High content in vitro assessing of cardiotoxic risk and adjuvant chemotherapy effects in breast cancer

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New anticancer agents have led to higher life expectancy for cancer patients. However, treatment related morbidity factors such as cardiac toxicity have become important issues for long-term cancer survivors. Cardiotoxic side effects such as arrhythmia, thromboembolism and myocardial ischemia are common with anti-cancer drugs. This led to the development of cardio-oncology field, to promote cardiovascular health while providing the best cancer therapy.

Using change in impedance, we monitored breast cancer cell regrowth after chemotherapy treatment *in vitro*, coupled with the acute and chronic effects of this treatment on human stem cell derived cardiomyocytes (hsc-CMs). One of the standard clinical regimens for breast cancer is a combination of cyclophosphamide, adriamycin (doxorubicin) and 5-fluorouracil (CAF). Even though initially successful, tumor recurrence after this therapy remains a major cause of mortality in breast cancer patients. We investigated responses from murine H8N8 (immortal mammary carcinoma cell line with tumor stem cell properties) and H8N8 T3.2 (once-treated recurrent tumor variant) cells, to single and recurrent CAF treatment. Changes in impedance and confluency of these cells were used as a measure of toxicity, with cell viability monitored under physiological conditions for 500h. Dose- and treatment dependent effects of CAF clinical treatment on cycle- regrowth of tumor cells were observed.

We further investigated putative cardiovascular side effects of CAF mix and paclitaxel (acute and chronic) on hsc-CMs viability. We observed the cardiotoxic effects of paclitaxel (a microtuble stabilizing drug approved for the treatment of breast, ovarian and lung cancer). Paclitaxel and CAF also induced negative changes in cell contraction properties. hsc-CMs´ viability and beating patterns were monitored over 190 h. Paclitaxel showed a time and dose dependent decrease in base impedance and impedance amplitude, cyclophosphamide and 5-fluouracil shown no or small effect, while doxorubicin shown significant toxic effects in all combinations.

In summary, long-term high-resolution impedance monitoring provides amenable insights into dynamics of cell proliferation and contraction, for in vitro investigations of adjuvant chemotherapy in both cancer and cardio-oncology fields.