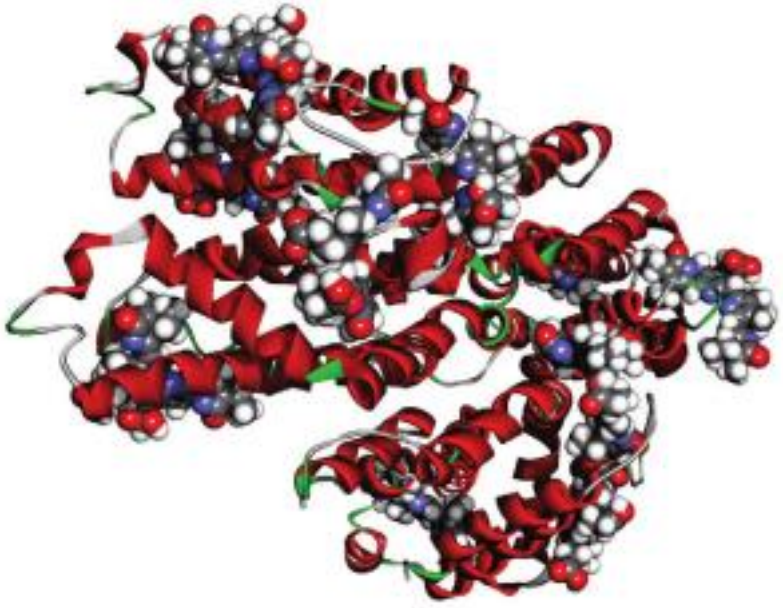
Polymer-drug conjugates

Supervisor: Dr. Mazda Rad-Malekshahi

Presented by: Zahra Kheyri

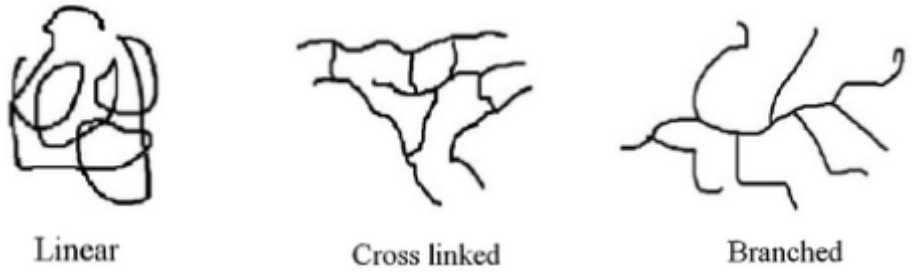
2022/06/21



Introduction

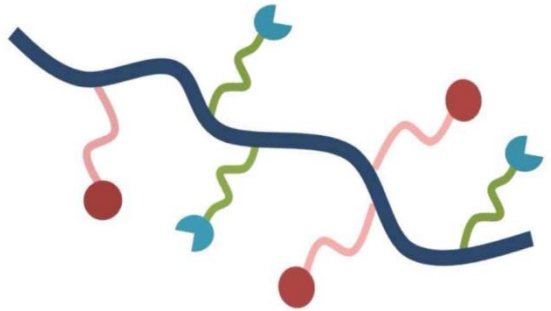
- The concept of polymer-drug conjugates (PDCs) had already been described in the 1970s.
- **Drug**, describes any entity with a therapeutic effect:

  small molecules, peptides, proteins (e.g. antibodies or enzymes) or even RNA/DNA strands.
- **Polymer**, **natural** or **synthetic** origin and feature any architecture, from linear to branched to crosslinked.



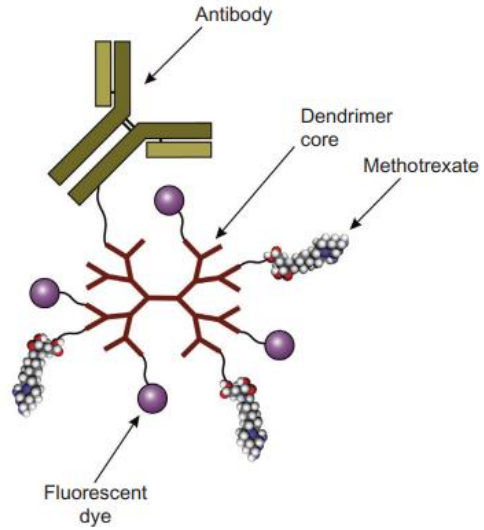
- There is a covalent bond between the drug and the polymer, making it a conjugate

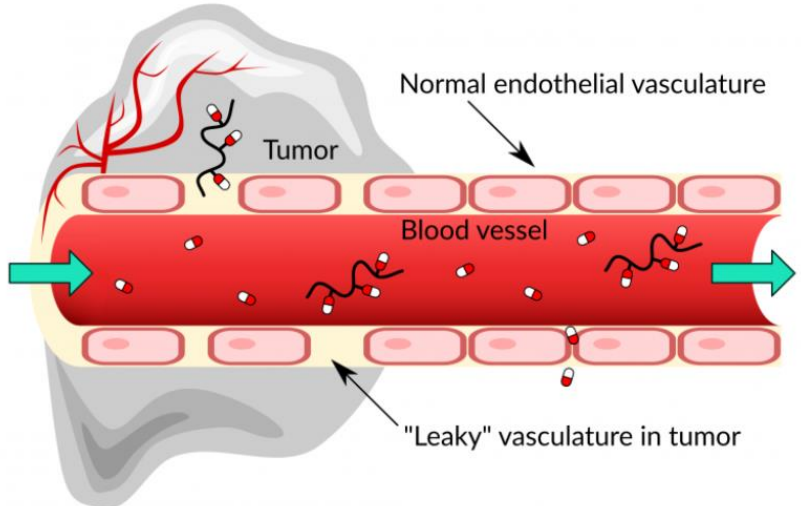
1. Polymer-drug conjugates, where the **drug is active**
2. Polymer prodrugs, where the **drug is inactive**



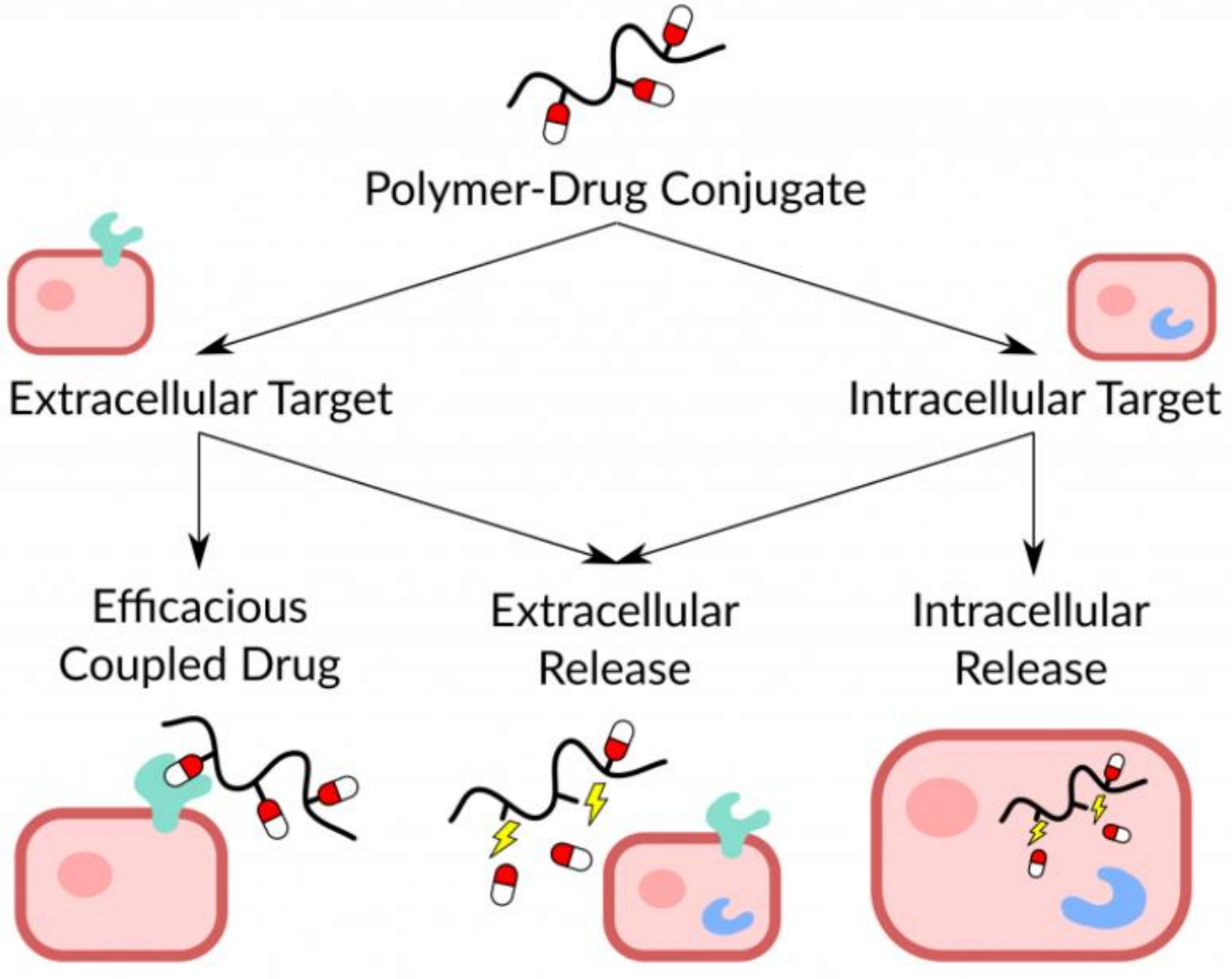
Benefits of polymer-drug conjugates

- Enhances their solubility and stability in body fluids
- Reduces their toxic side effects in healthy tissues
- The covalent bonds allow for incorporation of higher drug loads
- Control the release profile
- Additional functional groups of the polymer can be used to attach ligands
- Enhance residence time in the body and drug targeting





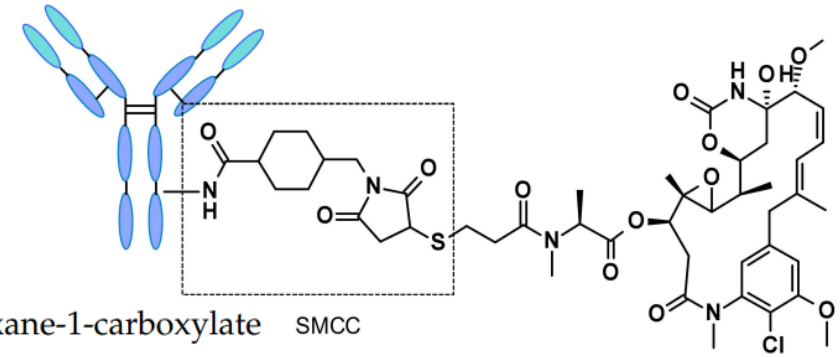
Polymer-drug conjugates classified by target site



Linker types

- The linkages between polymers and drugs can be:

  1- stable (non-cleavable),

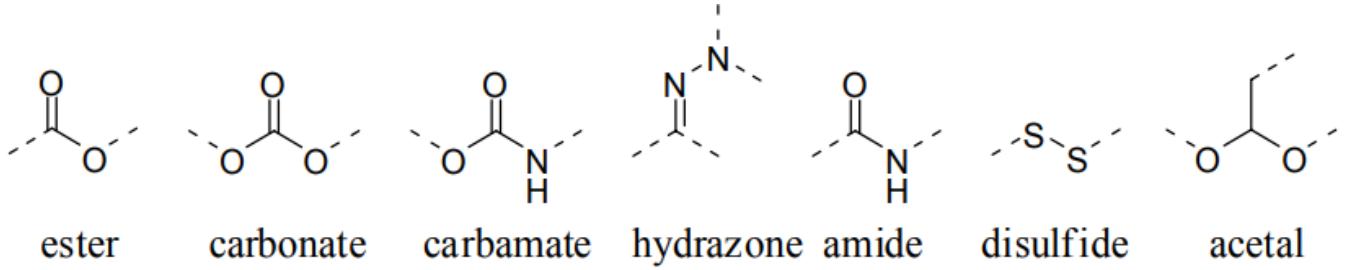


N-succinimidyl-4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate SMCC

  2- or they can be chemically or enzymatically cleavable

  Chemical triggers: pH, oxidative/reductive environments or the presence of reactive groups.

  - ✓**Disulfide bonds**
  - ✓**Ester bonds**
  - ✓**Hydrazones** and **acetals**
  - ✓**Peptide linkers**



Polymer–drug conjugate therapeutics: advances, insights and prospects

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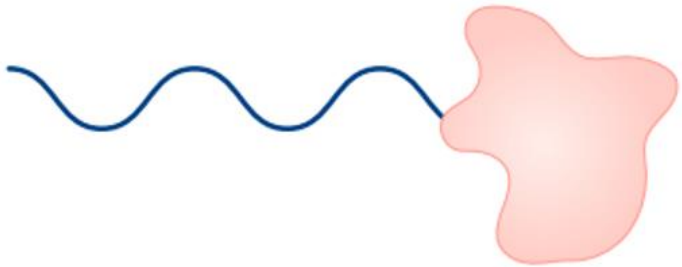
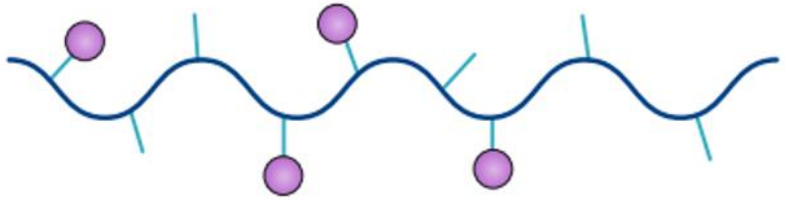
Abstract | Polymer–drug conjugates have long been a mainstay of the drug delivery field, with several conjugates successfully translated into clinical practice. The conjugation of therapeutic agents to polymeric carriers, such as polyethylene glycol, offers several advantages, including improved drug solubilization, prolonged circulation, reduced immunogenicity, controlled release and enhanced safety. In this Review, we discuss the rational design, physicochemical characteristics and recent advances in the development of different classes of polymer–drug conjugates, including polymer–protein and polymer–small-molecule drug conjugates, dendrimers, polymer nanoparticles and multifunctional systems. Current obstacles hampering the clinical translation of polymer–drug conjugate therapeutics and future prospects are also presented.

Classes of polymer–drug conjugates

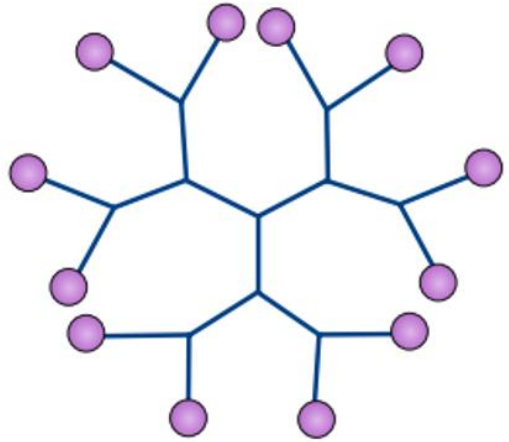
a Polymer–protein conjugate



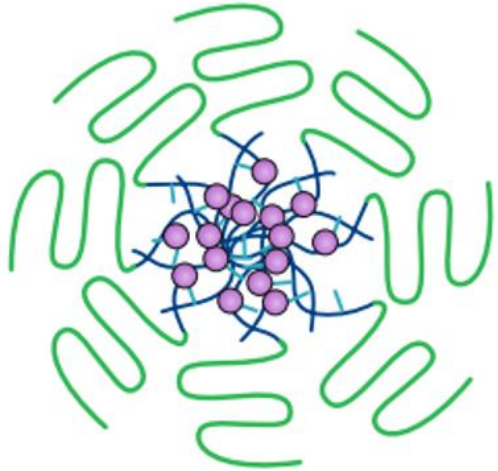
b Polymer–small-molecule drug conjugate



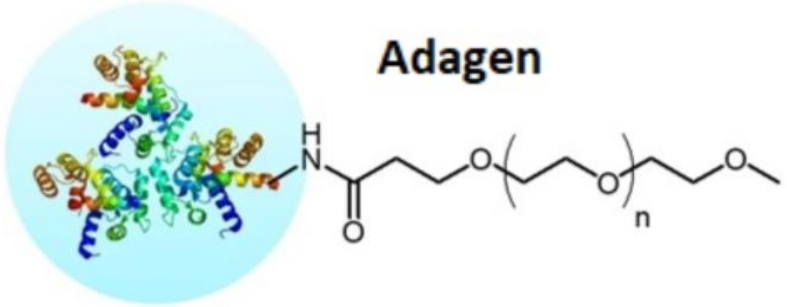
c Dendrimer



d Polymer nanoparticle



a) Polymer–protein conjugates



PEGylation in 1977

Recombinant insulin in **1982**

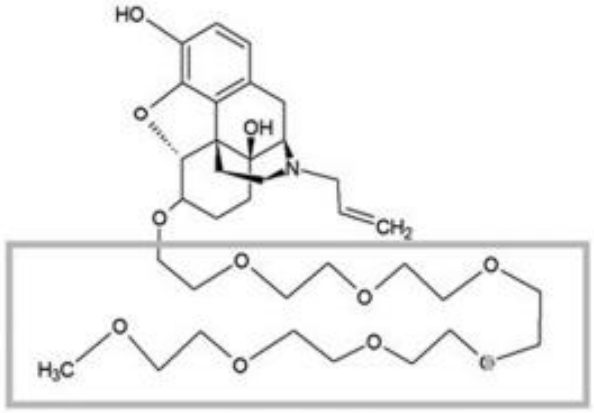
The first marketed PEG–protein therapeutic, **Adagen**, in **1990**

Peginterferon alfa-2b (PegIntron, **2001**) and peginterferon alfa-2a (Pegasys, **2002**)

PEG–epoetin beta conjugate, Mircera, in **2007**

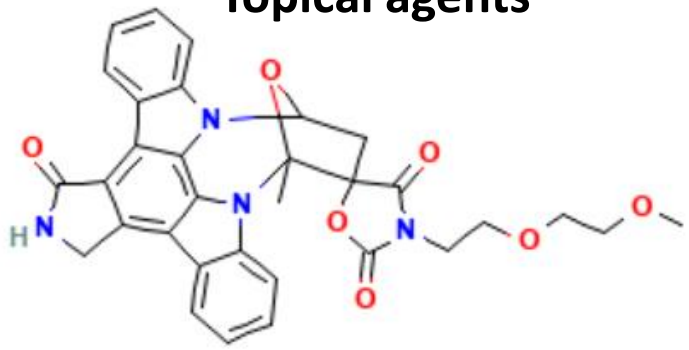
- PEGylated protein therapeutics employ PEGs of ≤40 kDa molecular mass
- Alternative: polysaccharides, including dextran and hyaluronic acid

b) Polymer–small-molecule drug conjugates



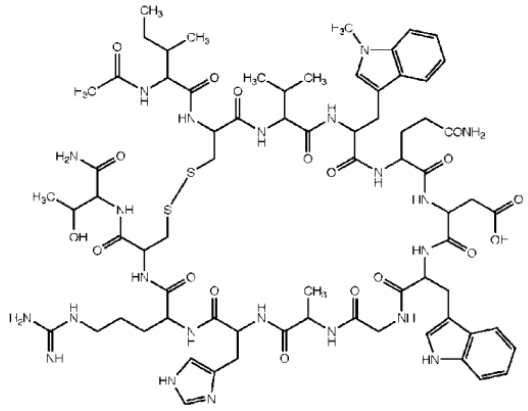
Naloxegol (In 2014)

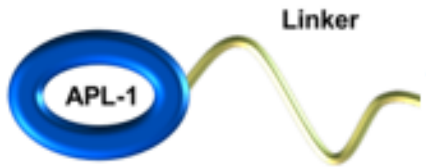
Topical agents



Pegcantratinib, a PEGylated small- molecule TrkA kinase inhibitor for psoriasis (phase II trials)

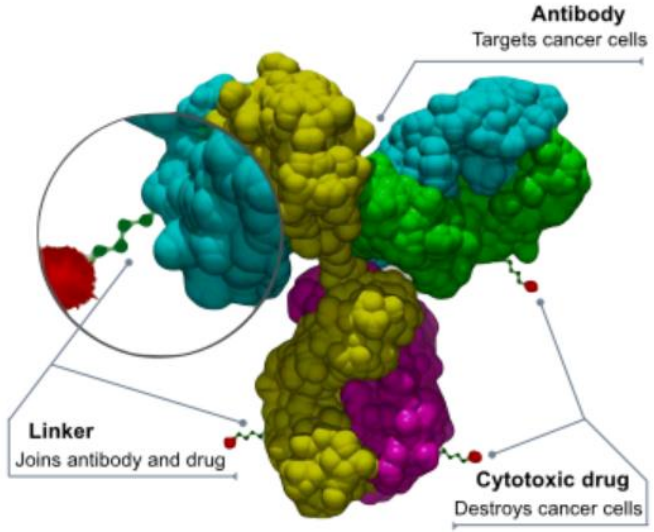
APL-1 Structure





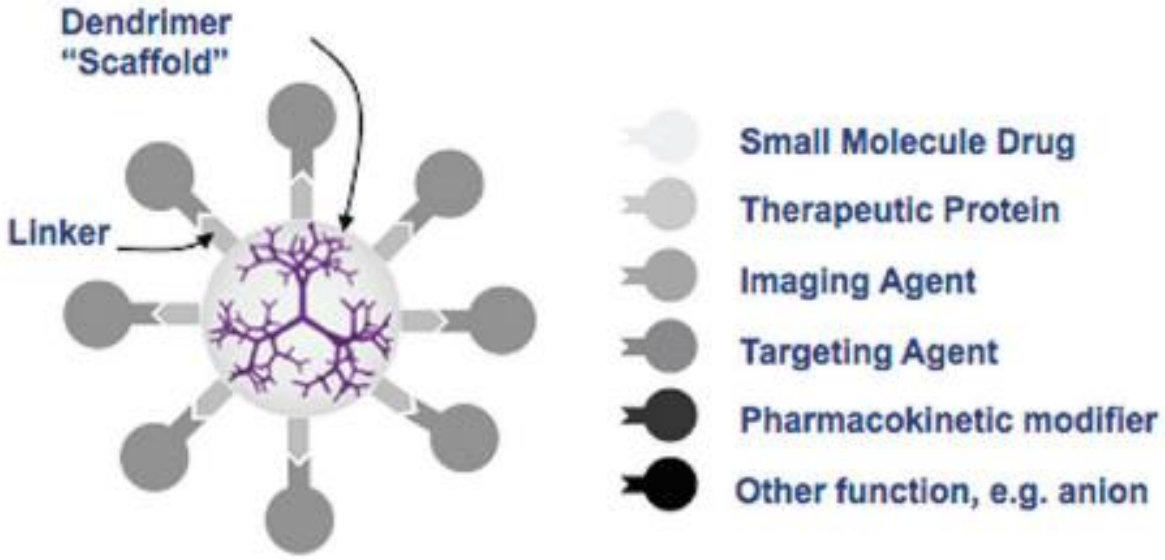
APL-2

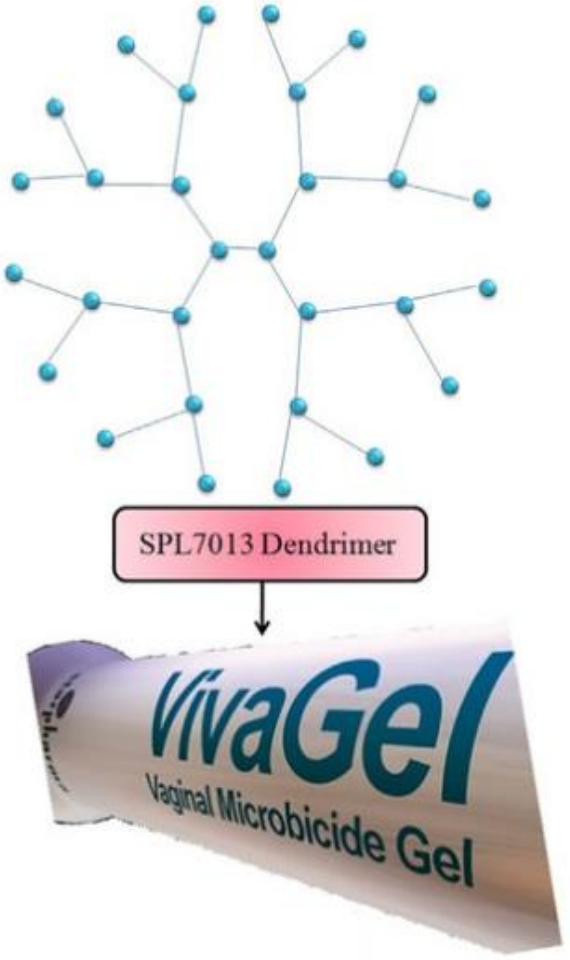
APL-2 PEGylated cyclic peptide inhibitor of complement C3, for Paroxysmal Nocturnal Hemoglobinuria (phase III trials)



c) Dendrimers

- Highly branched, 3D polymeric macromolecules
- Large hydrodynamic radii: **reduced renal clearance** and **greater plasma exposure** than linear polymers of similar molecular mass
- The first dendrimer-based drug product, (VivaGel)
- PAMAM, PPI, …





FULL PAPER

Polymer-from-Polymer Release

Macromolecular Bioscience
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Hyaluronic Acid Graft Copolymers with Cleavable Arms as Potential Intravitreal Drug Delivery Vehicles

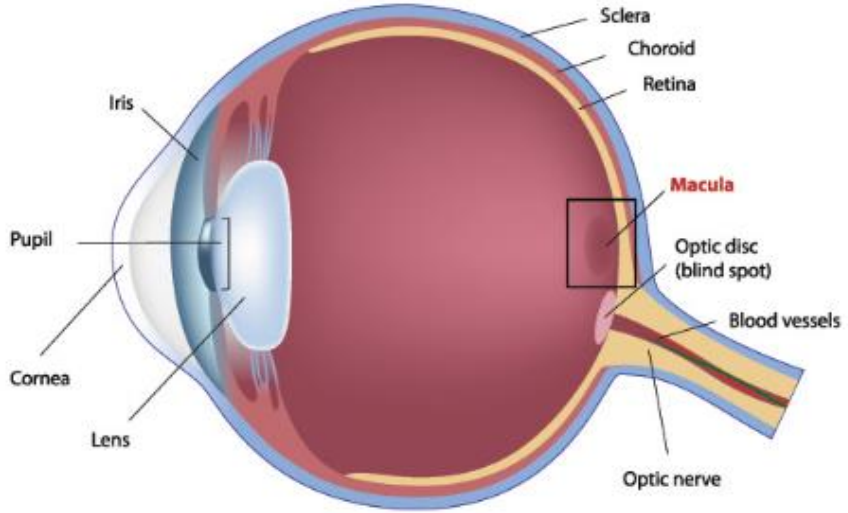
Tina Borke, Mathie Najberg, Polina Ilina, Madhushree Bhattacharya, Arto Urtti, Heikki Tenhu, and Sami Hietala**

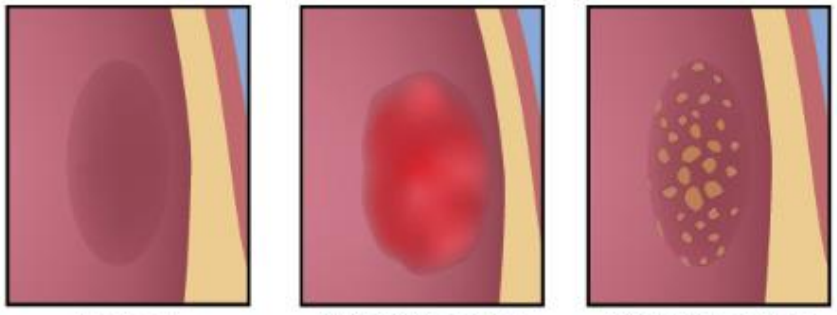
Macromol. Biosci. **2017**, 1700200

DOI: 10.1002/mabi.201700200

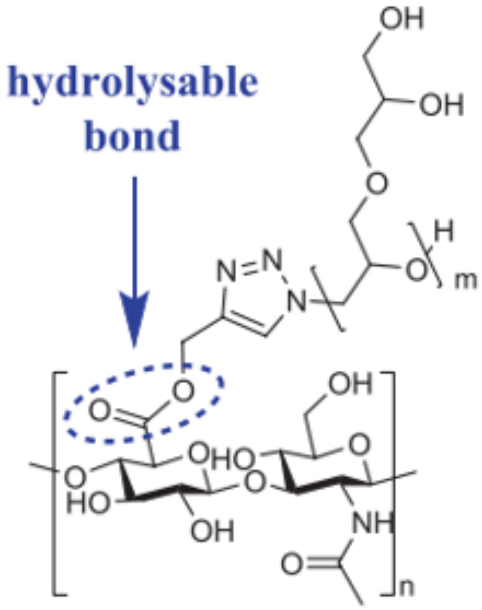
Hyaluronic acid graft copolymers as potential vehicles for intravitreal drug delivery

Age-related macular degeneration (AMD)

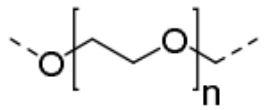




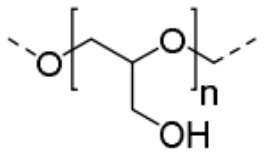
- HA backbone
- Poly(glyceryl glycerol) (PGG)



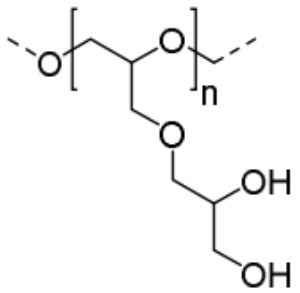
Poly(ethylene glycol) (PEG)

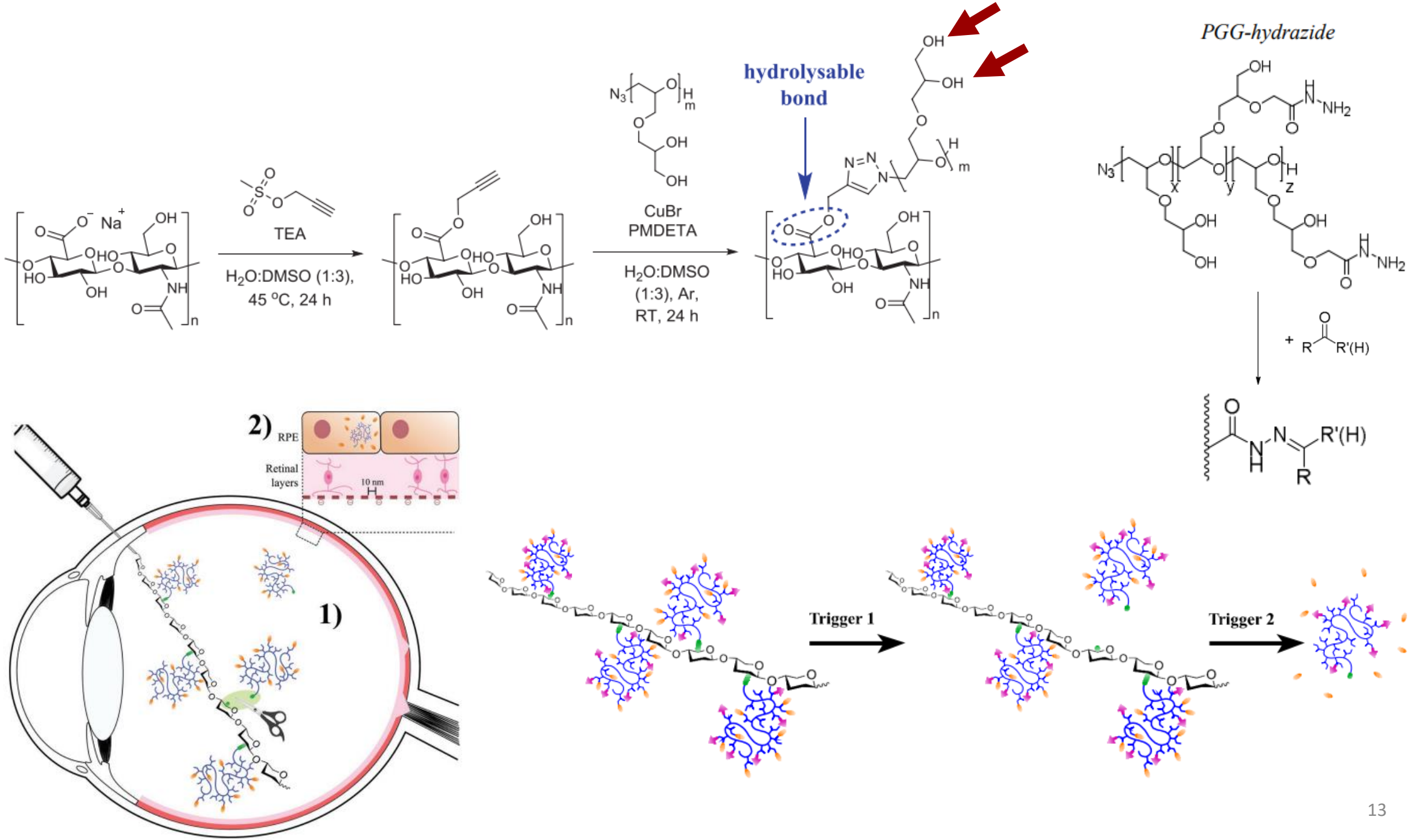


Polyglycerol (PG)



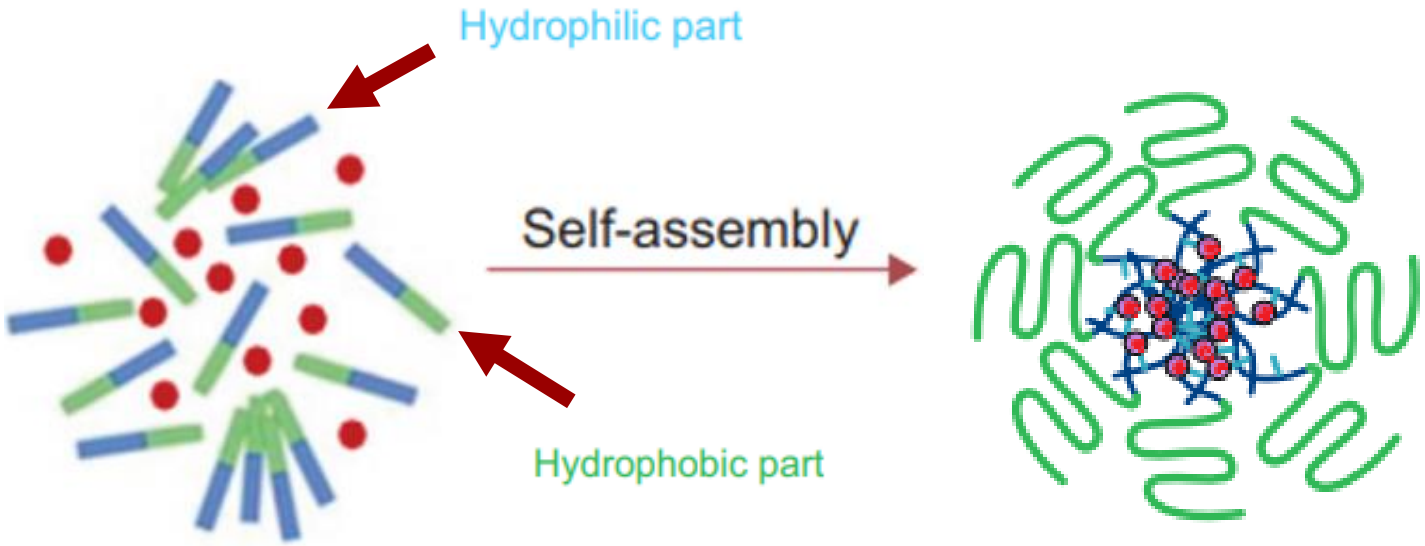
Poly(glyceryl glycerol) (PGG)




TEA
H2O:DMSO (1:3),
45 °C, 24 h
CuBr
PMDETA
H2O:DMSO
(1:3), Ar,
RT, 24 h
hydrolysable
bond
PGG-hydrazide
2)
RPE
Retinal
layers
10 nm
1)
Trigger 1
Trigger 2

d) Polymer nanoparticles

- Polymeric nanoparticles, which are colloidal carriers with dimensions on the nanoscale (30-100 nm), have since been widely employed as drug delivery vehicles.



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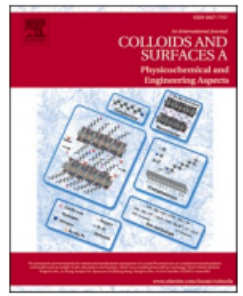
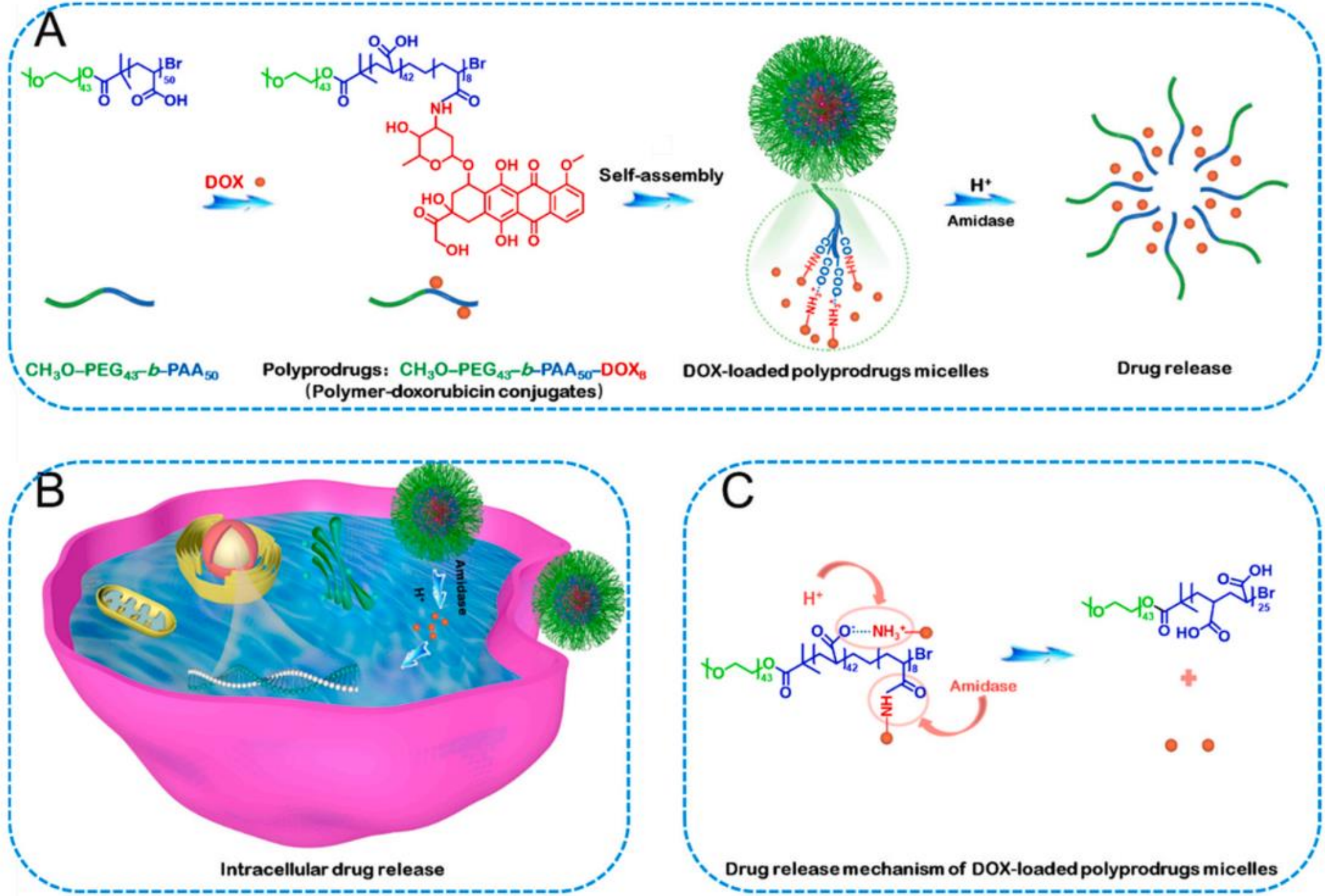
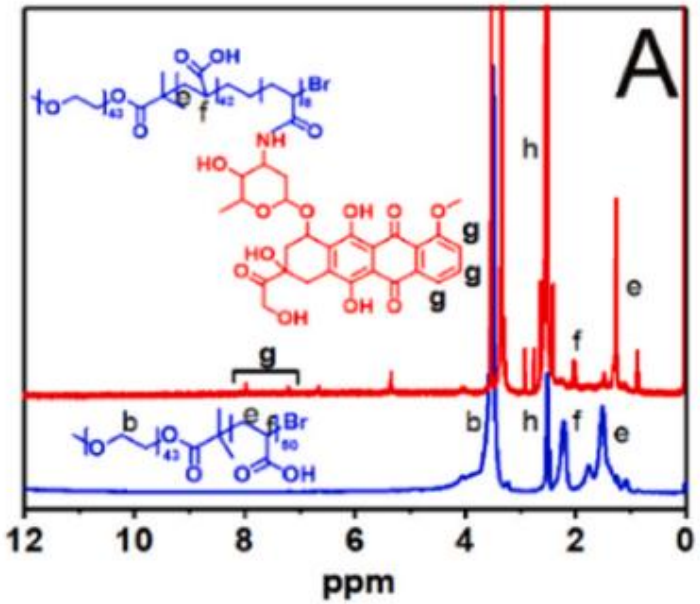


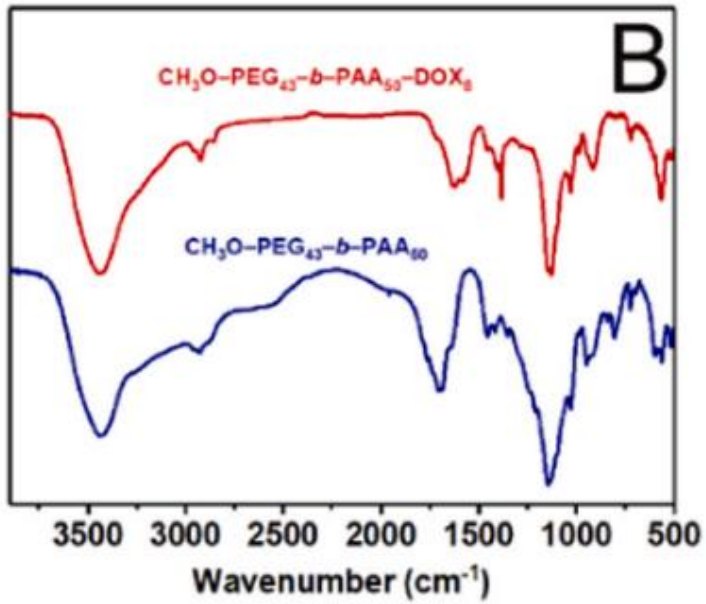
Self-assembly of polymer-doxorubicin conjugates to form polyprodrug micelles for pH/enzyme dual-responsive drug delivery

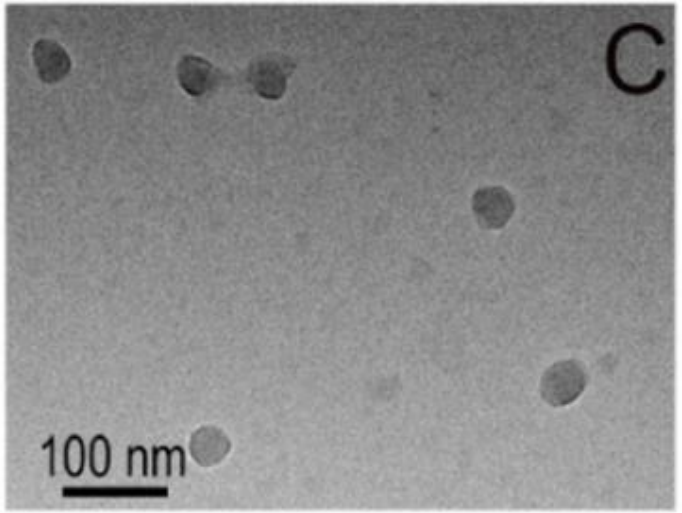
Mengna Zhang [a], Shujing Zhang [a], Kun Zhang [a], Zongyuan Zhu [b], Yalei Miao [a], Yudian Qiu [a], Panke Zhang [a,*], Xubo Zhao [a,*]

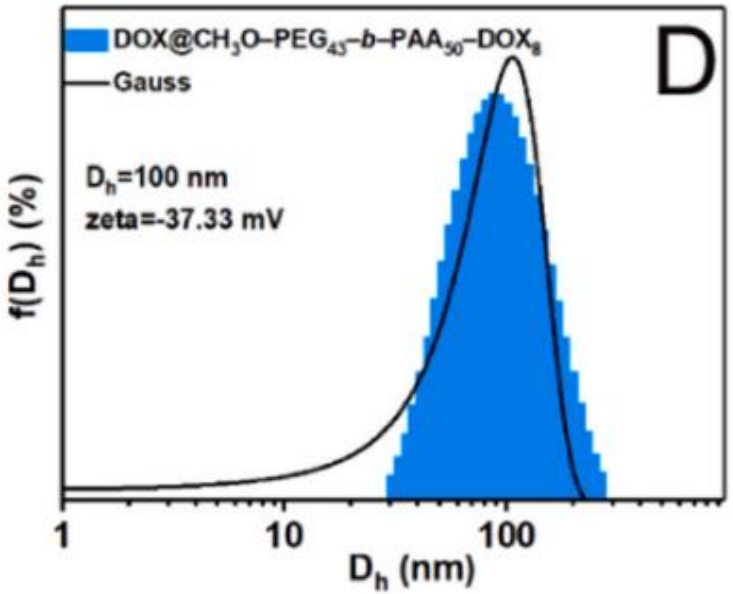
[a] *Green Catalysis Center, College of Chemistry, School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou 450001, China*
[b] *Energy and Power Department, Jiangsu University of Science and Technology, Zhenjiang 212003, China*

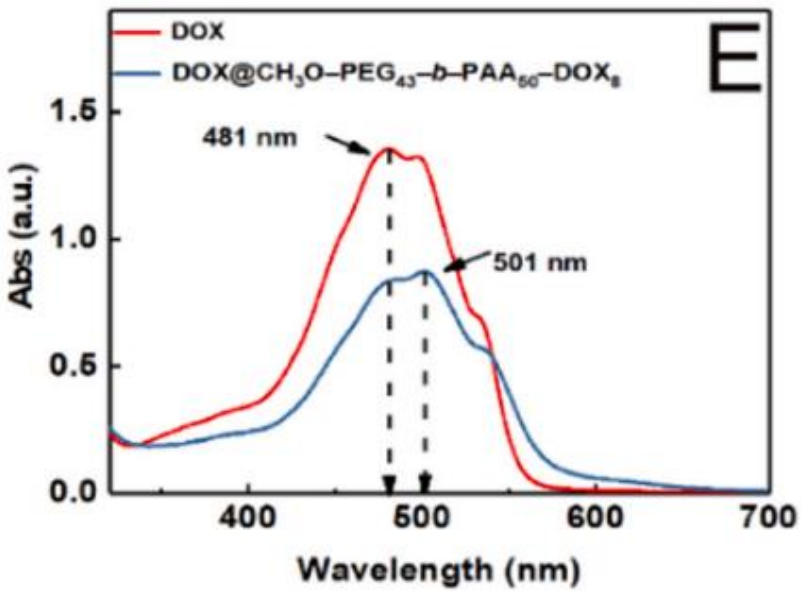

A
DOX
Self-assembly
H+
Amidase
CH3O–PEG43–b–PAA50
Polyprodrugs: CH3O–PEG43–b–PAA50–DOX8
(Polymer-doxorubicin conjugates)
DOX-loaded polyprodrugs micelles
Drug release
B
Amidase
H+
Intracellular drug release
C
H+
Amidase
Drug release mechanism of DOX-loaded polyprodrugs micelles

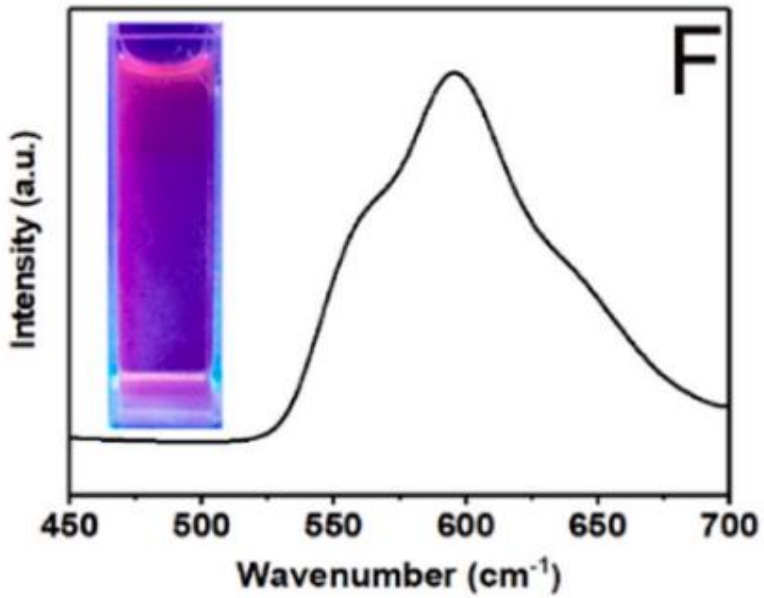

A
h
g
g
g
e
f
g
b
e
b
h
f
e
12
10
8
6
4
2
0
ppm

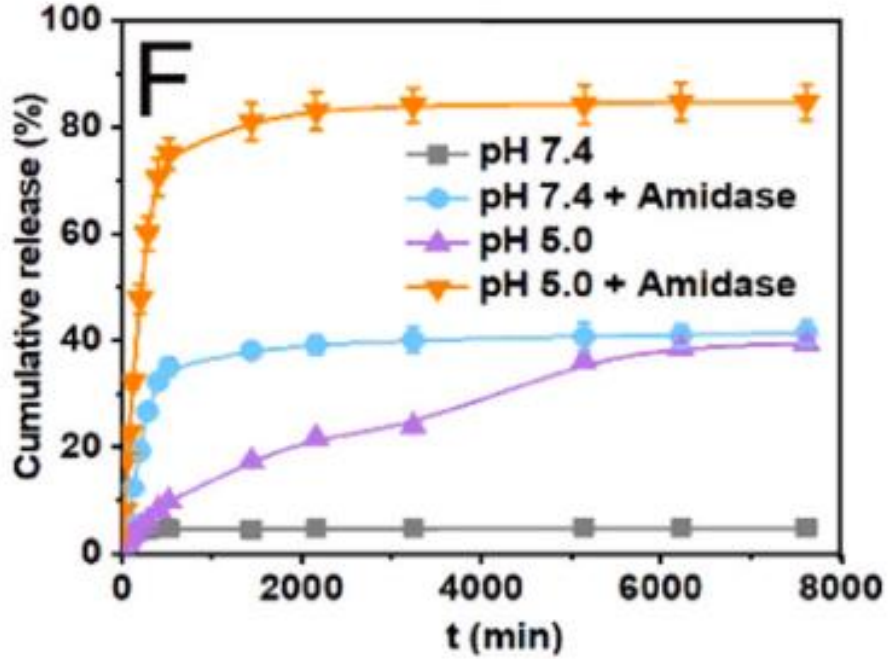

B
CH3O–PEG43–b–PAA50–DOX8
CH3O–PEG43–b–PAA60
3500
3000
2500
2000
1500
1000
500
Wavenumber (cm-1)

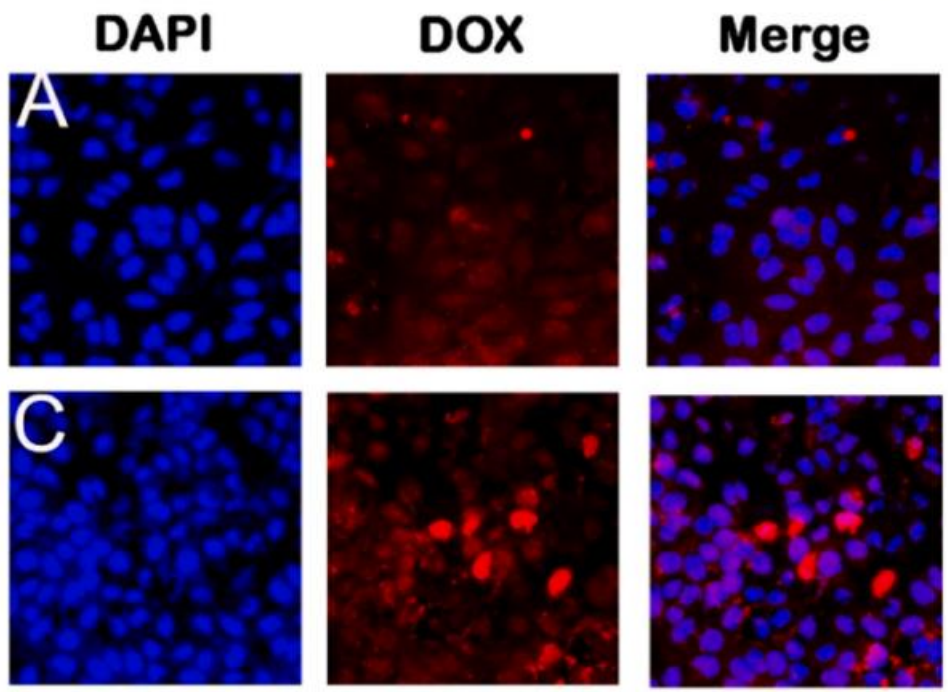

C
100 nm


D
DOX@CH3O–PEG43–b–PAA50–DOX8
Gauss
Dh=100 nm
zeta=-37.33 mV
f(Dh) (%)
1
10
100
Dh (nm)

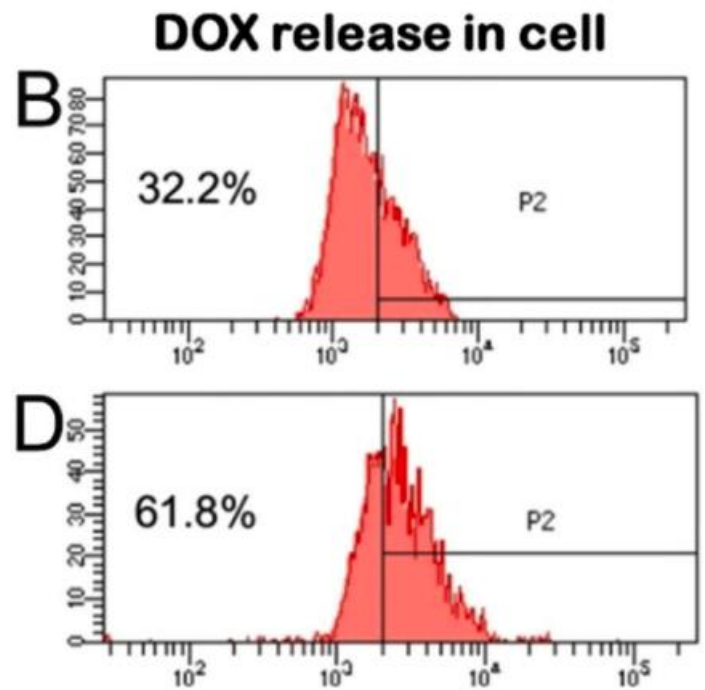

E
DOX
DOX@CH3O–PEG43–b–PAA60–DOX8
481 nm
501 nm
Abs (a.u.)
1.5
1.0
0.5
0.0
400
500
600
700
Wavelength (nm)


F
Intensity (a.u.)
450
500
550
600
650
700
Wavenumber (cm-1)



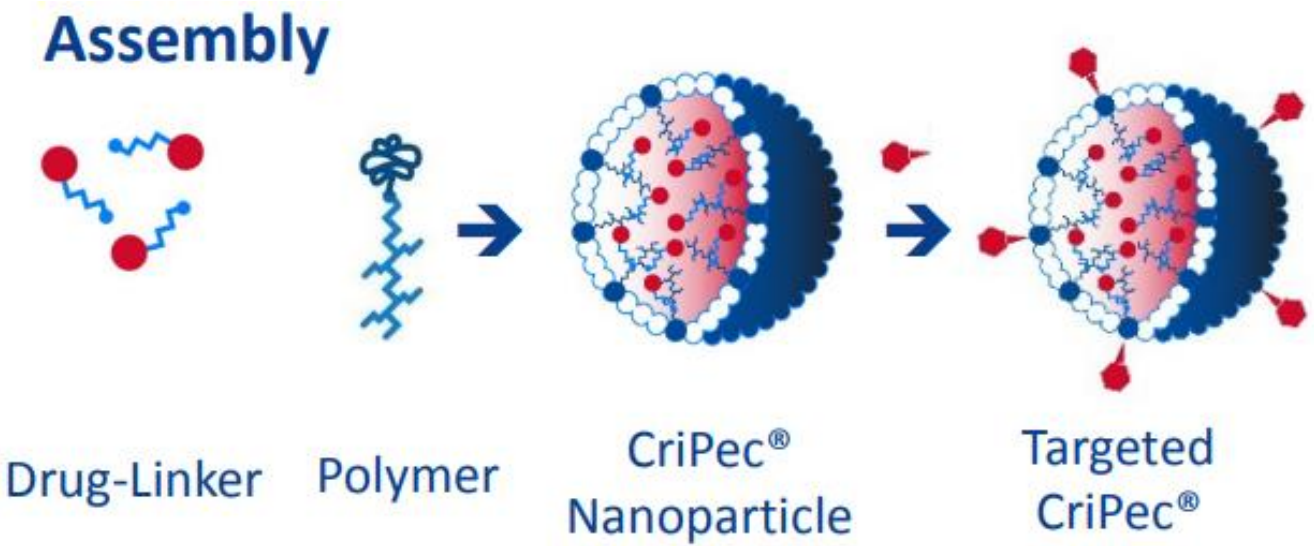


MCF-7 cells (CLSM technique)



Flow Cytometric Analyses

CriPec® nanoparticle



Cristal Therapeutics

Biomaterials 53 (2015) 370–378

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

Complete regression of breast tumour with a single dose of docetaxel-entrapped core-cross-linked polymeric micelles

Qizhi Hu [a, b], Cristianne J. Rijcken [b], Ruchi Bansal [a], Wim E. Hennink [c], Gert Storm [a, c], Jai Prakash [a, d, *]

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[b] *Cristal Therapeutics, Oxfordlaan 55, Maastricht 6229EV, The Netherlands*
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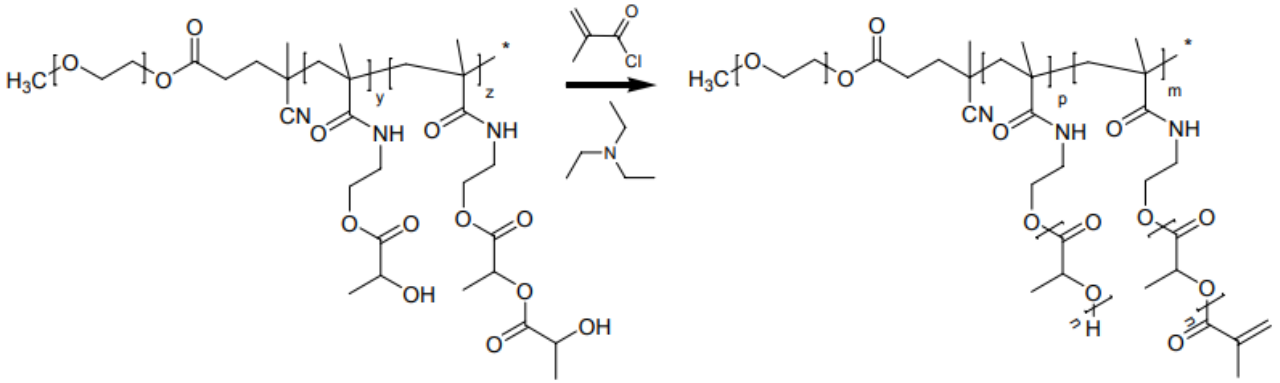
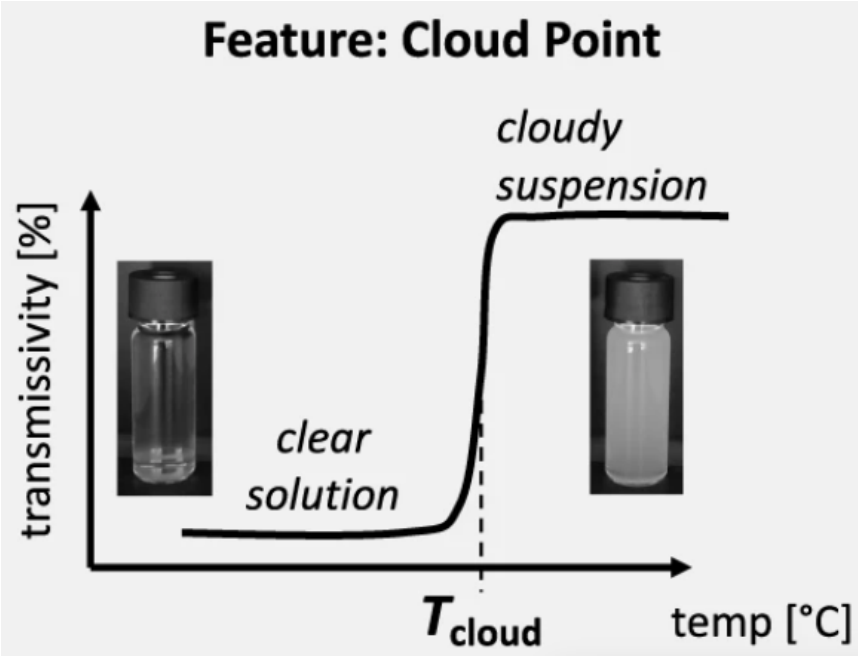
[d] *Cancer Centre Karolinska, Karolinska Institutet, Stockholm SE-171 76, Sweden*

A methacrylated block copolymer containing

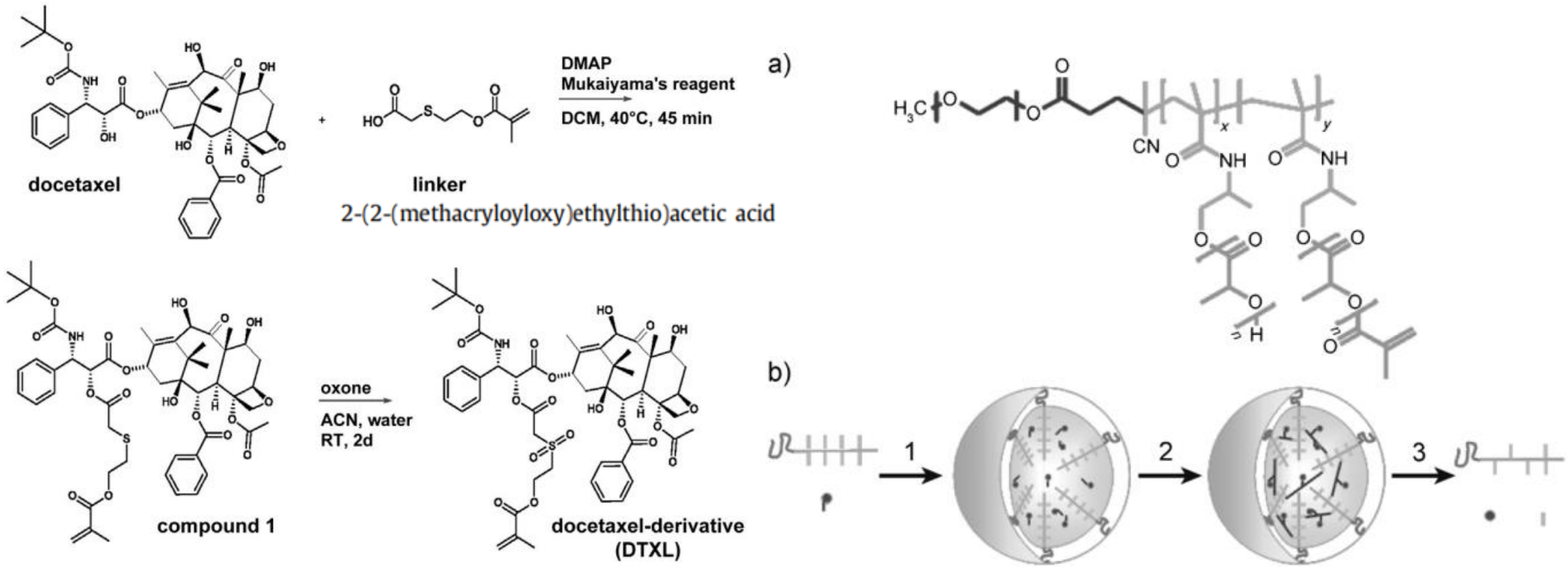
- Mono-methoxy poly(ethylene glycol) (mPEG, Mn = 5000) as **hydrophilic block**
- A random copolymer of N-2-hydroxypropyl methacrylamide monolactate (HPMAmLac1) and N-2-hydroxypropyl methacrylamide dilactate (HPMAmLac2) as **thermosensitive block**



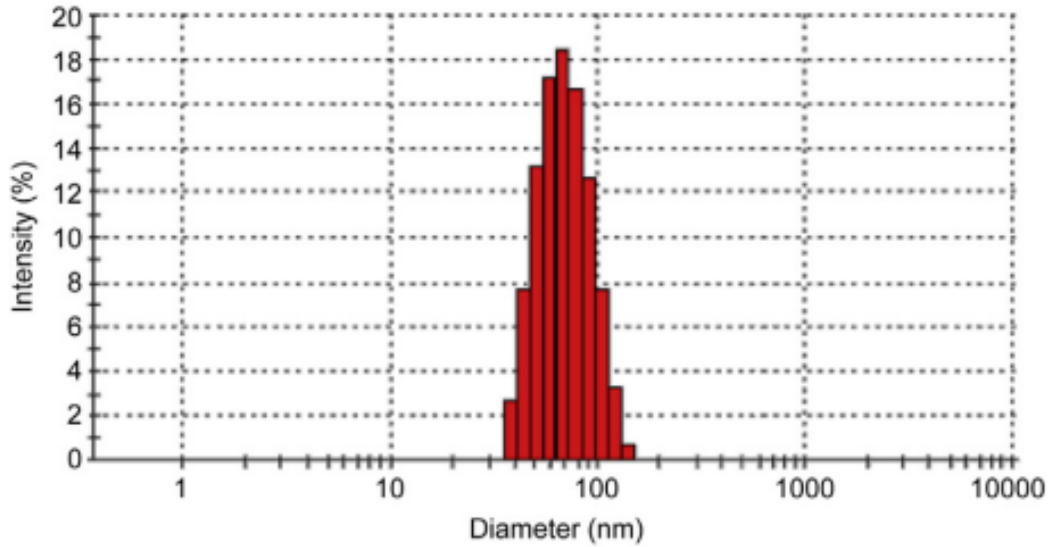


docetaxel-entrapped core-cross-linked polymeric micelles

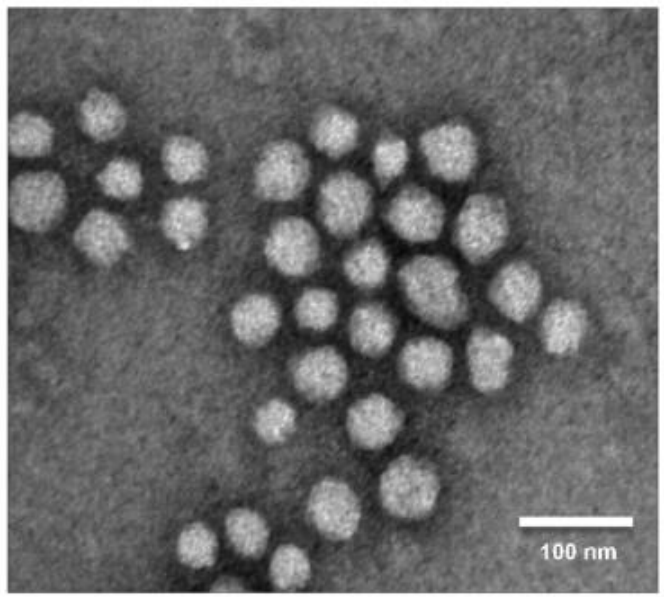
Docetaxel entrapped core-cross-linked polymeric micelles (DTX-CCL-PMs) were prepared essentially using the fast heating method.



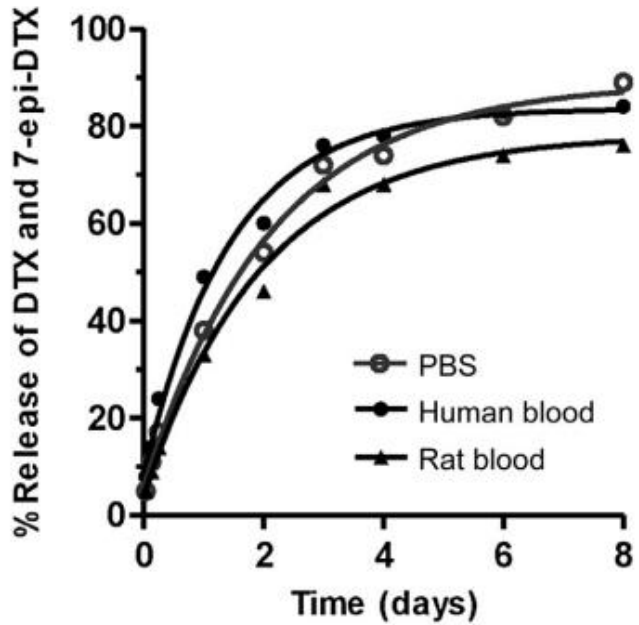
B


Intensity (%)
20
18
16
14
12
10
8
6
4
2
0
1
10
100
1000
10000
Diameter (nm)

