TARGETING ITGB3 MEDIATED INTERCELLULAR COMMUNICATION: A THERAPEUTIC STRATEGY TO PREVENT METASTATIC DISEASES PROGRESSION IN BREAST CANCER PATIENTS

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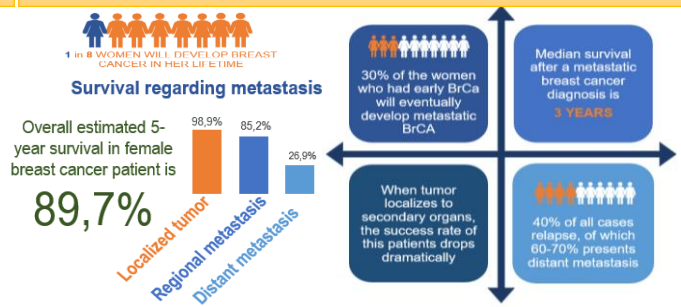
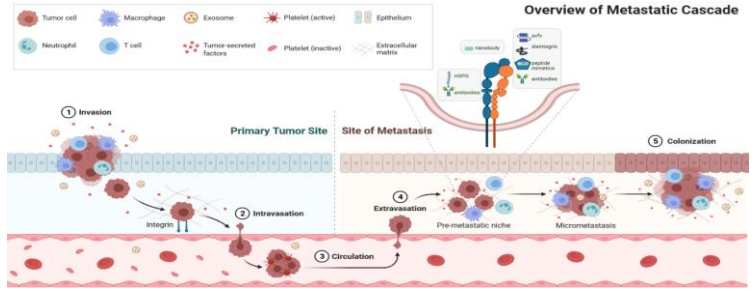
Abstract

Despite numerous advances in cancer research, the lethality of metastatic tumors has practically not been improved in recent years. In breast cancer, the progression of metastatic disease has a poor prognosis, with 5-year survival rates of less than 20%. In a screening of new factors involved in resistance to tumor stress, the beta 3 integrin (ITGB3) has been identified, moreover, it has been shown that it is essential in intracellular communication through the uptake of extracellular vesicles (EV), key part in the progression of breast cancer metastasis. The identification of the molecular agents involved in the uptake of EVs by breast cancer cells allows for in vitro and in vivo screening of inhibitors to be able to identify selective inhibitors that prevent this process and, therefore, may delay or prevent the progression of breast cancer metastasis. Among the molecules that interfere with this metastasis-promoting process, we have identified and produced a scfv that, according to preliminary experiments, blocks the internment of EV by a significant percentage.

Introduction





The ITGB3 model

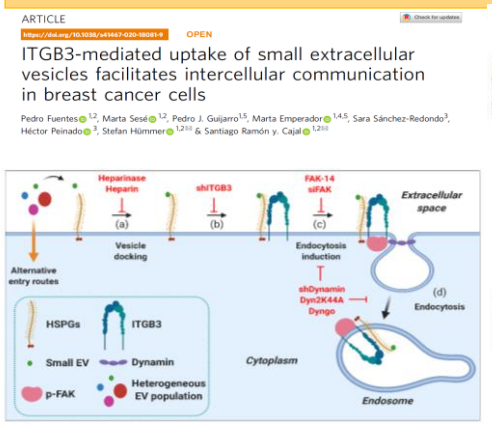


Fig. 1 Model for the proposed role of ITGB3 in vesicle uptake and exosome biogenesis: (a) EV-HSPG interaction; (b) αvβ3 recruitment; (c) pFAK -DYNAMIN recruitment to endocytosis complex; (d) Dynamin-mediated internalization of Evs and EE formation. Fuentes et al, 2020

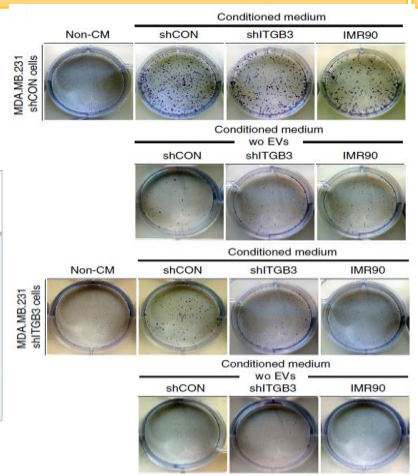


Fig. 2 ITGB3 is required for EV-induced colony formation : Representative pictures are shown for each cell population and condition. Fuentes et al, 2020

Inhibition of ITGB3

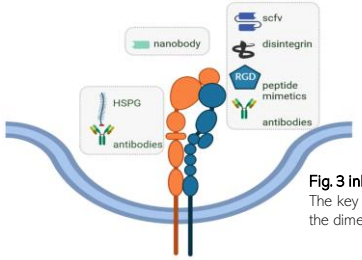


Fig. 3 inhibition products; The key in this proyect is to inhibit the dimer with a mix of drugs.

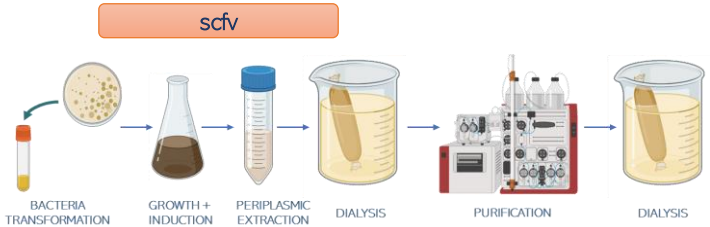


Fig. 4 scfv production: The scfv sequence was found in a paper and cloned in to the pHEN6. The scfv was produce in wk6 modified E.coli by inducing a periplasmic production. Then the scfv was extracted from the periplasmic, dyalized in PBS and purified by äkta (HPLC). A second dyalisis is needed to remove the buffers from the purification.

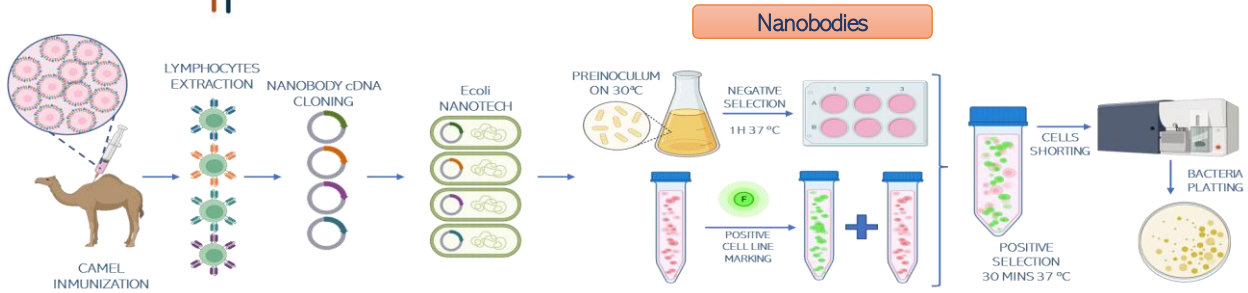


Fig 5 Nanobodies libraries: Nanobodies are generated by camelid immunization, cDNAs corresponding to VHHs regions from lymphocytes are amplified and cloned in pNeae2 vector for *E. coli* display in the outter membrane. The selection of the nanobodies that recognizes the protein of interest can be selected by FACS for cells expressing the antigen.

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