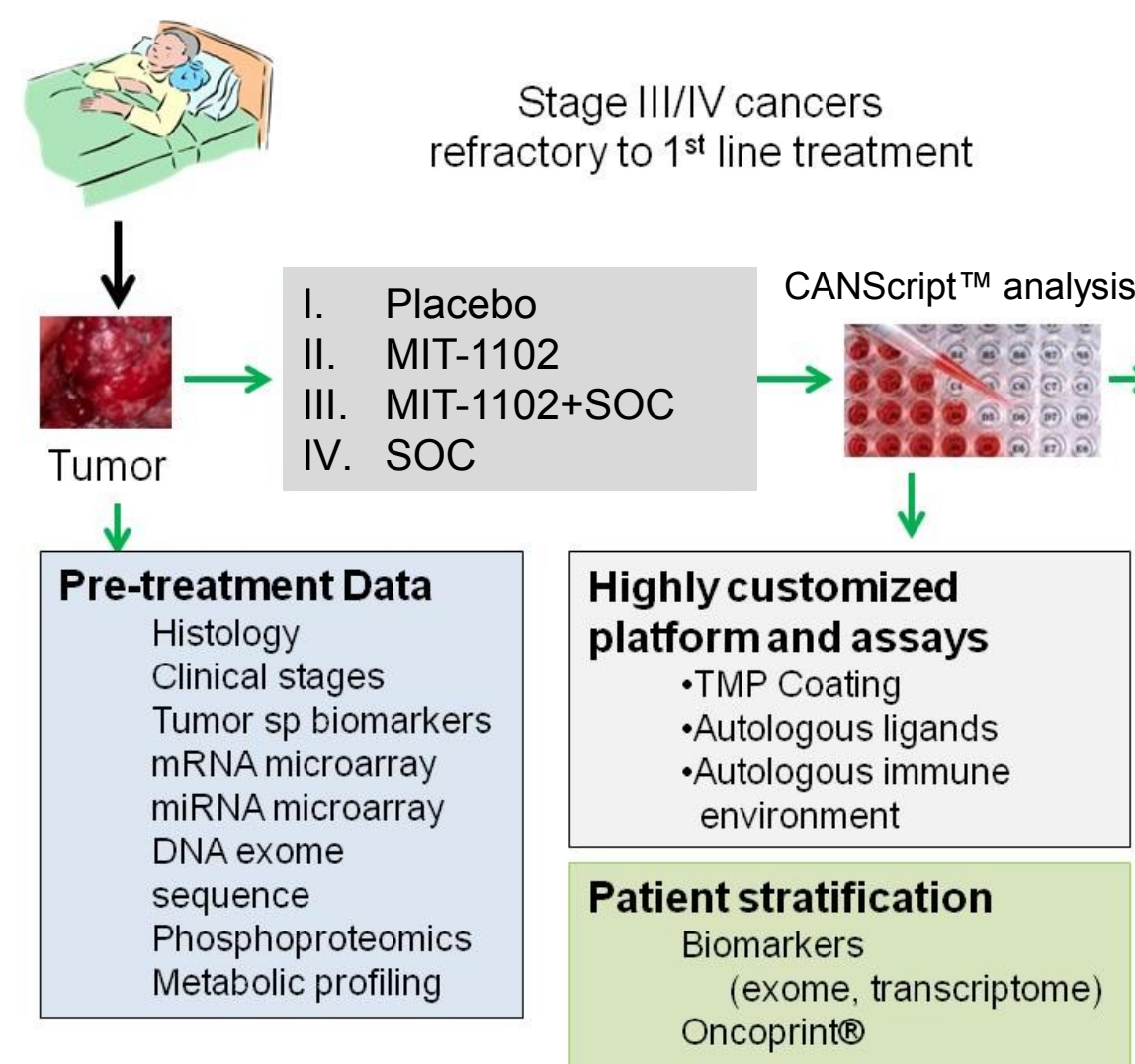
- Identification of best in class HDAC inhibitor for solid cancer
- Application of novel CANScrip™ technology for faster and cheaper clinical development
- Mechanism of sensitivity and resistance of HDAC inhibitor in solid cancer

