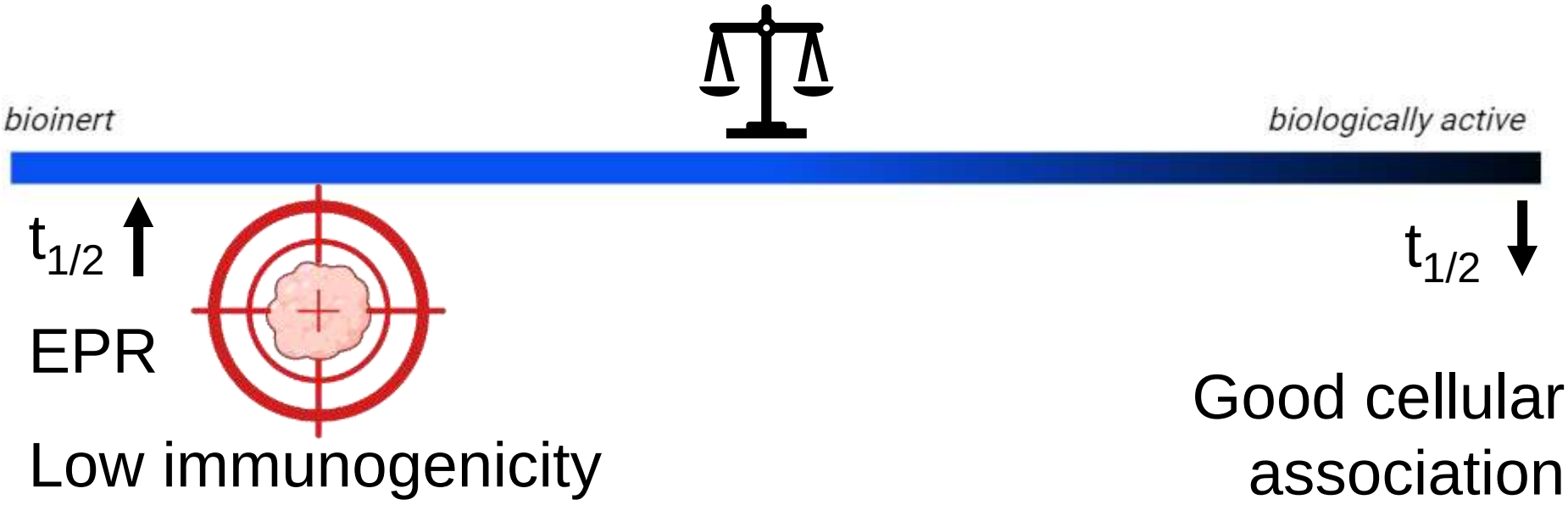
THE UNIVERSITY OF QUEENSLAND
AUSTRALIA
CREATE CHANGE

Using pH-responsive PEG cleavage to improve association of cationic hyperbranched polymers with tumours

Thomas Jarrett

Supervisors: Prof Kris Thurecht, Dr Craig Bell, Dr Rhia Stone, Dr Nick Fletcher

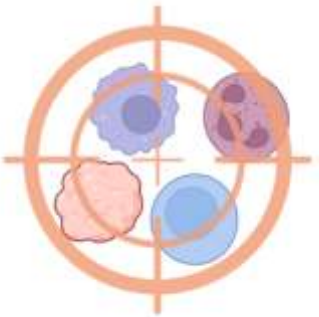
Polymers for drug delivery



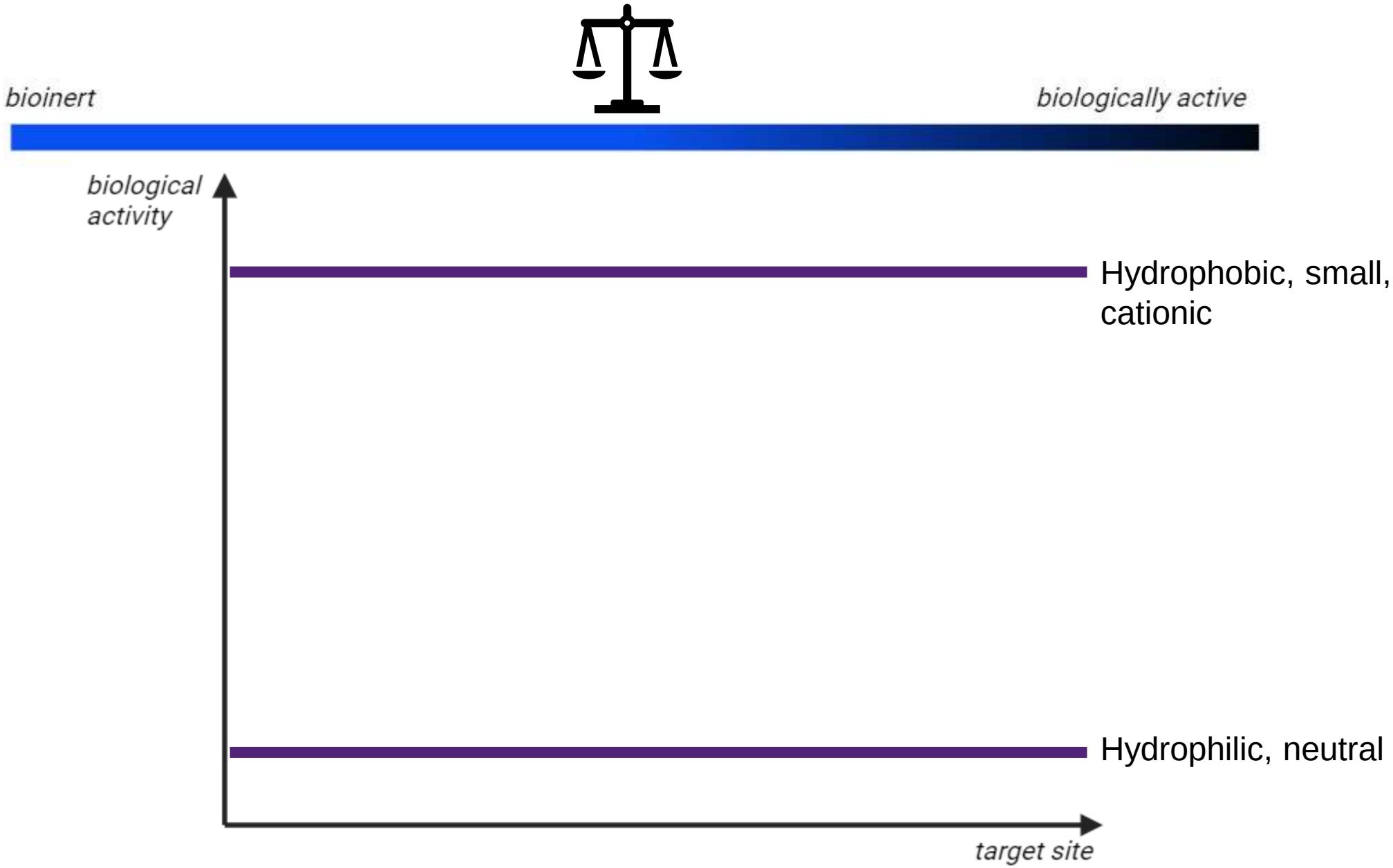
Review article

Stealth nanoparticles in oncology: Facing the PEG dilemma

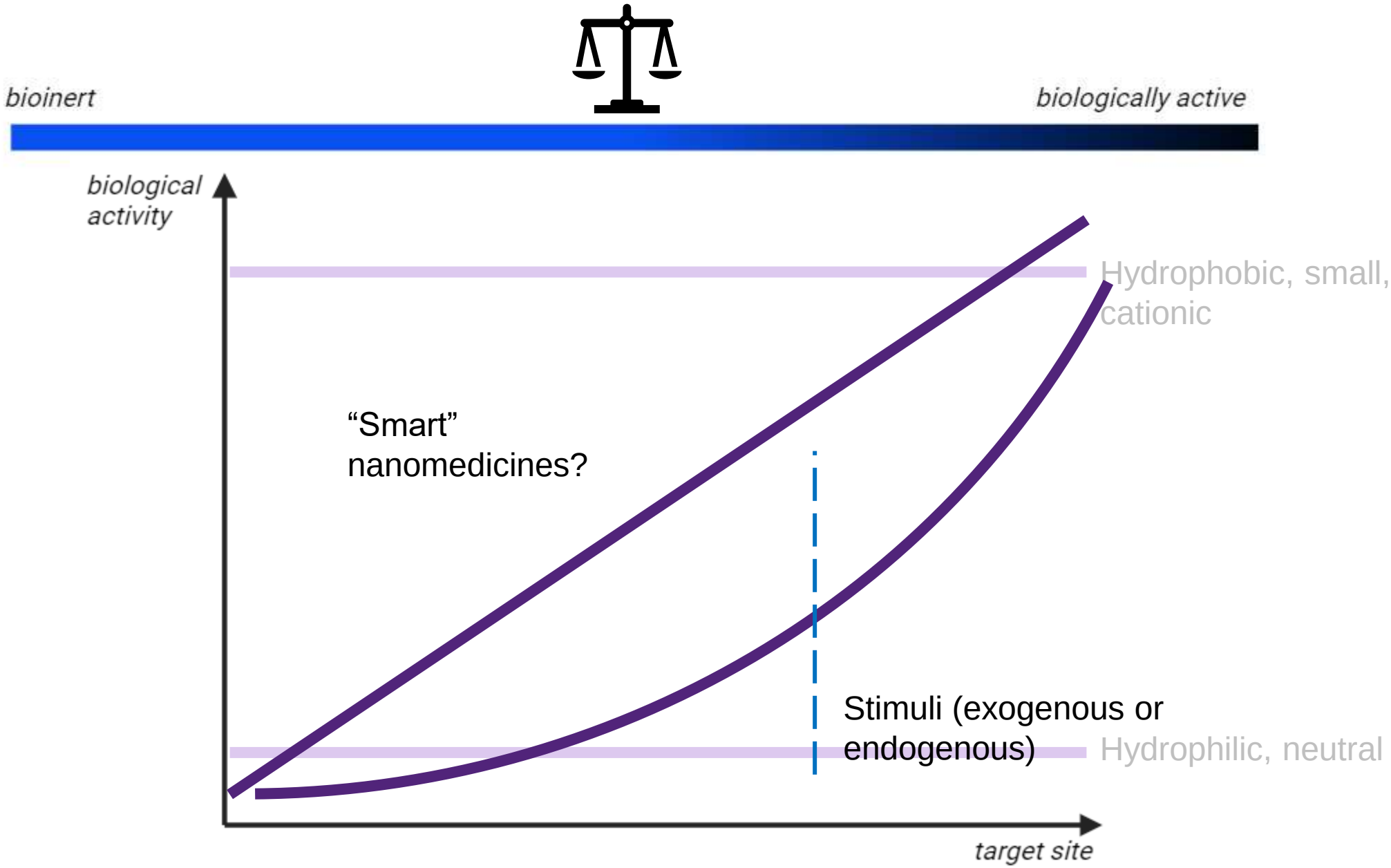
Sara Zalba [a b], Timo L.M. ten Hagen [c], Carmen Burgui [a], María J. Garrido [a b]



