Hierarchical Clustering of Growth Response Patterns (GI50s) for investigational oncology agents

Abstract: We have acquired >400 investigational oncology agents, comprised primarily of targeted small molecules currently in clinical and/or preclinical evaluation. An oncology investigational new agent (INAA) is a potential therapeutic agent, and the NCI-60 human tumor cell line panel is an ideal community-wide tool to further understanding of the disease targets of new agents. The panel consists of 60 cell lines from five tumor types, and is extremely well characterized at the molecular level, with both in-house and novel sequenced characterization, including genome assays for mutations, snps, copy number variation, methylation, mRNAs, microRNAs, and proteins. Each drug is tested against the panel at multiple drug concentrations, including IC50, GI50, IC90, GI90, and growth inhibition, resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells.

Growth inhibition of 50% (GI50) is calculated from \[
\frac{(Ti-Tz)}{(C-Tz)} \times 100 = 50
\]
where \(Ti\) is the compound concentration measurement (time zero, \(Tz\)), \(C\) is control growth, and \(Ti\) is test growth. The % growth is calculated.

For staining, sulforhodamine B (SRB) solution (100 µL) at 0.4 % (w/v) in 1 % acetic acid is added to each well, and plates are diluted and measured for staining.

For compound addition, the solution is diluted to twice the desired final concentration with complete medium, 1 log hours after plating densities ranging from 5,000 to 40,000 cells/well.

Methods and Materials: We have acquired >400 investigational oncology agents, comprised primarily of targeted small molecules currently in clinical and/or preclinical evaluation. An oncology investigational new agent (INAA) is a potential therapeutic agent, and the NCI-60 human tumor cell line panel is an ideal community-wide tool to further understanding of the disease targets of new agents.

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Summary: The leukemia cell line SR displays high sensitivity to all ARA inhibitors, including crizotinib, NVP-ARC-105, LDK378, TLG-177, TAK-582 and CH-5424802. High expression of ARA is known to be associated with the SR line. In addition, the content is enabled with high expression of ARA and CASP8, suggesting the involvement of an unrelated mechanism.

References: