Synergistic enhancers of TRAIL-mediated apoptosis: A quantitative parallel comparison of TRAIL-small molecule synergies using cHTS™

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Abstract

TRAIL-resistant apoptotic inducing ligand (TRAIL) is an extensively studied cytokine known to selectively induce apoptosis in a variety of cancer cell lines through the activation of the extrinsic apoptotic signaling cascade. Although TRAIL is regarded as a potentially useful clinical therapeutic, many TRAIL-resistant cell lines have been discovered. While the mechanisms of TRAIL resistance are diverse, CombinatoRx scientists and collaborators have demonstrated that TRAIL combination with various chemotherapy agents elicits synergistic antiproliferative activity, most notable of which is the large quantitative correlation of TRAIL sensitivity is parallel to the determination of the most efficacious TRAIL-drug combinations. Using CombatoRx high-throughput screening (cHTS), we have compared various TRAIL-small molecule drug combinations to determine the resulting synergies to identify a subset of compounds that synergistically enhance TRAIL-mediated apoptosis. We show that these drug combinations can reconstitute the targeted pathway and sensitize the TRAIL-sensitive line, two compounds are capable of overcoming TRAIL resistance. Of the drug classes studied, certain classes and topoisomerase poisons show utility in overcoming TRAIL resistance while maintaining a degree of selectivity toward NSCLC lines. These drug pairs, in combination with TRAIL, circumvent resistance and promote synergy. Therefore, through the identification of potent Partners, these data demonstrate the utility of using cHTS to quantitatively compare TRAIL-small molecule combinations to select the most efficacious drug-drug combinations that circumvent a common mechanism of TRAIL resistance.

Combination High Throughput Screening

- Allows the discovery of novel multi-target therapies and co-therapies
- Characterizes complex pathways of drug synergy and antagonism
- Reveals synthetic response surfaces that are indicative of underlying pathway connectivity
- Guides clinical co-therapy development decision making

Selection of Synergies

- Selects the most efficacious drug-drug combinations
- Identifies potential co-therapy combinations

Methods

**Screen Rationale:**

- Classic mechanisms of TRAIL resistance are observed in various tumor cell lines across various issues
- Many drugs and probes have been reported to synergize with TRAIL, and overcome TRAIL resistance by modulating the extrinsic and intrinsic apoptotic signaling cascade

**Data Interpretation:**

- From the known TRAIL synergies, which drugs promote the largest synergistic effects in NSCLC?
- Can any of these drug-induced synergies overcome TRAIL resistance?
- Are any of these drug-induction synergies selective with respect to intrinsically cell types?

**Screening System:**

- Cytostatic Potentiation
- Allows the discovery of novel multi-target therapies and co-therapies
- Reveals synthetic response surfaces that are indicative of underlying pathway connectivity
- Guides clinical co-therapy development decision making
- Selects the most efficacious drug-drug combinations
- Identifies potential co-therapy combinations

**References**


**Conclusion:**

- High-resolution combination of life
- Cytostatic Potentiation
- Synergy profile of a null p53 cell line (H1299) most closely resembles A549 which is p53 competent
- Synergy in H1295 is not due to p53 loss of function but PTEN
- Synergistic activation of MAPK/ERK in H1295 may play a role in shaping co-stimulatory synergy topology
- Cyp3a 3 dependent apoptosis in H1295 shows that extrinsic apoptotic signaling is reestablished