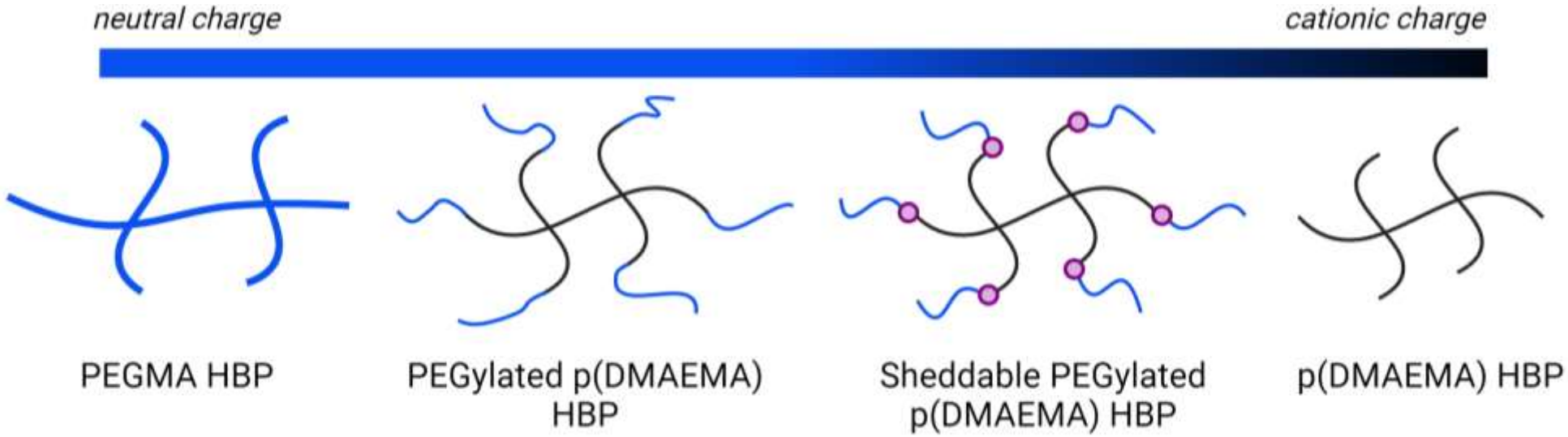
Polymers for drug delivery

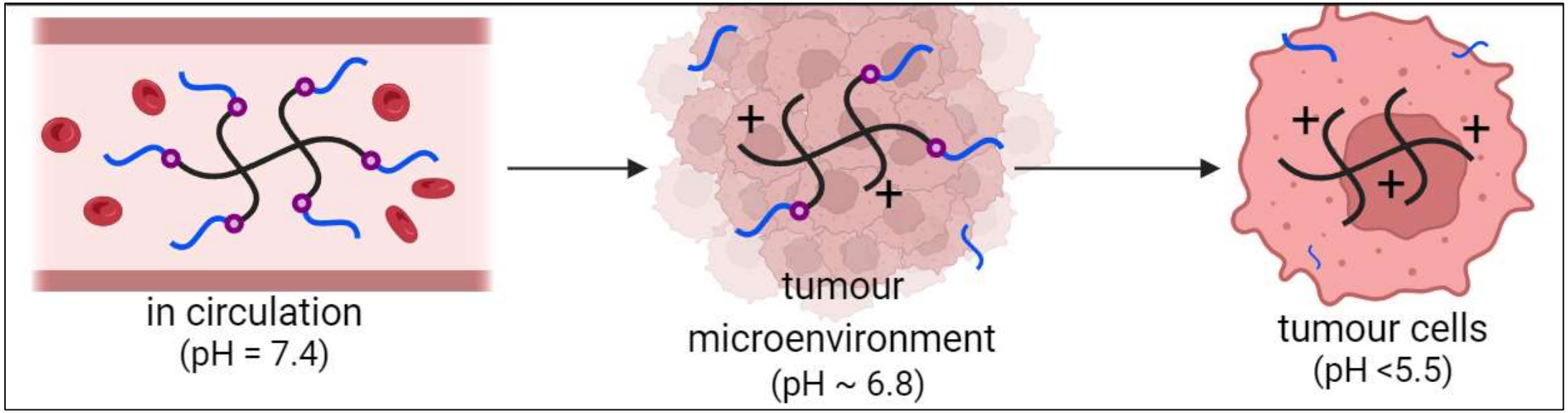


Polymers for drug delivery



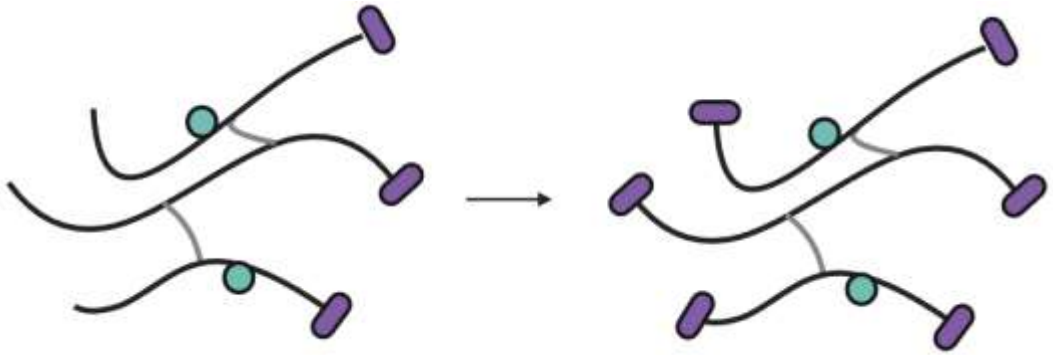
System aim


neutral charge
cationic charge
PEGMA HBP
PEGylated p(DMAEMA) HBP
Sheddable PEGylated p(DMAEMA) HBP
p(DMAEMA) HBP

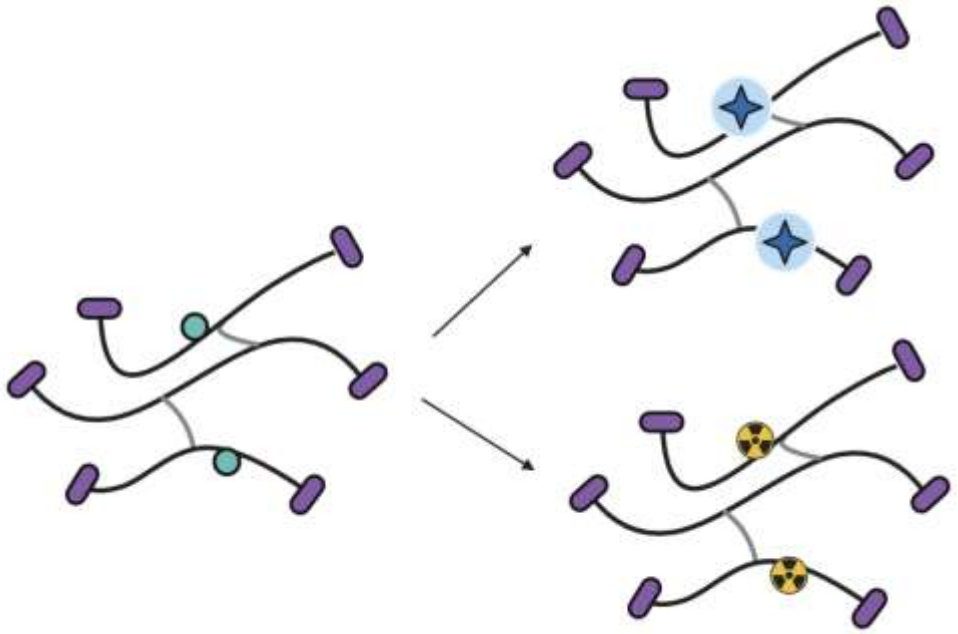

in circulation
(pH = 7.4)
tumour microenvironment
(pH ~ 6.8)
tumour cells
(pH <5.5)

Synthetic vision

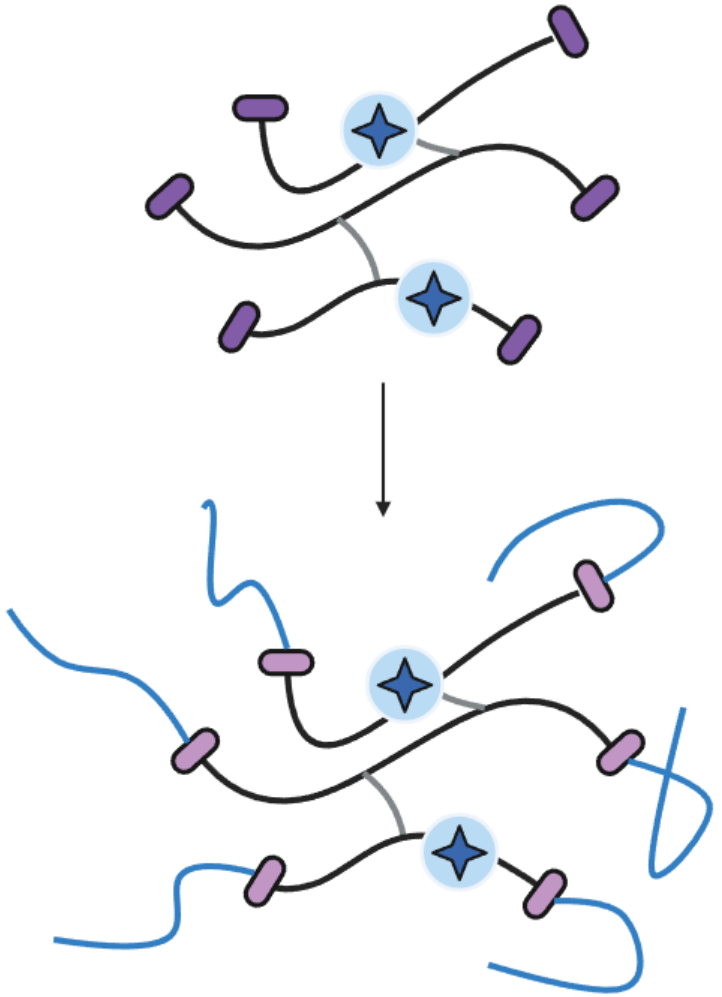
1. Polymerisation & modification



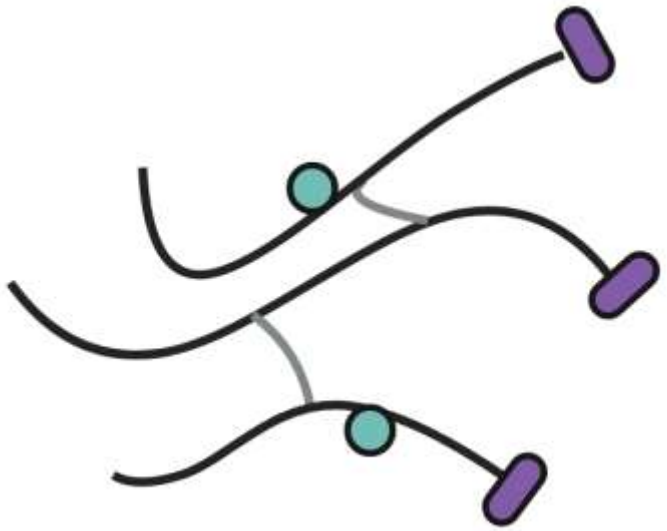
2. Incorporate imaging modality

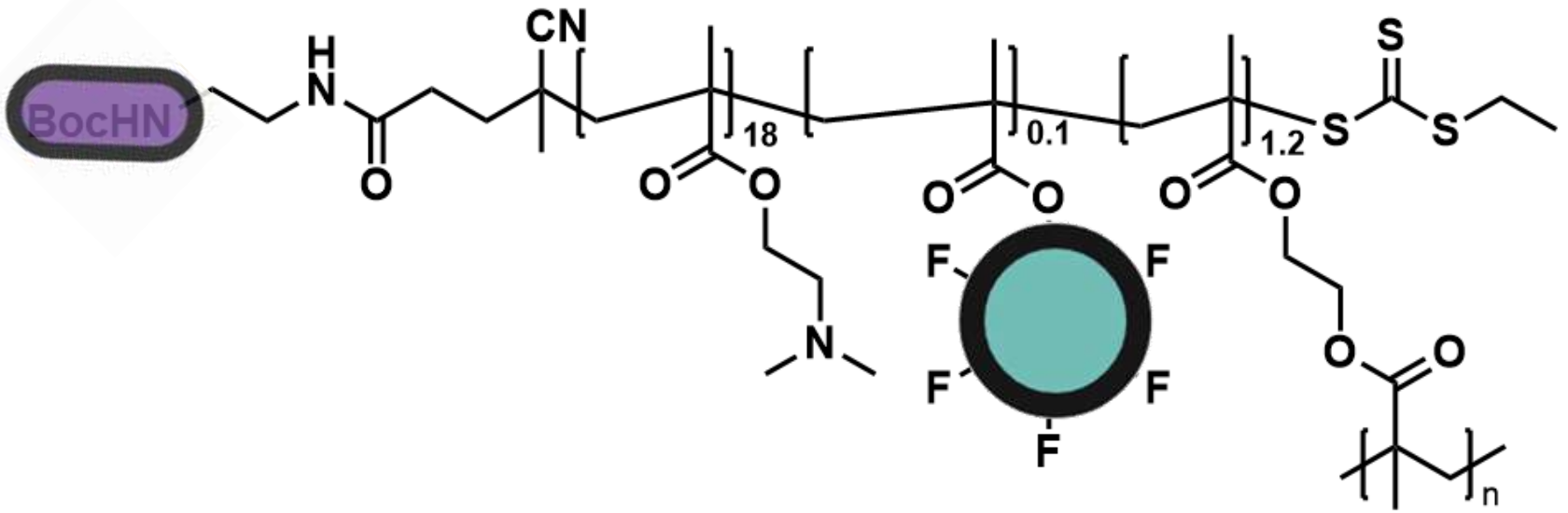


3. Incorporate PEG moiety

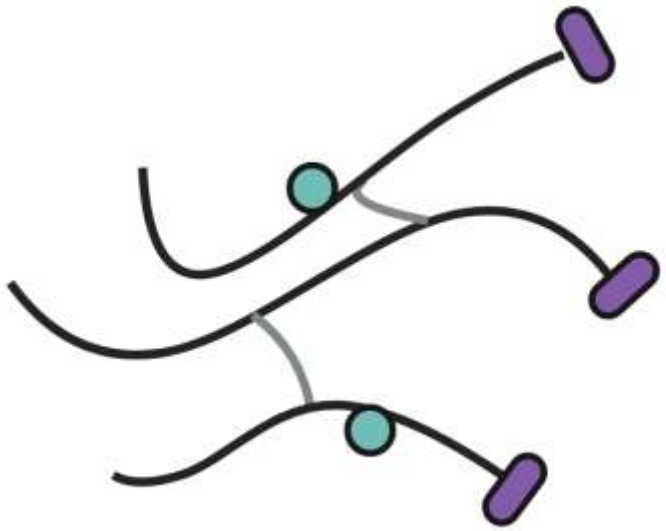


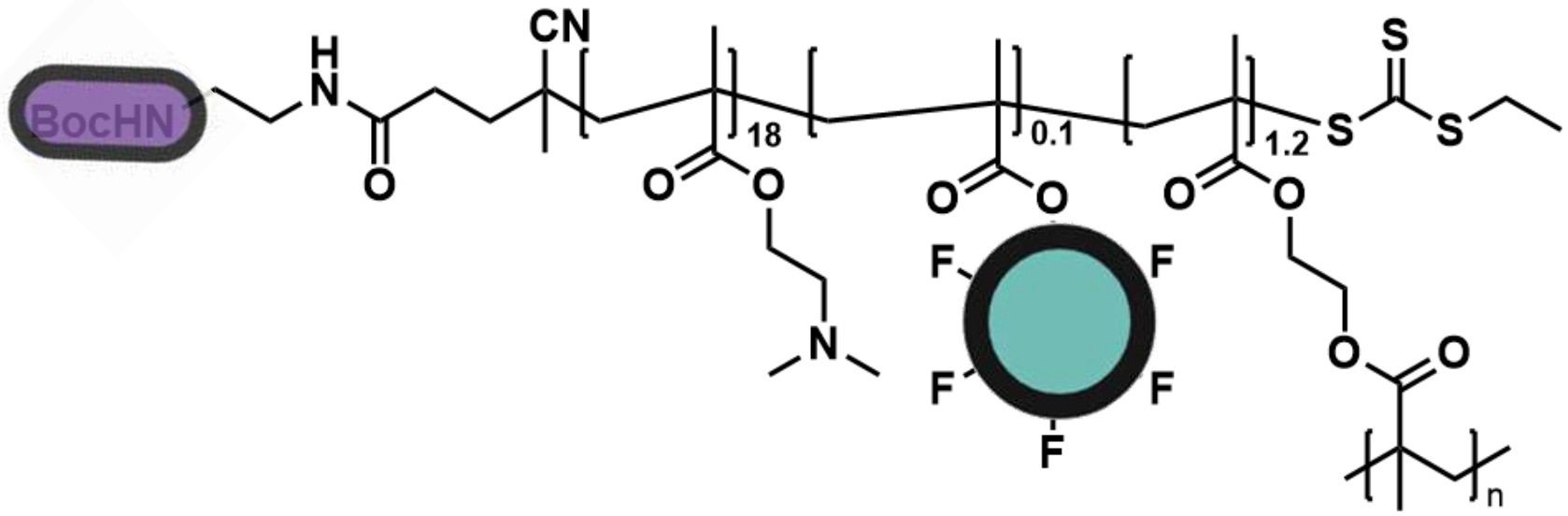
1. Synthesis and modification

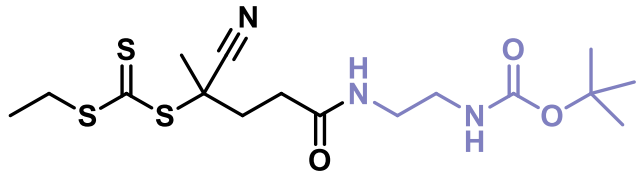




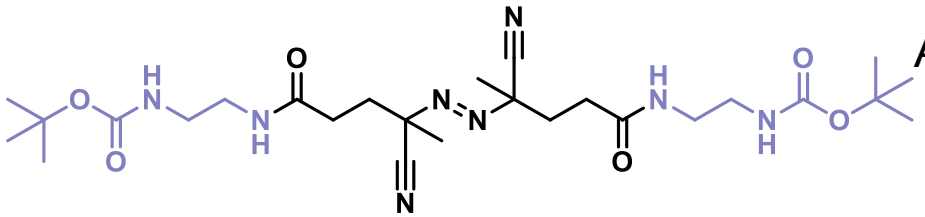
1. Synthesis and modification





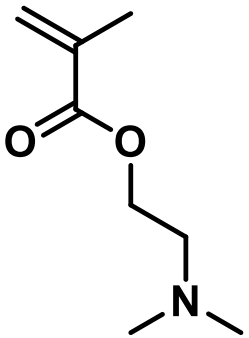


CEPA-NHBoc
(1.0 equiv)

