Design, synthesis, and applications of self-immolative polymers

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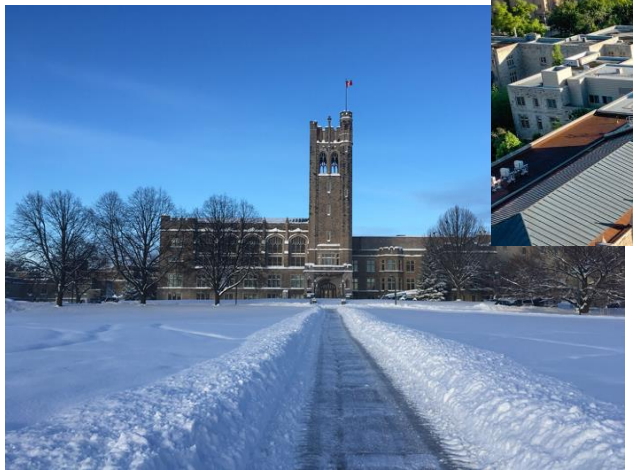
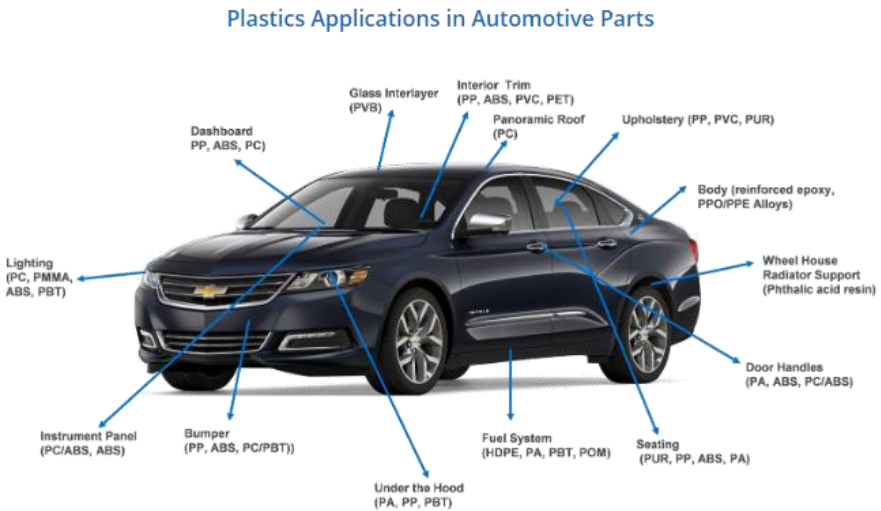
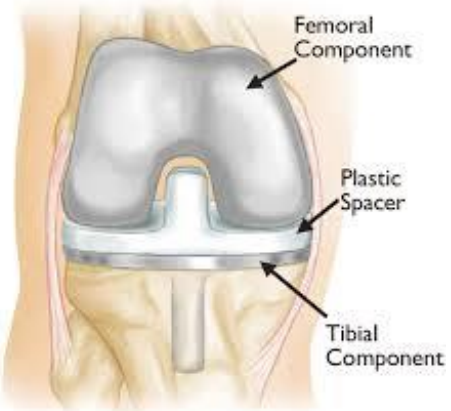
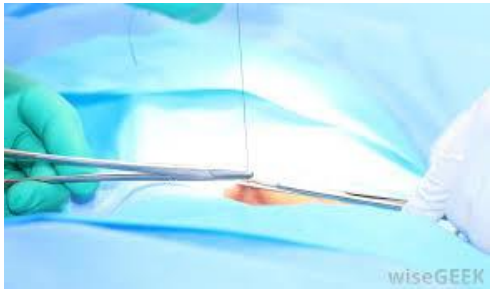


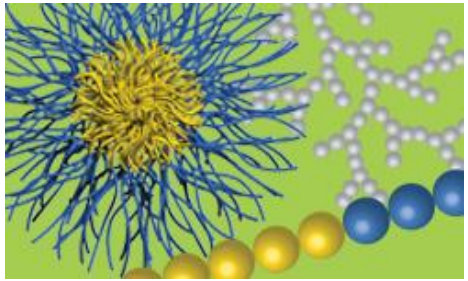
Polymers are traditionally slow to degrade

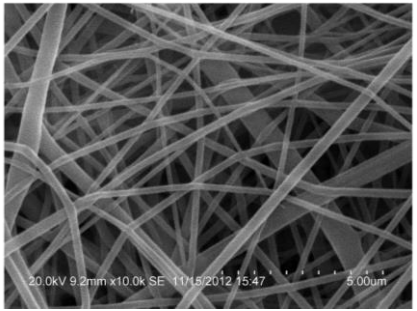




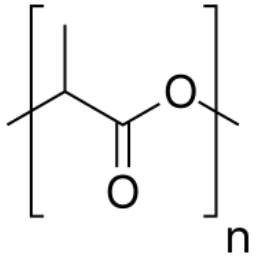
But there is increasing interest in degradable polymers



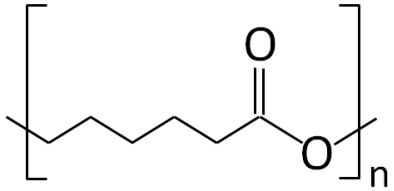




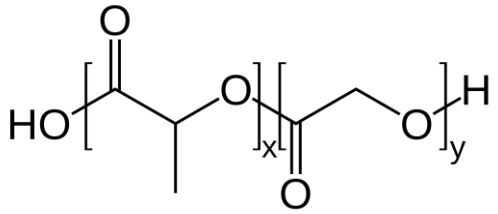
Traditional biodegradable polymers



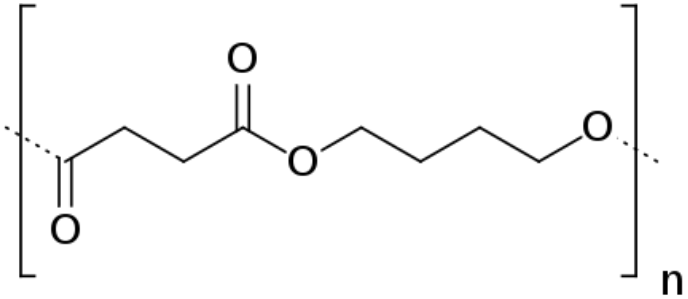
Polylactide



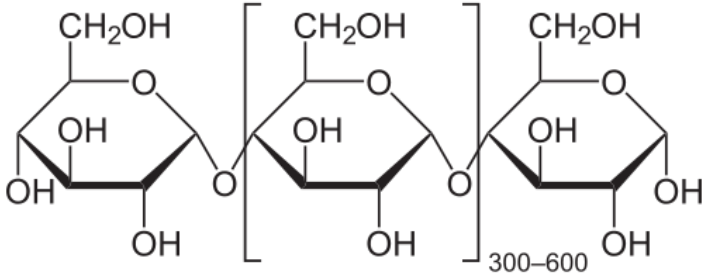
Polycaprolactone



Poly(lactide-*co*-glycolide)



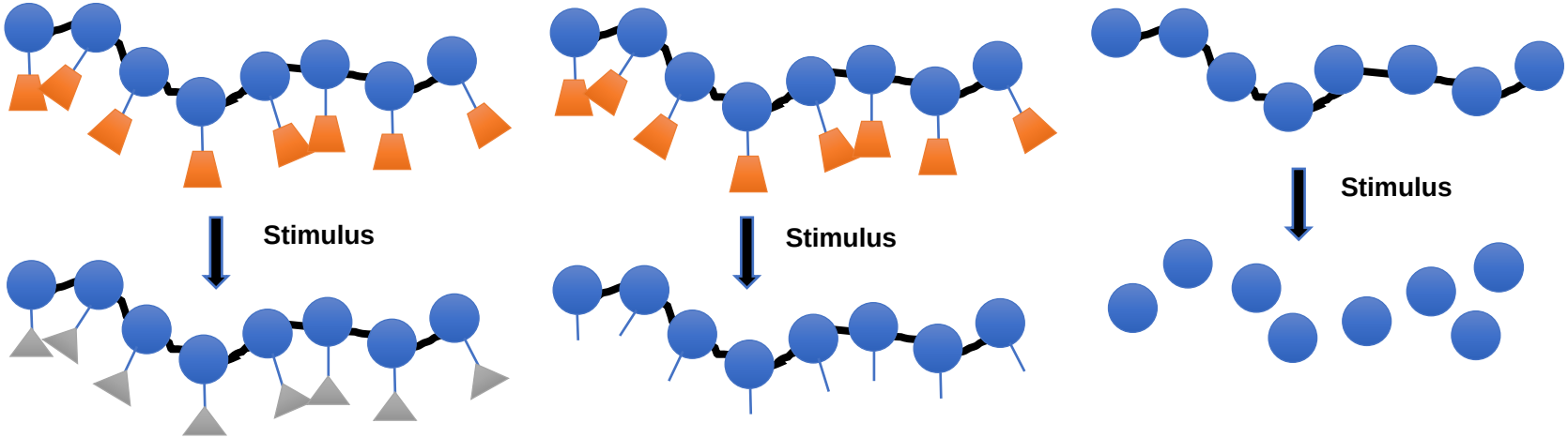
Poly(butylene succinate)



Starch

Generally not possible to “turn on” degradation

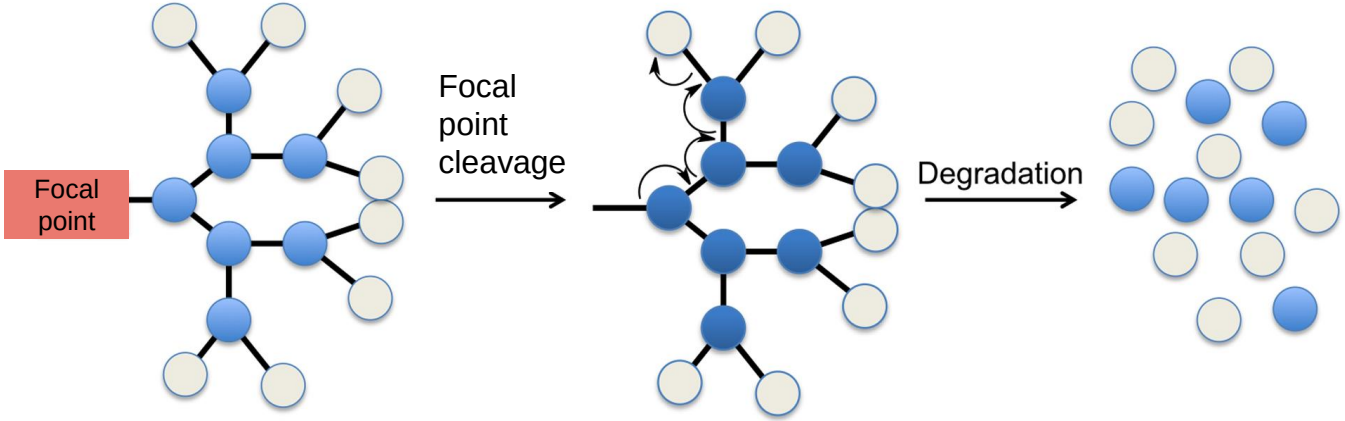
Stimuli-responsive/switchable polymers



One stimulus, one response

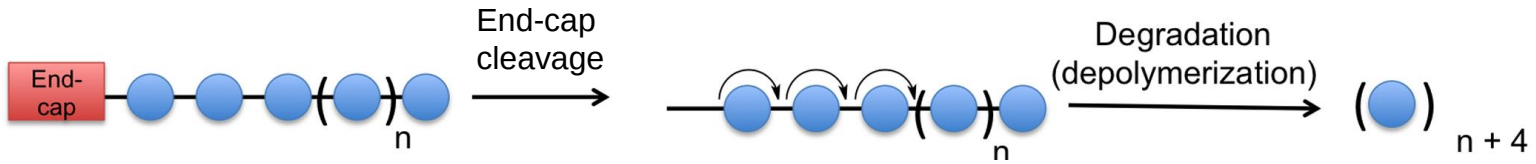
Can we amplify the response by creating a cascade?

