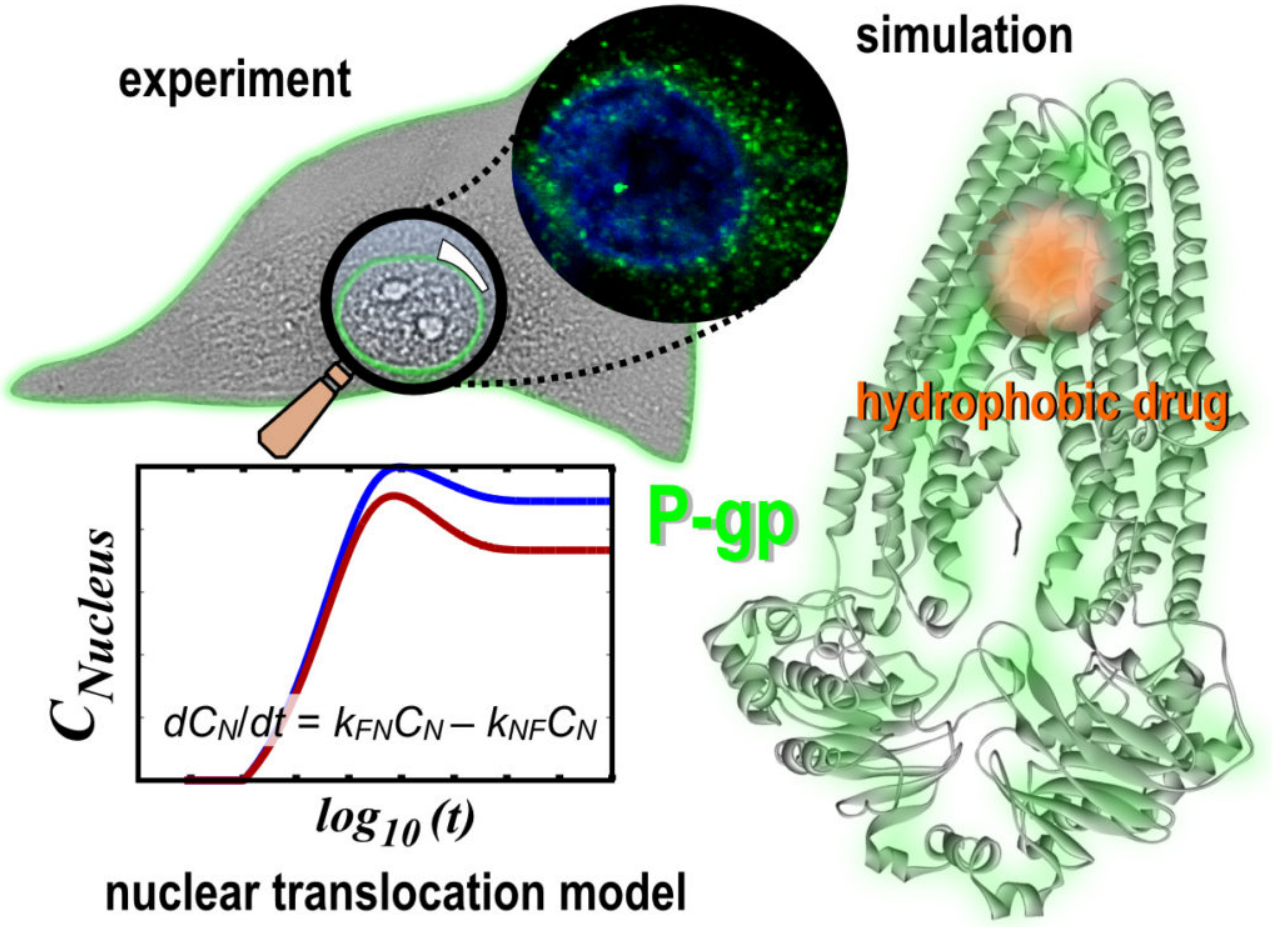
# Modalities to overcome cancer cells safeguard

The increase of intracellular concentration without raising the applied drug doses is big challenge for cancer treatments. Cancer cells employ multiple mechanisms to resists the anticancer drugs action. One of the mechanisms involves P-glycoprotein. The role of P-gp, a *mdr1* (multi-drug resistance) gene product in humans, is to detoxify cells by exporting chemically unrelated toxins. The nuclear envelope is considered to be the main barrier that protects nuclear DNA from interaction with anticancer drugs. The efficacy of anticancer drug molecules, targeting nuclear DNA could be thus improved by facilitating their transport through the nuclear envelope. Nuclear envelope can be perforated after photo-activation of selected molecules allowing them to pass inside the nucleus. Small anthraquinone derivatives hypericin, quinizarin and emodin belong to a class of compounds that exhibit stimulatory properties for regulation of P-gp activity. They are naturally occurring plant pigments that possess anti-viral, anti-tumoral and anti-inflammatory properties and can be light activated.




In this study we suggested new possibility how to increase drug concentration in cancer cells and nuclear targeting by regulation of P-glycoprotein activity and/or organelle-specific light activation of

the drug. Our docking models based on combined quantum chemical/molecular mechanics methodology demonstrate significant affinity of hypericin, emodin and quinizarin towards P-glycoprotein. Following the drug and proteins, lipids or DNA interaction we demonstrated that mainly hydrophobic character of these drugs is responsible for their positive or negative nuclear localization. By combining the empirical results and docking simulation models we constructed the subcellular inter-compartmental model of the drug dynamics, which can be used to predict intracellular distribution of drugs with different hydrophobic properties.

This study offers new insight on the drug delivery through the cellular membranes and also on the therapy improvement that will dramatically decrease the side effects frequently caused by high anti-cancer drug concentration.

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## Publication

Deeper insights into the drug defense of glioma cells against hydrophobic molecules.
Verebova V, Belej D, Joniova J, Jurasekova Z, Miskovsky P, Kozar T, Horvath D, Stanicova J, Huntosova V
*Int J Pharm. 2016 Apr 30*