Otago Spotlight Series
Cancer Research

Transforming existing drugs; one more step in the fight against cancer

Khaled Greish MD, Ph.D

Khaled.greish@ otago.ac.nz

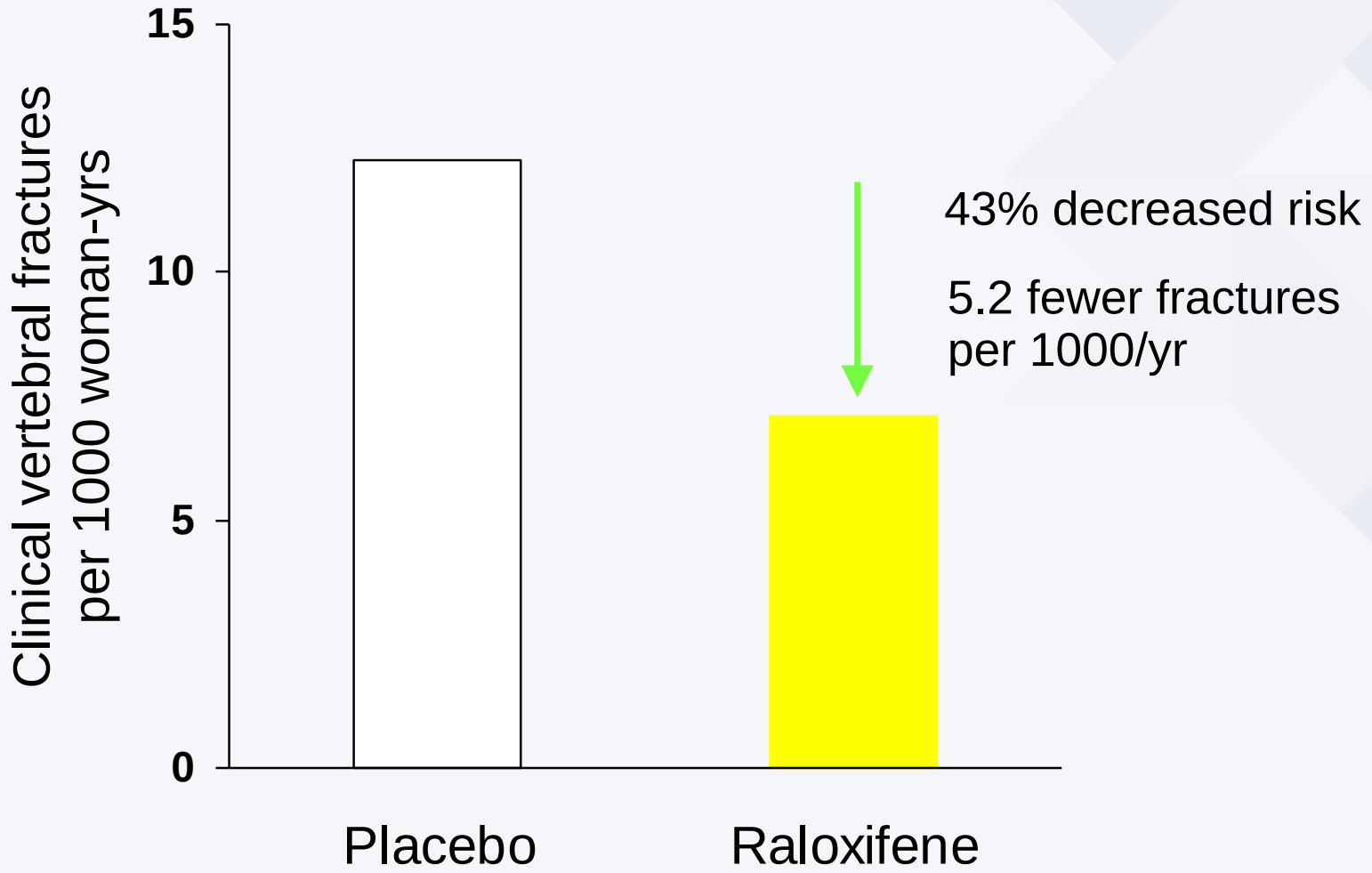
New Zealand Cancer Registry 2011

- ✓ Cancer was the most common cause of death for both males and females in New Zealand in 2011, accounting for nearly a third of all deaths.
- ✓ The most commonly registered cancer was colorectal (3030 registrations), followed by prostate cancer (3023 registrations), together accounting for 28.8% of registrations. Breast cancer and melanoma were the next most commonly registered cancers.

Raloxifene is a Selective Estrogen Receptor Modulator

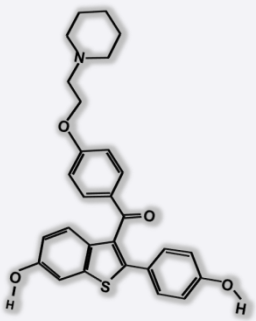
- Non-steroidal ligand of the estrogen receptor
- Has estrogen-like effects in some tissues (bone)
- Blocks estrogen effects in other tissues (breast, endometrium)
- Evista® (raloxifene HCl 60 mg/day) is approved for the prevention and treatment of osteoporosis

Raloxifene is approved for the prevention and treatment of osteoporosis



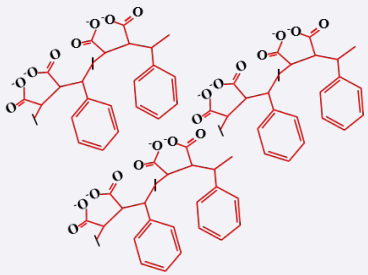
Raloxifene encapsulation

- Poor bioavailability (~2% due to extensive metabolism by glucuronidation in intestine and liver
- SMA micellar formulation results in :
  - ✓ High water solubility
  - ✓ Higher concentration in the plasma by protection from metabolic enzymes
  - ✓ Enhanced tumor (inflammatory tissues) concentration due to enhanced permeability in these tissues



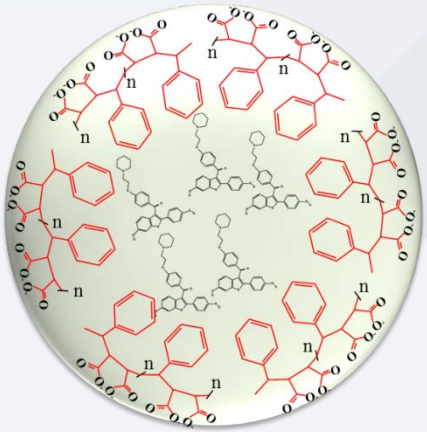
Raloxifene

+



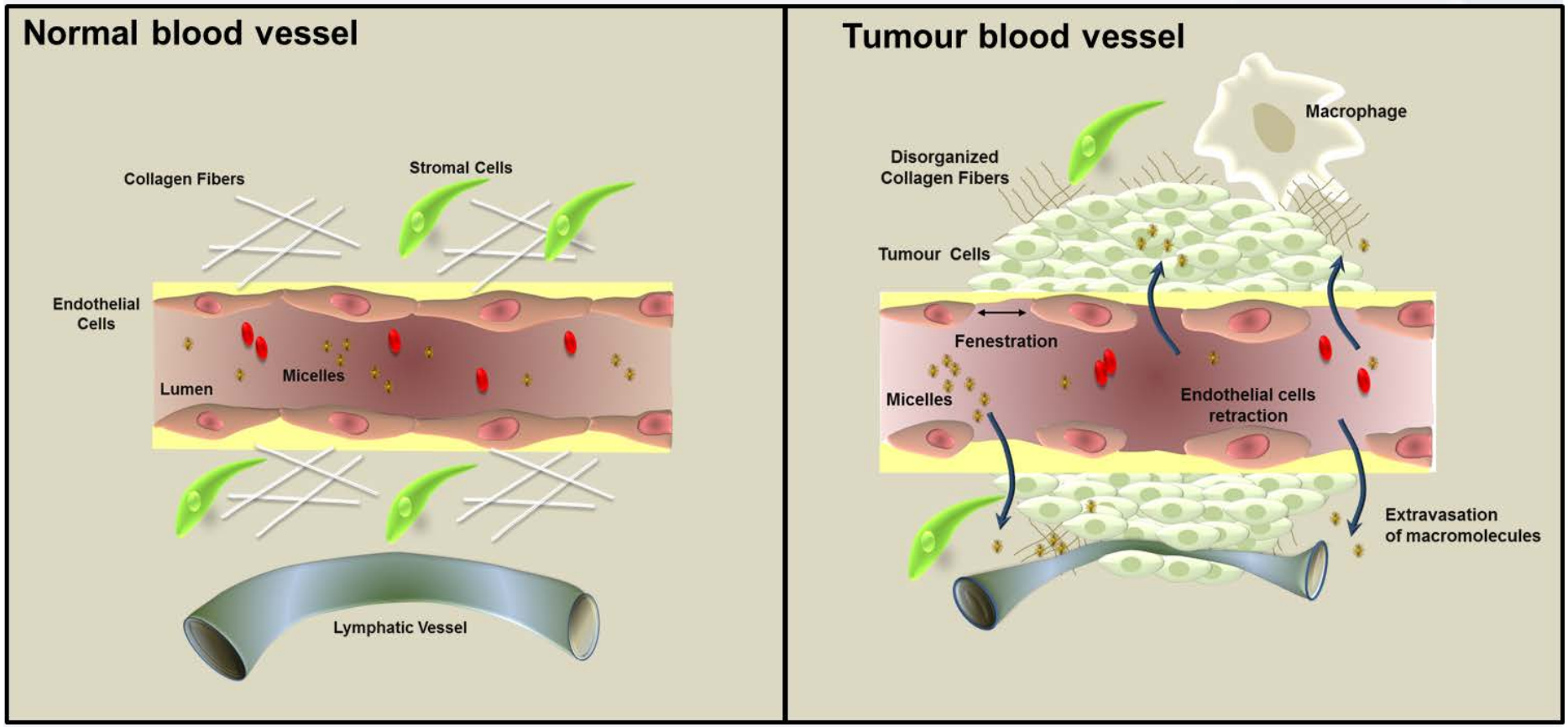
Poly(styrene-co- maleic acid) (SMA)

pH dependent encapsulation



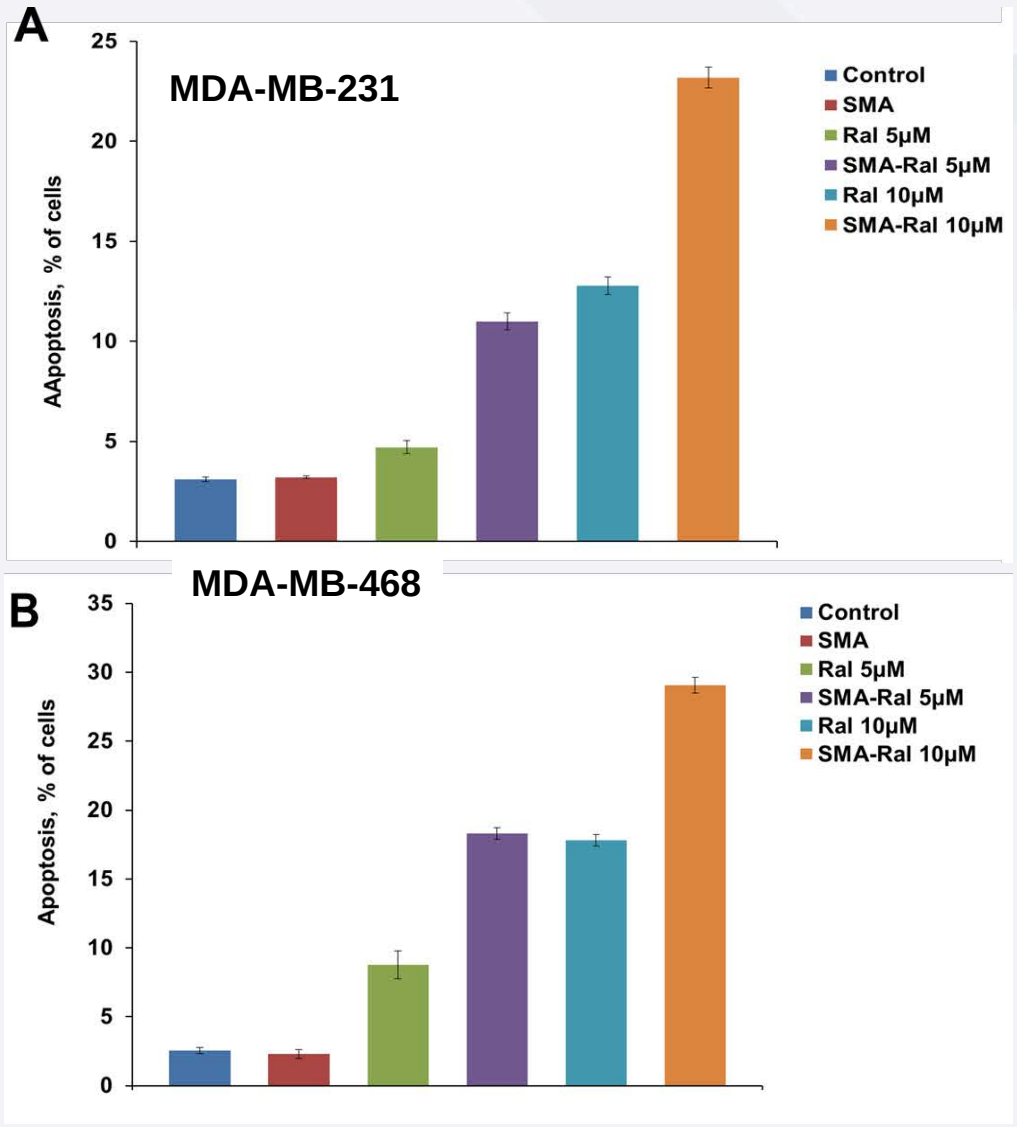
SMA-Raloxifene

Enhanced Permeability and Retention Effect in inflammation and cancer



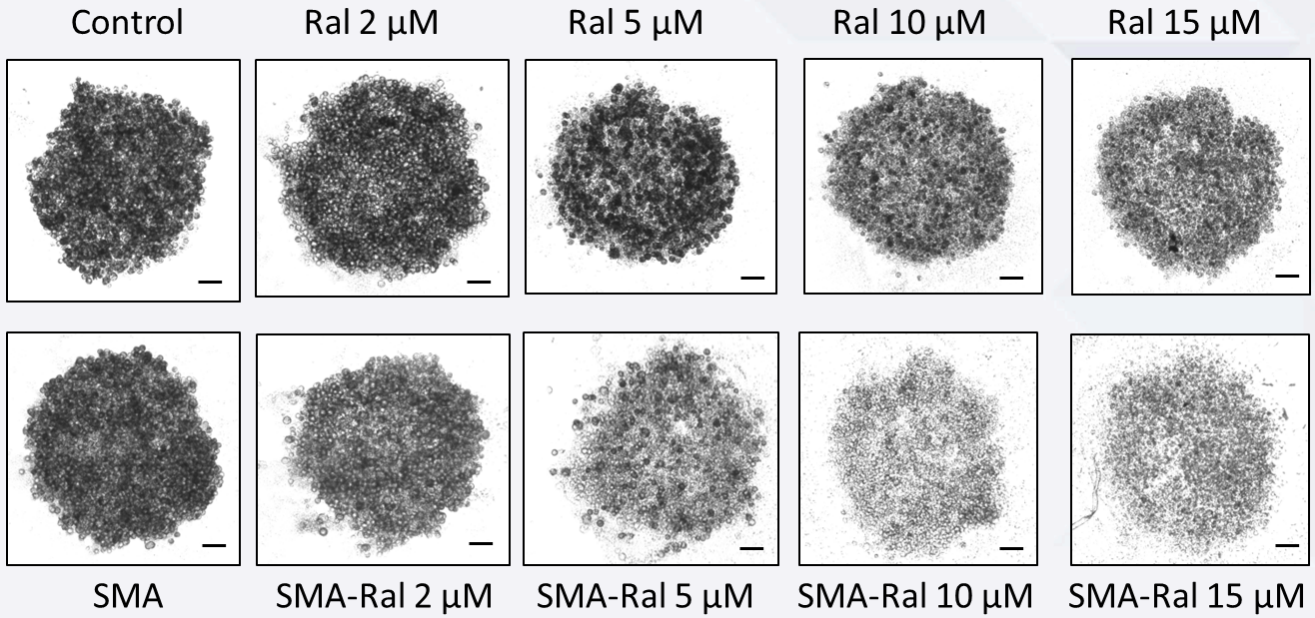
S. Taurin, H. Nehoff, K. Greish, Anticancer nanomedicine and tumor vascular permeability; Where is the missing link?, Journal of controlled release, 164 (2012) 265-275.