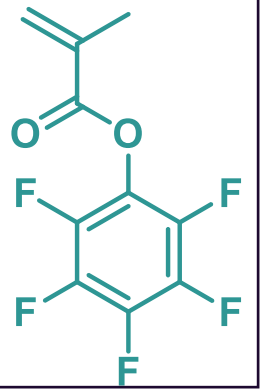


ACVA-NHBoc
(0.2 equiv)

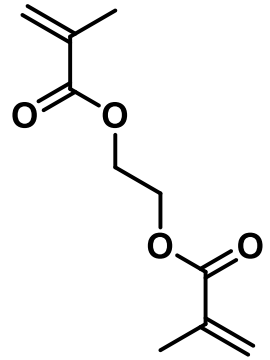
DMAEMA
(20 equiv)



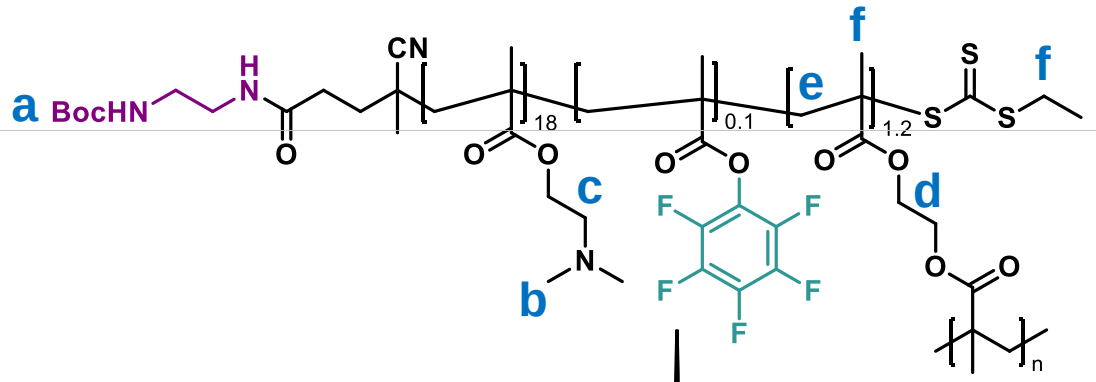
PFMA
(0.1 equiv)



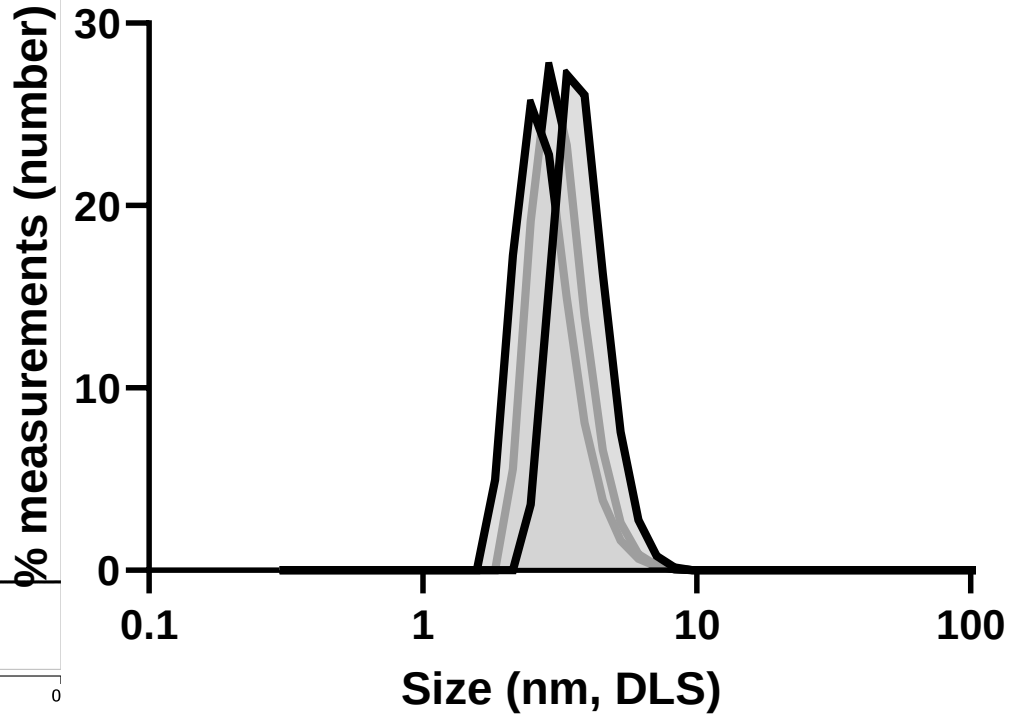
EGDMA
(1.2 equiv)



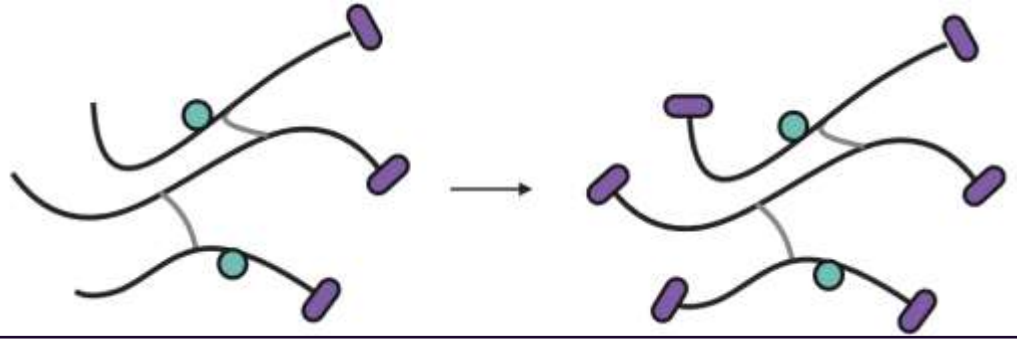
1. Synthesis and modification

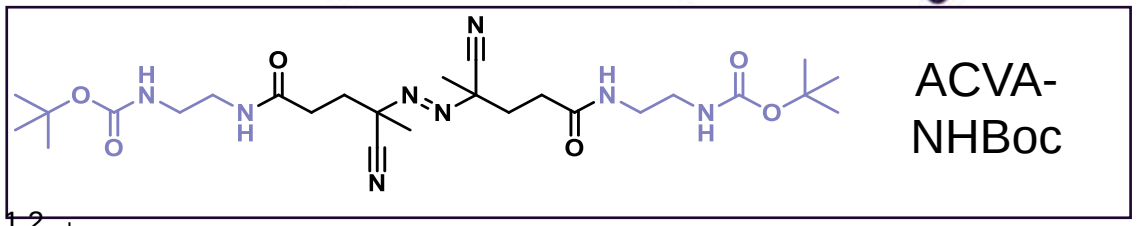


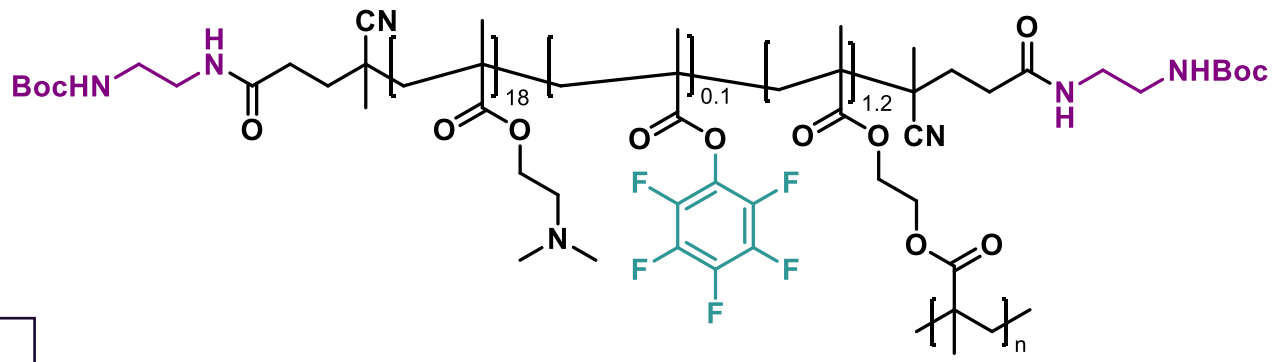
DP	Arm M_n	M_n (MALS)	No. arms
18.3	3650 Da	31.1 kDa	8.5
PDI	**Conv. %**	**DLS**	**Charge**
1.34	97%	2.8 nm	33 mV

