Madeira et al. BMC Proceedings 2014, 8(Suppl 4):P22
http://www.biomedcentral.com/1753-6561/8/S4/P22

BMC Proceedings

POSTER PRESENTATION Open Access

In vitro antineoplastic activity in triple-negative breast cancer cell line and *in vivo*

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From 5th Congress of the Brazilian Biotechnology Society (SBBIOTEC)
Florianópolis, Brazil. 10-14 November 2013

Background

Triple negative breast cancer (TNBC) is a heterogeneous subgroup (ER-, PR-, and HER2-) of invasive breast cancer, associated to poor prognosis, partially due to its resistance to available drugs. Therefore, it is imperative to discover new treatment options for the disease. In this context, we have synthesized and screened novel naphtoquinone-derived drugs (patent-protected), rationally designed to act through multiple pathways to avoid tumor chemoresistance.

Methods

Drugs antineoplastic efficacy (AE) was accessed in the claudin-low TNBC cell line, MDA-MB231, by cellular metabolic viability (CMV) and IC_{50} calculation (MTT method; GraphPad Prism version 5.1). Drugs toxicity was studied in healthy mice, following the Guideline 423 (for test of chemicals) of OECD; blood cells and tissues were analyzed by a Pathologist. Computational molecular dock studies were conducted to investigate the molecules tridimensional conformation and bounding energy to topoisomerase 2 (TOPO) and PI3K (Autodock Vina software).

Results and conclusions

We screened the AE of 43 novel drugs in MDA-MB231 (CMV ≤ 50% with 7 drugs). Of these, the most promising drugs PIC 20 (IC_{50} $1.38x10^{-5}$M; CMV = 10%) and PIC21 (IC_{50} $5.00x10^{-5}$M; CMV = 30%) showed significantly higher AE than cisplatin (IC_{50} $1.56x10^{-4}$M; CMV>90%), doxorubicin (IC_{50} $1.76x10^{-4}$M; CMV = 62%), and paclitaxel (IC_{50} $5.05x10^{-7}$M; CMV = 80%). None of the treated mice died, neither demonstrated symptoms of toxicity, following 14-days treatment with PIC. Indeed, there was no significant change in the animals' weight and general activity/behavior. Major organs showed no significant morphological changes, congestion, edema, necrosis, degeneration or inflammation. On the other hand, there was a 48.98% decrease in their hematocrit count. Finally, based on the crystalline structure of proteins deposited on PDB (1QZR, TOPO; 1E7U, PI3K), and PIC20 and PIC21 tridimensional structures, we concluded that the novel molecules bind to the ATP domain of the proteins with similar interaction energy (E) than the TOPO - Doxorubicin (E = -5.6) and Etoposide (E = -5.7) - or PI3K inhibitors - LY294002 (E = -9.5) and Wortmannin (E = -8.8): PIC20: E = -5.3 and -8.9; PIC21: E = -5.7 and -8.2, for TOPO and PI3K, respectively. In conclusion, we present novel and potentially safe drugs to treat TNBC, in an innovative and economically viable approach.

Acknowledgements
Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Fundação de Amparo à Pesquisa do Espírito Santo (FAPES).

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Published: 1 October 2014

doi:10.1186/1753-6561-8-S4-P22
Cite this article as: Madeira *et al.*: *In vitro* antineoplastic activity in triple-negative breast cancer cell line and *in vivo*. *BMC Proceedings* 2014 **8** (Suppl 4):P22.

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