Drug-initiated synthesis of polymer-drug conjugates

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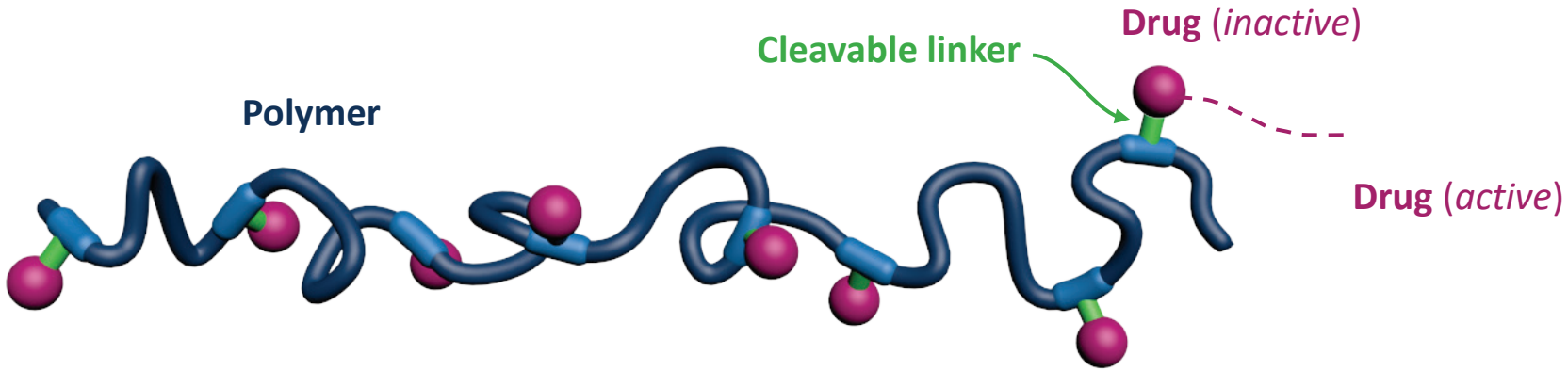
CONTROLLED RELEASE SOCIETY
CRS 2024 Annual Meeting AND Exposition
JULY 8-12, 2024 • BOLOGNA, ITALY

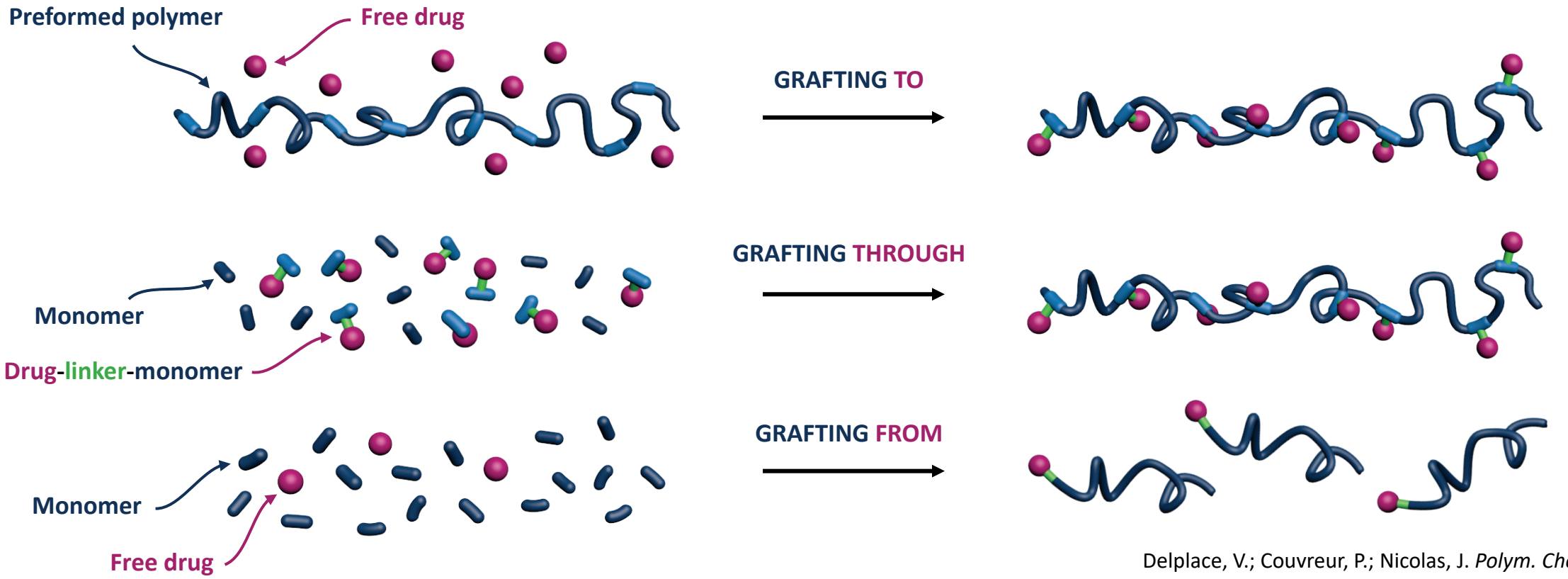
INTEGRATING
Delivery Science
ACROSS DISCIPLINES

POLYMER-DRUG CONJUGATES

Main synthesis strategies

- ✓ No burst release
- ✓ Higher drug loadings
- ✓ Greater drug miscibility
- ✓ Extended plasma half-life
- ✓ Enhanced stability
- ✓ Improved safety & efficacy (EPR effect)



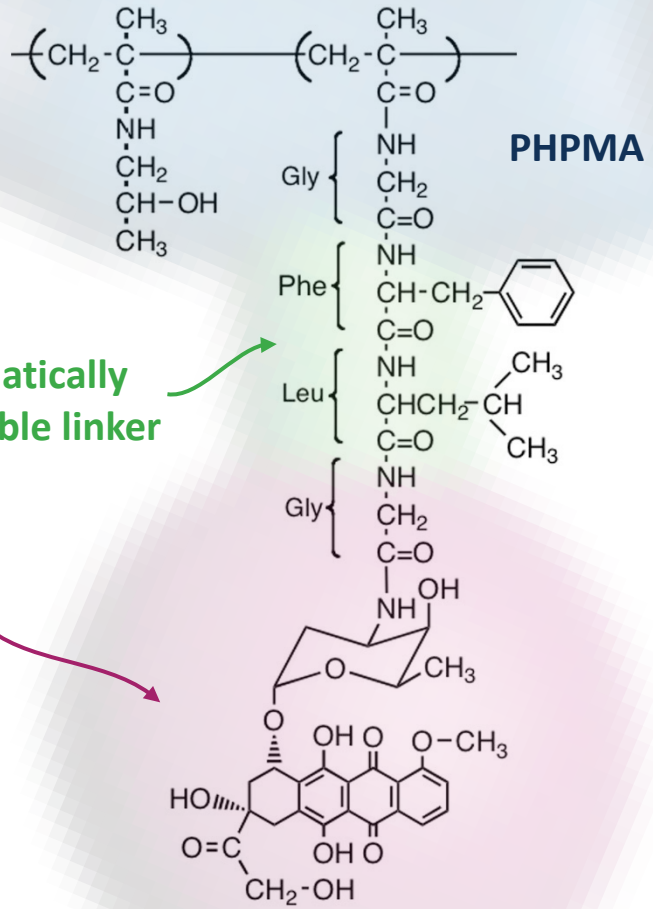


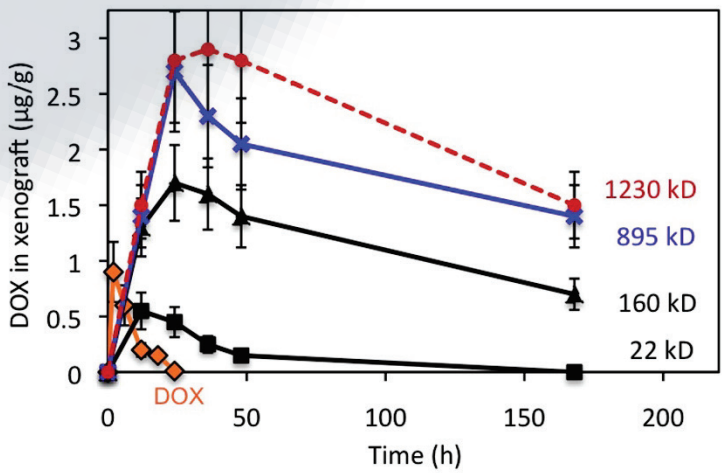
Delplace, V.; Couvreur, P.; Nicolas, J. *Polym. Chem.* **2014**, *5*, 1529

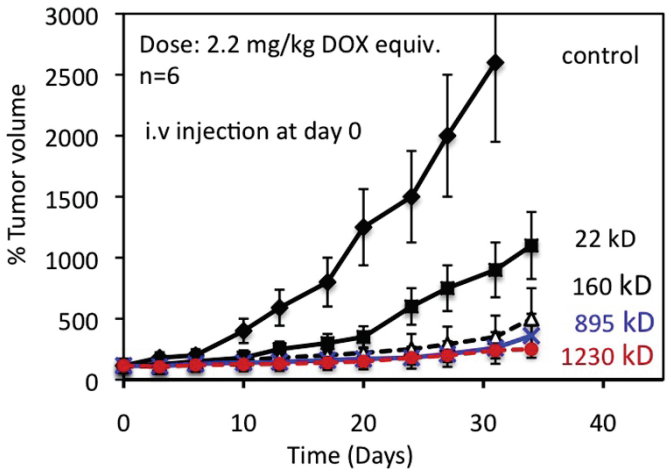
Ekladious, I., Colson, Y.L.; Grinstaff, M.W. *Nature Rev. Drug Discov.* **2019**, *18*, 273

POLYMER-DRUG CONJUGATES

A representative example of polymer drug conjugate



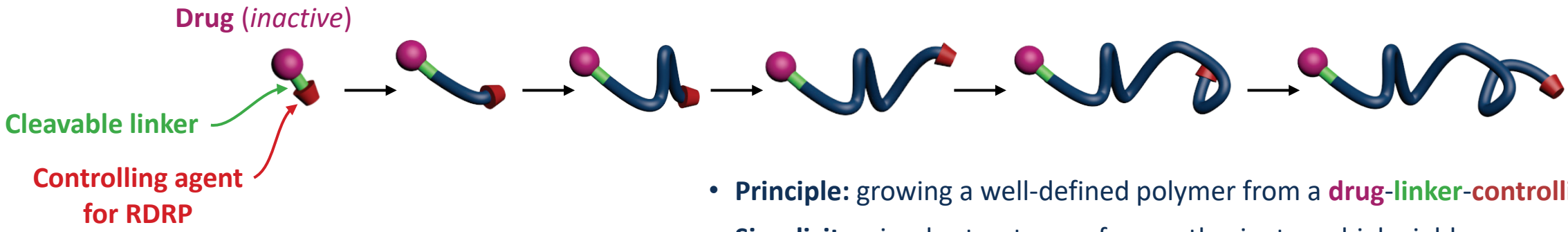




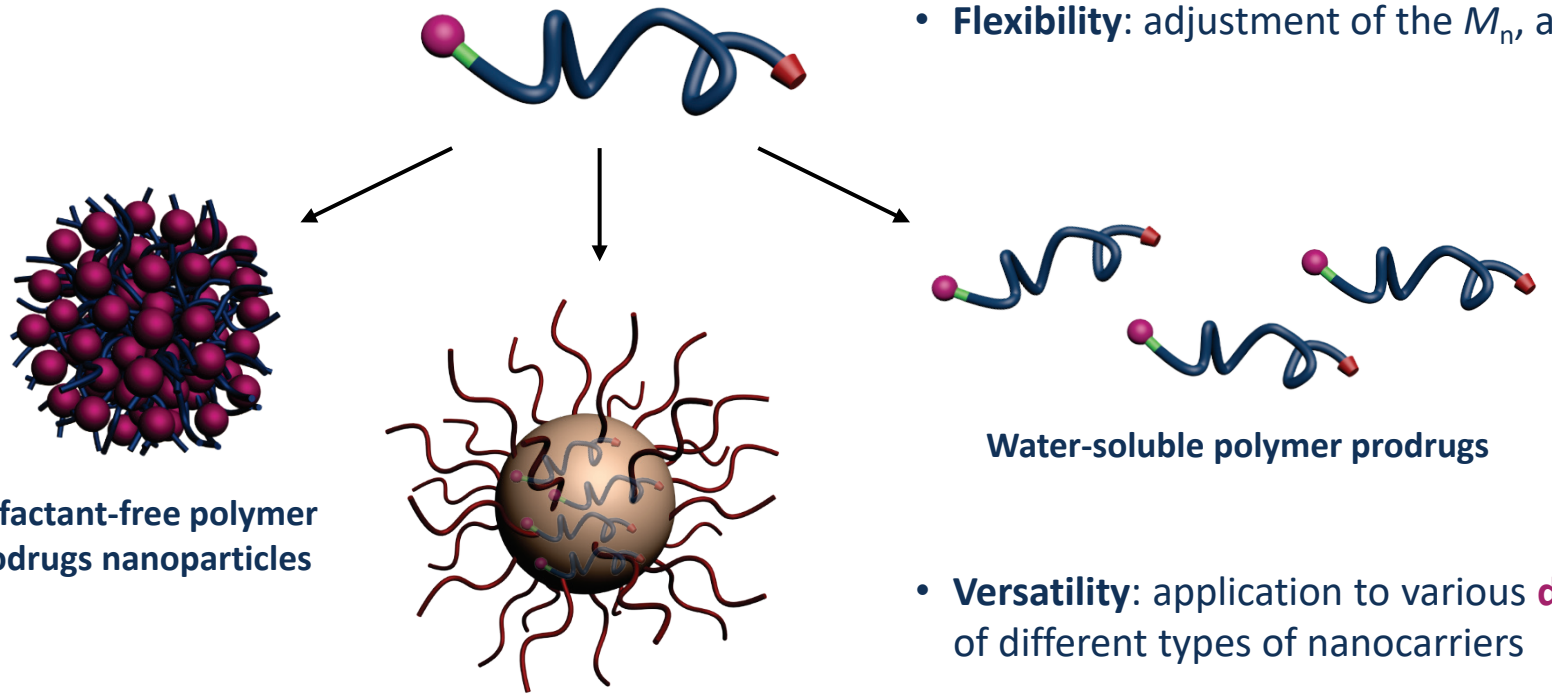
- Broad variety of **linkers** (hydrolytic, enzymatic) and **drugs** (small molecules, peptides, antibodies)
- **Effective EPR effect** by targeting high molar masses → long circulating properties
- **Clinical trials: phase II** PK1 (Dox) and **phase II** PK2 (Dox + galactosamine) in breast, lung and colorectal cancers

Kopeček, J.; Kopečková, P. *Adv. Drug Delivery Rev.* **2010**, 62, 122
Yang, J.; Kopeček, J. *Curr. Opin. Colloid. Interface Sci.* **2017**, *31*, 30

GRAFTING FROM / THE DRUG-INITIATED METHOD



- **Principle:** growing a well-defined polymer from a **drug**-**linker**-**controlling agent**
- **Simplicity**: simple structure, a few synthesis steps, high yields, easy workup
- **Flexibility**: adjustment of the M_n, and thus of drug loading

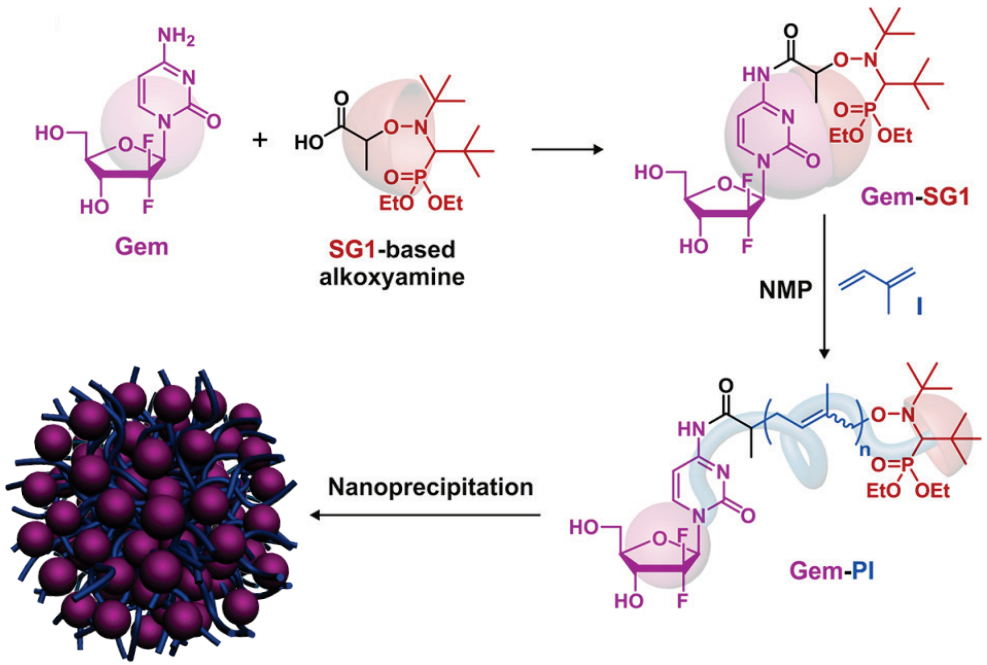


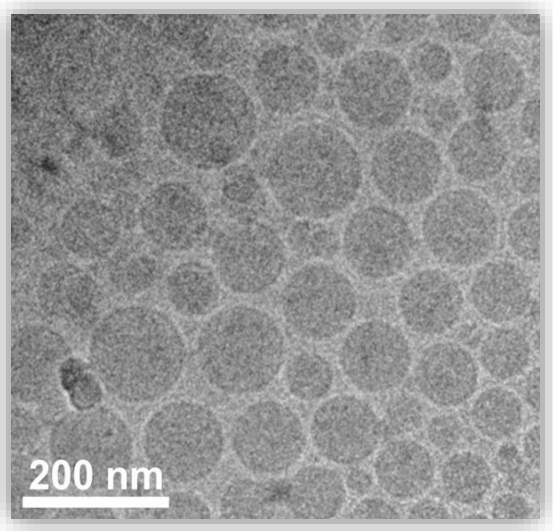
- **Versatility**: application to various **drugs**, **linkers** and **polymer**, and preparation of different types of nanocarriers

Nicolas, J. *Chem. Mater.* **2016**, *28*, 1591

GEMCITABINE-POLYISOPRENE PRODRUGS

Synthesis and nanoparticle formation





	M_n (g.mol^{-1})	DP_n	$Đ$	Diameter (nm)	PSD	Gem (wt %)
P1	840	~3.5	1.35	159	0.10	31.2
P2	1200	~9	1.29	137	0.10	22.1
P3	1560	~14	1.28	133	0.11	16.9
P4	2510	~28	1.40	138	0.11	10.5

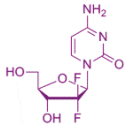
- Only 3 steps (~50% yield), easy workup
- Well-defined Gem-PI prodrugs
- Stable nanoparticles, with narrow size distributions
- **High drug loading nanoparticles** (> 30 wt %)

Harrisson, S.; Nicolas, J.; Maksimenko, A.; Bui, D.T.; Mougin, J.; Couvreur, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 1678
Vinciguerra, D.; Denis, S.; Mougin, J.; Jacobs, M.; Guillaneuf, Y.; Mura, S.; Couvreur, P.; Nicolas, J. *J. Control. Release* **2018**, *286*, 485

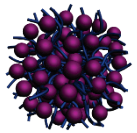
GEMCITABINE-POLYISOPRENE PRODRUGS

In vivo anticancer efficacy

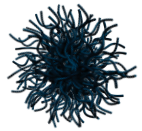
NaCl 0.9 %



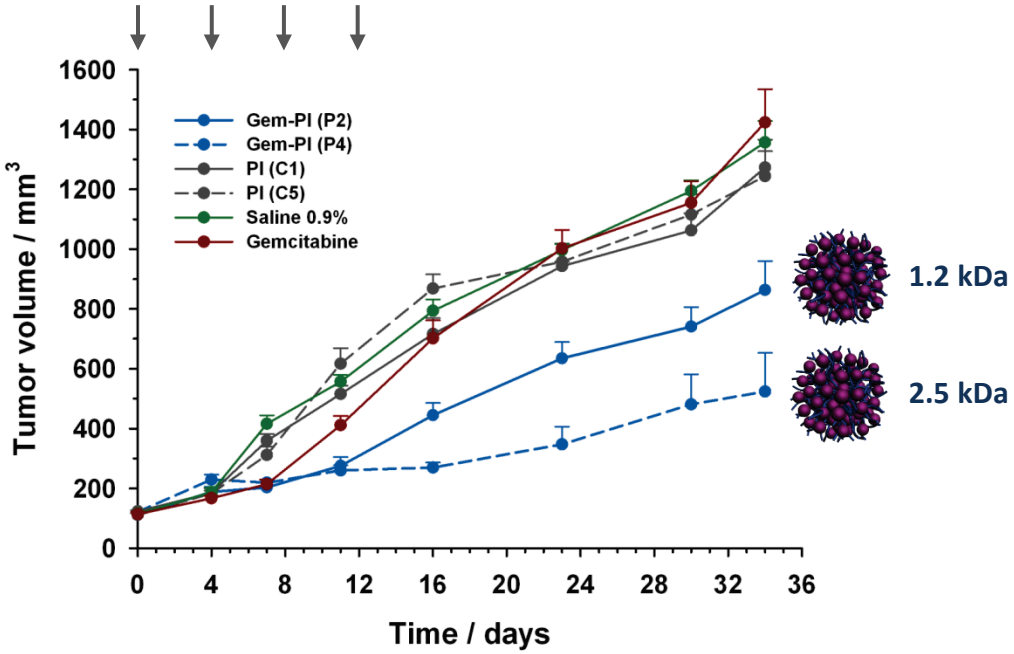
Gemcitabine
7 $mg_{Gem}.kg^{-1}$



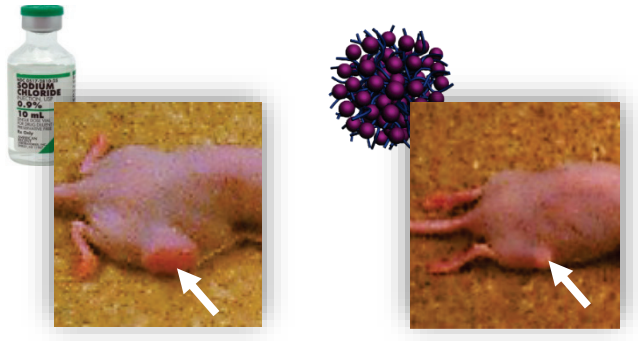
Gem-PI (1.2 / 2.5 kDa)
7 $mg_{Gem}.kg^{-1}$

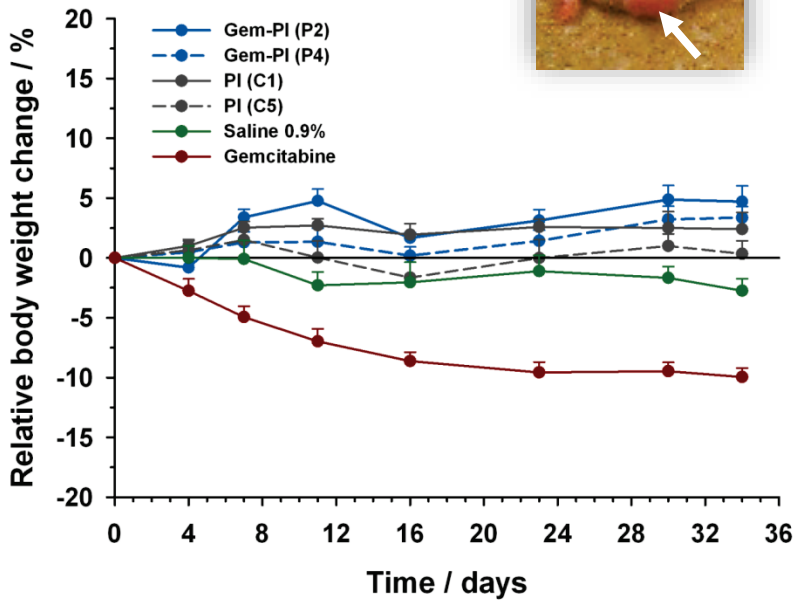


PI (1.2 / 2.5 kDa)



2.5 kDa



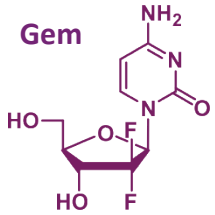


- **Significant *in vivo* anticancer efficacy**
- The higher the DP_n, the higher the anticancer activity
- No toxicity of the nanoparticles

Harrisson, S.; Nicolas, J.; Maksimenko, A.; Bui, D.T.; Mougin, J.; Couvreur, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 1678

GRAFTING FROM / THE DRUG-INITIATED METHOD

Versatility and applicability



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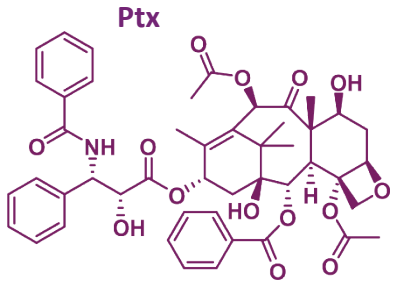
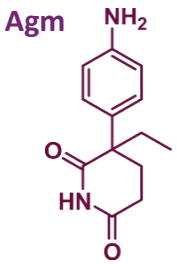
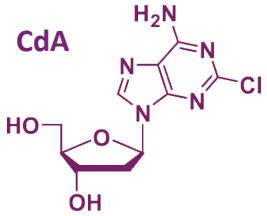
Biomacromolecules **2013**, *14*, 2837



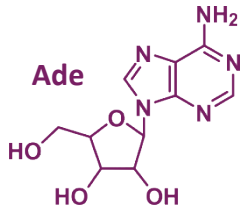
Polym. Chem. **2018**, *9*, 687



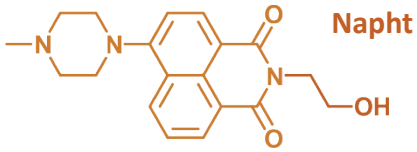
J. Control. Release **2018**, *286*, 485



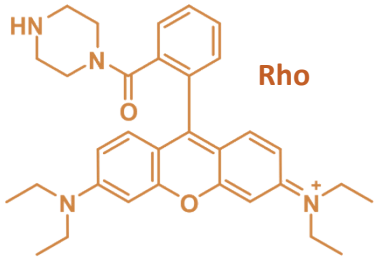
Chem. Mater. **2016**, *28*, 2268
Polym. Chem. **2017**, 8, 5174



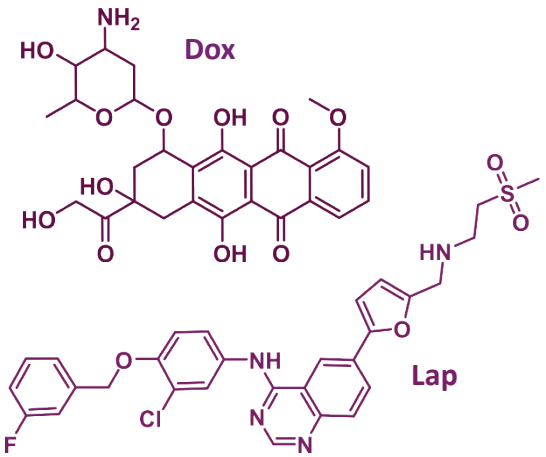
Eur. J. Pharm. Biopharm. **2019**, *142*, 70



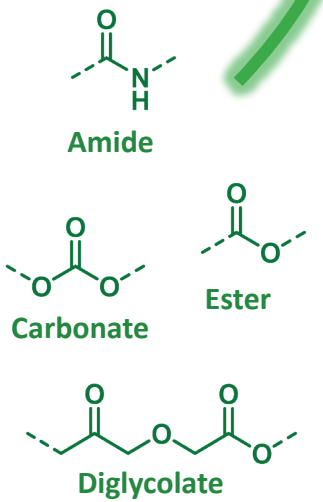
Chem. Commun. **2017**, *53*, 4489

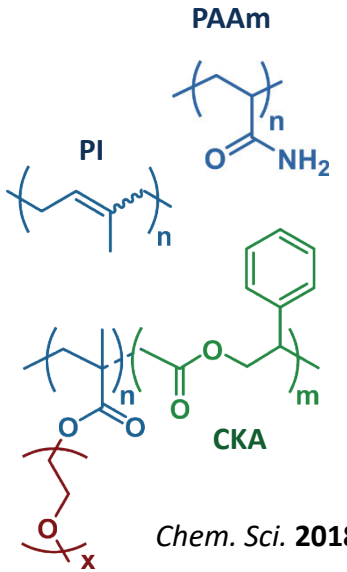


Biomacromolecules **2019**, *20*, 2464

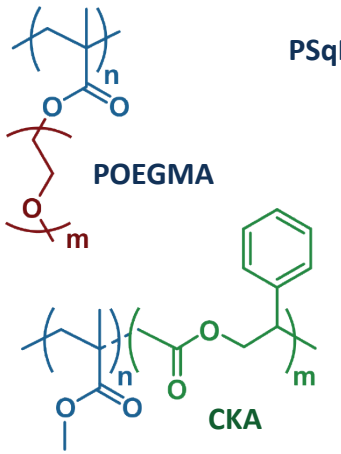


J. Control. Release **2019**, *295*, 223

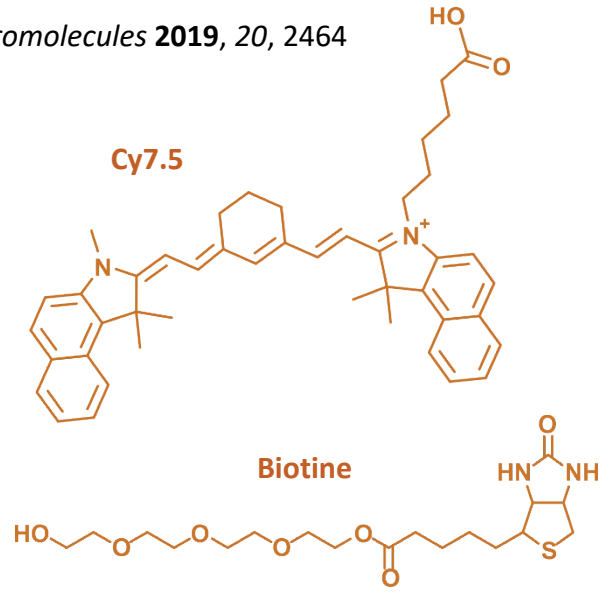




Chem. Sci. **2018**, *9*, 8291



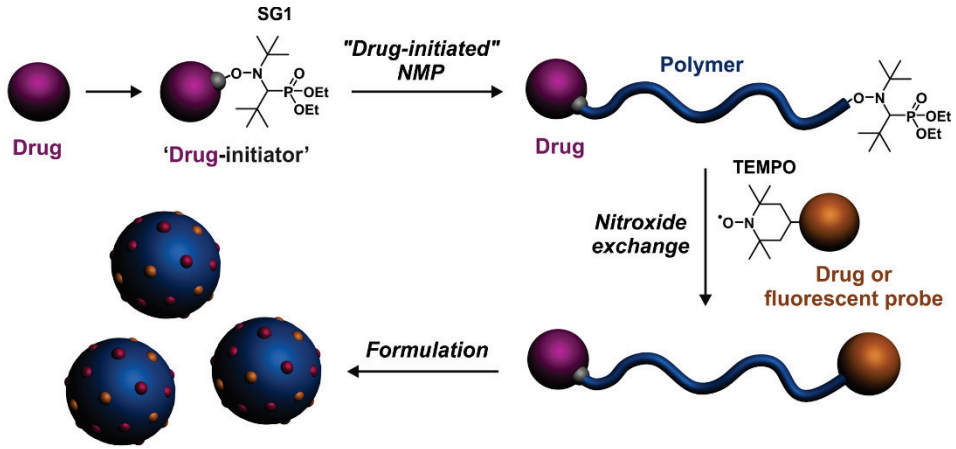
Chem. Mater. **2014**, *26*, 3606



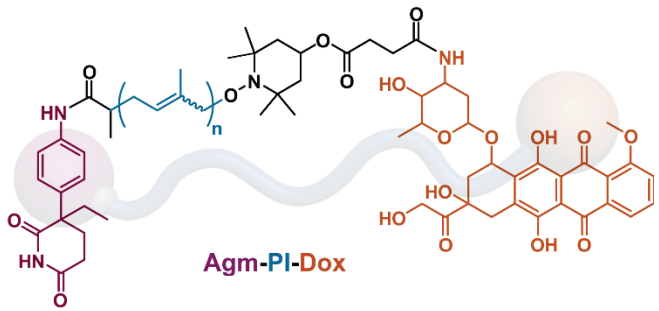
Biomacromolecules **2019**, *20*, 2464

GRAFTING FROM / THE DRUG-INITIATED METHOD

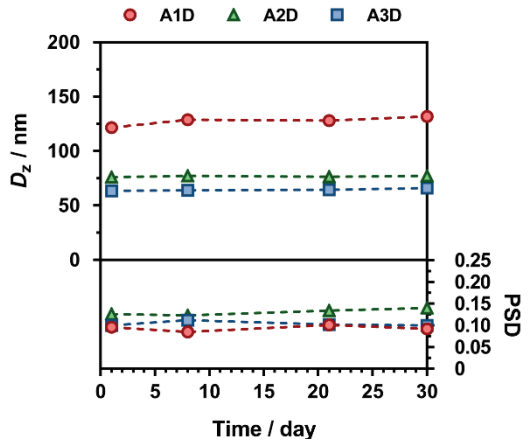
Heterotelechelic polymer prodrugs

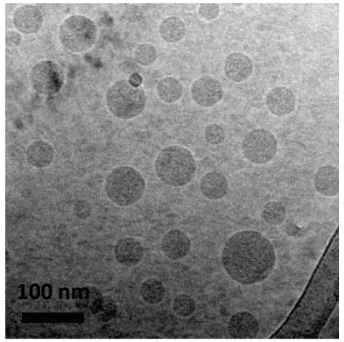


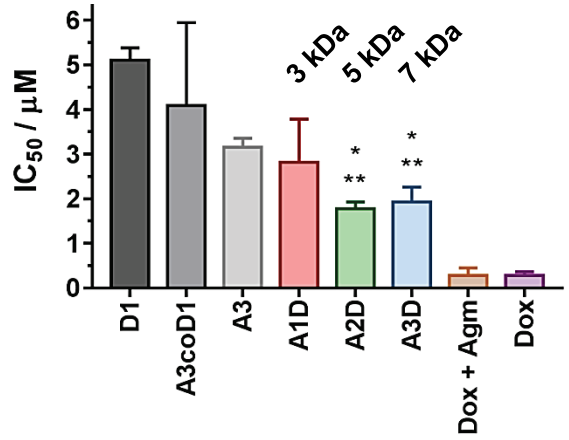
- Facile synthetic route, 1 equiv. TEMPO
- Driving force : more stable bond
- Few steps, quantitative yields
- Versatility



A1D = 3 kDa
A2D = 5 kDa
A3D = 7 kDa







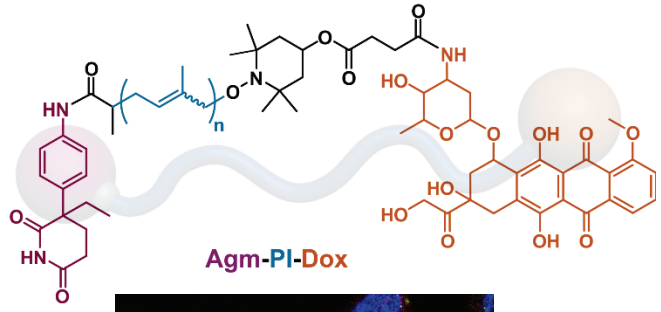
- **Heterotelechelic** > monofunctional
- **CI** = 0.91 (synergistic)

Vinciguerra, D.; Denis, S.; Mougin, J.; Jacobs, M.; Guillaneuf, Y.; Mura, S.; Couvreur, P.; Nicolas, J. *J. Control. Release* **2018**, *286*, 425

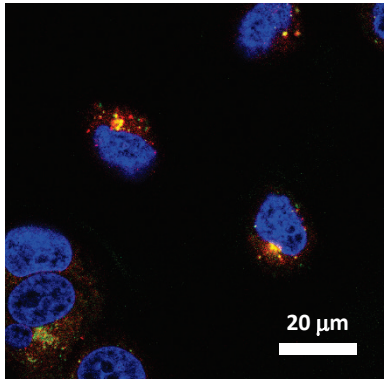
Vinciguerra, D.; Jacobs, M.; Denis, S.; Mougin, J.; Guillaneuf, Y.; Lazzari, G.; Zhu, C.; Mura, S.; Couvreur, P., Nicolas, J. *J. Control. Release* **2019**, *295*, 223

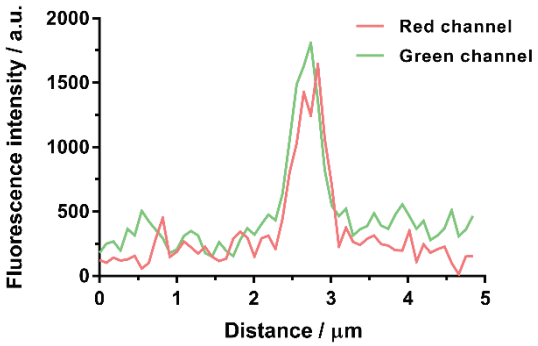
GRAFTING FROM / THE DRUG-INITIATED METHOD

Towards theranostic systems

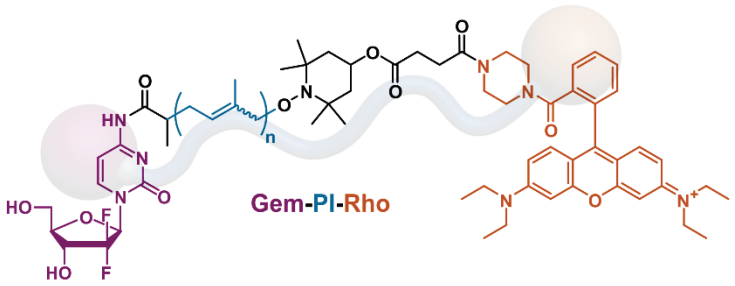


MCF-7 cells

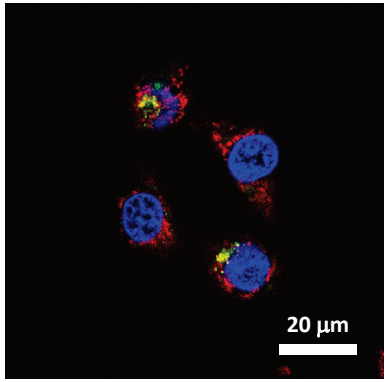


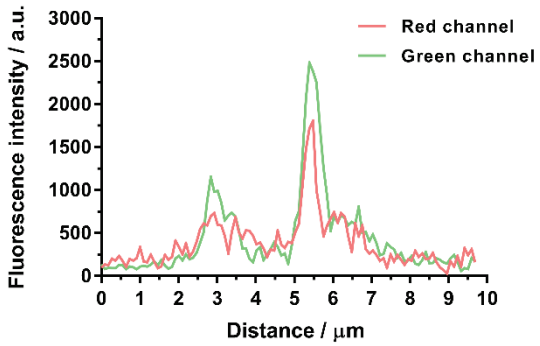


5 wt.%

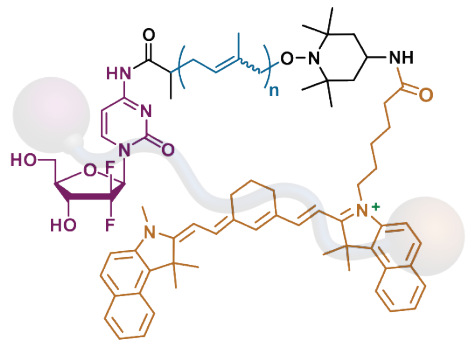


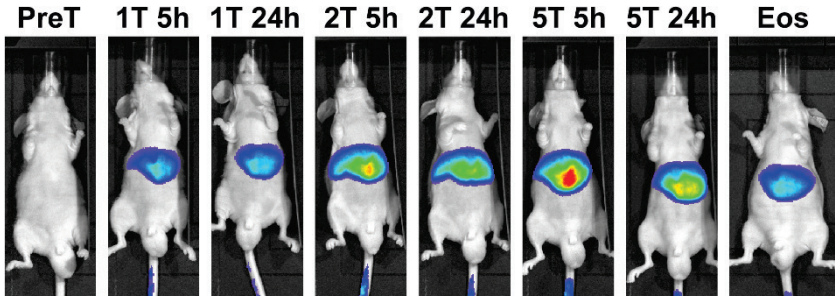
MCF-7 cells

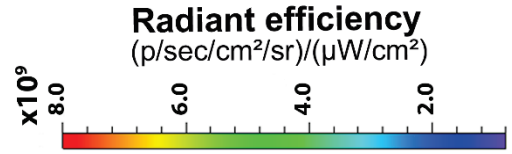




10 wt.%





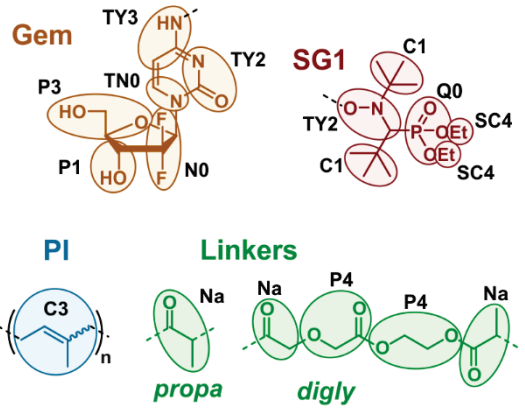


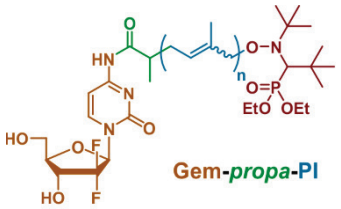
Vinciguerra, D.; Degrassi, A.; Mancini, L.; Mura, S.; Mougin, J.; Couvreur, P.; Nicolas, J. *J. Biomacromolecules* **2019,** *20*, 2464