Self-immolative polymers



Shabat and coworkers, *Angew. Chem. Int. Ed*. **2003**, *42*, 4494-4499.
de Groot and coworkers, *Angew. Chem. Int. Ed.* **2003**, *42*, 4490-4494.
McGrath and coworkers, *J. Am. Chem. Soc.* **2003**, *125,* 15688–15689.

Linear polymer analogue:



Stable polymer backbone with end-to-end depolymerization stimulated by removal of the end-cap

Advantages of self-immolative polymers

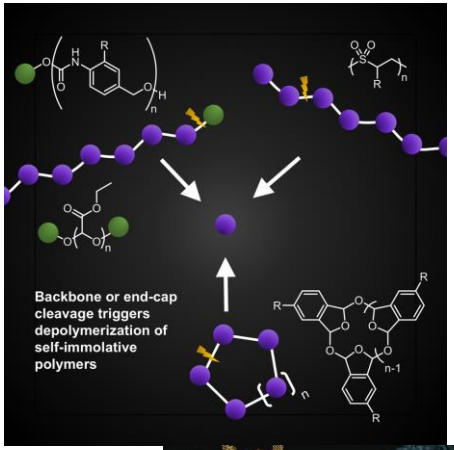
Amplification of the stimulus

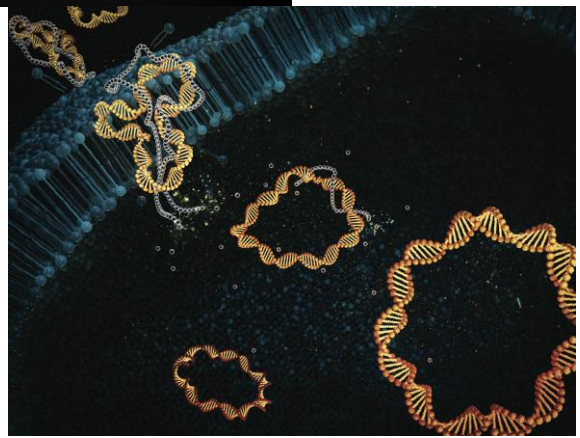
Degradation of single polymer triggered under different conditions

End-cap removal can be triggered under various conditions

e.g. light, enzymes, change in pH or redox potential

Outline



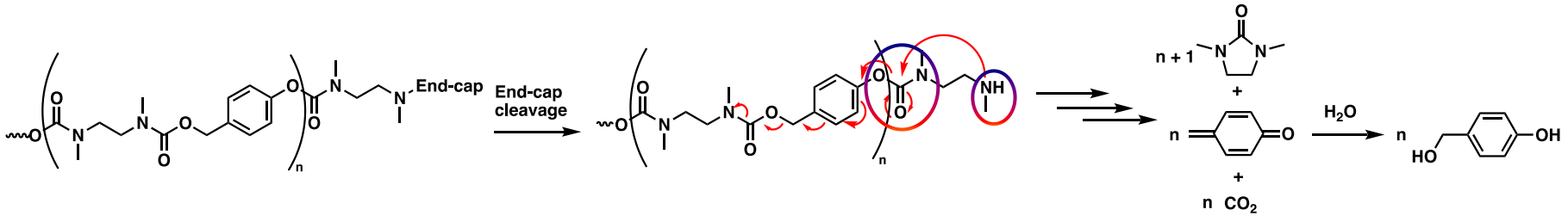


Chemistry of depolymerizable polymer backbones

Applications

- Micropatterning
- Imaging contrast agents
- Hydrogels

Polymers can depolymerize by alternating cyclization and elimination reactions

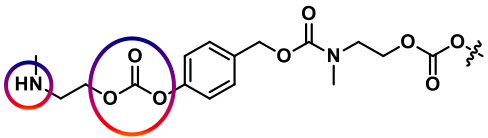


DeWit, Gillies *J. Am. Chem. Soc.* **2009**, *131*, 18327-18334.

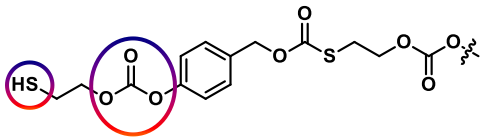
Cyclization reaction can control the rate

Matt DeWit

Tuning the rate:



Carbonates stronger electrophiles than carbamates



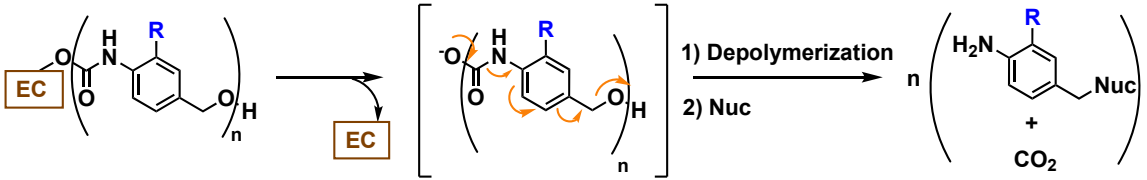
Thiols can be stronger nucleophiles (depending on conditions)

Eric Chen

Chen, McBride, Gillies, *Macromolecules*, **2012**, *45*, 7364-7374.

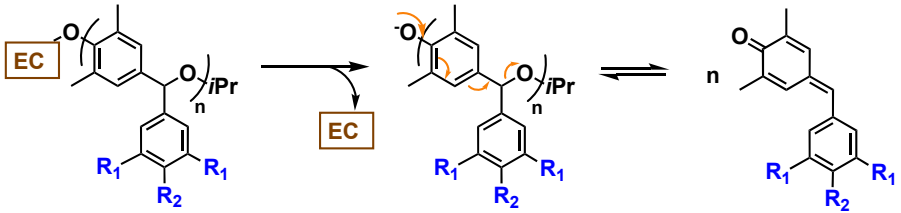
Other self-immolative backbones

Polycarbamates



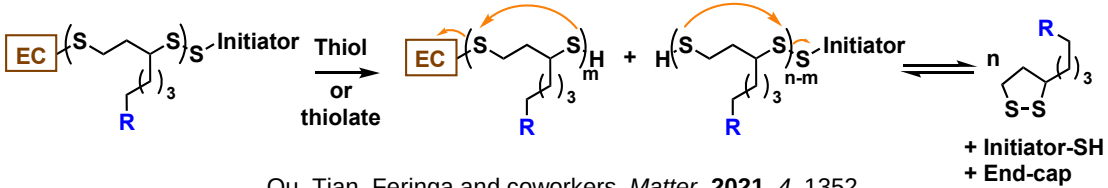
Shabat and coworkers *J. Am. Chem. Soc.* **2008**, 130, 5434.

Poly(benzyl ether)s



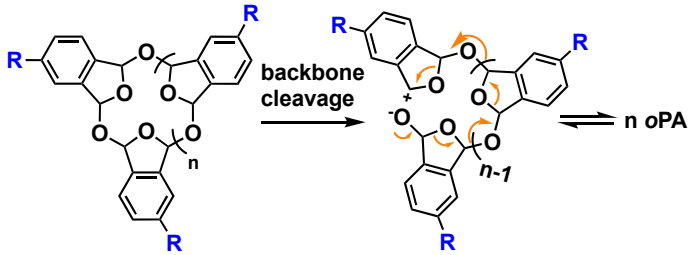
Phillips and coworkers, *Macromolecules*, **2013**, *46*, 5924.

Polydisulfides



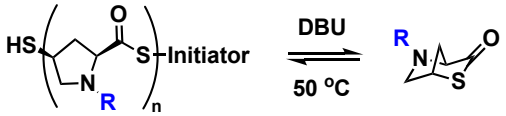
Qu, Tian, Feringa and coworkers, *Matter*, **2021**, *4*, 1352.

Polyphthalaldehydes



Moore and coworkers, *J. Am. Chem. Soc.* **2013**, *135*, 12755.

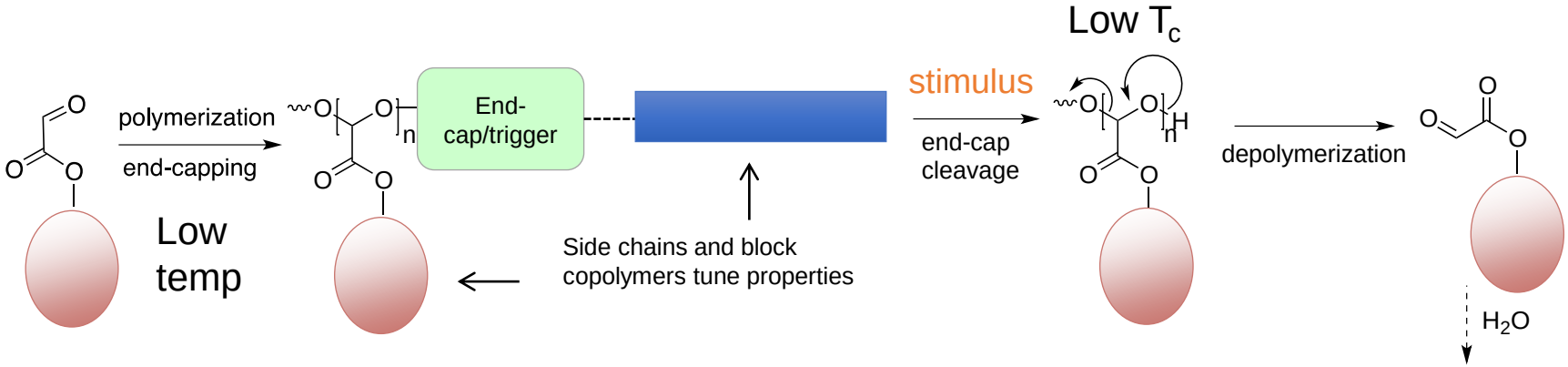
Polythioesters

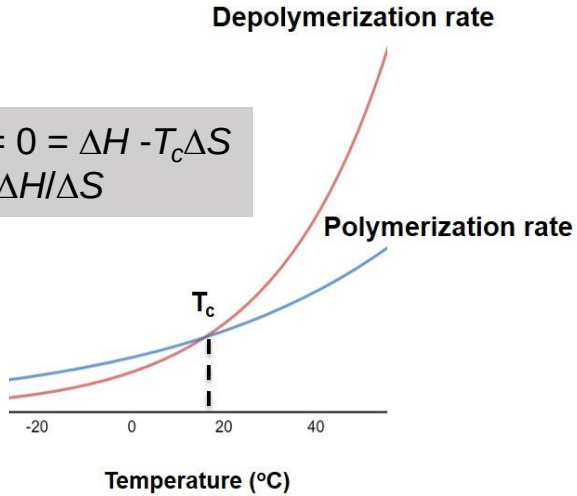


Lu and coworkers, *J. Am. Chem. Soc.* **2019**, *141*, 4928

Yardley, Rabiee Kenaree, Gillies, Perspective in *Macromolecules*, **2019**, *52*, 6342.
Deng, Gillies, Perspective in *JACS Au*, **2023**, *3*, 2436.

