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LETTER TO THE EDITOR

Comment on the Article "Theoretical Analysis of Interplay of Therapeutic Protein Drug and Circulating Soluble Target: Temporal Profiles of 'Free' and 'Total' Drug and Target"

Peiming Ma

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In their article titled "Theoretical Analysis of Interplay of Therapeutic Protein Drug and Circulating Soluble Target: Temporal Profiles of 'Free' and 'Total' Drug and Target", Tang and Prueksaritanont assumed a rapid binding (RB) model under the RB assumption (equation (1)) and described features of the model. I would like to point out an area of inaccuracy in their work.

A major conclusion of the article is that the ratio of the total and the free drug concentration (C_{tot} and C, respectively) at terminal phase increases as the steady-state free target concentration (R_{ss}) increases. In fact, they stated "predictions by the model showed a linear relationship between R_{ss}/K_D and C_{tot}/C, which is outlined in Fig. 3b", where K_D is the dissociation constant, and in the figure notes "the results indicate that the ratio of R_{ss}/K_D determines the magnitude of the difference between C_{tot} and C at terminal phase".

However, it is unclear if the authors realized that the above statement and Fig. 3b were a direct consequence of making the RB assumption. Indeed, the equation $C_{tot}/C = 1 + R/K_D$ is equivalent to the RB assumption (equation (1)), where R is the free target concentration. At steady state and the terminal phase an exact relationship bears out (i.e., $C_{tot}/C = 1 + R_{ss}/K_D$). This is the reason that Fig. 3b is a line given by $y = x + 1$. Therefore, no simulation or prediction is needed for the statement. The statement is not a 'result' but part of the initial assumption of the RB model as a simplification of the system.

P. Ma (✉)
GSK Research and Development, Shanghai, China
e-mail: peiming.p.ma@gsk.com