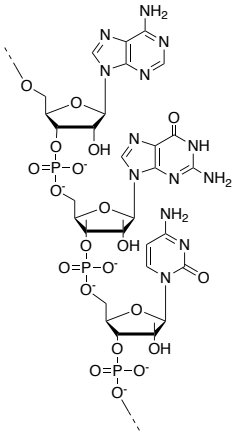
ARNA

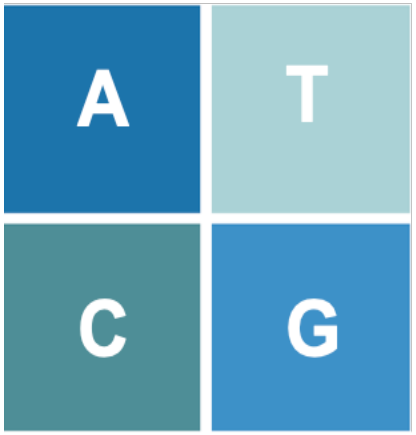
January 22-27, 2023
Les Houches (Haute-Savoie, France)

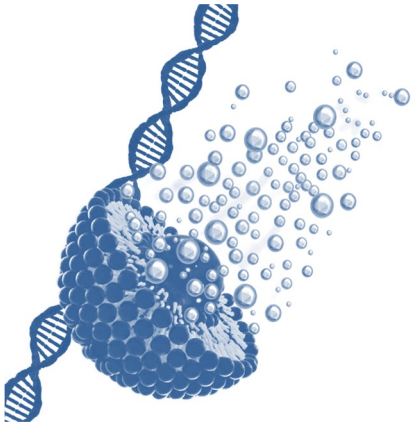
SNOSCELLS

NUCLEIC ACID BASED BIOCONJUGATES

FOR BIOMEDICAL APPLICATIONS







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ChemBioPharm

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université de BORDEAUX

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NUCLEIC ACID BASED BIOCONJUGATES

FOR BIOMEDICAL APPLICATIONS

- INTRODUCTION
  - NUCLEIC ACID
  - BIOMATERIALS
  - SUPRAMOLECULAR PROPERTIES
- I/ NUCLEOLIPIDS (PART A)
  - SYNTHESIS
  - BIOMATERIALS
  - DRUG DELIVERY
  - DECONTAMINATION
- II/ GLYCOSYL-NUCLEOLIPIDS
  - SYNTHESIS
  - BIOMATERIALS
  - DRUG DELIVERY
- III/ LIPID OLIGONUCLEOTIDE CONJUGATES
- CONCLUSION

PART A

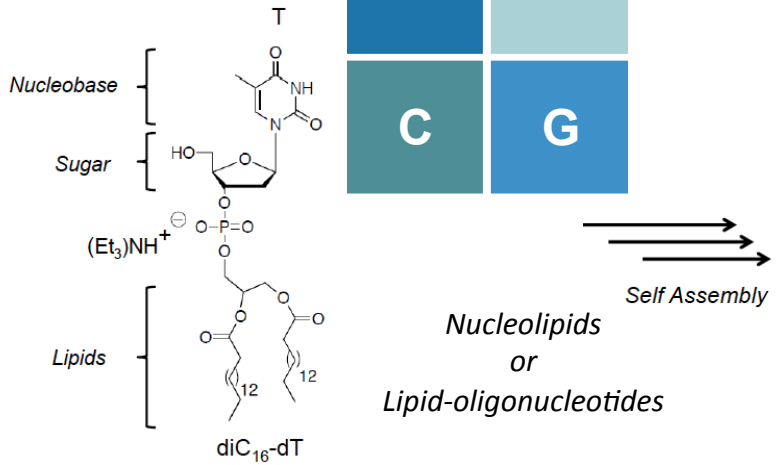
PART B

http://chembiopharm.fr

Abstract Part A

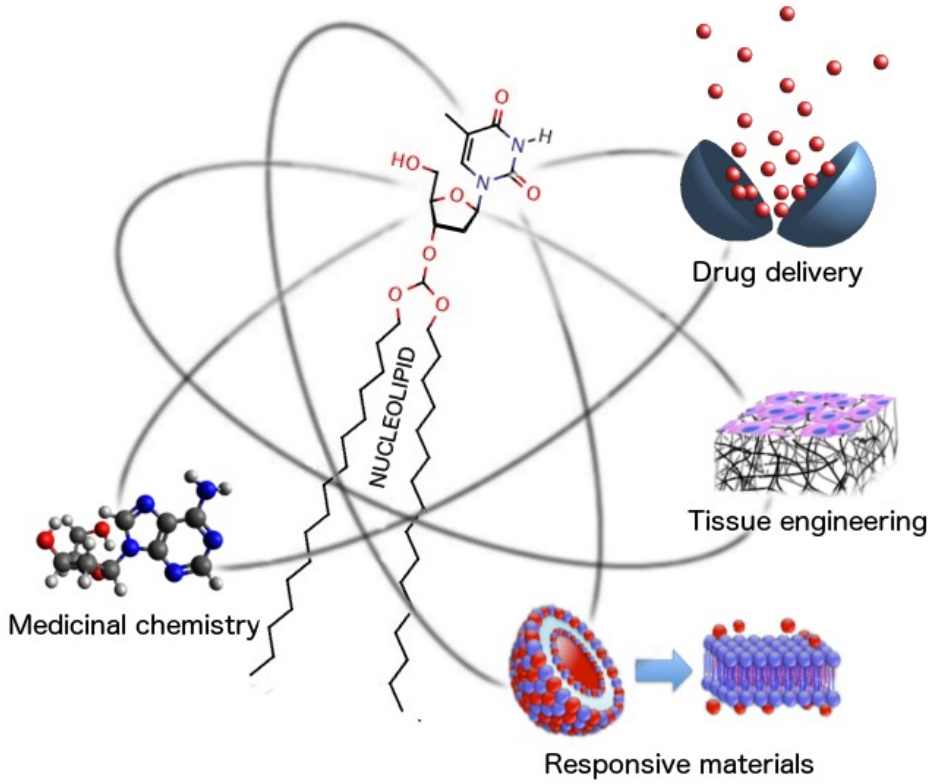
Nucleotide lipids at the biological interface

- ✓ Hydrogen bonding
- ✓ π–π stacking
- ✓ Van der Waals forces
- ✓ Hydrophobic effect



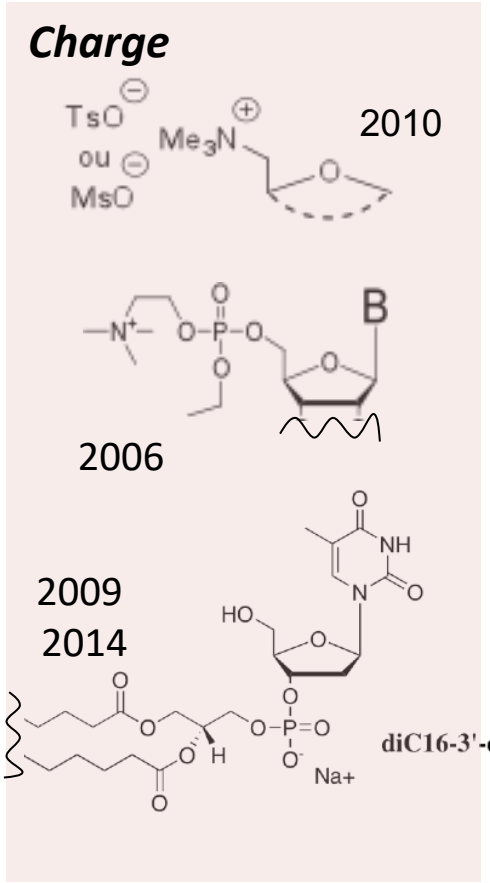
Self Assembly

Nucleolipids
or
Lipid-oligonucleotides



CHEMBIOPHARM

Part B Nucleic acid conjugates at the biological interface



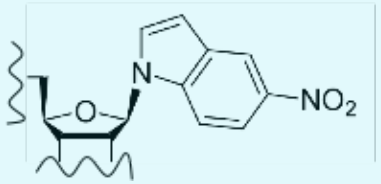
Oligonucleotides
(2008, 2010, 2012, 2013, 2014…)

Amino acids (2013)

LNA (2013)

Sugars
(2005, 2009, 2010, 2012, 2013, 2014…)

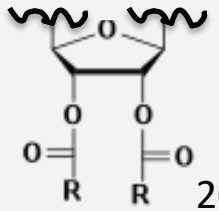
Natural and universal bases



A,T,C, G,
Nitro indole, imidazole, pyrrole
a, b anomers

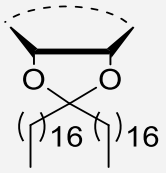
2009/2010

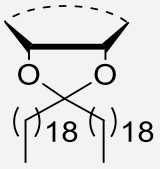
Acyclic (2011)



2002

Hydrophobic moieties





2008

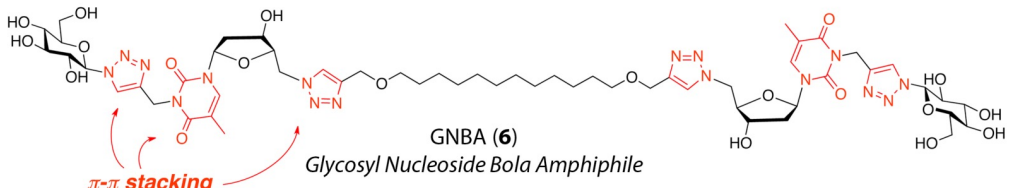
2010, 2013

STRATEGY

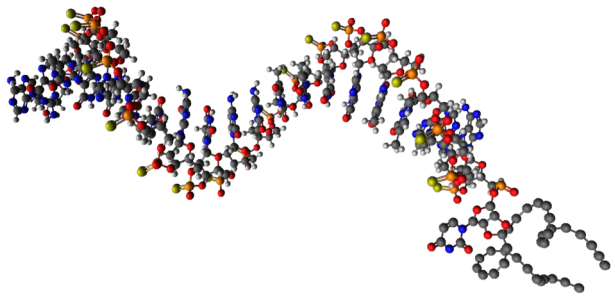
- Explore new advanced materials
- Open new therapeutic landscapes

Part B Nucleic acid conjugates at the biological interface

- **Advanced Materials =>** Modulation of the rheological properties?



- **New therapeutics =>** Insert nucleic acid code in supramolecular systems?



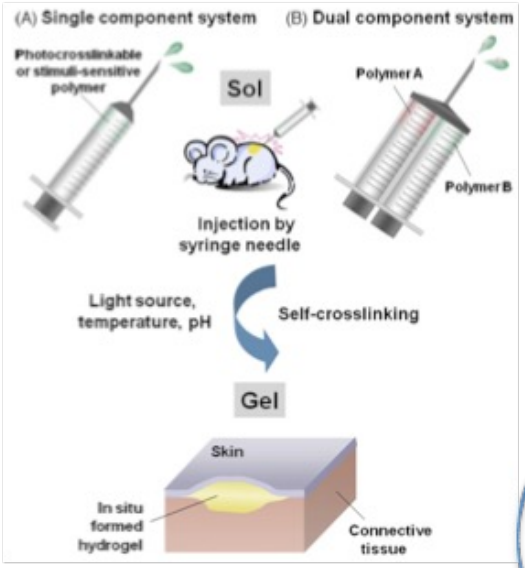
J. Baillet, V. Desvergnes, A. Hamoud, L.Latxague, and P. Barthélémy ***Adv. Mater.* 2018**, 1705078

Smart gels for biomedical applications

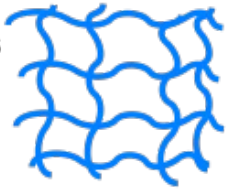
Drug delivery / Stem cell delivery / Tissue engineering / Regenerative medicine / Biocompatible interfaces etc

Background

Injectable scaffold



Hydrogels:
3D network of polymer chains

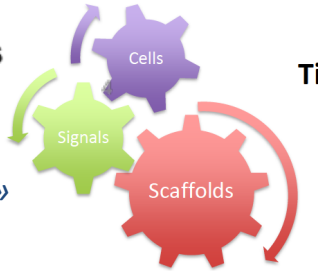


Requested Properties:
- Biocompatibility
- Injectability
- Nontoxic
- Easy to handle,
- Biocompatible rheology (thixotropic behavior)

Polymers drawbacks
- Biocompatibility
- Poor degradability
- Complex and difficult to control
- Immunogenicity…

Low Molecular Weight Gelators

J. H. Wen, *et al.*, ***NATURE MATERIALS (2014)***
« Interplay of matrix stiffness and protein tethering in stem cell differentiation »



Tissue Engineering triad

Gel scaffold plays a major role in the stem cell fate

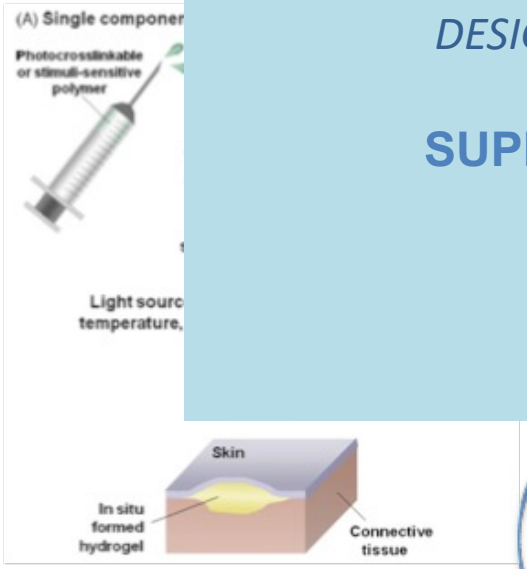
Smart gels for biomedical applications

Drug delivery / Stem cell delivery / Tissue engineering /
Regenerative medicine / Biocompatible interfaces etc

Background

Injectable scaffold

Hydrogels:
3D network of polymer chains



DESIGN OF SOFT BIOINSPIRED MATERIALS

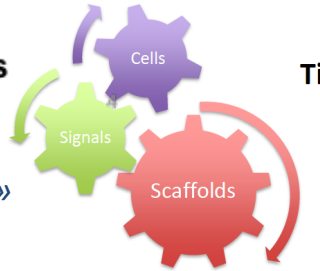
SUPRAMOLECULAR GELS (LMWG);

AN ALTERNATIVE TO POLYMERS?

- Biocompatibility
- Poor degradability
- Complex and difficult to control
- Immunogenicity…

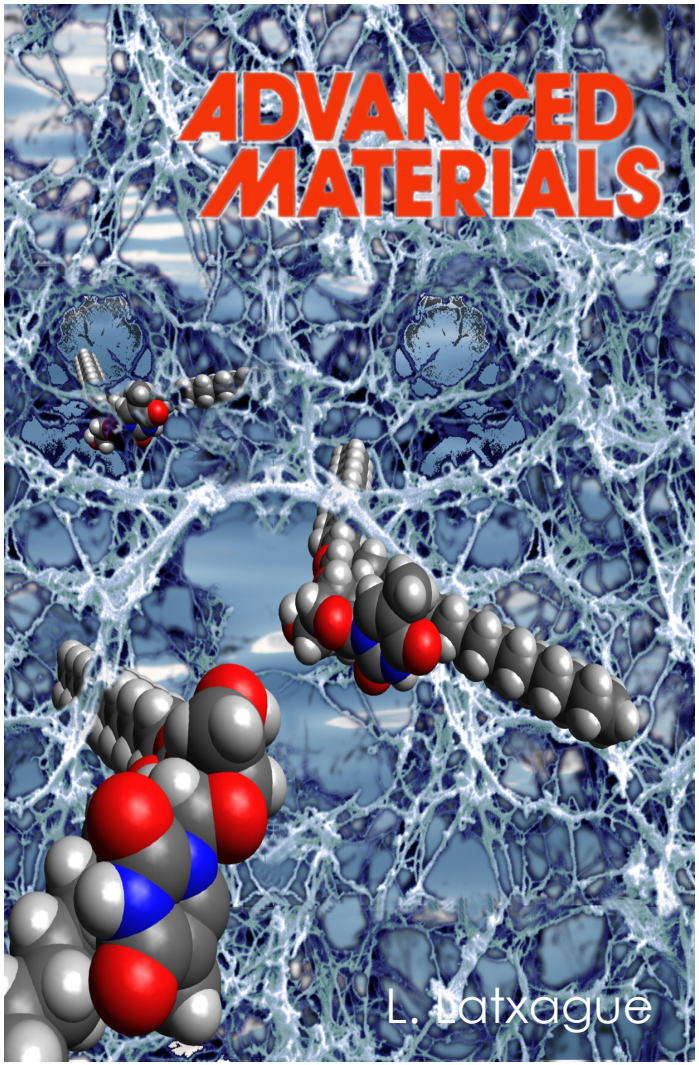
Low Molecular Weight Gelators

J. H. Wen, *et al.*, ***NATURE MATERIALS (2014)***
« Interplay of matrix stiffness and protein tethering in stem cell differentiation »



Tissue Engineering triad

Gel scaffold plays a major role in the stem cell fate



GLYCOSYL-NUCLEOLIPIDS

J. Baillet, V. Desvergnes, A. Hamoud, L. Latxague, and P. Barthélémy ***Adv. Mater.* 2018**, 1705078

Specifications

- Easy synthetic access to **Glycosyl-Nucleoside-Lipids (GNLs)**

- Tunable compounds

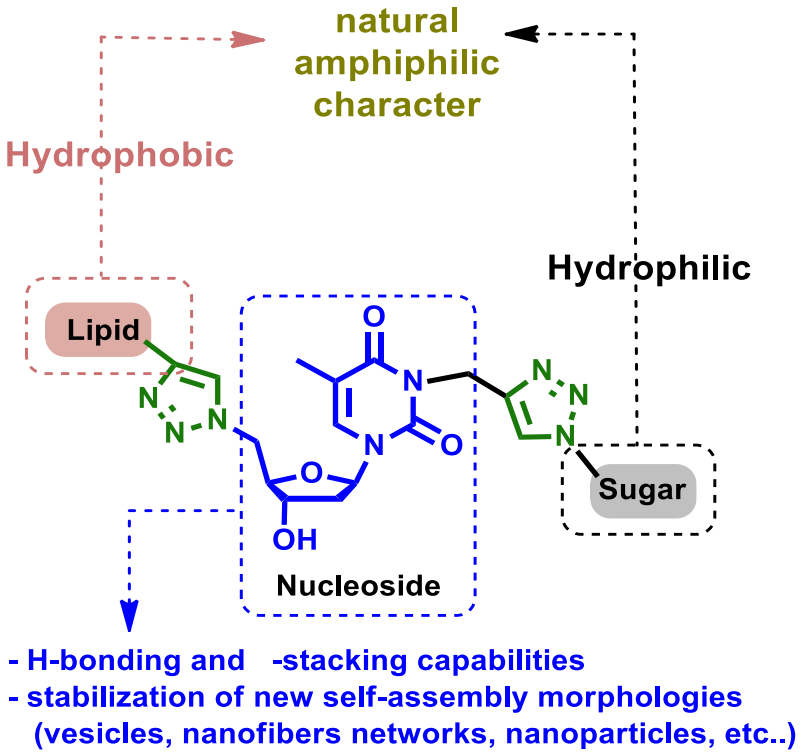
- Neutral compounds

- Very low concentration of gelation

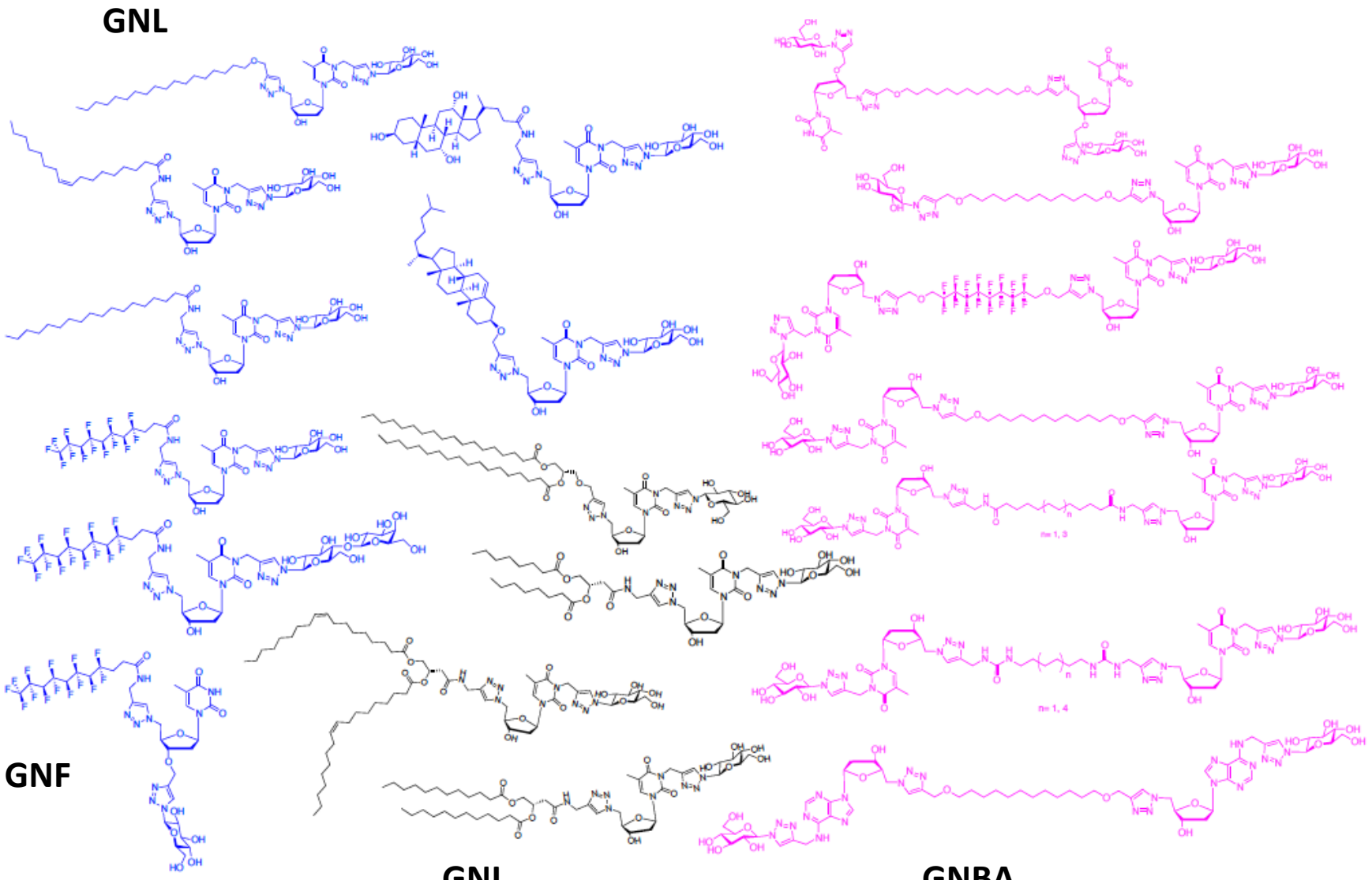
- Tunable rheological properties

- Non toxic

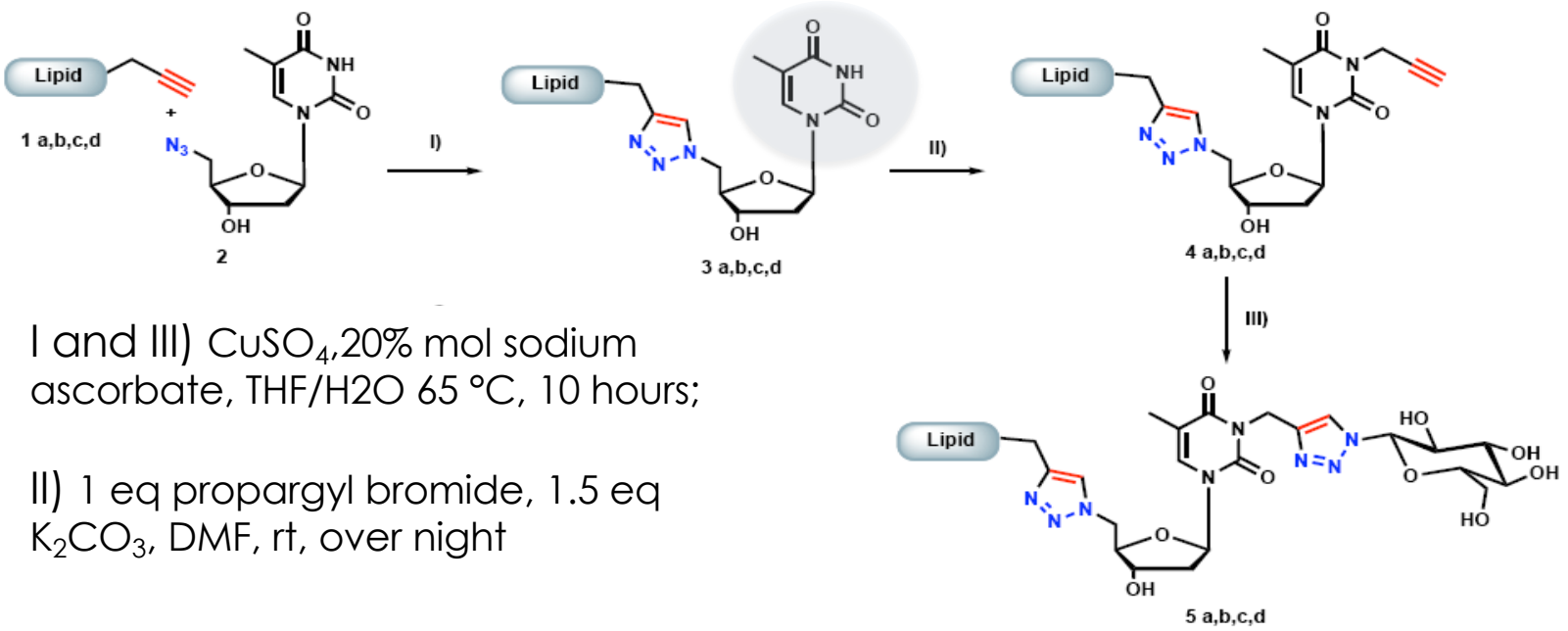
- Biocompatible



Glycosylated Nucleoside Lipids (GNLs)


GNL
GNF
GNL
GNBA
Bola-amphihiles

Synthesis of GNLs



I and III) $CuSO_4$,20% mol sodium ascorbate, THF/H2O 65 °C, 10 hours;

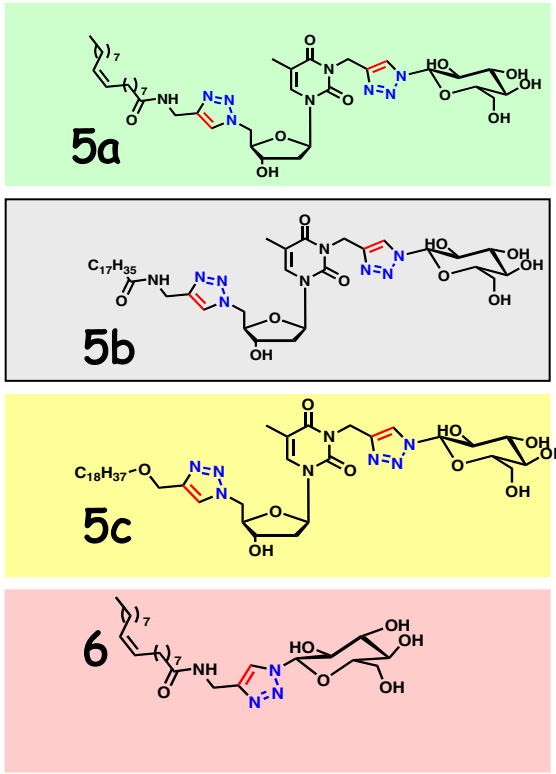
II) 1 eq propargyl bromide, 1.5 eq K_2CO_3, DMF, rt, over night

Guilhem G. et al. *Langmuir.* **2009**

Guilhem G. et al. *Chem. Commun.* **2009**

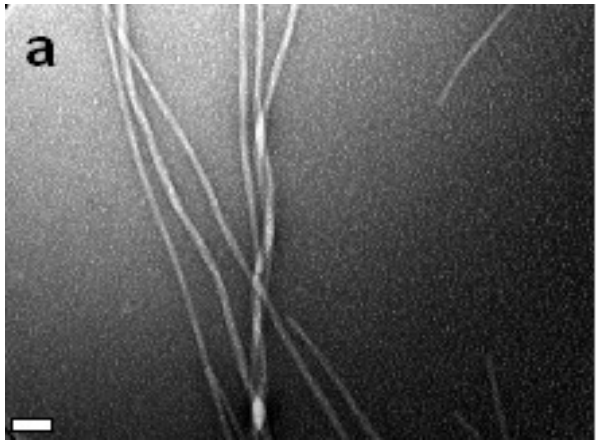
Summary of gelation properties of GNLs in water and organic solvents

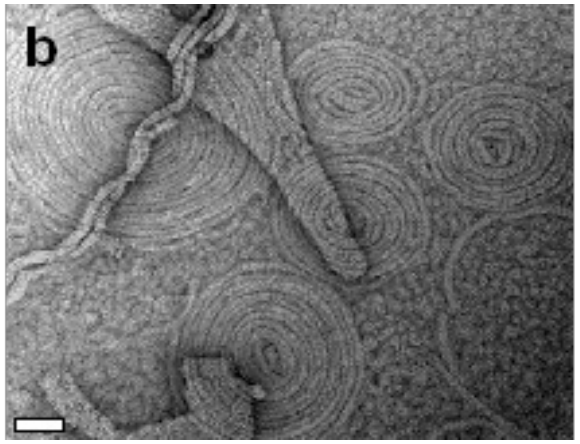
Compounds	5a	5b	5c	5d	6
Water	CG (2.5%)	G (0.1%)	OG (3%)	P	P
Chloroform	CG (2.5%)	G (8%)	Sol	OG (5%)	P
Toluene	P	P	CG (6%)	CG (9%)	/
Hexane	P	P	P	P	/
DMSO	Sol	Sol	Sol	Sol	/
n-Butan-1-ol	Sol	Sol	Sol	OG (9%)	/

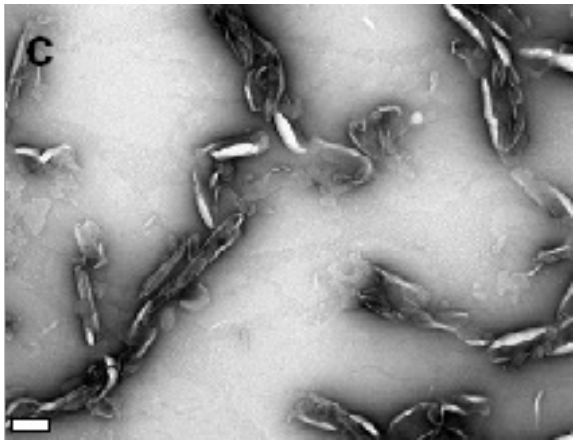


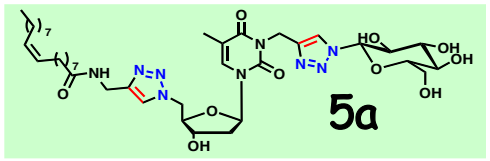
Gelation concentrations w/w
CG, clear gel;
G, gel; OG, opaque gel; P, partially soluble and/or precipitate; Sol, soluble.

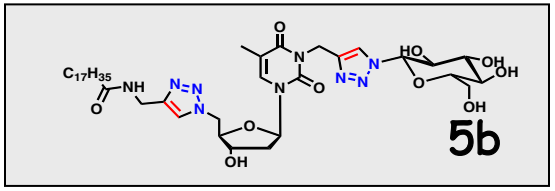
Electron microscopy studies (samples from water)

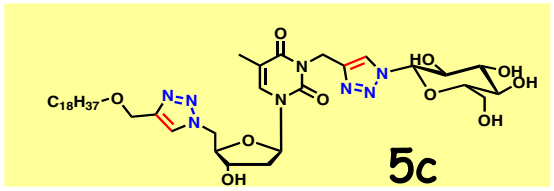












a) Networks made of nanofibers (oleylamide 5a scale 100 nm)

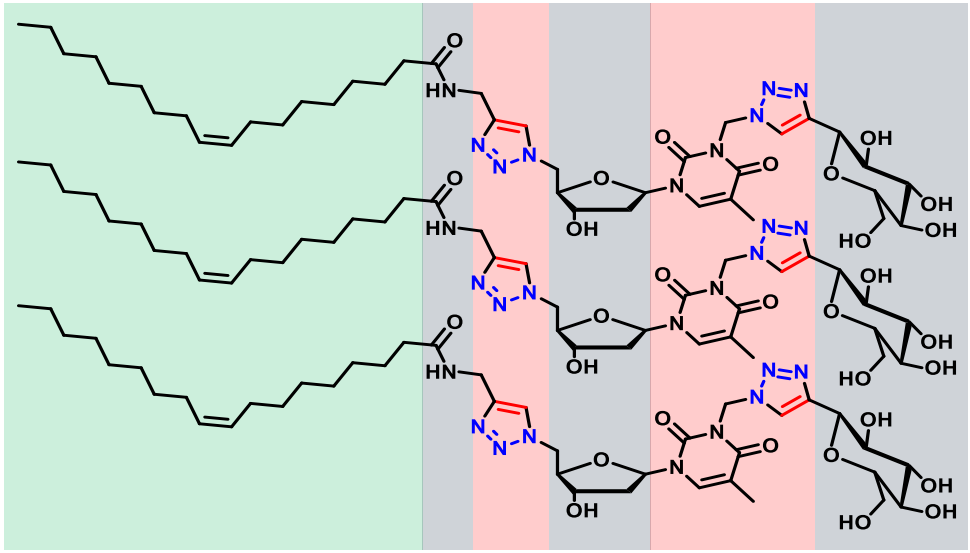
b) Circular fine fibers circularly organized (octadecylamide 5b, scale 50 nm).

c) Ether derivative 5c semi-tubular objects (c, scale 200 nm).

Godeau G. et al. ***Langmuir* (2009)**

Glycosyl-Nucleoside-lipids (**GNLs**) provide

LMWH and **LMOG (hydro and organogels)**



Hydrophobic effect (pyrene)

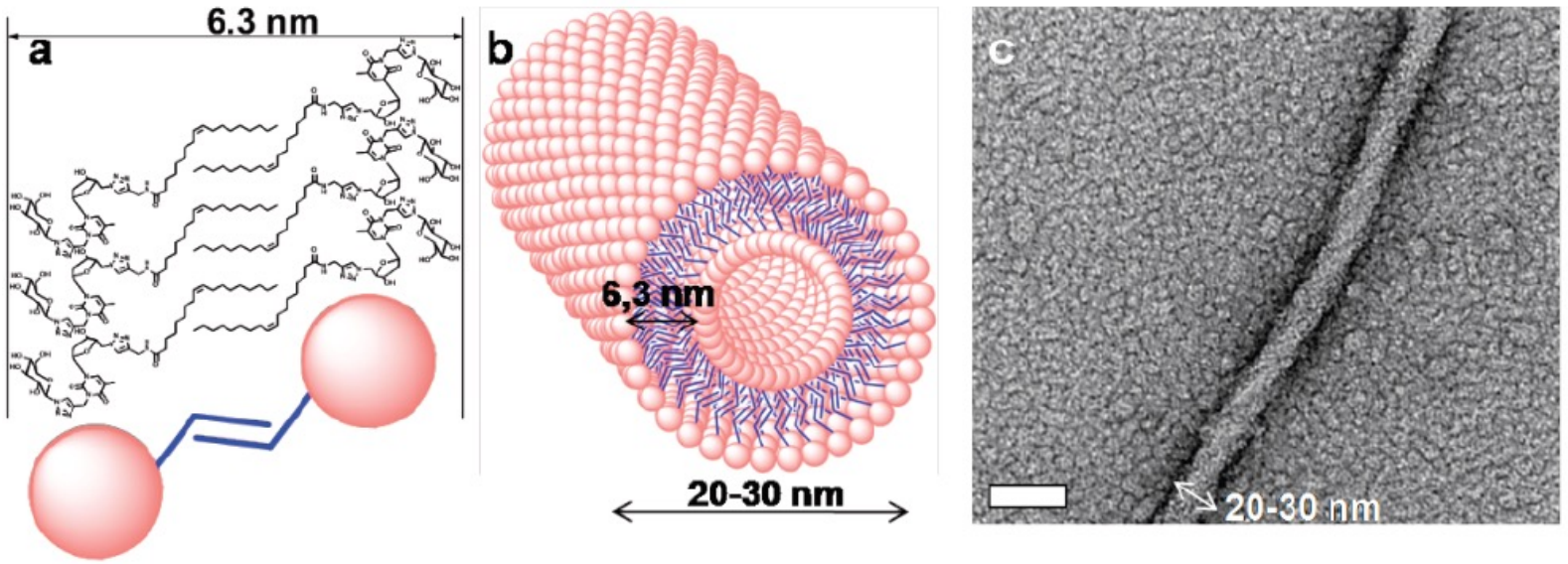
H bonding (IR)

π – π Stacking (UV, molar absorptivity)

Godeau G. et al. ***Langmuir*** **(2009)**

Glycosyl-Nucleoside-lipids (**GNLs**) provides

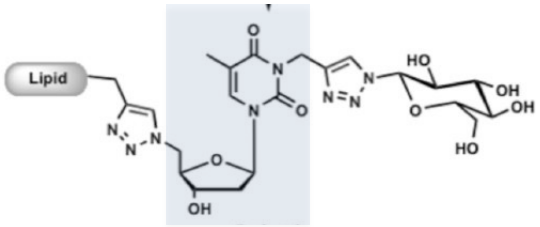
LMWH (Low-Molecular-Weight-Hydrogelators)
and **LMOG** (Low-Molecular-mass-Organic-Gelators).



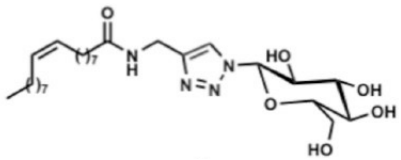
Bi-dimensional (a) and tri-dimentional (b) arrangements for the polysaccharidic like assembly of oleyl derivatives (c, TEM image of a GNL nanotube scale: 50 nm).

Glycosyl-Nucleoside-lipids (**GNLs**) entrap oligonucleotides and favor their cellular uptake

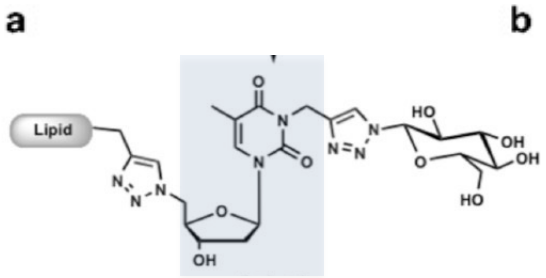
Guilhem G. et al. *Langmuir.* **2009**
Guilhem G. et al. *Chem. Commun.* **2009**



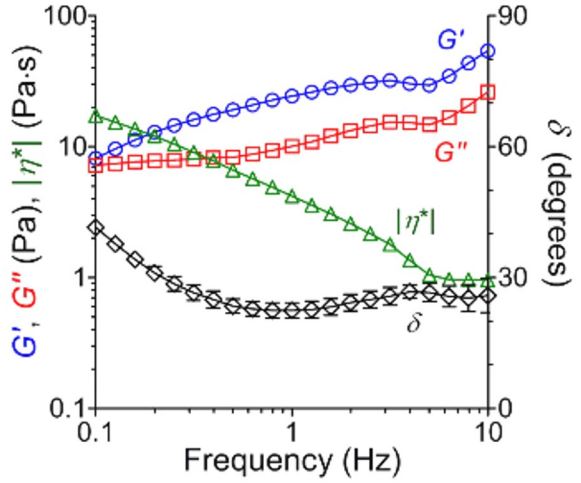
GNL → gels

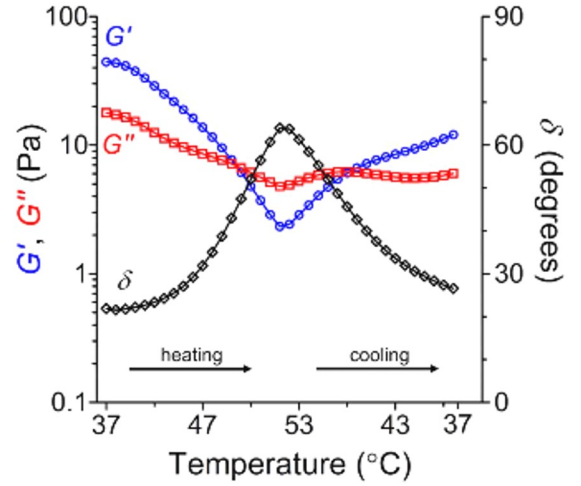


GL → No gel

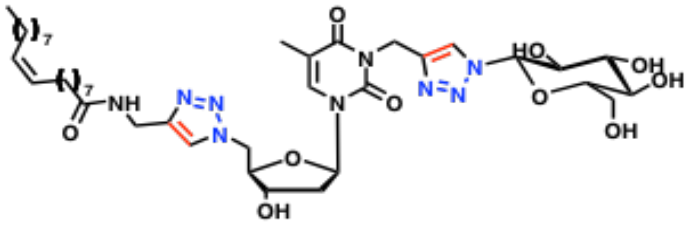


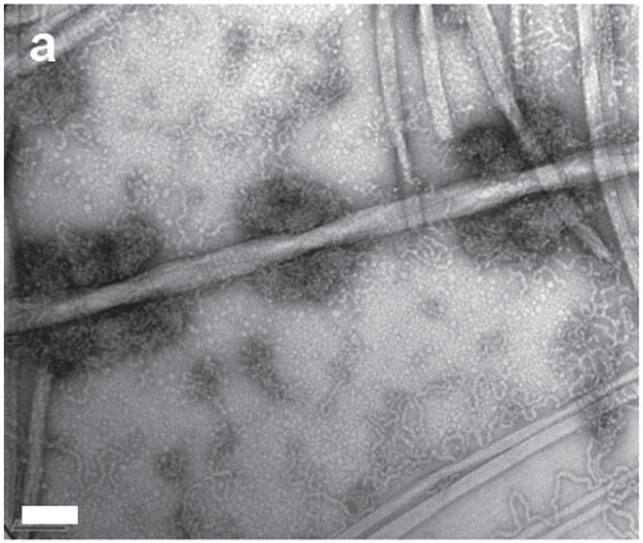
Frequency sweep of GNL hydrogel (τ = 3.0 Pa, 37 °C).