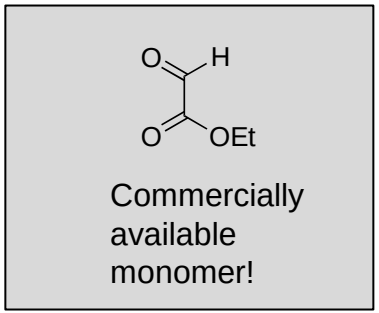
Polyglyoxylates



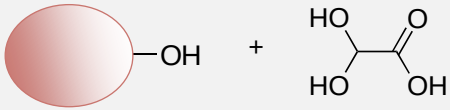


$\Delta G = 0 = \Delta H - T_c \Delta S$

$T_c = \Delta H / \Delta S$

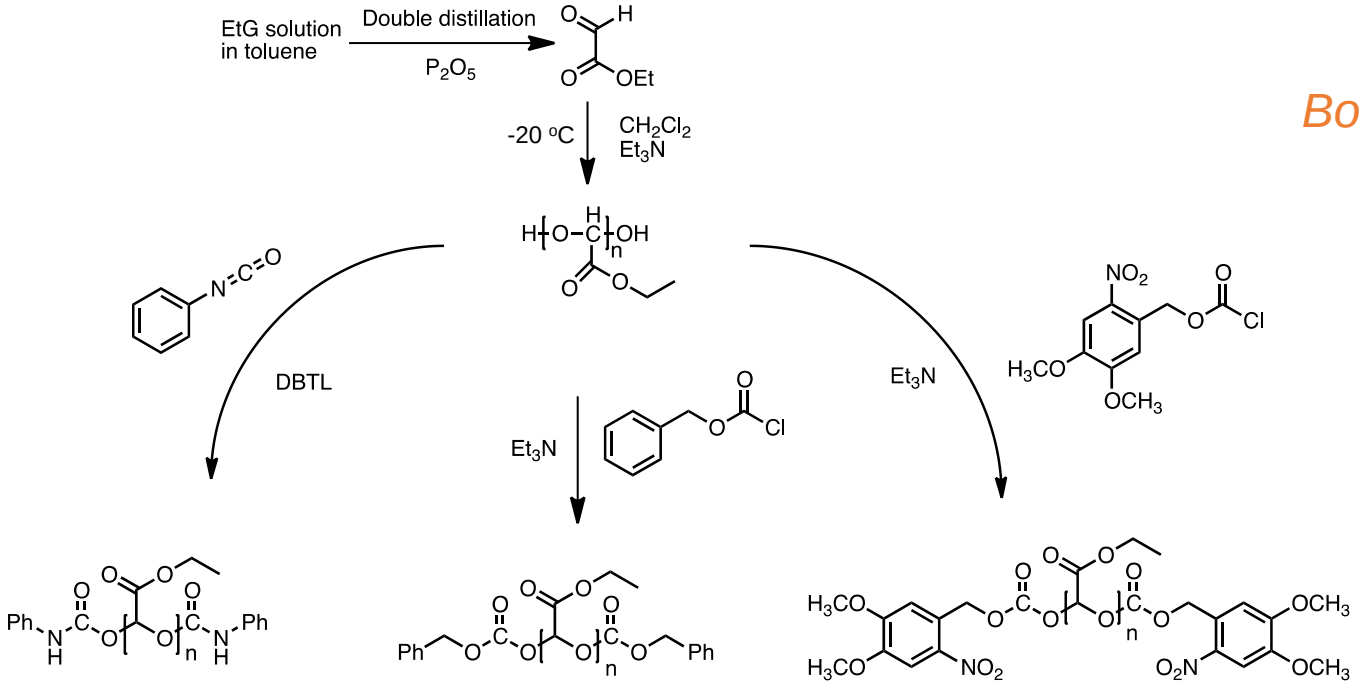


Commercially available monomer!



Non-toxic products ?

Synthesis of end-capped poly(ethyl glyoxylate)



Bo Fan

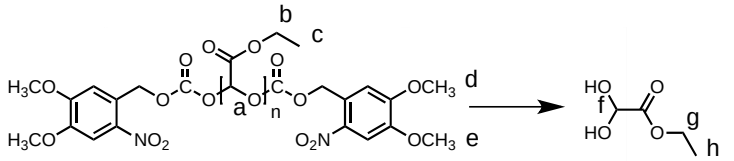
Carbamate
M_n = 27 kg/mol
$Đ$ = 2.5

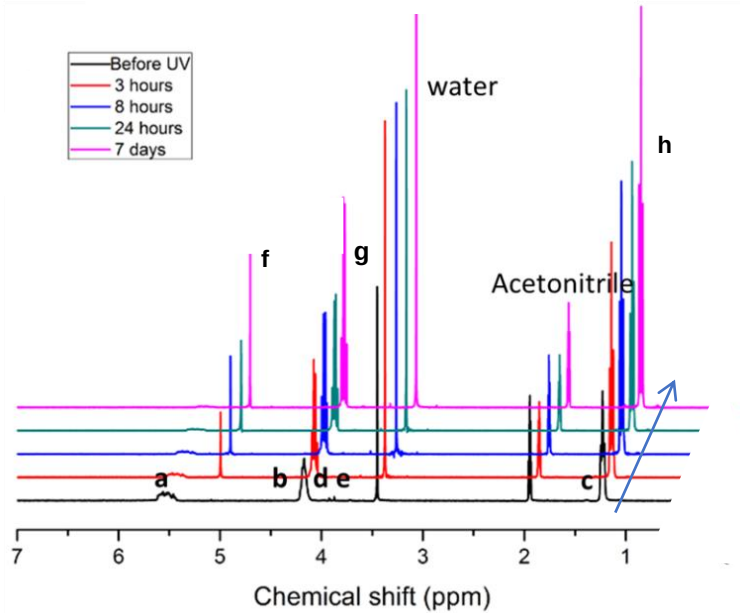
Carbonate, control
M_n = 31 kg/mol
$Đ$ = 1.9

Photosensitive
M_n = 53 kg/mol
$Đ$ = 1.7
T_g = -9 °C

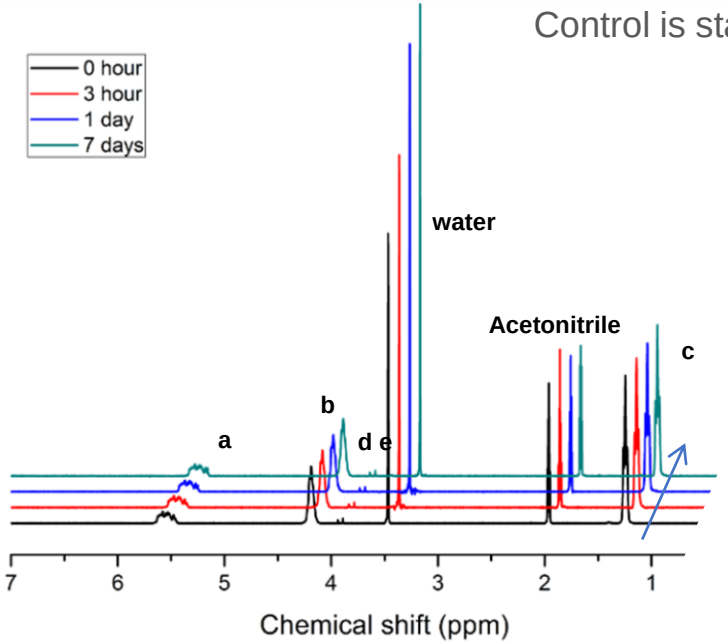
Fan, Trant, Wong, Gillies, *J. Am. Chem. Soc.* **2014**, *136*, 10116.

Light selectively induces depolymerization





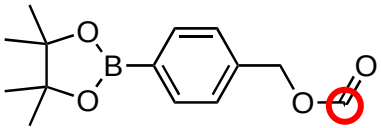
Control is stable



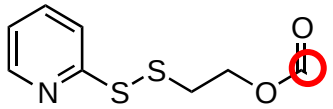
Fan, Trant, Wong, Gillies, *J. Am. Chem. Soc.* **2014**, *136*, 10116.

Diverse end-caps can be incorporated

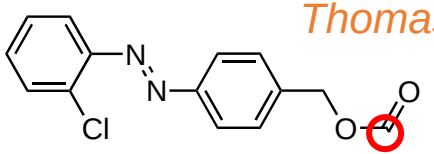
Bo Fan
Andrew Wong
John Trant
Thomas Gungor



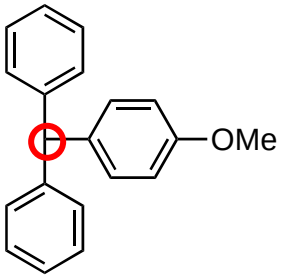
Hydrogen peroxide



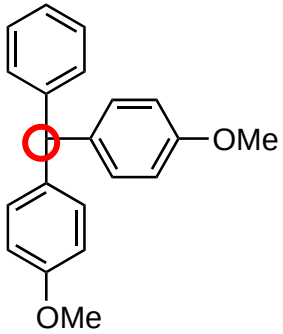
Reducing conditions



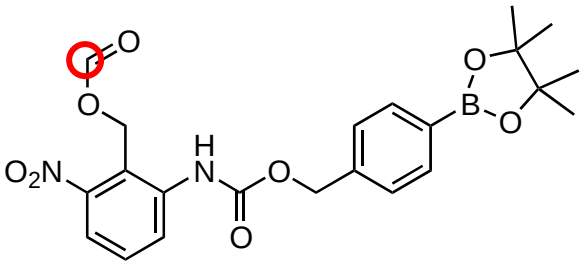
Reducing conditions,
enzymes in the colon



Acid



Milder acid

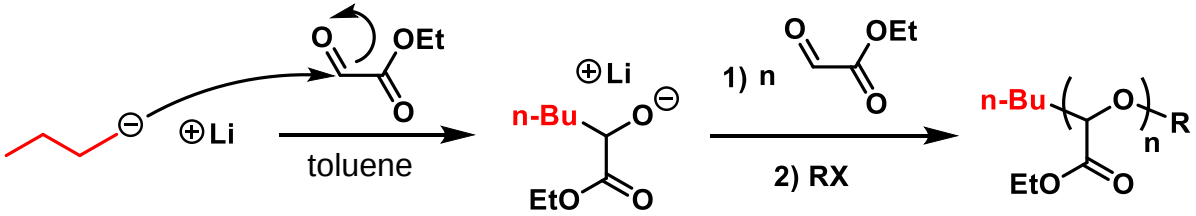


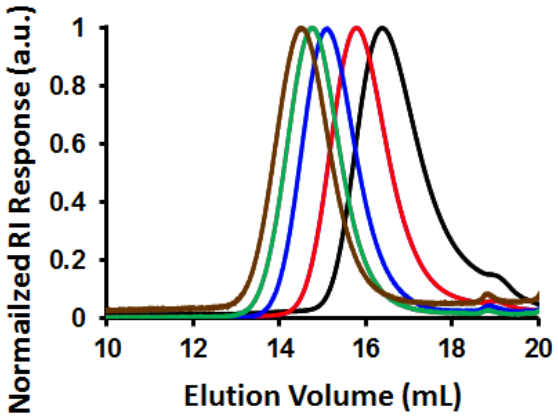
Multiple stimuli
-reduction, light, H_2O_2

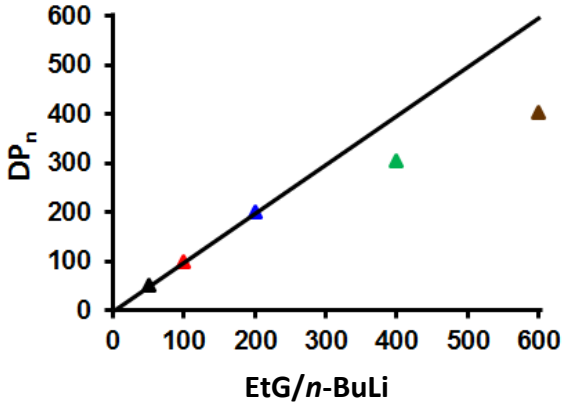
Fan, Trant, Gillies, *Macromolecules*, **2016**, *49*, 9309.
Wong, Gungor, Gillies, *ACS Macro Lett.* **2014**, *3*, 1191.
Fan, Trant, Hemery, Sandre, Gillies, *Chem. Commun.*, **2017**, *53*, 12068.

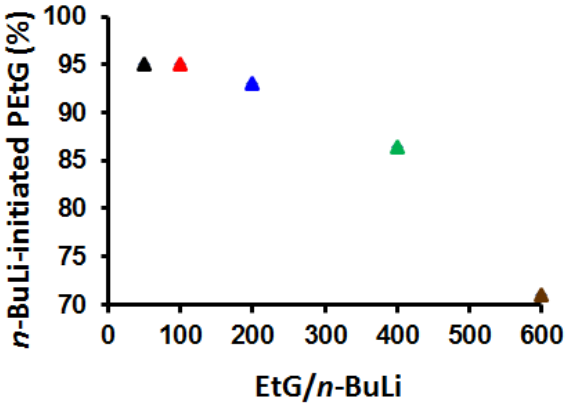
Controlling molar mass

Amir Rabiee Kenaree







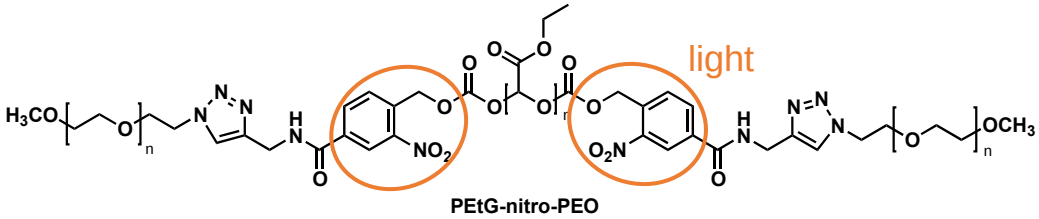


Rabiee Kenaree, Gillies, *Macromolecules*, **2018**, *51*, 5501-5510.

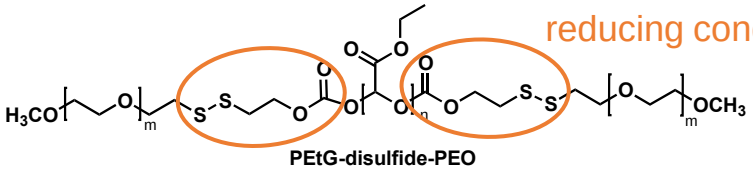
Can also initiate from an alcohol or thiol with NEt_3

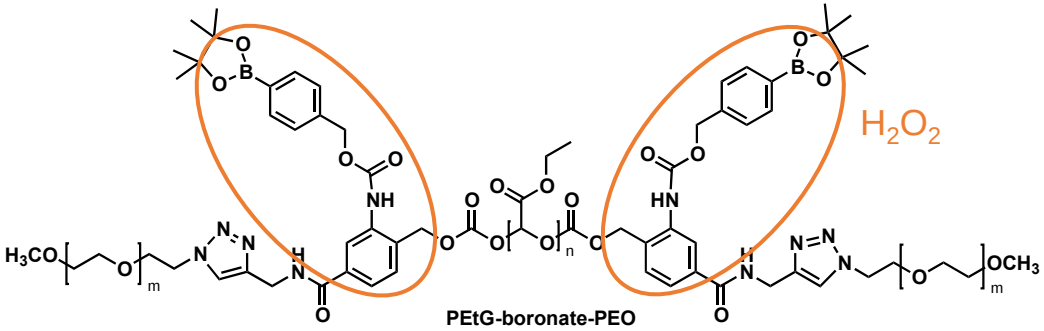
Hewitt, Grubbs, *ACS Macro Letters* **2021**, 10, 3, 370-374.

We can make block copolymers

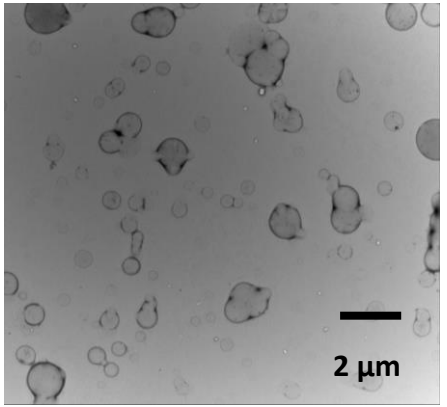


Bo Fan

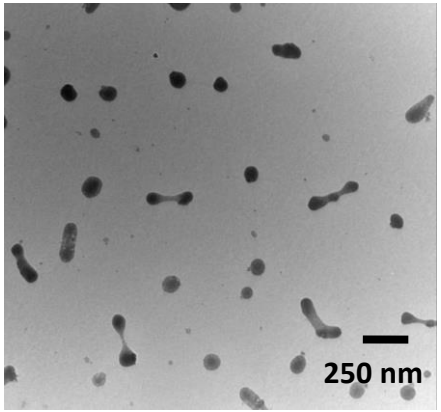




PEO750-PEtG64K-PEO750



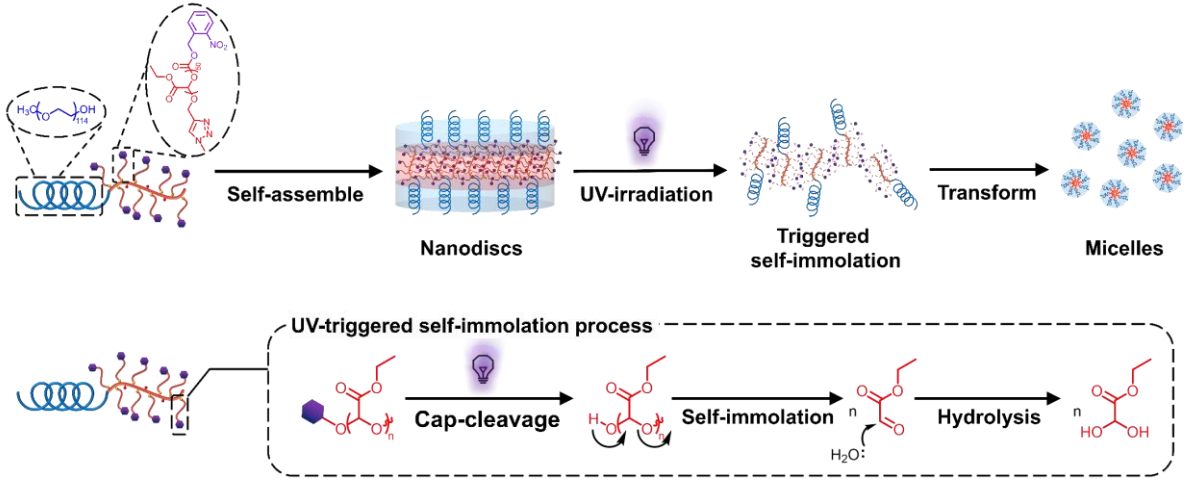
PEO5K-PEtG64K-PEO5K

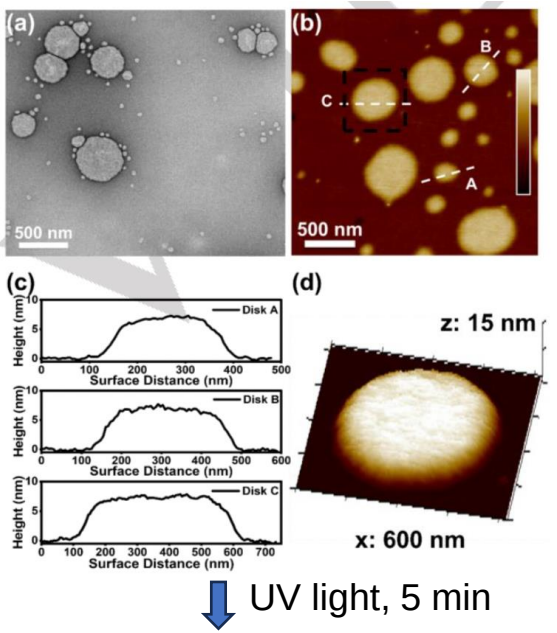


Fan, Trant, Hemery, Sandre, Gillies, *Chem. Commun.*, **2017**, *53*, 12068.

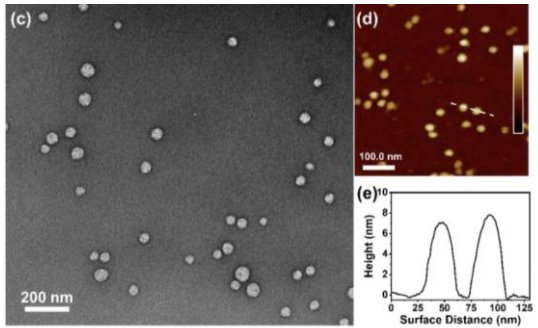
Fan, Gillies, *Mol. Pharmaceutics,* **2017**, *14*, 2548.

Shape transformations in polymer nanodiscs





UV light, 5 min

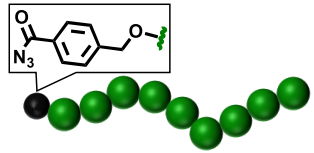


with Müllner group, Univ. Sydney
Haoxiang Zeng, Derrick Roberts

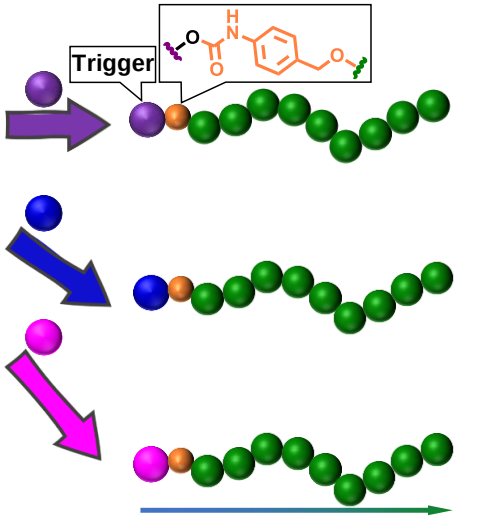
Advances in Polymer Synthesis and Characterisation session
Tasman 1, **Tuesday**, 11:30AM

Zeng, Liang, Roberts, Gillies, Müllner*, *Angew. Chem. Int. Ed.* **2024**, *63*, e202317063.

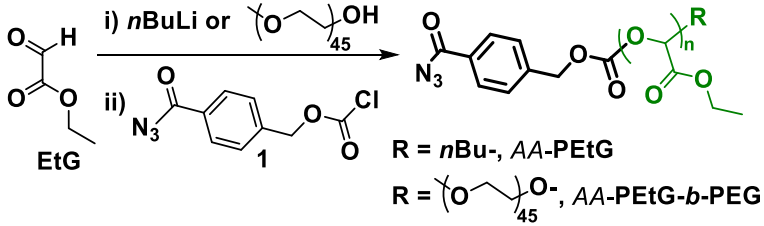
Introduction of the end-cap by aroyl azide “click” chemistry

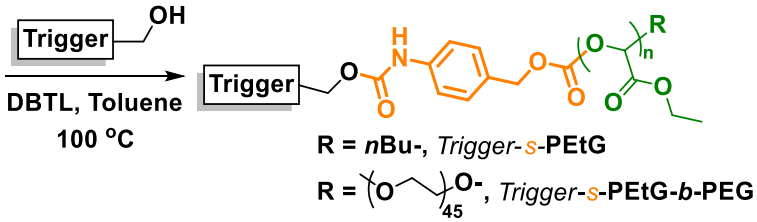


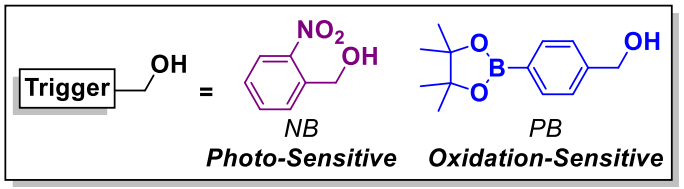
Aroyl azide-Terminated
(Co)Polymer Precursor