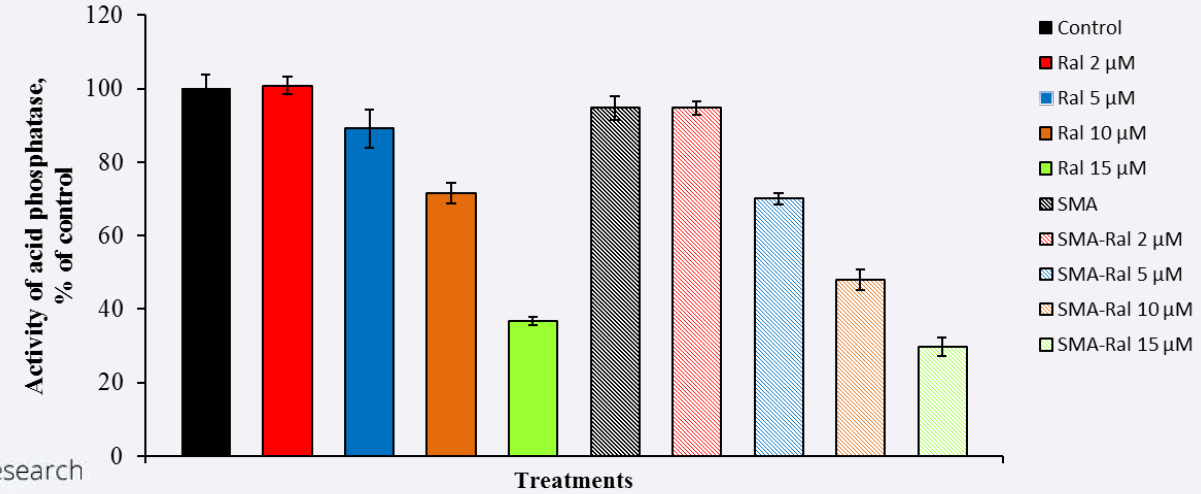
Effect of raloxifene on apoptosis in breast cancer cells in vitro



Taurin, S.; Nehoff, H.; Van Aswegen, T.; Rosengren, R. J.; Greish, K. A Novel Role for Raloxifene Nanomicelles in Management of Castrate Resistant Prostate Cancer. *BioMed Research International(* 2014**),** *2014*, 14.

SMA-raloxifene reduces tumor spheroid viability





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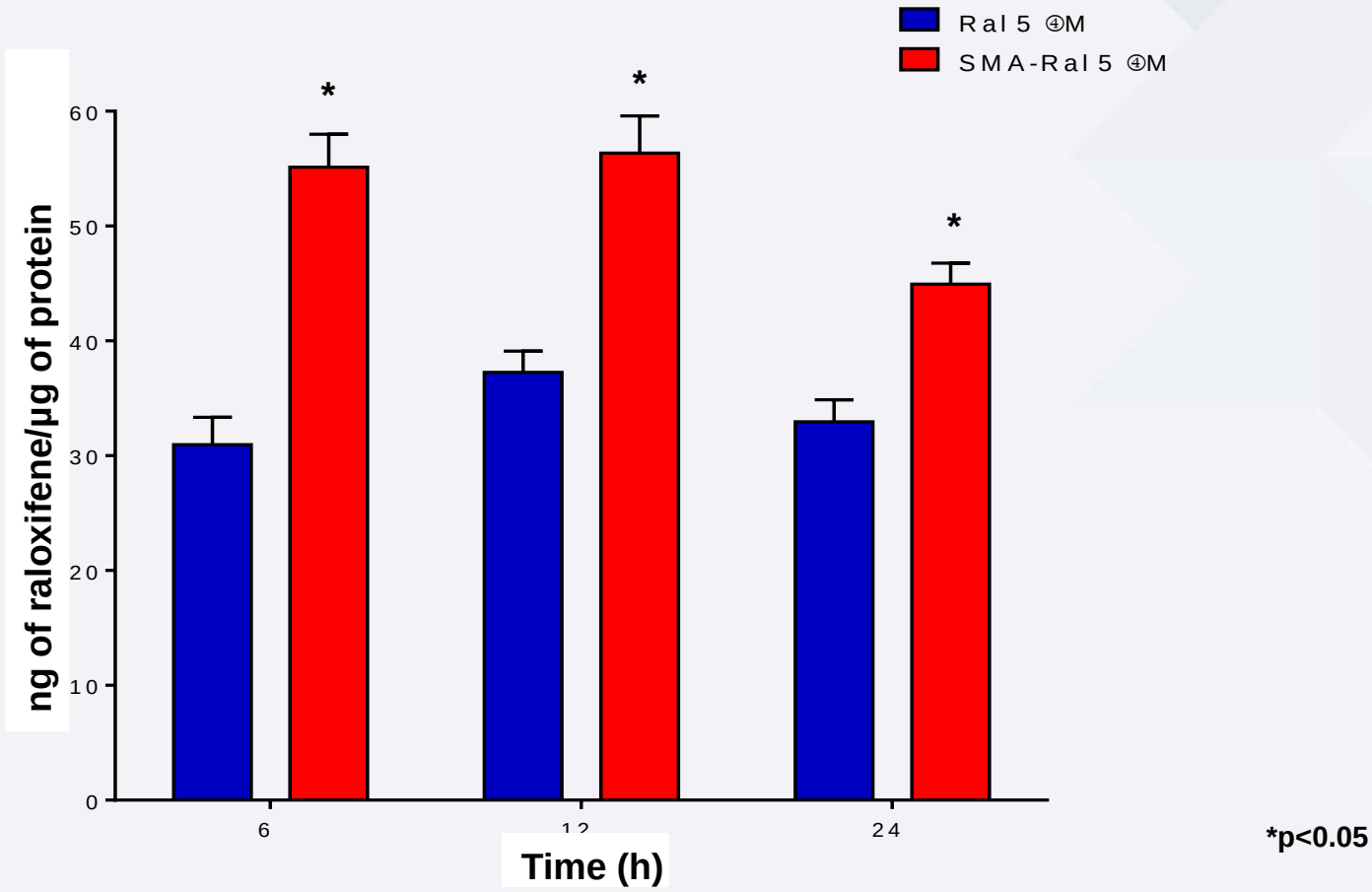
SMA-Raloxifene enhances intracellular drug accumulation in tumor cells



*p<0.05

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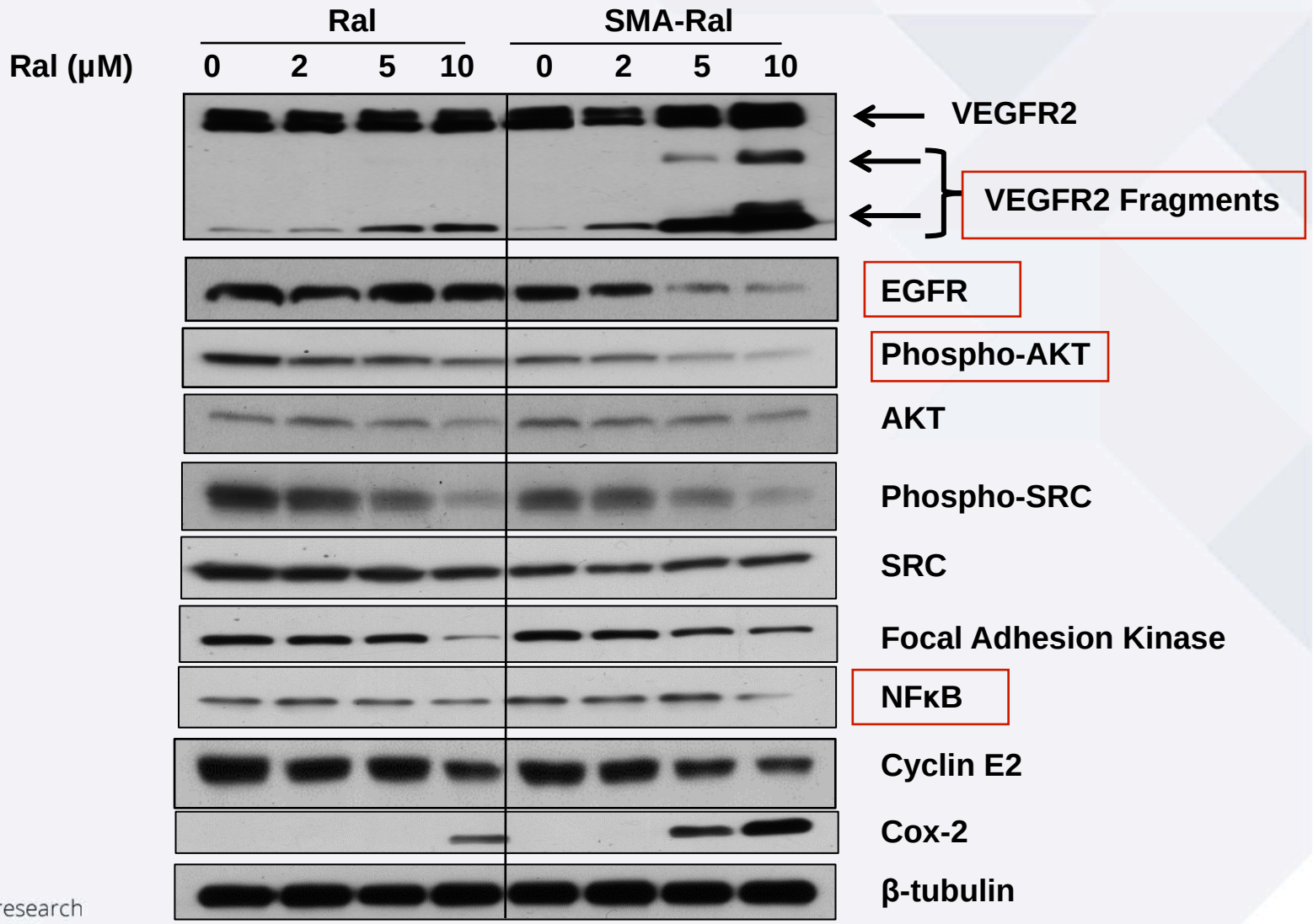
Pritchard T, Rosengren RJ, Greish K, Taurin S. Raloxifene nanomicelles reduce the growth of castrate-resistant prostate cancer. Journal of Drug Targeting. 2015:1-9.