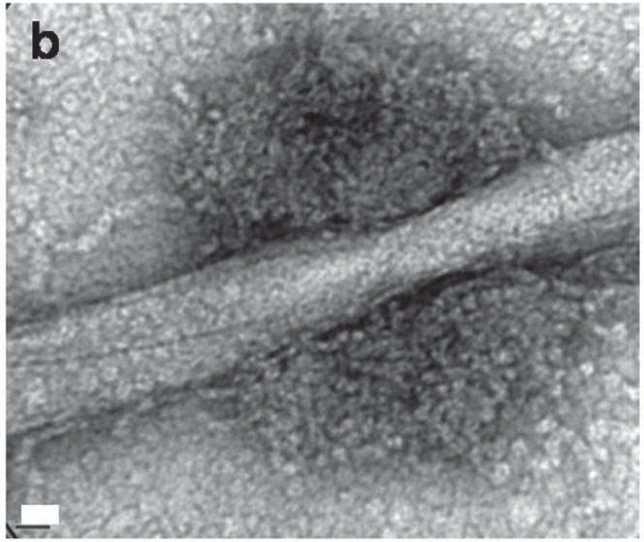


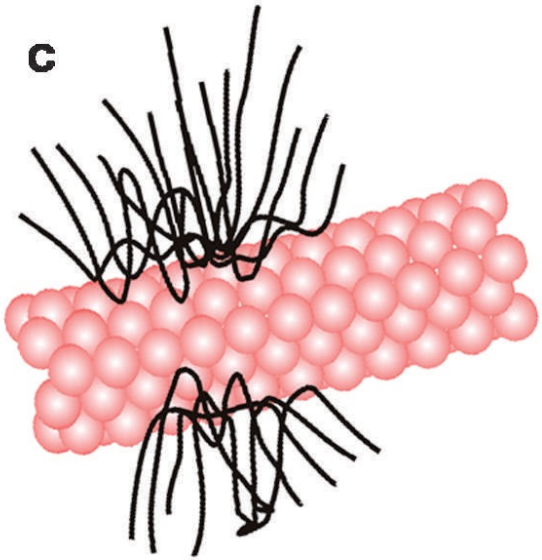


Interaction of nucleic acids (Oligo) with GNLs



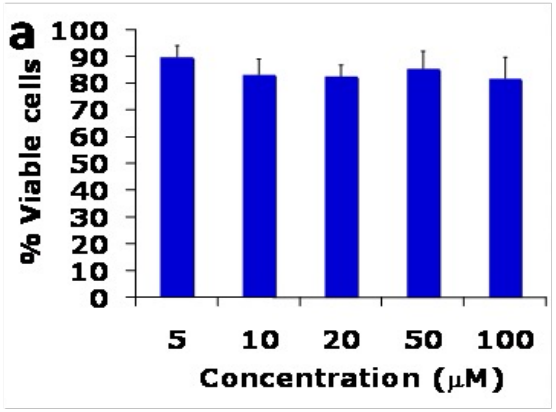


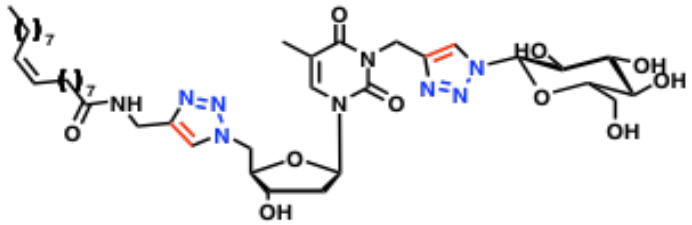


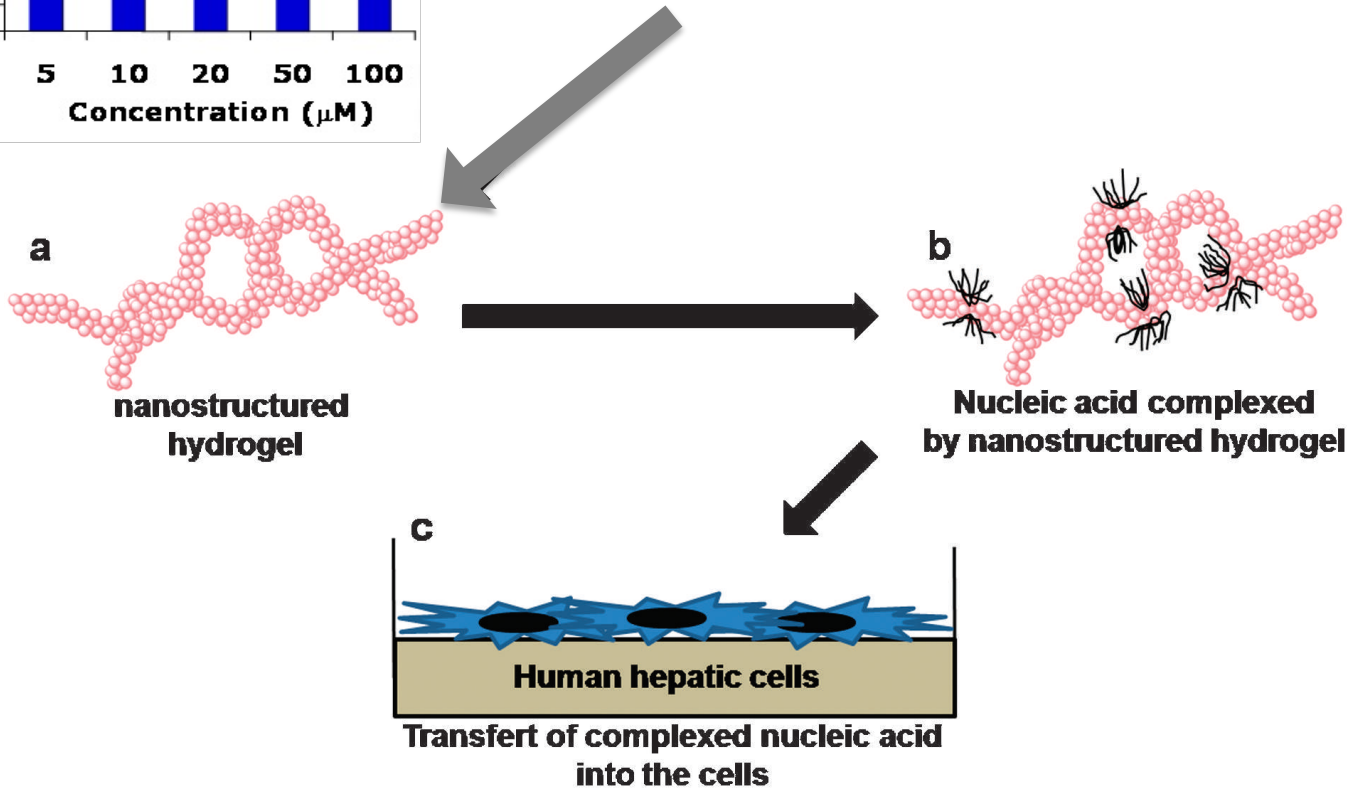


Godeau G. et al. ***Chem. Commun.* (2009)**

Cell viability is not affected by GNLs

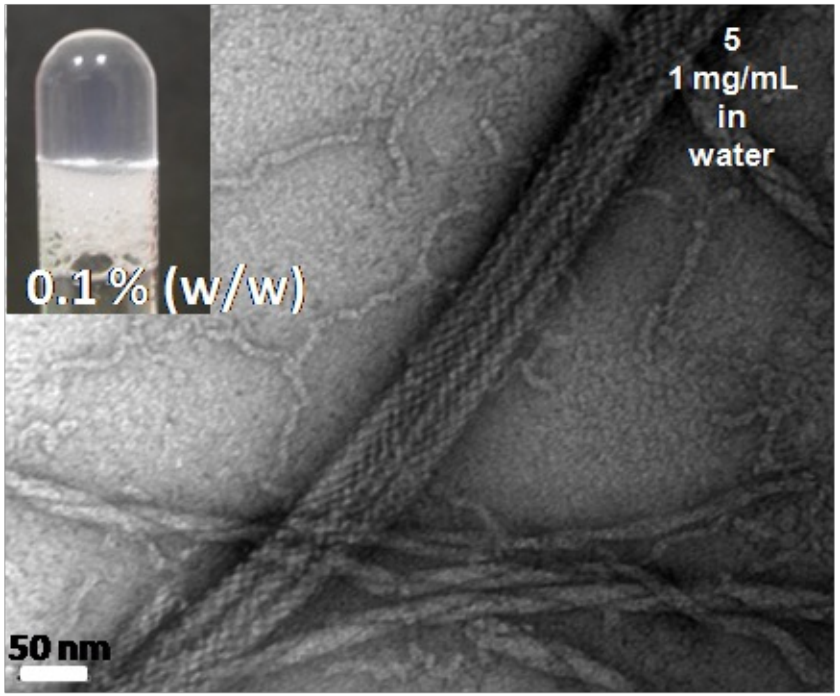


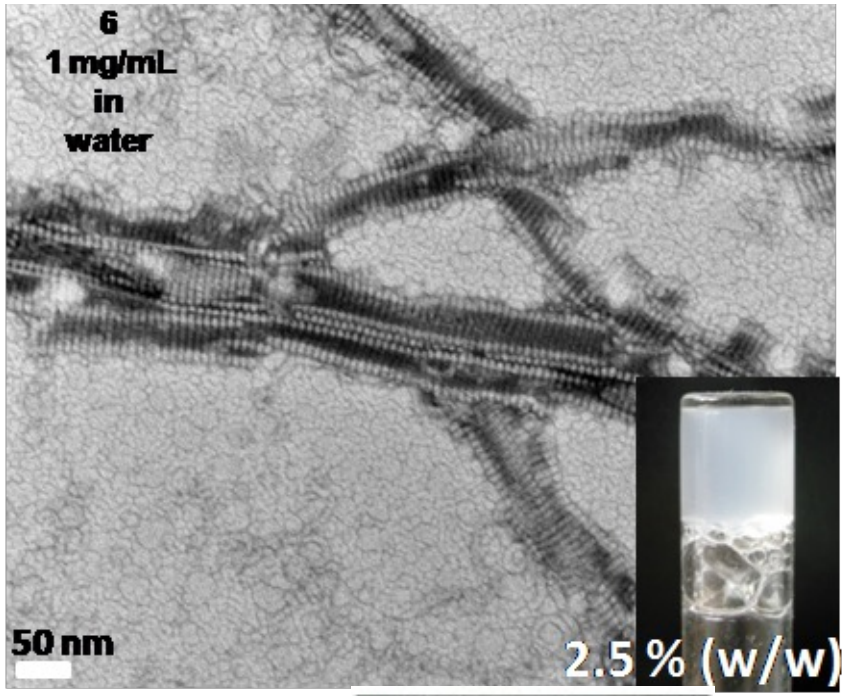


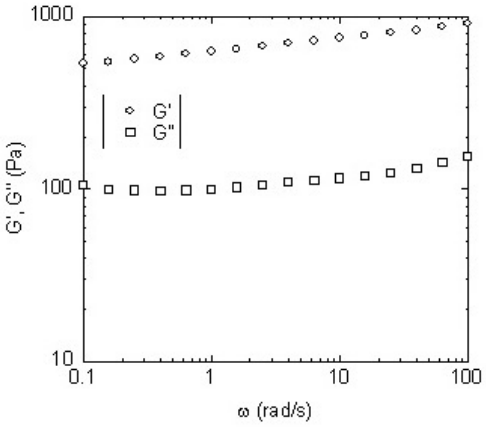


Godeau G. et al. ***Chem. Commun.* (2009)**

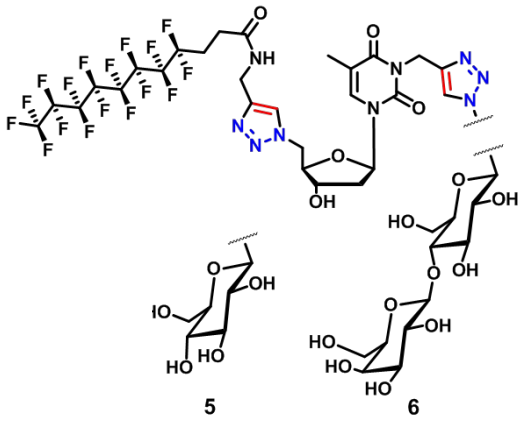
Improvement of gel properties G' ↗

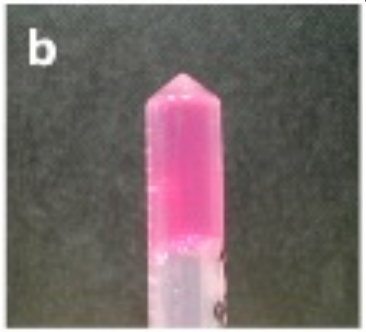






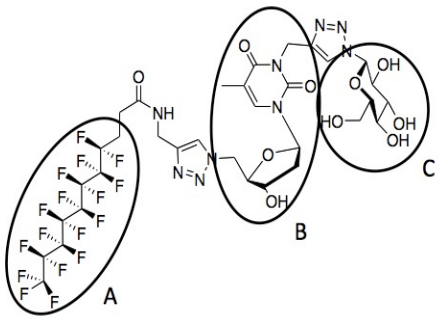
GNF



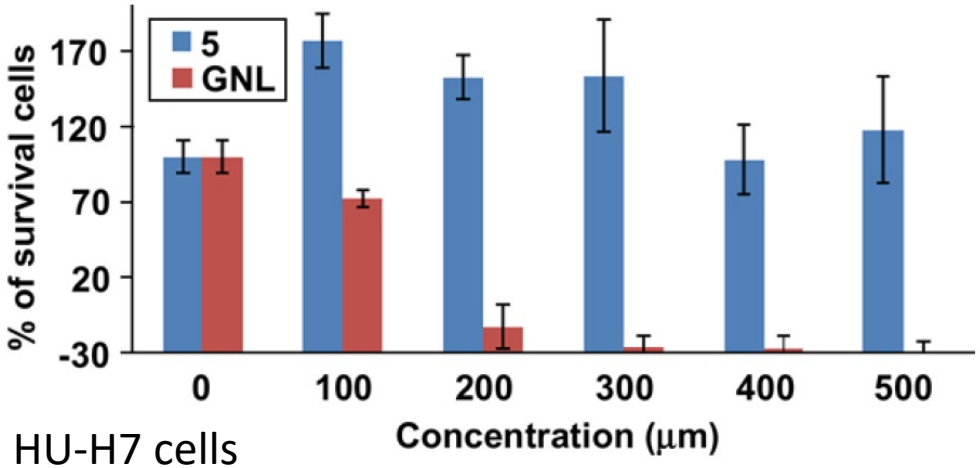


0.1% w/w (1 mM) in DMEM (medium)

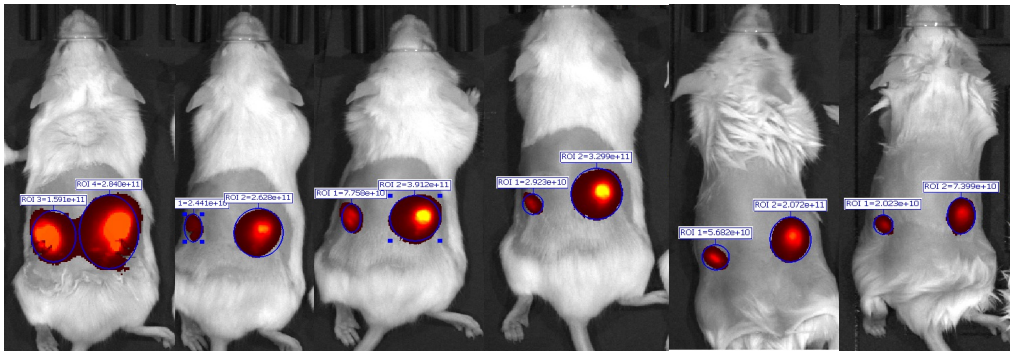
Guilhem G. *et al. Tetrahedron Letters* **2010**



GNF



HU-H7 cells

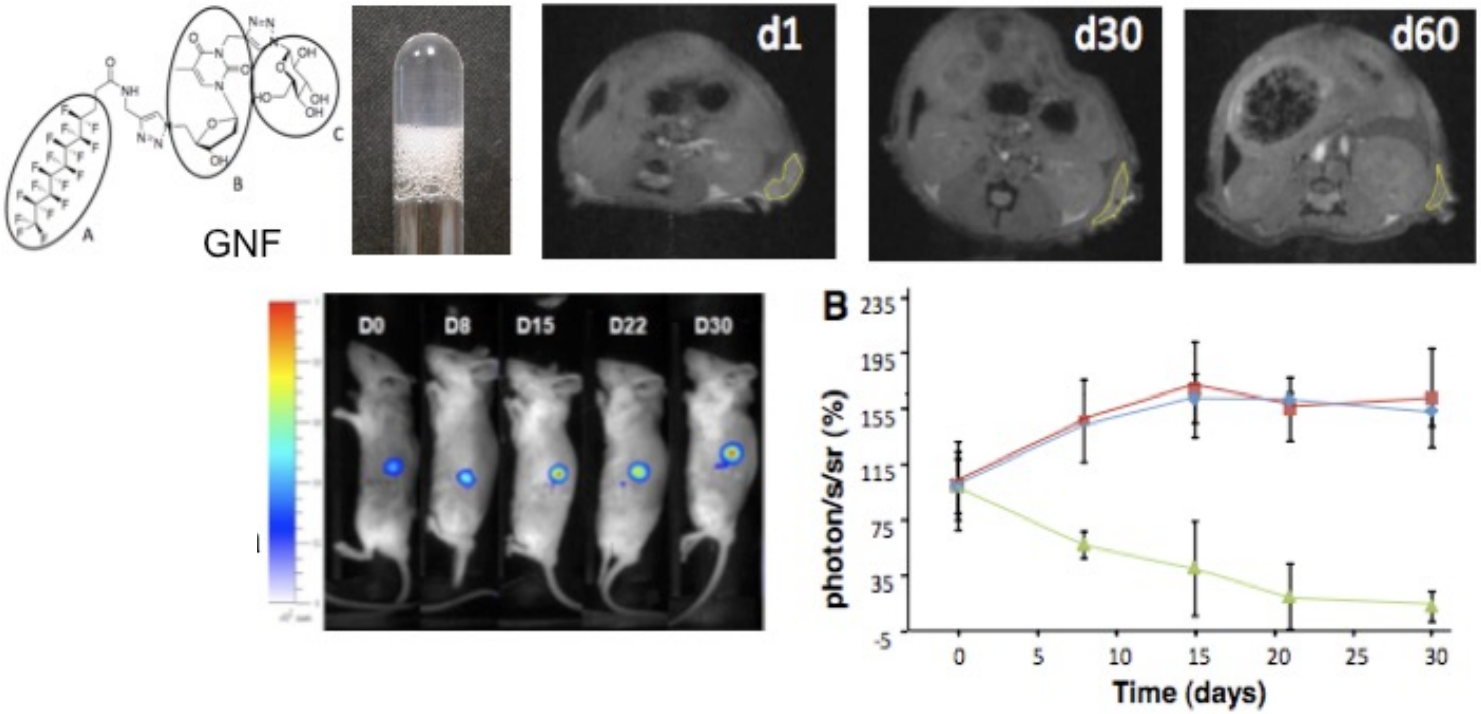


Day 0 Day 2 Day 5 Day 7 Day 14 Day 21

No immunogenic effect
Biocompatible

Guilhem G. *et al. Tetrahedron Letters* **2010**

Degradable LMW hydrogels for tissue engineering
(grafting Stem Cells)

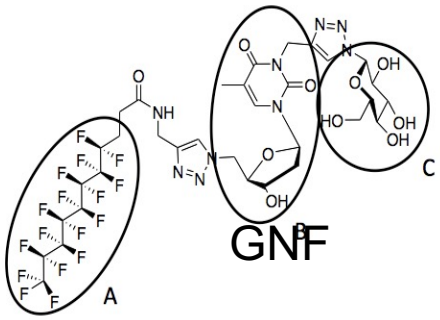


Human adipose tissue-derived mesenchymal stem cells (ASCs)

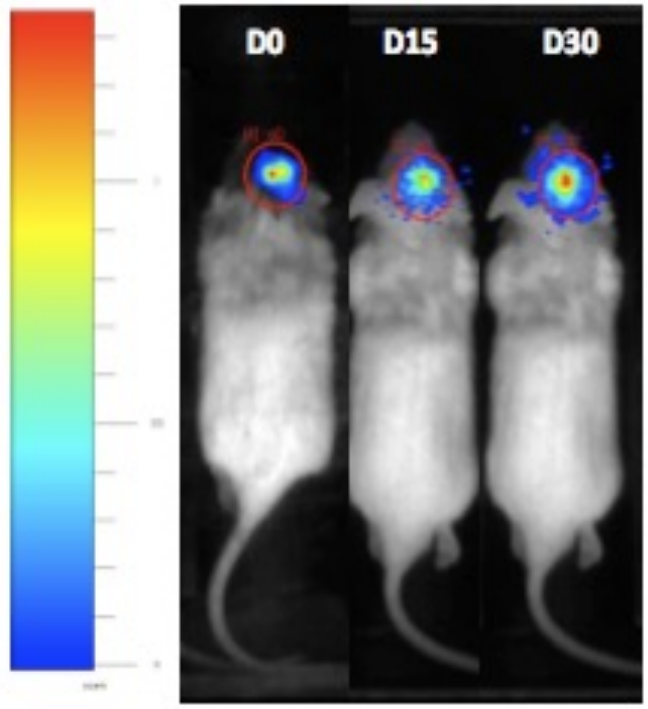
Weak supramolecular hydrogel (scaffold) allowing stem cells growth as clusters (Spheroid)

S. Ziane *et al.* *European Cells and Materials* ***2012***

Degradable LMW hydrogels for tissue engineering (grafting Stem Cells)



GNF hydrogel promotes the differentiation of ASCs into functional osteoblasts
In vitro and in vivo.

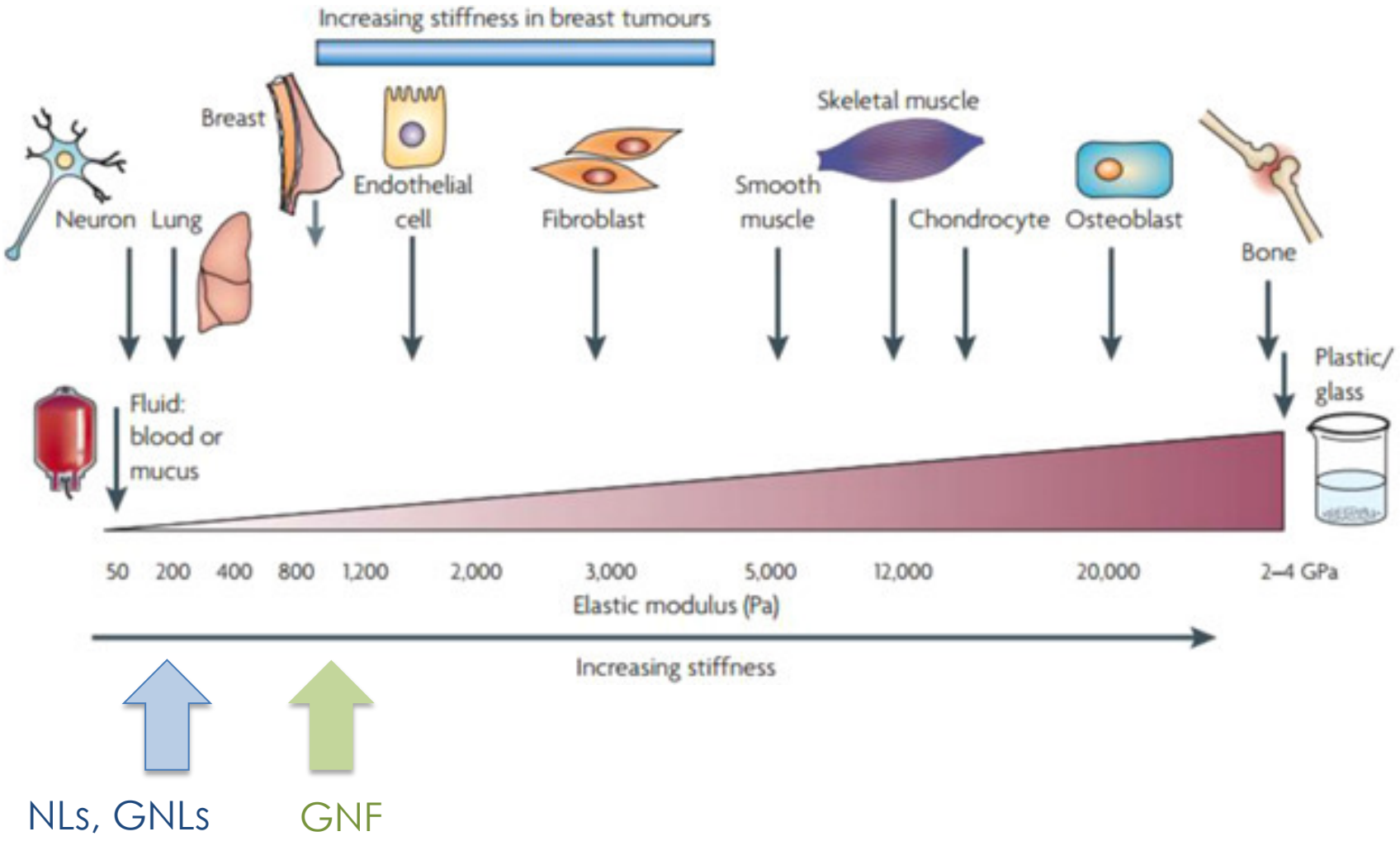


In vivo

Weak supramolecular hydrogel (scaffold) allowing stem cells growth as clusters (Spheroid)
No immunogenic effect
Biocompatible

S. Ziane *et al. European Cells and Materials* ***2012***

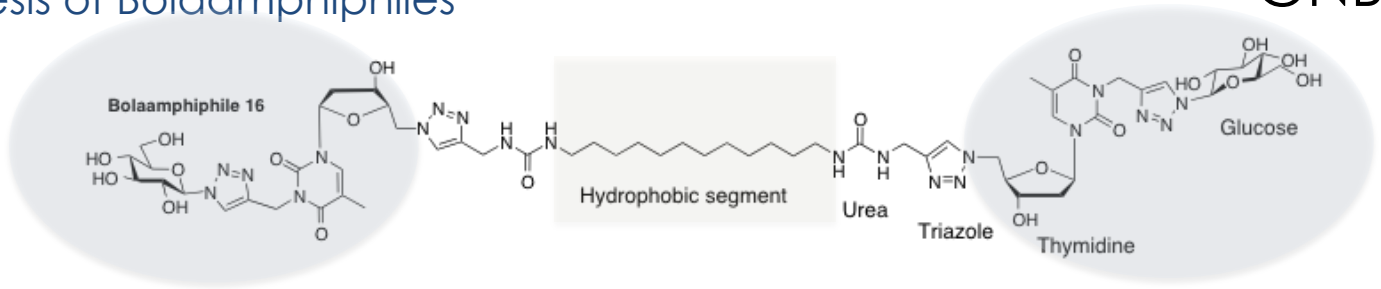
Supramolecular gels are useful materials for biomedical applications



Prince, E.; Kumacheva, E. Design and applications of man-made biomimetic fibrillar hydrogels. *Nat. Rev. Mater.* **2019**, 4, 99–115.