Triggerable PEtG



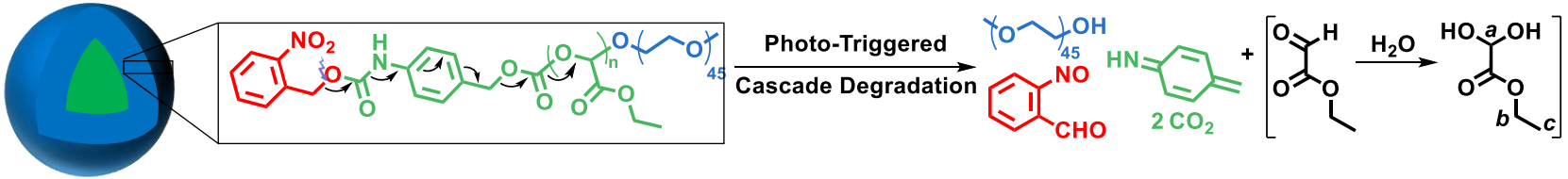


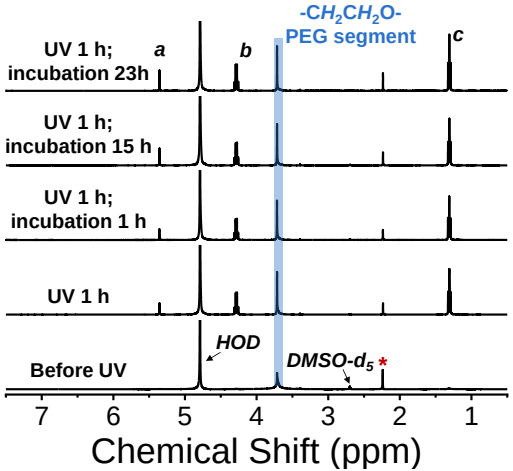


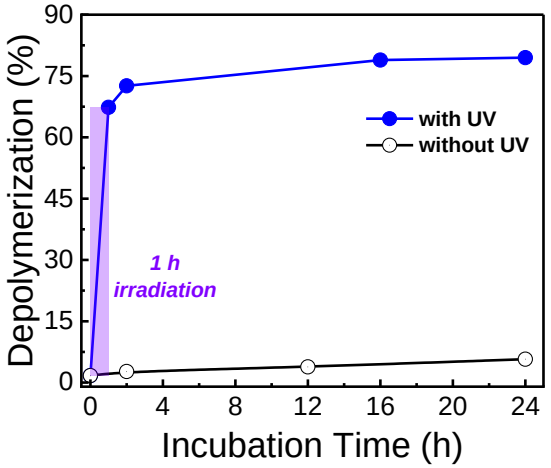
Zhengyu Deng

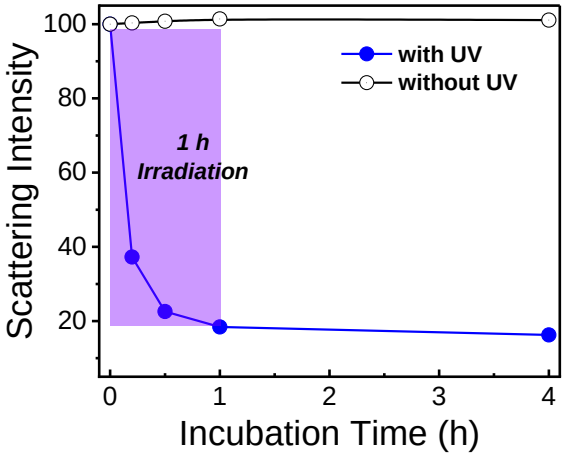
Deng, Liang, Gillies, *Angew. Chem. Int. Ed.* **2024**, *63*, e202317063.

End-cap triggering translates to the PEtG backbone



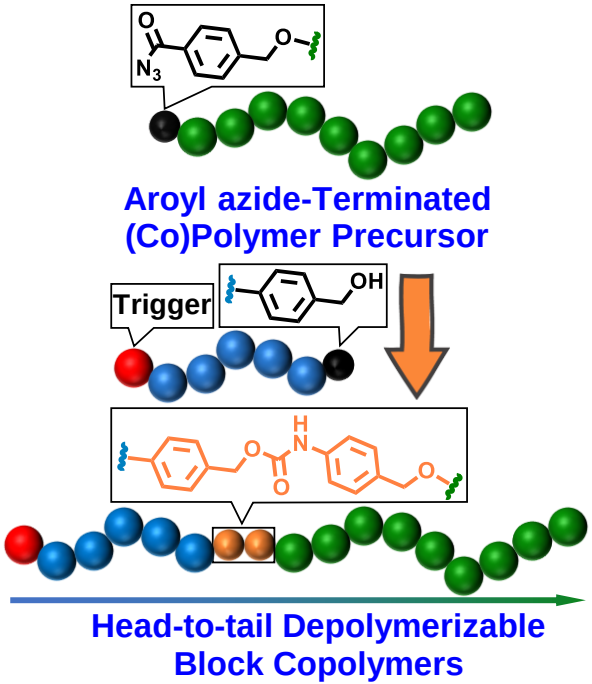


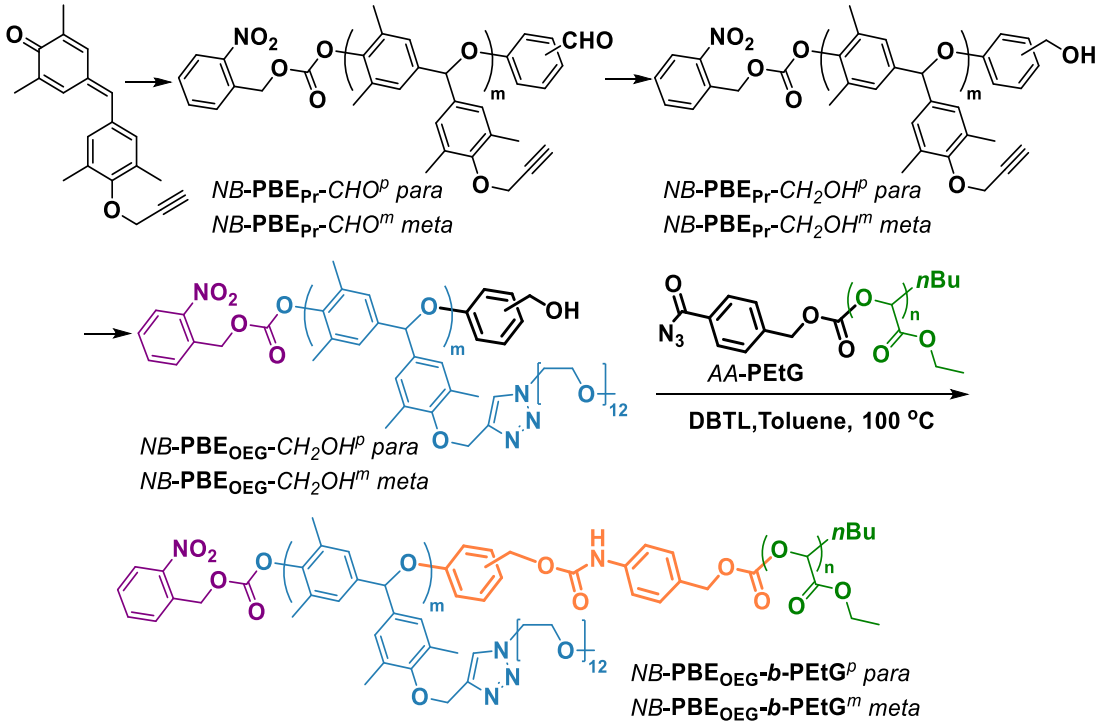




Deng, Liang, Gillies, *Angew. Chem. Int. Ed.* **2024**, *63*, e202317063.

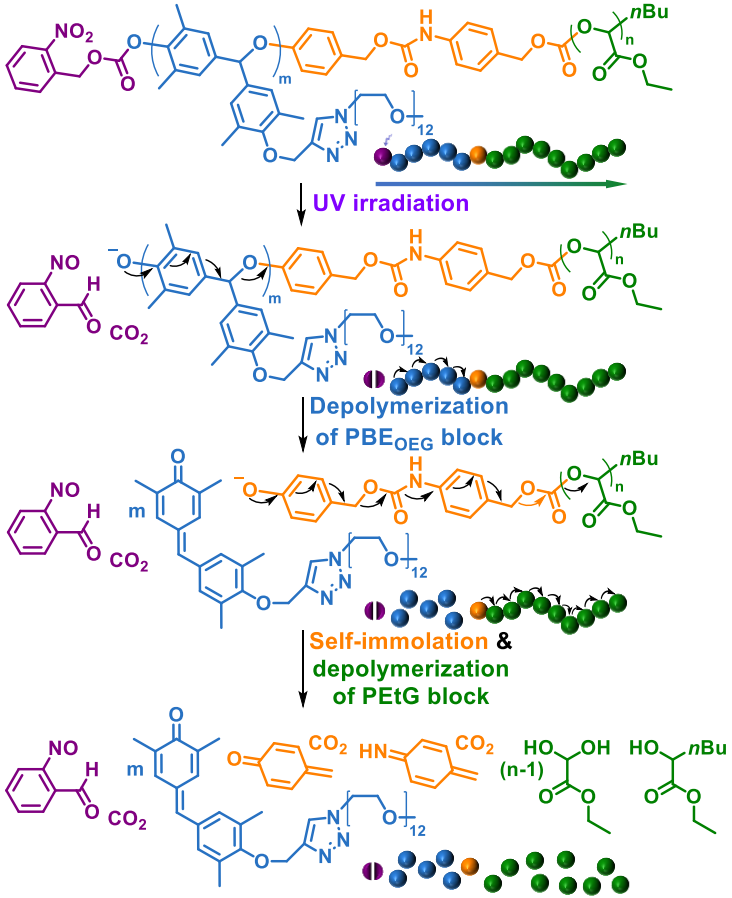
End-to-end depolymerizable block copolymers

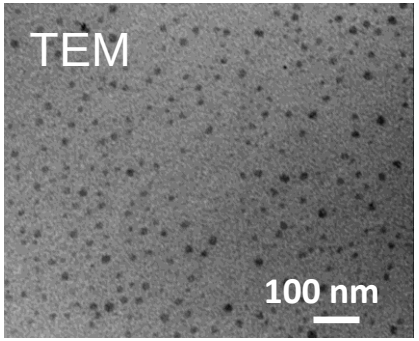


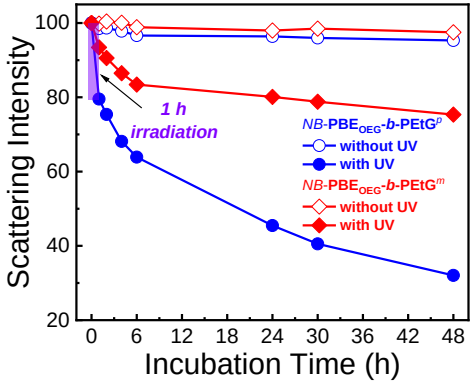


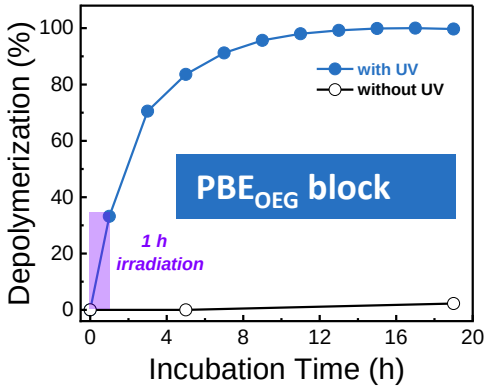
Deng, Liang, Gillies, *Angew. Chem. Int. Ed.* **2024**, *63*, e202317063.