Vinciguerra, D.; Denis, S.; Mougin, J.; Jacobs, M.; Guillaneuf, Y.; Mura, S.; Couvreur, P.; Nicolas, J. *J. Control. Release* **2018**, *286*, 425

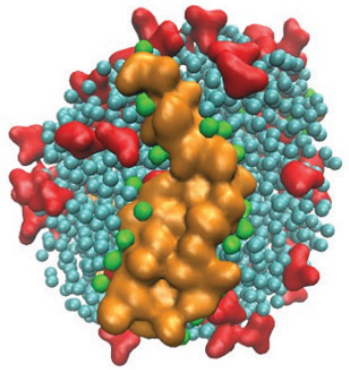
MODELING OF POLYMER PRODRUGS

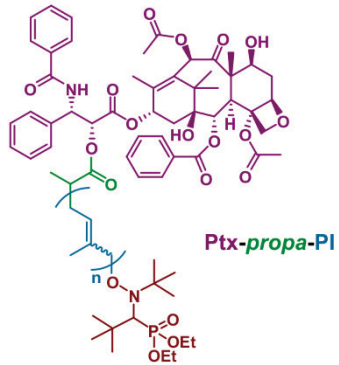
Coarse-Grained (CG) simulations



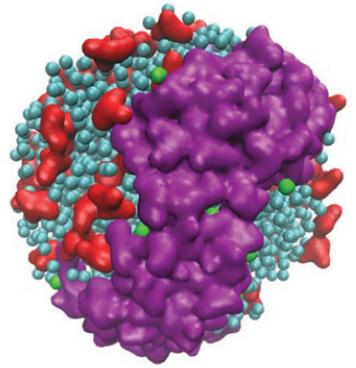


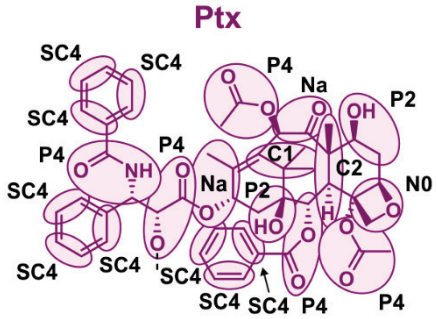
Gem-*propa*-PI

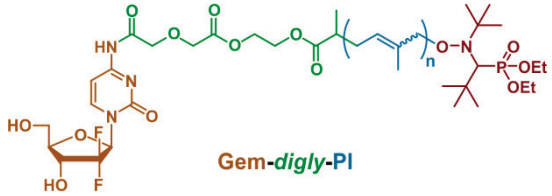




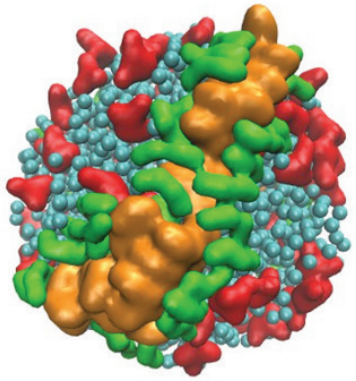
Ptx-*propa*-PI

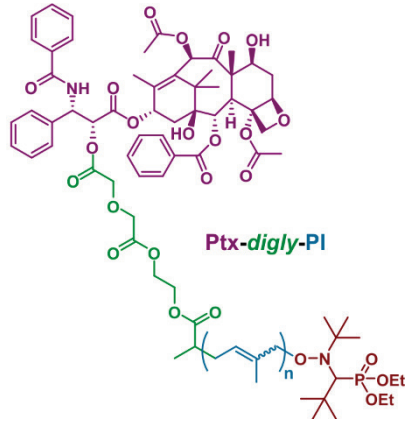




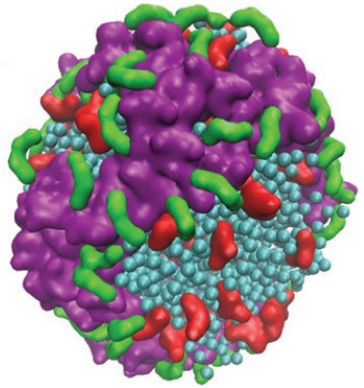


Gem-*digly*-PI





Ptx-*digly*-PI



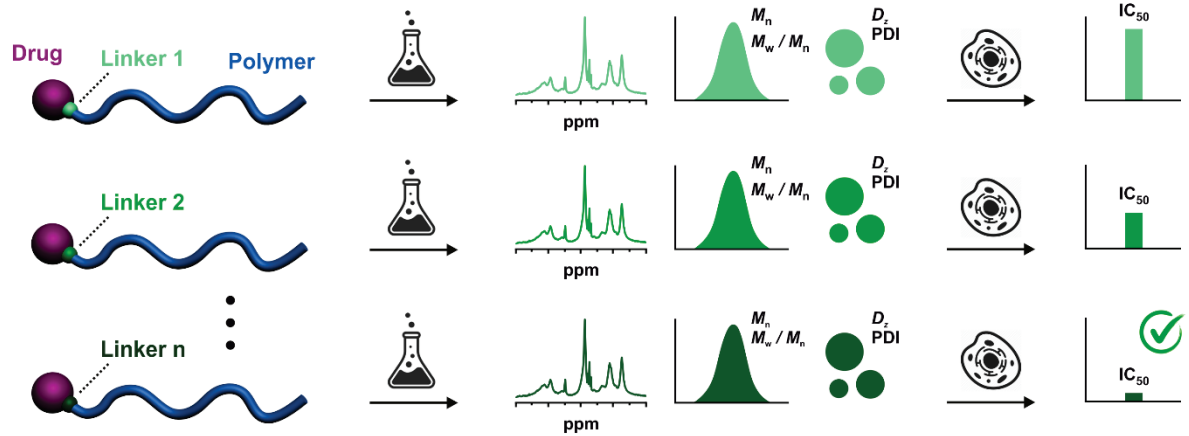
- Atom-to-bead mapping to construct the coarse-grained (CG) model using the MARTINI force field
- **Supramolecular organization** described by CG molecular dynamics simulations
- Influence of the nature of the linker on its localization in the nanoparticle surface

Gao, P.; Nicolas, J.; Ha-Duong, T. *J. Am. Chem. Soc.* **2021**, 143, 17412

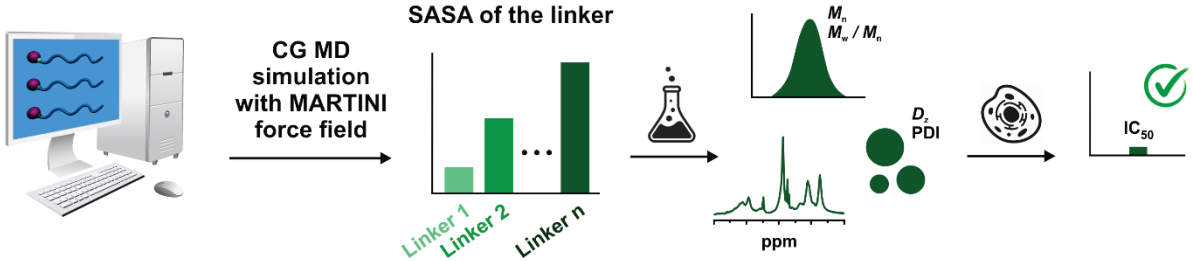
MODELING OF POLYMER PRODRUGS

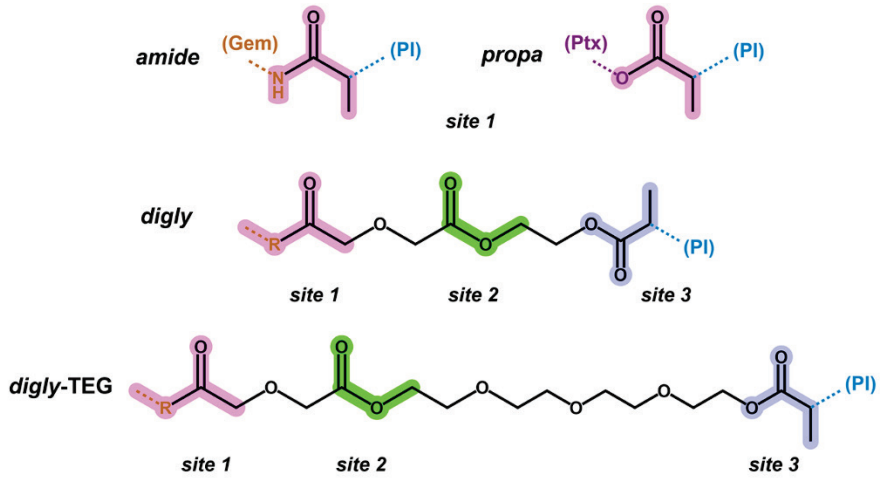
CG-assisted design of optimized polymer prodrugs

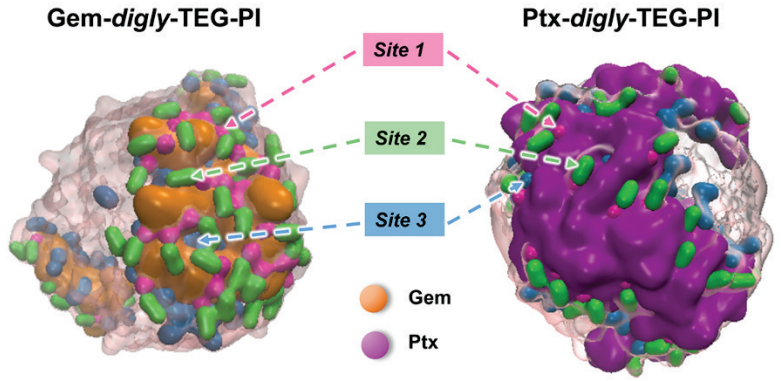
Traditional approach: trial and error



This work: coarse-grained-assisted design





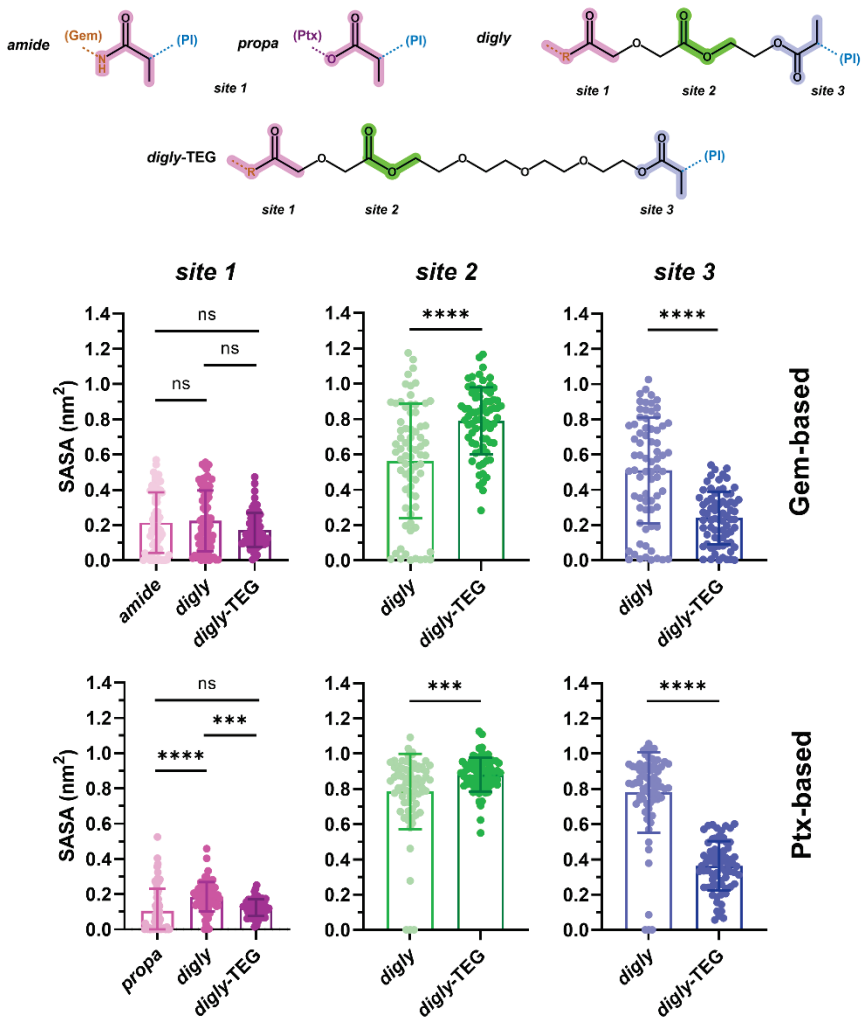


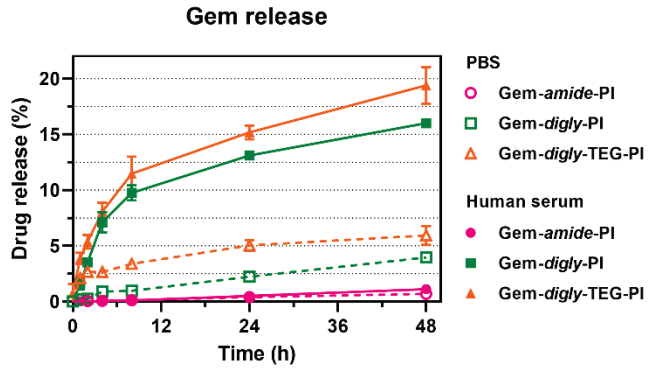
- Trial and error is time- and resource-consuming
- Use of the solvent accessible surface area (SASA) of the linker to predict drug release and cytotoxicity
- Investigation of a new linker: TEG-diglycolate

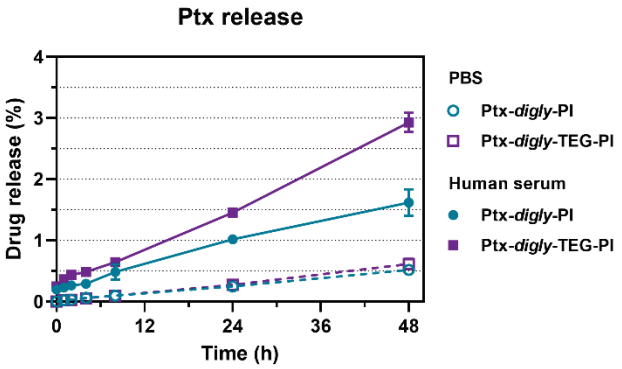
Gao, P.; Ha-Duong, T.; Nicolas, J. *Angew. Chem.; Int. Ed.* **2024**, 136, e202316056

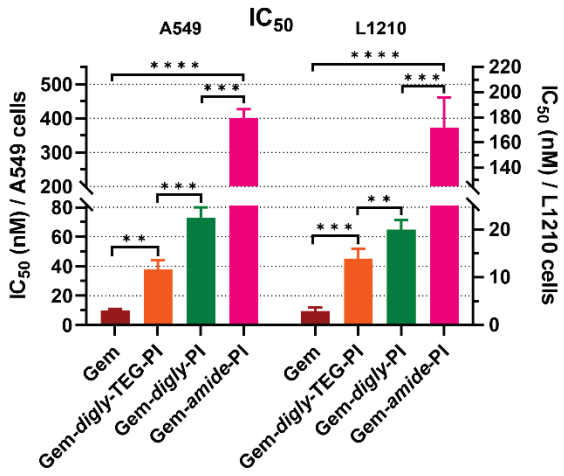
MODELING OF POLYMER PRODRUGS

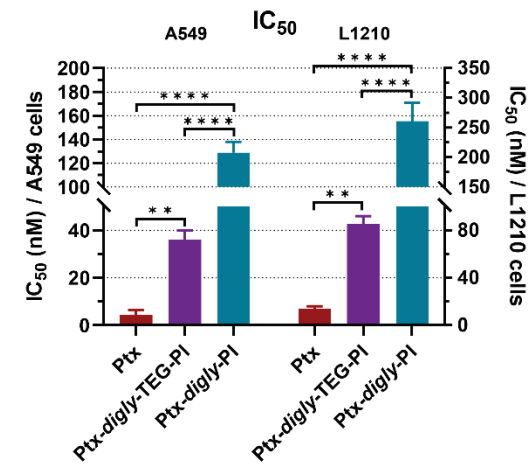
CG-assisted design of optimized polymer prodrugs











- Higher SASA values for site 2 in TEG-*digly* for both Gem- and Ptx-based polymer prodrugs
- Higher drug release with Gem-TEG-*digly*-PI and Ptx-TEG-*digly*-PI → greater cytotoxicity

Gao, P.; Ha-Duong, T.; Nicolas, J. *Angew. Chem.; Int. Ed.* **2024**, 136, e202316056

SWITCHING FROM IV TO SC ADMINISTRATION

Rationale

Conventional chemotherapy protocols

- **~95% by intravenous (IV) injection**
- Invasive treatment, patient discomfort
- Qualified staff, long hospital stay (€€€)
- Maximum tolerated dose (MTD)
  - Adverse effects (toxicity)
  - Tumor rebound
  - Resistances
- Other routes?
  - Oral route: poor/variable bioavailability
  - **Subcutaneous (SC) route?**

SC administration of anticancer drugs

- ↘ inpatient hospital stays (€)
- ↗ patient comfort
- High bioavailability (~80%)
- Tackle the pitfalls of MTD chemotherapy
- Self-administration & chemotherapy at home

- Not applicable to irritant/vesicant drugs (taxanes, Dox, Pt-based drugs, Gem, etc.) → *local toxicity*

How to switch from IV to SC administration of irritant/vesicant chemotherapeutics?

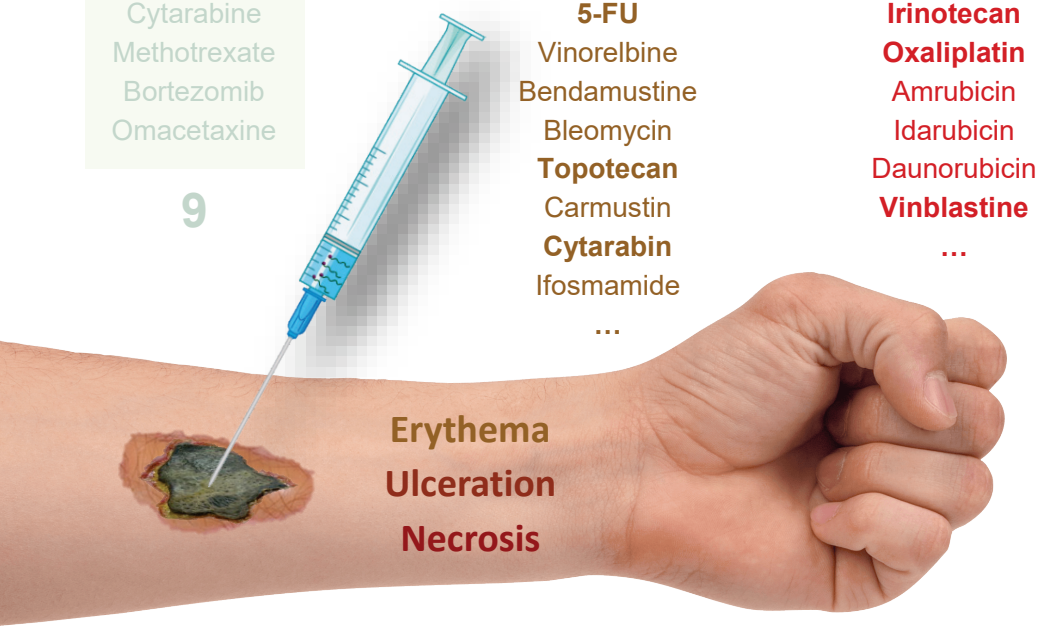
Tomasini, L.; Ferrere, M.; Nicolas, J. *Nature Rev. Bioeng.* **2024**, *2*, 501

SWITCHING FROM IV TO SC ADMINISTRATION

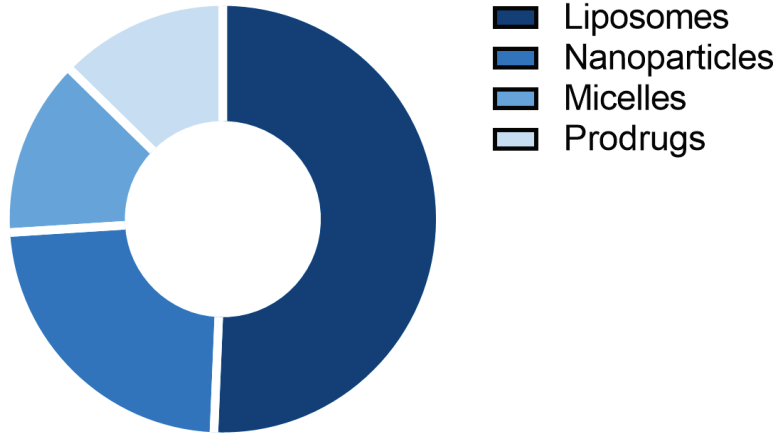
Rationale

Local toxicity of anticancer drugs

Neutrals	Irritants	Vesicants
Bleomycin	Carboplatin	**Docetaxel**
Decitabine	**Cisplatin**	**Doxorubicin**
Azacitidine	Cyclophosphamide	Epirubicin
Guadecitabine	Dacarbazine	**Paclitaxel**
Cladribine	**Gemcitabine**	Pirarubicin
Cytarabine	**5-FU**	**Irinotecan**
Methotrexate	Vinorelbine	**Oxaliplatin**
Bortezomib	Bendamustine	Amrubicin
Omacetaxine	Bleomycin	Idarubicin
9	**Topotecan**	Daunorubicin
	Carmustin	**Vinblastine**
	Cytarabin	…
	Ifosmamide	
	…	



Nanoscale drug delivery systems for SC administration

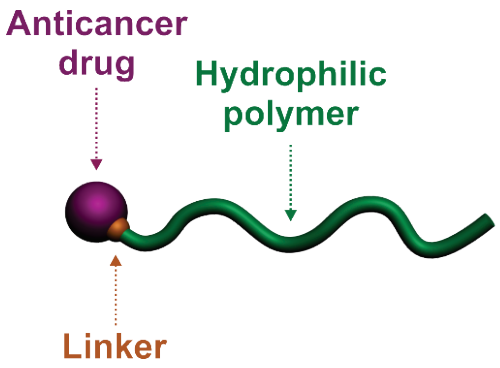


- Mainly against inflammations, diabetes, hematological diseases, infections, immunological diseases, pain, etc.
- **No marketed products or clinical trials with vesicant/irritant anticancer drugs**
- Plenty of room for innovation

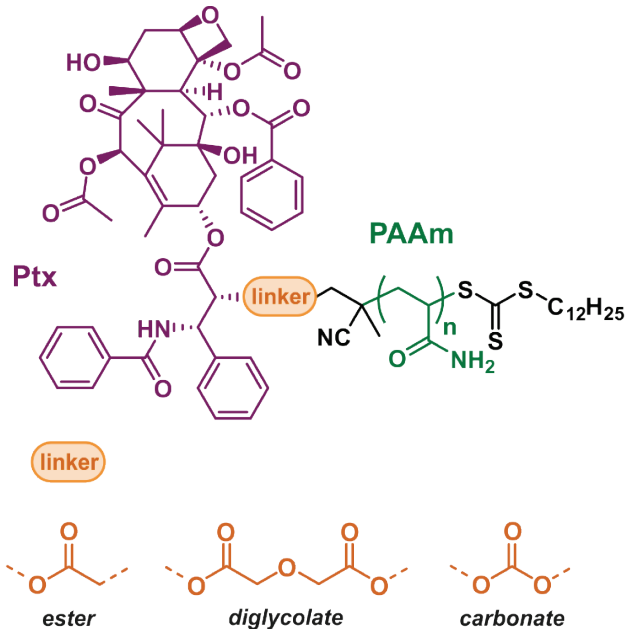
Tomasini, L.; Ferrere, M.; Nicolas, J. *Nature Rev. Bioeng.* **2024**, *2*, 501