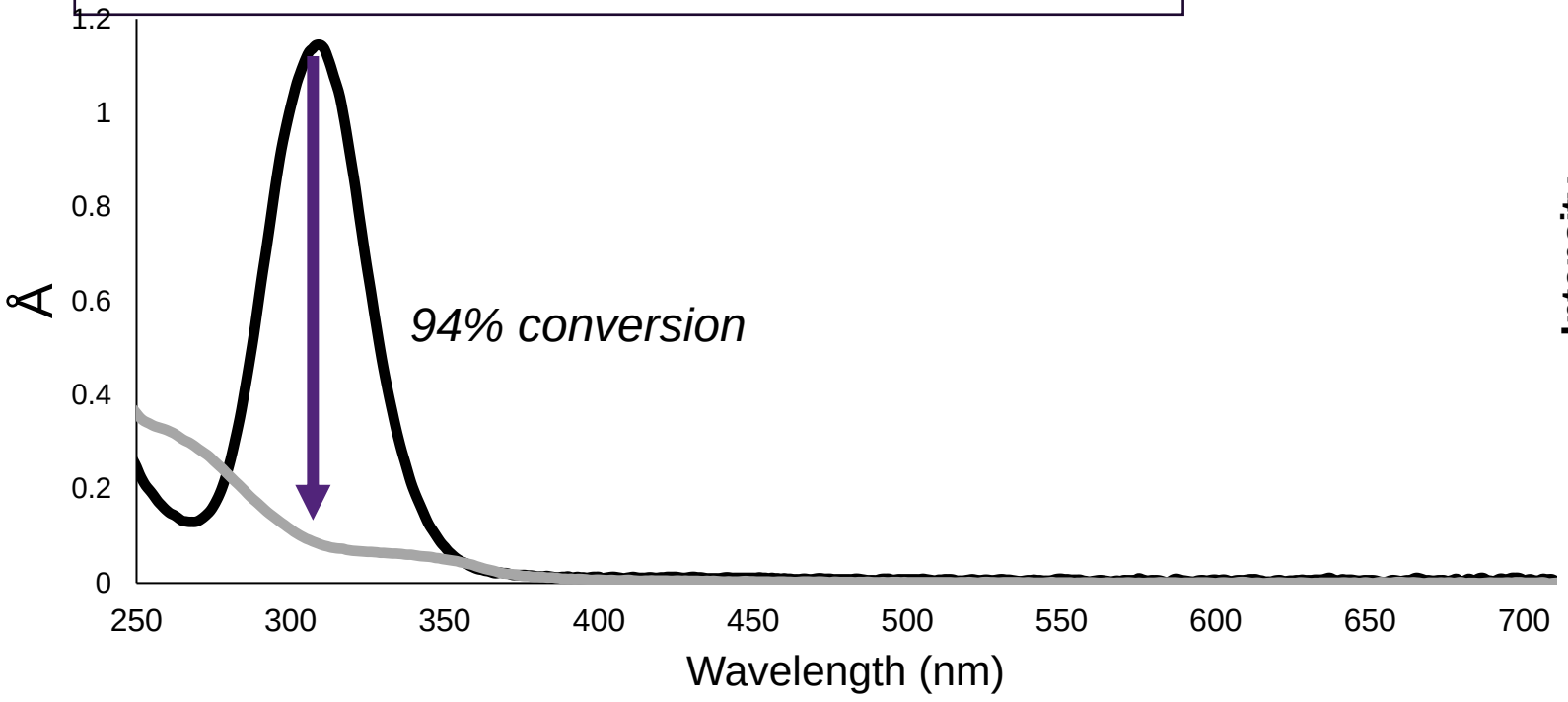


1. Synthesis and modification

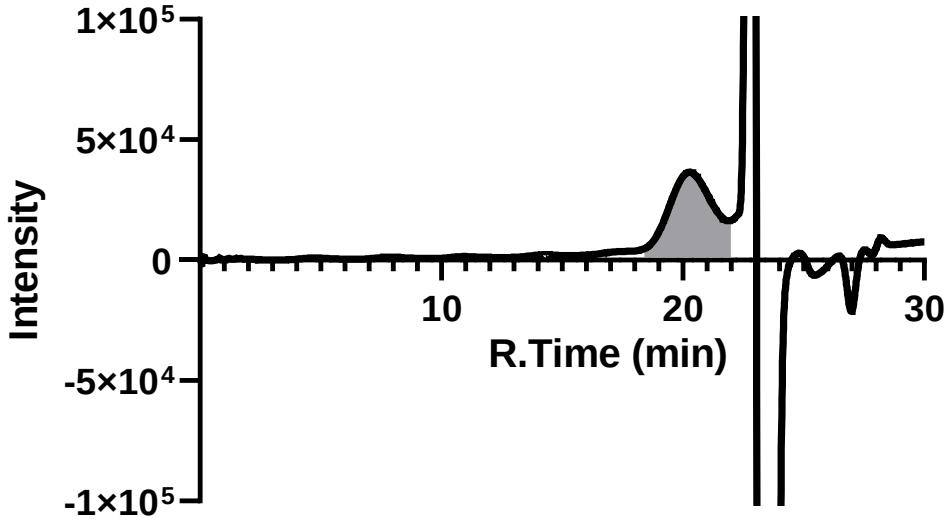


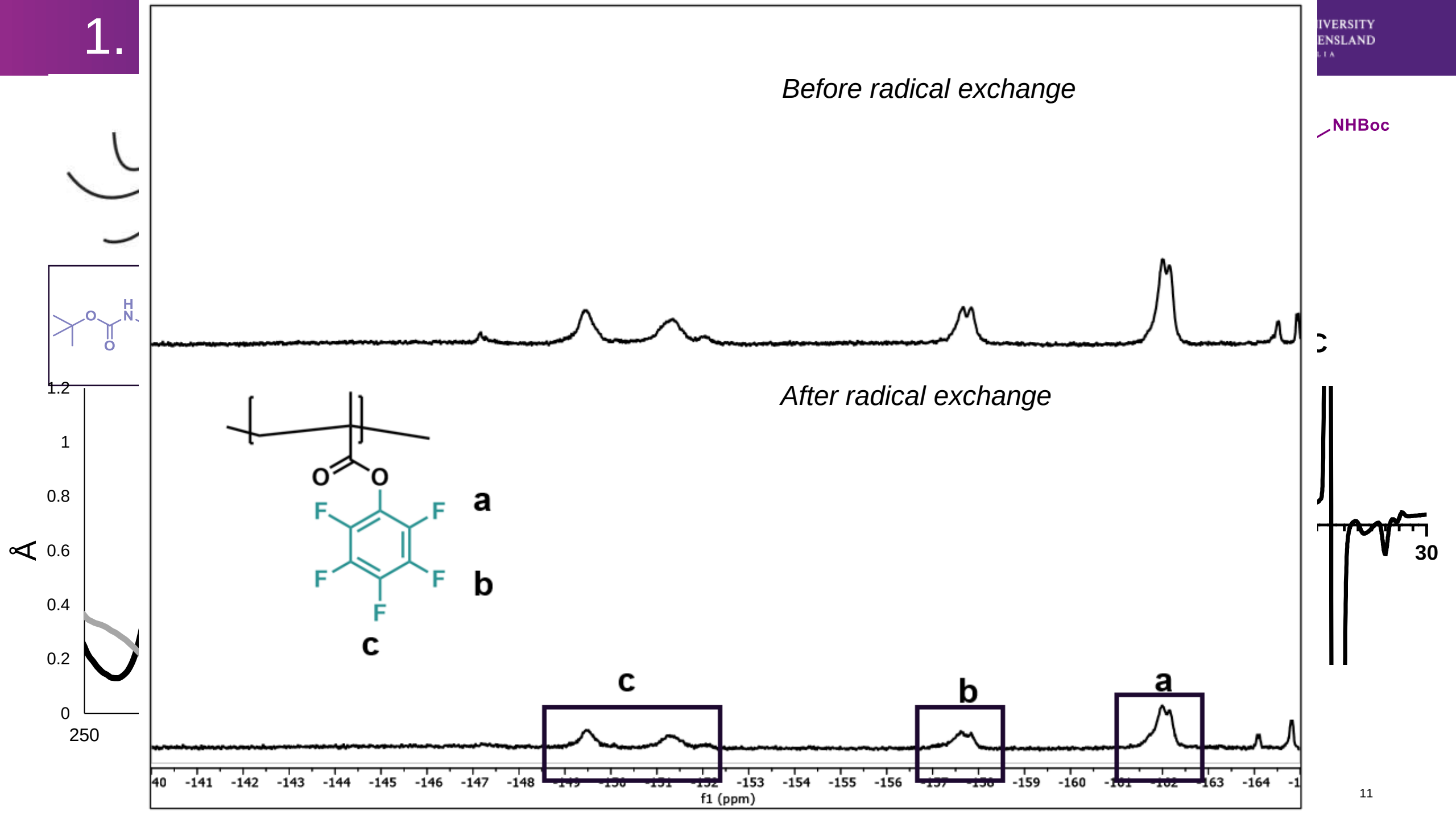




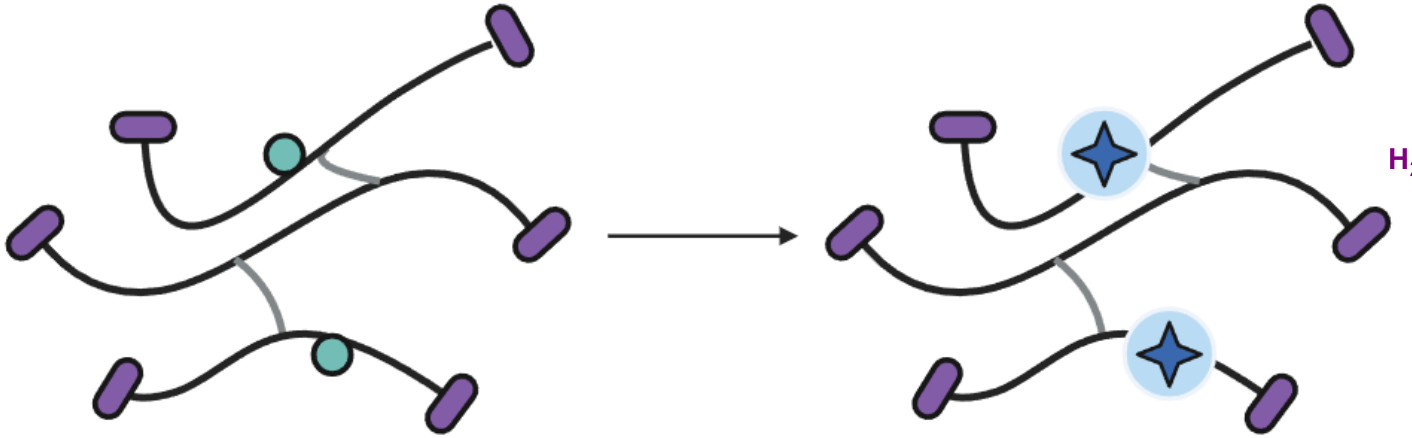


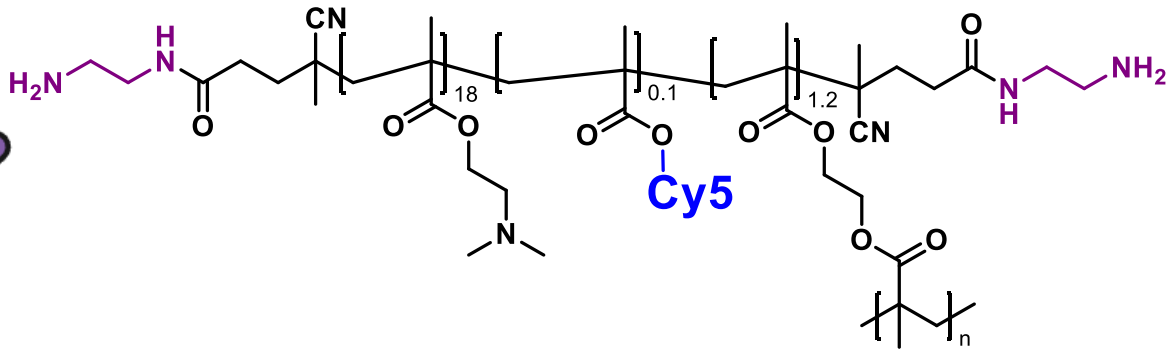
HBP-NHBoc GPC

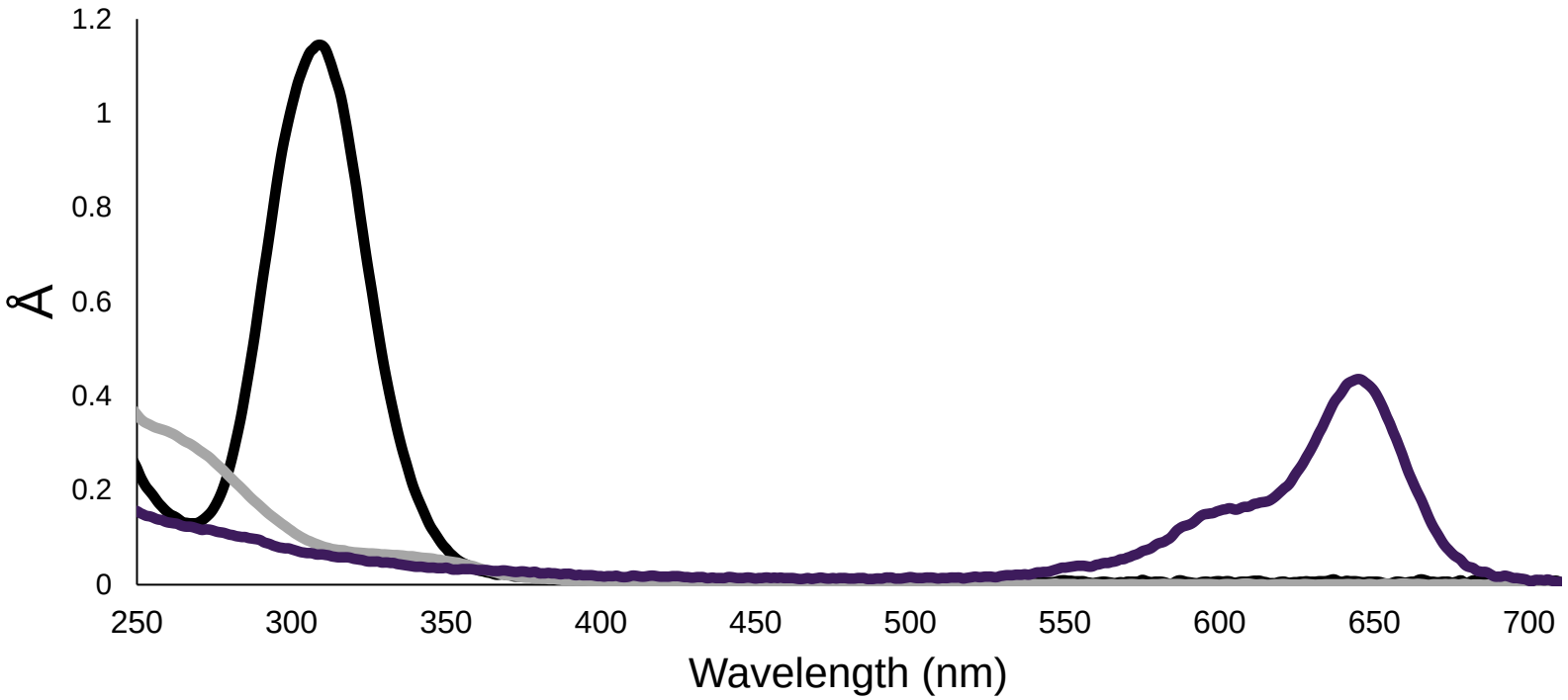



Before radical exchange
After radical exchange
a
b
c
c
b
a
f1 (ppm)
NHBoc
30
A
1.2
1
0.8
0.6
0.4
0.2
0
250