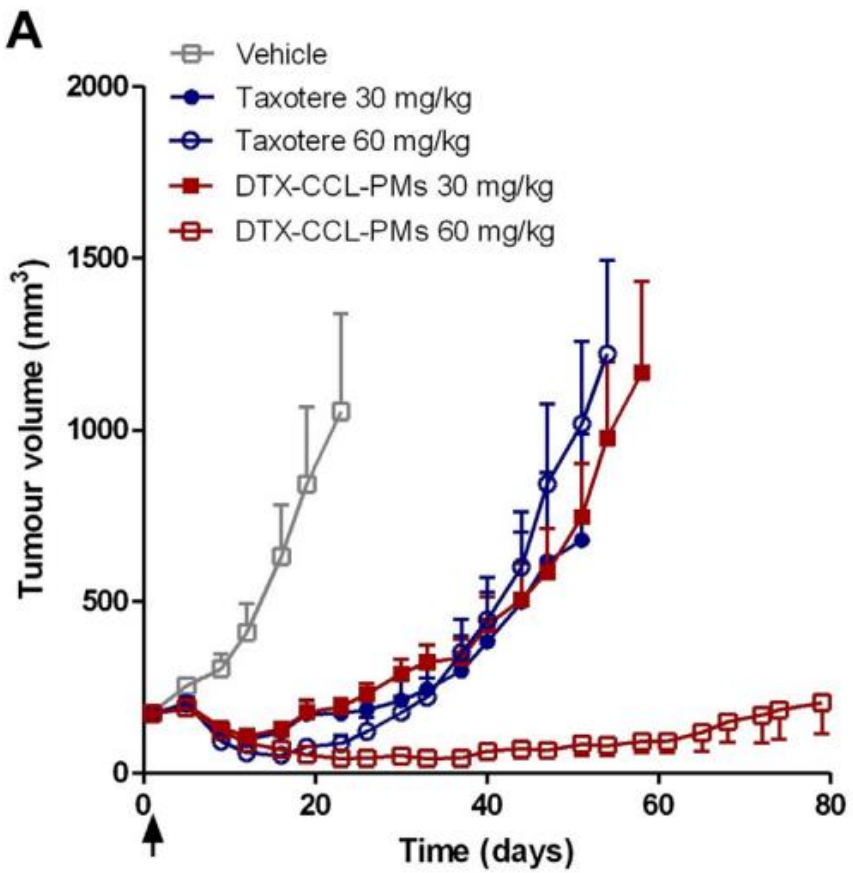
C

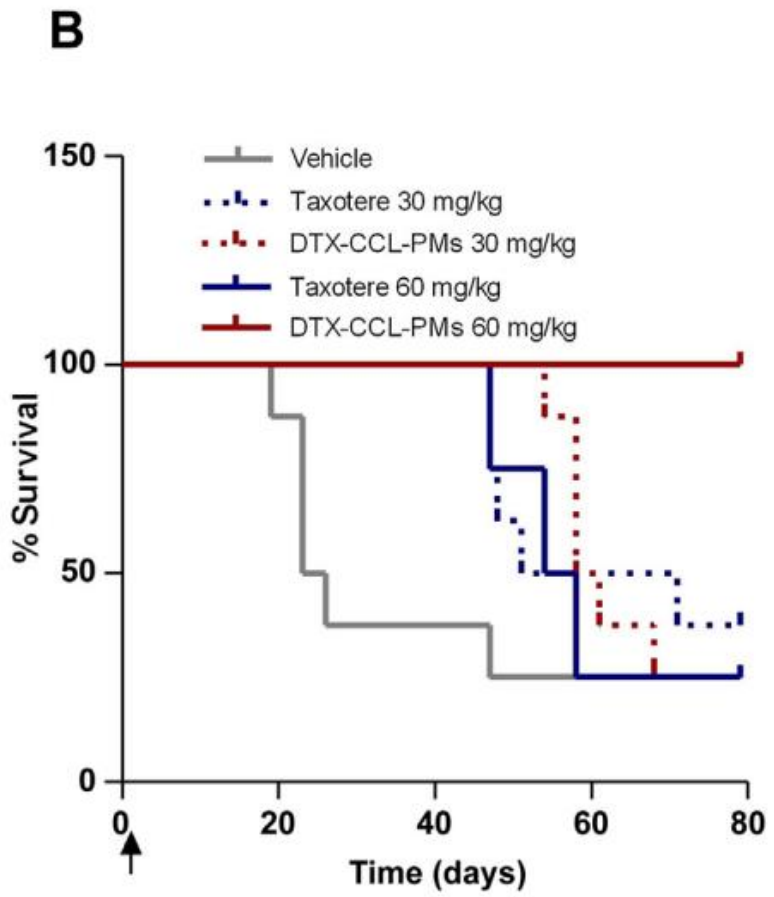

100 nm

D


% Release of DTX and 7-epi-DTX
100
80
60
40
20
0
0
2
4
6
8
Time (days)
PBS
Human blood
Rat blood

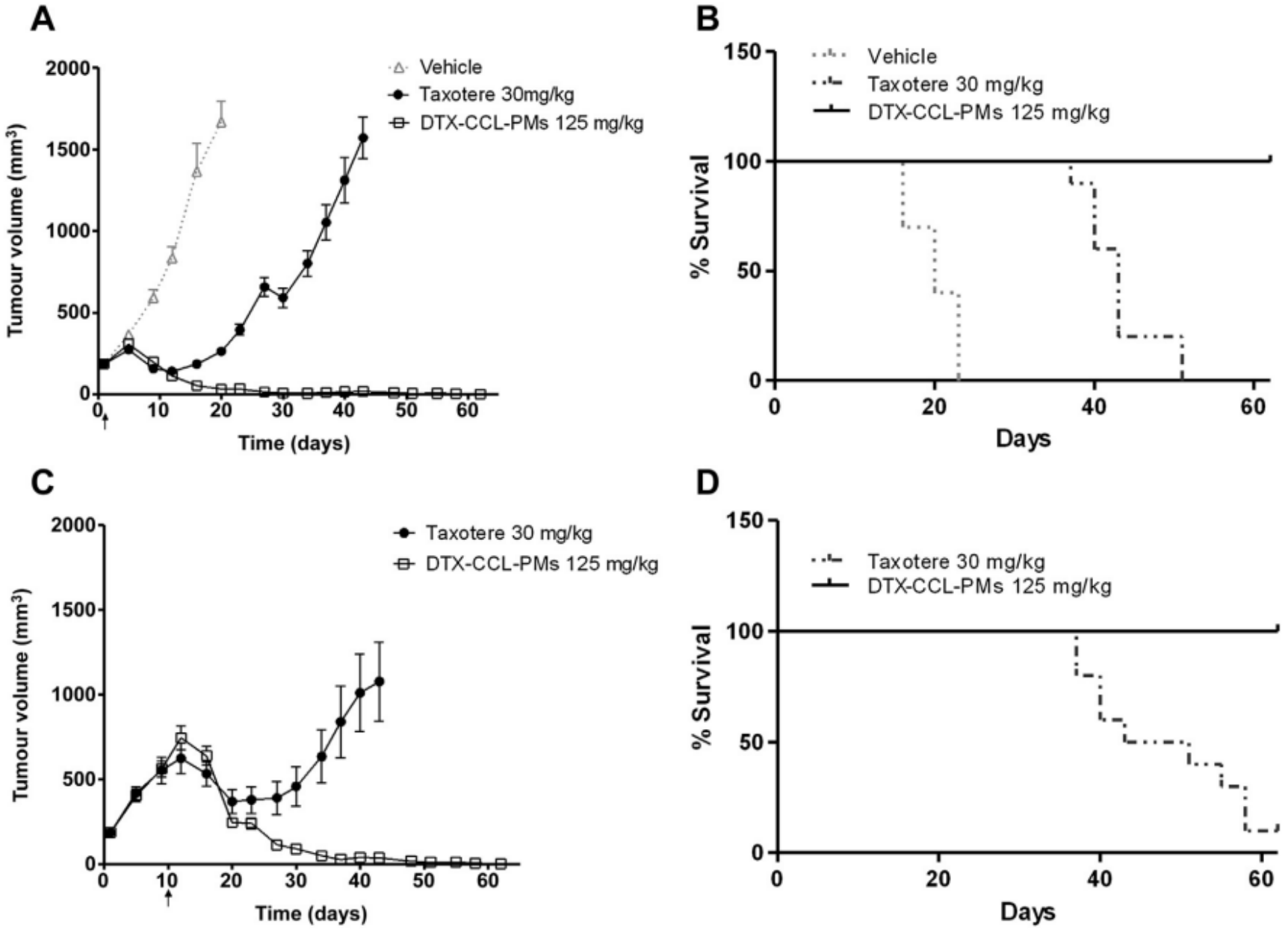
Antitumour effect of DTX-CCL-PMs at a single dose of 30 and 60 mg DTX/kg



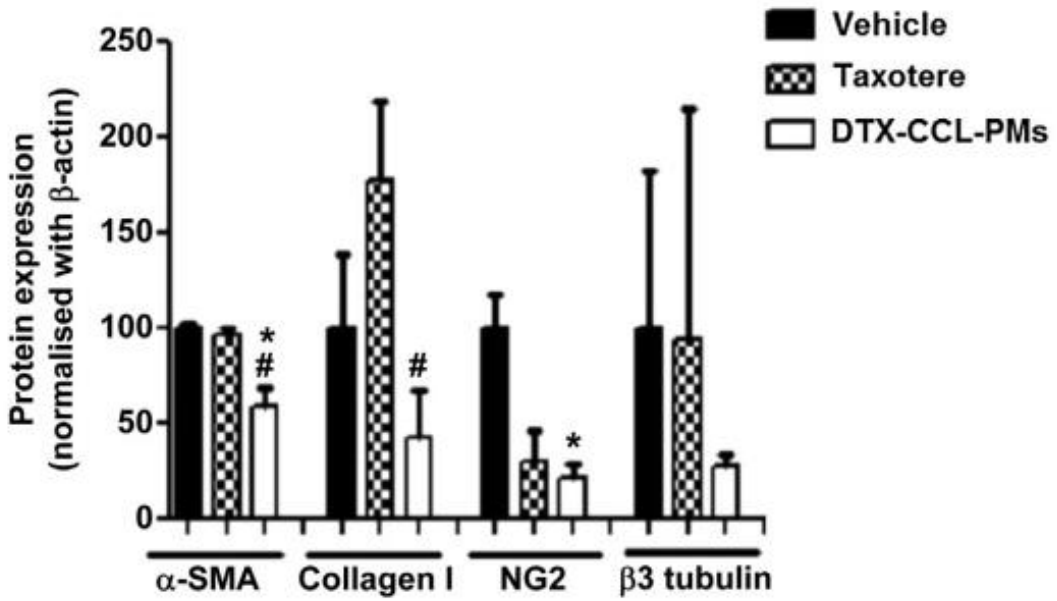


Tumour growth curve

% survival of mice bearing MDA-MB-231 xenografts



Antitumour effect of DTX-CCL-PMs (125 mg DTX/kg) in early and established MDA-MB-231 xenografts tumours



Intratumoural effect of DTX-CCL-PM
(using Western Blot analyses)

Critical issues of polymeric micelles:

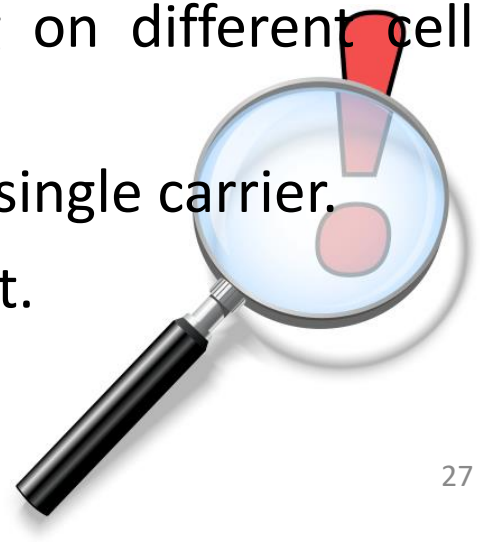
- **Low stability of micelles in circulation**
- **Uncontrolled drug release rate because of degradation of the polymers and/or diffusion of the drug from the micelles**

In this study:

- **Covalent conjugation of docetaxel (DTX) to CCL-PMs provided <u>stable micellar nanoparticles</u>**
- **A hydrolysis-sensitive covalent linkage of DTX to the CCL-PMs resulted in <u>sustained release of the drug</u>**

Conclusion

- The field of polymer–drug conjugates has matured substantially in the past two decades.
- Polymeric carriers are being developed to deliver a wide range of therapeutic modalities, including **small molecules**, **peptides**, **aptamers** and **proteins**.
- Active and passive targeting
- Combination therapy: combinations of active agents can maximize therapeutic efficacy by targeting different molecular pathways or acting on different cell subpopulations.
- The concurrent integration of therapeutics and diagnostics in a single carrier.
- Polymeric immunotherapies, are already in clinical development.




thank
you