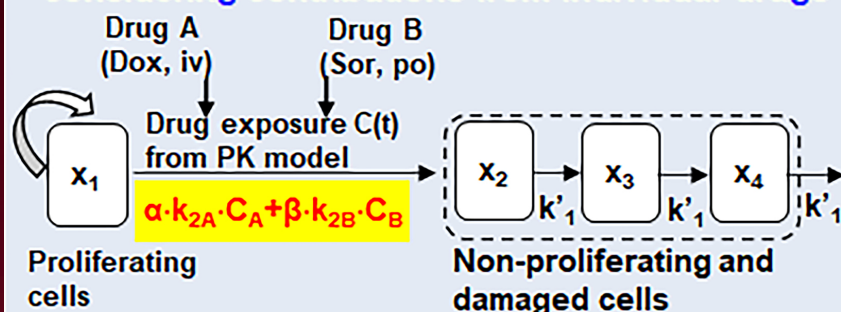# The Journal of
PHARMACOLOGY
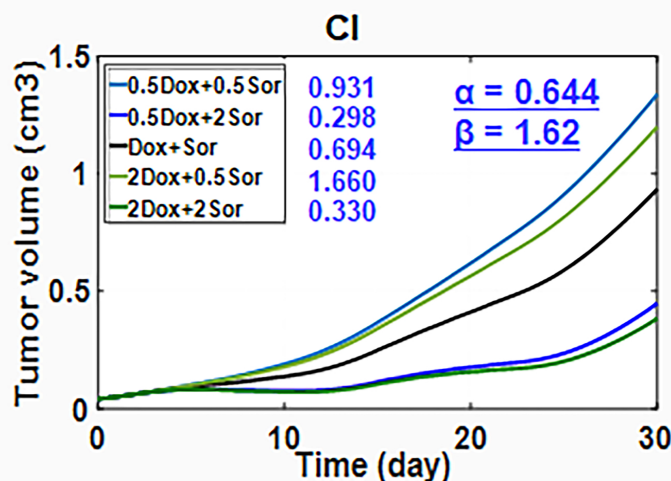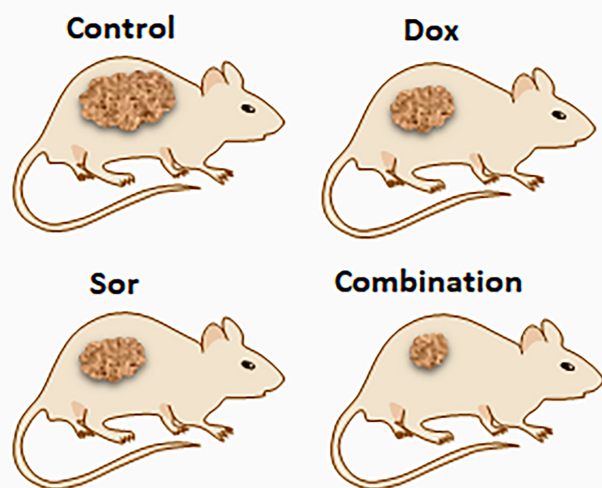## And Experimental Therapeutics

New PK-PD model for combination therapy by considering contributions from individual drugs

Drug A (Dox, iv)   Drug B (Sor, po)

Drug exposure C(t) from PK model

$\alpha \cdot k_{2A} \cdot C_A + \beta \cdot k_{2B} \cdot C_B$

x_1

Proliferating cells

$x_2 \xrightarrow{k'_1} x_3 \xrightarrow{k'_1} x_4 \xrightarrow{k'_1}$

Non-proliferating and damaged cells

Combination Index (CI) Method is integrated into the predictive PK-PD model to critically define *in vivo* pharmacologic synergism.

- CI > 1, antagonism
- CI = 1, addition
- CI < 1, synergism

Control   Dox

Sor   Combination

CI

	CI
0.5Dox+0.5Sor	0.931
0.5Dox+2Sor	0.298
Dox+Sor	0.694
2Dox+0.5Sor	1.660
2Dox+2Sor	0.330

$\alpha = 0.644$
$\beta = 1.62$

Tumor volume (cm3) — Time (day)

The new model 1) offers one definitive prediction of the responses to drug combinations, and 2) discloses a much greater contribution from sorafenib (Sor) to tumor growth inhibition than co-administered doxorubicin (Dox).