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Using nanotechnology to target cancer associated neurons as a tool for treating breast cancer

Maya Kaduri, Mor Sela, Maria Poley, Janna Shainsky-Roitman, Jeny Shklover, and Avi Schroeder

Laboratory for Targeted Drug Delivery and Personalized Medicine Technologies, Department of Chemical Engineering, Technion, Haifa, Israel.

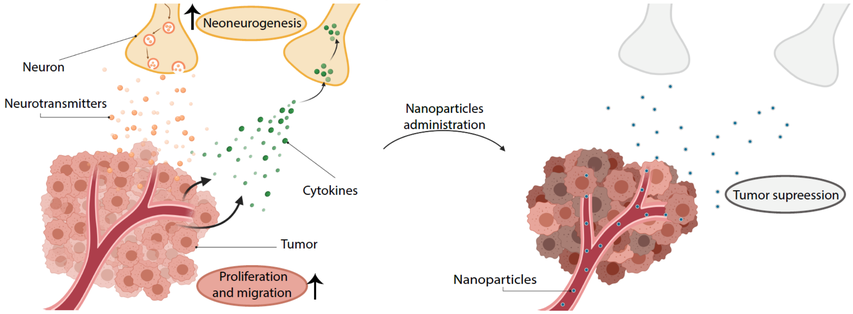
mayakad@campus.technion.ac.il

Introduction

It has been discovered that **there is a connection between the nervous system and cancer progression.** Nerves and their axons actively infiltrate the tumor tissue and stimulate cancer-cell growth, proliferation, invasion and migration. Moreover, cancer cells can grow and invade the nerves in the tumor tissue, causing extreme pain and using the nerves as a means for metastatic spread.

Objectives

Study the nerve–cancer cell interactions and develop a new class of **nanotechnologies that will treat breast cancer by interrupting the signaling between the tumor and the nerves**. To achieve this goal, we have developed liposomes contain the local anesthetic bupivacaine, and delivered it to the tumor microenvironment to be taken up by the neurons and cause their destruction.



Take home message

There are collaborative interactions between nerves and cancer that support cancer development and progression. **By using nanotechnology** that reduces nerve invasion we aim to **inhibit tumor growth and metastasis.**

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Results:

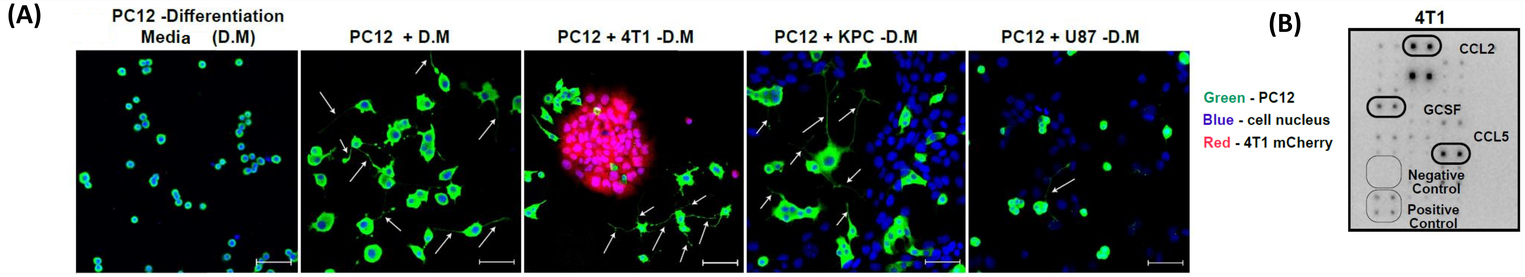

Fig.1 Cancer cells stimulate neurite growth: **(A)** Confocal microscopy analysis demonstrates the effect of different cancer cell types presence on neuron-like cells (PC12) during 72 hours. PC12 axons represented by arrows. The scale bar is 50µm. 4T1, triple negative breast cancer cells; KPC, pancreatic cancer cells; U87, glioblastoma cells. **(B)** Cancer cells secrete cytokines that might promote neurites outgrowth, as was identified by cytokine antibody array.

