Targeting of non-cancer cells in the tumor microenvironment

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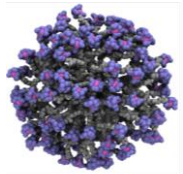
COST ACTION CA 17140 – NANO2CLINIC
Working group 3 workshop
Preclinical Development of Cancer Nanomedicines: State of the Art and Future Perspectives
March 24-25th 2022, Institute of Oncology Research-IOR, Bellinzona, CH

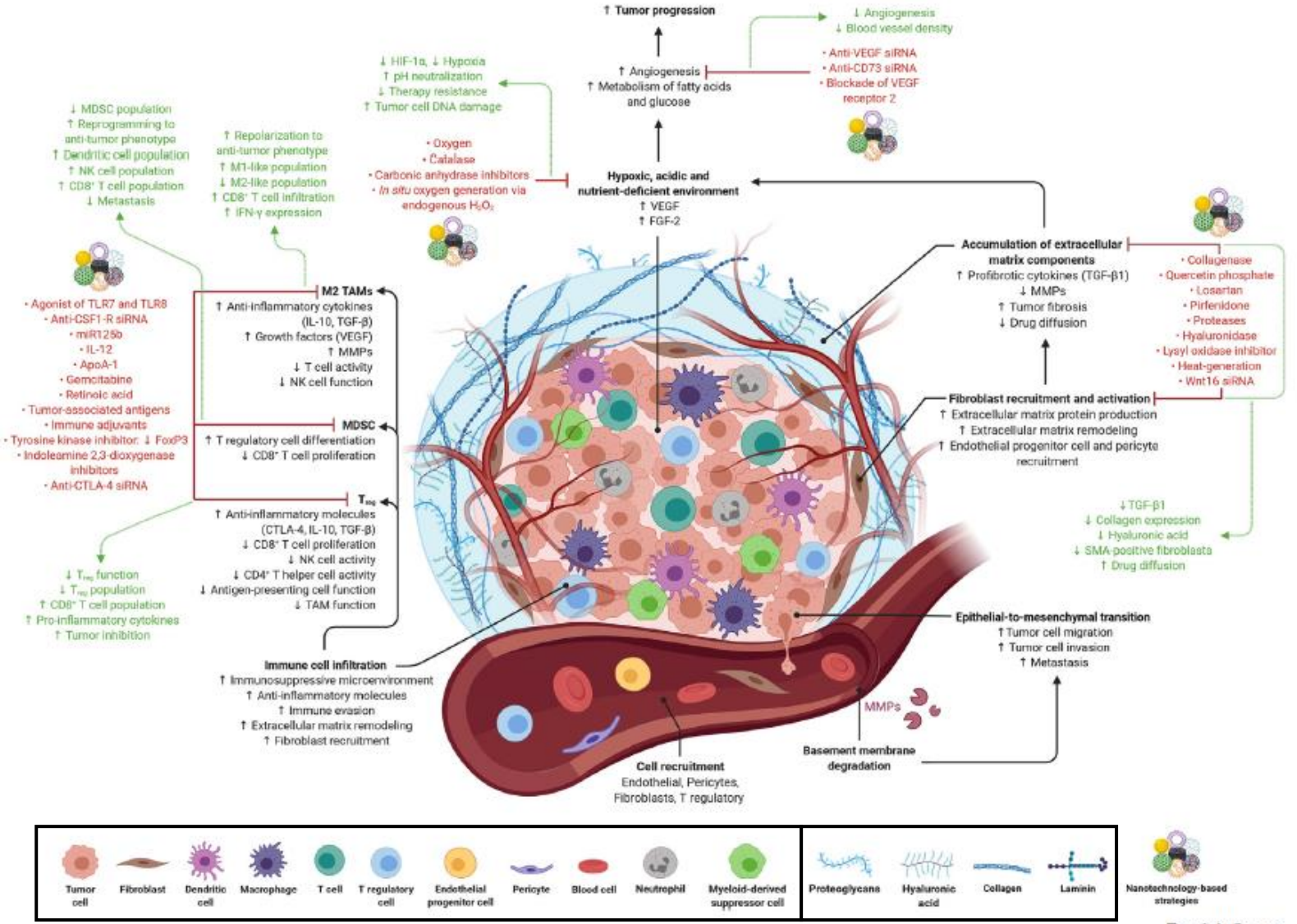
COST ACTION CA 17140
NANO2CLINIC
CANCER NANOMEDICINE - FROM THE BENCH TO THE BEDSIDE

cost
EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Funded by the European Union