Synthesis of Bolaamphiphiles

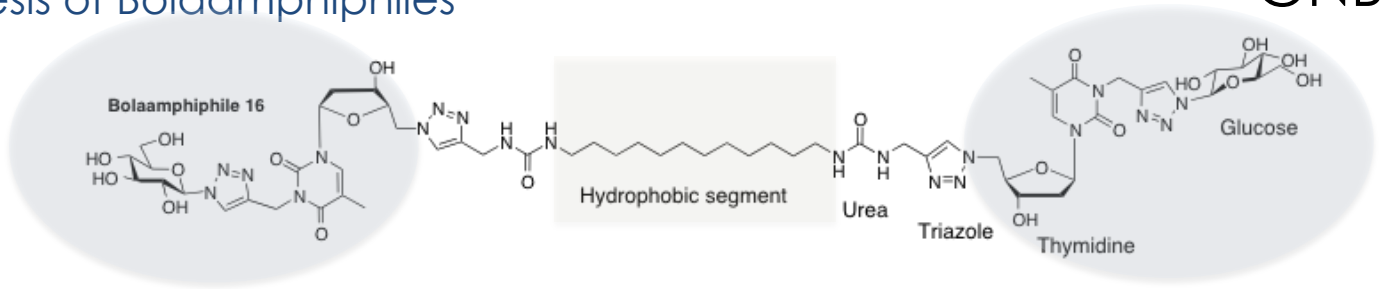
GNBAs

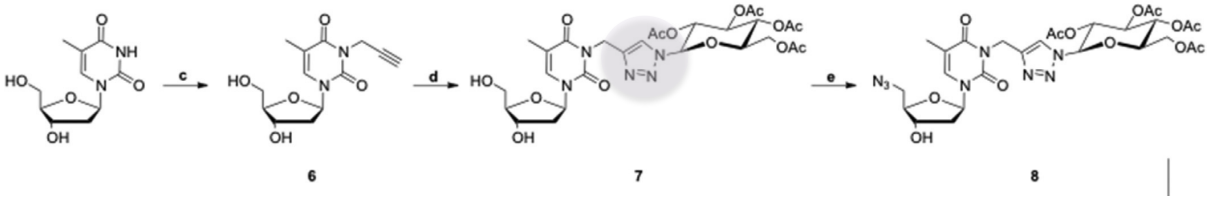


Ramin M. *et al. Biomaterials* (**2017**)

Synthesis of Bolaamphiphiles

GNBAs

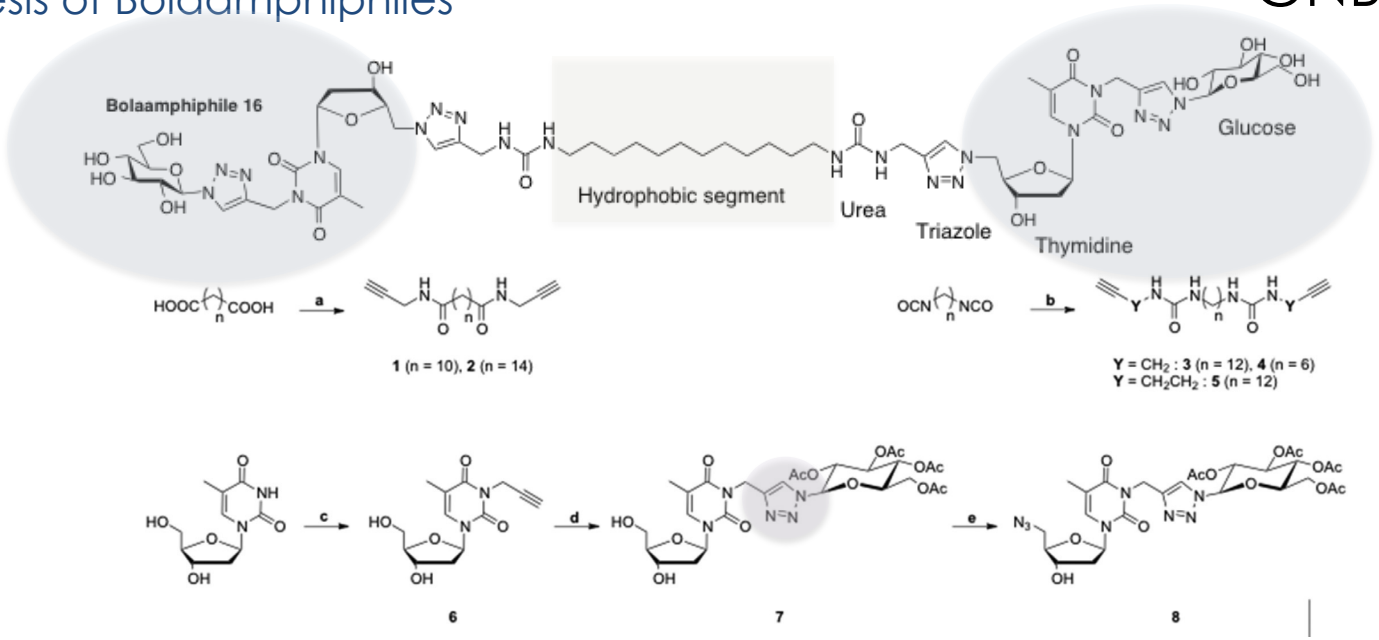




Ramin M. *et al. Biomaterials* (**2017**)

Synthesis of Bolaamphiphiles

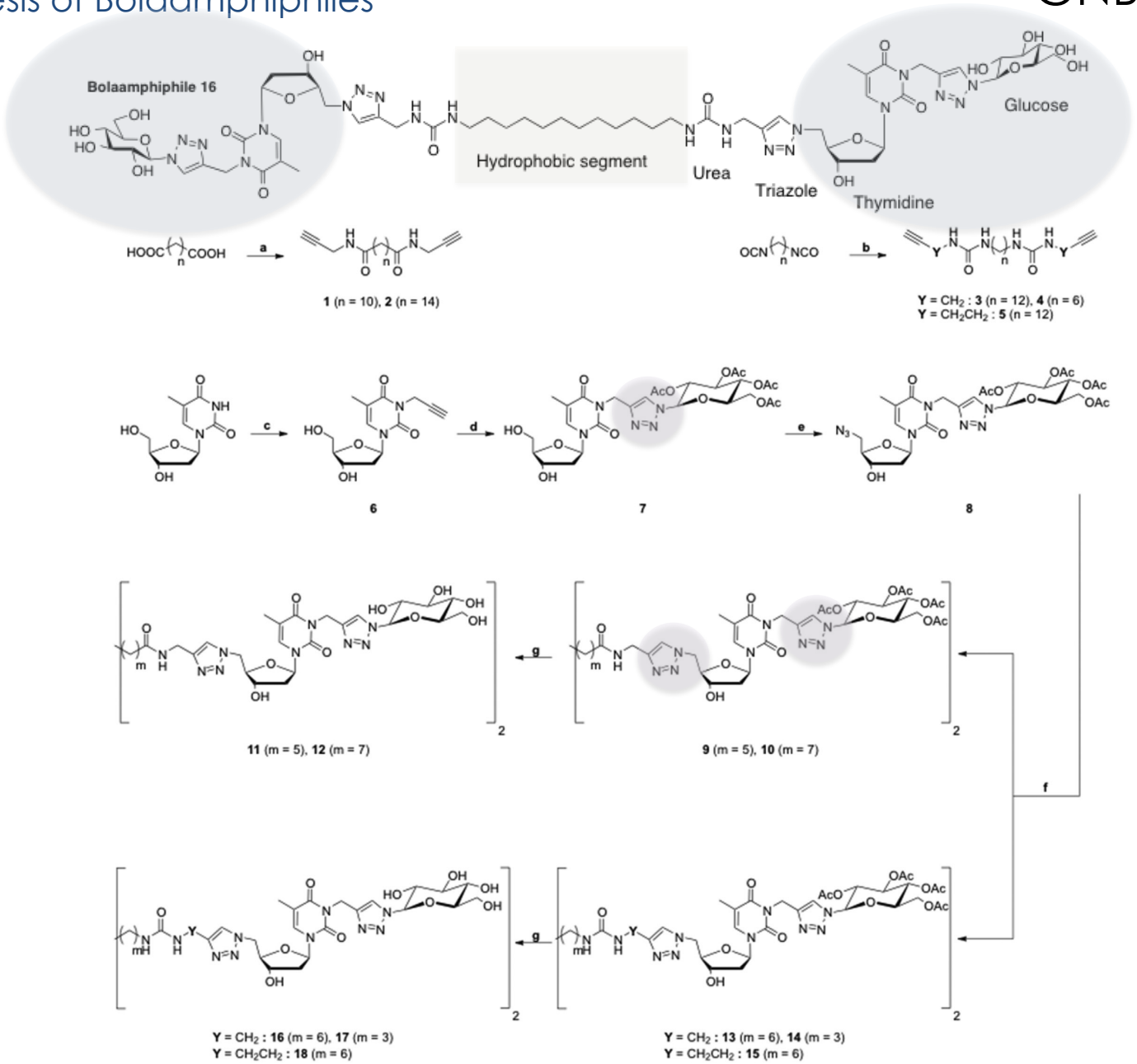
GNBAs



Ramin M. *et al. Biomaterials* (**2017**)

Synthesis of Bolaamphiphiles

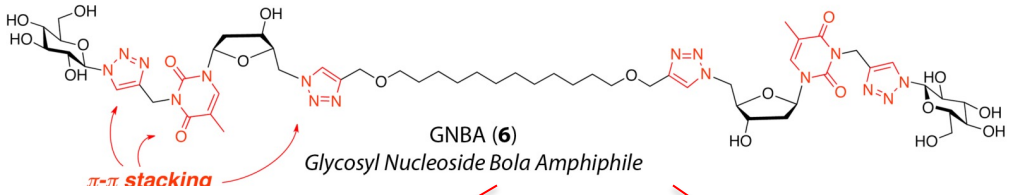
GNBAs



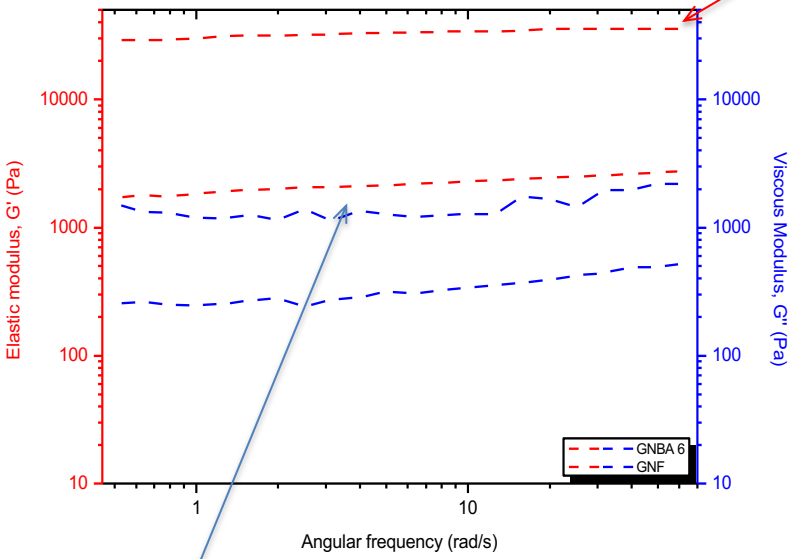
Ramin M. *et al. Biomaterials* (**2017**)

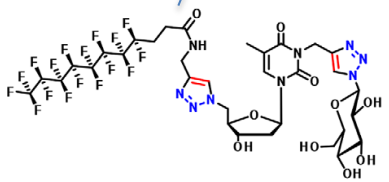
Bolaamphiphile

G’

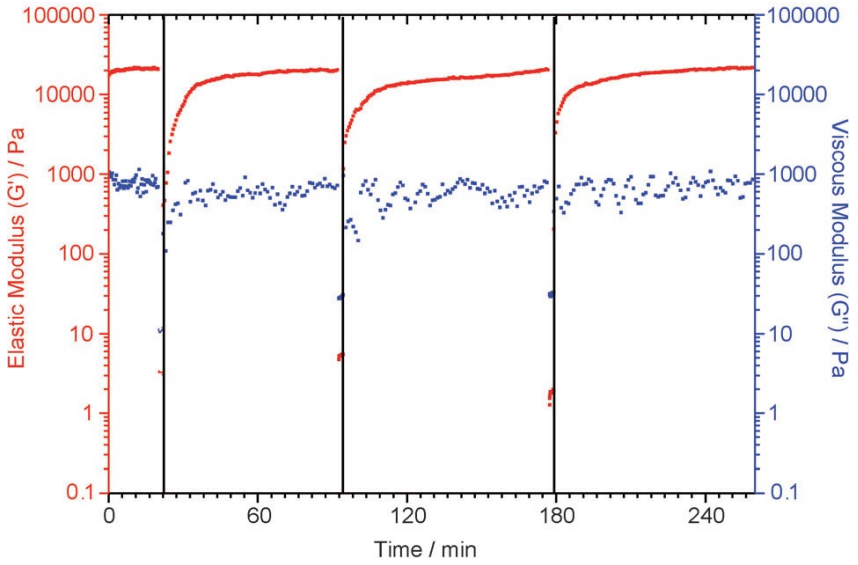


Bola based GNLs





GNF



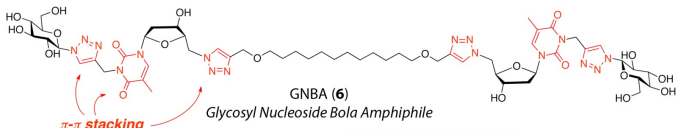
P. Barthélémy *et al.* *PCT*, ***2014***,

Thixotropy

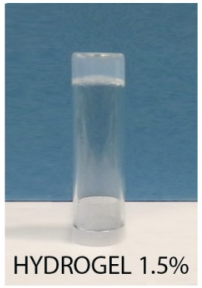
Latxague *et al. Angewandte Chemie (2015)*

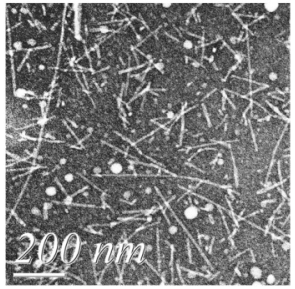
Scaffold for stem cells

STEM CELLS BIOMATERIALS



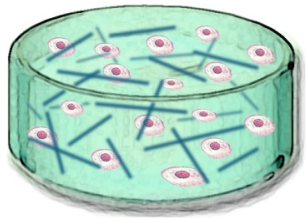
GNBA → Low Molecular Weight Gel (LMWG)



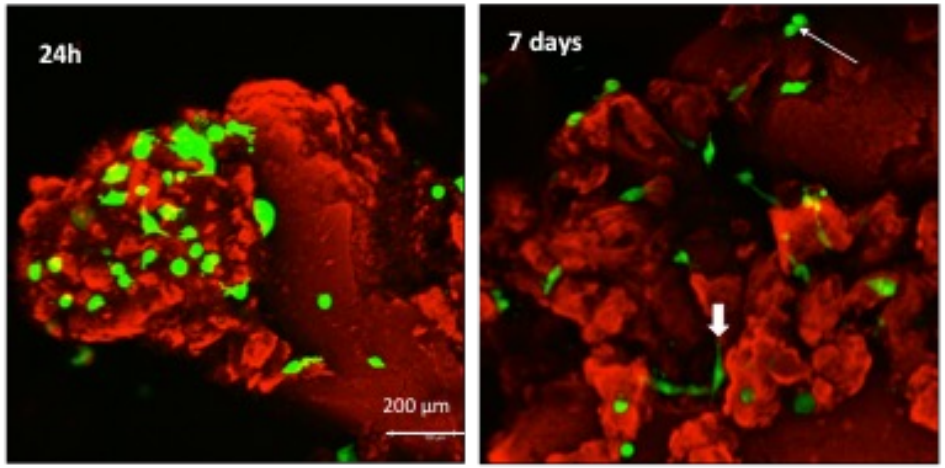


STABLE AND STRAIGHT FIBERS
HIGH ELASTIC MODULUS
SELF-HEALING MATERIAL

Isolated Stem Cells →



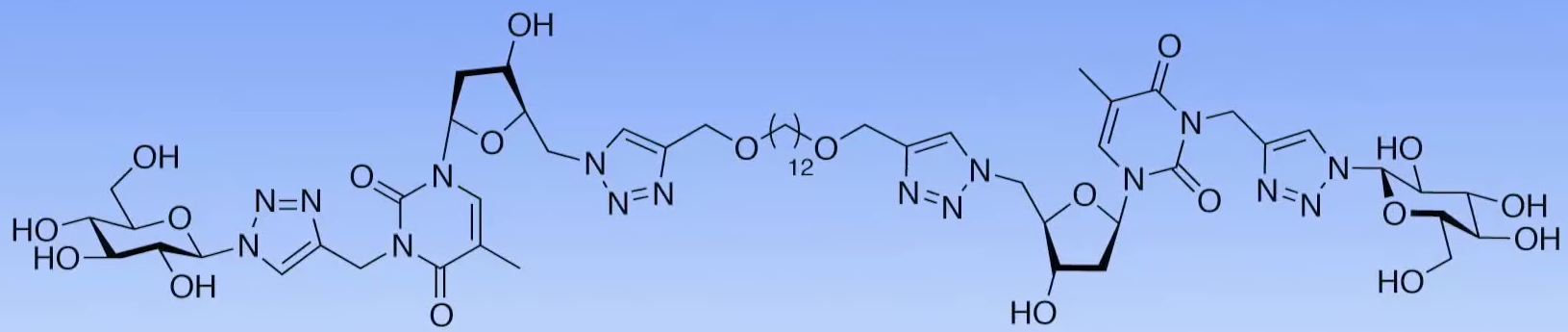
STEM CELLS ADHESION AND PROLIFERATION



Biocompatible supramolecular scaffolds allowing stem cells adhesion and proliferation Isolated cells

P. Barthélémy *et al. PCT,* ***2014****,*

Latxague *et al. Angewandte Chemie (2015)*



GNBA 1

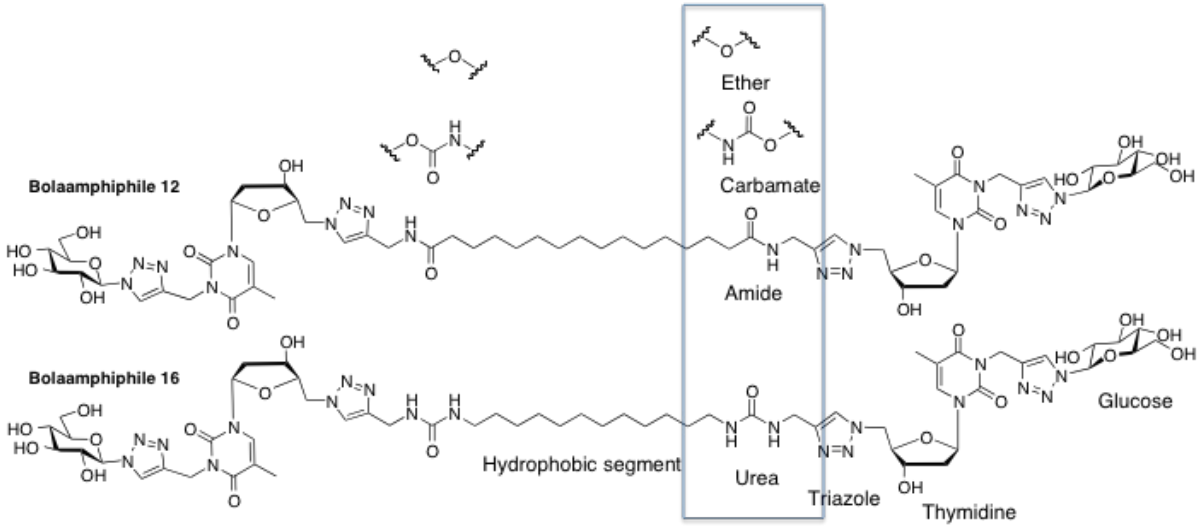
A. Thixotropic Properties

B. *in vivo* Injectability

Latxague *et al. Angewandte Chemie (2015)*

Hydrogels

Molecular modulation



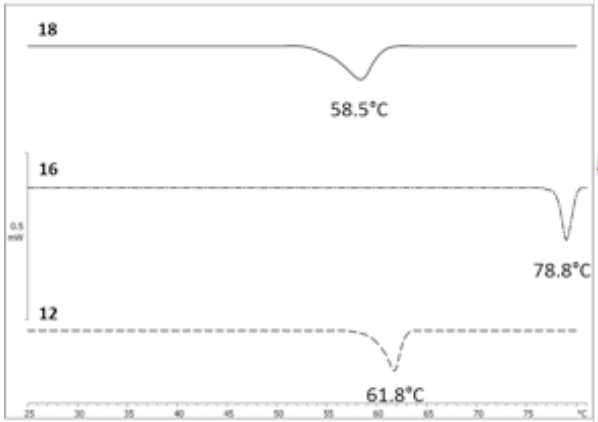
Bola based GNLs

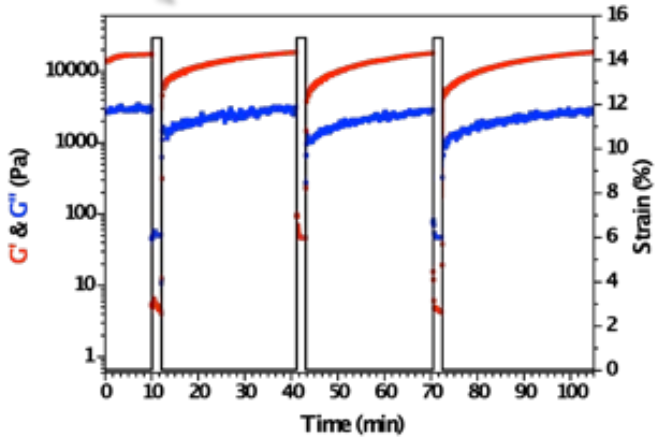
G'>20kPa

Amide

Urea

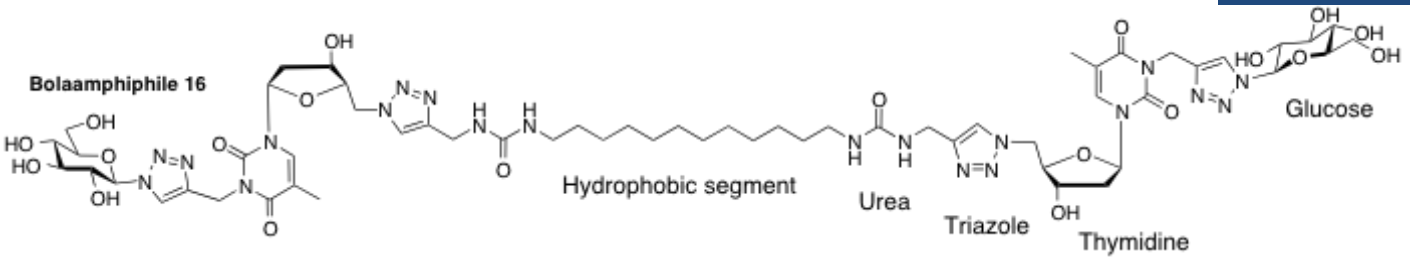
Amide



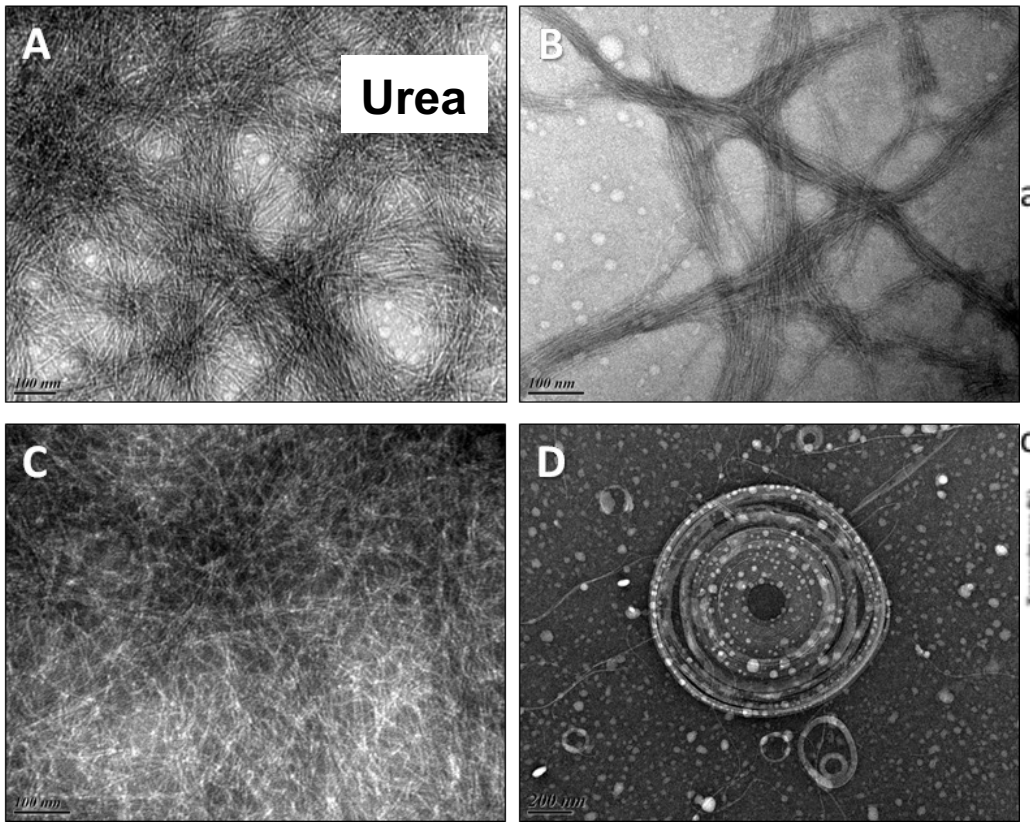


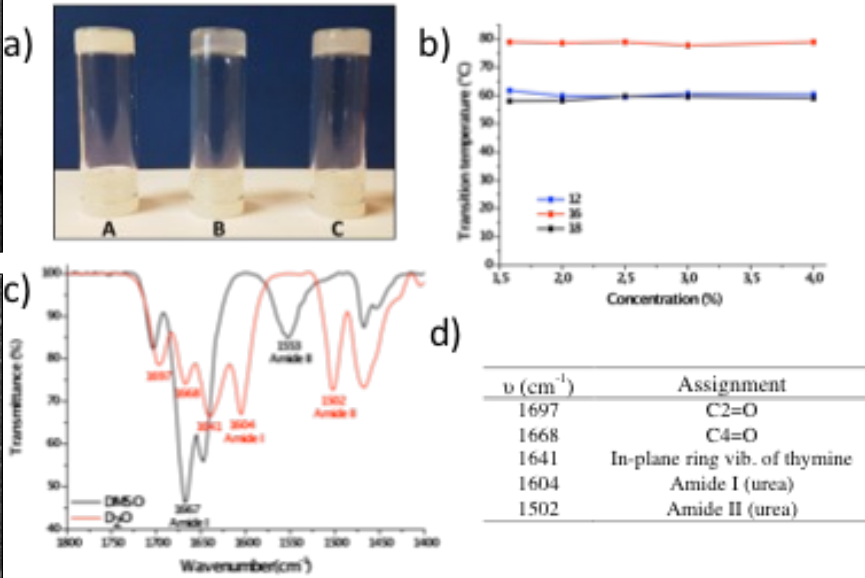
Thixotropy

Ramin M. *et al. Biomaterials* (2017)



