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Screening of mixed co-poly(ester-carbonate) PEG-based nanoparticles for breast cancer therapy

10th APS International PharmSci Conference

Robert Cavanagh

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Introduction

Triple negative breast cancer (TNBC)

- ~ 200,000 patients diagnosed per year [1]
- Negative for expression of Oestrogen, Progesterone and Her2
- Poor prognosis, high levels of local recurrence
- Typical therapy involves; **radiation**, **surgery** and **chemotherapeutics**
- **Chemotherapeutics are applied intravenously at maximum tolerated dose**

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Serious adverse effects

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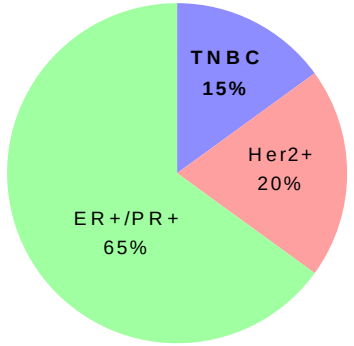
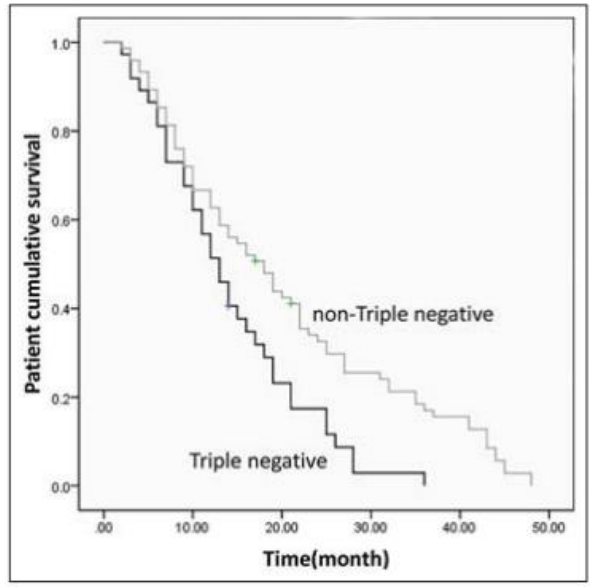
Requirement for delivery system capable of minimizing off site toxicity



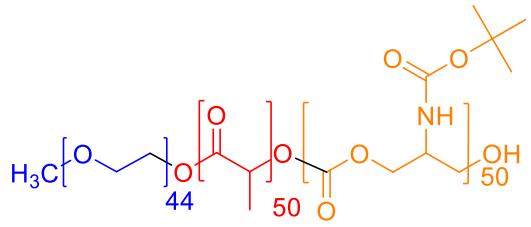
Breast cancer subtypes by incidence [2]



Survival rate of TNBC [3]

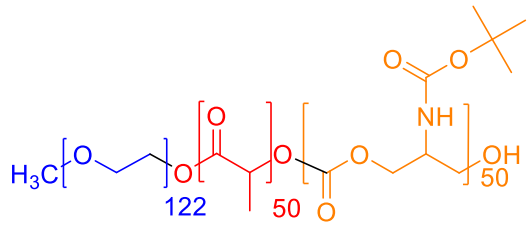
[1] Trivers et al., Can. Causes. Control. (2009), 20, 1071-82
[2] Newman et al., Ann. Surg. Oncol. (2015), 22:874-82
[3] Wu et al., J. Can. Res. Ther. (2013), 9(7), 169-72

Project Polymers overview



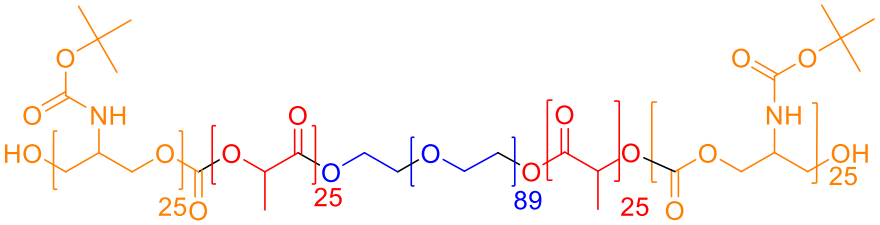
$mPEG_{2000}$-$(LA)_{50}$-$(CT)_{50}$

- Size: 126 nm
- Z-potential: -24.4 mV



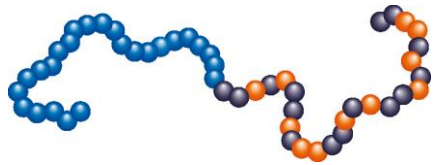
$mPEG_{5000}$-$(LA)_{50}$-$(CT)_{50}$

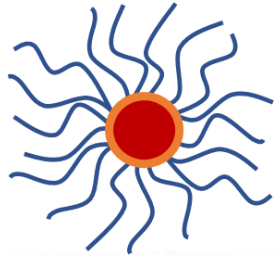
- Size: 82 nm
- Z-potential: -14.4 mV



PEG_{4000}-$(LA)_{50}$-$(CT)_{50}$

- Size: 88 nm
- Z-potential: -14.1 mV





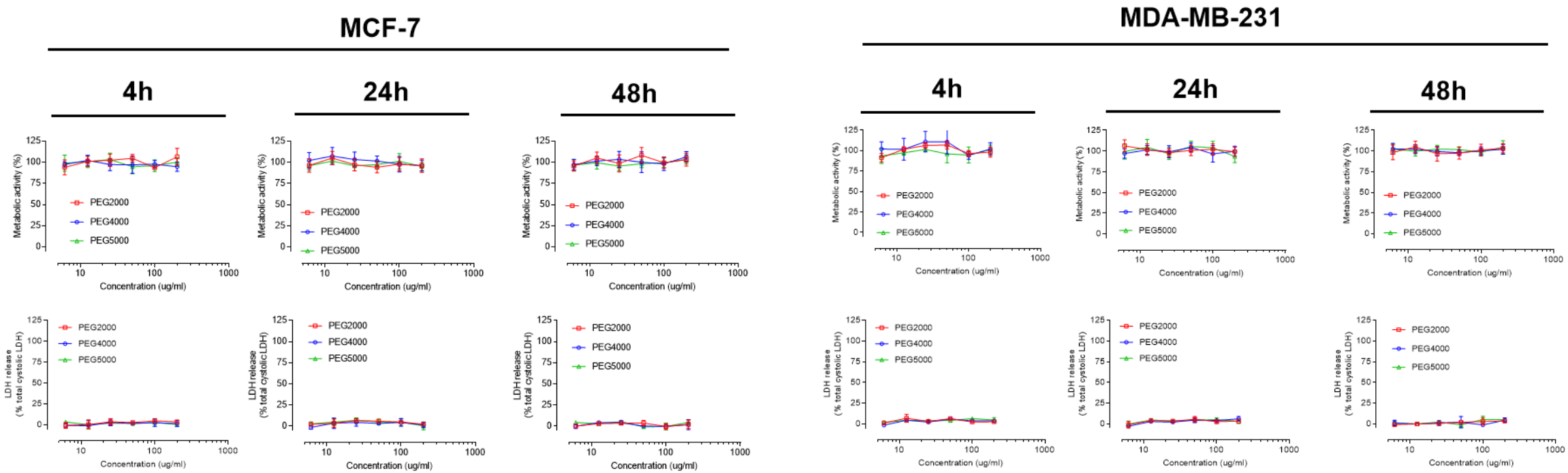
Micelle-like self-assembling

Linear di-blocks

Flower micelle-like self-assembling

