

# **SPECIAL THEMED ISSUE: CARDIOTOXICITY**

## **EDITORIAL**

### **NEW INSIGHTS INTO CARDIOTOXICITY CAUSED BY CHEMOTHERAPEUTIC AGENTS**

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Every year 1 in 200 people in the Western world are diagnosed with cancer and despite major improvements in treatment, it is still currently responsible for approximately 25% of all mortality. Although agents such as anthracyclines and tyrosine kinase inhibitors, are effective anti-neoplastic agents which have been widely utilised for many years in the successful treatment of cancer, their clinical application is severely limited by dose-dependent cardiotoxicity which is characterised by progressive maladaptive remodelling of cardiomyocytes and the extracellular matrix, ultimately leading to contractile dysfunction and congestive heart failure (Bloom *et al.*, 2016). Whilst several mechanisms have been proposed, including mitochondrial dysfunction, reactive oxygen species generation, lipid peroxidation, reduced sarcoplasmic reticulum Ca<sup>2+</sup>-ATPase activity and impaired myocyte energetics, understanding of the underlying pathways remains generally poor with no significant advances in clinical prevention or treatment strategies (McGowan *et al.*, 2017). In addition to cardiotoxicity linked with established cancer therapies, there is huge pre-clinical attrition of potential drugs during the transition from the laboratory bench to hospital bedside, with 89% of drugs that pass current in vitro and animal model screening tests being withdrawn in the clinical phase due to cardiotoxicity, which accounts for up to 33% of drug trial failure (Roberts *et al.*, 2014). This themed issue was inspired by an embedded symposium at Pharmacology 2015 organised by the British Society for Cardiovascular Research and entitled ‘Targeting cardiotoxicity’. It comprises several review articles and original research papers addressing key topics in the field to provide an up-to-date overview of current understanding of cardiotoxicity, novel approaches to its diagnosis and future directions towards eradicating this hugely detrimental side-effect of otherwise effective anti-cancer therapies.

The anthracycline agent, doxorubicin, is commonly used to treat a diverse range of cancers and is notorious for associated risk of cardiomyopathy, which may largely be mediated by oxidative stress. To specifically investigate the role of Nox2 NADPH oxidase, previously

implicated in doxorubicin-induced cardiotoxicity (Zhao *et al.*, 2010), McLaughlin *et al.* performed microarray analysis of left ventricular tissue from doxorubicin-treated Nox2<sup>-/-</sup> and wild-type mice, which highlighted particular involvement of cell death and survival pathways (McLaughlin *et al.*, 2017). They specifically focussed on mitofusin-2 (Mfn2), a mitochondrial shaping protein which has been implicated in cardiomyocyte health and survival (Ong *et al.*, 2017), and reported that activation of Mfn2 signalling appears to be protective against doxorubicin cardiotoxicity. On a similar theme, Cappetta *et al.* report that administration of ranolazine, a selective blocker of late Na<sup>+</sup> current, to doxorubicin-treated rats, decreases systolic and diastolic dysfunction and associated mortality by reducing myocardial Nox2 NADPH oxidase expression and oxidative/nitrosative stress (Cappetta *et al.*, 2017.). A study by Altieri *et al.* investigated a different class of chemotherapeutic agents, known as fluoropyrimidines. Although 5-fluorouracil (5FU) and its prodrug, capecitabine, are widely employed for treatment of solid tumours, they are linked with myocardial ischaemia secondary to vasospasm and/or coronary microvascular dysfunction. These authors report that 5FU causes endothelial cell senescence and dysfunction which may underlie its cardiovascular side effects (Altieri *et al.*, 2017). Of potential clinical significance, 5FU-mediated endothelial cell damage was prevented by glucagon-like peptide-1 (GLP-1), indicating that GLP-1 analogues, which are widely prescribed for glycaemic control and confer cardiovascular benefit (Tate *et al.*, 2015), may also be used to treat 5FU and capecitabine-induced vascular toxicity. Other therapeutic approaches to doxorubicin cardiotoxicity include iron chelators, such as dexrazoxane, which are sometimes used clinically but are not universally effective (McGowan *et al.*, 2017).

Cardiotoxicity also occurs in some breast cancer patients treated with Trastuzumab (Herceptin<sup>®</sup>), a humanised monoclonal antibody directed against epidermal growth factor receptor-2 (HER-2), which is expressed by ~25% of such tumours (HER-2 positive). Although associated cardiotoxicity is likely to be dependent upon cardiac HER-2 expression, the exact

mechanism is still unknown. In this regard, Nemeth et al. have contributed a comprehensive review of Trastuzumab clinical trial data and current understanding of Trastuzumab cardiotoxicity, with a view towards emerging pharmacological approaches and candidate biomarkers which may indicate drug sensitivity in cancer patients (Nemeth *et al.*, 2016).

