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# Too early to say, "no targeting of mitosis!"

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I recently read the article by Komlodi-Pasztor *et al.* (Mitosis is not a key target of microtubule agents in patient tumors. *Nat. Rev. Clin. Oncol.* **8**, 244–250)[1] and have serious concerns about the rationales that led to their conclusions.

Komlodi-Pazstor *et al.*[1] state that many mitotic inhibitors have been unsuccessful in clinical trials in patients with cancer, and conclude that targeting the mitotic process is not useful. While current drugs predominantly target microtubule proteins, targeting other proteins involved in mitosis is in its infancy. Inhibitors of only three (all kinases) of more than 100 mitotic proteins[2] have been assessed and discussed in the Review article.

The central tenet of the Komlodi-Pasztor *et al.*[1] manuscript is that the doubling times of human tumors are very long when compared with *in vitro* tissue culture or xenograft systems. This assessment of the data is my major concern with the manuscript. The assumption is that tumor doubling time correlates directly with cell-cycle duration. Tumor 'growth' (increase in physical dimensions) is a product of cell division and cell death. The authors assume that it takes approximately 140 days for cells in tumors to divide and cited the article by Tubiana and Malaise[3] to support this claim. However, in addition to the tumor doubling time, the article reported that the mean cell-cycle duration of human tumors is approximately 48 h.[3] Increased growth rate of colon tumor xenografts is due largely to a decreased cell loss factor, rather than increased growth fraction. The increased response rates to antimitotic treatments in xenograft models, compared with response rates in humans, is likely a consequence of greater drug tolerance of the host (mouse) compared with that of humans, increasing the 'apparent' therapeutic index,[4] and not necessarily increased growth rate. This was shown for other classes of cancer drugs that are dependent on proliferation to induce cytotoxicity.[4,5]

The argument that mitosis is very short (approximately 0.5 h) and mitotic cells in tumors are rare, is then used to conclude that mitosis (and mitotic proteins) cannot be the major target of anticancer drugs.[1] If cells progress through mitosis in the presence of a microtubule inhibitor (such as the spindle checkpoint-deficient Mad2-depleted cells[6–8]), the cells could then die or enter senescence in interphase. Thus, whether a cell arrests in mitosis or not is irrelevant. Of importance is the exposure of the target to the drug at concentrations required for target inhibition, and the cell cycle transit time. Most data show that where a drug is retained, cell death occurs only after the cell engages mitosis. For tumors lacking drug-efflux transporters, very prolonged accumulation of mitotic cells following a single drug administration was observed.[9]

The failure to detect mitotic cells in ixabepilone-treated breast tumors (Figure 4 of the article)[1] was used to support their argument. This observation could be explained by the fact that the breast cancers that they examined did not have a functional spindle checkpoint (which often occurs in breast cancer[10]), where cells may die in the subsequent interphase (as shown with inhibitors of Aurora B kinase). The observed lack of mitotic arrest in tumors does not mean that the drug did not kill cells by inhibition of some event in mitosis. More effective use of antimitotics may require dosing based on tumor kinetic characteristics, although this may result in enhanced toxicity—or lack of selectivity versus bone marrow or other proliferating tissues. However, with increased understanding of tumor-specific defects in checkpoint functions that protect cells from specific antimitotic agents, it might be possible to individualize drug treatments based on the tumor genotype to selectively kill malignant cells by targeting specific proteins engaged during mitosis.

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**Competing interests**
The author declares no competing interests.

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