Nanomedicine targeting of the TME





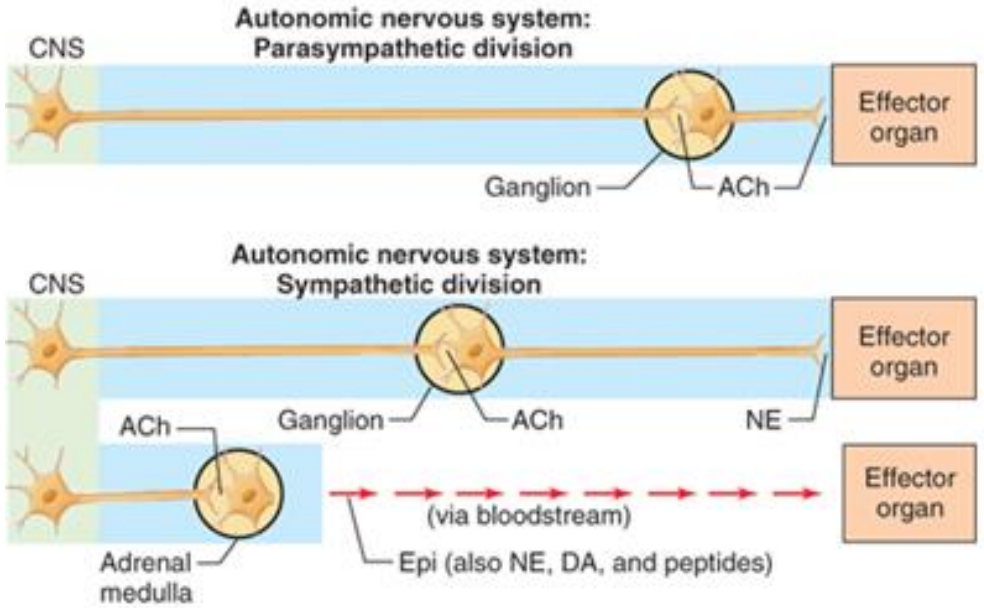
Cellular components

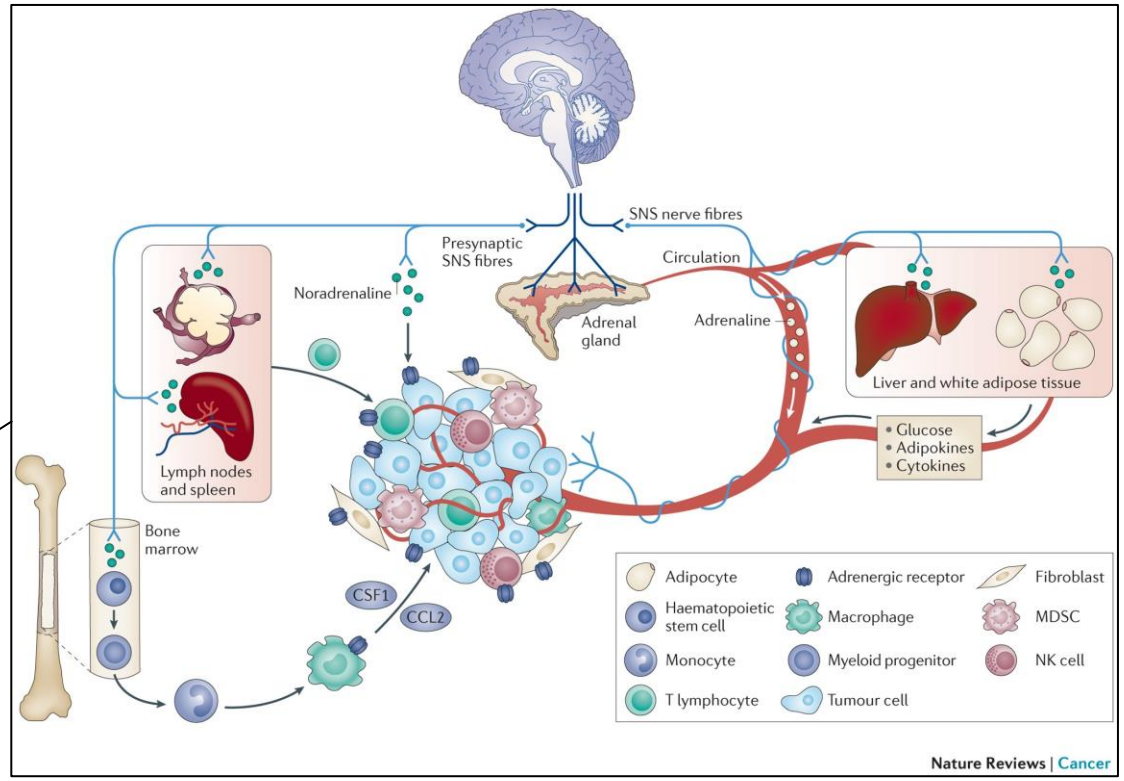
Non-cellular components

"Nanomedicine-based strategies to target and modulate the tumor microenvironment"
Bárbara B. Mendes et al; Cell Press, 2021

Targeting of tumor-infiltrating nerves

Pheripheral nervous system



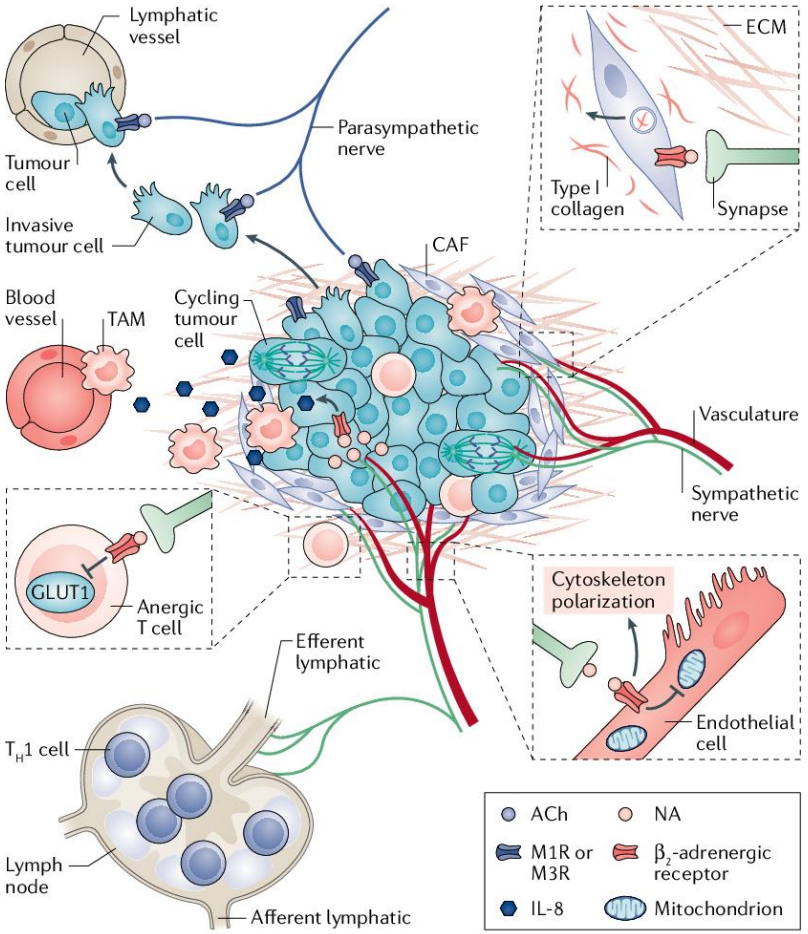


"Vander's Human Physiology".
Vander et al; NY: McGraw-Hill; 2008.

"*Nerves in cancer*"
Ali H. Zahalka et el; Nature reviews, Cancer; 2020

Sympathetic nervous system (SNS) regulation of tumor progression: an emerging hallmark of cancer

Immunosuppressive effects



Metastasis formation

Angiogenesis and lympho-angiogenesis

"*Nerves in cancer*" Ali H. Zahalka et el; Nature reviews, Cancer; 2020

Table 1. Evidence for neural regulation in cancer and cancer cell–induced axonogenesis