FAST GELATION KINETICS

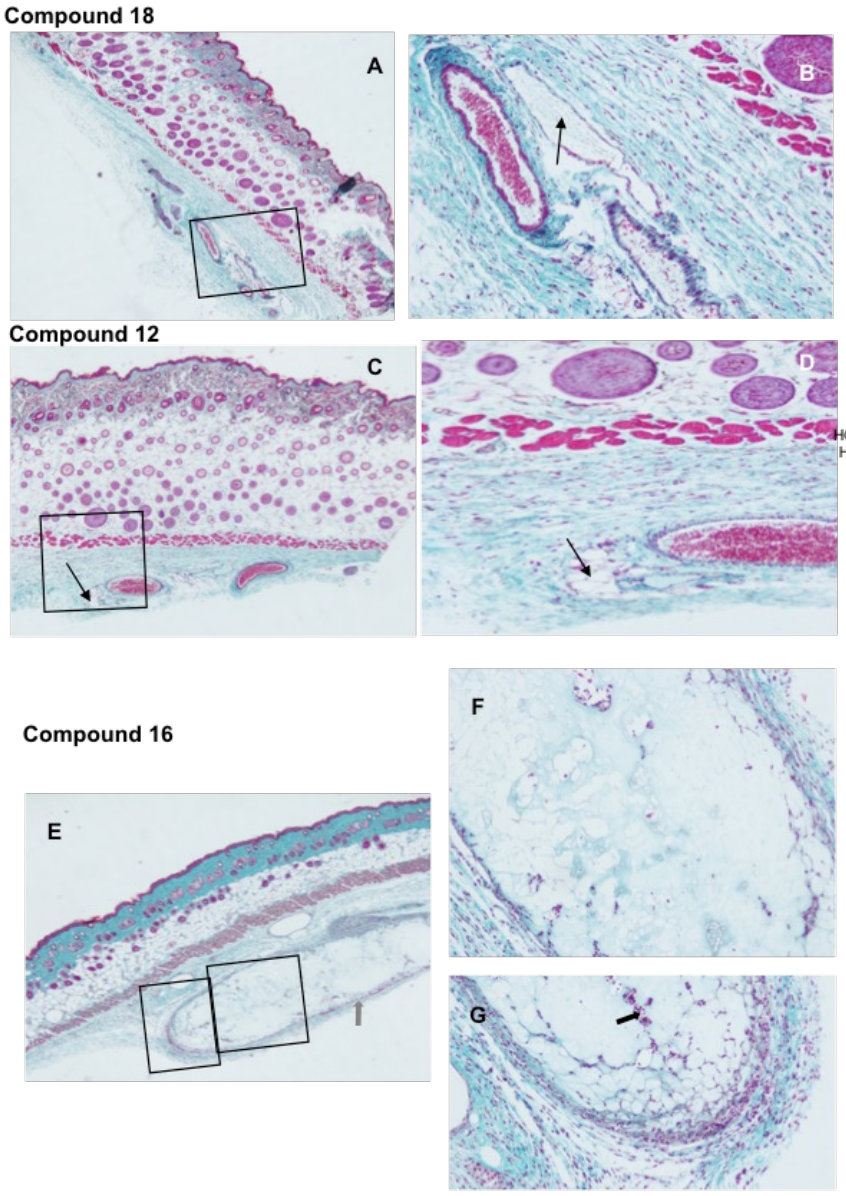




υ (cm^{-1})	Assignment
1697	C2=O
1668	C4=O
1641	In-plane ring vib. of thymine
1604	Amide I (urea)
1502	Amide II (urea)

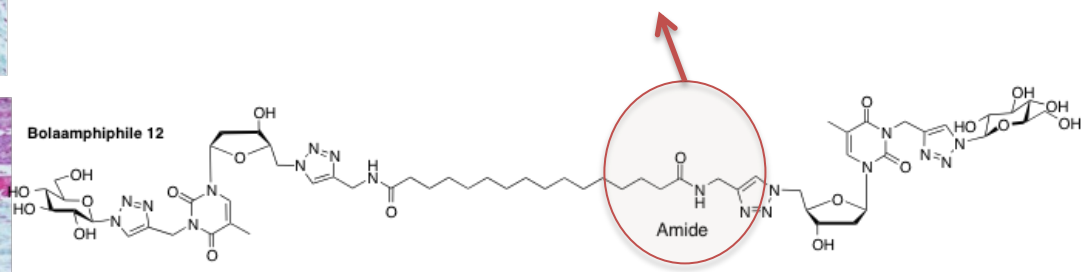
TEM images of aqueous samples at 2 % w/v obtained for Bolaamphiphiles (A) **16**, (B) **18**, (C) **12** and (D) **11**

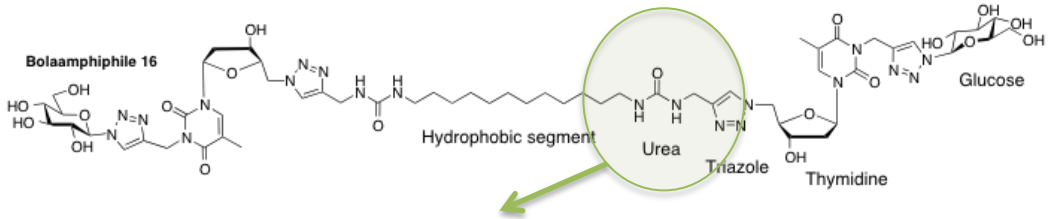
Ramin M. *et al. Biomaterials* (2017)



Bolas

almost completely degraded 21 days after implantation (black arrows)





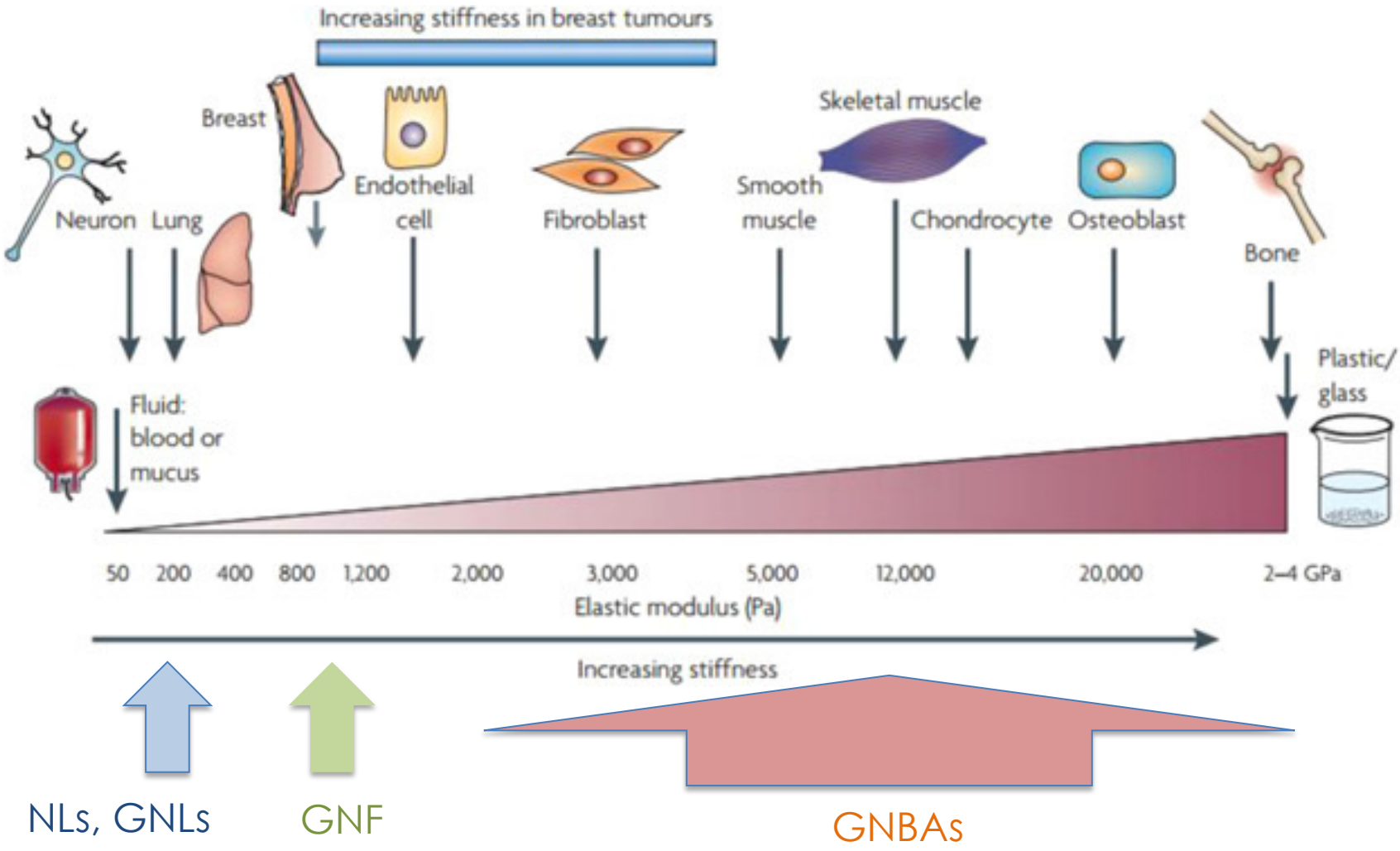
The urea-Bola feature a **fast gelation kinetic and high *in vivo* stability**.

This hydrogel **inhibits recognition by macrophages and fibrous deposition**

Ramin M. *et al. Biomaterials (*2017**)**

Supramolecular gels are useful materials for biomedical applications

BIOMATERIALS

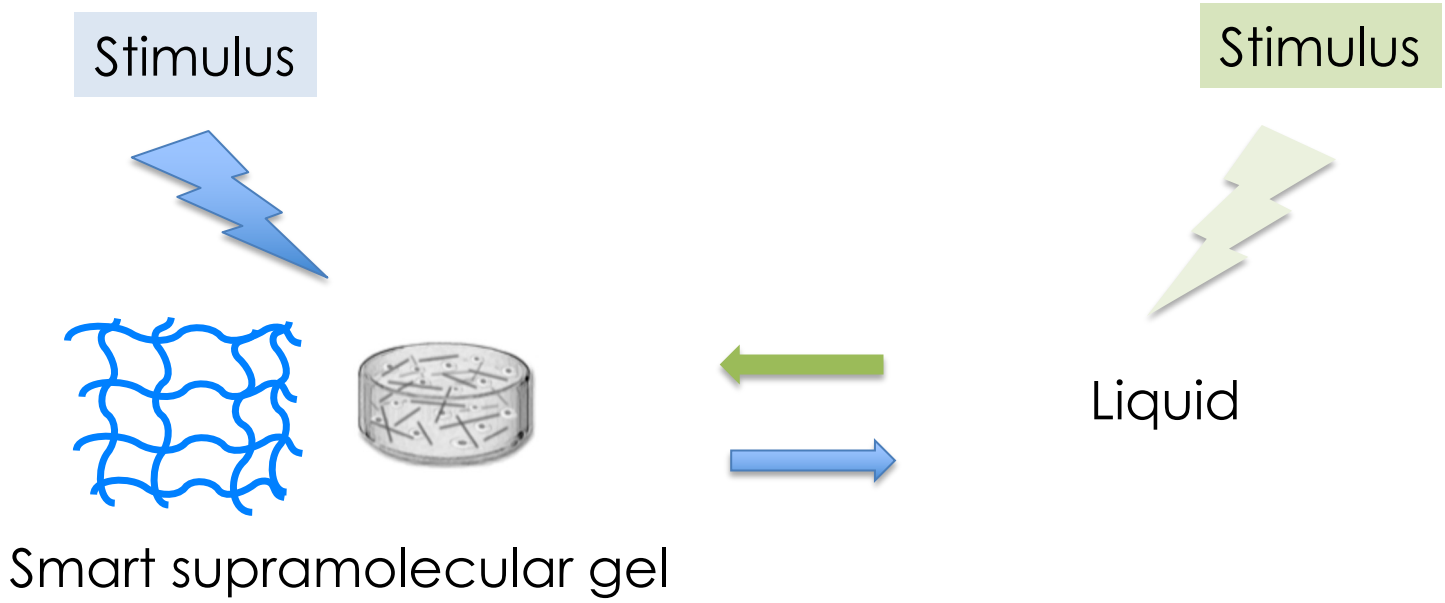


Prince, E.; Kumacheva, E. Design and applications of man-made biomimetic fibrillar hydrogels. *Nat. Rev. Mater.* **2019**, 4, 99–115.

"Smart polymer-free soft materials"

-> Responsive supramolecular materials

Molecular modulation of the mechanical, rheological and biological properties on demand



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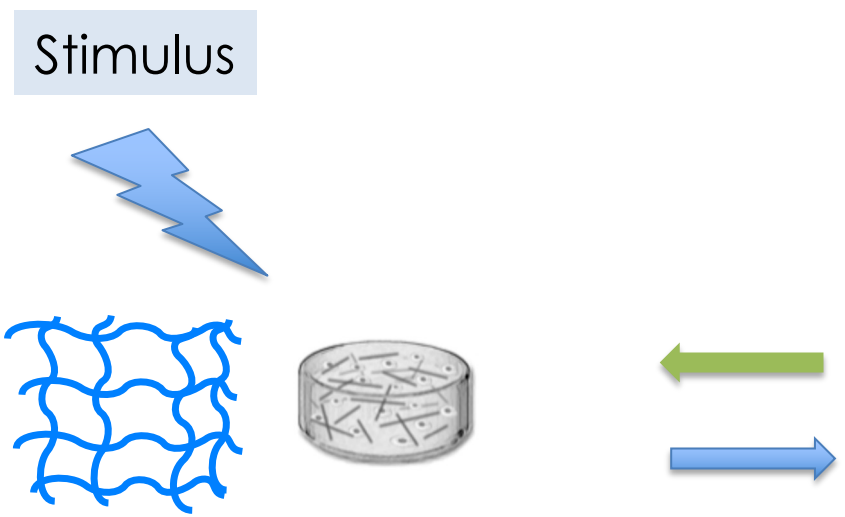
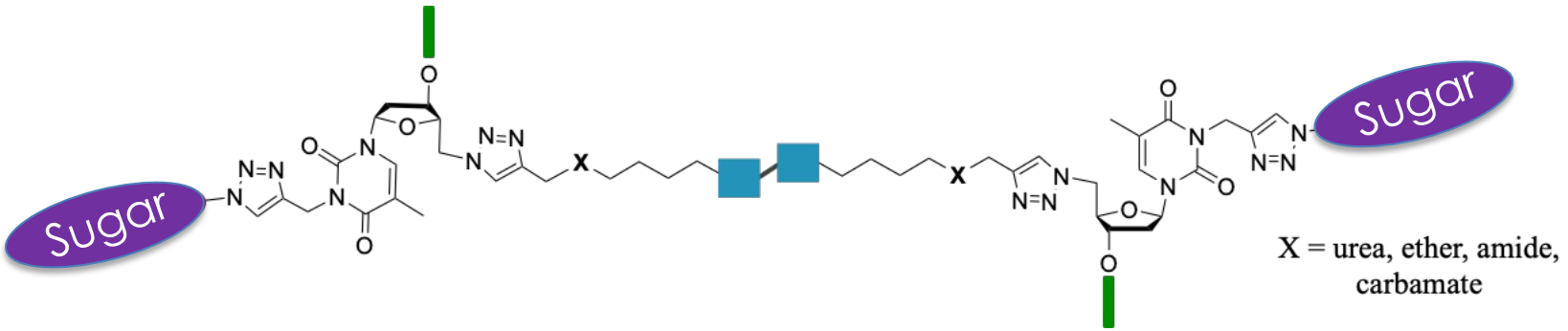
Molecular modulation of the mechanical, rheological and biological properties on demand



Smart supramolecular gel

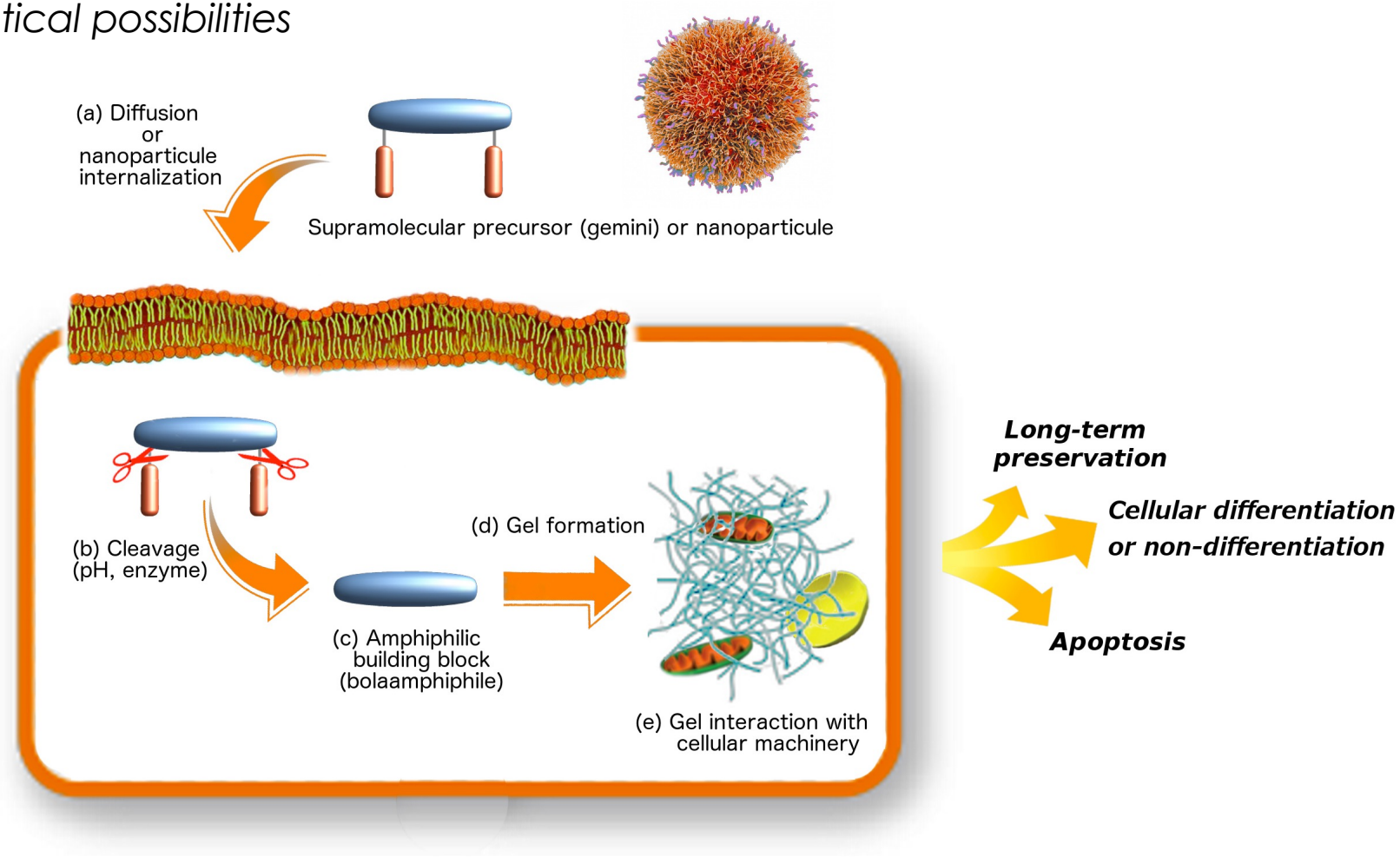


"Smart polymer-free soft materials"

-> Responsive supramolecular materials

Molecular modulation of the mechanical, rheological and biological properties on demand

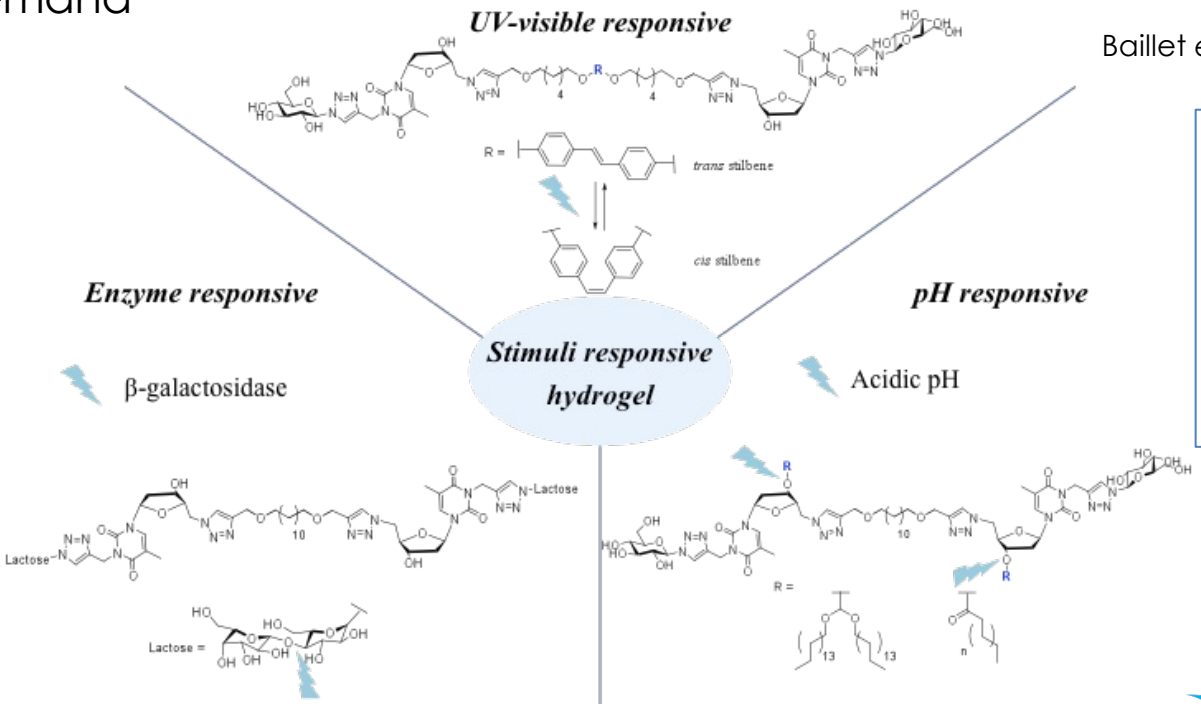
Theoretical possibilities



"Smart polymer-free soft materials"

-> Responsive supramolecular materials

Molecular modulation of the mechanical, rheological and biological properties on demand



