# XXXIX JCET LECTURE, 13.06.2014, 9.00

Oxidative stress, apoptosis and topoisomerase II in anthracycline-induced cardiotoxicity and pharmacological cardioprotection



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Anthracyclines (doxorubicin, daunorubicin or epirubicin) rank among the most effective anticancer drugs, but their clinical usefulness is hampered by the risk of cardiotoxicity. The most feared are the chronic forms of cardiotoxicity, characterized by irreversible cardiac damage and congestive heart failure. Although the pathogenesis of anthracycline cardiotoxicity seems to be complex, the pivotal role has been traditionally linked to the iron-catalyzed intramyocardial production of reactive oxygen species (ROS). To date, dexrazoxane (ICRF-187) is the only clinically approved cardioprotectant. Its metal chelating metabolite ADR-925 may take iron from its complex with anthracycline and inhibit ROS formation. However, in our studies, despite effective protection by dexrazoxane against daunorubicin-induced apoptosis in vivo (which correlated with severity of heart failure), we have observed neither significant reduction in myocardial malondialdehyde content nor correlation between this marker of lipoperoxidation and cardiac apoptosis or function. Dexrazoxane is also catalytic topoisomerase II inhibitor, which could protect DNA from the anthracycline-induced double strand breaks. We have demonstrated significant protection against the daunorubicin cardiotoxicity with several topoisomerase catalytic inhibitors, while none was able to protect cardiomyocytes from the model oxidative injury by hydrogen peroxide. Cardioprotective experiments with other chelators (stronger and more selective for iron than dexrazoxane) yielded at best mixed outcomes - both in vitro and in vivo. Hence, rather than by simple antioxidant action, dexrazoxane apparently protects the heart by other mechanism(s), such as the interaction with topoisomerase II. Different expression of its isoforms in cardiac and cancer cells may be responsible for selective modulation of anthracycline action.

References:

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- Štěrba M., Popelová O., Vávrová A., Jirkovský E., Kovaříková P., Geršl V., Šimůnek T. Oxidative stress, redox signaling and metal chelation in anthracycline cardiotoxicity and pharmacological cardioprotection. Antiox Redox Signal. 2013; 18(8): 899-929.

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- Šimůnek T., Štěrba M., Popelová O., Kaiserová H., Adamcová M., Hroch M., Hašková P., Poňka P., Geršl V. Anthracycline toxicity to cardiomyocytes or cancer cells is differently affected by iron chelation with salicylaldehyde isonicotinoyl hydrazone. Br J Pharmacol 2008; 155(1): 138-48.

## CURRICULUM VITAE Tomáš Šimůnek, Pharm.D., Ph.D.

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Born 16 April 1976 in Liberec, Czech Republic

## Present Position:

• Dean of the Charles University Faculty of Pharmacy

• Principal investigator, University Research Center for the Study of Toxic and Protective Effects of Drugs on Cardiovascular System

• Group Leader - Molecular and Cellular Toxicology Research Group

## Previous Education and Training

• 2003-2004: Postdoctoral Fellowship, Laboratory for Physiology, Institute for Cardiovascular Research, Free University Amsterdam, The Netherlands (13 months, Huyghens Scholarship)

• 1999-2003: Doctoral Study - Charles University in Prague, Faculty of Pharmacy in Hradec Králové, (Ph.D. in Pharmacology and Toxicology; PharmD in Pharmacy);

• 1998-1999: Department of Pharmacology and Toxicology, University of Vienna, Austria (6 months, M.Sc. Diploma Thesis Project, ERASMUS)

• 1994-1999: Masters Study - Charles University in Prague, Faculty of Pharmacy in Hradec Králové, (M.Sc. in Pharmacy)

## **Research Interests**

• Cardiovascular pharmacology, toxicology and molecular biology

- *in-vitro* models of diseases
- drug-induced cardiotoxicity
- oxidative stress-related diseases
- role of free iron and copper ions in various pathologies
- development and evaluation of potential cardioprotective and anticancer agents

## Teaching

• since 2012: mentor of three post-doctoral research associates

• since 2006: tutor of five Ph.D. students; member of the Examination Board of Ph.D. programs Pathobiochemistry and Xenobiochemistry, Pharmacology and Toxicology

• since 2004: supervisor of >40 B.Sc. and M.Sc. (Pharmacy and Medical Bioanalytics) diploma theses

• since 2004: principal lecturer and examiner of Molecular Biology study courses for B.Sc. and M.Sc. students (Pharmacy and Medical Bioanalytics), Charles University in Prague, Faculty of Pharmacy in Hradec Králové

#### Professional Memberships

• President of the Scientific Council, Charles University in Prague, Faculty of Pharmacy in Hradec Králové

• Coordinator of the Charles University Reseach program "Research and Study of the Drugs" (PRVOUK P40)

• Grant Agency of the Charles University - Member of the Biology examination panel (section B)

• The Council of Higher Education Institutions of the Czech Republic - representative of the Charles University Faculty of Pharmacy and member of the Science and Economy committees

• International Society on Chelation and Metals (ISOCAM) - Co-chair of Cancer Subcommittee

• International Society for Heart Research (European Section)

• Czech Society for Experimental and Clinical Pharmacology and Toxicology

• Czech Pharmaceutical Society

• 1996-1998: President of the Czech Pharmacy Stdents' Association (CPSA)

#### Grants Received

• principal investigator, University Research Center for the Study of Toxic and Protective Effects of Drugs on Cardiovascular System (Charles University in Prague, UNCE 204019)

• principal investigator, Czech Science Foundation project GACR 13-15008S - New potential cardioprotective agents: study of structure-activity relationships in various types of myocardial injury (2013 - 2017)

• principal investigator, Czech Science Foundation, GACR P305/05/P156 "Study of protective effects of novel iron chelators in the heart injury induced by oxidative stress and anthracycline cytostatics"

• principal investigator, grant of the Czech Society of Cardiology "Study of the role of apoptosis in the anthracycline-induced myocardial damage" (2006-2008)

• co-investigator in other research grants and projects (5x GA CR, 7 x GA UK, 2 x IGA MZ CR, 3 x European Union - funded projects)

#### Awards/Prizes

• 2005: Winner - Prix de Pharmacie, organized by the French Embassy in Prague and Sanofi-Aventis pharma company

• 2009: Medal of the Charles University Faculty of Pharmacy

#### Publications

author and co-author of >40 papers in international peer-reviewed journals, 5 books chapters and proceeding papers, 3 textbooks; >500 citations (WoS; excluding self-citations); H-index: 15 (WoS)