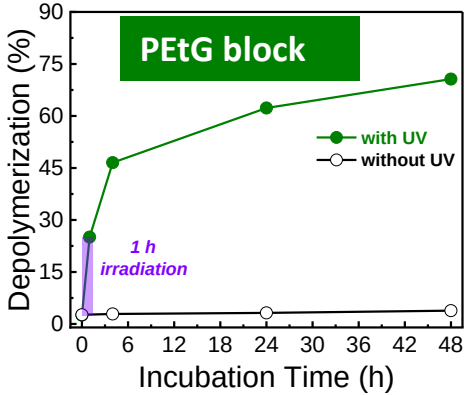
End-to-end depolymerizable block copolymers



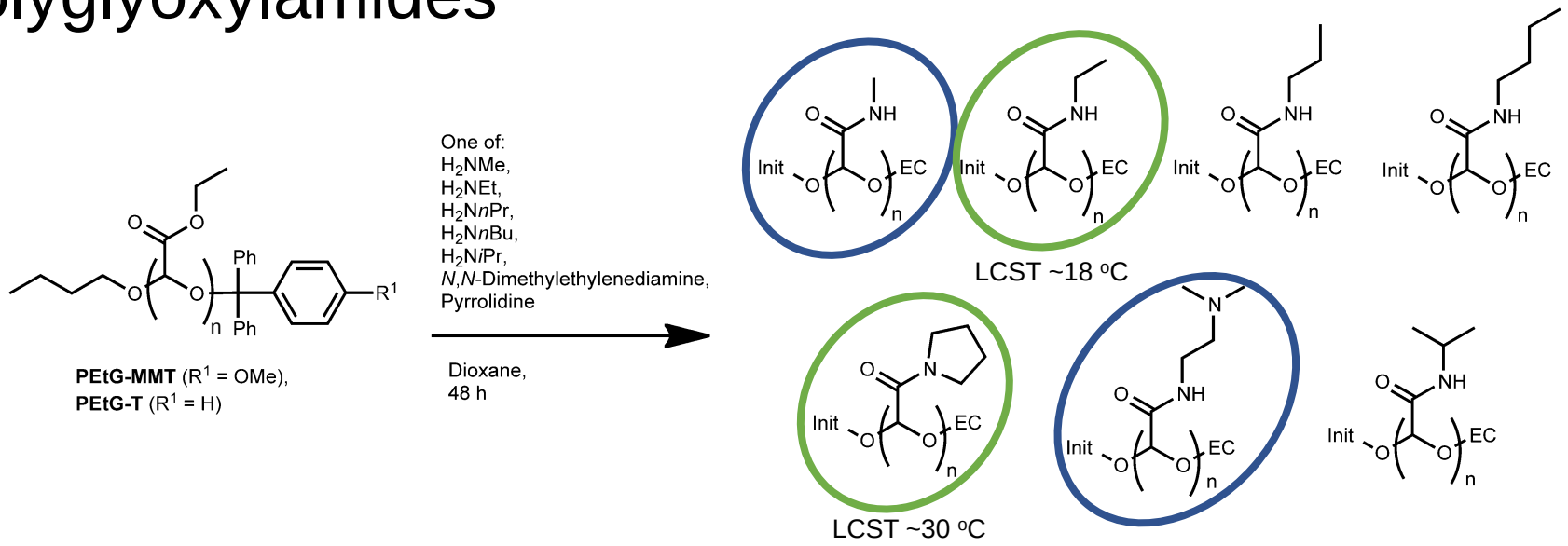








Polyglyoxylamides

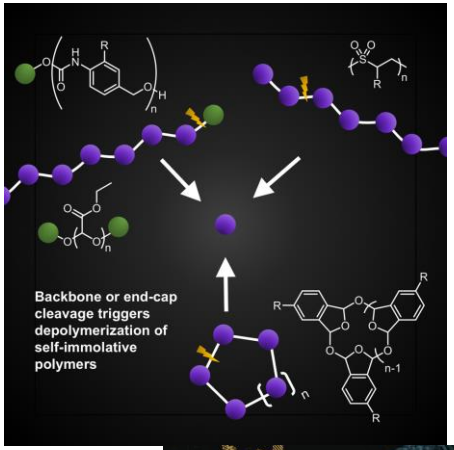


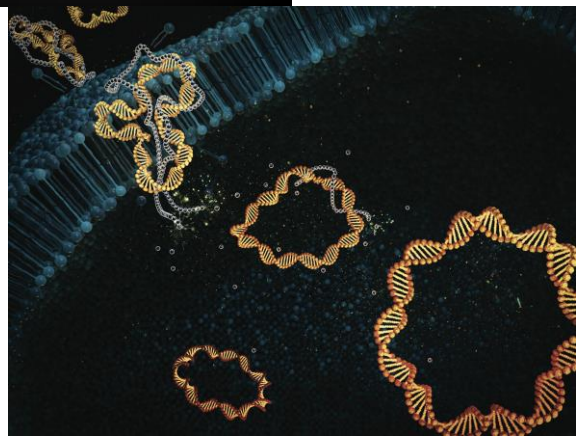
Quinton Sirianni
Amir Rabiee Kenaree

T_g ranges from 40 – 90 °C
Solubility varies
Can be cationic

Sirianni, Rabiee Kenaree, Gillies, *Macromolecules*, **2019**, *52*, 262–270.

Outline



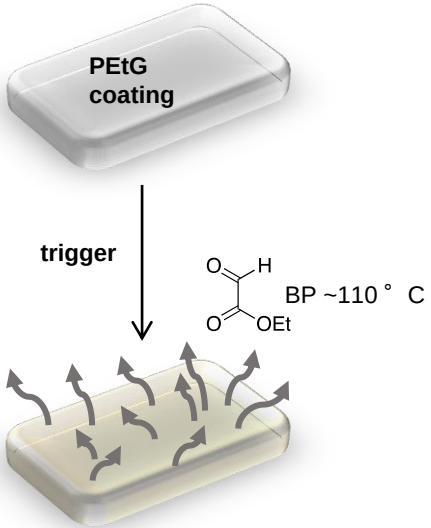


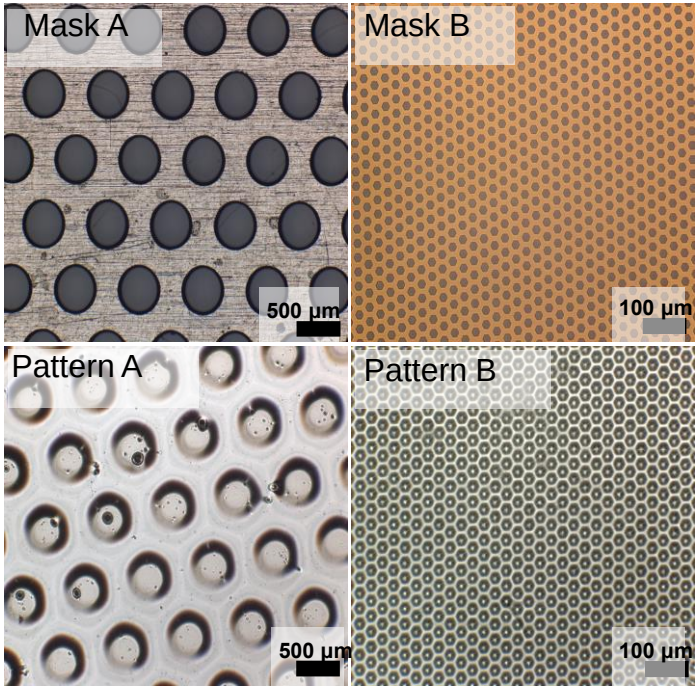
Chemistry of depolymerizable polymer backbones

Applications

- Micropatterning
- Imaging contrast agents
- Hydrogels

Micropatterning without chemical steps





Bo Fan
Prof. Francois Lagugne-Labarthet

Fan, Trant, Yardley, Pickering, Lagugné-Labarthet, Gillies, E. R. *Macromolecules,* **2016**, *49,* 7196-7203.

Contrast agents for vascular X-ray micro-CT

with Drangova group, Western

- Widely used to study vascular disease and response to therapy in small animals
- Lack suitable vascular contrast agents

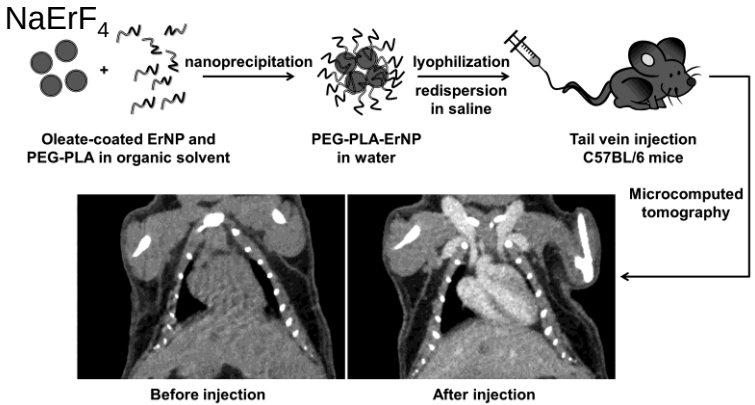
Needs

- Blood circulation time ~1 h
- Lanthanide (Er, Gd) ideal due to their k-edges
  - allow for dual energy CT
- High concentrations (100 mg/mL of metal)

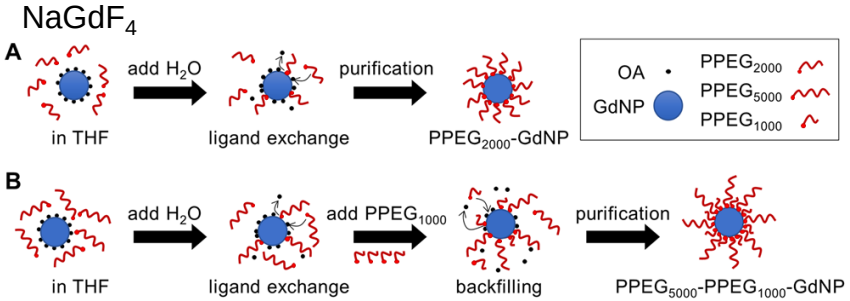
Challenges

- Toxicity (dose is > 0.5 g/kg)!
- Stability and viscosity at high concentration

Towards vascular contrast agents for micro-CT



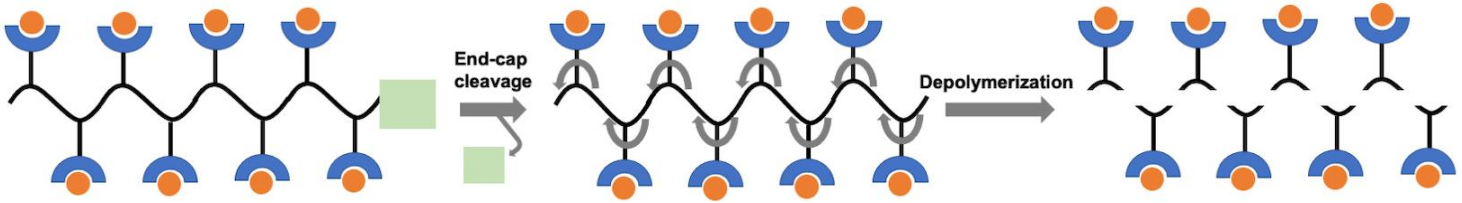
Cruje, C.; Dunmore-Buyze, J.; MacDonald, J. P.; Holdsworth, D. W.; Drangova, M.; Gillies, E. R. *Biomacromolecules* **2018**, *19*, 896.