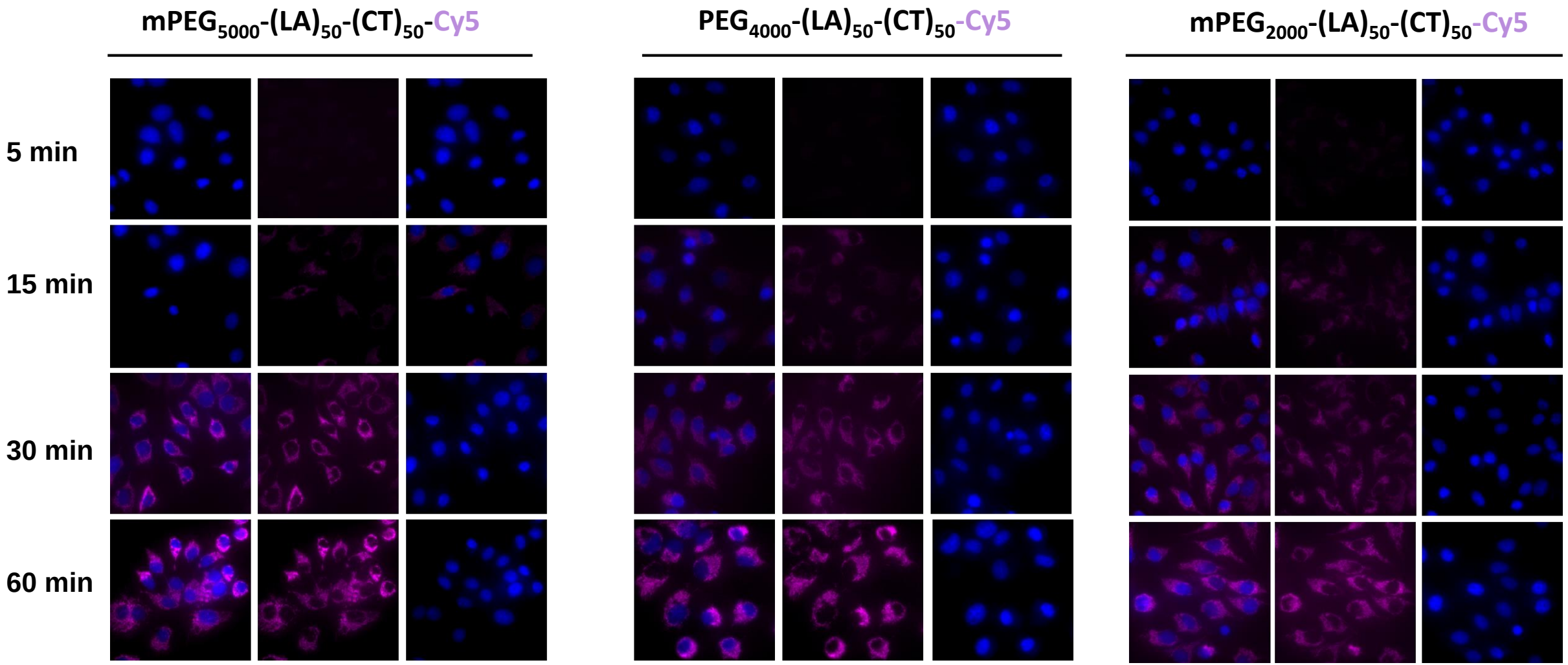
Linear tri-blocks

Biocompatibility



Linear polymer-based NPs demonstrate biocompatibility in MCF-7 and MDA-MB-231 cells. Metabolic activity (top row) was assessed using the resazurin-based PrestoBlue assay and membrane damage by the LDH release assay (bottom row). NPs were applied in DMEM containing 10% FBS. MDA-MB-231 cells were seeded at a density of $1x10^4$ cell/well, and MCF-7 cells at $5x10^3$cell/well in 96 well plates and cultured for 24h prior to dosing. Data represents mean ± S.D, and represents triplicates from three experiments.

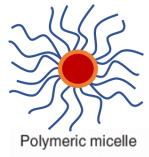
Uptake in BCC



Quantitative uptake

$mPEG_{2000}$-$(LA)_{50}$-$(CT)_{50}$

- **Size: 126 nm**
- Z-potential: -24.4 mV
- Micelle-like assemble



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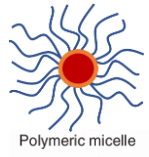
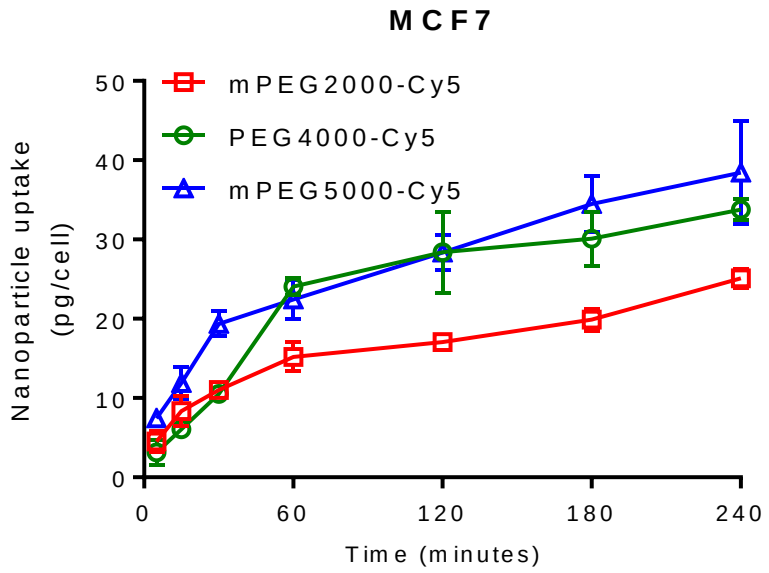
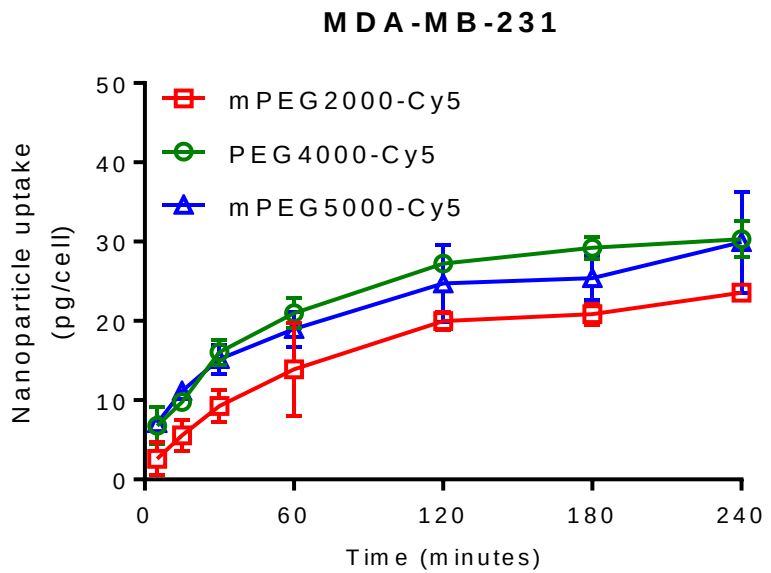
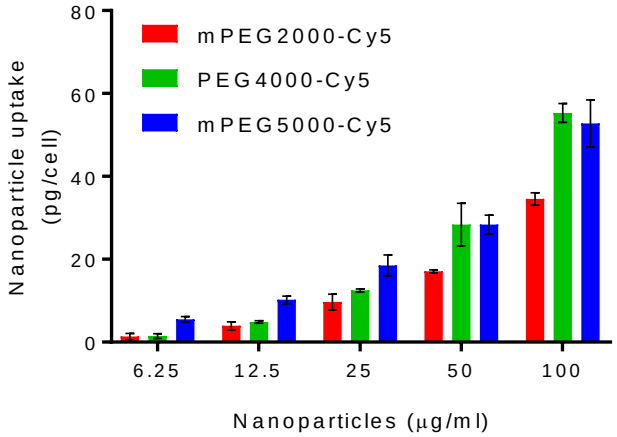
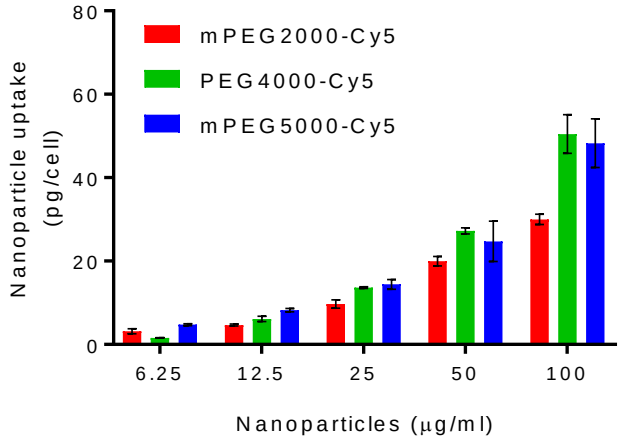


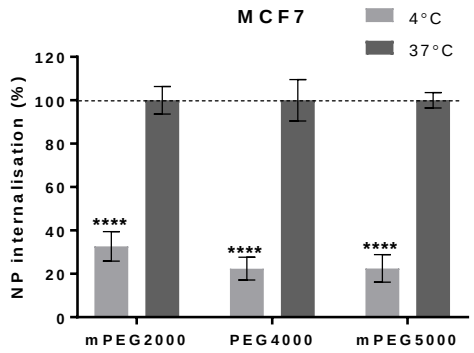


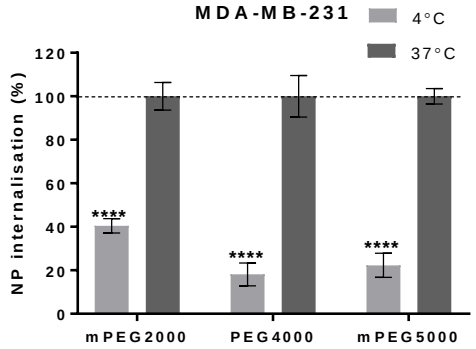


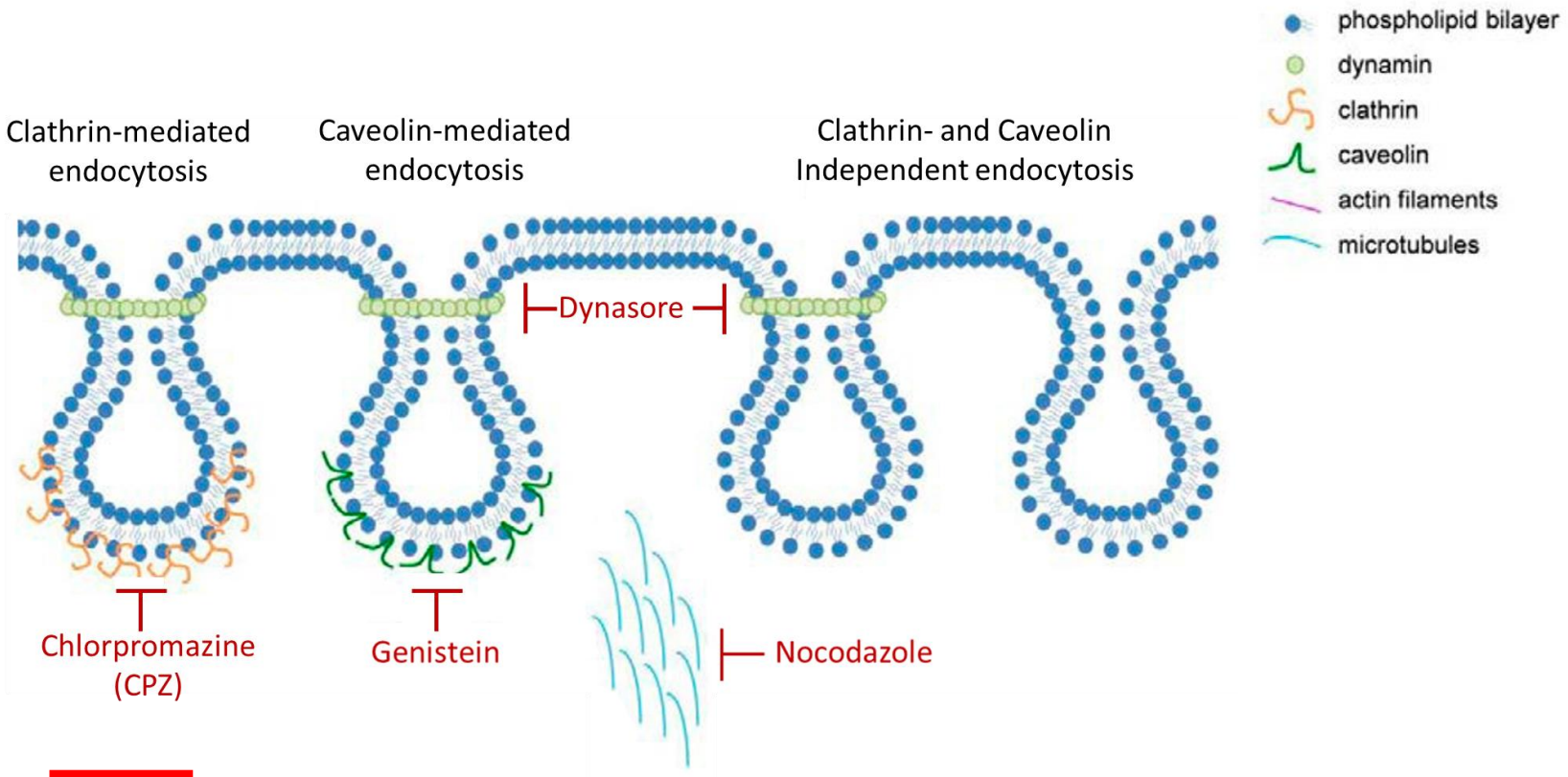


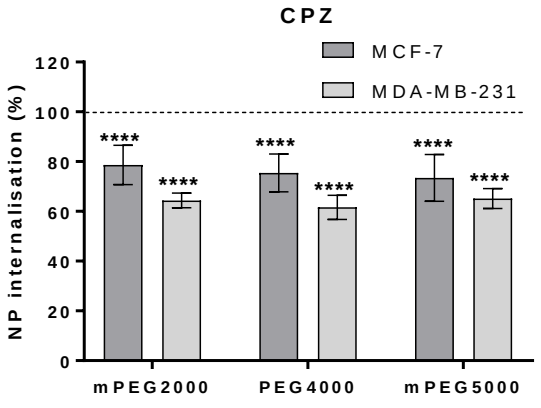


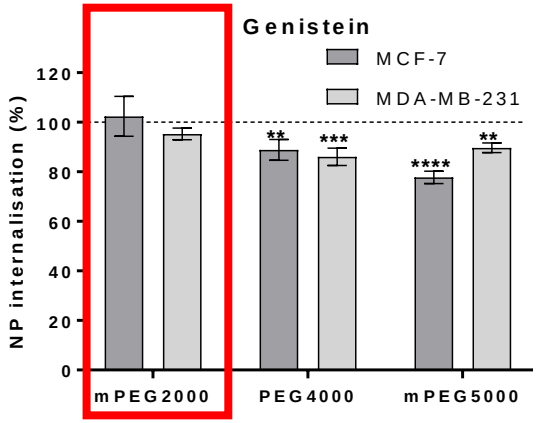
Endocytosis pathways

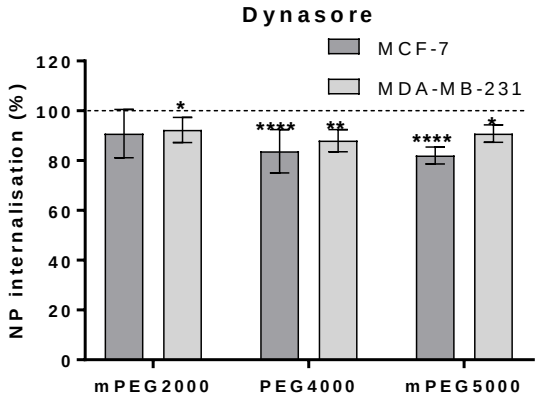


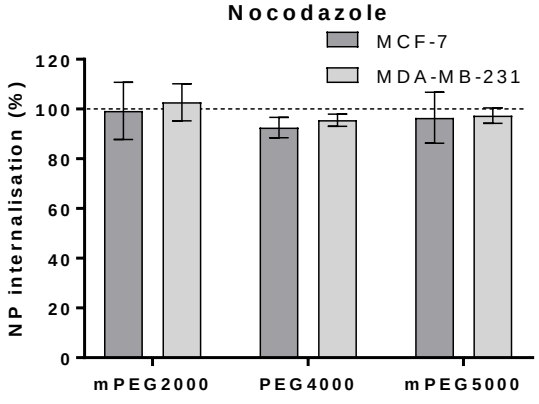




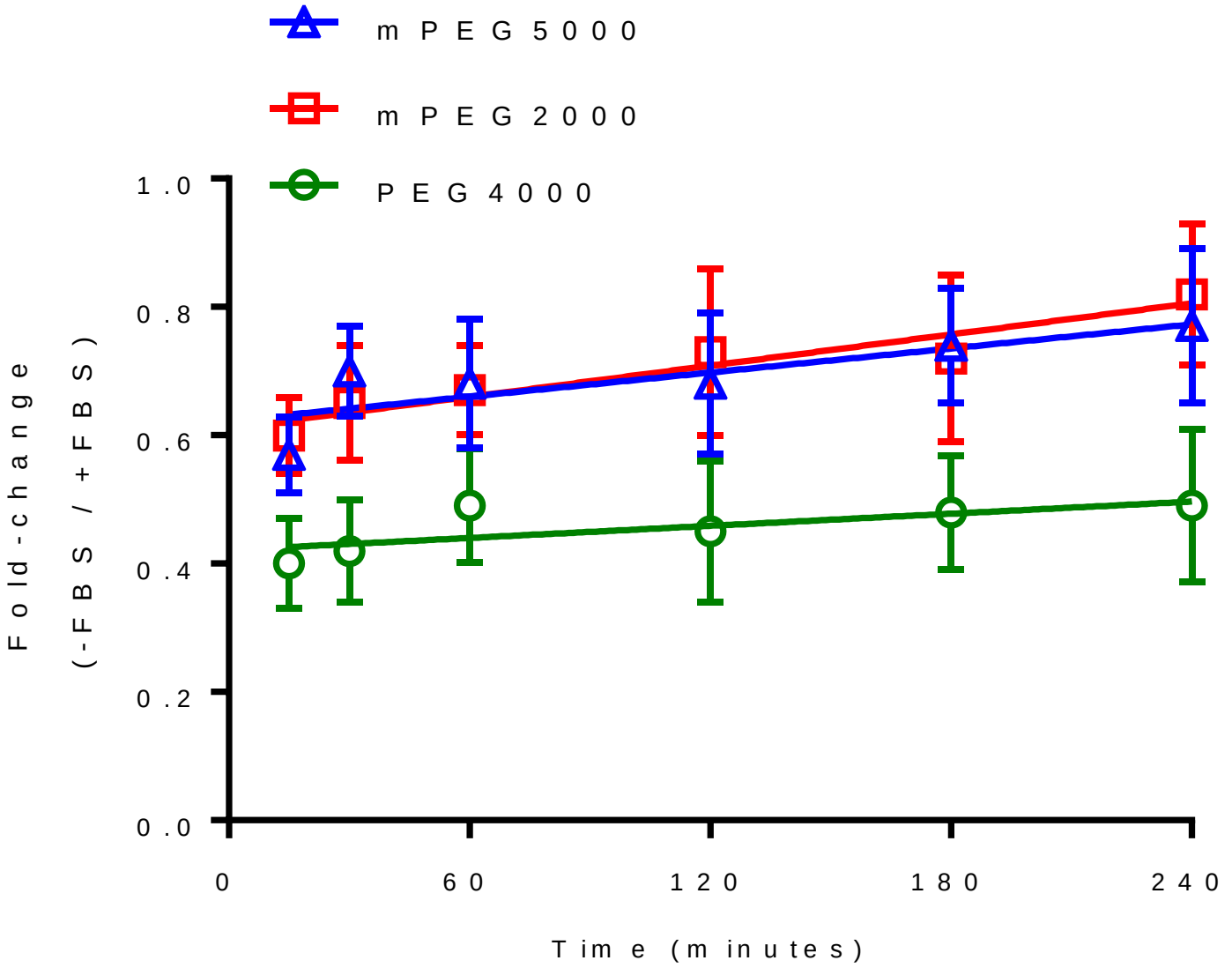


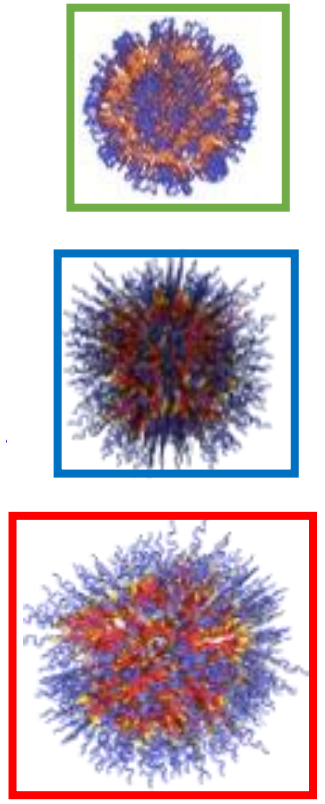






Macrophage uptake (RAW 264.7 cells)