Cancer type	Finding	Ref.
Prostate	Adrenergic and cholinergic nerves stimulate tumor progression	(5)
	Adrenergic nerves activate an angiogenic switch	(38)
	Botulinum toxin–based denervation induces cancer cell apoptosis	(74)
	Neurogenic expression in stem cells	(51)
	Neurotrophic factors drive tumor axonogenesis	(26, 27)
	Cancer incidence is lower in spinal cord injuries	(6)
Gastric	Vagus nerve stimulates cancer initiation and progression	(8)
	Cholinergic signaling stimulates cancer stem cell growth	(8, 28)
	Cholinergic signaling induces NGF secretion that in turn drives tumor axonogenesis	(28)
Pancreatic	Sensory nerves stimulate tumor progression	(9)
	Sympathetic nerve/NGF feed-forward loop promotes cancer progression	(10)
	Parasympathetic nerves suppress tumorigenesis and cancer stemness	(11)
	Neuronal cross-talk promotes tumorigenesis	(13, 14, 29)
Skin	Sensory innervation is necessary to tumor initiation and cancer stem cell growth	(15)
Breast	Axonogenesis is associated with tumor aggressiveness and driven by NGF	(30, 31)
Colon	Nerve infiltration is associated with tumor aggressiveness	(33, 34)
	Neuroimmune regulation of cancer progression	(62)
Ovary	Tumor axonogenesis is driven by BDNF	(71)
Head and neck	Axonogenesis is stimulated by cancer cell–released exosomes containing Ephrin B1	(73)
Glioma	Neurons stimulate cancer cell growth through the release of neuroligin-3 and pleiotropin	(16, 17)

NOTE: Nerves can stimulate cancer cells directly or indirectly through the tumor microenvironment.

"Tumor neurobiology and the war of nerves in cancer " Sam Faulkner et al; 2019

SCIENCE ADVANCES | RESEARCH ARTICLE

CANCER

Targeting neurons in the tumor microenvironment with bupivacaine nanoparticles reduces breast cancer progression and metastases

Maya Kaduri[1], Mor Sela[1], Shaked Kagan[1], Maria Poley[1], Hanan Abumanhal-Masarweh[1,2], Patricia Mora-Raimundo[1], Alberto Ouro[3,4,5], Nitsan Dahan[6], Dov Hershkovitz[7], Jeny Shklover[1], Janna Shainsky-Roitman[1], Yosef Buganim[4], Avi Schroeder[1]*

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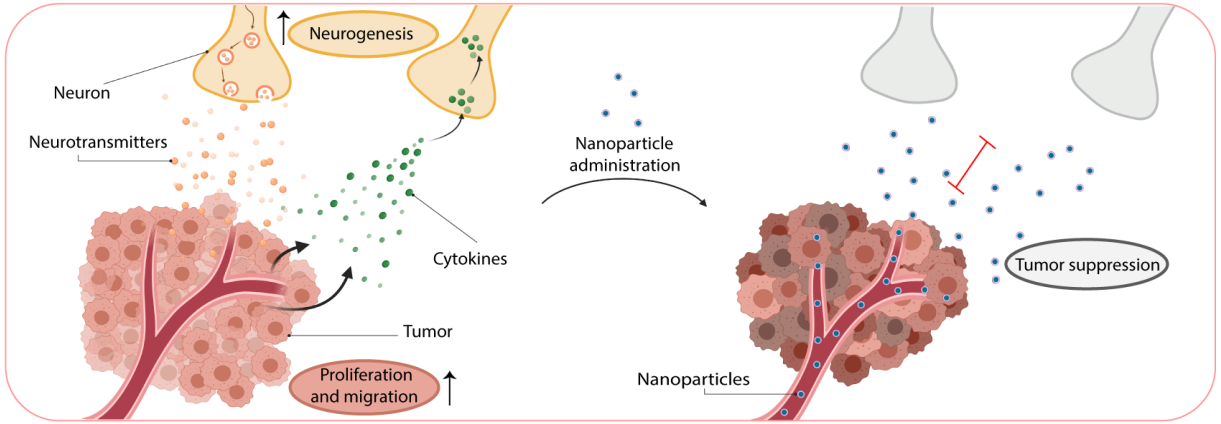
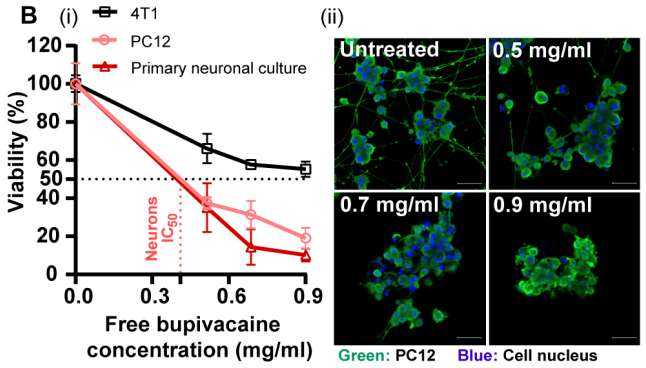
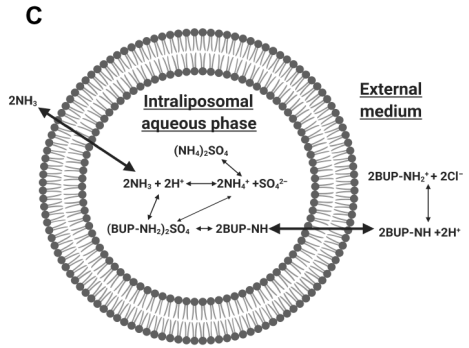
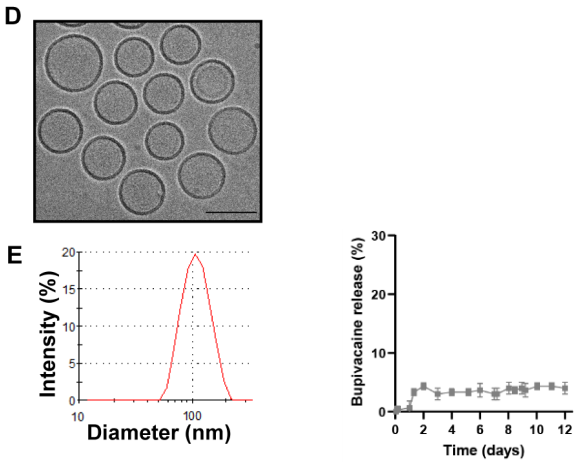


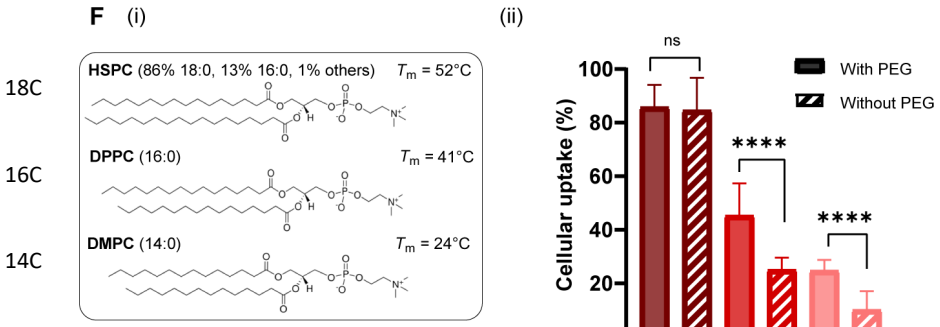
Analgesic NPs as tool for targeting neurons within breast cancer tumors