Cruje, C.; Dunmore-Buyze, P. J.; Grolman, E.; Holdsworth, D. W.; Gillies, E. R. Drangova, M. *Sci. Rep*. **2021**, *11*, 16603

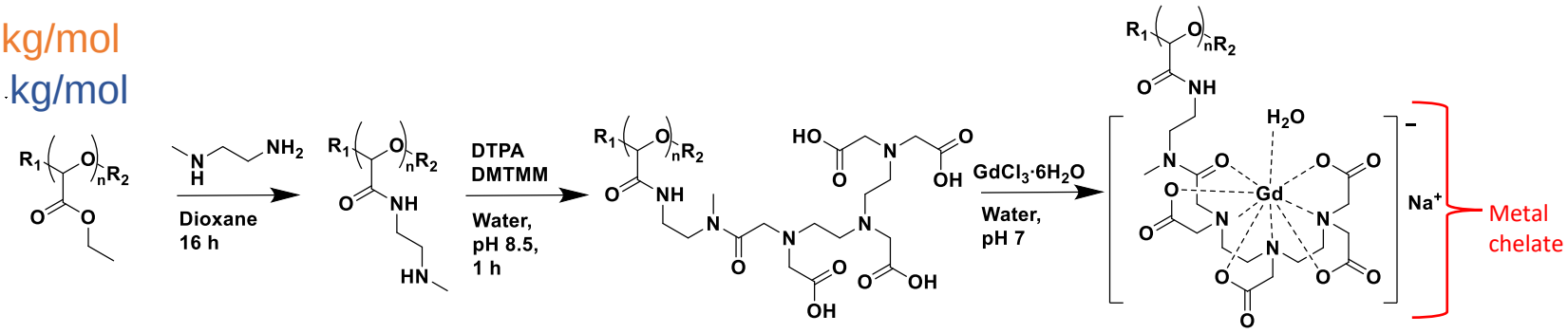
Good contrast and circulation times, but long term toxicity

Can self-immolative agents help by promoting excretion after imaging?

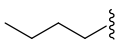
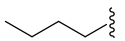
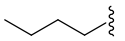
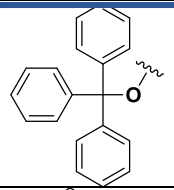
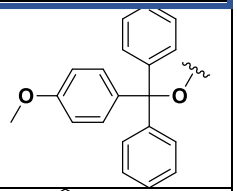
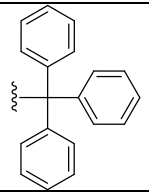
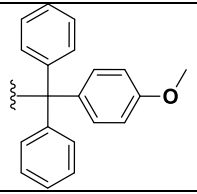
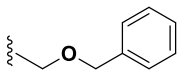
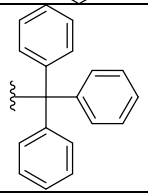
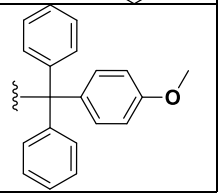


Synthesis of a self-immolative polymer chelate

L = ~25 kg/mol
H = ~45 kg/mol



Poly(ethyl glyoxylate) | Poly(glyoxylamide) | PGAm-DTPA | PGAm-DTPA-Gd

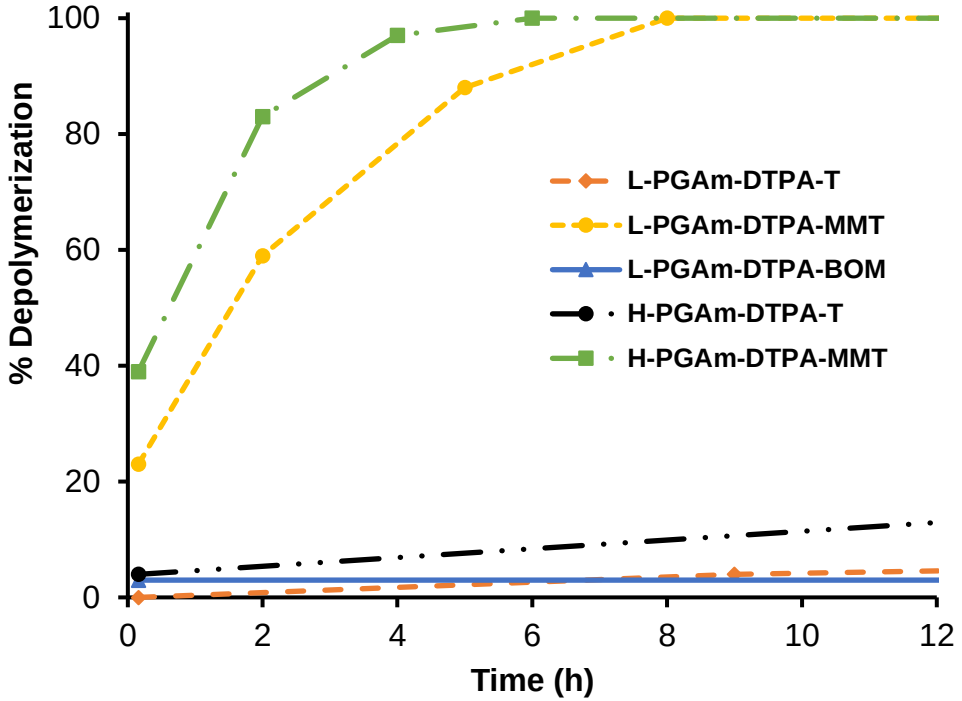
Polymer	L-PGAm-DTPA-T	L-PGAm-DTPA-MMT	L-PGAm-DTPA-BOM	H-PGAm-DTPA-T	H-PGAm-DTPA-MMT
R_1					
R_2					

Eric Grolman
Quinton Sirianni

Grolman, Sirianni, Dumore-Buyze, Cruje, Drangova, Gillies, *Acta Biomater.* **2023**, *169*, 530.

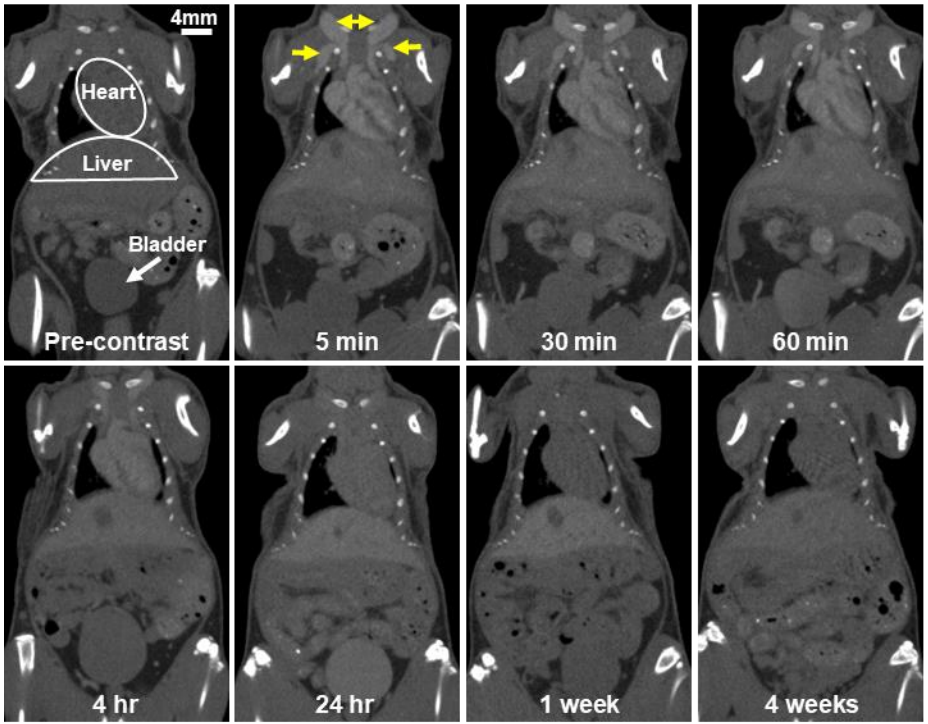
Depolymerization of the polymeric chelates

Polymer	Time to Fully Degrade
L-PGAm-DTPA-Gd-T	~1 month
L-PGAM-DTPA-Gd-MMT	~8 h
L-PGAm-DTPA-Gd-BOM	N/A
H-PGAm-DTPA-Gd-T	~14 days
H-PGAm-DTPA-Gd-MMT	~4 h

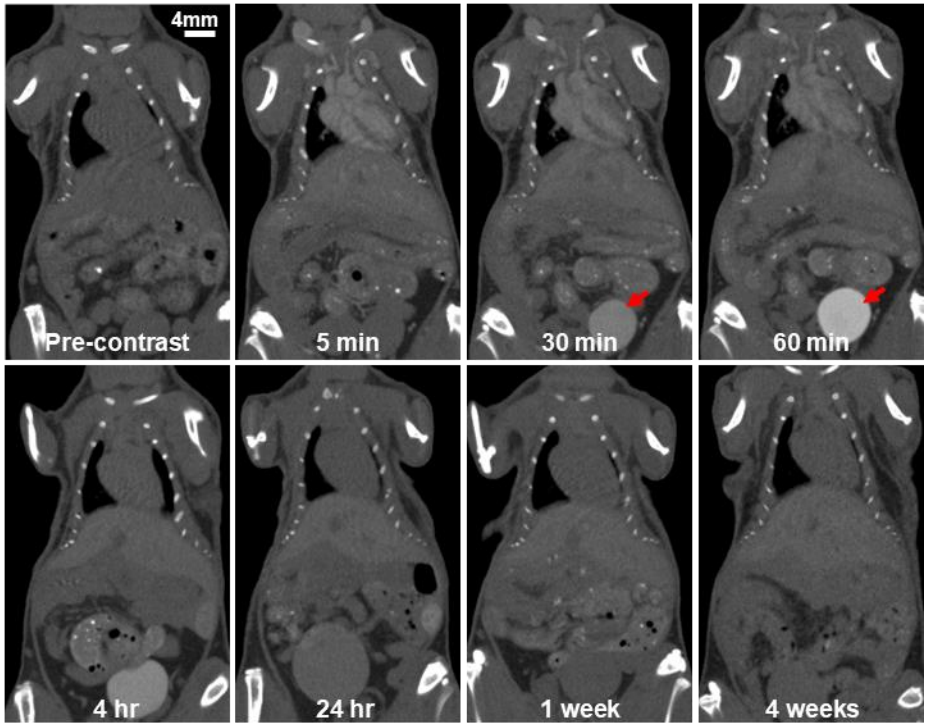


- Preliminary studies showed low molar mass polymers excreted too rapidly
- Focus on high molar mass polymers (T as stable control, MMT as degradable)

In vivo imaging after tail vein injection in mice



Trityl - degrades slowly, not observed in bladder

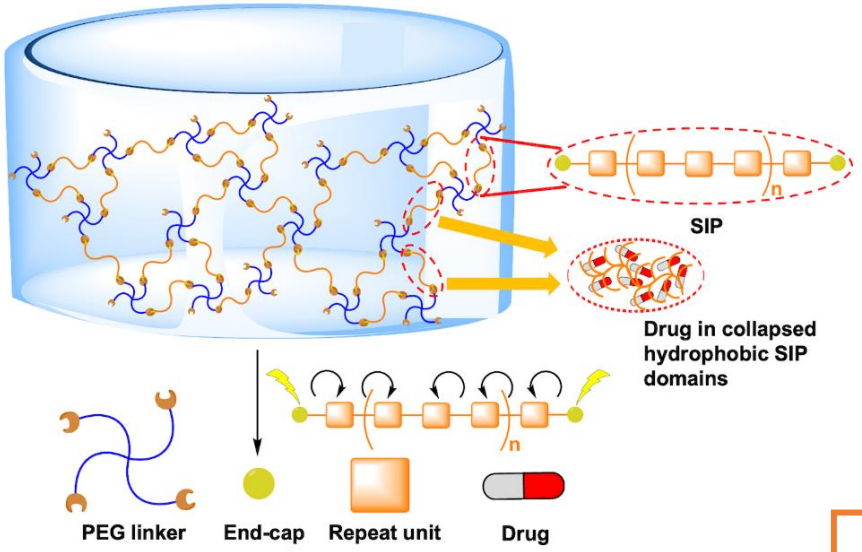


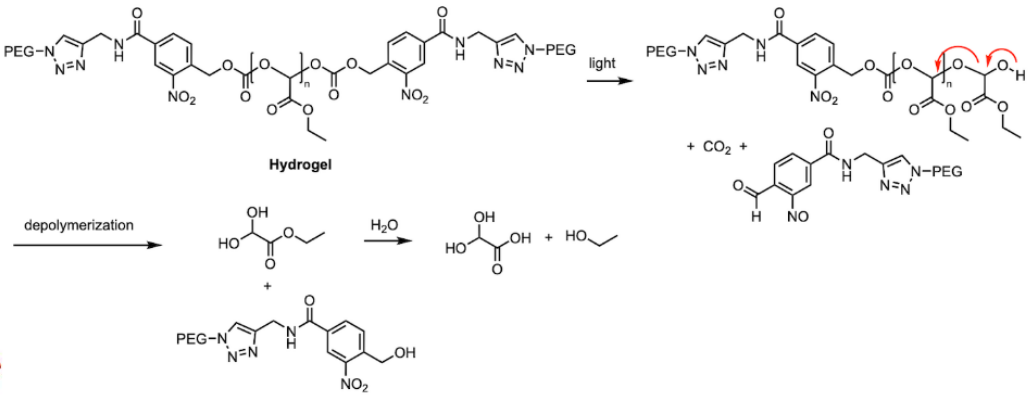
MMT – degrades rapidly, observed in bladder

Grolman, Sirianni, Dumore-Buyze, Cruje, Drangova, Gillies, *Acta Biomater.* **2023**, *169*, 530.