SMA-raloxifene alters the expression of proteins essential for tumor proliferation and survival



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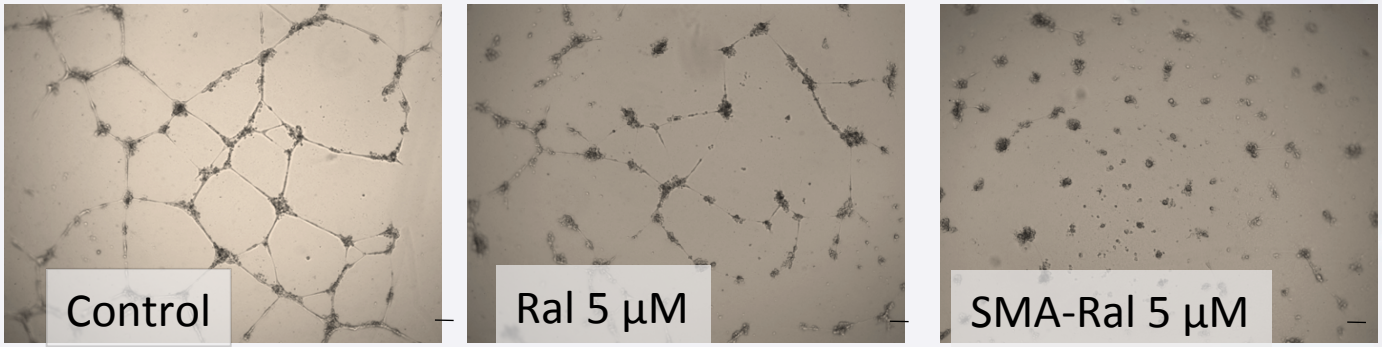
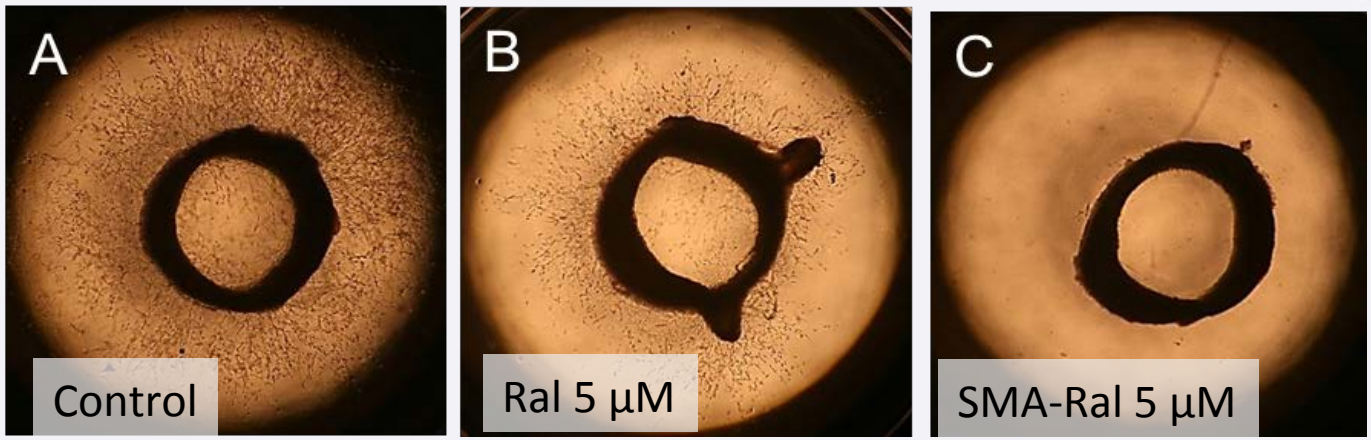
SMA-raloxifene suppresses angiogenesis

Huvec



Rat aortic ring



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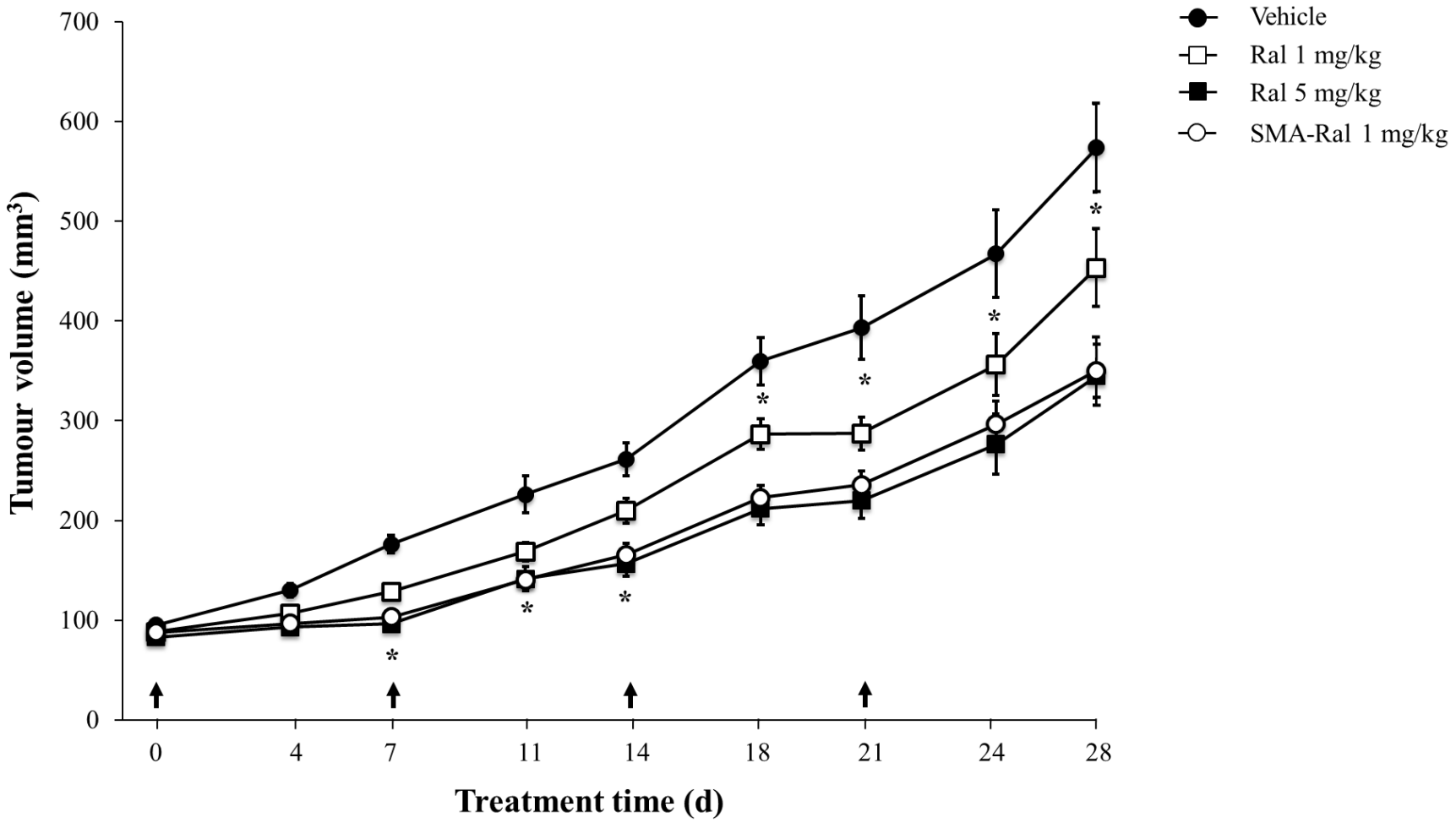
SMA-raloxifene reduces the growth of PC3 xenograft prostate tumours