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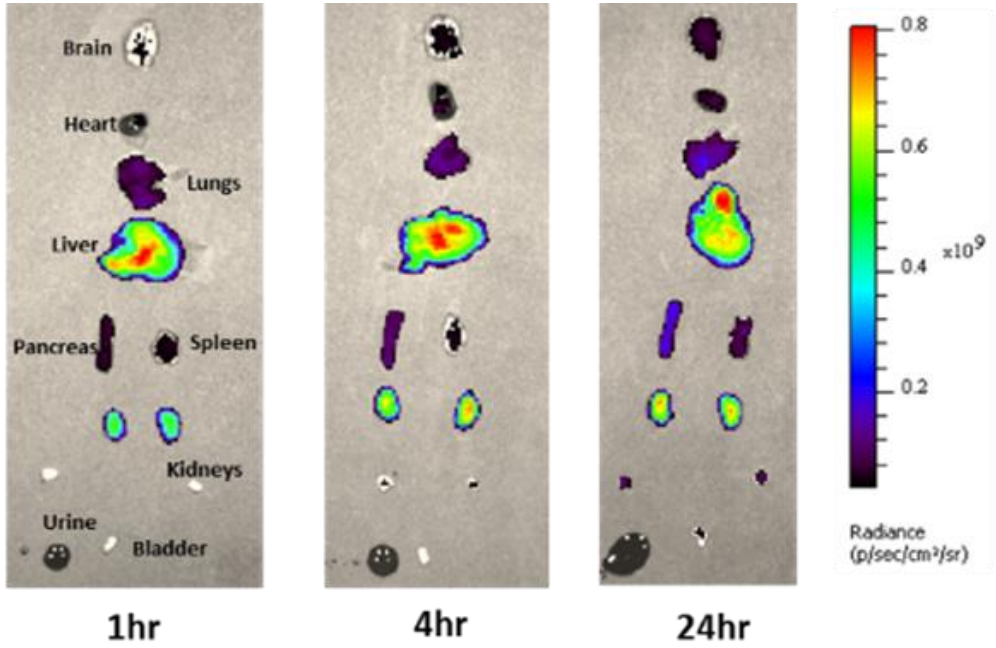
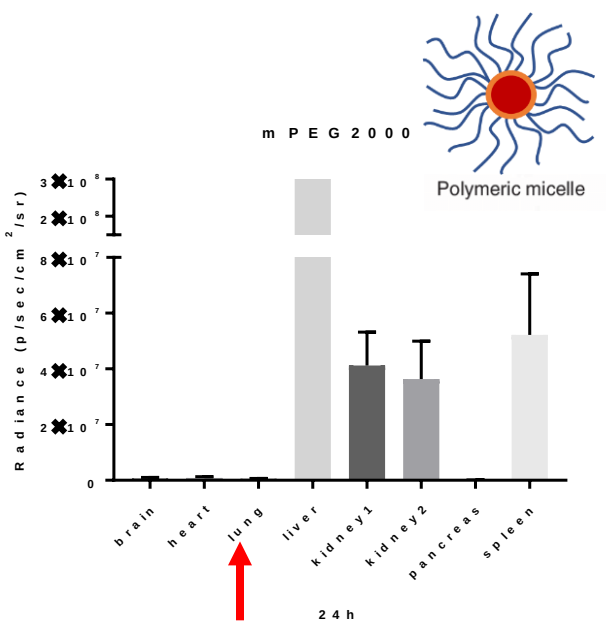
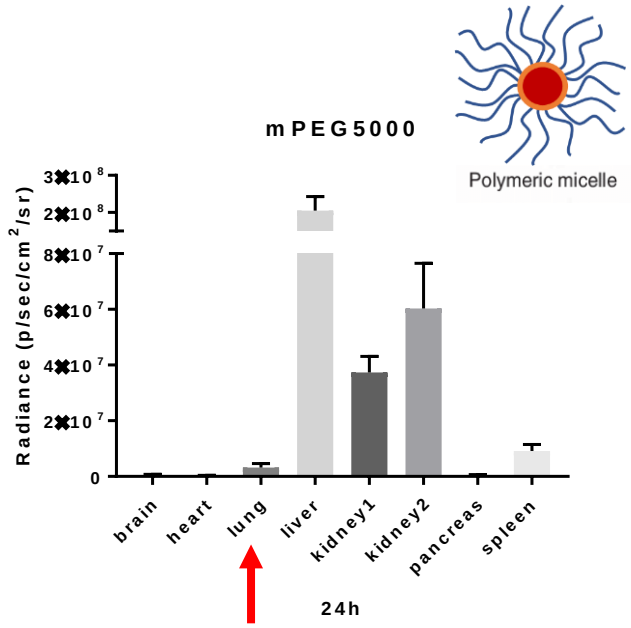
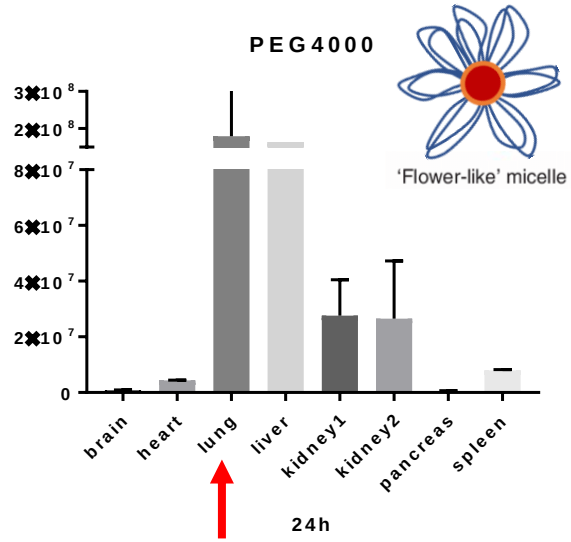
In vivo Biodistribution