Self-immolative hydrogels

Release drugs
Release encapsulated cells
Signals for sensor development

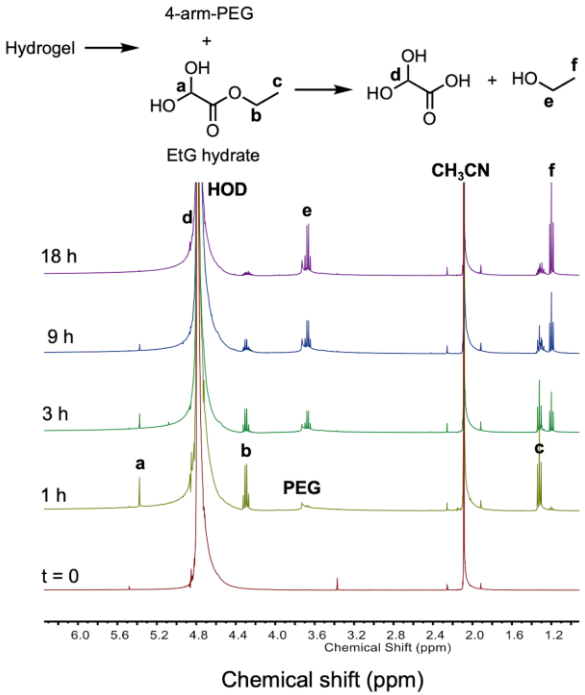


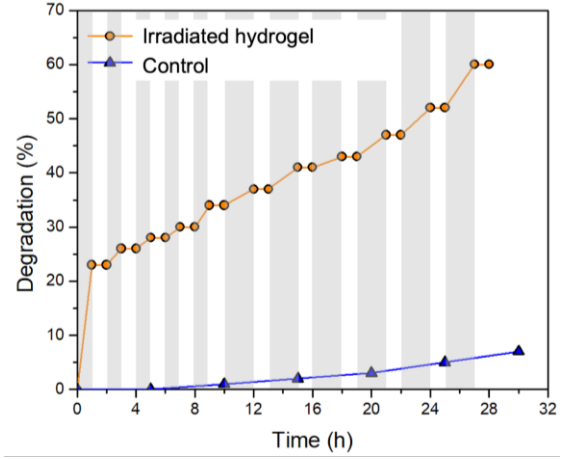


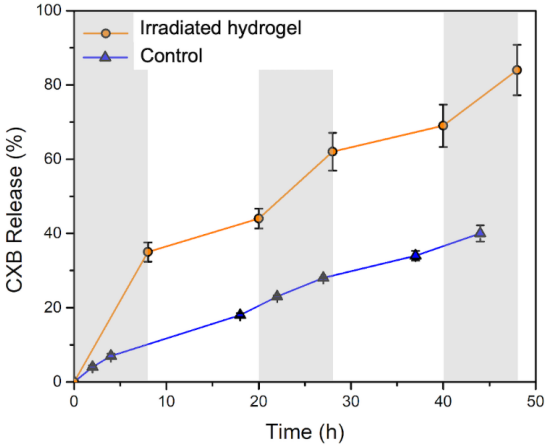
4-arm-PEG-azide Concentration (% w/v)	M_n of PEG-azide (kg/mol)	M_n of PEtG-alkyne (kg/mol)	Gel Content (%)	EWC (%)
10	2	1.2	91 ± 6	90 ± 3
10	2	5.4	83 ± 6	84 ± 3
10	5	5.4	85 ± 4	86 ± 3
15	2	1.2	90 ± 6	89 ± 3
15	2	5.4	81 ± 7	83 ± 3
15	5	5.4	81 ± 13	83 ± 6

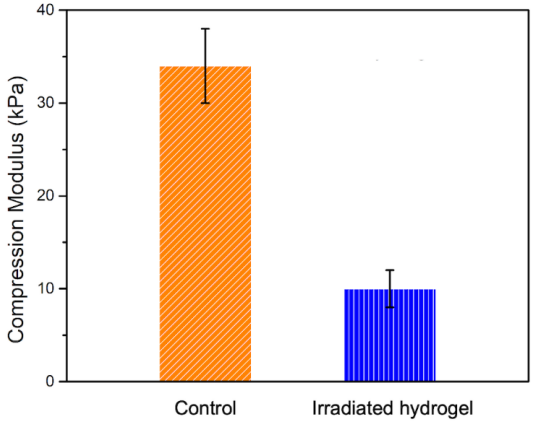
Jue Gong

On-off degradation and celecoxib (CXB) release



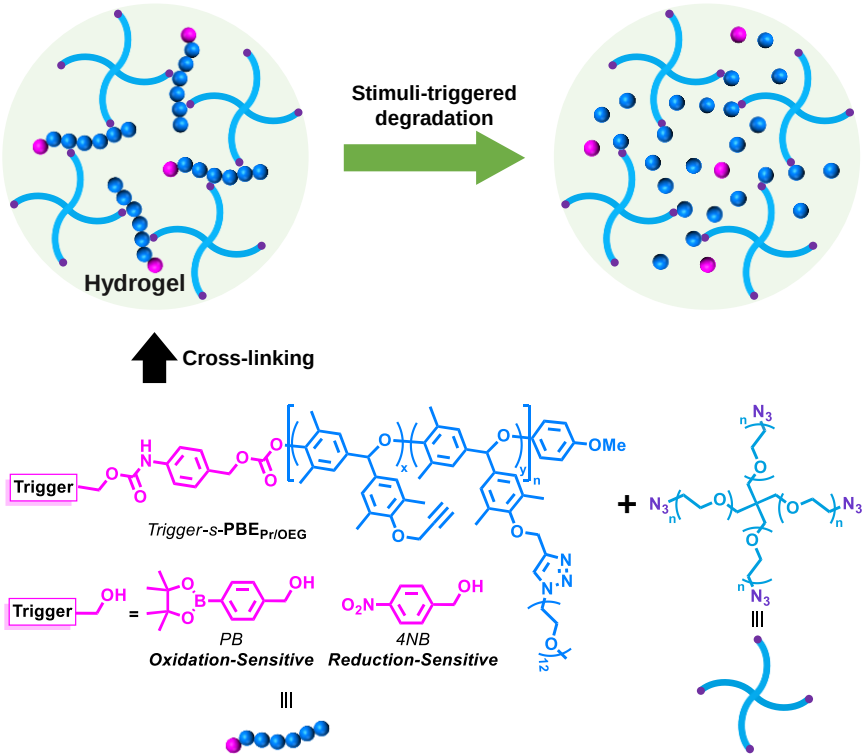




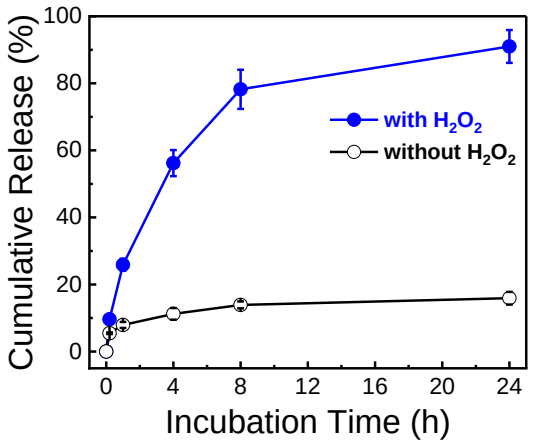


Gong, Borecki, Gillies, *Biomacromolecules*, **2023**, *24*, 3629.

Hydrogels using the aroyl azide end-capping approach



Release of doxorubicin (oxidation-sensitive hydrogel)



Zhengyu Deng

Deng, Liang, Gillies, *Angew. Chem. Int. Ed.* **2024**, *63*, e202317063.

Summary

- Self-immolative polymers with diverse end-caps can be synthesized
- Different pendent groups impart different properties and functions
- Block copolymers can be prepared by different approaches
- Depolymerization can be used in diverse applications

Challenges/future work

- New backbones, end-caps
- Mechanical and other physical properties
- Cost considerations for different applications
- Further biological studies needed

Acknowledgements

Graduate students
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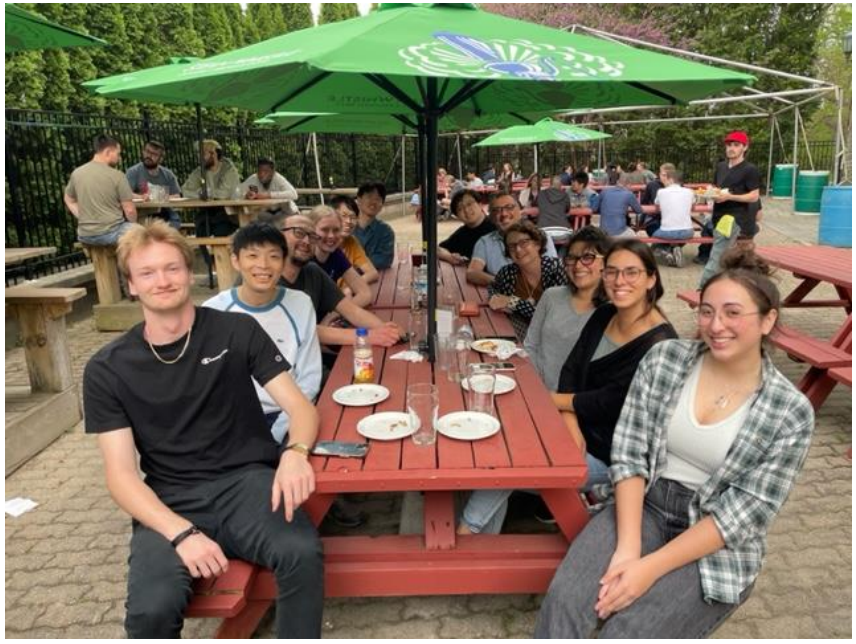
Saman Nadeem

Undergrads
Tristyn Snow
Tayte Bowron
Pierre-Christof Ascheri

Postdocs
Zhengyu Deng
Burak Tavsanli

Research Assistant
Aneta Borecki

Collaborators
Maria Drangova
Georgina Such
Derrick Roberts
Marcus Müllner
Frank Breitling
Daniela Wilson



Funding

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Ontario MINISTRY OF RESEARCH & INNOVATION
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Positions available!