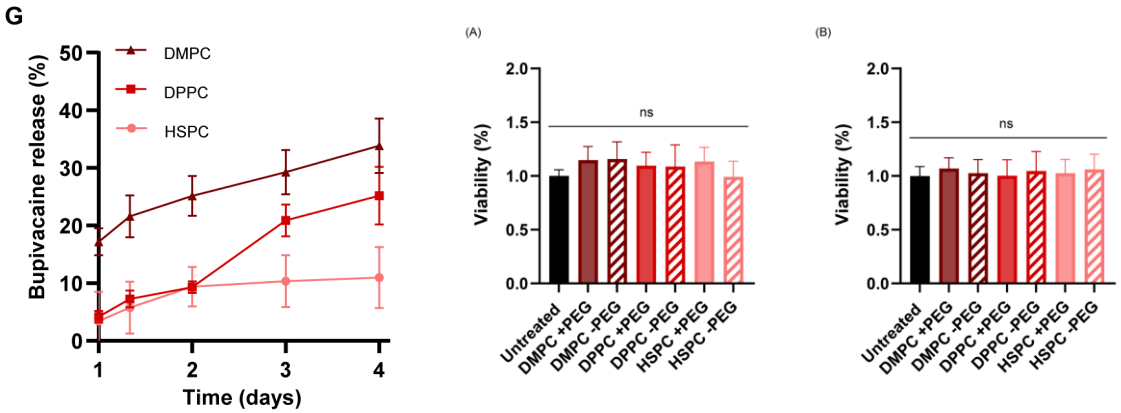
- Primary neurons
- Rat adrenal cells (PC12)
- TNBC cells (4T1)







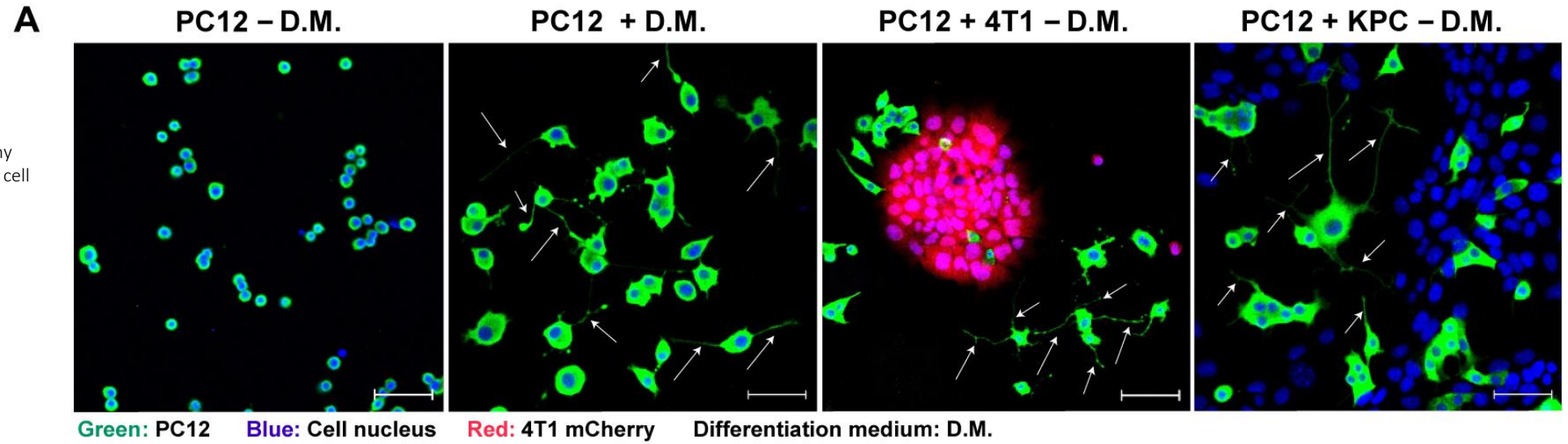


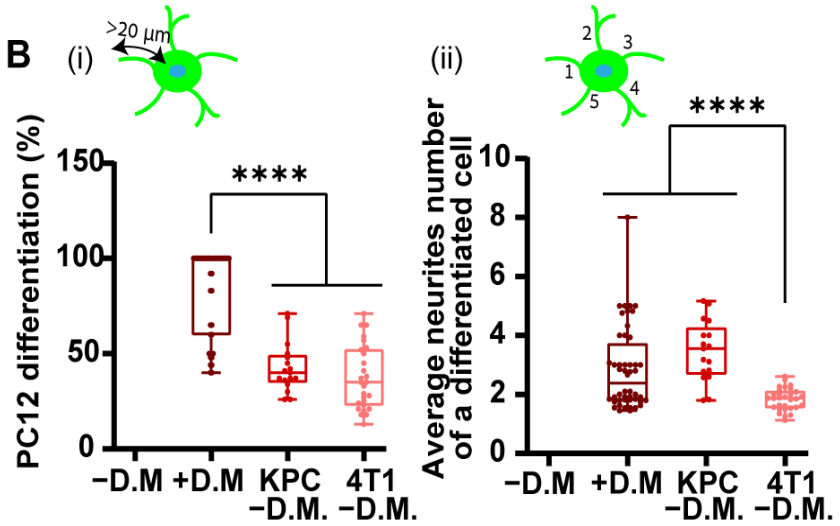


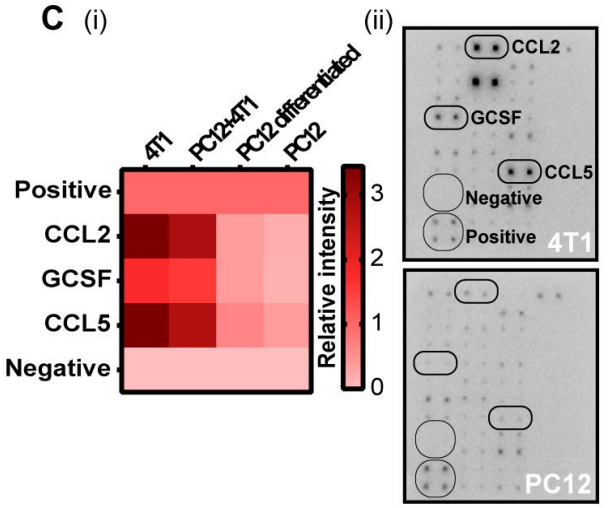
Kaduri et al; Science advances; 2021

Cancer cells promotes neurite growth

Neurite: refers to any projection from the cell body of a neuron.