Ex vivo images of mouse organs used for detection of NP-Cy5 signal and quantification of distribution. Representative image of mPEG5000







Screening summary

Biocompatibility → Uptake in Cancer cells → Immune cell evasion + In vivo biodistribution

PEG_{4000}-$(LA)_{50}$-$(CT)_{50}$
- **Size: 88 nm**
- Flower micelle-like assemble

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- **Size: 82 nm**
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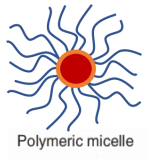

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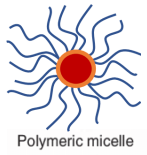

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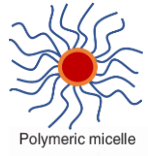

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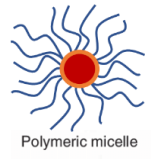
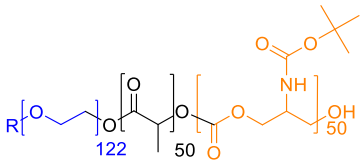
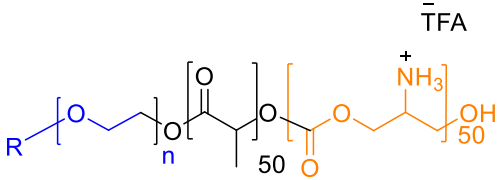
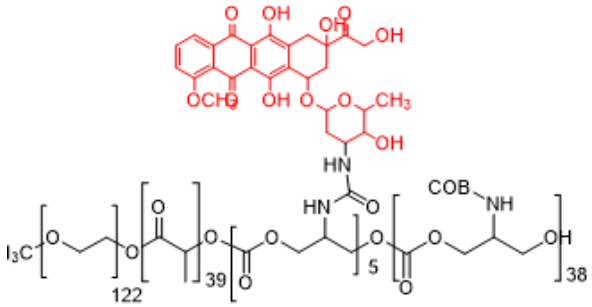


Functionalisation with Doxorubicin: In vitro potency

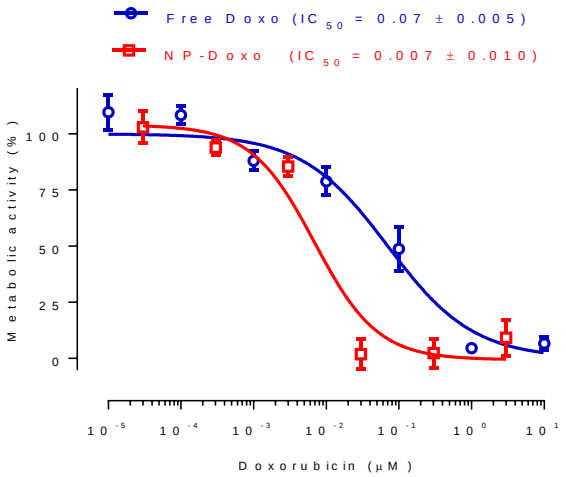




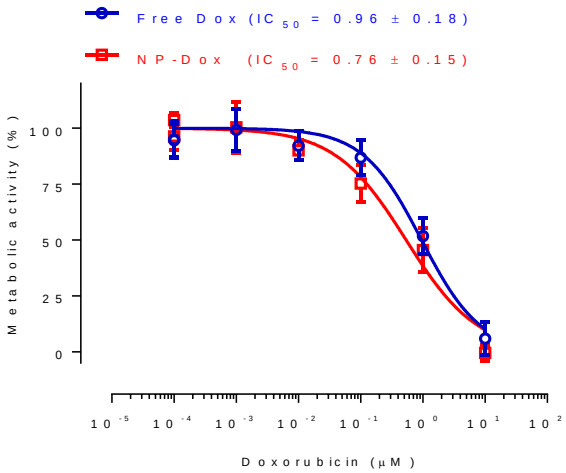


Drug coupling - Doxorubicin

MCF7
Luminal BC



MDA-MB-231
Triple Negative BC



Cell type	Doxorubicin IC50 (µM)	NP-Doxorubicin IC50 (µM)	Fold-Change
MCF-7	0.07 ± 0.01	0.007± 0.01	10-Fold
MDA-MB-231	0.96 ± 0.18	0.76 ± 0.15	1.3-Fold

Acknowledgments

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Dr Amanda Pearce

Catherine Vasey

Federica Sodano

Chiara Greco

The University of Nottingham

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