Baillet, J. *et al. Soft Matter*, **2020**,

Baillet *et al. Chem. Commun*. **2020**

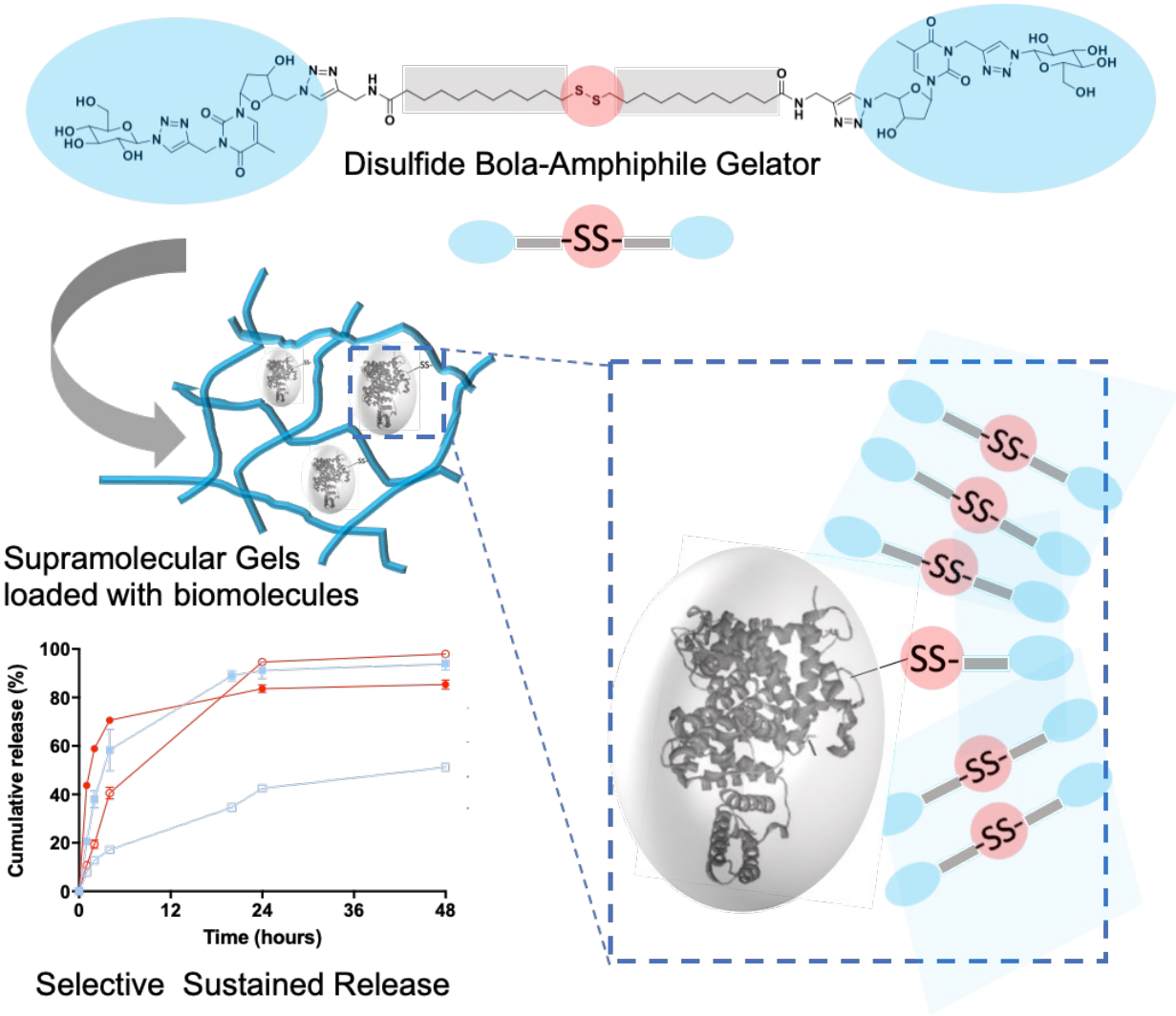
Red/Ox

Disulfide Based Low Molecular Weight Gel

Nitin D. Bansode, et al. Biomaterials Science **2020**

- Modulation of the biological properties (Promote angiogenesis, **gelator is a prodrug)**
- Gel formation intra cell (**Progelator-> generate gelation in cellulo**)

Sustained release of biomolecules

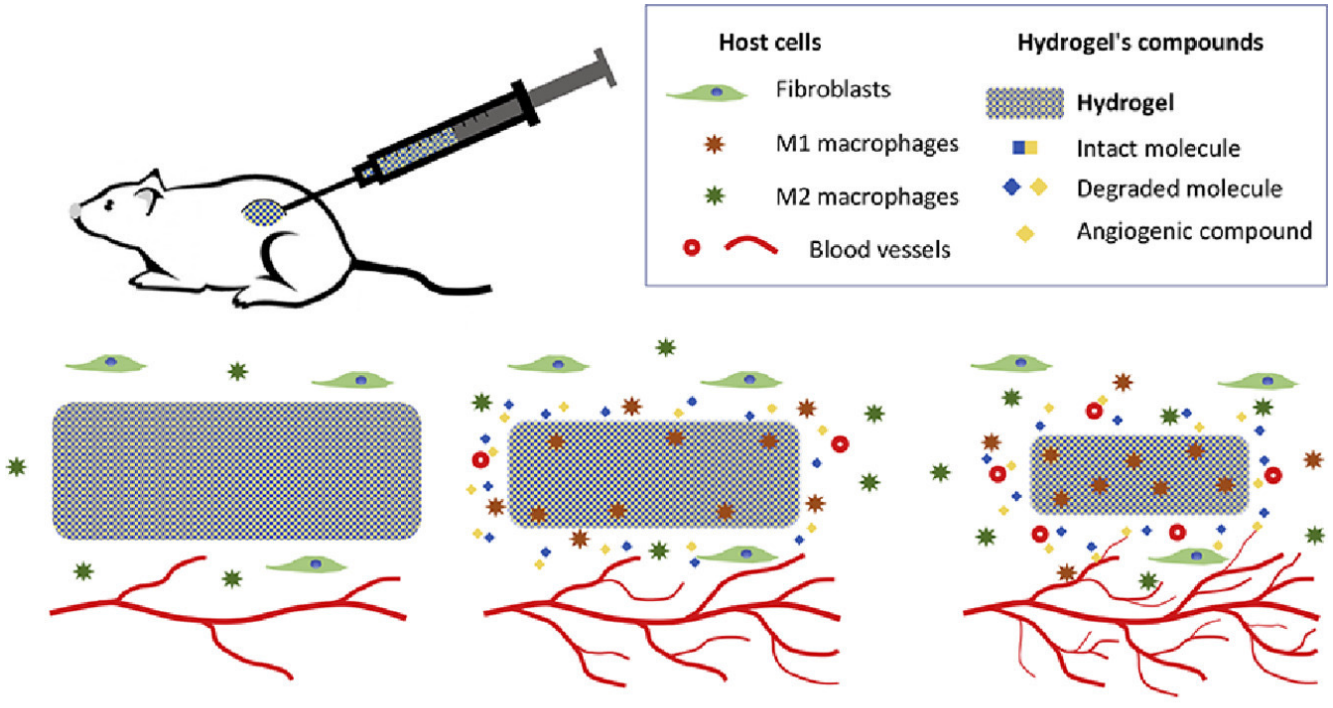


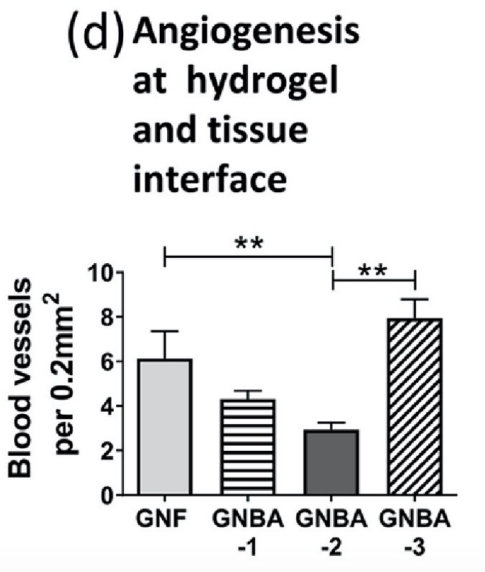
Disulfide Based Low Molecular Weight Gel For a Selective Sustained Release of Biomolecules

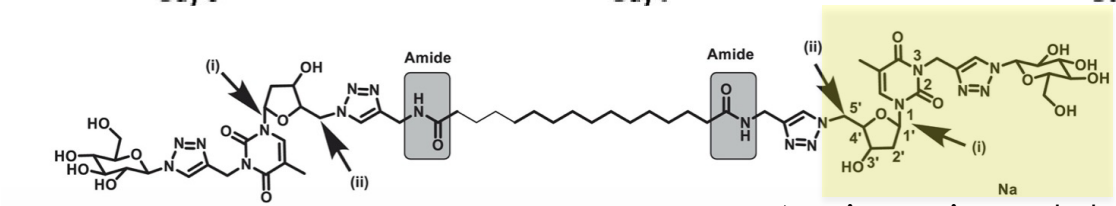
Nitin D. Bansode, et al. Biomaterials Science **2020**

« Prodrug gel »

Injectable supramolecular gel that **promote angiogenesis** through a bioactive degradation product







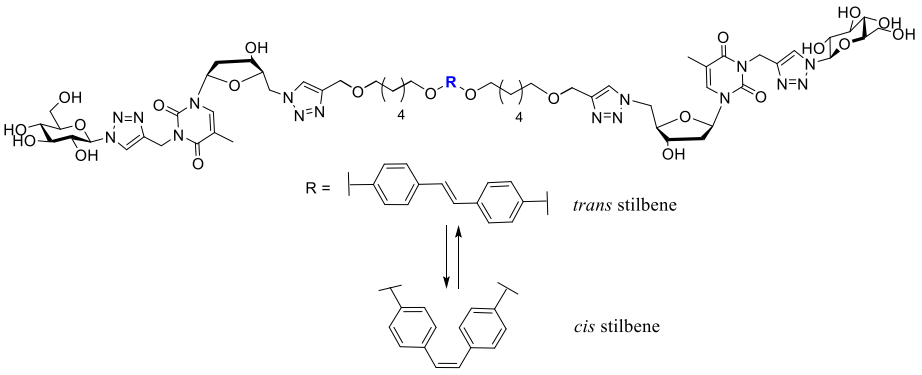
Angiogenic metabolite
(Probable agonist of the P2Y receptors (endothelial cells)

K.R. Sindhu *et al. Acta Biomaterialia*, **2020**, Vol 115, 197-209

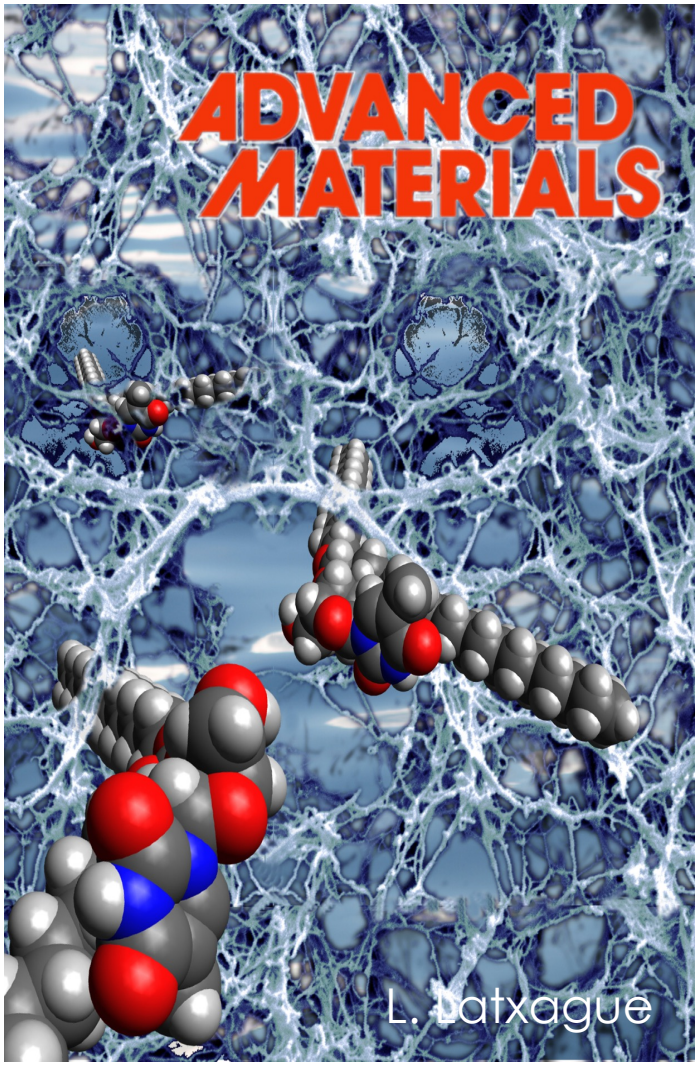
GLYCOSYL-NUCLEOLIPIDS SUPRAMOLECULAR GELS

SUPRAMOLECULAR SOFT MATERIALS IN SHORT (POLYMER FREE MATERIALS)

- ✓ Modulation of the mechanical and rheological properties
- ✓ Injectable (thixotropy)
- ✓ Stem cell culture
- ✓ Biocompatible materials
- ✓ No inflammation
- ✓ In vivo injection of stem cells (Regenerative medicine)
- ✓ Controlled/Sustained release of biologics and/or drugs
- ✓Smart supramolecular gels (pH, Ez, Light)
- ✓…

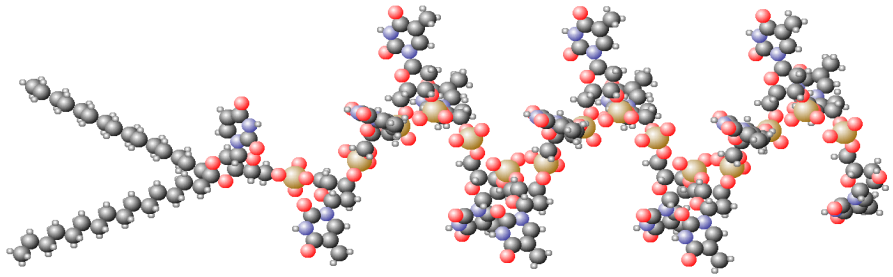


J. Baillet, V. Desvergnes, A. Hamoud, L.Latxague, and P. Barthélémy ***Adv. Mater*. 2018**, 1705078
L. Latxague, A. Gaubert and P. Barthélémy ***Molecules* 2018**, 23, 89

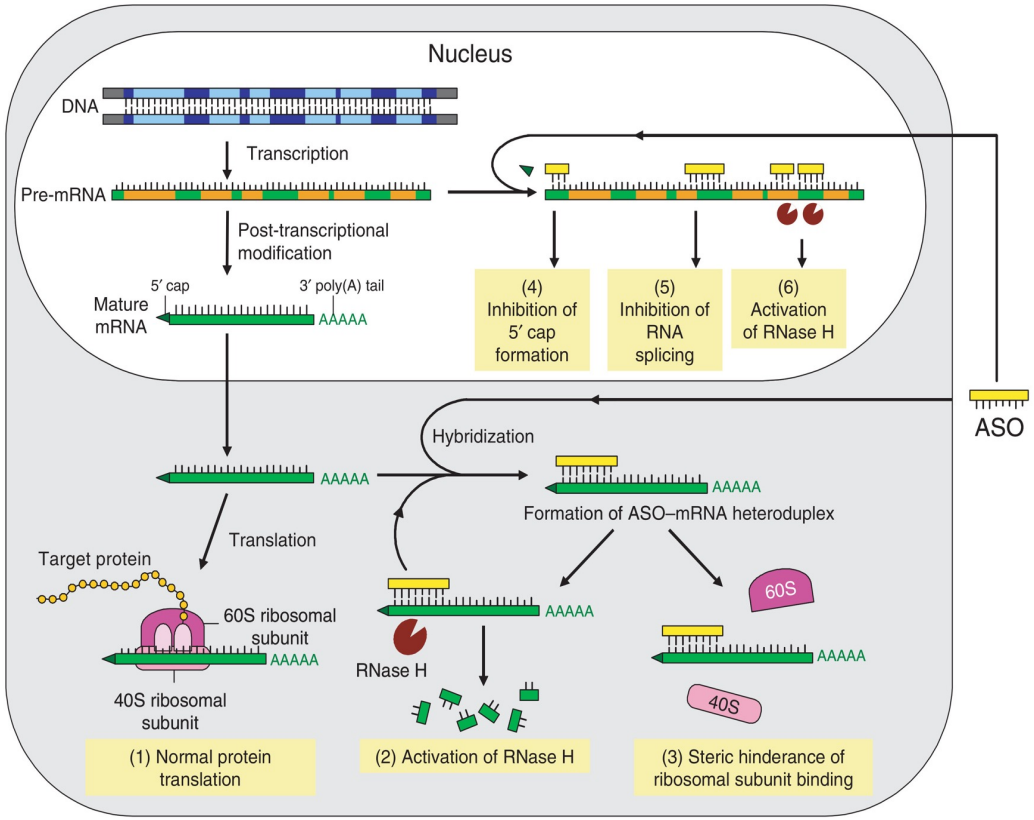


Part 3.

Lipid-Oligonucleotide Conjugates



Therapeutic Oligonucleotides, the context

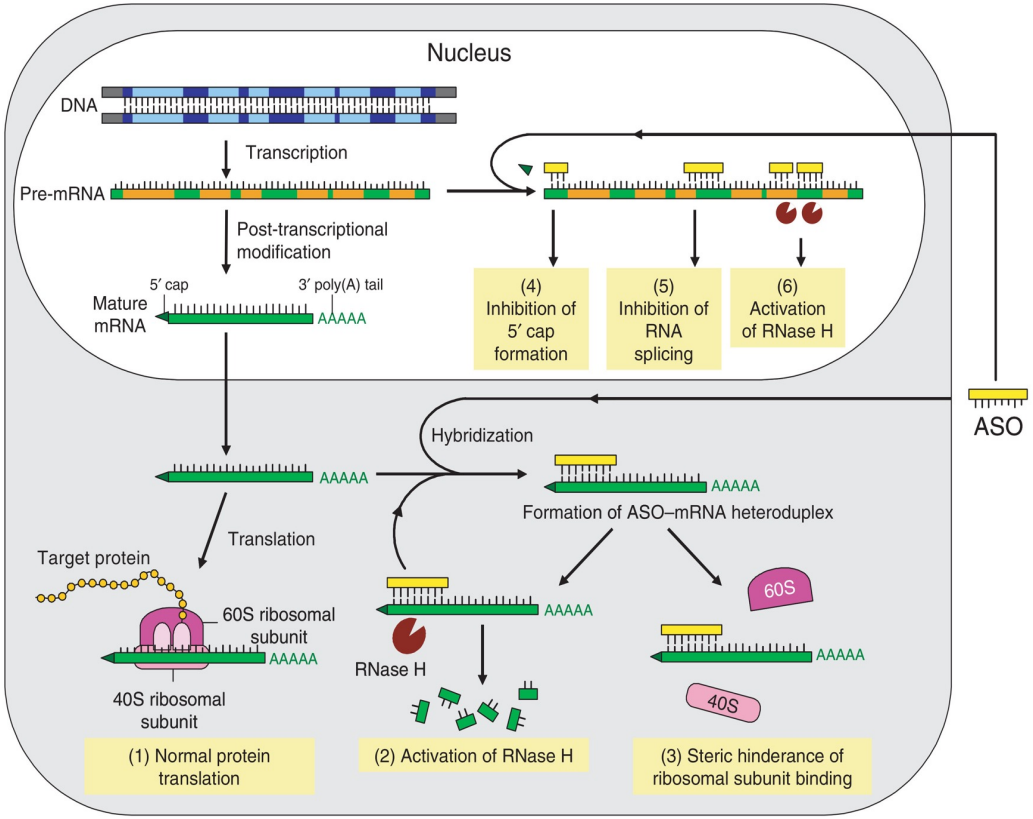


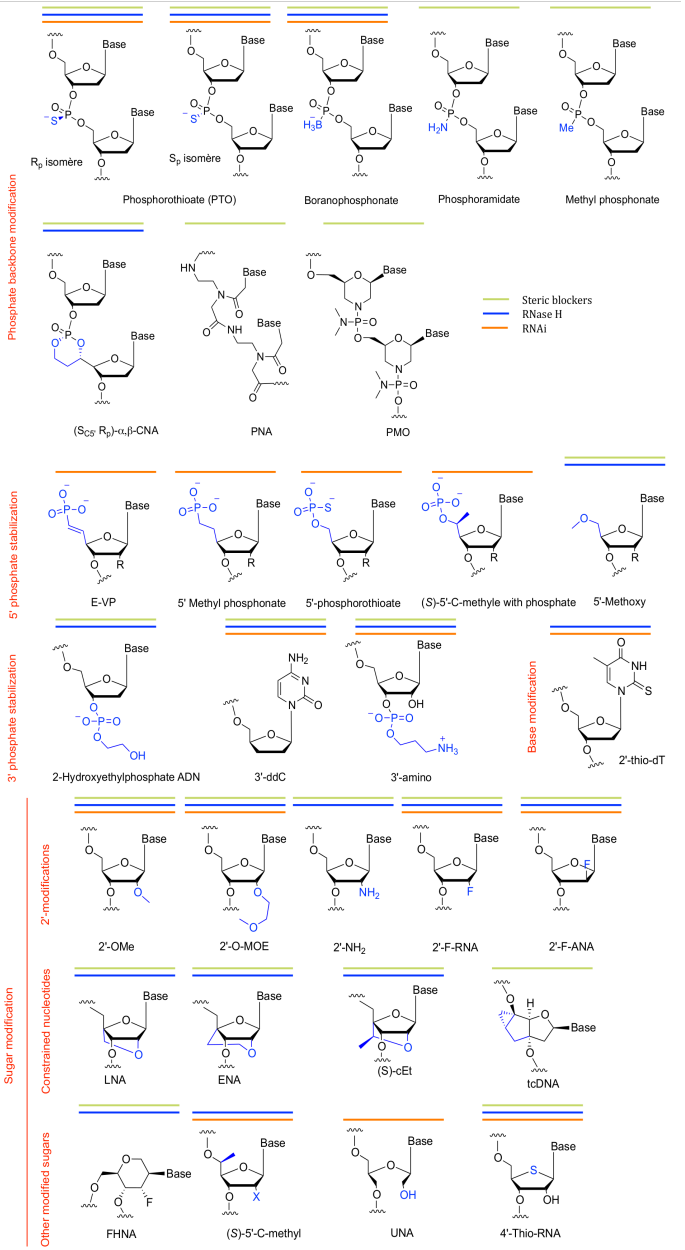
Therapeutic nucleic acids: antisense oligonucleotides (ASO)