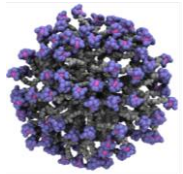


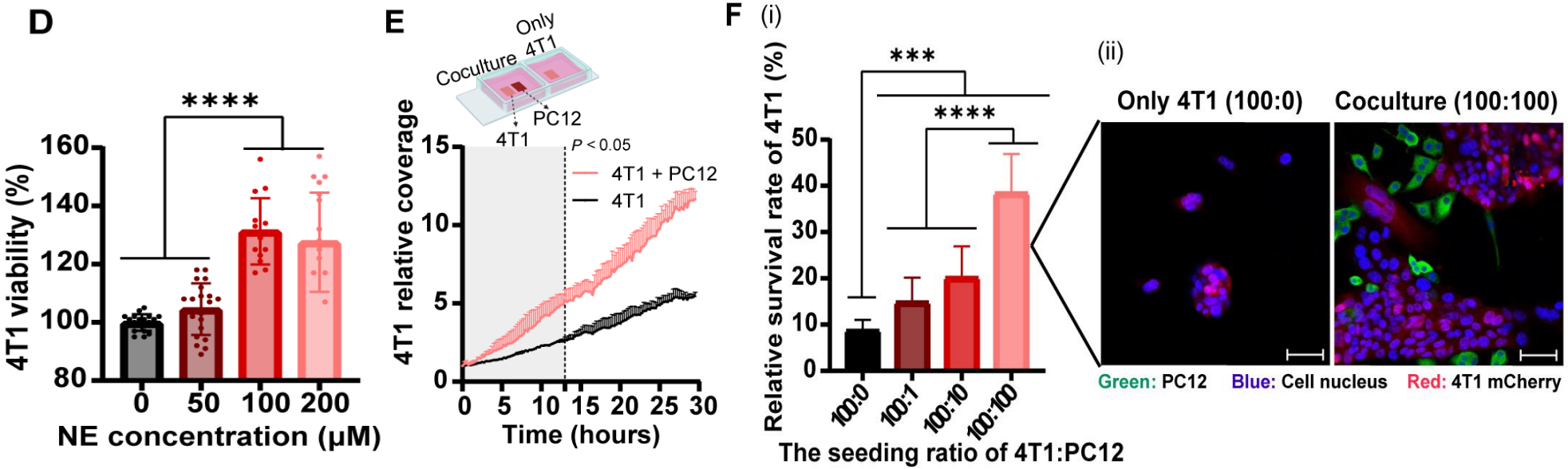


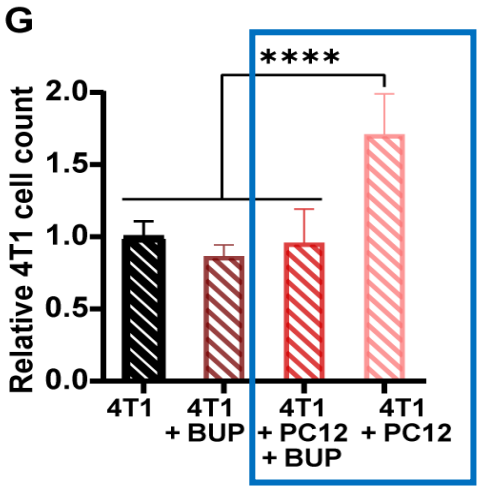


Kaduri et al; Science advances; 2021

Nerves induce cancer cell proliferation, migration and survival



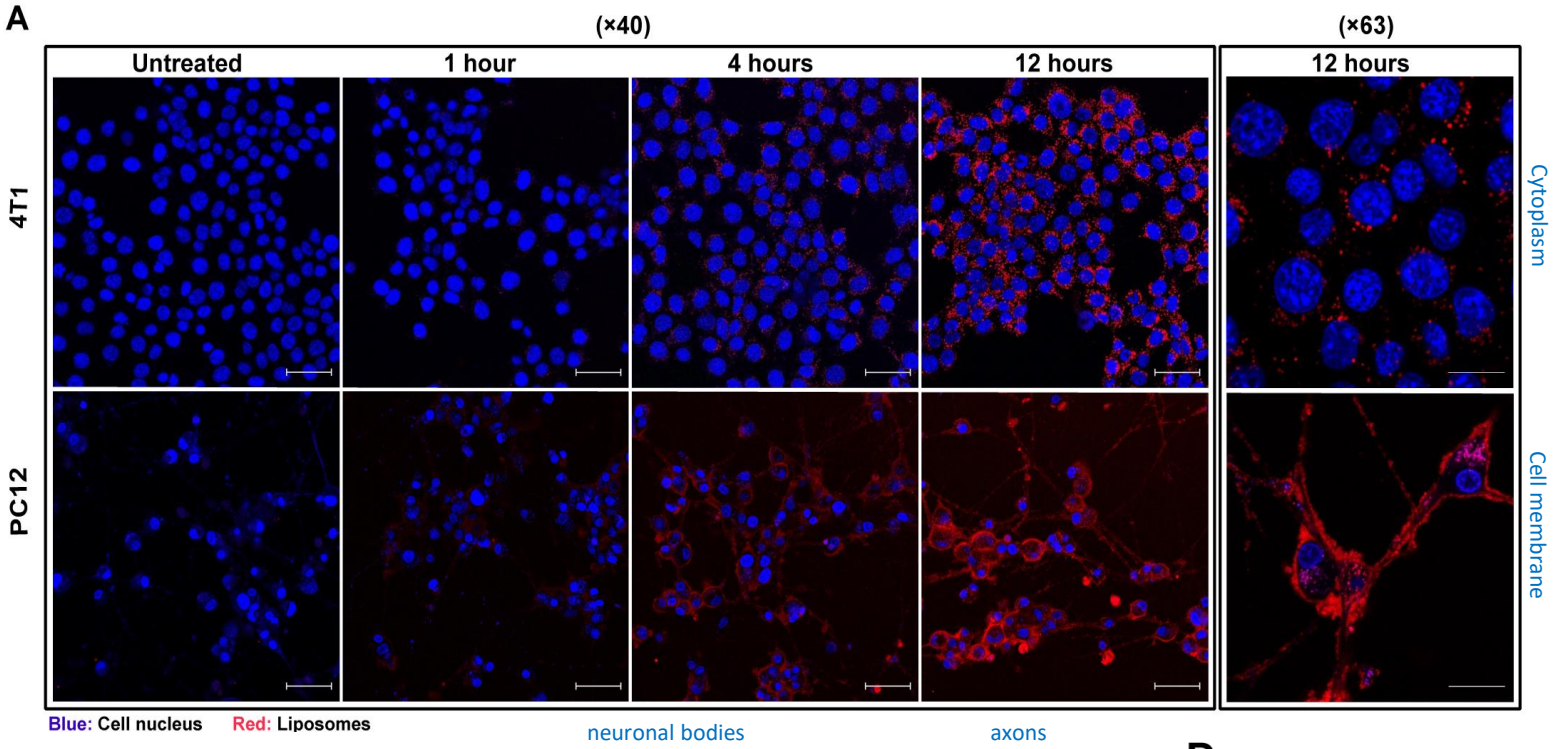


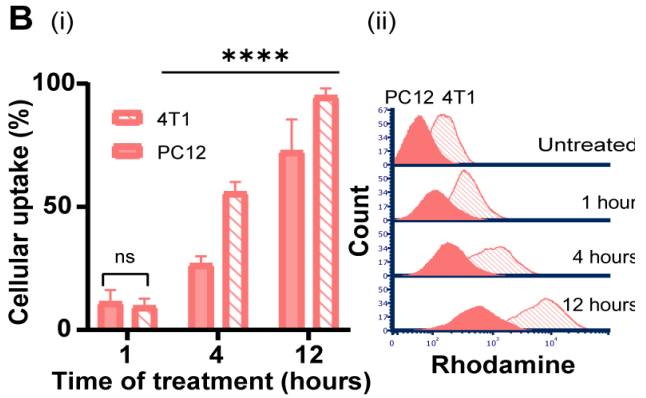


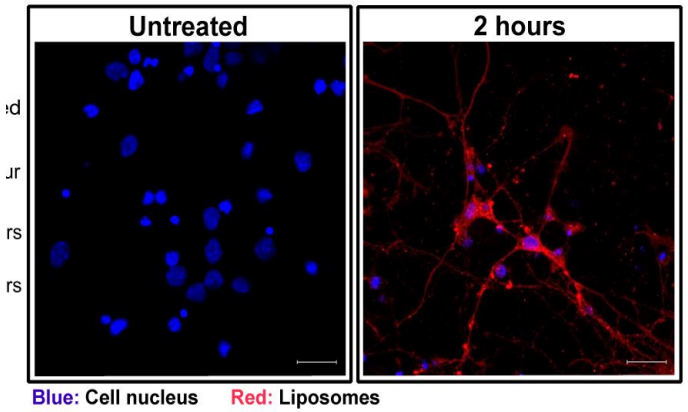
BUP target neurons and in turn influence tumor cells

