This Ph.D. thesis is a commented collection of 3 original articles published in international journals. The first part deals with cardiotoxicity of proteasome inhibitors (PI) bortezomib and carfilzomib, which are biologically targeted drugs with a suspected risk of cardiotoxicity and heart failure (HF). As PIs are now being combined with anthracycline (ANT) anticancer drugs, which are well known for their damaging impact on the heart, a special attention was paid to this potentially risky combination. *In vitro* experiments with primary cardiomyocytes yielded different results depending on the employment of either neonatal or adult rat cardiomyocyte model (NVCM and AVCM, respectively). In particular, both PIs significantly increased toxicity of ANTs to NVCM, but not to AVCM, even though they inhibited proteasome activity in AVCM even more effectively. Both PIs administered in maximally tolerated doses in combination with ANT did not have a significant impact on the development of chronic ANT cardiotoxicity and HF in rabbits. Both PIs induced significant but relatively short-lived inhibition of proteasome activity in the heart, which might explain why they did not have a significant impact on a protein homeostasis impairment found in hearts with chronic ANT cardiotoxicity. Hence, the experimental data show that the combination of PIs with ANTs is not accompanied by an exaggerated risk of cardiotoxicity and HF at least in young adult animal cardiomyocytes and hearts.

Inhibitors of angiotensin-converting enzyme (ACEi) have been recently hypothesized to be promising cardioprotective agents for prevention of the ANT-induced damage to the heart when used in primary prevention settings (i.e., throughout whole chemotherapy). This part aimed to address this question in animal experiments with focus on long-term outcomes of this intervention in post-treatment follow-up (FU). Using the model of chronic ANT cardiotoxicity in rabbits it was revealed that different benefits can be attributed to administration of clinically relevant doses of ACEi perindopril depending on the length of post-treatment FU. A week after the last ANT dose, perindopril administration seemed to completely overcome or markedly reduced most of the parameters describing toxic damage, including degenerative changes induced in cardiomyocytes. However, after additional 3–10-week FU, most of these cardiotoxicity parameters significantly deteriorated including occurrence of cases of end-stage HF with premature deaths. Continued administration of perindopril in the FU prevented cases of severe HF and related mortality but did not reverse the apparent trend for waning of benefits in the FU. These results were strikingly different from those obtained previously on the same rabbit model with clinically used DEX, where a sustained and robust cardioprotection was observed even after 10-week FU. Therefore, mechanistic differences in cardioprotective effects of these two drugs were studied. In sharp contrast to DEX, neither perindopril nor its active metabolite affected the activity of recombinant topoisomerase II beta (TOP2B) and prevented p53-mediated DNA damage signalling induced in the heart by a single ANT dose. Unlike DEX, ACEi provided largely only temporal benefits in the primary prevention of chronic ANT cardiotoxicity which may relate to their inability to prevent ANT induced and TOP2B-dependent DNA damage and related signalling in the myocardium.

In the last part of this thesis, mechanisms of cardioprotective effects of clinically used cardioprotectant DEX were investigated. Pharmacokinetic experiments showed that exogenous administration of the main DEX metabolite possessing metal chelating properties (ADR-925) induced even higher concentrations of this agent *in vitro* in NVCM and *in vivo* in rabbit's hearts than after administration of parent DEX. However, in head-to-head comparison with DEX, administration of ADR-925 did not show any cardioprotective potential both *in vitro* in NVCM and *in vivo* in rabbits. However, it was observed that parent DEX inhibited the activity of the recombinant TOP2B *in vitro* and depleted the same enzyme both *in vitro* in NVCM and *in vivo* in rabbit heart under the conditions it provides cardioprotective effects. Furthermore, DEX was also shown to protect cardiomyocytes against ANT-induced DNA damage. The mechanistic link towards TOP2B was further strengthened by experiments performed with diastereoisomers of a new derivative of DEX. Hence, these results supported a new mechanistic paradigm that attributes clinically effective cardioprotection against ANT cardiotoxicity to interactions with TOP2B, but not metal chelation.