2. Incorporate imaging modality

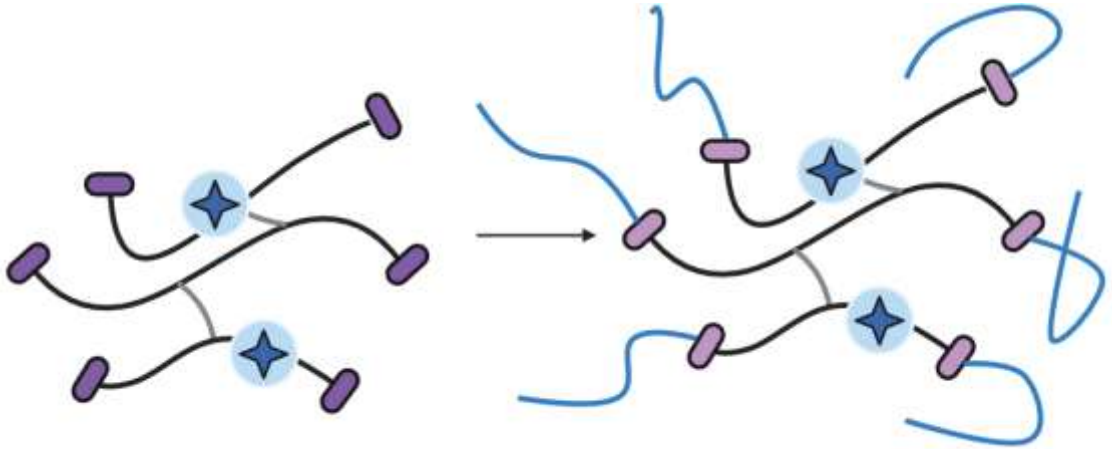


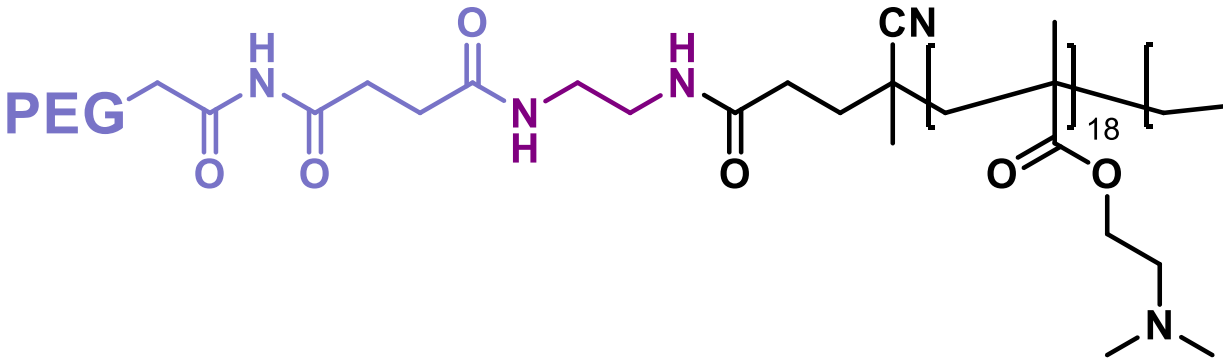


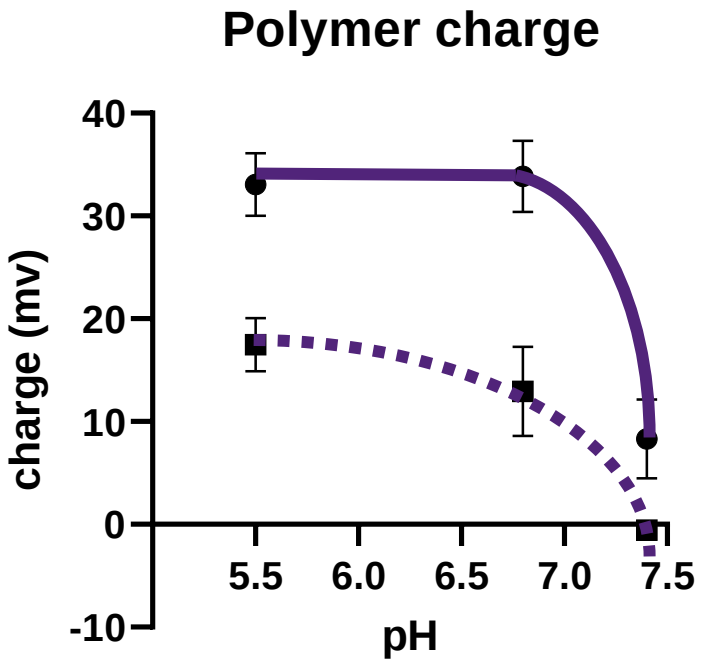


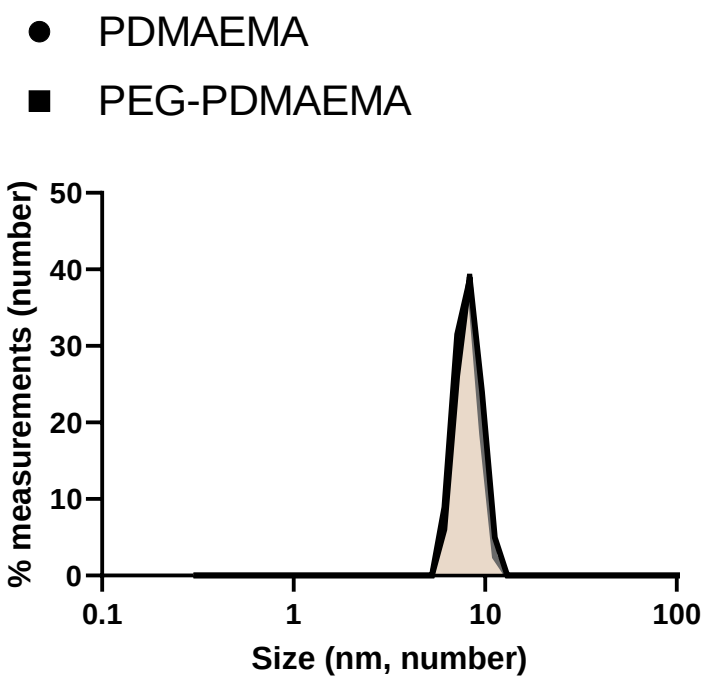
~2.5 dyes per HBP

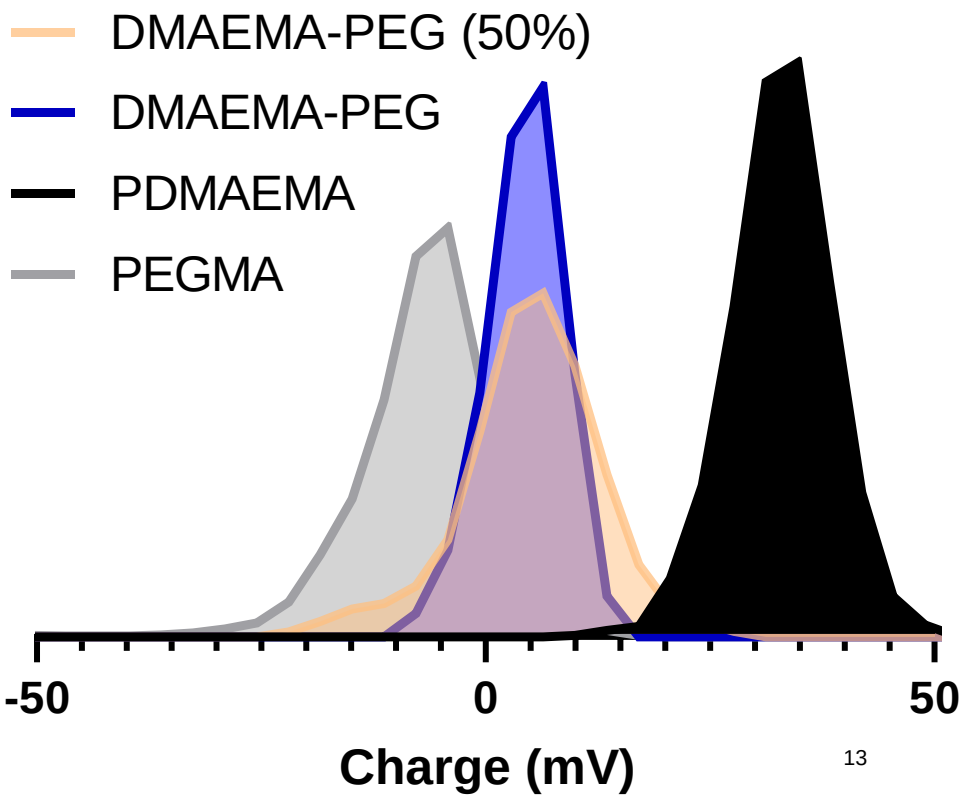
3. Incorporating PEG moieties







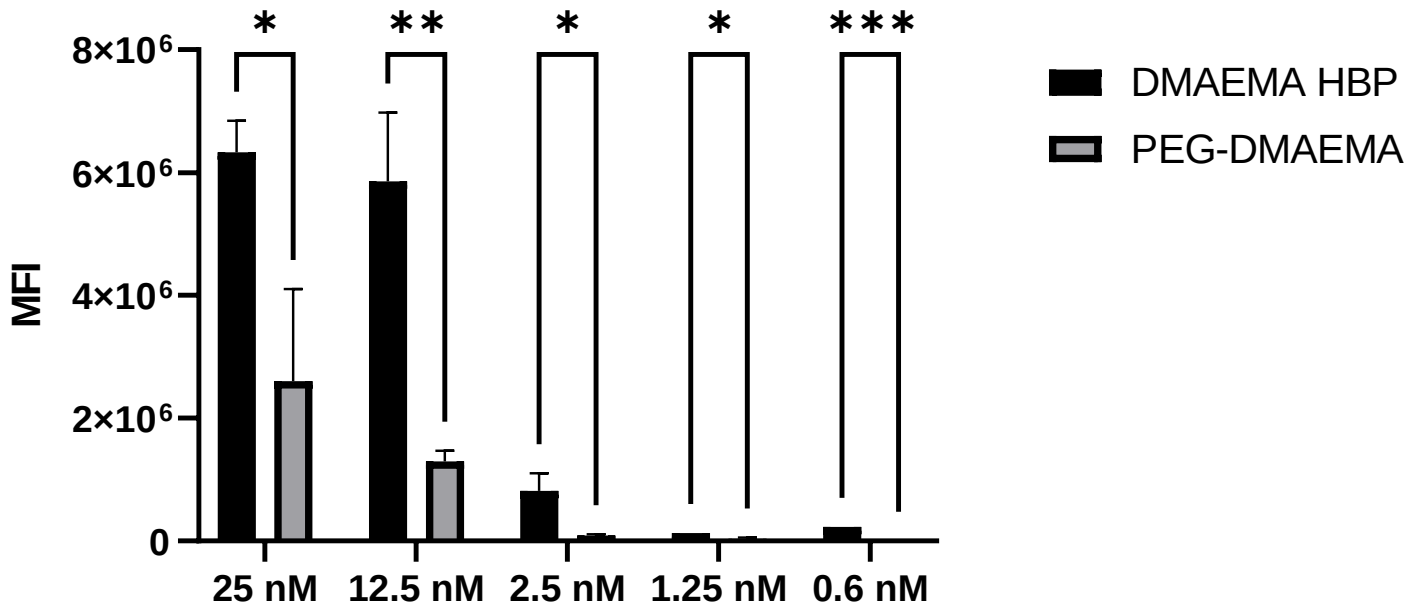


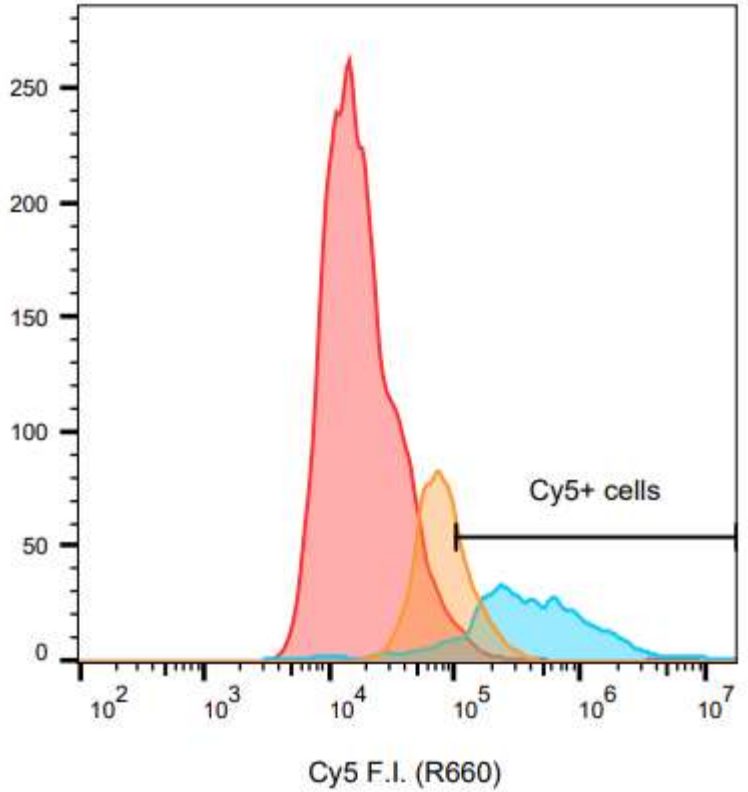


PDMAEMA vs PEG-DMAEMA

PEG increases polymer bioinertness across all concentrations

Cellular Association of PEGylated vs unPEGylated DMAEMA





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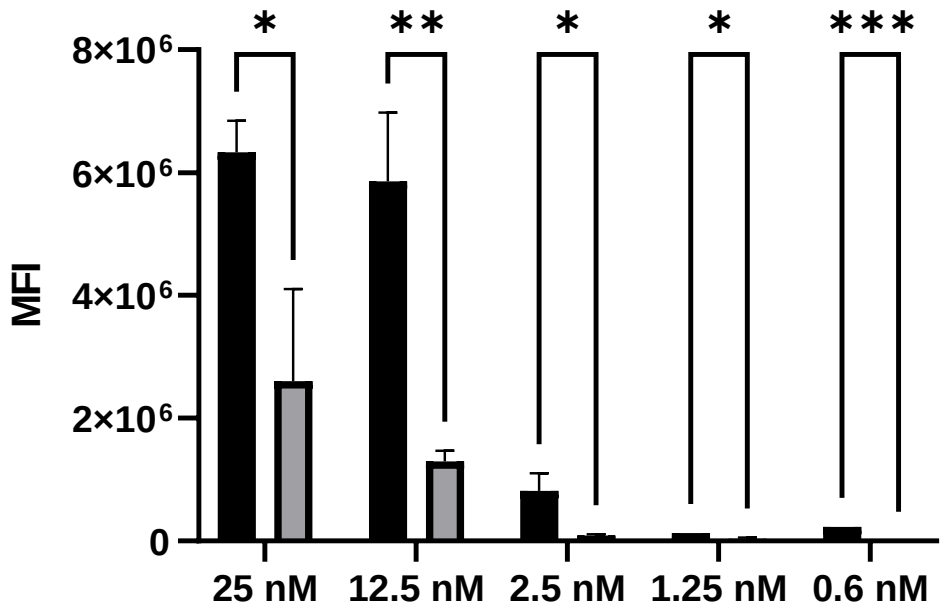
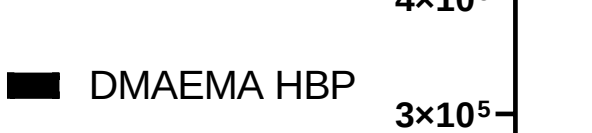
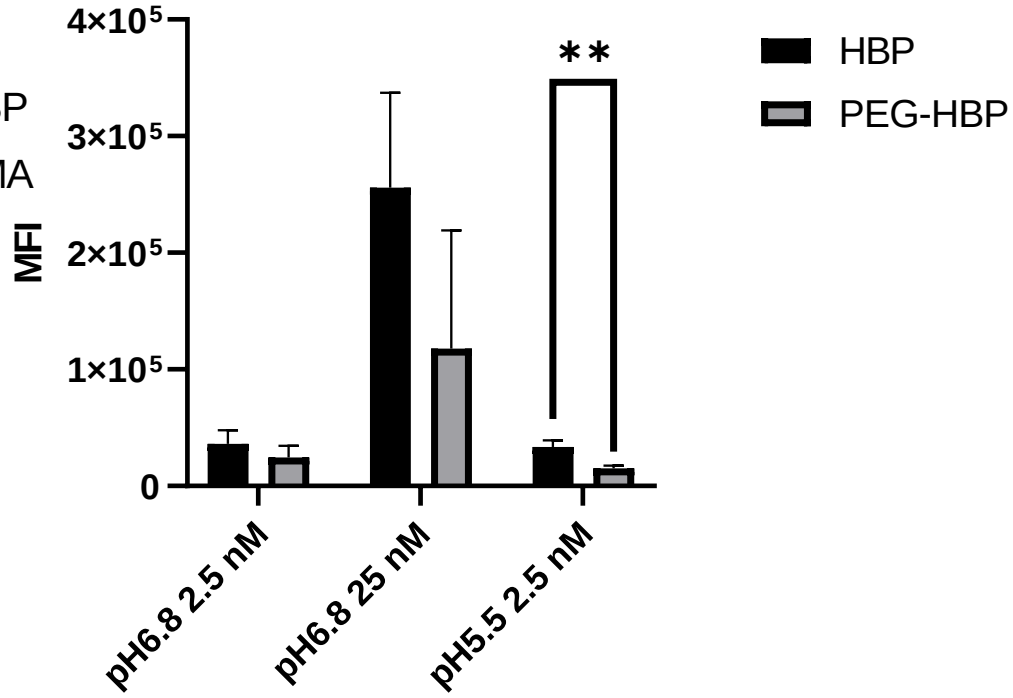