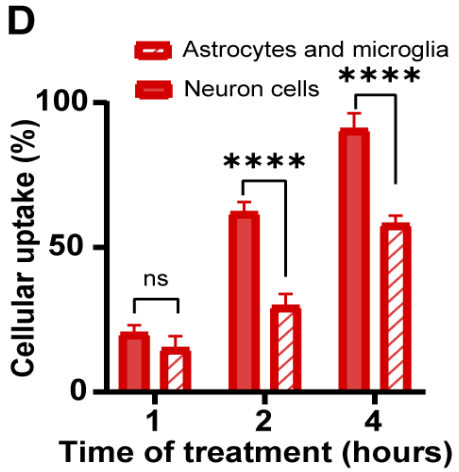
Kaduri et al; Science advances; 2021

Uptake of liposomes by neuron cancer cells



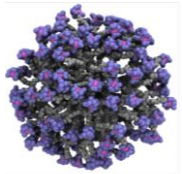




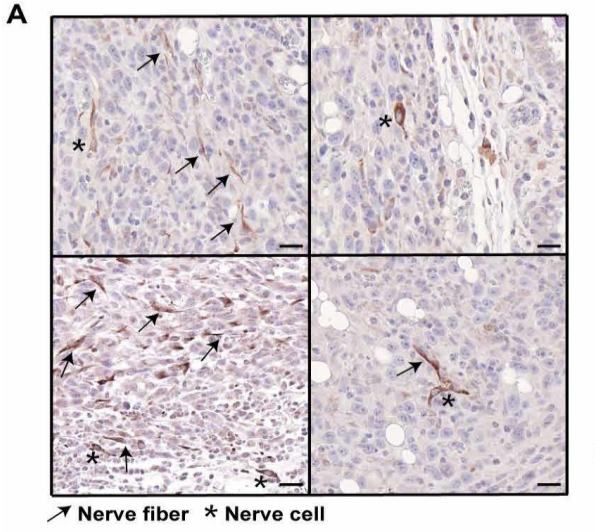


Kaduri et al; Science advances; 2021

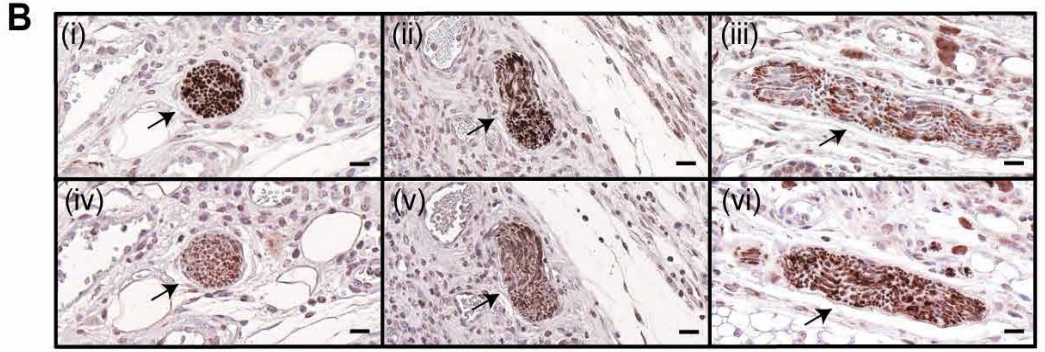
Neurons are integral in breast cancer tumors

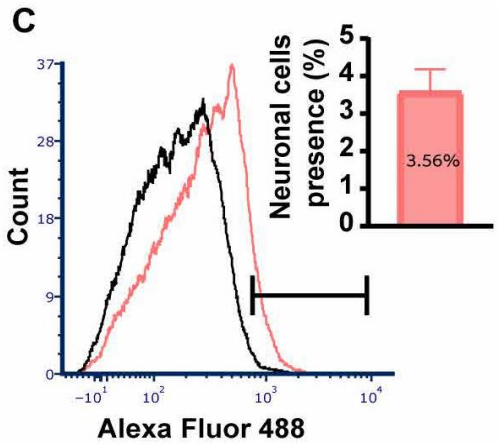


ßIII tubulin
PGP9.5
(neurons)



Nerve trunk

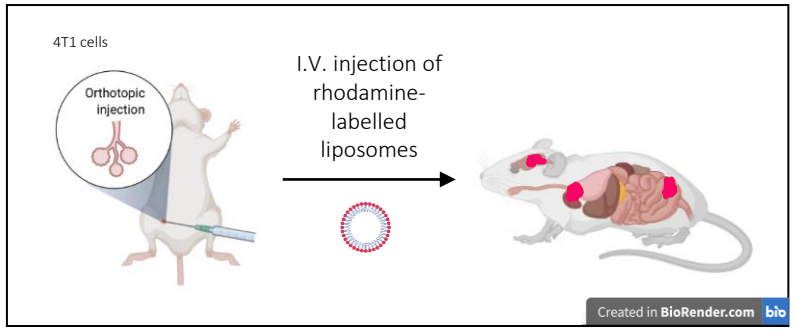


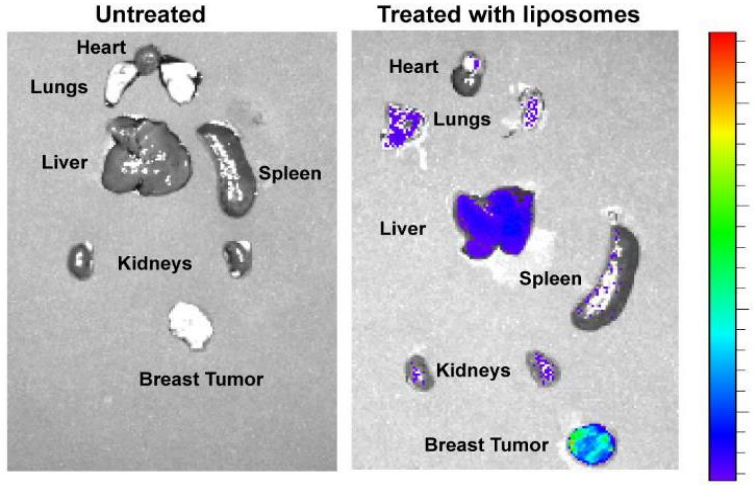


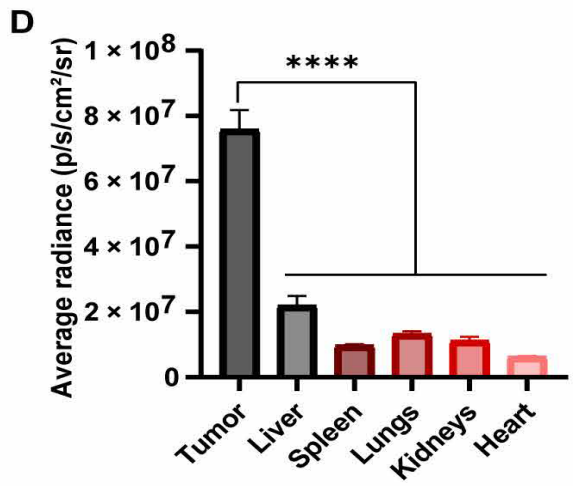
Tyrosine hydrolase, TH (adrenergic neurons)

