
CardioTox In Vivo

People Publications



The research is tightly coordinated with the other laboratories of the network **CardioTox Hradec Králové** (see the section Cooperation). We focus on the **cardiovascular toxicity of anticancer drugs**, especially those inducing heart failure, and the **possibilities of pharmacological cardioprotection**. The main subject is the cardiotoxicity of **anthracycline cytostatics (ANTs)**, e.g., doxorubicin or daunorubicin). Moreover, we have studied the toxicity of newer biologically targeted drugs, such as tyrosine kinase inhibitors (sunitinib) and proteasome inhibitors (bortezomib/carfizomib). Our goal is to deliver high-quality experimental and translational research in cardio-oncology.

Regarding ANT cardiotoxicity, we are studying molecular mechanisms of cardiotoxicity development. We are particularly interested in the **role of topoisomerase II beta (TOP2B)** and its poisoning by ANT which induces **DNA damage** and **DNA damage response (DDR) signaling in the heart**.

We have also studied the **mechanisms of action of clinically used cardioprotectant dexrazoxane (DEX)**. Our recent work shows that its cardioprotective effects are **not mediated by iron chelation**, as has been believed. However, DEX acts as a **catalytic inhibitor of TOP2B**, thereby preventing poisoning of the enzyme by ANT, and thus DNA damage and DDR will not happen in the heart.

We are also investigating **new pharmacological cardioprotectants targeting TOP2B**. We have shown that **DEX derivatives**, which are more potent as catalytic inhibitors of TOP2B, are also more potent in inhibiting ANT-induced DDR and, consequently, more effective as cardioprotectants. In this regard, we have identified compound GK-667, a prodrug of ICRF-193, as a promising cardioprotectant in vivo providing potent and dose-dependent cardioprotection in lower ratios to ANT than DEX. Besides that, we study the cardioprotective effects of **other TOP2B inhibitors than DEX and related agents**, including newly synthesized compounds, to develop **TOP2B selective, effective and safe cardioprotectants**.

Our recent interest is to analyze **DDR signaling induced by ANT in the heart and tumors in vivo** and its **pharmacological modulation by TOP2B inhibitors and DDR inhibitors**. For this purpose, we have established a model of mice bearing human tumor xenografts and their treatment with doxorubicin.

People

Group Leader

- Doc. PharmDr. Martin Štěřba, Ph.D.

Postdoctoral Researchers

- PharmDr. Olga Lenčová (born Popelová), Ph.D.
- Mgr. Petra Kollárová (born Brázdová), Ph.D.
- Daniel Diaz Garcia, Ph.D.

Former Group Members

- PharmDr. Jirkovský Eduard, Ph.D. (bývalý doktorand a postdoktorand)
- Mgr. Zuzana Pokorná, Ph.D. (bývalá doktorandka)
- Prof. MUDr. Vladimír Geršl, Ph.D. (bývalý vedoucí skupiny)

Publications

A full list of publications can be found in the [Scopus database](#).

Overview of last 10 years

- **26 papers** in journals with IF in total
- AIS D1 papers – 19.2 %, AIS Q1 papers – 73.1 %
- Group Leader as the corresponding author – 53.2 % (with an one exception, all are Q1 papers)

Selected publications

1. Pokorná Z., Kollárová-Brázdová P., Lenčová-Popelová O., Jirkovský E., Kubeš J., Mazurová Y., Adamcová M., Holečková M., Palička V., Šimůnek T., Štěřba M. Primary prevention of chronic anthracycline cardiotoxicity with ACE

inhibitor is temporarily effective in rabbits, but benefits wane in post-treatment follow-up. *Clinical Science (London)* 2022;136(1):139-161.

IF 6.876, AIS 1.456, AIS Q1

2. Jirkovský E., Jirkovská A., Bavlovič-Piskáčková H., Skalická V., Pokorná Z., Karabanovich G., Kollárová-Brázdová P., Kubeš J., Lenčová-Popelová O., Mazurová Y., Adamcová M., Lyon A. R., Roh J., Šimůnek T., Štěrbová-Kovářiková P., Štěrbá M. Clinically Translatable Prevention of Anthracycline Cardiotoxicity by Dexrazoxane Is Mediated by Topoisomerase II Beta and Not Metal Chelation. *Circulation Heart Failure* 2021;14(11):e008209.

IF 10.447, AIS 4.093, AIS D1

3. Kollárová-Brázdová P., Lenčová-Popelová O., Karabanovich G., Kocúrová-Lengvarská J., Kubeš J., Váňová N., Mazurová Y., Adamcová M., Jirkovská A., Holečková M., Šimůnek T., Štěrbová-Kovářiková P., Roh J., Štěrbá M. Prodrug of ICRF-193 provides promising protective effects against chronic anthracycline cardiotoxicity in a rabbit model in vivo. *Clinical Science (London)* 2021;135(15):1897-1914.

IF 6.876, AIS 1.456, AIS Q1

4. Pokorná Z., Jirkovský E., Hlaváčková M., Jansová H., Jirkovská A., Lenčová-Popelová O., Brázdová P., Kubeš J., Sotáková-Kašparová D., Mazurová Y., Adamcová M., Vostatková L., Holzerová K., Kolář F., Šimůnek T., Štěrbá M. In vitro and in vivo investigation of cardiotoxicity associated with anticancer proteasome inhibitors and their combination with anthracycline. *Clinical Science (London)* 2019;133(16):1827-1844.

IF 5.223, AIS 1.327, AIS Q1

5. Mladěnka P., Applová L., Patočka J., Costa V.M., Remiao F., Pourová J., Mladěnka A., Karlíčková J., Jahodář L., Vopršalová M., Varner K.J., Štěrbá M.; TOX-OER and CARDIOTOX Hradec Králové Researchers and Collaborators. Comprehensive review of cardiovascular toxicity of drugs and related agents. *Medicinal Research Reviews* 2018;38(4):1332-1403.

IF 9.791, AIS 2.096, AIS D1

6. Lenčová-Popelová O., Jirkovský E., Jansová H., Jirkovská-Vávrová A., Vostatková-Tichotová L., Mazurová Y., Adamcová M., Chládek J., Hroch M., Pokorná Z., Geršl V., Šimůnek T., Štěrbá M. Cardioprotective effects of inorganic nitrate/nitrite in chronic anthracycline cardiotoxicity: Comparison with dexrazoxane. *Journal of Molecular and Cellular Cardiology* 2016;91:92-103.

IF 5.055, AIS 1.470, Q1

7. Štěrbá M., Popelová O., Vávrová A., Jirkovský E., Kovářiková P., Geršl V., Šimůnek T. Oxidative stress, redox signaling and metal chelation in anthracycline cardiotoxicity and pharmacological cardioprotection. *Antioxidants & Redox Signaling* 2013;18(8):899-929.

IF 5.828, AIS 1.921, AIS D1/Q1