Eva Novotna et al., J Clinic Toxicol, 2018, Volume 8
DOI: 10.4172/2161-0495-C1-027

Roscovitine and purvalanol A effectively inhibit aldo-keto reductase 1C3 (AKR1C3) *in vitro* and synergistically potentiate cytotoxic effect of daunorubicin

Eva Novotna and **Vladimir Wsol**
Charles University Faculty of Pharmacy in Hradec Kralove, Czech Republic

Anthracyclines, in particular, doxorubicin (Dox) and daunorubicin (Dau), have been used as a key part of many cancer treatment regimes, but their usefulness is limited by intrinsic and/or acquired resistance. Pharmacokinetic anthracycline resistance is associated with the enzymatic detoxification and with changes in anthracycline absorption and retention. The major anthracycline metabolic pathway in humans is mediated by a group of cytosolic NADPH-dependent carbonyl reducing enzymes from AKR and SDR superfamilies that catalyze two-electron reduction of Dau and Dox to less active metabolites. Cyclin-dependent kinases (CDK) are key regulators of cell cycle progression, and defects in their regulation are associated with many human pathologies. The CDK inhibitors purvalanol A and roscovitine are purine analogs with different potencies and selectivities. Recent studies showed that roscovitine could effectively kill anthracycline-resistant cancer cells and increase the therapeutic activity of anthracyclines. Although beneficial effects of these combinations have been demonstrated, the molecular mechanisms have not been fully understood yet. In our study, we proved that both purvalanol A and roscovitine significantly inhibit recombinant AKR1C3 with IC_{50} values of 6.6 and 2.2 μM, respectively. Kinetic measurements showed that the ARK1C3-mediated reduction of Dau is inhibited in a noncompetitive manner. Both the drugs were also active at the cellular level in the experiments with transiently transfected HCT116 cells. In the follow up combination experiments, we demonstrated that the inhibition of AKR1C3 by roscovitine and purvalanol A has a potential to overcome the Dau resistance mediated by this enzyme. The dose reduction indices suggest a potential of the examined combinations to increase the safety of the treatment with the involved drugs.

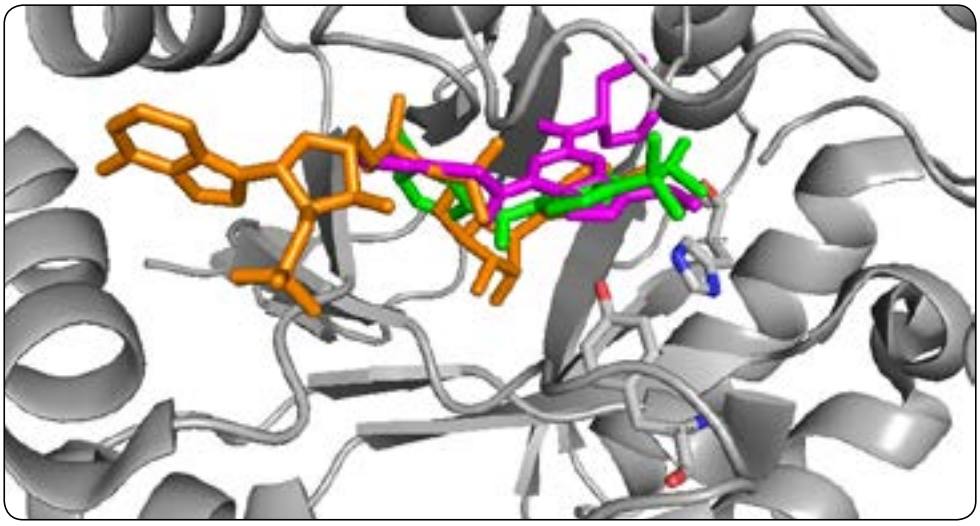

Figure 1: Roscovitine and purvalanol A probably occupy a part of the cofactor-binding site. Flexible molecular docking of roscovitine and purvalanol A into AKR1C3. Purvalanol A is depicted in green, roscovitine in magenta, $NADP^+$ in orange, and catalytic residues Tyr55 and His117 are shown as grey sticks.

Recent Publications:

1. Bains O S, Grigliatti T A, Reid R E, Riggs K W (2010) Naturally occurring variants of human aldo-keto reductases with reduced in vitro metabolism of daunorubicin and doxorubicin. J. Pharmacol. Exp. Ther. 335(3):533-545.
2. Roskoski R (2016) Cyclin-dependent protein kinase inhibitors including palbociclib as anticancer drugs. Pharmacol. Res. 107:249-275.
3. Hsieh W S et al. (2009) Pharmacodynamic effects of seliciclib, an orally administered cell cycle modulator, in undifferentiated nasopharyngeal cancer. Clin. Cancer Res. 15(4):1435-1442.
4. Raynaud et al. (2005) In vitro and in vivo pharmacokinetic-pharmacodynamic relationships for the trisubstituted aminopurine cyclin-dependent kinase inhibitors olomoucine, bohemine and CYC202. Clin. Cancer Res. 11(13):4875-4887.
5. Appleyard M V et al. (2009) Seliciclib (CYC202, R-roscovitine) enhances the antitumor effect of doxorubicin in vivo in a breast cancer xenograft model. Int. J. Cancer. 124(2):465-472.

Biography

Eva Novotna has her expertise in the preparation and purification of recombinant enzymes. She studies interactions of potential inhibitors with carbonyl reducing enzymes using human recombinant enzymes and cancer cell lines. Her research interest include: carbonyl reducing enzymes, inhibitors and cancer drug resistance.

eva.novotna@faf.cuni.cz

Notes: