THE SHORT ANSWER

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Correlating chemical sensitivity and basal gene expression reveals mechanism of action

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The scenario below is completely fictional but highlights real strategies including the one introduced in this paper.

Congratulations. Your phenotypic screen yielded a compound that kills this cell line.

YES! I'VE CURED CANCER!

What is the target of your compound? You will need to know that.

MISSION ACCOMPLISHED

WHAT'S THAT NOW?

You've identified your target. Well done. But does it kill any other cell lines?

ONE YEAR LATER...

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ARGHH1 MUTANT

Why don't you try giving the compound to 823 different cancer cell lines from various lineages (ie. skin, lung, etc.) and figure out how sensitive each one is. May help predict patient response.

UNRESPONSIVE

HIGHLY SENSITIVE

ONE BOX = ONE CELL LINE

OKAY, SO LUNG CANCER CELLS ARE PARTICULARLY SENSITIVE. BUT WHY IS THERE SO MUCH VARIABILITY?

Thanks to some massive parallel sequencing efforts there is a lot of sequence information on these cell lines. You could narrow down to cell lines with genetic variants of ARGHH1.

NOW I'M REALLY CONFUSED. I UNDERSTAND THAT DIFFERENT MUTATIONS SHOULD YIELD VARIABLE SENSITIVITY, BUT HOW CAN CELL LINES WITH THE SAME ARGHH1 MUTATION STILL RESPOND TO THE COMPOUND SO DIFFERENTLY? WHAT ELSE IS HAPPENING IN THERE?

SENSITIVITY OF ARGHH1 MUTANT CANCER CELL LINES

What if you could correlate the sensitivity of these cancer cell lines with up or down-regulation of particular genes? Not as a *result* of treatment, I'm talking about *basal* transcription levels. If a gene's expression correlates to sensitivity, it may play a role in drug's mechanism of action.

BASAL TRANSCRIPT LEVELS (RELATIVE TO ALL CELL LINES)

ABOUT 19,000 GENES (BARS ON EACH GRAPH)/CELL LINE

823 CELL LINES

THIS OUTLIER GENE, PTOOEY, ENCODES AN EFFLUX PUMP THAT EXPELS SMALL ORGANIC COMPOUNDS FROM THE CELL, SO WHEN IT IS LOW, THE COMPOUND IS MORE EFFECTIVE.

CORRELATION STRENGTH

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HI, FDA? I THINK WE'RE READY. MMM HMMM... WHAT'S THAT NOW?