ISSUES → **STABILITY**
DELIVERY

S. Benizri, A. Gissot, A. Martin, B. Vialet, M. W. Grinstaff, and P. Barthélémy Bioconjugate Chem., (**2019**)

Therapeutic Oligonucleotides, the context



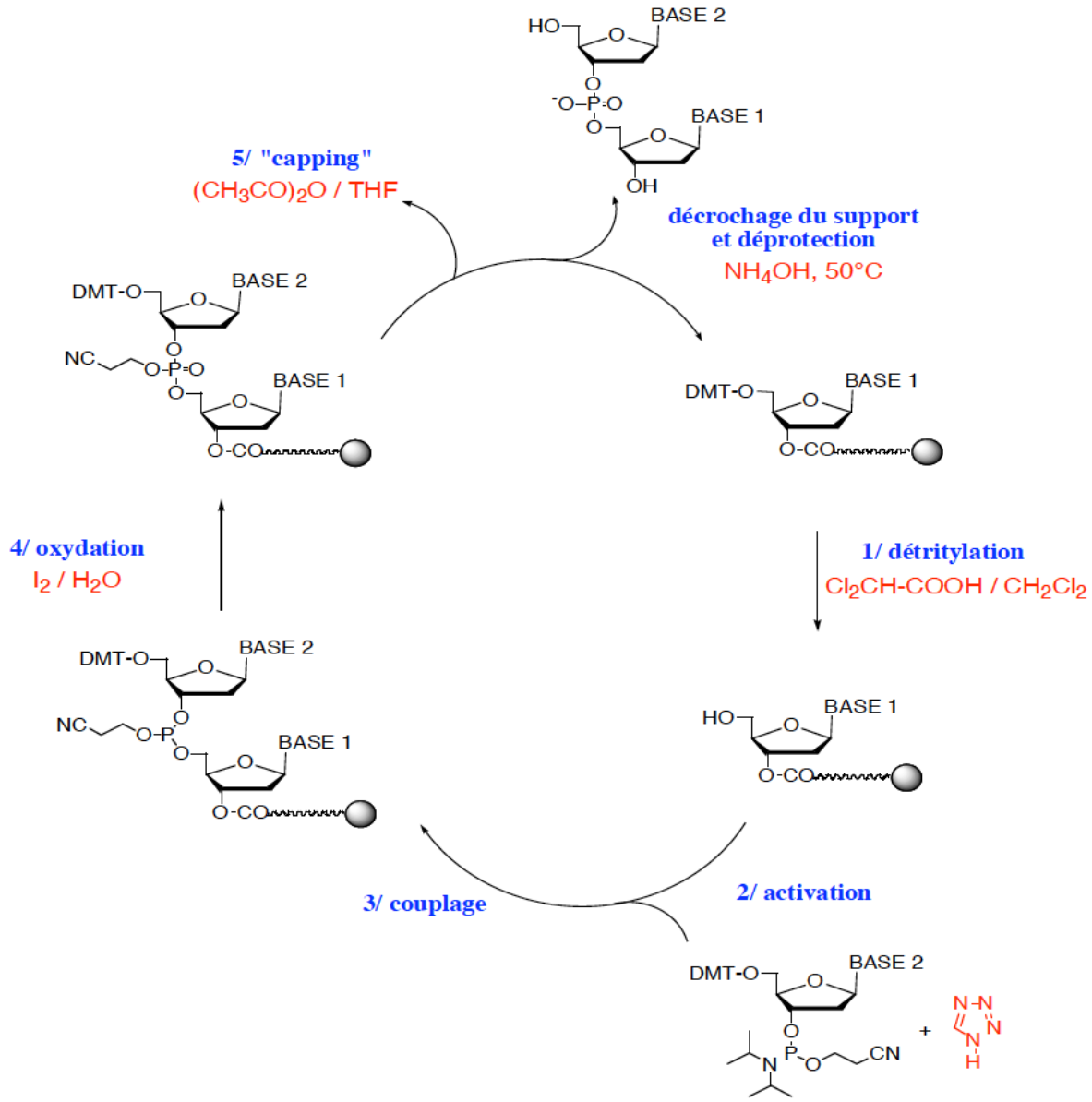


Therapeutic nucleic acids: antisense oligonucleotides (ASO)

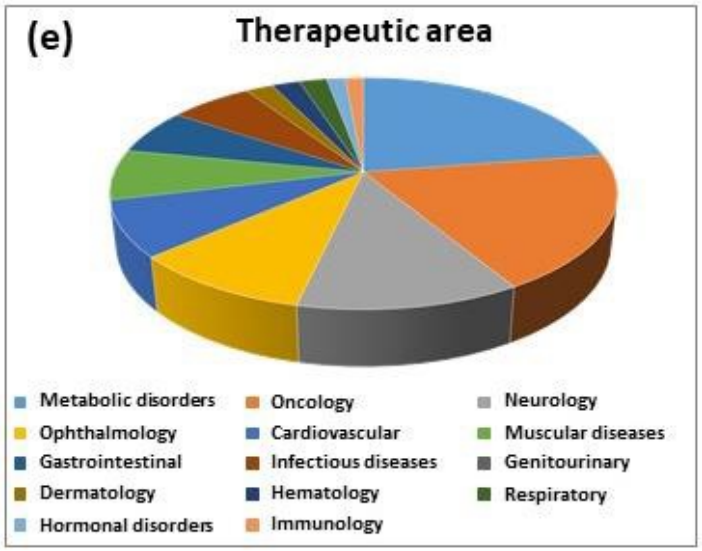
ISSUES → **STABILITY**
DELIVERY

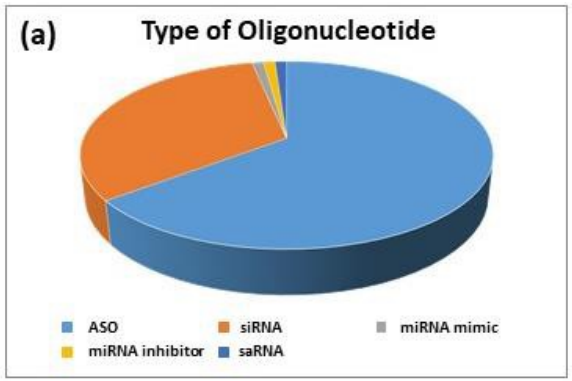
S. Benizri, A. Gissot, A. Martin, B. Vialet, M. W. Grinstaff, and P. Barthélémy Bioconjugate Chem., (**2019**)

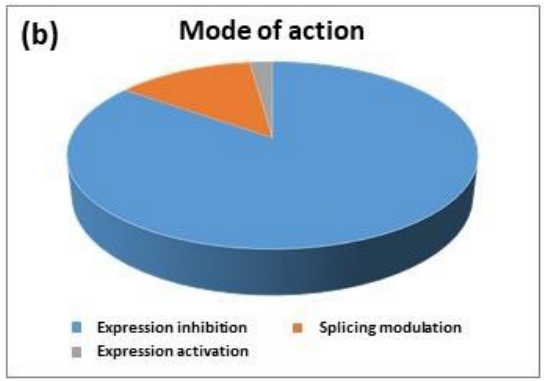
Oligonucleotide synthesis via phosphoramidite approach

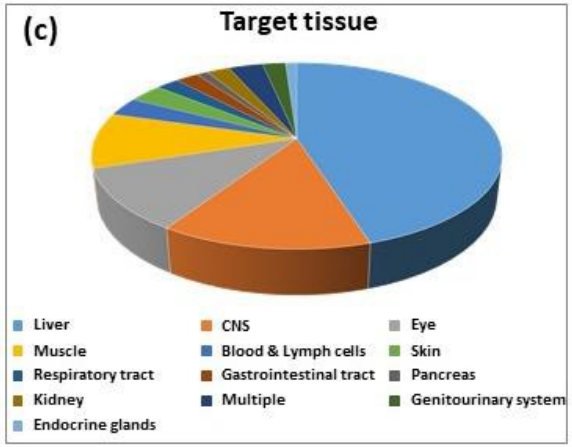


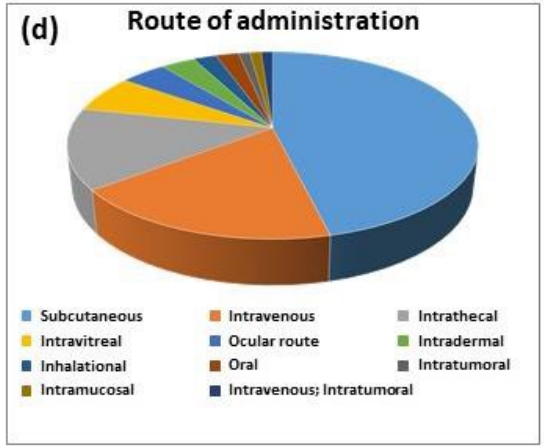
Therapeutic Oligonucleotides











- More than 12 oligonucleotides on the market
- More than 40 oligonucleotides in clinical developement

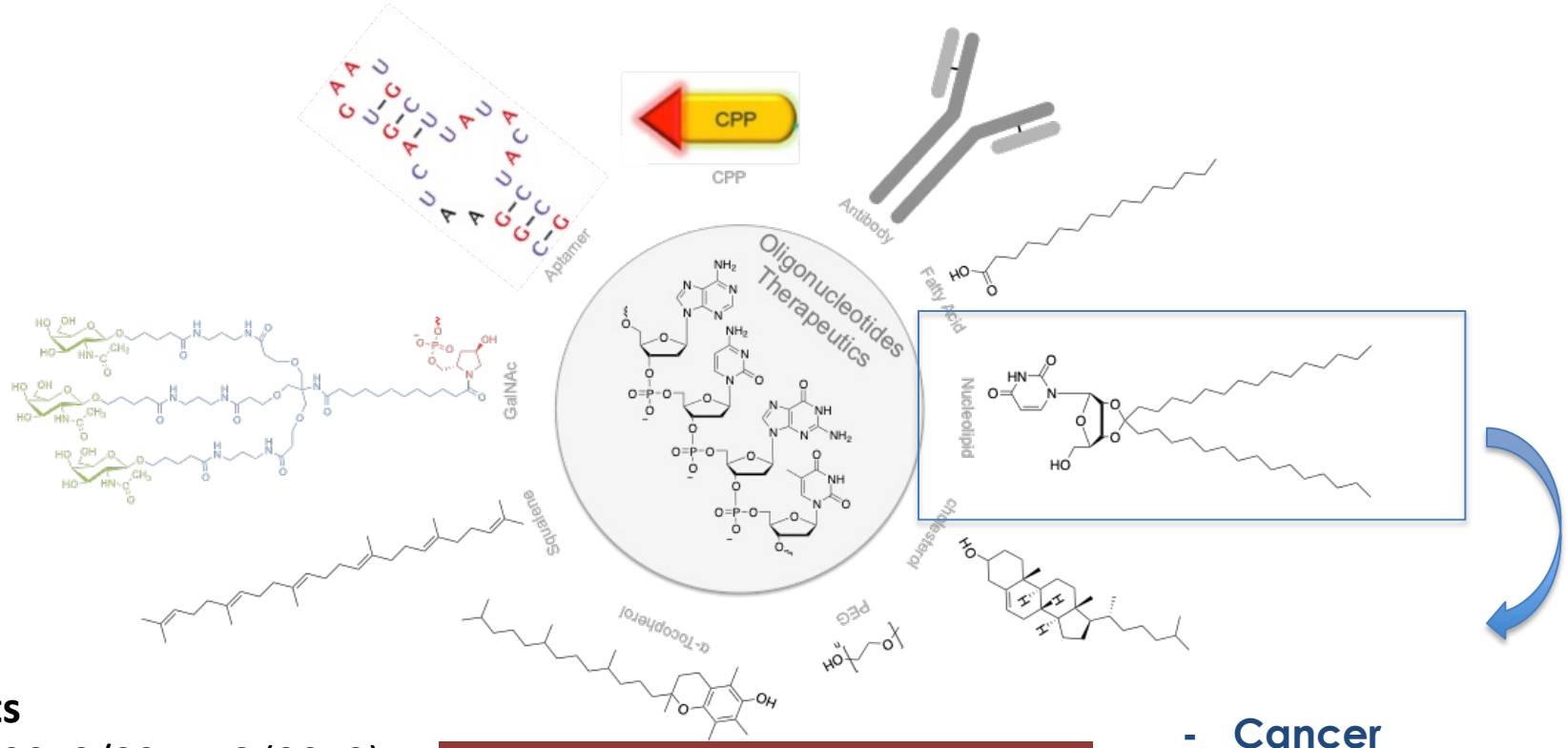
Moumné, L.; Marie, A.-C.; Crouvezier, N. Oligonucleotide Therapeutics: From Discovery and Development to Patentability. *Pharmaceutics* **2022**, *13*,

LIPID-OLIGONUCLEOTIDE CONJUGATES

InsermTransfert

Delivery of therapeutic nucleic acids?

- Nucleic acids carriers (SNALP, LNP, LPR etc)
- Bioconjugates



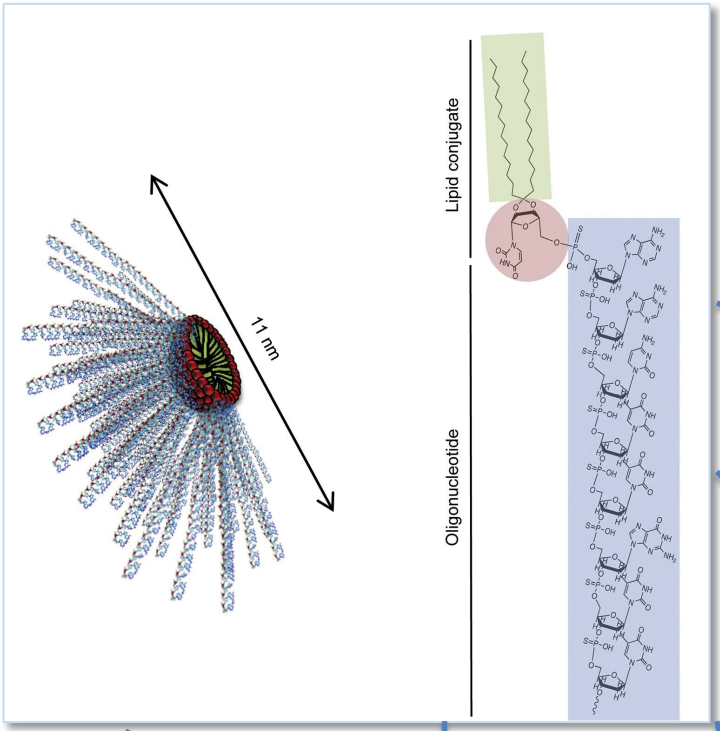
Patents
PCT/IB2013/001516 (2013)
PCT/IB2013/001517 (2013)

New Chemical Entities

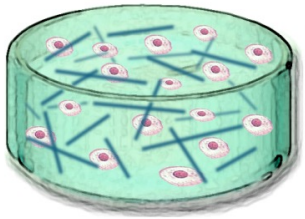
- **Cancer**
- **Antibiotic resistance**
- **…**

S. Benizri, A. Gissot, A. Martin, B. Vialet, M. W. Grinstaff, and P. Barthélémy Bioconjugate Chem., (**2019**)

LIPID-OLIGONUCLEOTIDE CONJUGATES

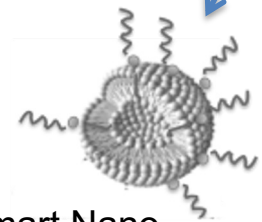


GEL



S. Benizri, et al.
Biomater. Sci., 2021,9, 3638-3644

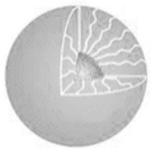
Coformulation with lipids and/or nucleolipid



Smart Nano

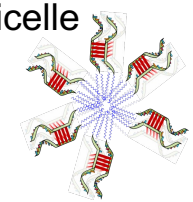
Gissot, A., et al.(2008)
Chemical Communications DOI: 10.1039/b812398e

Self-assemblies



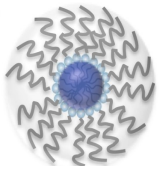
Micelle

G4-Micelle



Vialet, B., et al.
(2017) Chemical Communications,
DOI: 10.1039/c7cc05693a

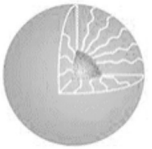
Self-assemblies + Drug



Responsive nano carriers

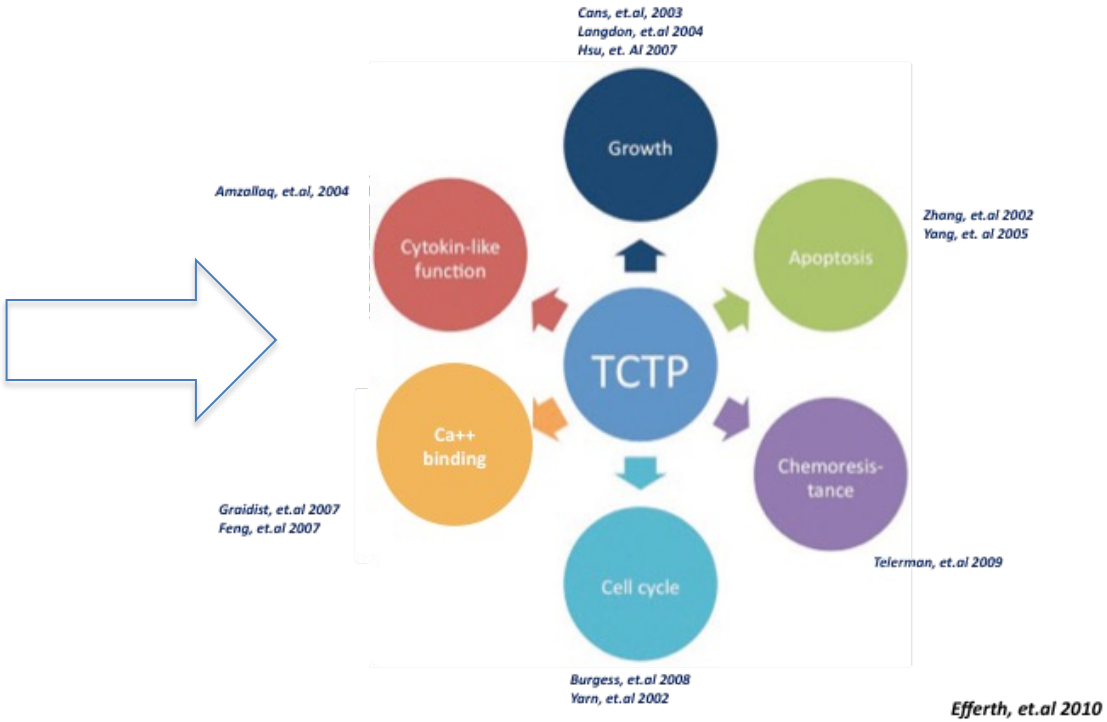
Pokholenko, O. et al.
Journal of Materials Chemistry B,
DOI: 10.1039/c3tb20357c

PROSTATE CANCER



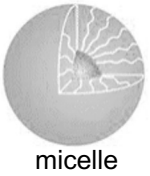
TCTP (Translationally controlled tumor protein) is a multifunctional protein

TCTP-LASO



Dr. Palma Rocchi
Centre de Recherche en Cancérologie de Marseille
CRCM, Inserm UMR 1068-CNRS UMR 7058

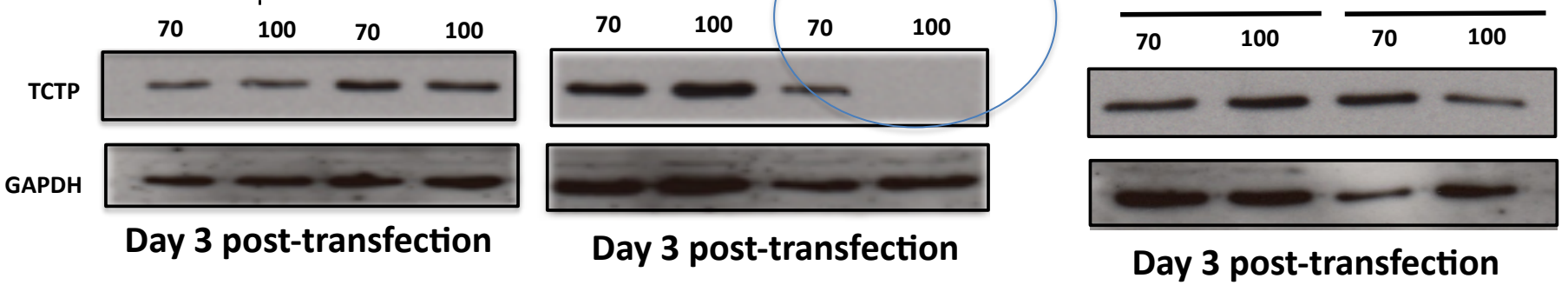
PROSTATE CANCER



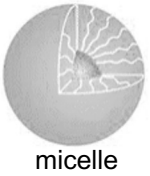
LASO 15 PTO Inhibits TCTP expression

~~without Oligofectamine~~

ASO ScrPTO ASO 15PTO LASO ScrPTO LASO 15PTO LASO ScrLNA LASO 15LNA

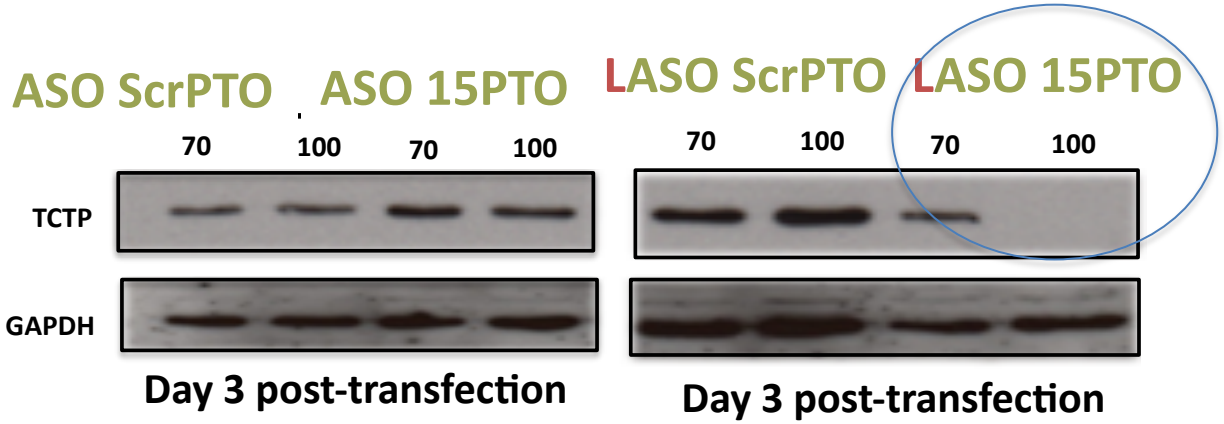


PROSTATE CANCER

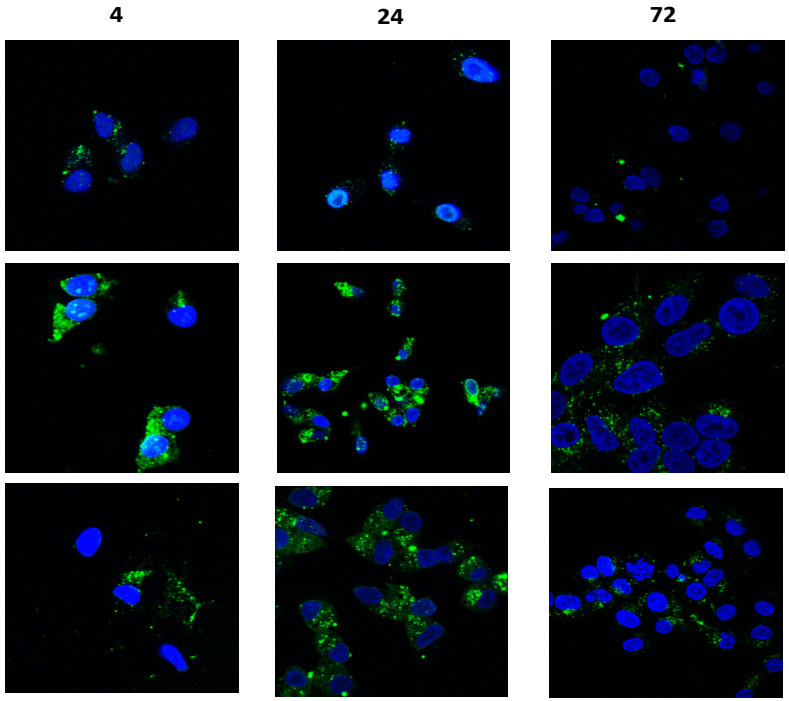


LASO 15 PTO Inhibits TCTP expression

~~without Oligofectamine~~



LASO 15PTO features the best stability and nuclear bioavailablity compared to ASO 15PTO and LASO 15LNA

