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Quo Vadis, Cardio-Oncology?

Nebigil CG[1], **Tounsi N**[2], **Fuhrmann G**[3]**and Désaubry L**[2,4*]

[1]*Department Cardiology, GPCRs in Cardiobiology Team, University of Strasbourg-CNRS, France*

[2]*Department Pharmacy, Laboratory of Therapeutic Innovation, Faculty of Pharmacy, University of Strasbourg-CNRS, France*

[3]*Department Pharmacy, Laboratory of Biophotonics and Pharmacology, Faculty of Pharmacy, University of Strasbourg-CNRS, France*

[4]*Department Medicinal Chemistry, Sino-French Joint Lab of Food Nutrition/Safety and Medicinal Chemistry, Tianjin University of Science and Technology, China*

[*]**Corresponding author:** Désaubry L, Department of Medical Chemistry, Laboratory of Therapeutic Innovation (UMR 7200) Faculté de Pharmacie de l' Université de Strasbourg 74 route du Rhin 67401 Illkirch Cedex, France, Tel: (+33) 03 68 85 41 41; Fax: (+33) 03 68 85 43 10; E-mail: desaubry@unistra.fr

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Cancer treatments including chemotherapy, targeted therapies and radiotherapy may cause irreversible cardiac damage with significant morbidity [1,2]. A recent survey followed cancer survivors for 7 years and indicated that 33% of patients died of heart diseases and 51% of cancer [3]. With the aging of the population, the incidence of both cancer and cardiac disease is rising, and there are more patients with cardiac problems developing cancer. In addition, increased life span of cancer patients brings a higher incidence of cardiac complications. These issues of public health have been reinforcing the cooperation between oncologists with cardiologists, leading to the recent creation of the "International CardiOncology Society", which is dedicated to the prevention, detection, and treatment of adverse cardiovascular effects induced by cancer treatments [4]. The ultimate objective of cardio-oncology is to exploit the benefits of modern cancer therapy while minimizing its adverse cardiovascular effects.

One of the typical examples of cardiotoxicity is the management of HER2-positive breast cancer survivors. These patients receive two of the most cardiotoxic classes of drugs: anthracyclines during chemotherapies and the human epidermal growth factor receptor 2 (HER2)-targeted monoclonal antibody trastuzumab (Herceptin). Anthracyclines, such as doxorubicin, epirubicin, daunorubicin and idarubicin have potent antitumor activity in many solid or hematologic malignancies, and have long been known to induce cardiotoxicity that may progress toward dilated cardiomyopathy and systolic heart failure [5]. Trastuzumab, which is *used as an adjuvant* (postoperative) treatment to decrease the risk of cancer recurrence, also promotes heart failure [6]. It was shown to induce a cardiotoxicity in 30% of older patients (mean age in the seventh decade) [7]. While anthracycline-related cardiotoxicity correlated with the cumulative administered dose [8], the cardiac adverse effect of trastuzumab was not related to either dose or duration, which allows the physician to discontinue its administration and allow the recovery of the heart. Thus, the cardiac function of these patients, and in particular the left ventricular ejection fraction (LVEF), needs to be monitored during trastuzumab administration to detect cardiac dysfunction early and prevent permanent damage.

Burgeoning research efforts in cardio-oncology aim to identify whether novel anticancer agents are cardiotoxic, decipher the mechanism of the adverse effects, develop biomarkers for patient susceptibility to cardiotoxicity, improve the monitoring and detection of patients at risk using enhanced imaging technologies and novel biomarkers, improve the clinical management of cancer survivors who have developed cardiac complications, and develop new cardioprotective strategies to ameliorate the adverse effects of cancer treatments [9]. Our lab has dedicated much effort to the latter issue for many years. Indeed, dexrazoxane (Zinecard,Cardioxane) an iron chelator, is currently the only cardioprotective agent approved to alleviate the adverse effects of anthracyclines. However, its efficacy is limited: a 2011 Cochrane meta-analysis found no difference in response rate or survival between the dexrazoxane and control group [10]. This meta-analysis examined the efficacy of six other cardioprotective agents: N-acetylcysteine, phenetylamines, coenzyme Q10, combination of vitamins E and C and N-acetylcysteine, L-carnitine, and carvedilol, as well. Only dexrazoxane showed a statistically significant cardioprotective effect.

Recently, we demonstrated that of a family of anticancer drugs, flavaglines, protect the heart against doxorubicin-induced toxicity in mice [11]. Flavaglines have been first isolated in 1992 from plants used in traditional Chinese medicine. These compounds have been shown to display a strong cytotoxicity in cancer cells without affecting non-cancer cells. This selectivity stems from their unique mode of action: - they bind to the scaffold proteins prohibitins-1 and 2 (PHB1/2) to block the activation of C-Raf by Ras and also to the translation initiation factor eIF4a to selectively inhibit the synthesis of proteins involved in oncogenesis and metastasis. The anticancer activity of flavaglines has been established by many labs, including ours [11]. In the course of our research, we identified flavaglines derivatives that display enhanced pharmacological properties compared to natural flavaglines [12-14]. We demonstrated that these drugs may relieve the resistance to B-Raf inhibitors in the targeted therapy of metastatic melanoma [15]. Prior studies indicated that flavaglines are neuroprotective. We discovered this protection extends to the heart and showed that our lead preclinical candidate, FL3, protects mice from acute doxorubicin cardiotoxicity [16]. We clarified the mechanism of this cardioprotection: we found that FL3 induces the heterodimerization of PHB1 with STAT3, the phosphorylation of STAT3 and also the translocation of these two proteins to mitochondria in cardiomyocytes [17]. Development of drugs that display both cardioprotective and anticancer activities illustrates the benefit of basic sciences in medicinal chemistry and cell biology and may contribute to the advancement of cardio-oncology.

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