**Title of the project:** Study of cardioprotective effects of ACE-inhibitor, dexrazoxane and its novel derivatives against chronic anthracycline cardiotoxicity in rabbits.

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**Project Number:** 680216  
**Principal Investigator:** Z. Pokorná  
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### Summary of 2018 results

**Title of the presentation:** Can ACEi prevent on-set of chronic anthracycline cardiotoxicity and provide long-lasting cardioprotection?  
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Chronic anthracycline (ANT) cardiotoxicity and resulting heart failure (HF) are feared complications of cancer chemotherapy. ACEi are commonly used to treat ANT-induced cardiac dysfunction and recently have been suggested to have potential to prevent induction of toxicity. However, the evidence for the letter hypothesis is lacking and it is unclear whether they can thereby offer true and long-lasting cardioprotection against ANT cardiotoxicity even after their withdrawal. Hence, the aim of this study was to evaluate cardioprotective effects of perindopril (PER) on the rabbit model of chronic ANT cardiotoxicity (daunorubicin - DAU, 3 mg/kg, weekly for 10 weeks). PER (0.05 mg/kg/day) was administered in drinking starting a week before 1st DAU dose and withdrawn 3 days after the last dose. Survivors were randomized for LV catheterization and sacrifice or for subsequent 3-week drug-free follow up (FU). In the treatment period PER prevented DAU-induced mortality, decline in systolic function, release of cardiac troponin T and increase of molecular markers of cardiac damage in the myocardium (e.g. expression of ANP, BNP, COL1A1). Interestingly, in the FU almost all parameters were gradually worsening. Hence, in other set of animals longer post-treatment FU (10 weeks – FU2) was employed to better describe the long-term trend and to estimate potential total benefit. Interestingly, the significant benefit was observed at the end of treatment and partial benefit noted after 3-week FU was attenuating further in the FU2 and several animals developed severe HF resulting into premature deaths. Also the incidence of blood congestion raised in this group. Interestingly, the protective effects of PER are strikingly different to the results obtained previously on the same model with DEX. Unlike PER, DEX showed the same and very effective protective effects at the end of the treatment as well as after 10-week FU. Hence, it seems that while DEX prevents the onset of ANT cardiotoxicity mechanistically (presumably due to the interaction with topoisomerase IIb in the heart), ACEi only temporally modulate some downstream pathogenic pathways and therefore, it is less effective. Supported by GAUK 680216.

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