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Rules of thumb for maximum percent tumor accumulation

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Dear Editor

During our previous investigations, we have obtained some observations on tumor accumulation and rationalized them using a model similar to that employed by a chemical engineer when considering a reactor. The model is explained, and the rationalized observations are summarized as rules of thumb. I hope these rules are of interest to my fellow researchers.

1. The “reactor” model

A fraction (f) of the cardiac output (F in mL/min) is continuously delivered into a tumor. The blood flow carries a tumor-targeting agent at a concentration of C_{blood} (in g/mL or any convenient unit), deposits a portion of the agent in the tumor at a trapping efficiency of E , and returns to the heart with the remaining agent at a lower concentration via the lymphatic and venous vessels. In an infinitely small time interval (dt in min), the increase in the tumor accumulation (dA in g) is $dA = F \times f \times C_{blood} \times dt \times E$. During this process, the agent may be excreted, metabolized, and/or accumulated into other organs, such that the value of C_{blood} decreases and becomes minimal after a sufficiently long time (theoretically $t \rightarrow \infty$). Assuming that the cardiac output F and the fraction f are constant, the total tumor accumulation is

$$A(g) = F \times f \times \int_{t=0}^{t=\infty} E \times C_{blood}(g/mL) \times dt. \quad (1)$$

After converting the units for the tumor accumulation and blood concentration to %ID/g by dividing both sides by the tumor weight W and the dose injected, we obtain

$$A(\%ID/g) = F \times f \times W^{-1} \int_{t=0}^{t=\infty} E \times C(\%ID/g)_{blood} \times dt. \quad (2)$$

Unlike the prevailing compartmental models used for data fitting, the “reactor” model at this stage represents only an understanding, although it does have potential for fitting. Based on this understanding, general ideas or ballpark values for tumor accumulation may be inferred from limited data. Observations from a particular agent may also provide useful insights for other agents.

In a study of a pretargeting system [1], we observed that the tumor-trapping efficiency E of a labeled cMORF effector (a DNA analogue targeting a MORF-antibody pretargeted in tumors) was constant during the targeting process under sub-saturation conditions. Thus, under sub-saturation conditions, the percent tumor accumulation of a stable tumor-targeting agent with a high binding affinity can be simplified to

$$\begin{aligned} MPTA (\%ID/g) &= F \times f \times W^{-1} \times E \times \int_{t=0}^{t=\infty} C(\%ID/g)_{blood} \times dt \\ &= F \times f \times W^{-1} \times E \times AUC_{blood}. \end{aligned} \quad (3)$$

In this equation, E is located outside the integral because E is constant and, because the percent tumor accumulation A is at its maximum, this variable was replaced by $MPTA$ (maximum percent tumor accumulation).

If the targeting sites can be saturated during the accumulating process, when the MORF-Ab in the tumor becomes close to saturation or saturated, the accumulation will be reduced or stopped (E becomes 0). A recent study with a larger dose range verified the plateau of absolute tumor accumulation (in g) beyond saturation [2]. In this case, Eq. (2) may not be simplified to Eq. (3), and the percent tumor accumulation is lower. Furthermore, for unpretargeted tumor (in the absence of a target), E is zero, and the tumor accumulation has been observed to be minimal as expected [3].

2. Rules of thumb

The $MPTA$ expression may help understanding not only how factors (including the mass dose of effectors and the number of binding sites) influence the tumor accumulation but also how $MPTA$ varies with the effector, the pretargeting agent, and the tumor model. Some rules of thumb for the changing trends are summarized below.

2.1. $MPTA$ does not change with the mass or activity dose of the agent

Due to its absence in the expression, the mass dose does not change the $MPTA$, and this finding is in agreement with the data obtained in our previous studies (Figs. 1A and B) [1,2]. The accumulations reach the $MPTA$ at doses to the left of the inflection point, but decrease at doses higher than the inflection point (the $MPTA$ is no longer expressed). The theoretical non- $MPTA$ curves were calculated by setting E to zero after saturation. Without the reactor model, it is unlikely to perceive a line with an inflection point.

2.2. $MPTA$ is independent of the pretargeting agents

Consultation with the $MPTA$ expression revealed that none of the parameters is directly related to a pretargeting agent. The influence of the pretargeting agent can only be reflected by its effect on the number of artificial binding sites in connection to the condition that holds the $MPTA$ expression. This lack of direct influence has been confirmed experimentally [4].

2.3. MPTA reached by pretargeting will not be improved by an amplification step

Similarly, another deduction is that an increase in the number of binding sites in the tumor does not change the *MPTA*, as confirmed experimentally [5] and in contrast to the previous anticipation of an increase [6].

2.4. MPTA ratio of agents A and B might be irrespective of tumor size

This independence was found previously during the examination of the nonlinear regression lines shown in Fig. 2 [7]. This finding further denotes an independence of the *E* ratio on the tumor size. It cannot be directly inferred from the *MPTA* expression and cannot be considered as a rule of thumb at this point, although it is very likely in theory.

2.5. MPTA can be independent of the administration route

In a more recent study [8], we found that the IP injection of cMORF did not compromise its bioavailability (the IP/IV *AUC* ratio). As indicated by the *MPTA* expression and confirmed experimentally, the tumor accumulation ratio is also 1.

3. Some insights

Currently, the rules of thumb inferred from the *MPTA* expression are only validated in the MORF/cMORF pretargeting system. Nevertheless, as the derivation is general, these equations should be applicable to other targeting agents and other targets in addition to tumor. Although validation is required, the insights into unknown areas are often more inspiring and useful than the delayed wisdom of later explanation.

3.1. Pre-injection of a blocking agent is theoretically more efficient

A defined receptor-binding agent different from the agent in question is often used in blocking studies. A co-injection of the blocking agent is recommended due to possible interference from its metabolites [9]. However, the reactor model suggests that a pre-injection would provide a higher blocking efficiency, although this hypothesis needs to be verified. Through the co-injection approach, target binding will still occur in the early phase of the targeting process.

3.2. The linear relationship between MPTA and $E \cdot AUC_{\text{blood}}$ may exhibit predictive power

In the MORF/cMORF pretargeting system, we have validated that the *MPTA* ratio of two agents is proportional to their *E*·*AUC* ratio, irrespective of the tumor size [7]. If this finding is generic for any irreversible tumor-binding agent, the variation in the tumor accumulation of an agent with a different tumor size may be estimated with much fewer experiments and the known accumulation-size curve of another agent. However, the validation of this hypothesis is required.

3.3. The MPTA expression may promote productivity

Most early stage radiopharmaceutical developments are basically on a path of trial and error. Although some studies are attempting to use a modeling approach [10,11], very often this is too complicated for radiochemists and physicians [12]. Investigations on the quantitative

relationship between structure and effect are more appealing but they are usually based on numerous existing molecules. There are also some rough guidelines to ensure solid science and to avoid repetitive studies [9], but few investigations have provided insights into the success possibility in target selection. Favorably, the rule-of-thumb approach may provide rough ideas on the outcomes at early stage under different conditions.

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Fig. 1.

The percent tumor accumulations from two previous studies (A and B). The inflection points of the dashed theoretical lines correspond to the saturation points of the MORF sites in the tumor.

Fig. 2.

Tumor accumulations (*MPTAs*) of (A) labeled cMORF and (B) labeled CC49 antibody. The solid lines are the best fits obtained through non-linear least square regression. Note: the *MPTA* ratio of the antibody to cMORF is 4.12, irrespective of the tumor size.