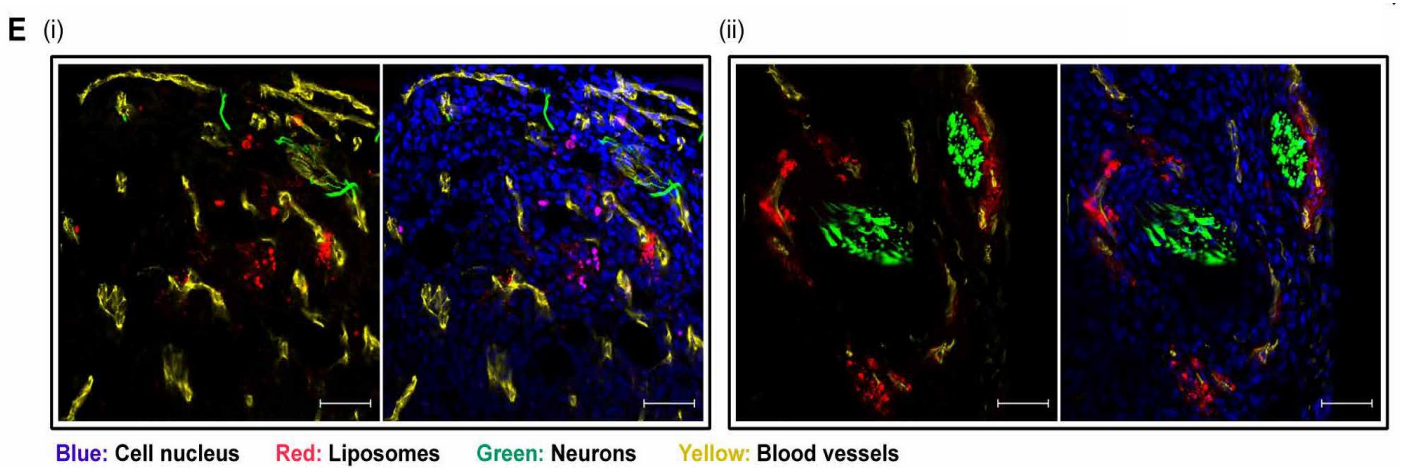
Kaduri et al; Science advances; 2021

Delivery of liposomes to tumor neurons



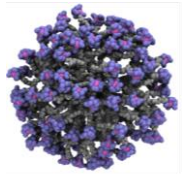


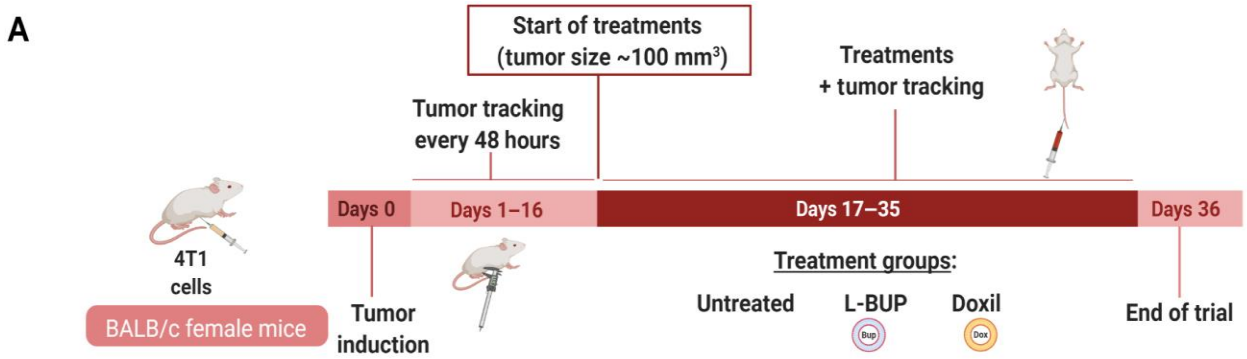


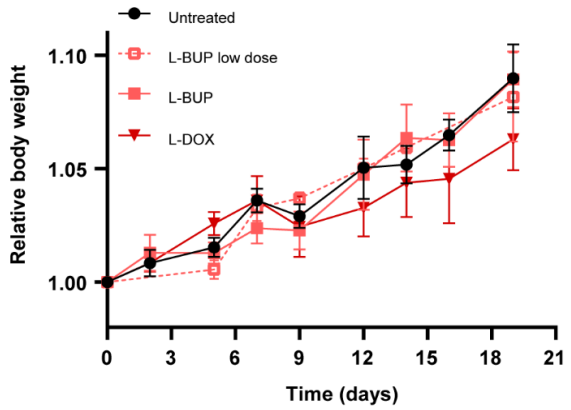


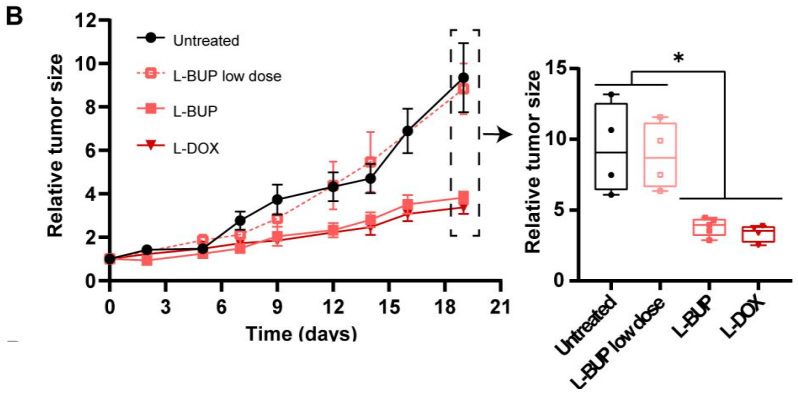
Kaduri et al; Science advances; 2021

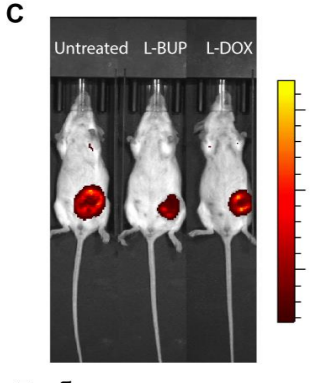
L-BUP inhibit tumor growth and metastasis in *in vivo* breast cancer models

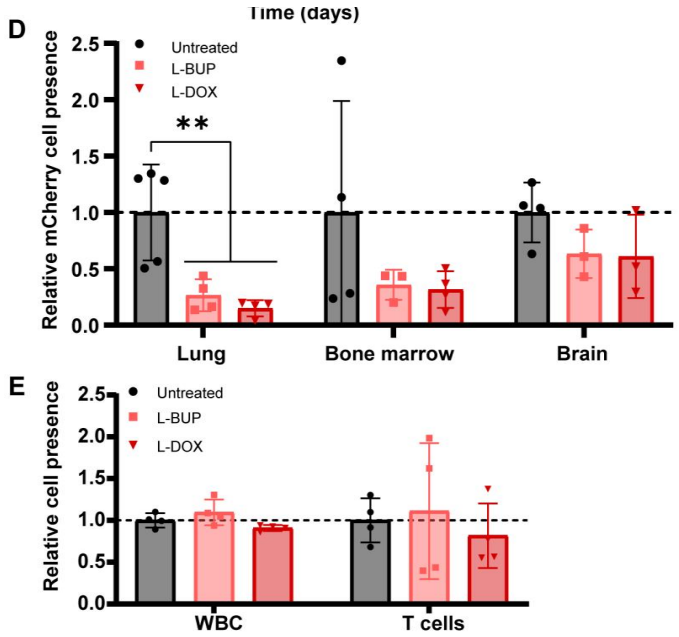


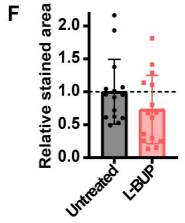


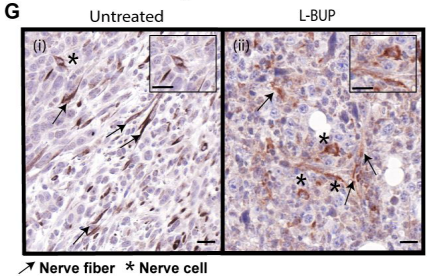












L-BUP treatment supress nerves within the tumors tissues and in turn inhibit tumor growth and reduce metastasis formation without causing any toxic or immunogenic effects

Kaduri et al; Science advances; 2021

Conclusions:

- In co-culture of PC12 and 4T1 cells free bupivacaine reduces the viability of neuronal cells
- Liposomes (100nm) intravenously injected to mice bearing TNBC are distributed specifically within the tumor neurons, curbing tumor growth
- Demonstration of the collaborative interaction between nerves and cancer and the potential of analgesic nanotechnology to supress this interaction

Targeting nerves in the tumor tissues using non-opioid anaesthetic nanoparticles could be a novel therapeutic strategy to improve treatment of breast cancer

Take-home message

Nanotherapeutic strategies that specifically target tumor infiltrating nerves within the tumor tissues are potentially new clinical approaches to improve cancer therapy

Prostate cancer

frontiers in Oncology

Investigation of Neural Microenvironment in Prostate Cancer in Context of Neural Density, Perineural Invasion, and Neuroendocrine Profile of Tumors

Dawid Sigorski[1,2], Jacek Gulczyński[3,4], Aleksandra Sejda[5], Wojciech Rogowski[6,7] and Ewa Iżycka-Świeszewska[3,4*]

2021

Science

Autonomic Nerve Development Contributes to Prostate Cancer Progression

2013

Liver cancer

cmgh CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

The Potential Implication of the Autonomic Nervous System in Hepatocellular Carcinoma

Romain Parent*

2019

Lung cancer

Thoracic Cancer

Autonomic nervous infiltration positively correlates with pathological risk grading and poor prognosis in patients with lung adenocarcinoma

Jing-Xin Shao[1], Bo Wang[2], Yi-Nan Yao[1], Zhi-Jie Pan[1], Qian Shen[1] & Jian-Ying Zhou[1]

2016

TME-targeting nanotechnology-based strategies are promising platform to improve targeting, modulation efficiency and treatment outcome in cancer patients

Thank for your attention!

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CANCER NANOMEDICINE - FROM THE BENCH TO THE BEDSIDE

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