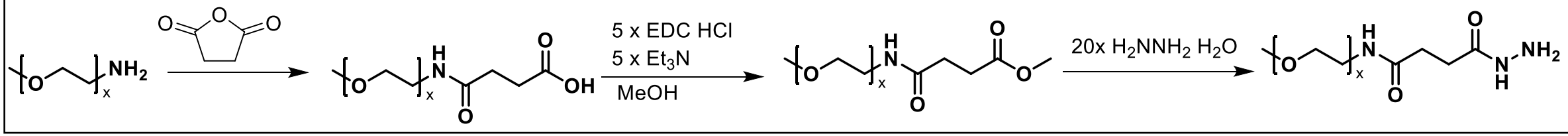


pH variable flow

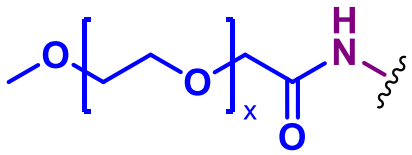


3. Incorporating PEG moieties

Acyl hydrazide

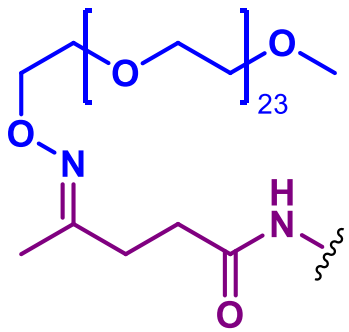


Non-sheddable



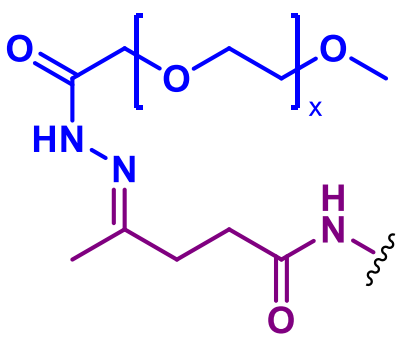
Amide stable in acid

Oxime



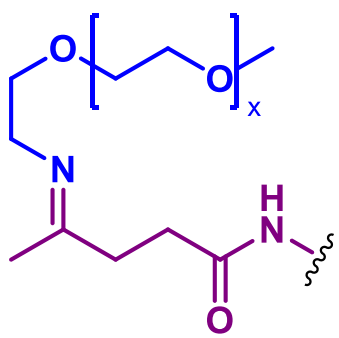
Slow cleavage

Hydrazone



Moderate cleavage

Imine

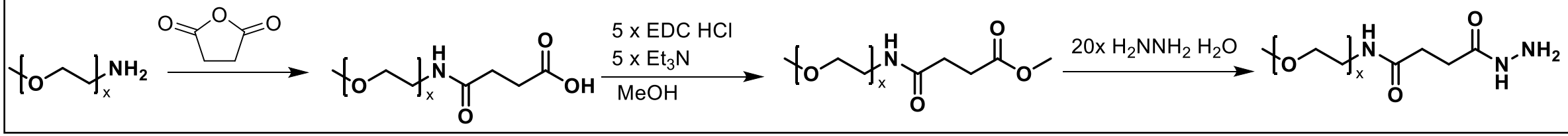


Fast cleavage in acid

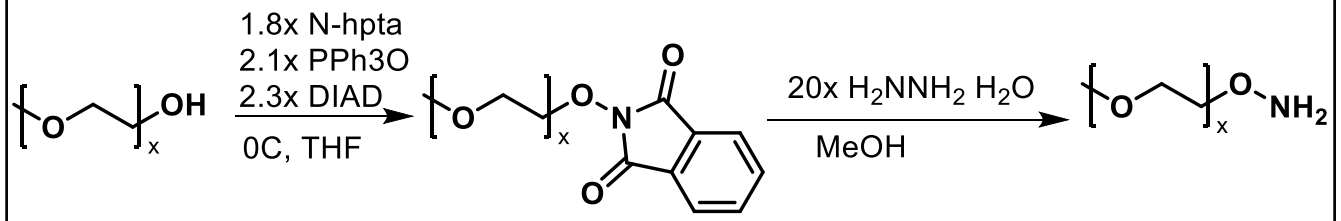
3. Incorporating PEG moieties

THE UNIVERSITY OF QUEENSLAND AUSTRALIA

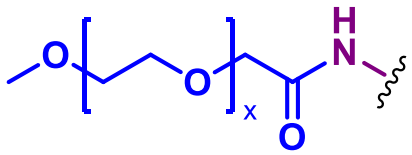
Acyl hydrazide



Hydroxylamine

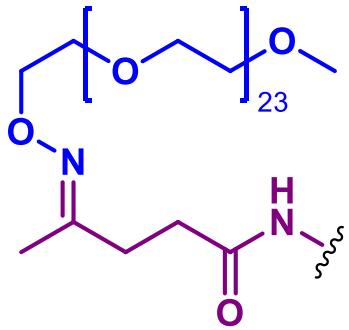


Non-sheddable



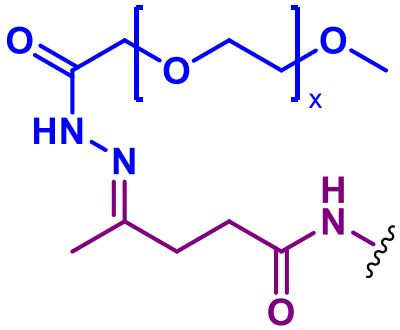
Amide <u>stable</u> in acid

Oxime



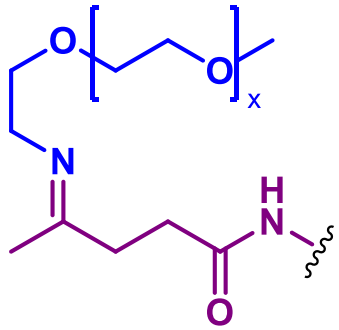
<u>Slow</u> cleavage

Hydrazone



<u>Moderate</u> cleavage

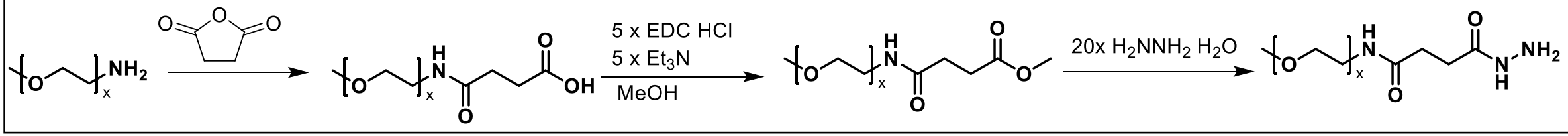
Imine