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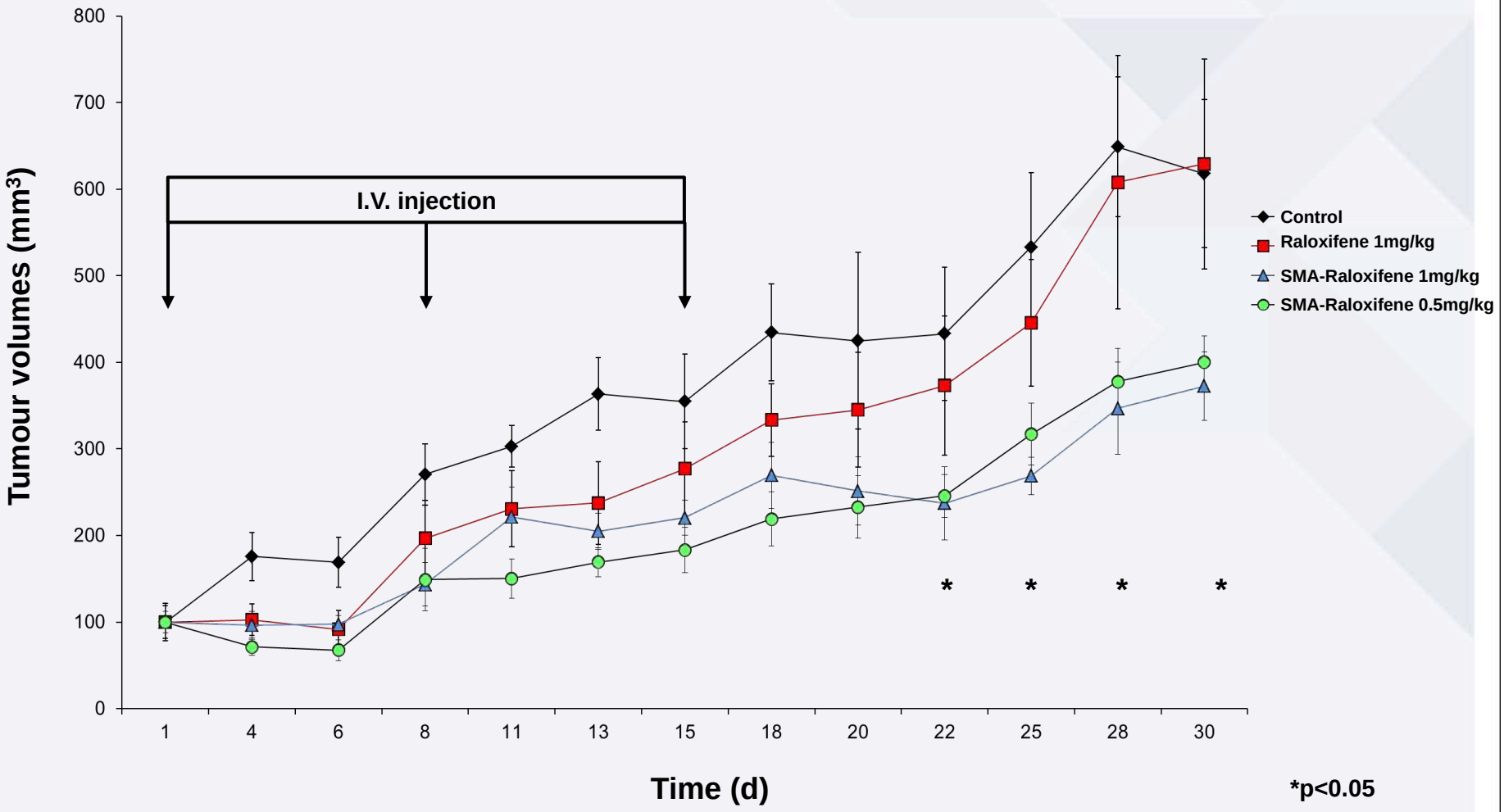
SMA-raloxifene reduces the growth of MDA-MB-231 breast tumours



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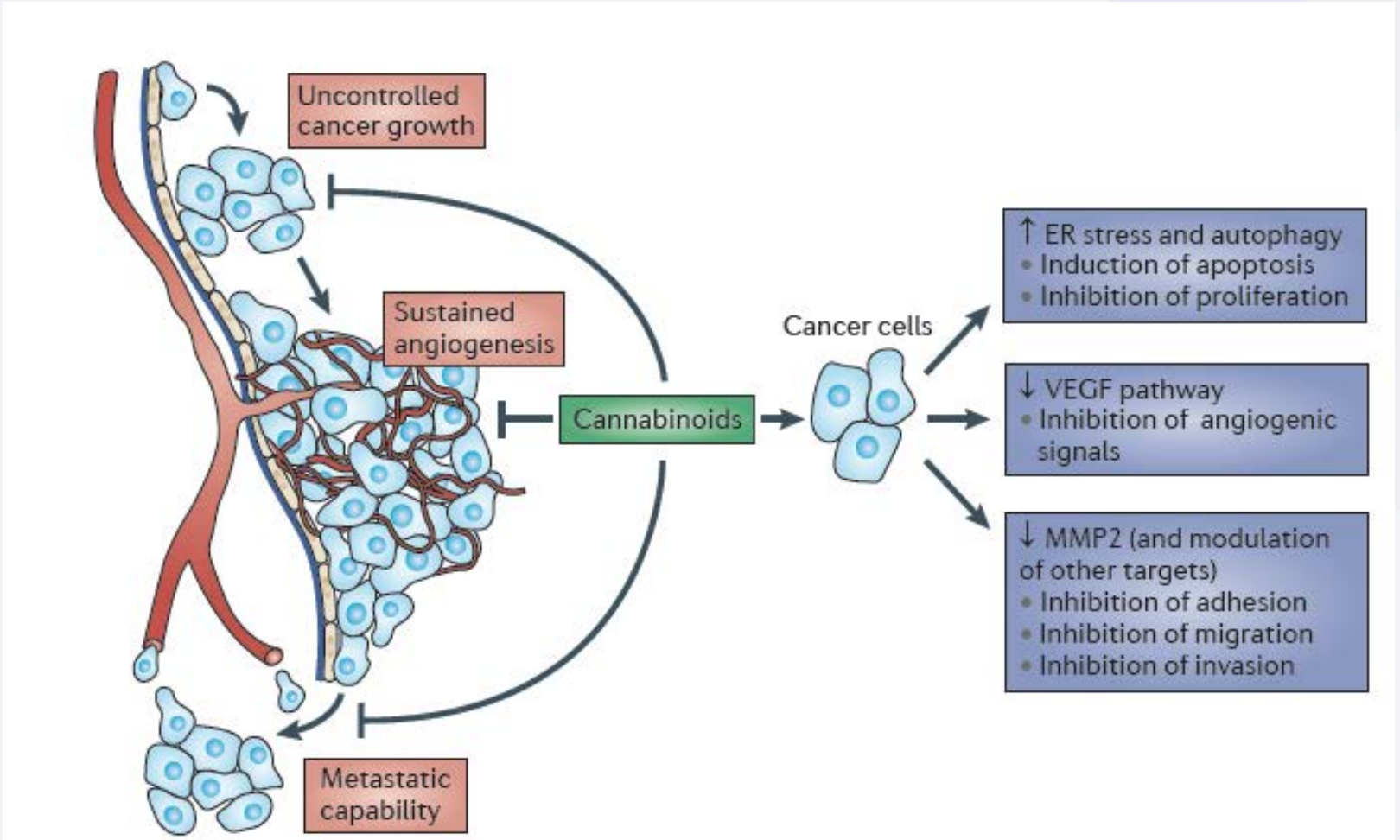
Cannabinoids for management of cancer



