ImmunoTools *special* Award 2018

Marisa P. Sarria, Research Fellow

Supervisor: Begoña Espiña

INL - International Iberian Nanotechnology Laboratory
Nano4Environment Unit - Water Quality Research Group
Av. Mestre José Veiga s/n - 4715-330 Braga - Portugal

Nanoliposomes for targeted delivery of marine phycotoxins as anticancer agents

Aquatic environments constitute the cradle of primitive molecules, which boosted the evolution to more complex life-forms and production of unique chemical entities, comprising a vast strategic natural resource to discover novel 'validated' structures as therapeutical agents. In general, the marine pharmaceutical pipeline remains very active. Yet, the momentum to deliver additional compounds to the near future implies tunable solutions to control their native cytotoxic potential and lack of in vivo bioactivity at sub-toxic concentrations.

To date, all marine-derived drugs, approved or under clinical trials, are from animal origin [1]. In opposition, investigation on therapeutical potential of marine floras of high-density proliferation is underexplored, a paradox given their prolific scope of potent poisoning metabolites [2]. Marine dinoflagellates blooms are among the most widespread distributed and harmful reported [3], producing powerful venoms [4], even at concentrations below detection limits [5]. Several emerging phyto-derived toxins and bioactives have been recognized as high added-value biomolecules and potential therapeutical tools [4].

Yet, their investigation as potential anticancer agents is unexplored, and even more if nanoscale vehicles are considered for their specific delivery to enhance biological properties, while reducing poisonous potency. Efficient targeting delivery of these bioactive agents with high cellular uptake is fundamental to minimize non-specific binding, reducing load-concentration and mitigating immunogenicity. In this context, targeted stealth pH-sensitive lipid-based nanoparticles are being developed at the INL as highly competent and biocompatible delivery nanosolutions for marine phycotoxins specific delivery and controlled release towards cancer cells. To identify with accuracy the limits within which these nanosystems can be applied safely preserving the bioavailability of the load, in vitro 2D models based testing is being pursued in different mammal cellular lines.

SDF-1 and CXCR4 were demonstrated to be up-regulated via VEGF inducing glioma cell invasion [6]. Taking into account that this angiogenic couple and respective

receptors are expressed in diverse cancer cells reporting alterations of cyclic nucleotide signalling [7], including modifications in expression and/or activity of important molecular targets of the phycotoxins, as phosphodiesterases of yessotoxins [8], cancer targeting via this strategy seems a promising and underexplored route to investigate. Yessotoxins are lipophilic polyethers capable of triggering paraptosis-like cell decadence of the cancer cells [8], from mitotic arrest to senescence, inducing subsequent secretion of soluble factors, as numerous proinflammatory chemo- and cytokines that regulate immune responses, and are intended to be determined taking advantage of ELISA-set(s) and reagents from ImmunoTools *special* Award 2018.

Our Project aims to compose advances on biomedical application of marine floras as sources of natural therapeutical agents, exploring emergent widespread-reported microalgae-derived bioactives; contribute for the development of innovative functionalized nanocarriers capable of their highly-specific delivery, and enhance pre-clinical data on pharmacological potential of microalgae-derived biomolecules as therapeutical agents. One of the most exciting outcomes of this project will surely be to allow for a mechanistic perspective of the perceived alterations, rather than a pure description of the phenotypical modifications.

[1] Mayer A.M.S., Rodríguez A.D., Taglialatela-Scafati O., Fusetani N., 2013. Marine pharmacology in 2009-2011: marine compounds with antibacterial, antidiabetic, antifungal, anti-inflammatory, antiprotozoal, antituberculosis, and antiviral activities; affecting the immune and nervous systems, and other miscellaneous mechanisms of action. Mar. Drugs 11(7):2510-2573.
[2] Boopathy N.S., Kathiresan K., 2010. Anticancer drugs from marine flora: an overview. J. Oncol. volume 2010, article ID 214186, 18 pages.
[3] Camacho F.G., Rodríguez J.G., Mirón A.S., García M.C., Belarbi E.H., Chisti Y., Grima E.M., 2007. Biotechnological significance of toxic marine dinoflagellates. Biotechnol Adv. 25(2):176-194.
[4] Dominguez H.J., Paz B., Daranas A.H., Norte M., Franco J.M., Fernández J.J., 2010. Dinoflagellate polyether within the yessotoxin, pectenotoxin and okadaic acid toxin groups: characterization, analysis and human health implications. Toxicon. 56(2):191-217.
[5] EFSA, 2009. Marine biotoxins in shellfish: summary on regulated marine biotoxins. The EFSA J. 1306:1-23.
[6] Hong X., Jiang F., Kalkanis S.N., Zhang Z.G., Zhang X.P., DeCarvalho A.C., Katakowski M., Bobbitt K., Mikkelsen T., Chopp M., 2006. SDF-1 and CXCR4 are up-regulated by VEGF and contribute to glioma cell invasion. Cancer Lett. 236(1):39-45.
[7] Fajardo A.M., Piazza G.A., Tinsley H.N., 2014. The role of cyclic nucleotide signaling pathways in cancer: targets for prevention and treatment. Cancers (Basel). 6(1):436-458.
[8] Alfonso A., Vieytes M.R., Botana L.M, 2016. Yessotoxin, a promising therapeutic tool. Mar. Drugs 14(2):30.

ImmunoTools *special* AWARD for **Marisa P. Sarria** includes 25 reagents

FITC - conjugated anti-human Annexin V-FITC

recombinant human cytokines: rh EGF, rh IL-1beta, rh IL-2, rh IL-6, rh IL-10, rh LIF, rh MIP-4/CCL18, rh SDF-1α/CXCL12a, rh SDF-1β/CXCL12b, rh TNFα, rh VEGF-A

Biotin- rh IL-2, Biotin- rh IL-6

human ELISA-set (for one 96 plate): rh IL-6, rh IL-8, rh TNF-a (each ELISA set contains 4 reagents)

recombinant mouse cytokines: rm LIF

DETAILS more AWARDS