The laboratory of Christine Mummery has pioneered differentiation of stem cells in to cardiomyocytes and their application for evaluation of drug cardiotoxicity. Such cardiomyocytes derived from human induced pluripotent stem cells (hiPS-CMs) hold clear promise for this purpose, although there are still limitations including phenotypic immaturity and variable phenotype. This group provides a comprehensive review of present and future preclinical cardiotoxicity screening, whilst suggesting directions to promote forward movement of the field (Sala *et al.*, 2016). In this regard, Kopljar et al. describe development of a novel video microscopy-based method of motion waveform imaging to assess chronic drug-induced changes in hiPS-CMs whilst highlighting biomarker potential of cardiac troponin I and heart fatty acid binding protein (FABP3), which represents an important advance towards optimisation of cardiomyocyte damage detection.

We hope that readers will find this up-to-date collection of cardiotoxicity-themed articles informative and inspiring.

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## **CONFLICTS OF INTEREST**

The authors have no conflicts of interest to declare.

## REFERENCES

- Altieri P, Murialdo R, Barisione C, Lazzarini E, Garibaldi S, Fabbi P et al. (2017). 5-fluorouracil causes endothelial cell senescence: potential protective role of glucagon-like peptide 1. *Br J Pharmacol* Jan 27. doi: 10.1111/bph.13725.
- Bloom MW, Hamo CE, Cardinale D, Ky B, Nohria A, Baer L et al. (2016). Cancer therapy-related cardiac dysfunction and heart failure: Part 1: definitions, pathophysiology, risk factors, and imaging. *Circ Heart Fail* **9**: e002661.
- Cappetta D, Esposito G, Coppini R, Piegari E, Russo R, Ciuffreda LP et al. (2017). Effects of ranolazine in a model of doxorubicin-induced left ventricle diastolic dysfunction. *Br J Pharmacol* Mar 20. doi: 10.1111/bph.13791.
- Kopljar I, De Bondt A, Vinken P, Teisman A, Damiano B, Goeminne N et al. (2017). Chronic drug-induced effects on contractile motion properties and cardiac biomarkers in human induced pluripotent stem cell-derived cardiomyocytes. *Br J Pharmacol* Jan 17. doi: 10.1111/bph.13713.
- McGowan JV, Chung R, Maulik A, Piotrowska I, Walker JM & Yellon DM (2017). Anthracycline chemotherapy and cardiotoxicity. *Cardiovasc Drugs Ther* **31**: 63-75.
- McLaughlin D, Zhao Y, O'Neill KM, Edgar KS, Dunne PD, Kearney AM et al. (2017). Signalling mechanisms underlying doxorubicin and Nox2 NADPH oxidase-induced cardiomyopathy: involvement of mitofusin-2. *Br J Pharmacol* Mar 6. doi: 10.1111/bph.13773.
- Nemeth BT, Varga ZV, Wu WJ & Pacher P (2016). Trastuzumab cardiotoxicity: from clinical trials to experimental studies. *Br J Pharmacol* Oct 7. doi: 10.1111/bph.13643.
- Ong SB, Kalkhoran SB, Hernandez-Resendiz S, Samangouei P, Ong SG & Hausenloy DJ (2017). Mitochondrial-shaping proteins in cardiac health and disease - the long and the short of it! *Cardiovasc Drugs Ther* **31**: 87-107.
- Roberts RA, Kavanagh SL, Mellor HR, Pollard CE, Robinson S & Platz SJ (2014). Reducing attrition in drug development: smart loading preclinical safety assessment. *Drug Discov Today* **19**: 341-347.
- Sala L, Bellin M & Mummery CL (2016). Integrating cardiomyocytes from human pluripotent stem cells in safety pharmacology: has the time come? *Br J Pharmacol* Sep 19. doi: 10.1111/bph.13577.
- Tate M, Chong A, Robinson E, Green BD & Grieve DJ (2015). Selective targeting of glucagon-like peptide-1 signalling as a novel therapeutic approach for cardiovascular disease in diabetes. *Br J Pharmacol* **172**: 721-736.
- Zhao Y, McLaughlin D, Robinson E, Harvey AP, Hookham MB, Shah AM et al. (2010). Nox2 NADPH oxidase promotes pathologic cardiac remodeling associated with doxorubicin chemotherapy. *Cancer Res* **70**: 9287-9297.