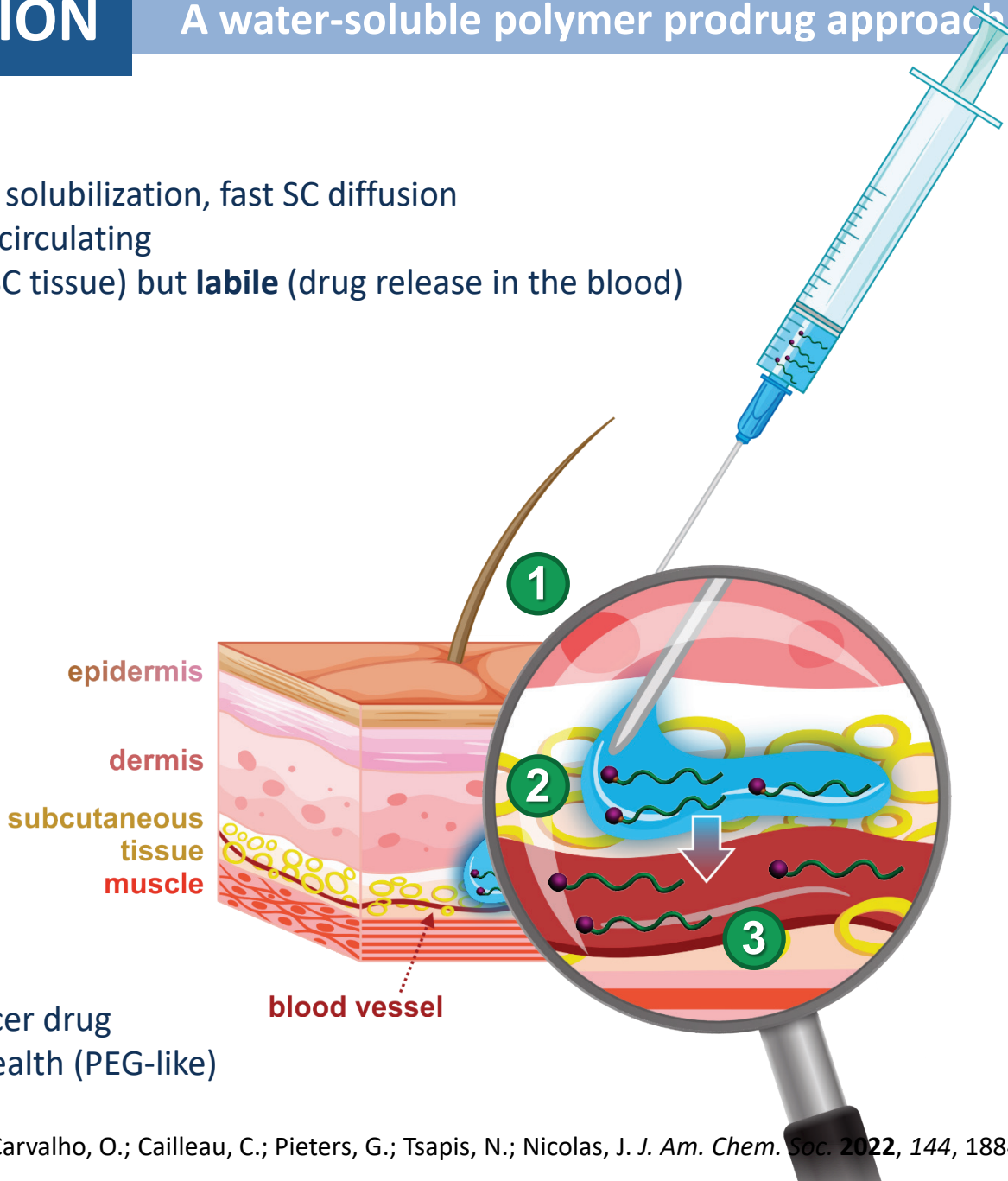
SWITCHING FROM IV TO SC ADMINISTRATION

A water-soluble polymer prodrug approach



- **Water-soluble polymer prodrug**: drug solubilization, fast SC diffusion
- **Biocompatible, stealth polymer**: long circulating
- **Linker**: **stable** (no drug release in the SC tissue) but **labile** (drug release in the blood)



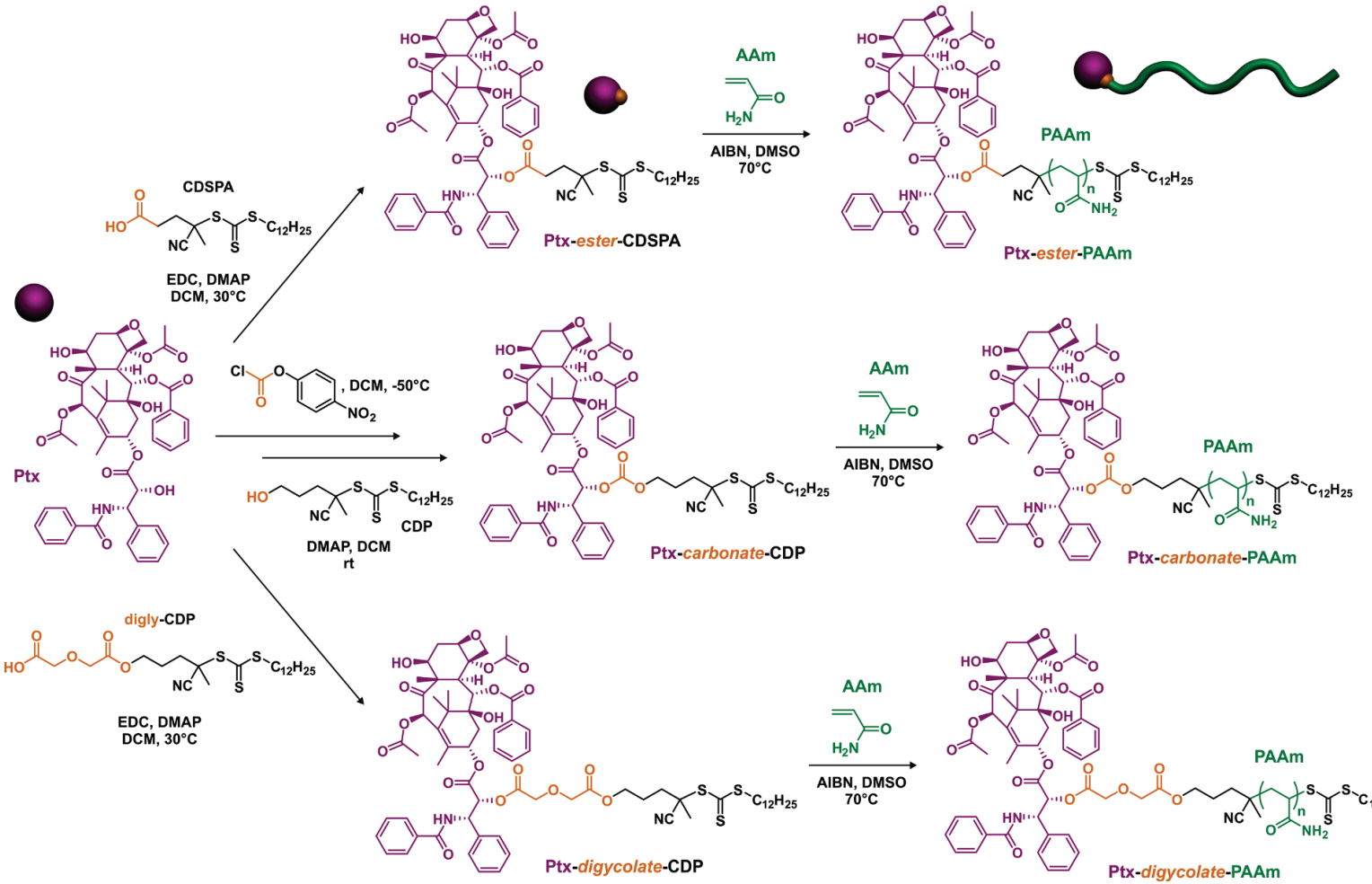


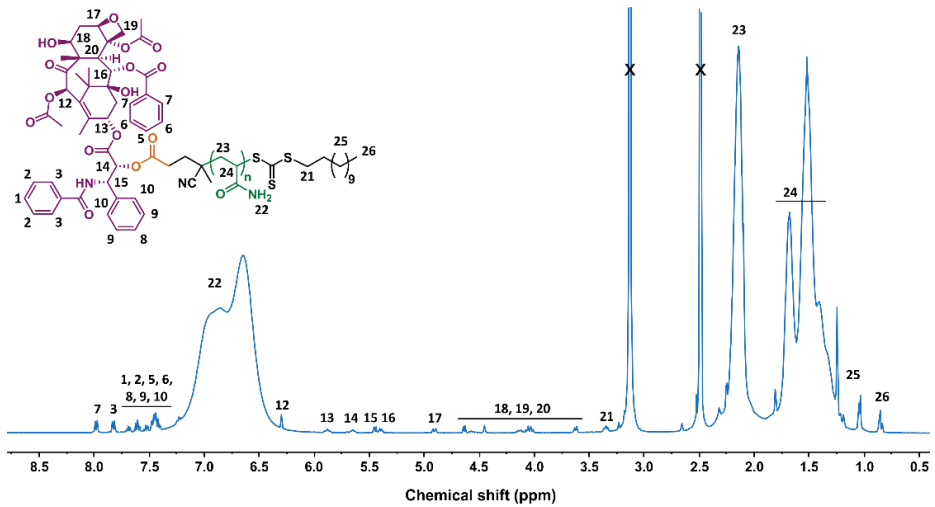
- **Paclitaxel**: hydrophobic, vesicant anticancer drug
- **PAAm**: biocompatible (Aquamid®) and stealth (PEG-like)

Bordat, A.; Boissenot, T.; Ibrahim, N.; Ferrere, M.; Levêque, M.; Denis, S.; Garcia-Argote, S.; Carvalho, O.; Cailleau, C.; Pieters, G.; Tsapis, N.; Nicolas, J. *J. Am. Chem. Soc.* **2022**, *144*, 18844

POLYMER PRODRUGS FOR SC ADMINISTRATION

Synthesis of Ptx-PAAm polymer prodrugs





	Linker	$M_{n,NMR}$ (g.mol^{-1})	$Đ$	Solubility
P1e	*ester*	6 200	1.07	**Insoluble**
P2e	*ester*	9 400	1.28	**Insoluble**
P3e	*ester*	21 600	1.12	**Soluble**
P3d	*digly*	27 300	1.10	**Soluble**
P3c	*carbonate*	23 000	1.09	**Soluble**

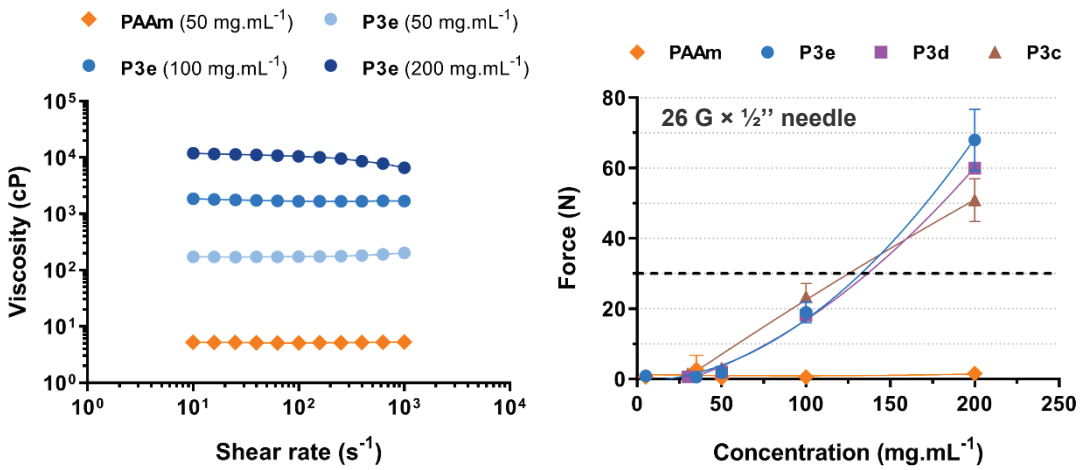
- Well-defined Ptx-PAAm prodrugs with different linkers
- **Water-solubility** achieved for M_n ~ 20 kg.mol^{-1}

Bordat, A.; Boissenot, T.; Ibrahim, N.; Ferrere, M.; Levêque, M.; Denis, S.; Garcia-Argote, S.; Carvalho, O.; Cailleau, C.; Pieters, G.; Tsapis, N.; Nicolas, J. *J. Am. Chem. Soc.* **2022**, *144*, 18844

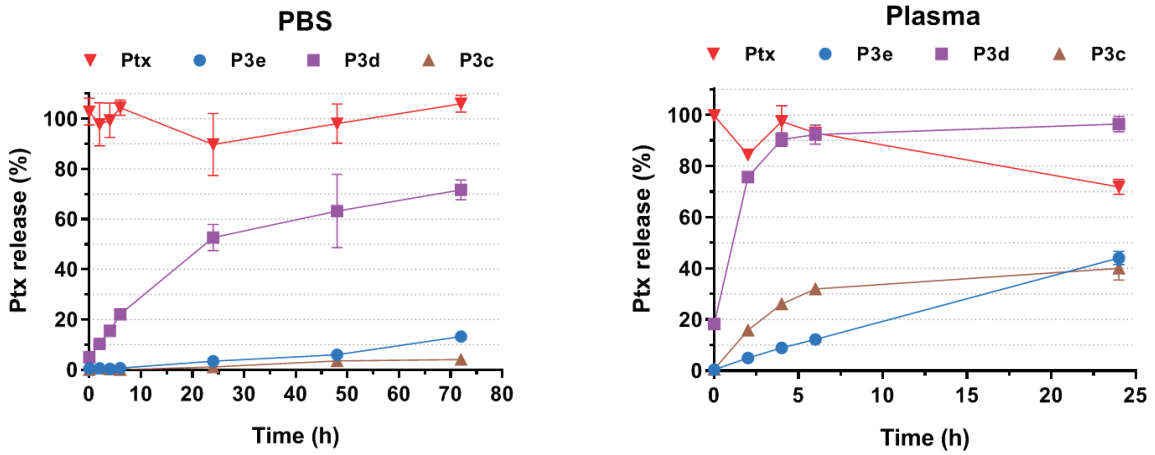
POLYMER PRODRUGS FOR SC ADMINISTRATION

Injectability and in vitro evaluations

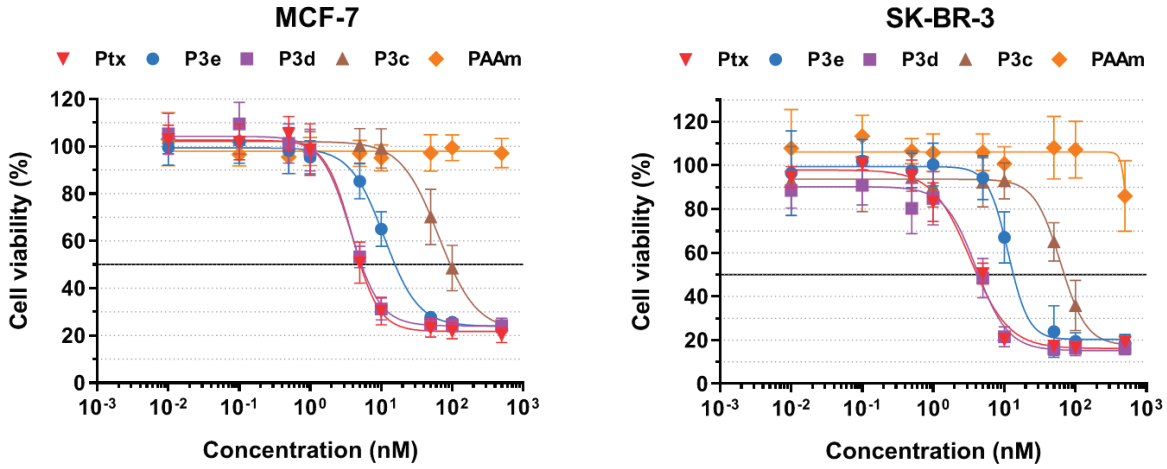
Viscosity measurements



Ptx release



Cytotoxicity



- **SC injectability**: up to ~130 mg.mL^{-1} (~6 mg.mL^{-1} in Ptx)
- **Ptx release**: governed by the nature of the linker:

