

## **Pharmacology of Paclitaxel Sensitive to Its Delivery Vehicles Drives Distinct Clinical Outcome of Paclitaxel Formulations**

Paclitaxel is an effective antitumor agent formulated in various vehicles, which serve as carriers to deliver the hydrophobic paclitaxel from blood to tissue. The approved formulations in US are Cremophor EL formulated paclitaxel (CrEL-paclitaxel) and nanoparticles albumin-bound paclitaxel (nab-paclitaxel), while others are in development. In spite of the same active ingredient paclitaxel, different formulations produce distinct products with unique efficacy and safety profiles in animals and humans. Why the same paclitaxel behaves drastically different with distinct delivery vehicles? A recently analysis demonstrated that the rapid decline of total paclitaxel concentration following IV administration of nab-paclitaxel and CrEL-paclitaxel was attributed to rapid tissue distribution of the paclitaxel-carrier complexes, with minor contribution of free and protein bound paclitaxel. Distribution of nab-paclitaxel to peripheral tissue is 4-fold faster and 10-fold more extensive than that of CrEL-paclitaxel micelles resulting in distinct tissue paclitaxel profiles. While tissue distribution of paclitaxel is carrier complex system dependent, different delivery systems results in distinct tissue paclitaxel profile but similar paclitaxel concentration-time profiles in plasma or blood, rendering paclitaxel plasma profile a poor surrogate for its clinical outcome.

**Tissue distribution, a forgotten pharmacologic property, is a key determinant of the clinical efficacy and safety of anti-cancer agents**

Drug tissue distribution, an important aspect of drug disposition with direct impact on drug efficacy and safety, is difficult to characterize in humans and has often been overlooked and reduced to overall plasma drug exposure in clinical drug development. Recent findings indicate that tissue distribution of anti-tumor agents is a key determinant of its potential efficacy and safety. Abraxane has favorable distribution characteristics over Taxol, resulting in better and distinct efficacy and safety profile. Ibrutinib has favorable distribution characteristics that more than 40% of circulating drug deposited into tissues relative to elimination. A competitor drug candidate with less than 15% of circulating drug deposited into tissues relative to elimination had inferior clinical efficacy in spite of stronger in vitro potency and higher plasma drug levels. Similarly, everolimus more than 65% of the circulating drug deposited into tissues as compared to less than 10% deposited into tissues for a competitor mTOR inhibitor. Distribution difference accounted for the different clinical efficacy of ibrutinib and everolimus, compared to their respective competitor drug candidates. Continual research to improve tissue distribution characteristics has good potential of breakthrough anti-tumor therapeutics.