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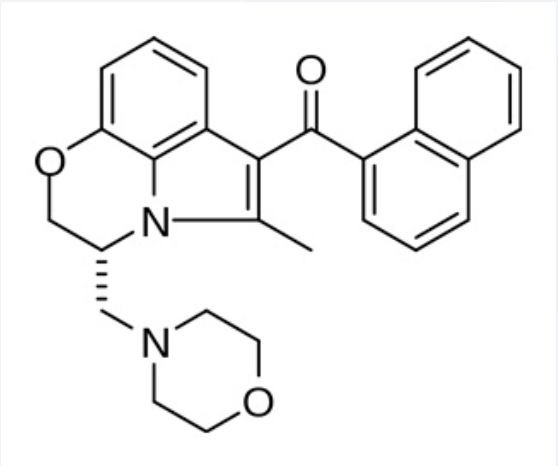
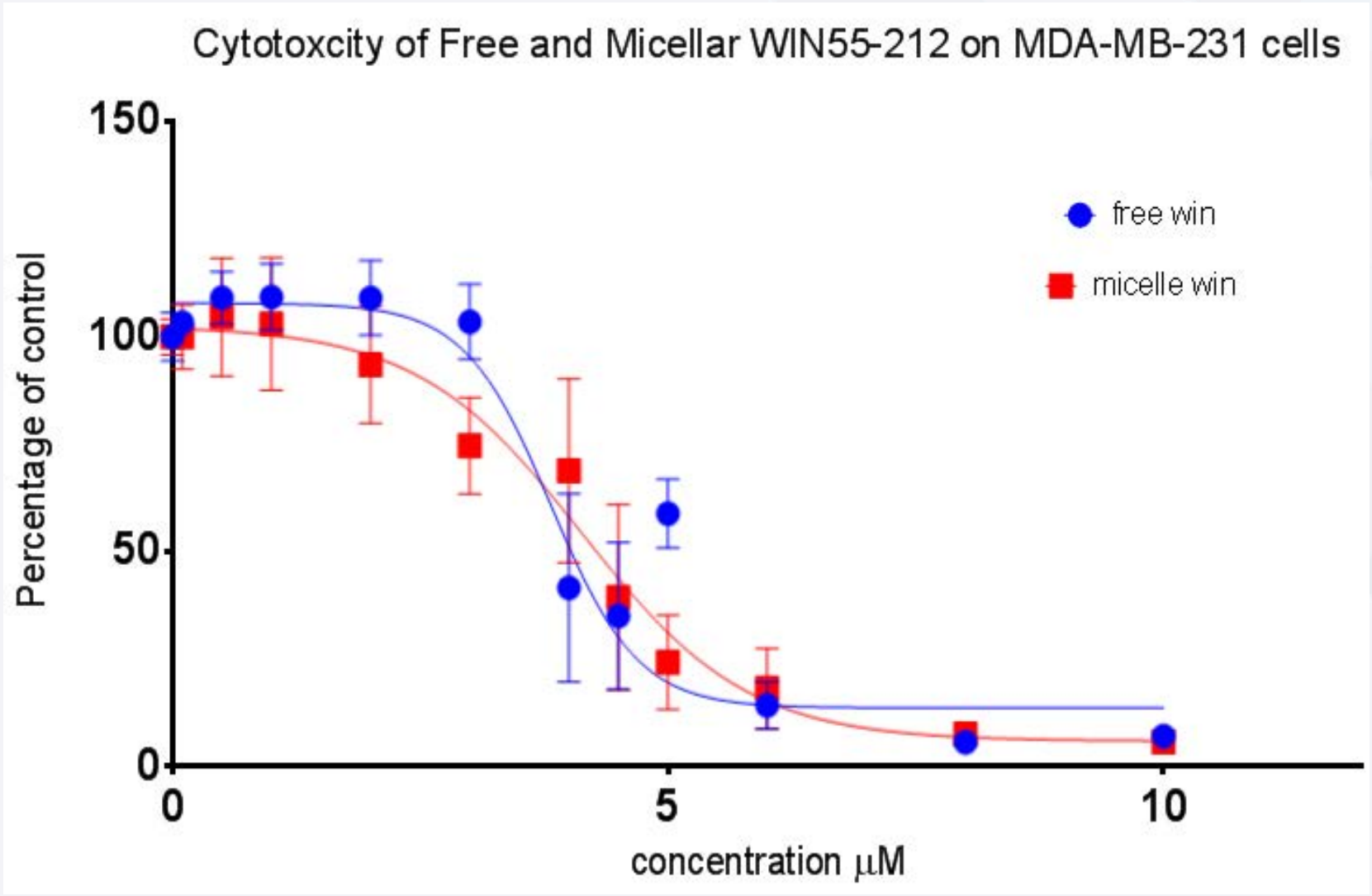
Velasco G, Sánchez C, Guzmán M. Towards the use of cannabinoids as antitumour agents. Nat Rev Cancer. 2012;12:436-44.

SMA-WIN for management of cancer

- WIN 55,212-2 is a potent cannabinoid receptor agonist that has been found to be a potent analgesic in neuropathic pain
  - ❑ Poorly water soluble
  - ❑ Target both CB1 and CB2
  - ❑ Side effect;
    - ➢ **Psychoactive effects**



[*include euphoria, alteration of sensory perception, sensation of relaxation / calmness, loss of sense of time and space , higher perception of colour and sound, and flight of ideas*]



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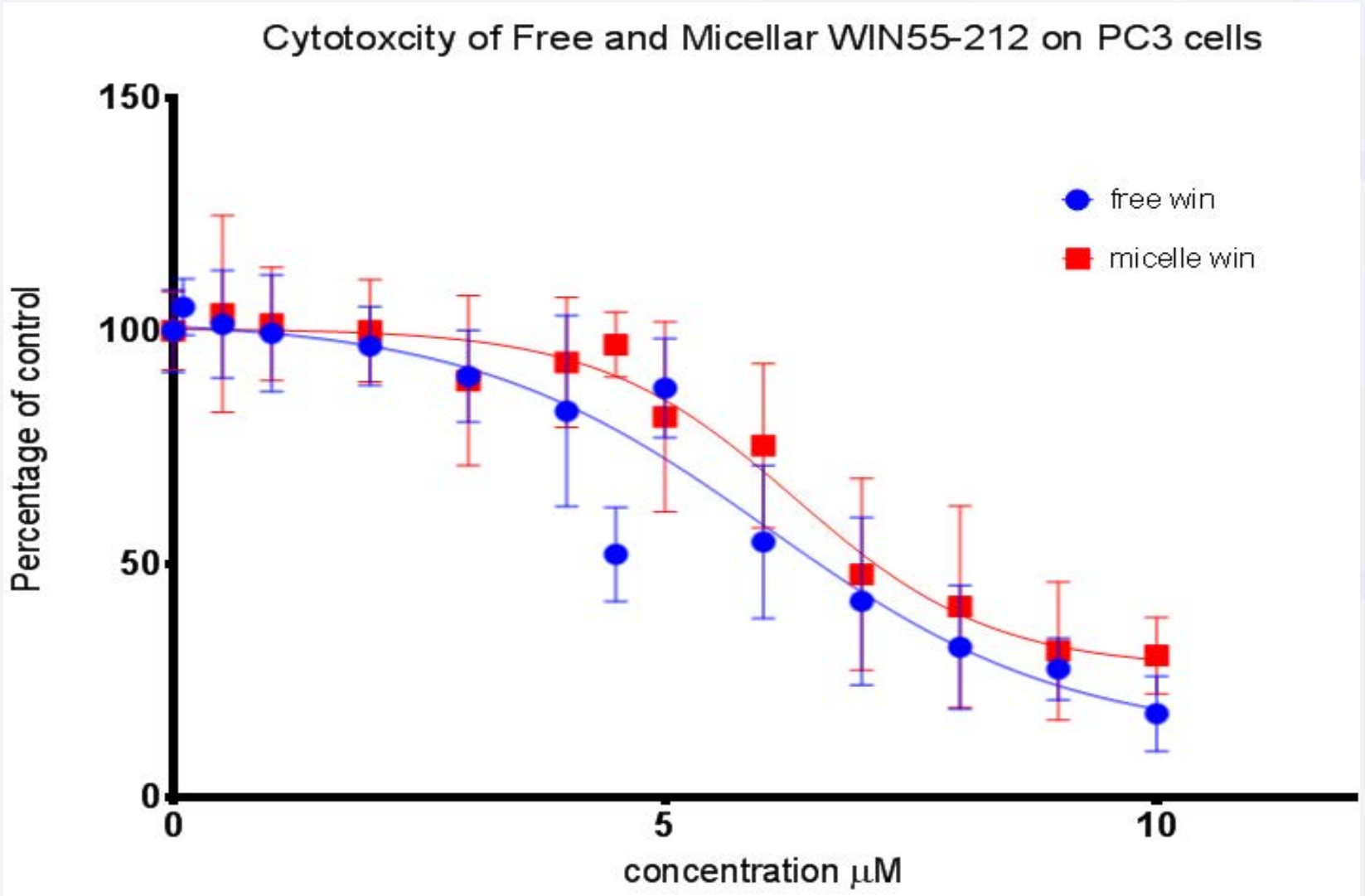
XIAN S, PARAYATH NN, NEHOFF H, GILES NM, GREISH K. The Use of Styrene Maleic Acid Nanomicelles Encapsulating the Synthetic Cannabinoid Analog WIN55, 212-2 for the Treatment of Cancer. Anticancer Research. 2015;35:4707-12.



