A New Method to Measure Serum Drug Levels to Improve the Safety of Cancer Therapies

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It is crucial that cancer patients receive the proper medication dosage. Too high of a dose can be toxic; too low of a dose will not effectively kill cancer cells. Accurate dosing requires a method to monitor drug levels to guide dose adjustment. However, the vast majority of drugs do not have such a method available. To address this, I developed a new method for drug measurement, a "modified thermal shift assay." In this assay, a probe derived from a drug's intended protein target undergoes thermal stabilization upon drug binding. I provided proof of concept that this method can measure the levels of the drug trametinib, a MEK1 inhibitor used to treat melanoma. However, due to the high affinity of MEK1 binding to trametinib, the initial formulation of this assay was highly sensitive but also saturated at low drug concentrations. To address this, I have here modified this assay by expressing and purifying a series of mutant MEK1 protein probes with reduced trametinib binding affinities. Utilization of these mutant MEK1 probes in parallel with wild type MEK1 greatly increased assay dynamic range and precision. The modified assay displays a <12% coefficient of variation across over 5 logs, characteristics superior to most current clinical drug monitoring assays. This assay only requires widely available equipment, is simple and rapid to conduct, and can be easily modified to measure other drugs. Thus, this approach could provide the first generalized method for clinical measurement of drug concentrations to guide dosing and improve drug safety.

Awards Won:

The Knowledge Society: 3rd Place