  ➡ diglycolate >> ester > carbonate

- **Cytotoxicity**: 2 cancer cell lines (MCF-7, SK-BR-3), in agreement with Ptx release profiles:

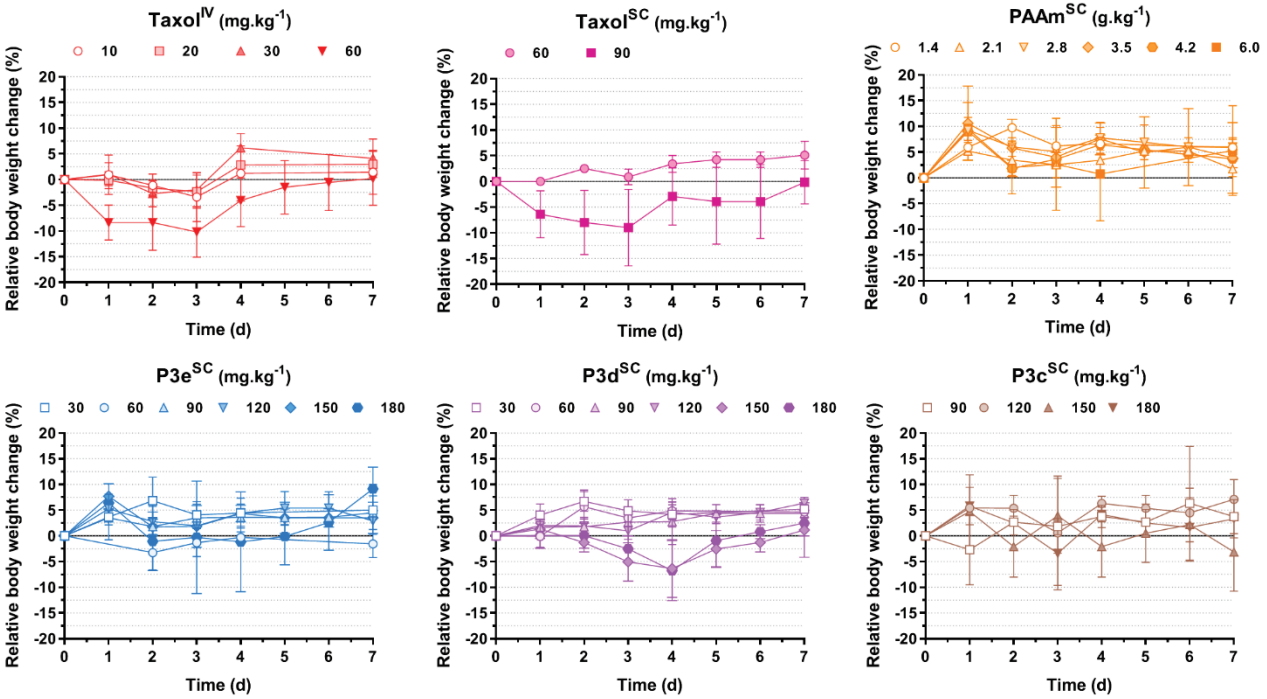
  ➡ IC_{50} Ptx ≈ IC_{50} diglycolate << IC_{50} ester < IC_{50} carbonate

Bordat, A.; Boissenot, T.; Ibrahim, N.; Ferrere, M.; Levêque, M.; Denis, S.; Garcia-Argote, S.; Carvalho, O.; Cailleau, C.; Pieters, G.; Tsapis, N.; Nicolas, J. *J. Am. Chem. Soc.* **2022**, *144*, 18844

POLYMER PRODRUGS FOR SC ADMINISTRATION

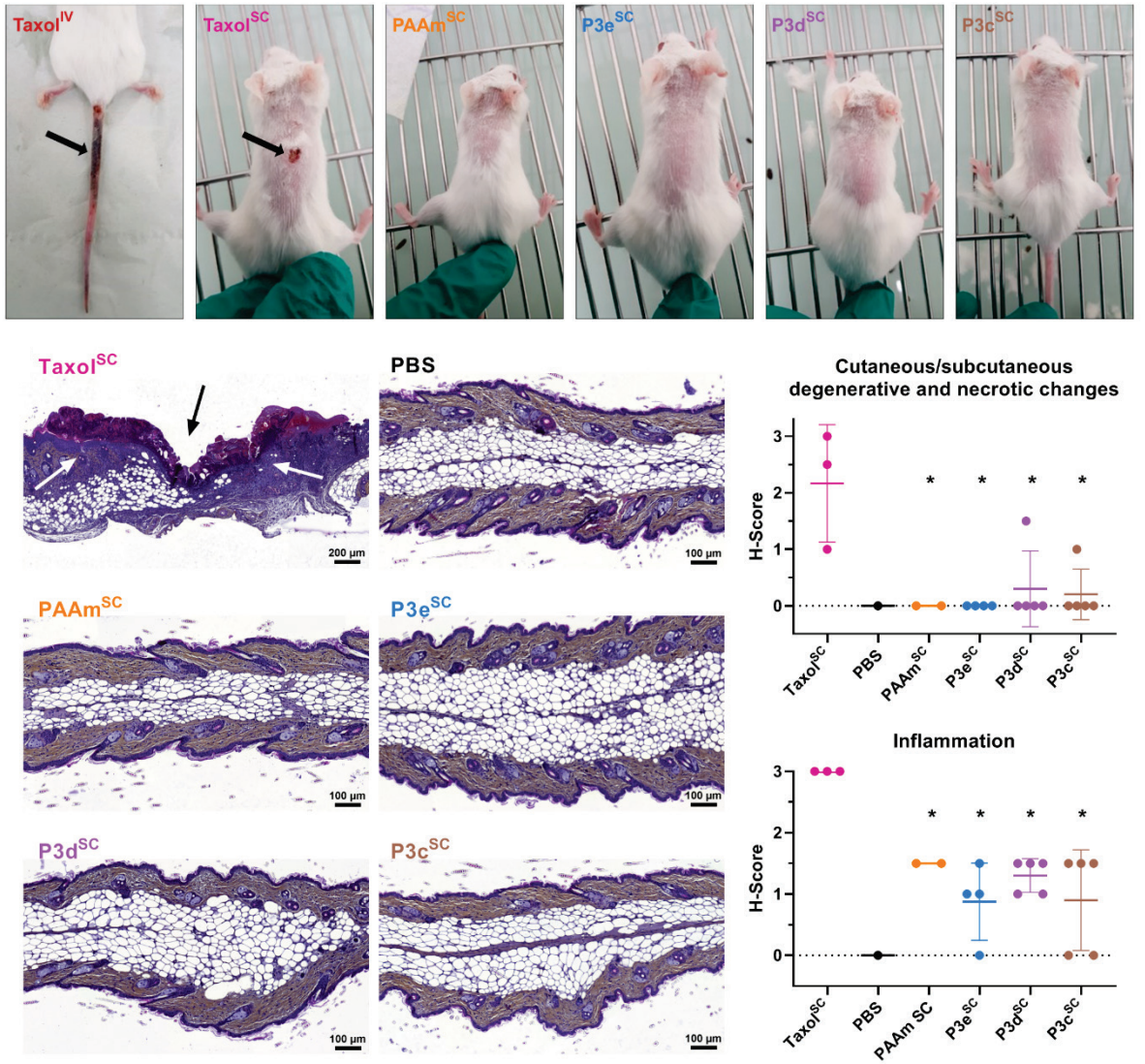
Systemic and local toxicity in vivo

Systemic toxicity



- **Systemic toxicity:** All prodrugs gave MTD ≥ 180 mg.kg^{-1} (x3 Taxol IV)
- **Local toxicity**:
  - Taxol IV leads to extravasation (necrosis)
  - Taxol SC leads to necrosis
  - No Ptx-PAAm prodrugs exhibit local toxicity

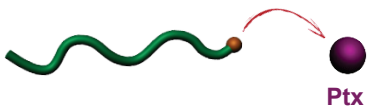
Acute local toxicity

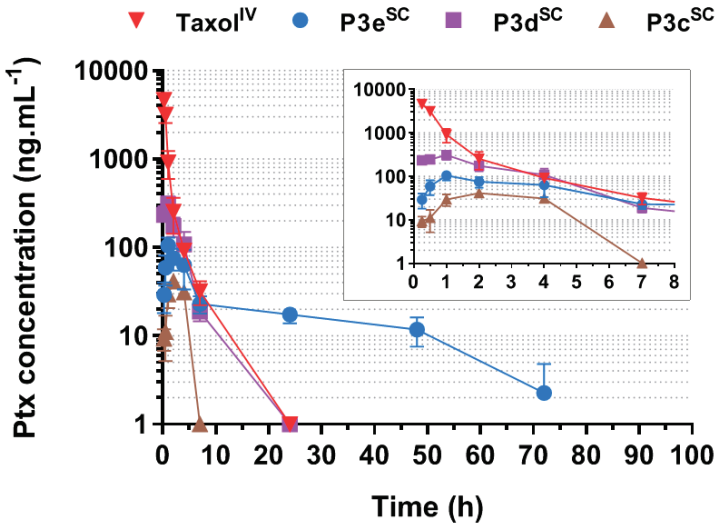


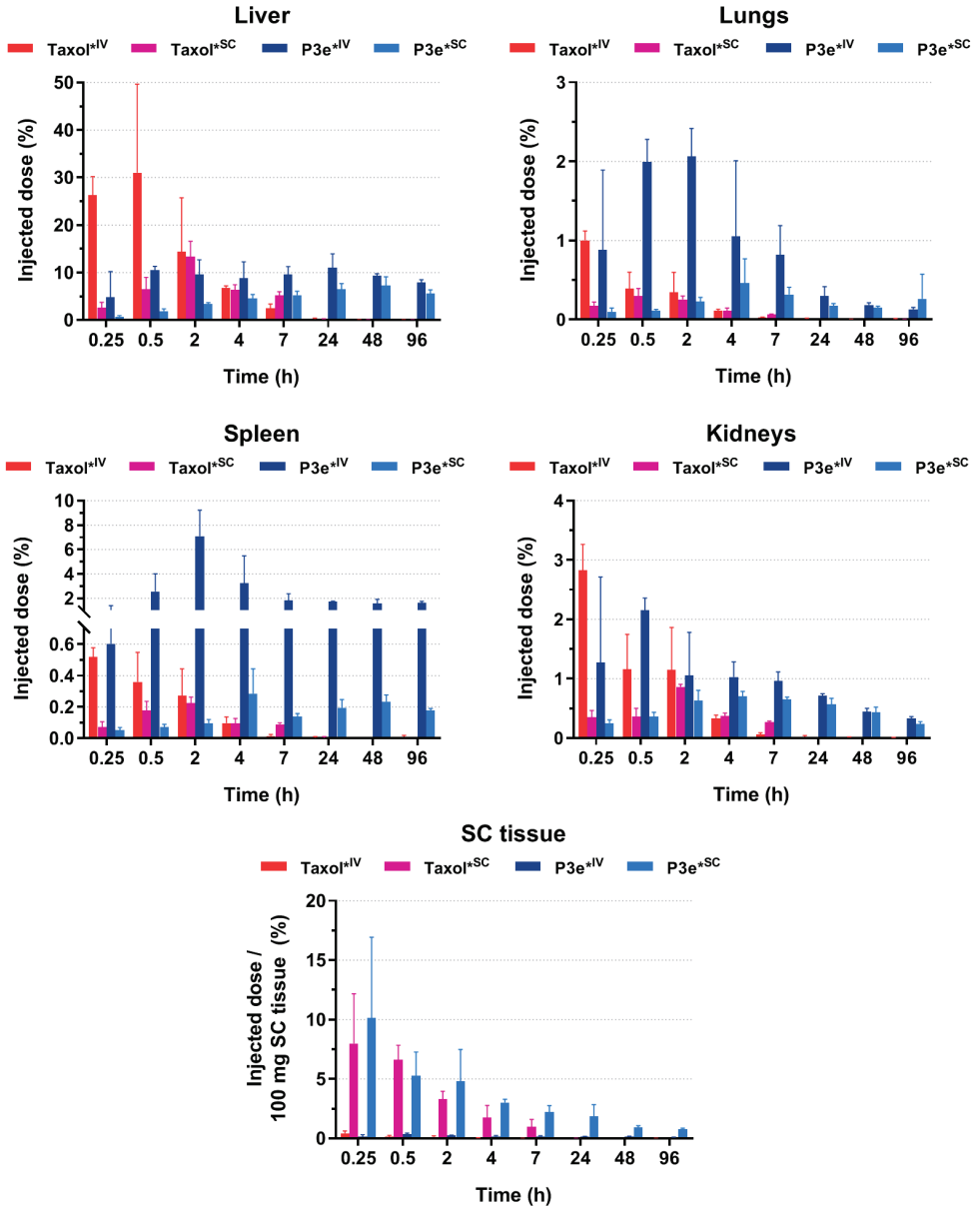
Bordat, A.; Boissenot, T.; Ibrahim, N.; Ferrere, M.; Levêque, M.; Denis, S.; Garcia-Argote, S.; Carvalho, O.; Cailleau, C.; Pieters, G.; Tsapis, N.; Nicolas, J. *J. Am. Chem. Soc.* **2022**, *144*, 18844