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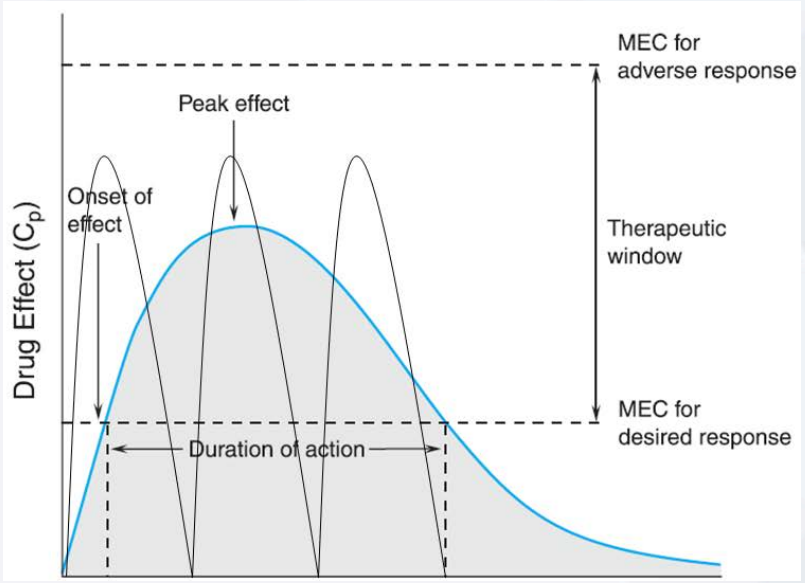
Why Oral Chemotherapy

- Non-invasive - reduces patient trauma
- Sustained pharmacokinetic profile
- Economical
- Interest to the pharmaceutical industry



- Most anticancer drugs exhibit poor oral bioavailability

  Paclitaxel on oral administration showed less than 1% bioavailability.

  (Eiseman, J., et al., Cancer Chemotherapy and Pharmacology, 1994. 34(6): p. 465-471)

Oral Anticancer Nanomedicine

- Nanocarrier protects the drug from harsh GI environment
- Reduced toxicity
- Can increase oral absorption
- Tumor targeting through EPR effect

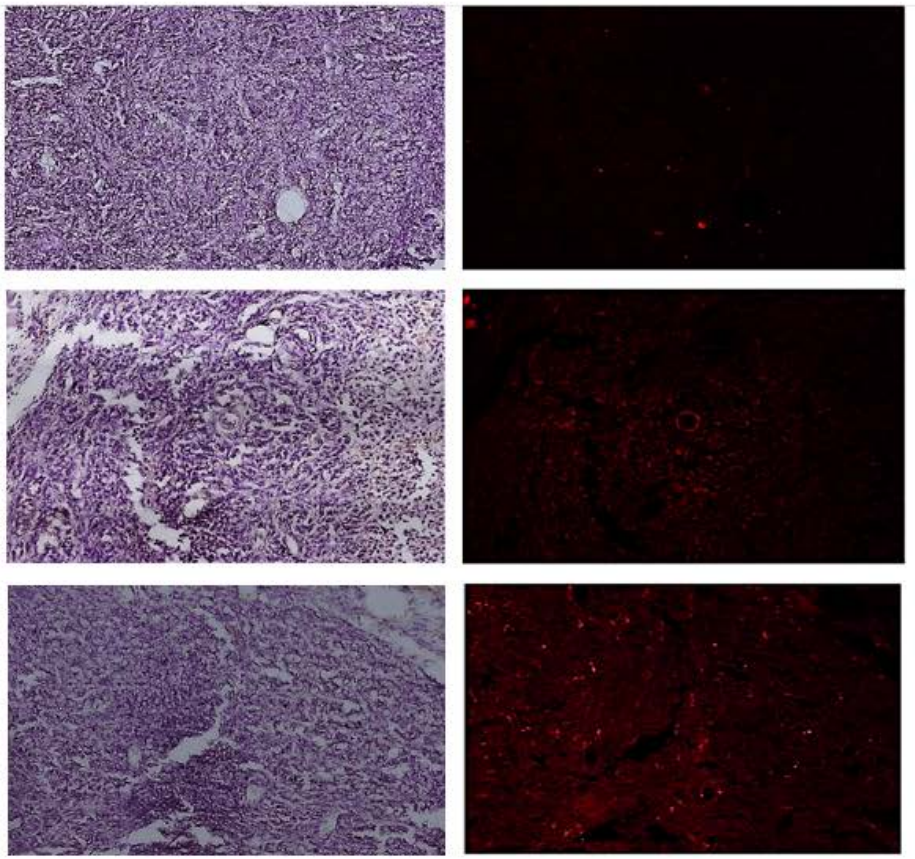
To date - No Oral Anticancer Nanomedicine in clinical use.

Tumor accumulation of oral SMA- micelles in tumor tissues

Oral gavage of free DiI

Oral gavage of SMA-DiI

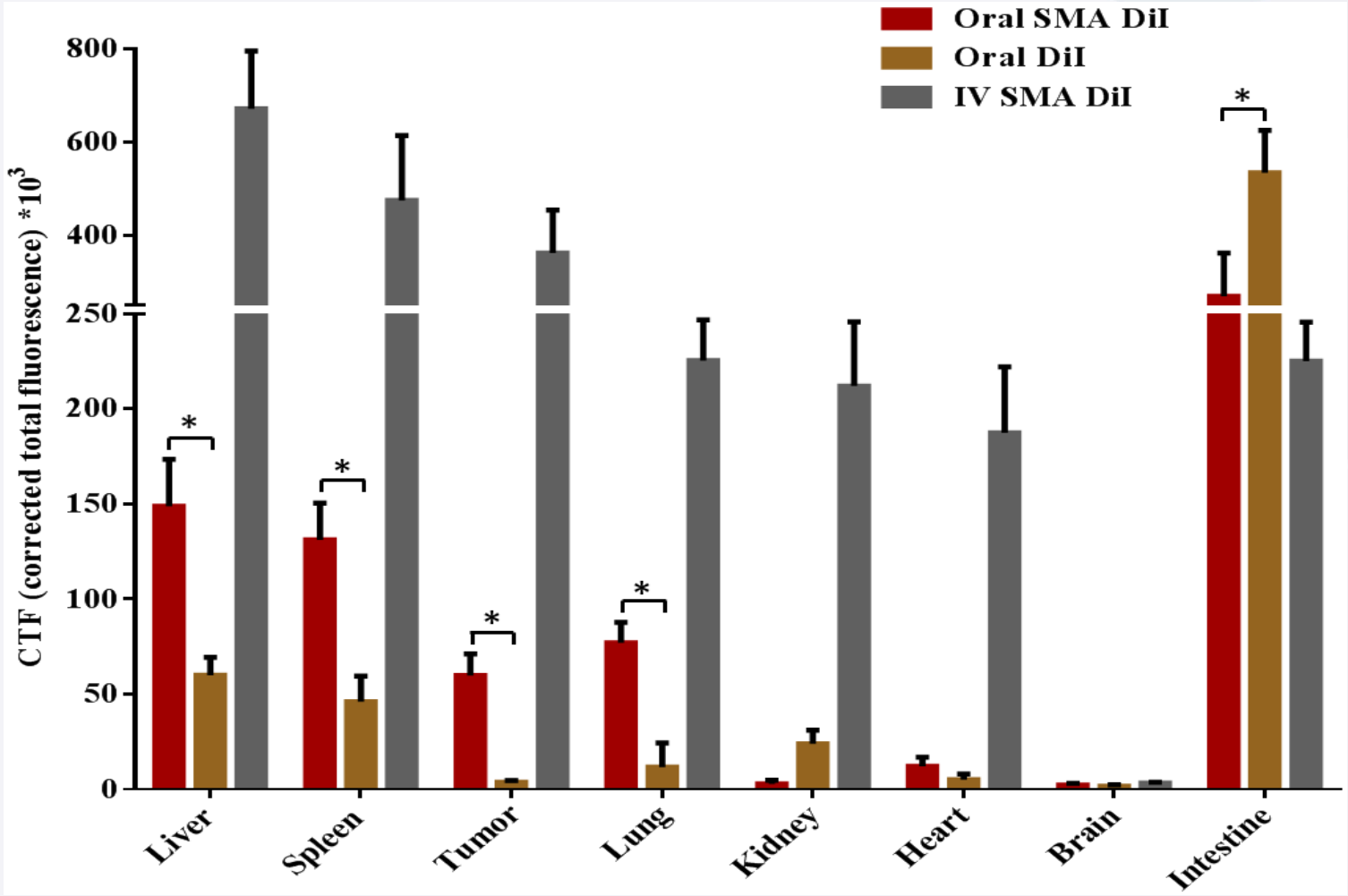
Intravenous SMA-DiI



Haematoxylin staining SMA-DiI Flourescence

Parayath NN, Nehoff H, Müller P, Taurin S, Greish K. styrene maleic acid micelles as a nanocarrier system for oral anticancer drug delivery–dual uptake through enterocytes and M-cells. International journal of nanomedicine. 2015;10:4653.