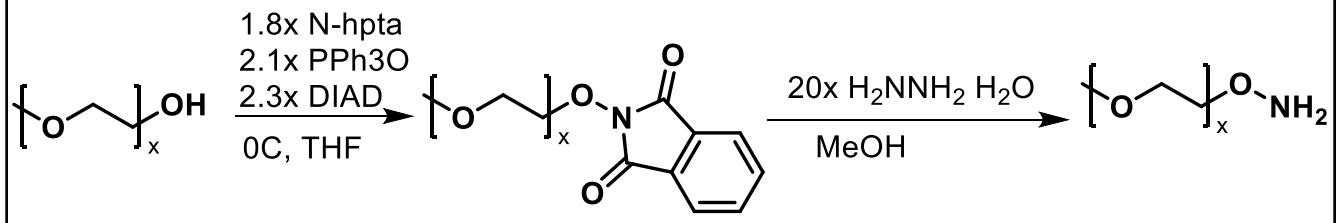
<u>Fast</u> cleavage in acid

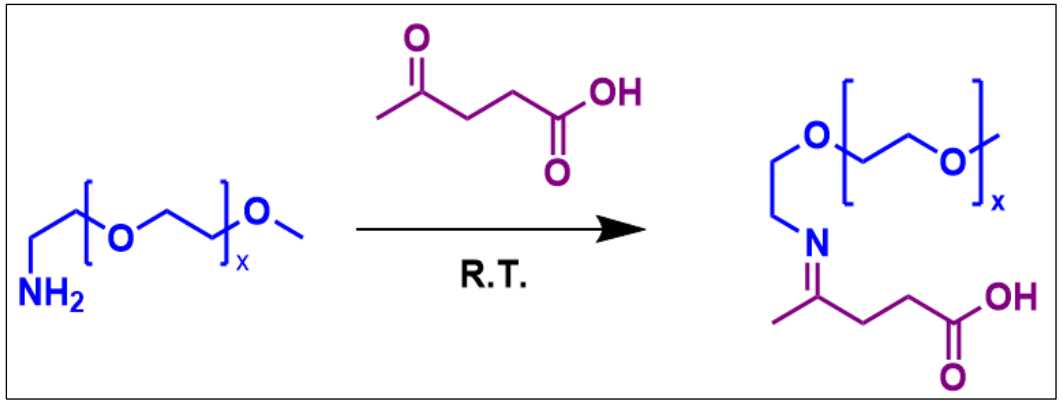
3. Incorporating PEG moieties

Acyl hydrazide

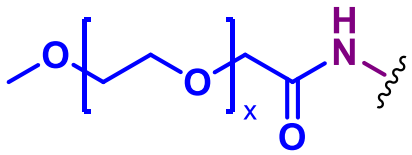


Hydroxylamine



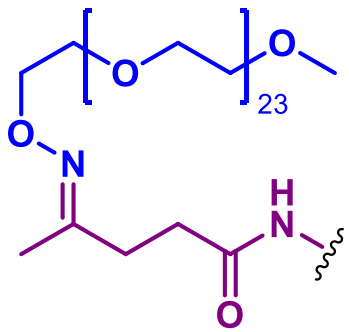


Non-sheddable



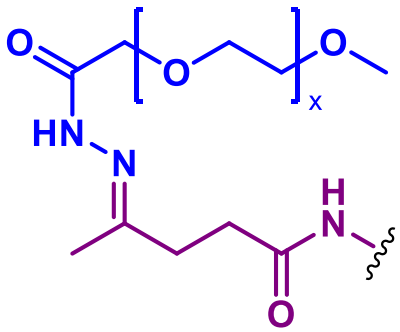
Amide <u>stable</u> in acid

Oxime



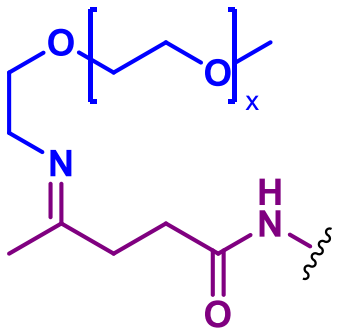
<u>Slow</u> cleavage

Hydrazone



<u>Moderate</u> cleavage

Imine

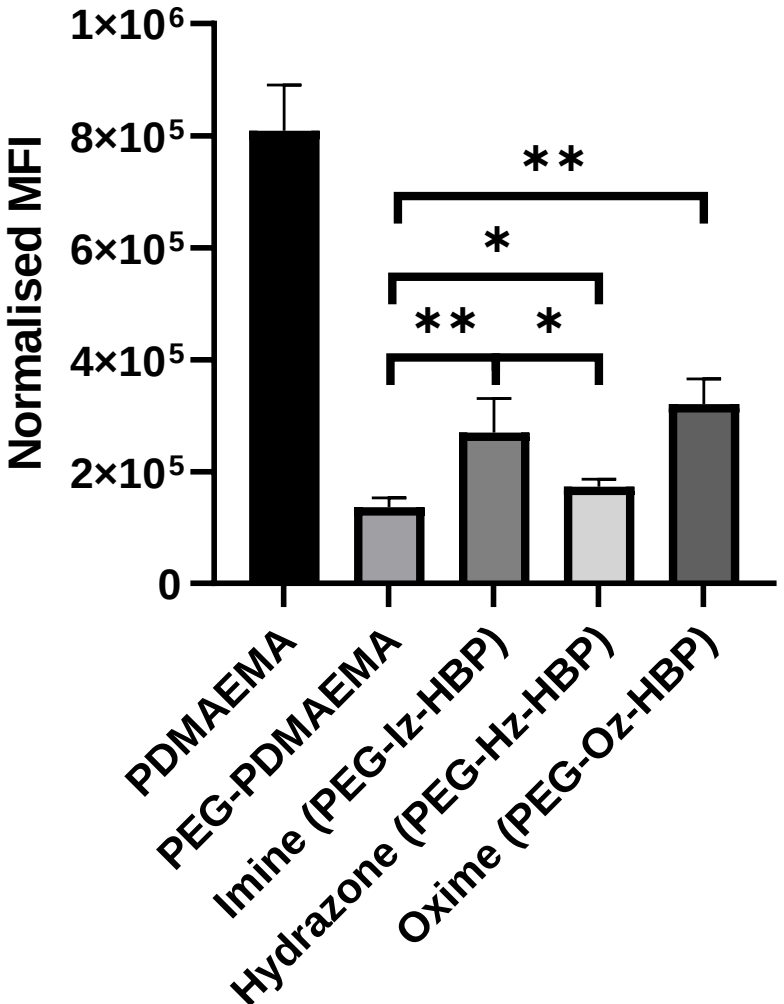


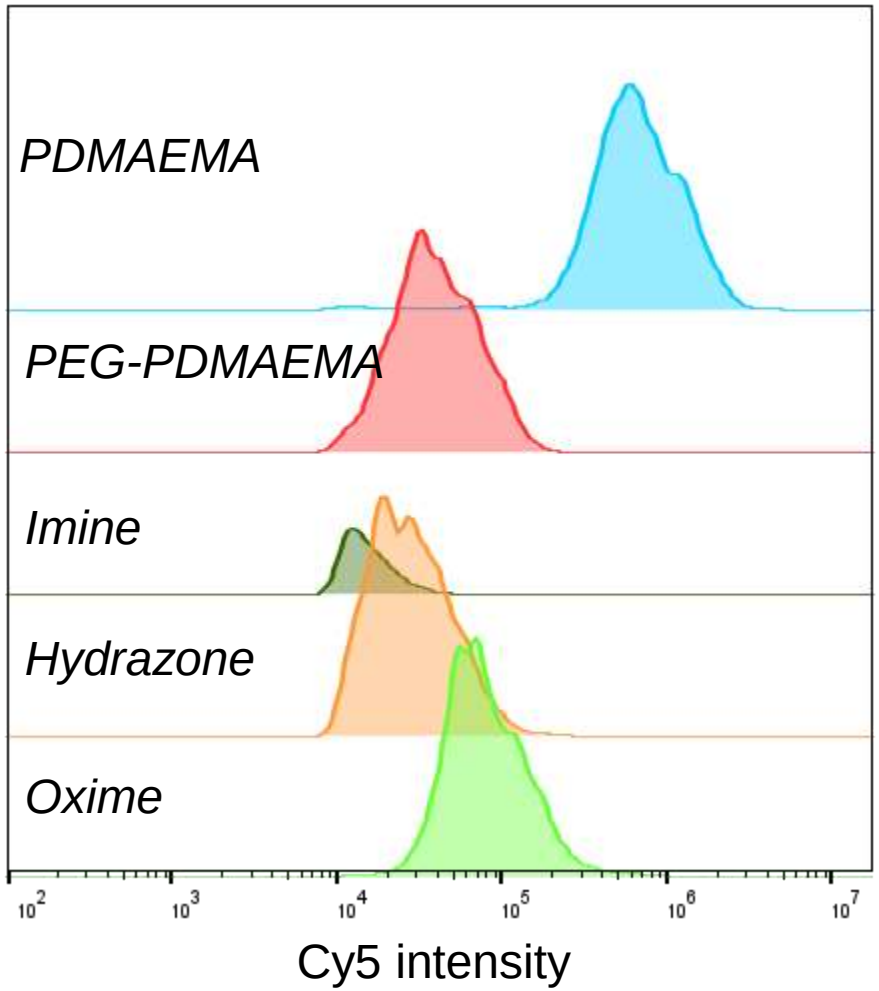
<u>Fast</u> cleavage in acid

Cellular association – sheddable PEG

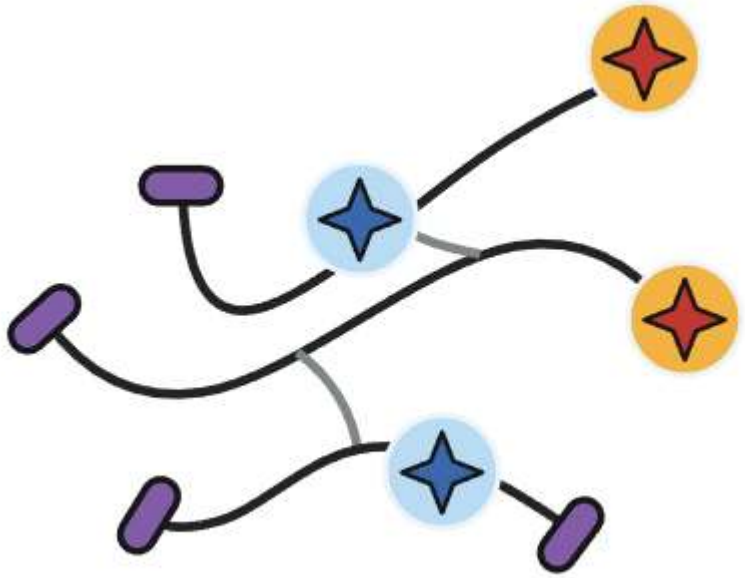
Increased lability = increased cellular association

How? Extra- or intra-cellular shedding?

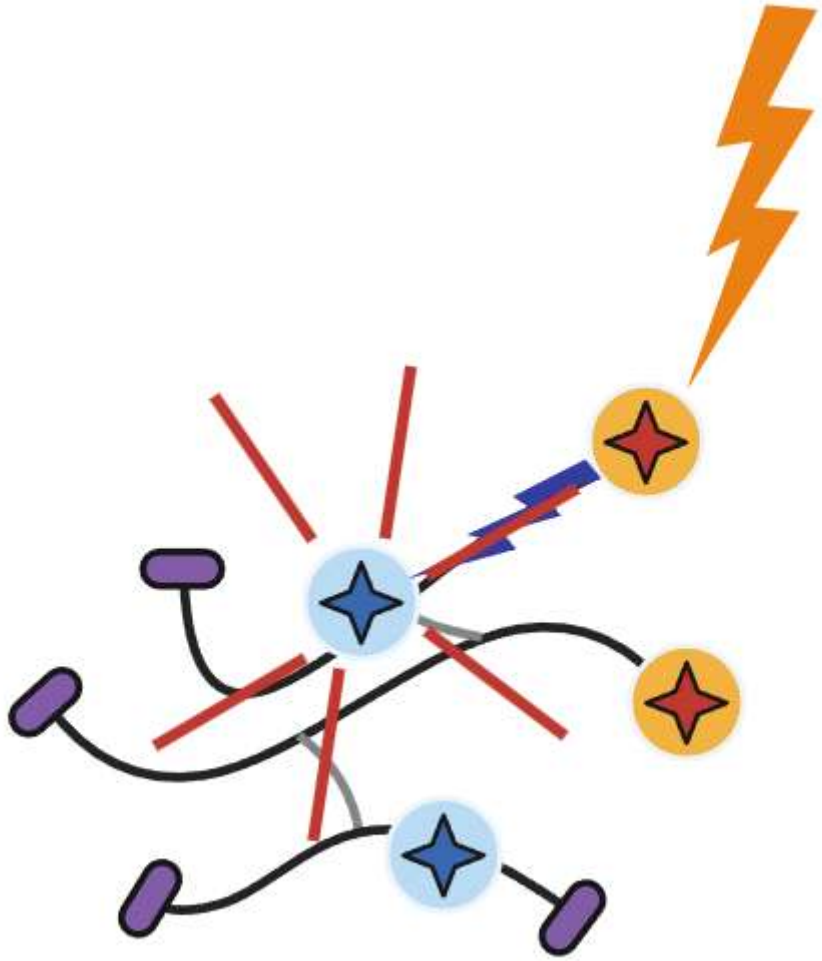




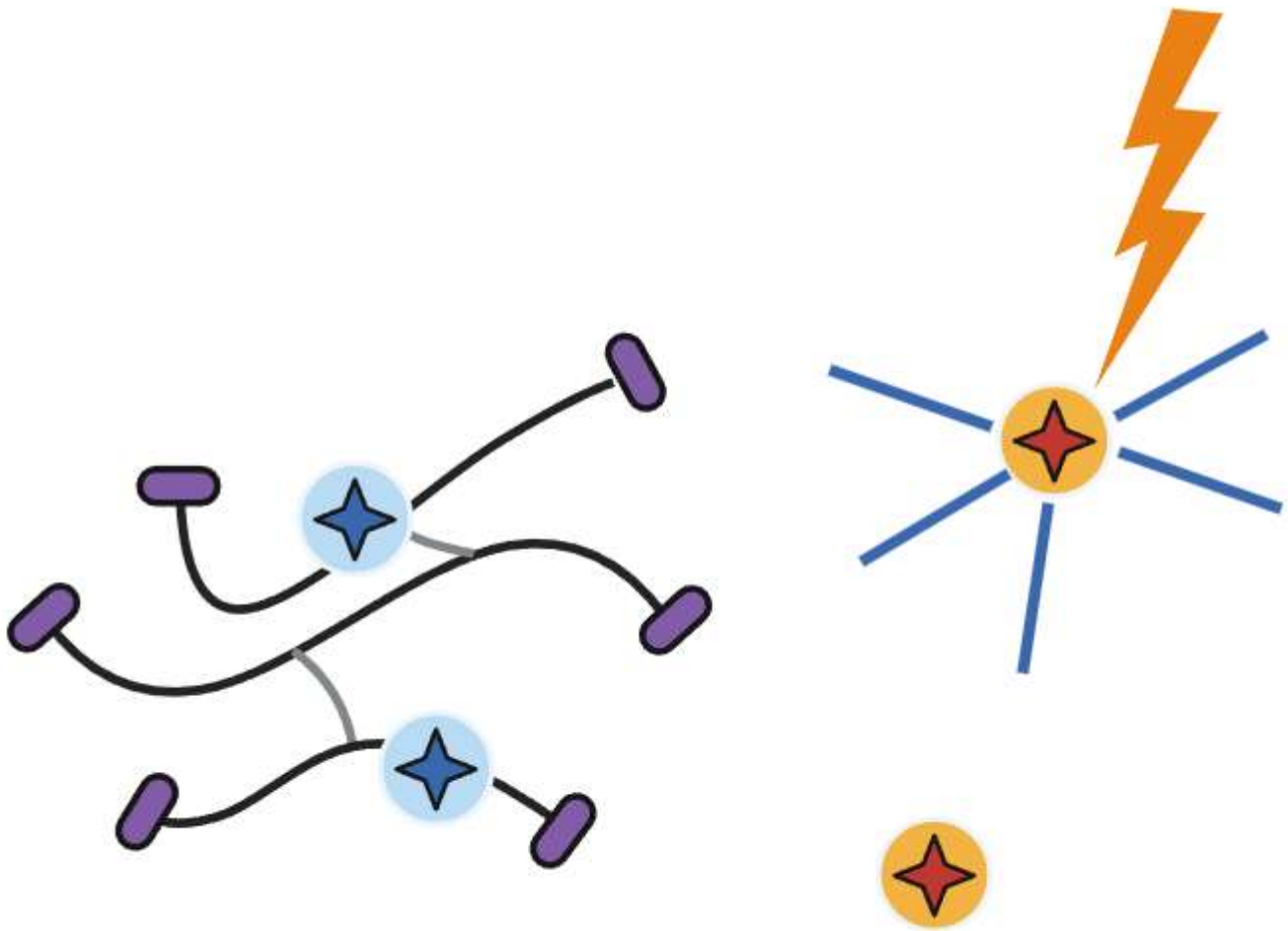
Sheddable PEG – biological mechanism?



Sheddable PEG – biological mechanism?