POLYMER PRODRUGS FOR SC ADMINISTRATION

Pharmacokinetics and biodistribution







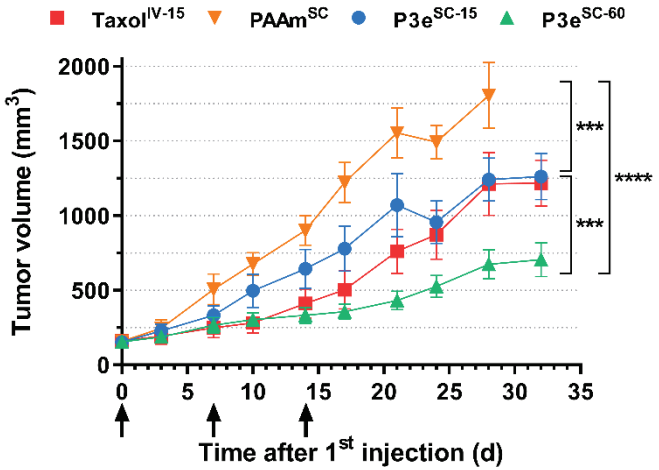
- **Pharmacokinetics:**
  - 15-114x lower C_{max} for the prodrugs vs. Taxol IV
  - Ptx-*ester*-PAAm = prolonged exposure to Ptx ($t_{1/2}$ = 14 h)
  - 84% bioavailability
  - Ptx-*digly*-PAAm = too rapid Ptx release
  - Ptx-*carbonate*-PAAm = too slow Ptx release
- **Biodistribution:**
  - Limited accumulation in the liver (< 10 % injected dose)
  - Rapid diffusion in the SC tissue and passage into the blood

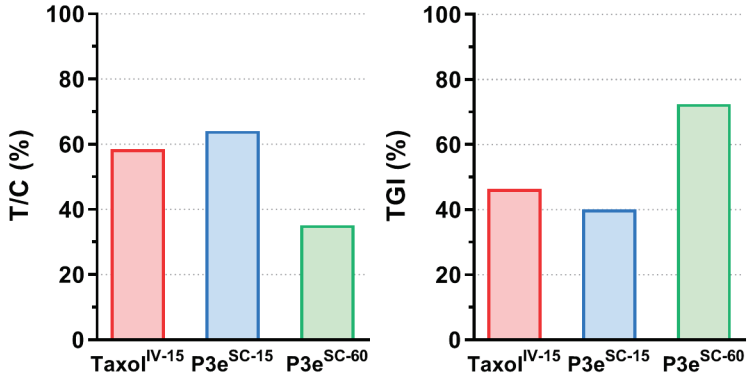
Bordat, A.; Boissenot, T.; Ibrahim, N.; Ferrere, M.; Levêque, M.; Denis, S.; Garcia-Argote, S.; Carvalho, O.; Cailleau, C.; Pieters, G.; Tsapis, N.; Nicolas, J. *J. Am. Chem. Soc.* **2022**, *144*, 18844

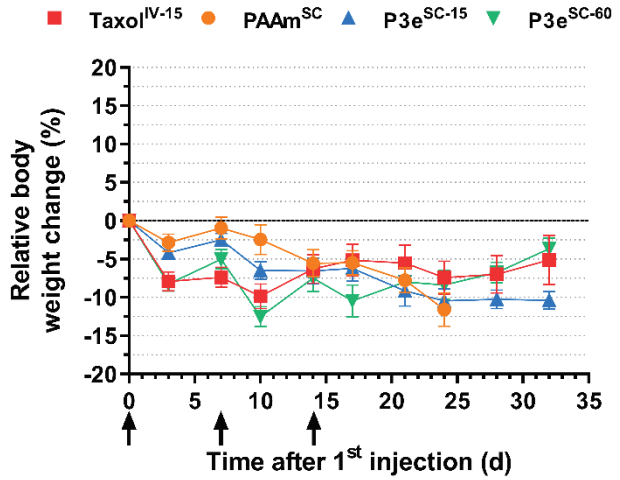
POLYMER PRODRUGS FOR SC ADMINISTRATION

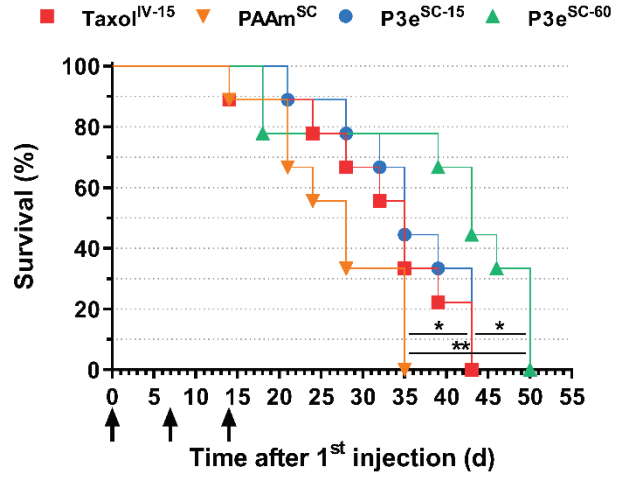
Anticancer efficacy

[MCF-7, sc/sc]





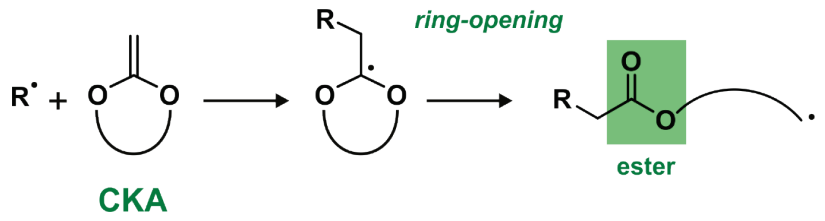


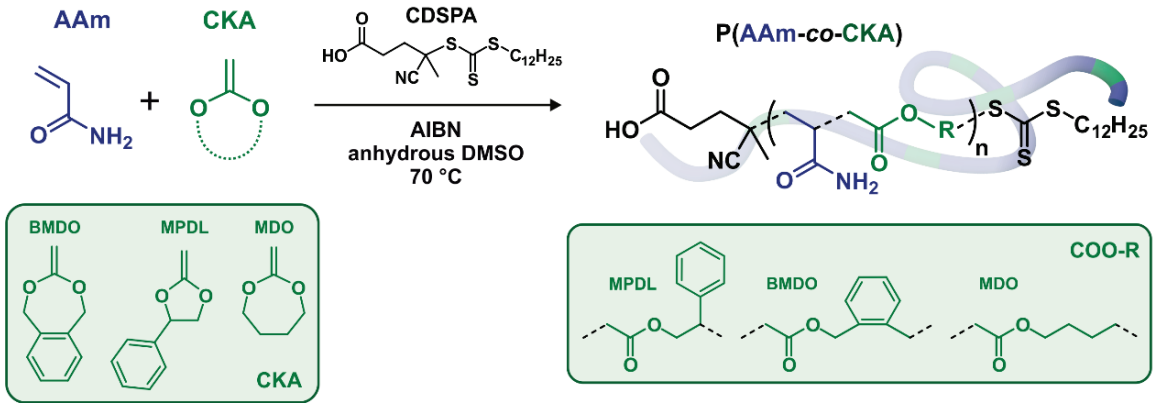


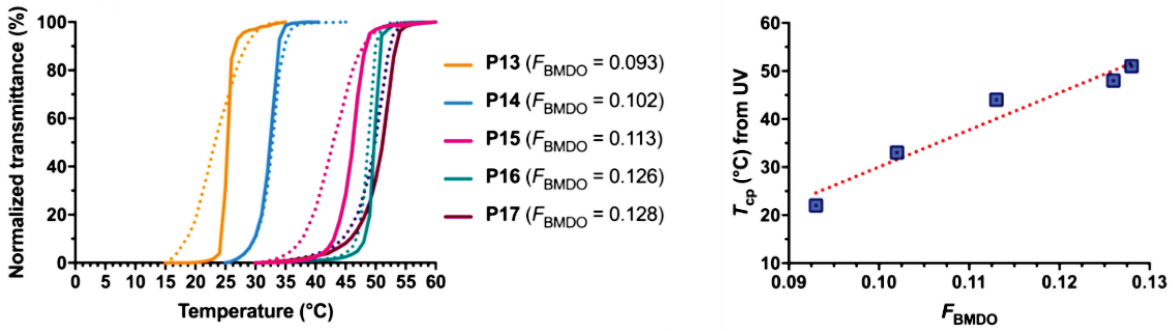
- Rapid tumor growth for PAAm-treated mice
- Anticancer efficacy for Taxol IV @ 15 $mg.kg^{-1}$
- At 15 $mg.kg^{-1}$: Ptx-*ester*-PAAm ≈ Taxol IV → **safe switch from IV to SC**
- At 60 $mg.kg^{-1}$: Ptx-*ester*-PAAm > Taxol IV → **the prodrug SC can outperfom Taxol IV**
- No significant body weight loss
- Highest survival rate (~78%) for Ptx-*ester*-PAAm, 25 days after treatment termination (day 39)

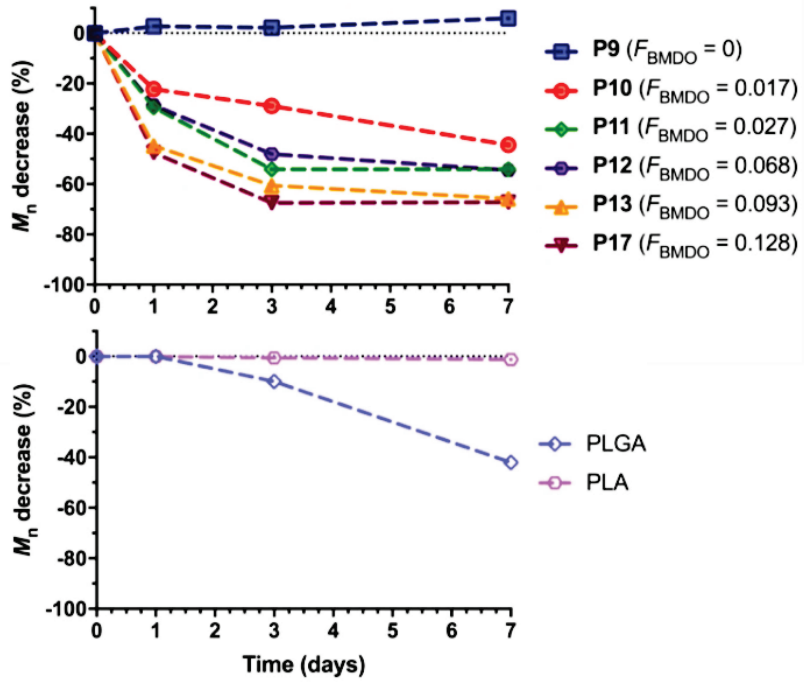
Bordat, A.; Boissenot, T.; Ibrahim, N.; Ferrere, M.; Levêque, M.; Denis, S.; Garcia-Argote, S.; Carvalho, O.; Cailleau, C.; Pieters, G.; Tsapis, N.; Nicolas, J. *J. Am. Chem. Soc.* **2022**, *144*, 18844

DEGRADABLE POLYACRYLAMIDE BY rROP









- Successful RAFT-mediated synthesis of P(AAm-*co*-CKA) copolymers
- High conversions, low dispersities, tunable CKA content (4–15 mol %)
- **Sharp and tunable UCST transitions** ($T_{cp,\ BMDO}$ = 23–55°C)
- **Hydrolytic degradation** in PBS (up to -75% M_n)
- Faster hydrolytic degradation than PLA and even PLGA!

Bossion, A.; Zhu, C.; Guerassimoff, L.; Mougin, J.; Nicolas, J. *Nature Commun.* **2022**, *13*, 2873

CONCLUSIONS

THE GRAFTING FROM / DRUG-INITIATED METHOD

- Well-defined polymer prodrugs by controlled radical polymerization
- High versatility (polymer, linker, drugs)
- Water-soluble or nanoparticulate systems
- Prediction of drug release and cytotoxicity by CG simulations

SC ADMINISTRATION OF ANTICANCER DRUGS

- Water-soluble Ptx-PAAm prodrugs
- Successful SC administration: no local toxicity and significant anticancer efficacy
- Outperforms Taxol (MTD, Ptx exposure, efficacy)
- Applicable to other irritant/vesicant anticancer drugs

DEGRADABLE POLYACRYLAMIDE BY rROP

- rROP = Imparts degradability to vinyl polymers
- Use of CKA as precursors of ester bonds in the backbone
- Successful copolymerization of AAm and CKA
- UCST copolymers
- Hydrolytic degradation faster then aliphatic polyesters

ACKNOWLEDGEMENTS

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