Tumor accumulation of oral SMA- micelles in different tissues



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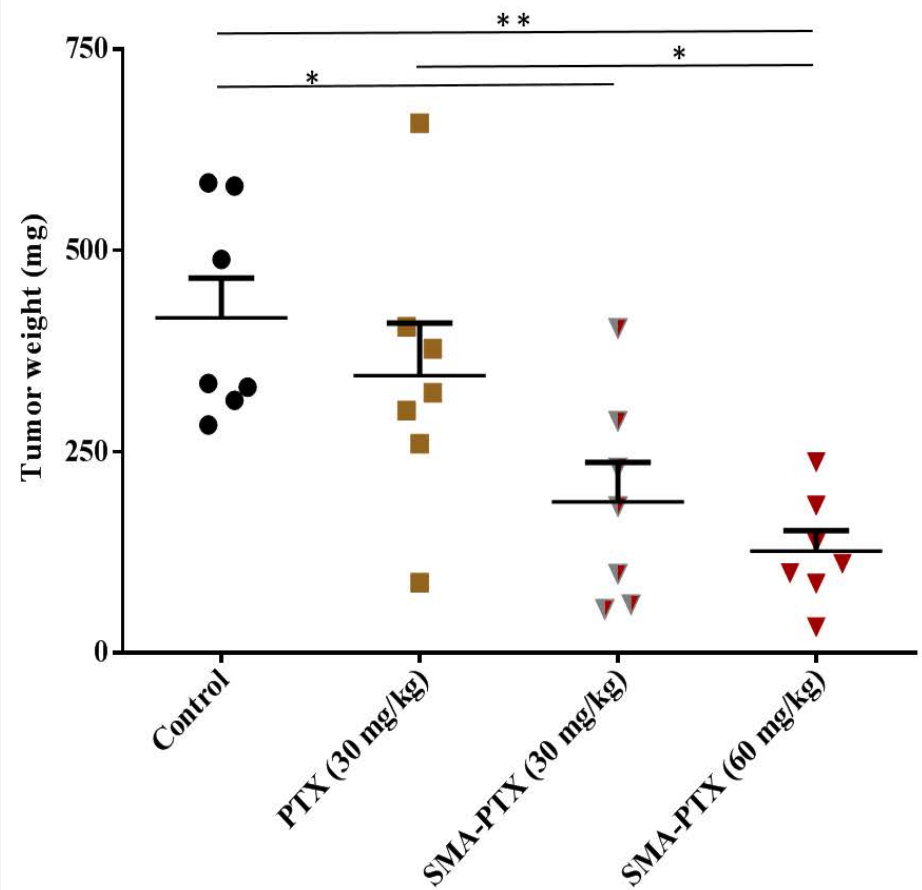
Maximum tolerated dose (MTD) of SMA-PTX micelles following oral administration

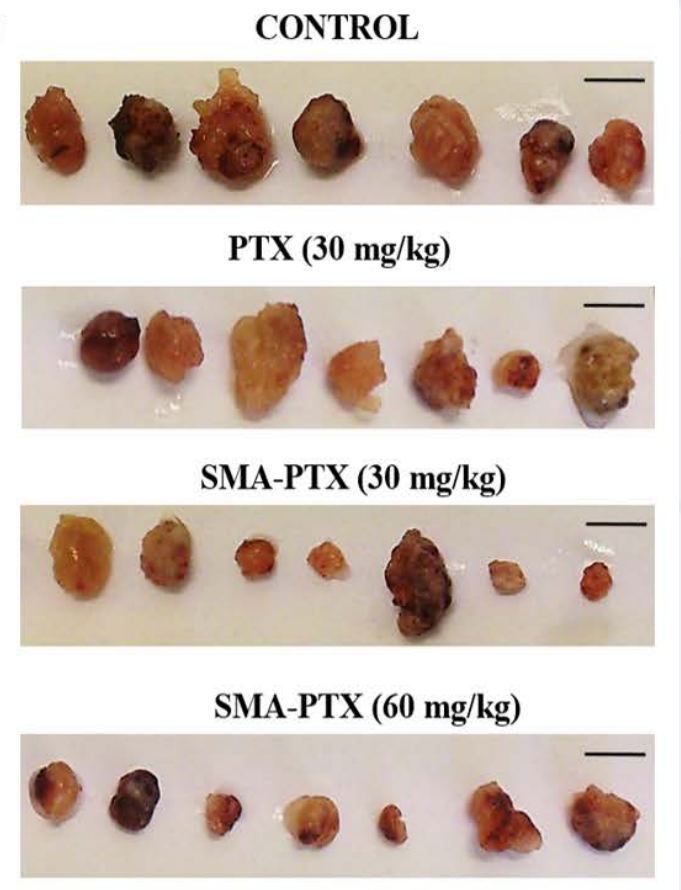
Single dose MTD
Healthy female BALB/c mice n = 6
Mice survival and variation in body weight

Repeated dose MTD
Healthy female BALB/c mice n = 4
Mice survival and variation in body weight

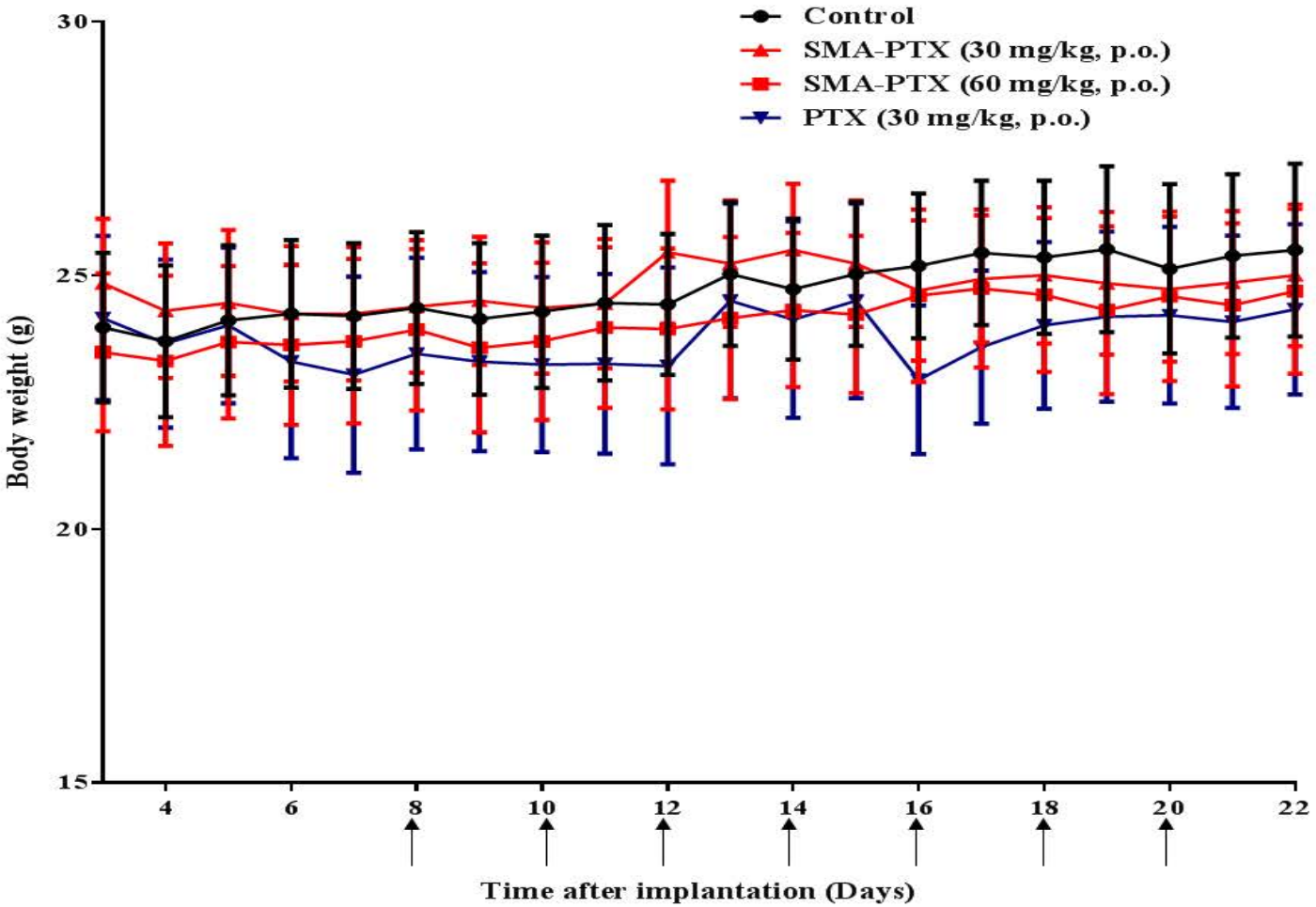
MTD in BALB/c mice	PTX (Ebewe)	SMA-PTX
Single dose	60 mg/kg	120 mg/kg
Repeated dose (doses every alternate days for 8 days)	30 mg/kg	60 mg/kg

Antitumor efficacy of SMA-PTX following oral administration in orthotopic colon cancer model





Safety of SMA-PTX following oral administration in orthotopic colon cancer model



Acknowledgments

Collaborators:

Sebastian Taurin

Rhonda Rosengren

Graduate Students:

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- Neha Parayath
- Tara Prichard
- Susan Xian

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