Results

Parameters	Value
IC ₅₀	3nM
GI ₅₀ (HCT 116 cell)	0.1µM
IC ₅₀ in cancer cell panel	1.89µM
Water solubility	5.1(mg/ml)
CYP inhibition	7
CL	681
C _{max}	1313
AUC	586
Oral bioavailability	9.8
TGI	73%

	MIT-1102	Belinostat	Vorinostat	SB-939
Company	Mitra Biotech /Anthem	Topotarget	Merck	SBio
HDAC inhibition in Hela nuclear extract (IC ₅₀ , nM)	3	27	78	24
GI ₅₀ , HCT-116	0.1 ± 0.0	0.2	2.2 ± 0.0	0.53 ± 0.24
Cytotoxicity tumor cell panel mean IC ₅₀ (µM)	1.89	NA	5.22	NA
Efficacy in HCT-116, TGI at dose (mg/kg), p.o. qd x 21	73% (150 mpk)	42% (200 mpk)	59% (200mpk)	97% (100 mpk)

MIT-1102 is a novel best in class small molecule



Outline of CANScrip™ technology for MIT-1102 development

Assays:

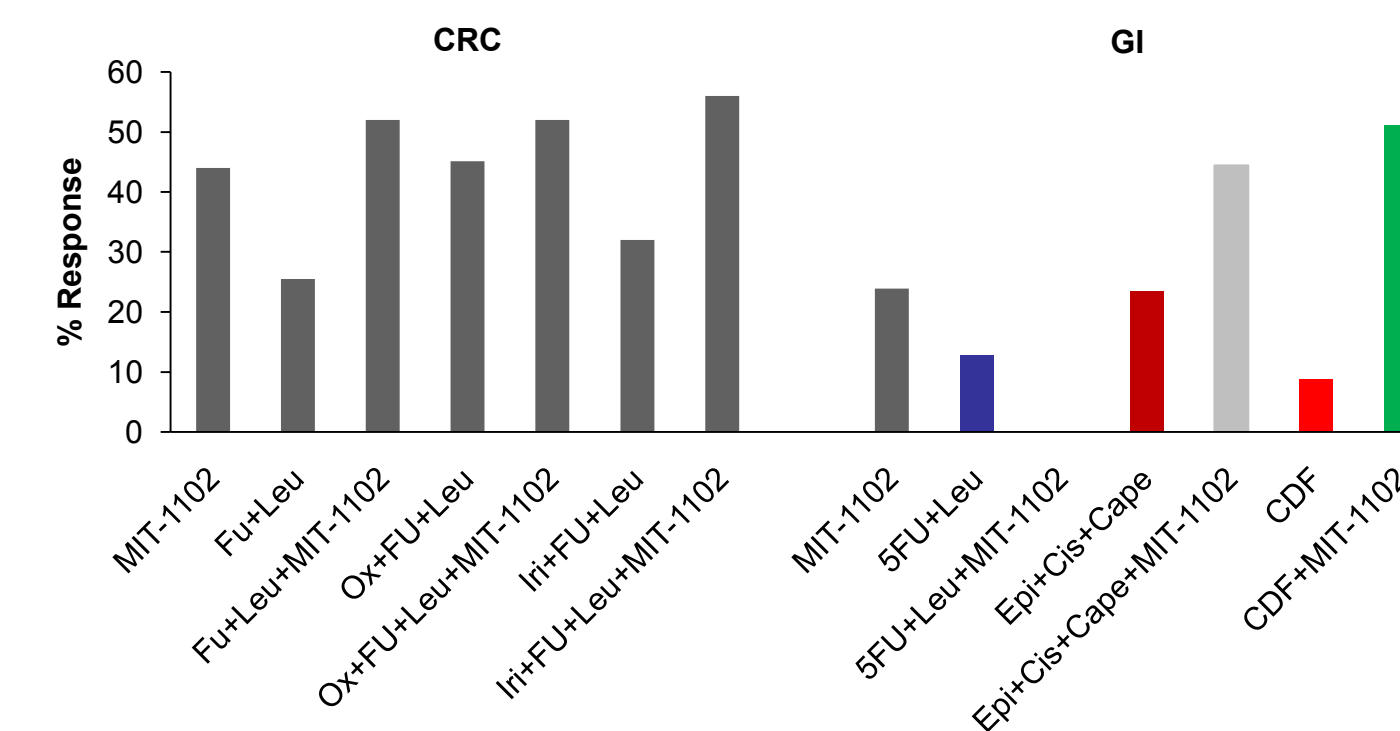
1. Kinetic Assays:

- Cell proliferation (ATP uptake)
- Tumor Metabolism (Glucose, galactose, pyruvate etc)
- Apoptosis (Caspase 3 & Caspase 8)
- Cell death (LDH release)

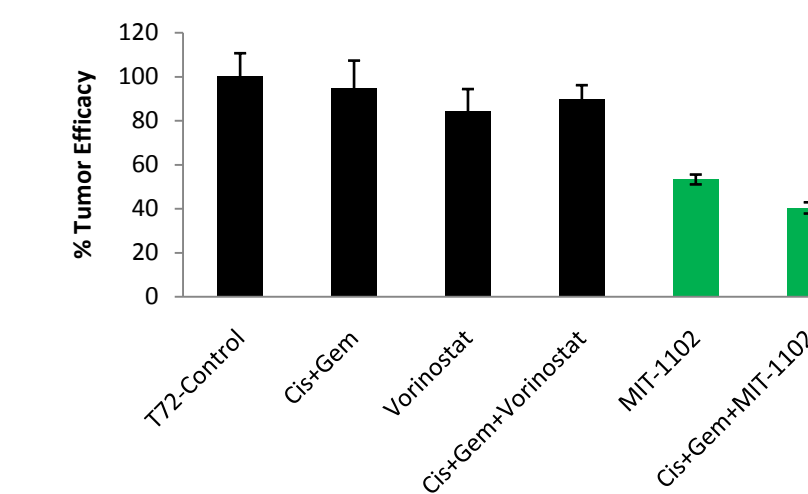
2. End Point Assays:

- Cell Viability (WST)
- Cell Proliferation (Ki-67, ATP uptake)
- Apoptosis (Caspase 3 & Caspase 8)
- Cell death (LDH release)
- Tumor Angiogenesis (CD31, VEGF etc)

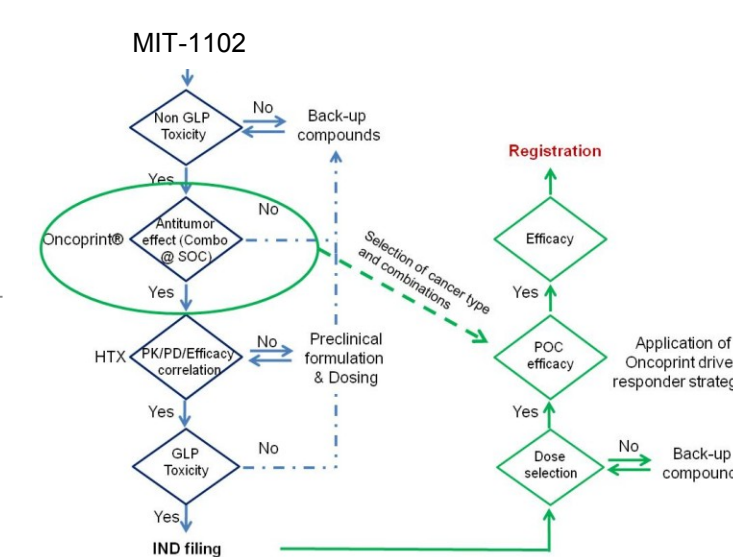
Results



CANScrip™ technology has been applied to identify best cancer indication and best SOC combination using more than 400 patient derived tumors in four cancer indications



Primary patient tumor derived data suggests MIT-1102 is superior than Vorinostat®



Development strategy of MIT-1102

Summary

- Identified best in class pan-HDAC inhibitor
- Applied CANScrip™ technology to identify best cancer indication, optimal combination and patient profile for clinical development of MIT-1102
- Expected FIM at the end of 2013