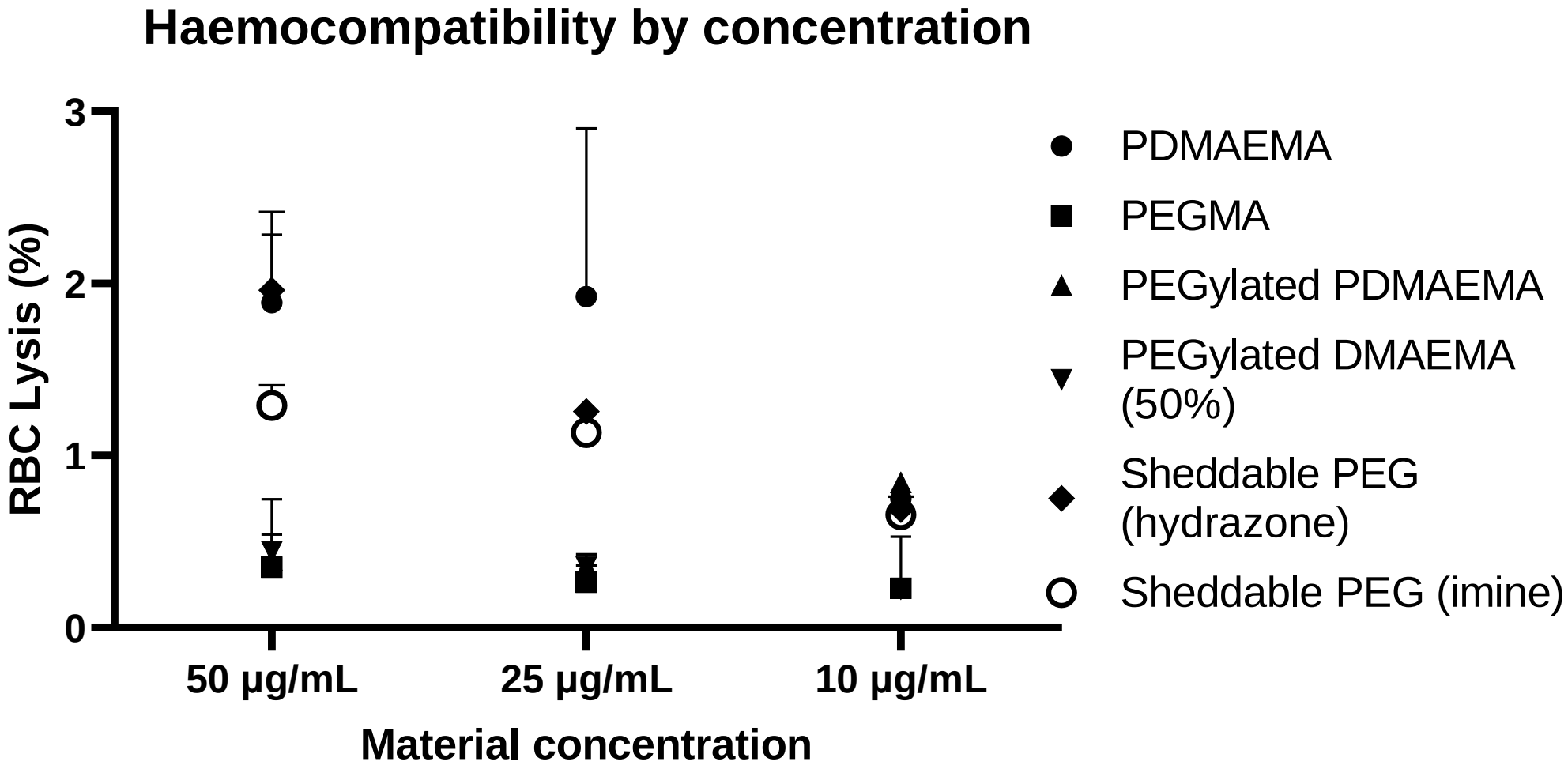
FRET on – no shedding



FRET off – shedding

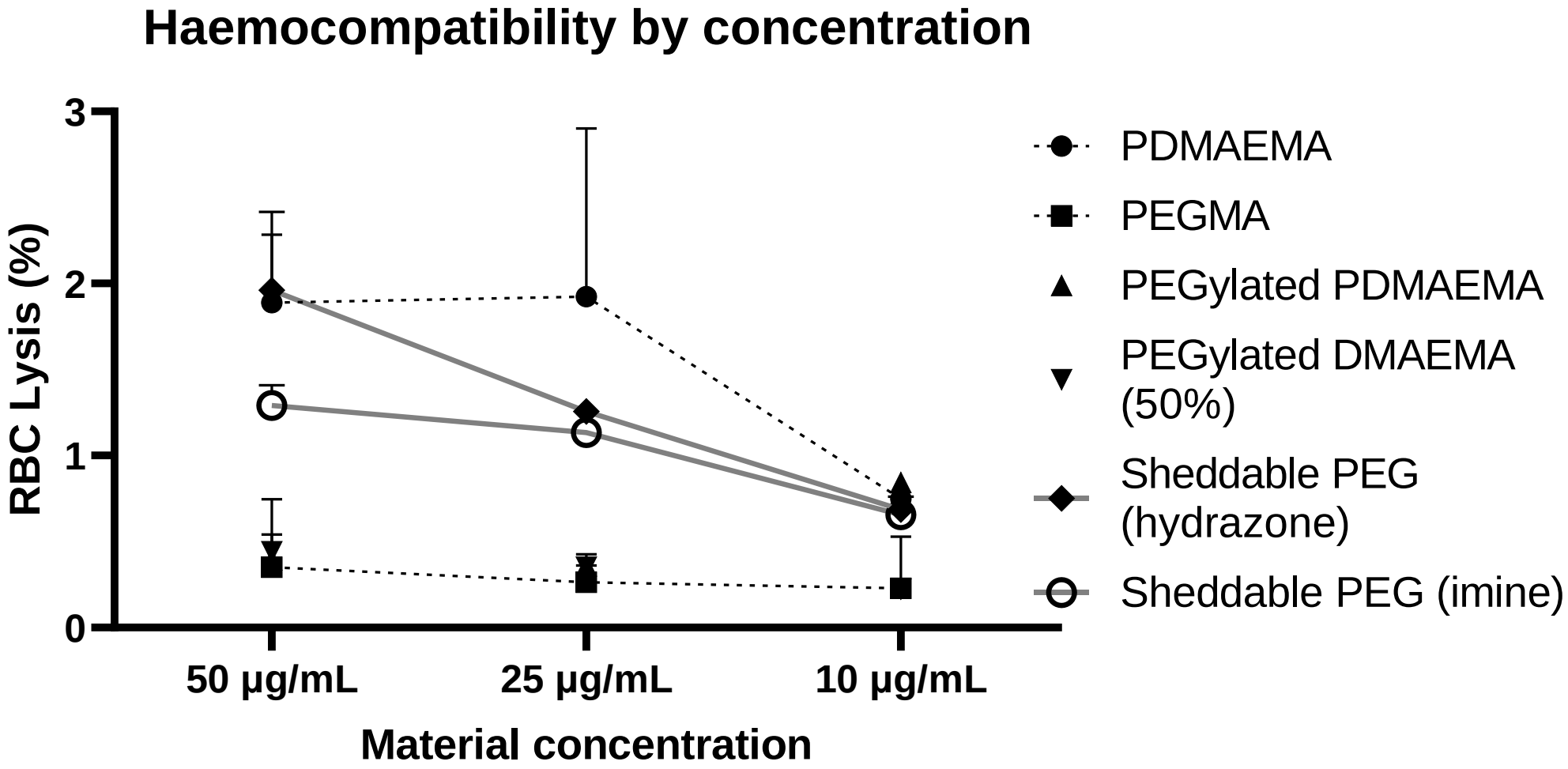
Towards *in vivo*

Haemolytic activity: PEGylated material < sheddable PEG < unPEGylated material

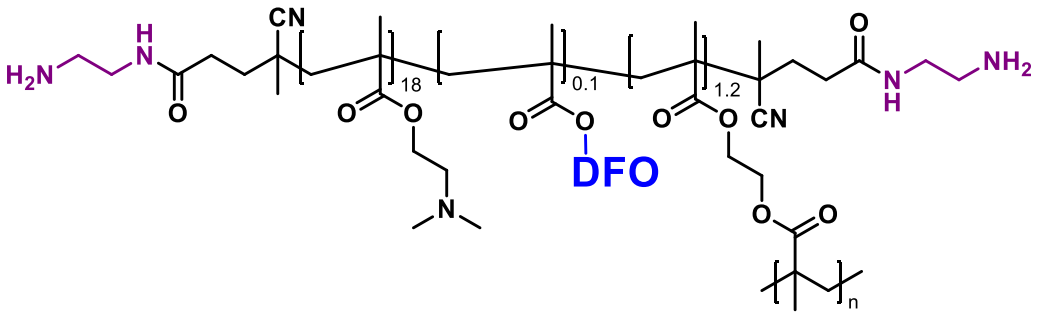


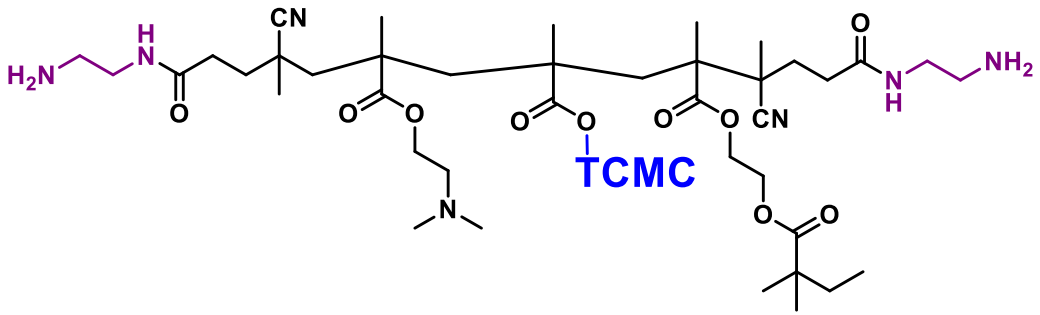
Towards *in vivo*

Haemolytic activity: PEGylated material < sheddable PEG < unPEGylated material

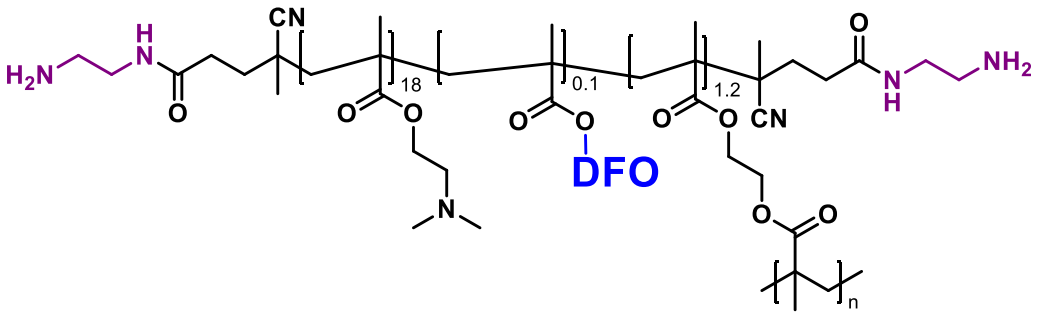


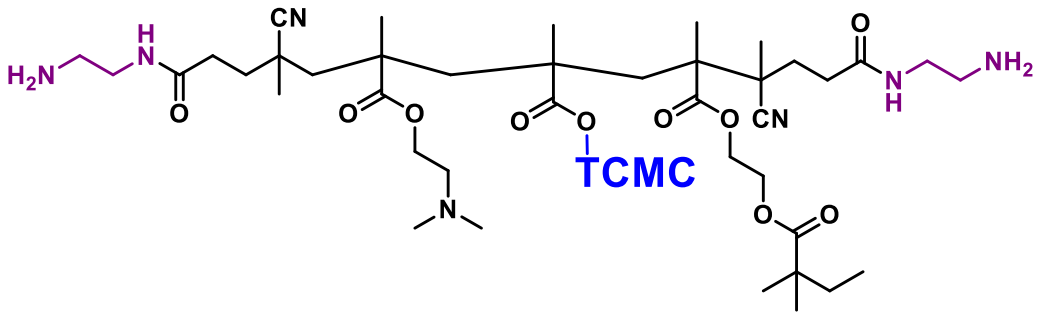
Towards *in vivo*

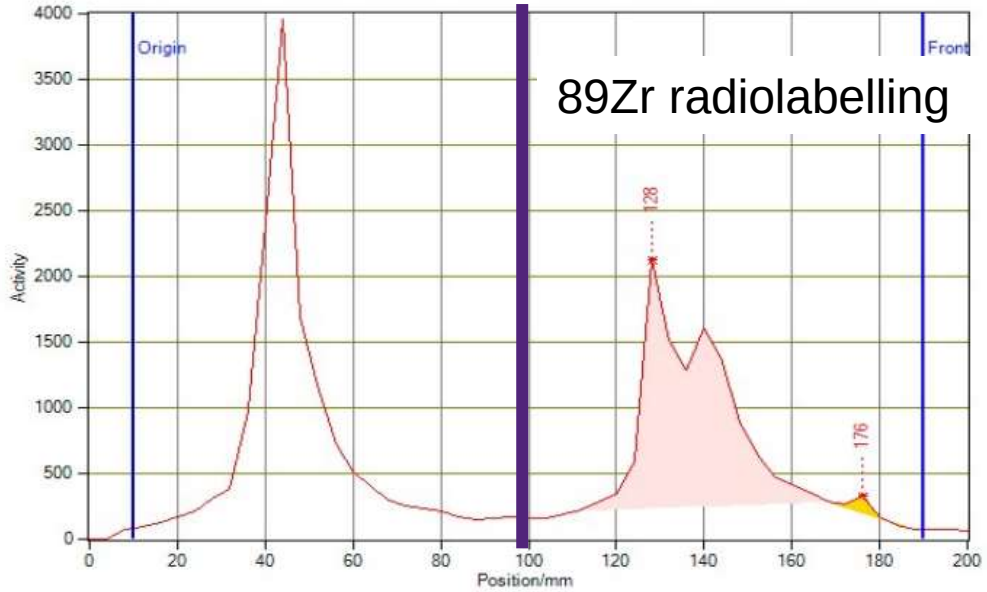


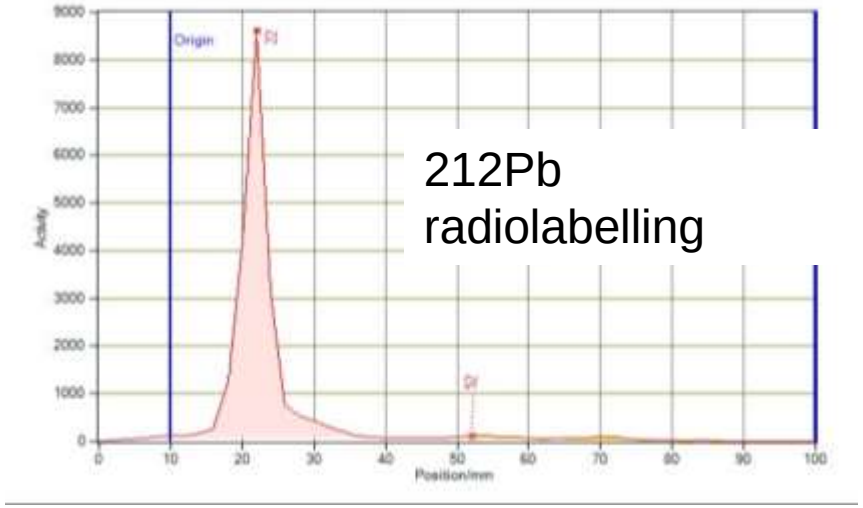


Towards *in vivo*









Conclusions & future direction

Conclusions

- Polymer which increases charge inversely to pH has been synthesised
- % shedded ≠ % charge increase
- Schiff base formation can occur simply by dissolving primary amines in levulinic acid
- Sheddable PEG-PDMAEMA behaviour *in vitro* dictated by linker kinetics
- Charged polymers are well within hemocompatibility limits for *in vivo* work
- Placement of chelators in PDMAEMA core does not inhibit effective radiolabelling

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Thank you