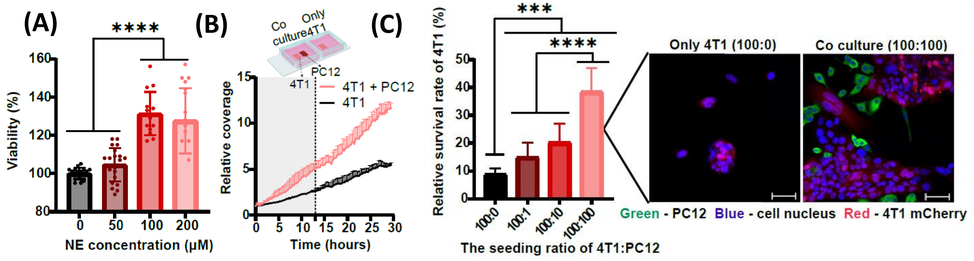

Fig.2 Neuron cells enhance the potency of cancer cells: **(A)** Increased concentrations of norepinephrine (NE) promote 4T1 cell proliferation **(B)** The increased coverage of 4T1 cells due to PC12 cells presence. The area cover obtained at the beginning of the experiment was set to 100%, and all the other values were normalized according to that. **(C)** An enhanced survival of 4T1 in starvation medium due to PC12 cells presence. Scale bar is 50µm.

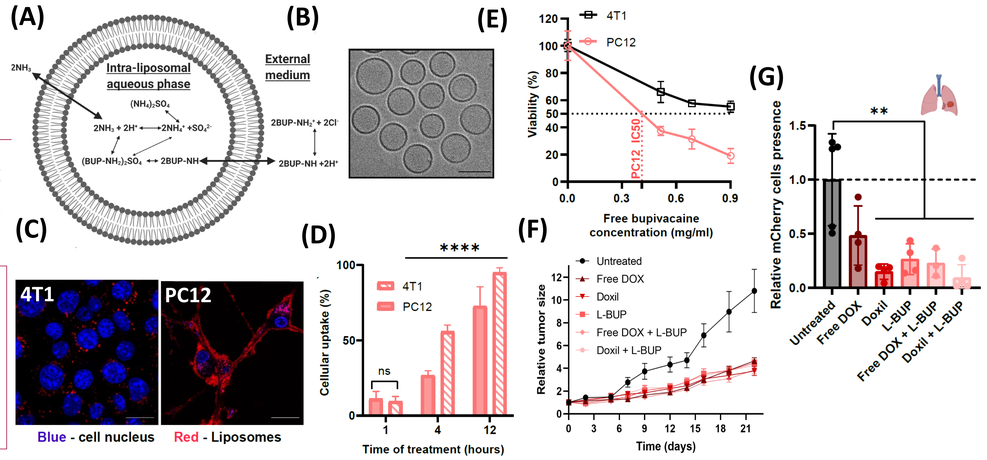

Fig.3 Liposomal bupivacaine inhibit cancer progression: **(A)** 100nm bupivacaine liposomes were prepared using the ammonium sulfate gradient method. **(B)** The L-BUP were characterized by Cryo-TEM images (100nm). **(C,D)** The increased cellular uptake of liposomes by PC12 and 4T1 cells, was observed using confocal microscopy (20µm) and flow cytometry respectively. **(E)** Toxicity of free bupivacaine after 6 hours of treatment on 4T1 and PC12. **(F)** The relative tumor size of BALB/c mice bearing orthotopic 4T1 mCherry tumors in the mammary fat pad. DOX, free doxorubicin; Doxil, liposomal doxorubicin; L-BUP, liposomal bupivacaine; **(G)** Decrease in metastasis formation due to L-BUP treatment. The percentage of positive mCherry cells for each tissue was divided by the value of the untreated group. Therefore, a value which is below 1 represent an decrease in the metastasis formation.