**S2. Model-based computation of drug synergy index**

Different drug synergy scores were used to numerically evaluate drug combination effect: the Chou-Talalay’s Combination Index, (CI score) [1], Bliss Independence (BI score) (28) and Coefficient of Drug Interaction (CDI score) (29). These are explained below.

The coefficient of drug interaction (CDI) is a simple model to the synergistically inhibitory effect of the drug combination [2,3]. CDI is calculated as follows: CDI=*E12*/(*E1*×*E2*), where *E12*is a normalized biological response (e.g., cell survival) at combination treatment of Drug A and Drug B by its control group, and *E1* and *E2* are the response measured at single drug treatment, respectively. CDI <1, = 1 or >1 indicates that the drugs are synergistic, additive or antagonistic, respectively. For instance, if cell survival is inhibited 50% by a combined drug treatment, and 30% and 20% inhibited by single drug treatment, respectively, then we have CDI=(1-0.5)/((1-0.3)×(1-0.2))=0.89, implying that the combined treatment has a synergistic effect.

Bliss Independence (BI) is another statistical model to assess the combination efficacy of two drugs based on the assumption that the individual drugs do not directly interfere with each other and drugs contribute to a common result [4,5]. The combined activity () at concentration C1 and C2 can be predicted using the complete activity of probability theory [5] as

BI is defined as follows: BI=/, where denotes the observed combined effect at concentration C1 and C2. For instance, if cell survival is inhibited 50% by a combined drug treatment, and 30% and 20% inhibited by single drug treatment, respectively, then we have and , thus BI=0.44/0.5=09. BI <1, = 1 or >1 indicates that the drugs are synergistic, additive or antagonistic, respectively.

The combination index (CI) is the preferred additive reference model devised by Loewe and generalized by Chou and Talalay for analysing combination effects based on the principle of mass action [4,6]. The central assertion of this model is that a compound must be addictive when combined with itself [4]. *CIx* for quantification of synergism or quantification for two drugs is calculated as follows:

+

where (*Dx*)1 is the concentration of *Drug 1* alone that inhibits a system *x*%, and (*Dx*)2 is the concentration of *Drug 2* alone that inhibits a system *x*%. (D)1 and (D)2 are the concentrations that inhibits x% in combination. The (*Dm*)*i* and *mi*, *i*=1,2 values can be determined by fitting the median-effect equation (that describes dose-effect relation) of the individual compound to measured experimental data [6].

**SUPPLEMENTARY REFERENCE**

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