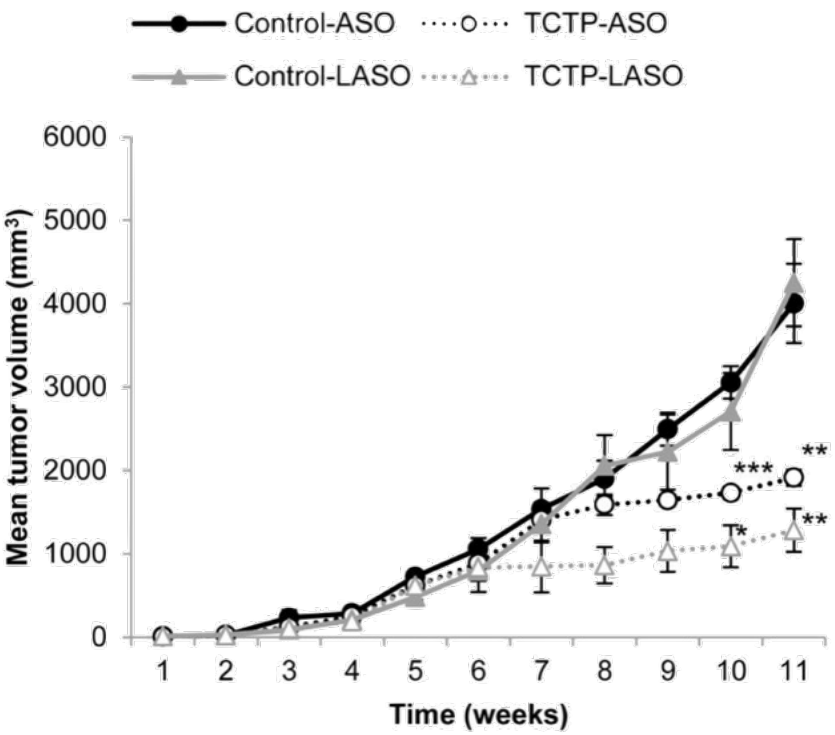


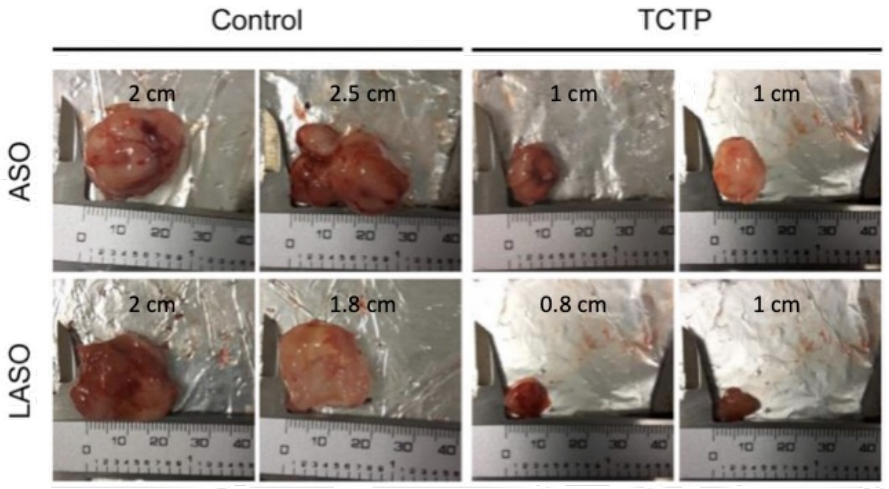
Barthélémy *et al.* PCT/IB2013/001516 (2013)
Barthélémy *et al.* PCT/IB2013/001517 (2013)

PROSTATE CANCER

LASO 15 Inhibits TCTP expression

micelle





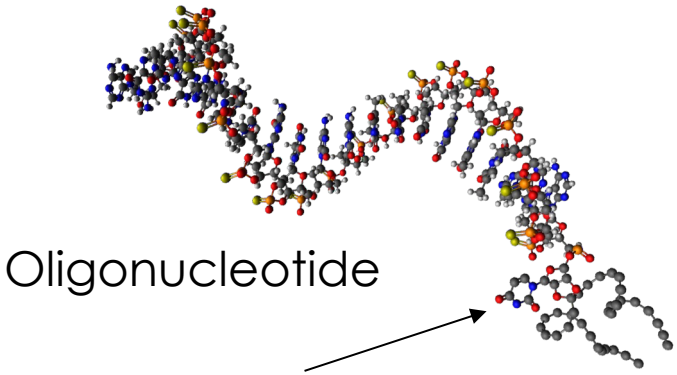
Sara Karaki *et al. J. Controlled Release* **2017**

Animals: mice xenografted with PC3 (hormono- resistant) cells, 8 animals/ group

Treatment: IP injection; 10mg/kg; daily injection for 7 days, then 3 injections/ week for 9 weeks.

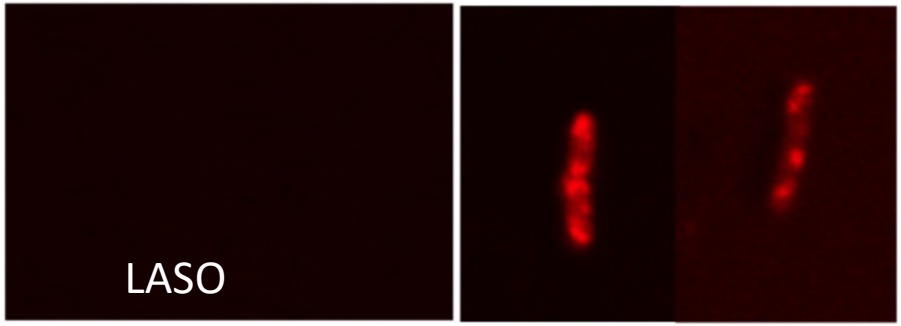
Concept : LASO targeting mRNA $bla_{CTX\text{-}M\text{-}15}$?

Can we takes advantage of LASO supramolecular properties for antisense delivery in bacteria?



Supramolecular

yes



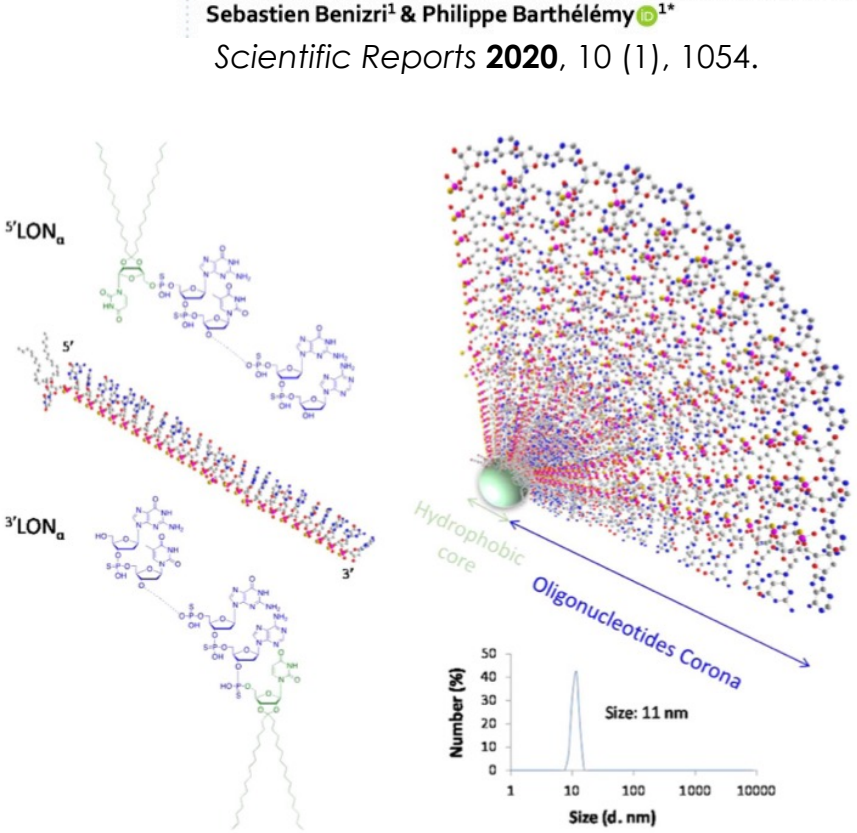
Internalization in *E. coli* observed by confocal microscopy

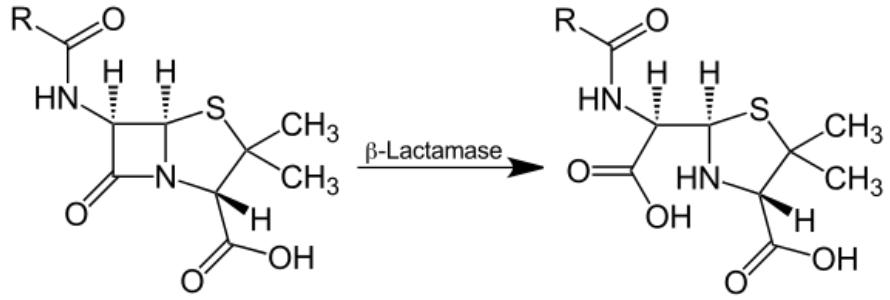
OPEN

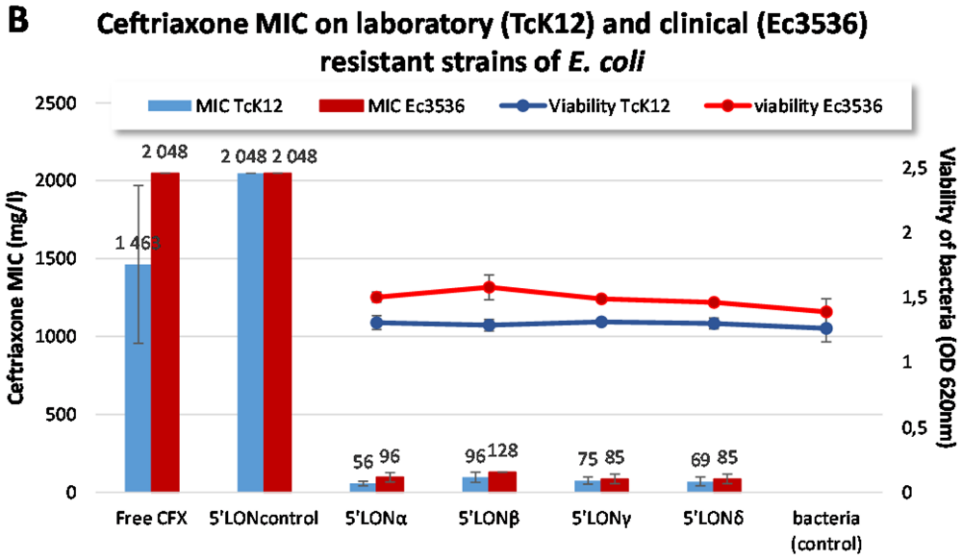
Lipid oligonucleotides as a new strategy for tackling the antibiotic resistance

Tina Kauss[1*], Corinne Arpin[2*], Léa Bientz[2,3], Phouc Vinh Nguyen[1,3], Brune Vialet[1], Sebastien Benizri[1] & Philippe Barthélémy[1*]

Scientific Reports **2020**, 10 (1), 1054.

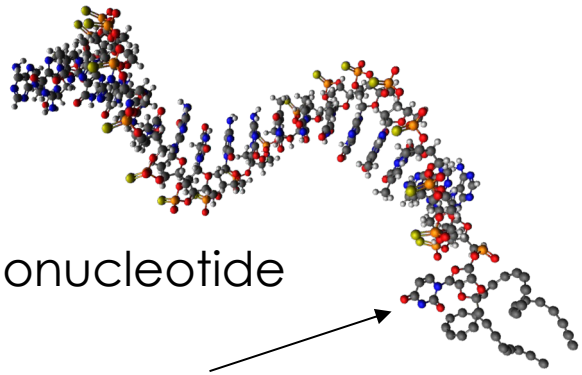






- *Delivery of the oligonucleotide sequences in the prokaryotic cells*
- *Decrease the Minimum inhibitory concentration of resistant bacteria to a third generation cephalosporin, the ceftriaxone.*

Can we takes advantage of LASO supramolecular properties for sustained release?



Oligonucleotide

Nucleolipid

Supramolecular

?

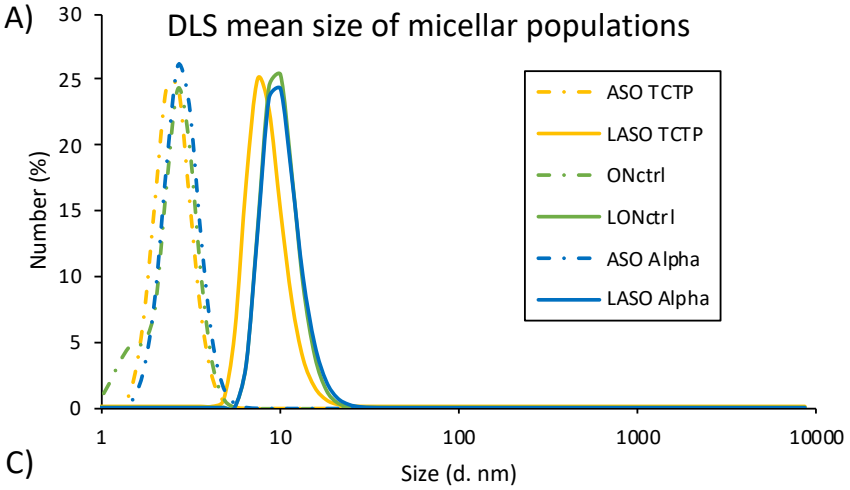
Table 1 Sequences of tested ONs and LONs

Name[a]	Length (mers)	Sequence (5′→3′)
ASO_{TCTP}	20	5′ AAC TTG TTT CCT GCA GGT GA 3′
$LASO_{TCTP}$	21	5′ (C_{15})U* AAC TTG TTT CCT GCA GGT GA 3′
ASO_{α}	25	5′ GCG CAG TGA TTT TTT AAC CAT GGG A 3′
$LASO_{\alpha}$	26	5′ (C_{15})U*GCG CAG TGA TTT TTT AAC CAT GGG A 3′
ON_{Ctrl}	19	5′ CGT GTA GGT ACG GCA GAT C 3′
LON_{Ctrl}	20	5′ (C15)U* CGT GTA GGT ACG GCA GAT C 3′

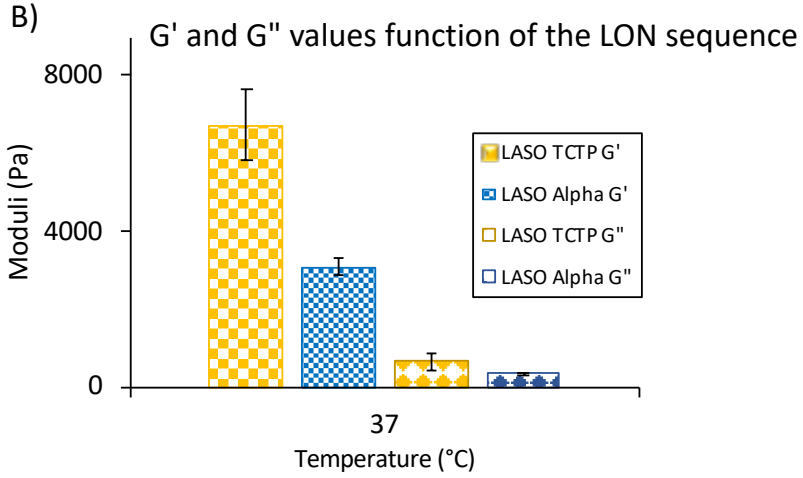
[a] LONs being 5′ conjugates of the ON sequence with ketal bis-C_{15} lipid.

Physico-chemical studies of ON/LON

A)



B)

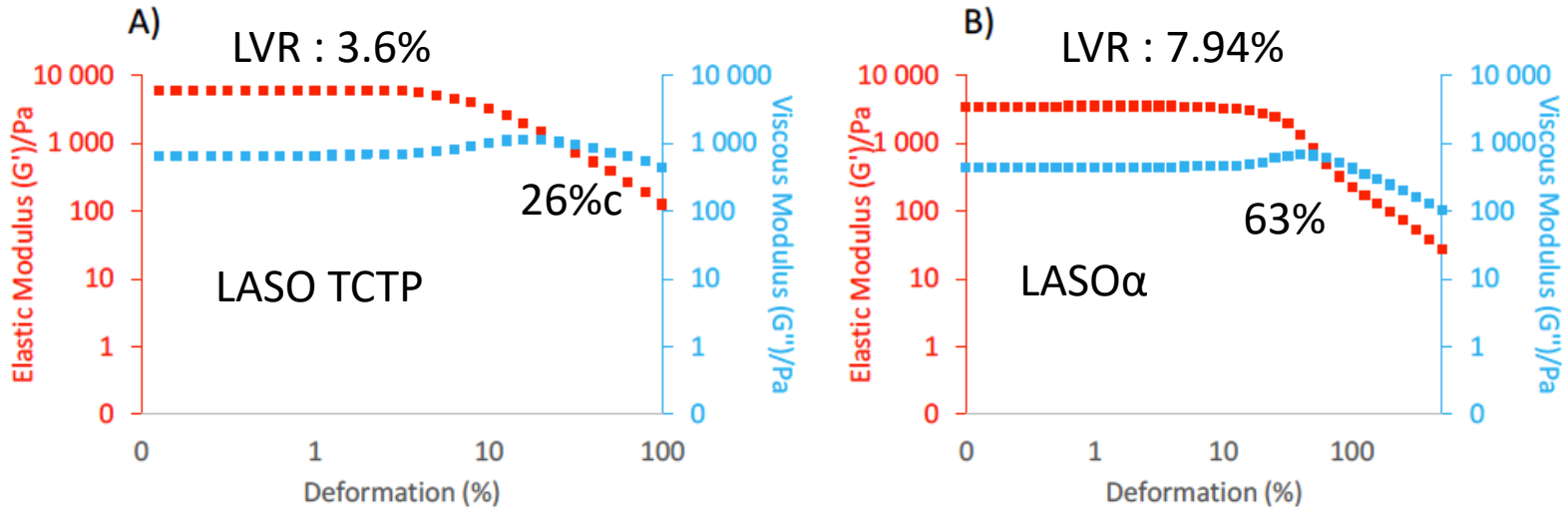


C)

	Size (nm)	G' (Pa)	G'' (Pa)	LVR (%)	Breaking point (%)	Thixotropy
ASO_{TCTP}	3.16 ± 0.41			No Gelation		
$LASO_{TCTP}$	14.12 ± 0.17	6740 ± 927	684 ± 21	3.16	26 ± 5	Yes
ON_{ctrl}	3.52 ± 0.55			No Gelation		
LON_{ctrl}	14.35 ± 0.56			No Gelation		
ASO_{α}	3.91 ± 0.34			No Gelation		
$LASO_{\alpha}$	15.05 ± 0.48	3088 ± 225	368 ± 2	7.94	63 ± 8	Yes

Viscoelastic properties

Amplitude sweep experiments



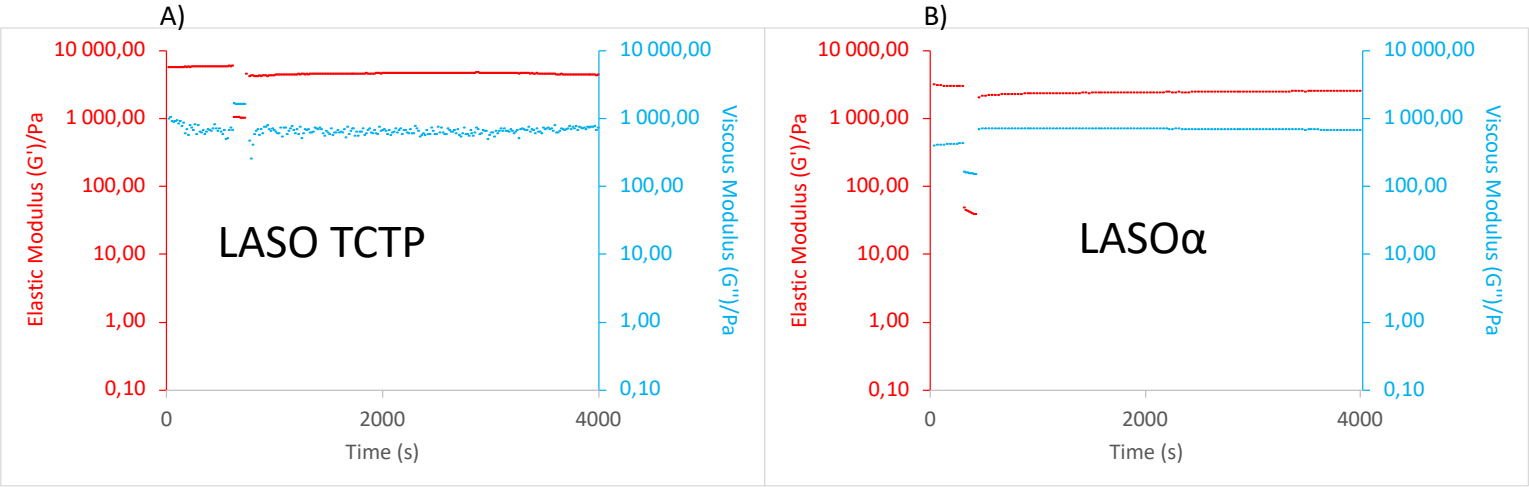
Amplitude sweep experiments of hydrogels at13.9 mM (T° 37°C, 1 Hz, shear strain 0.01% to 100%).

LASOα is a tougher material compared to LASO TCTP

⟹ **Viscoelastic properties are sequence dependent**

Viscoelastic properties

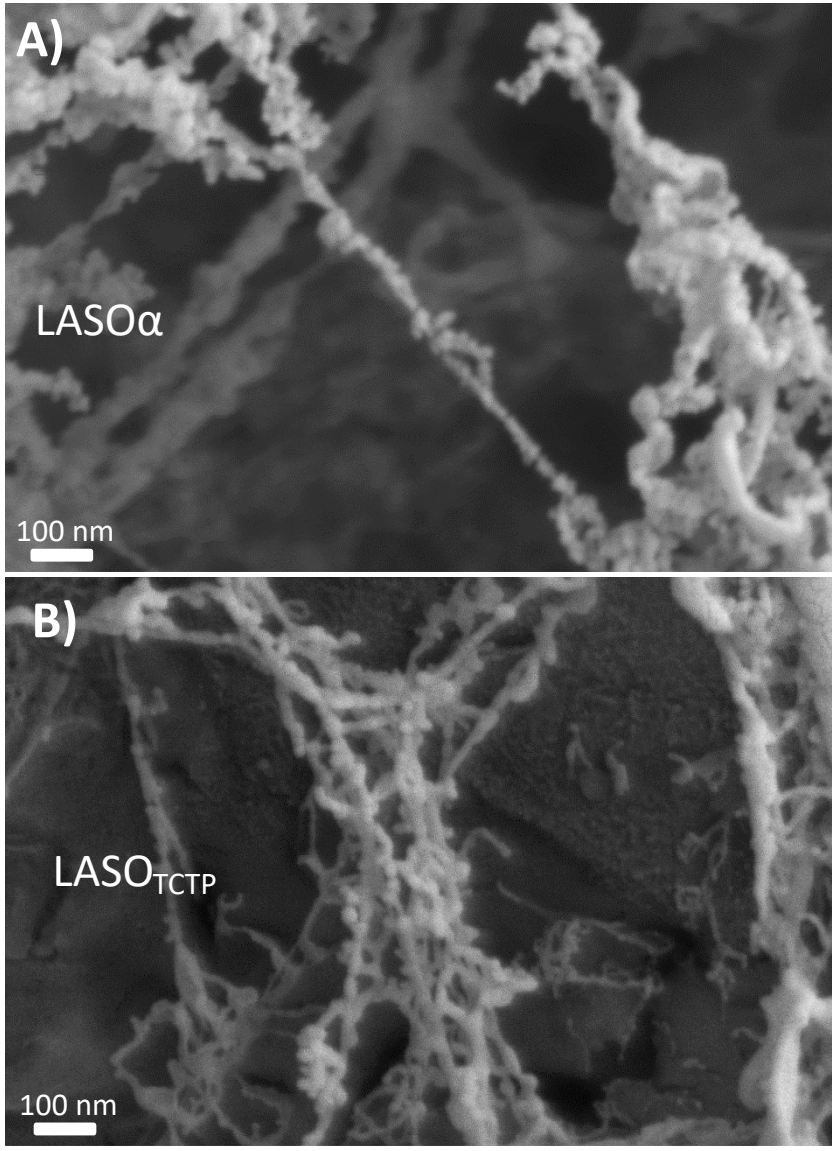
Step-strain measurements



Step-strain experiments of A) LASOTCTP and B) LASOα hydrogels (13.9 mM) at 37°C and with a fixed angular frequency of 1 Hz. The gels were swept from 0.03% (structuration step) to 30% (destructuration step) shear strain and then back to 0.03% (structuration step) shear strain.

⟹ Both LASOa and LASO TCTP biomaterials are **thixotropic**

Gel morphologies

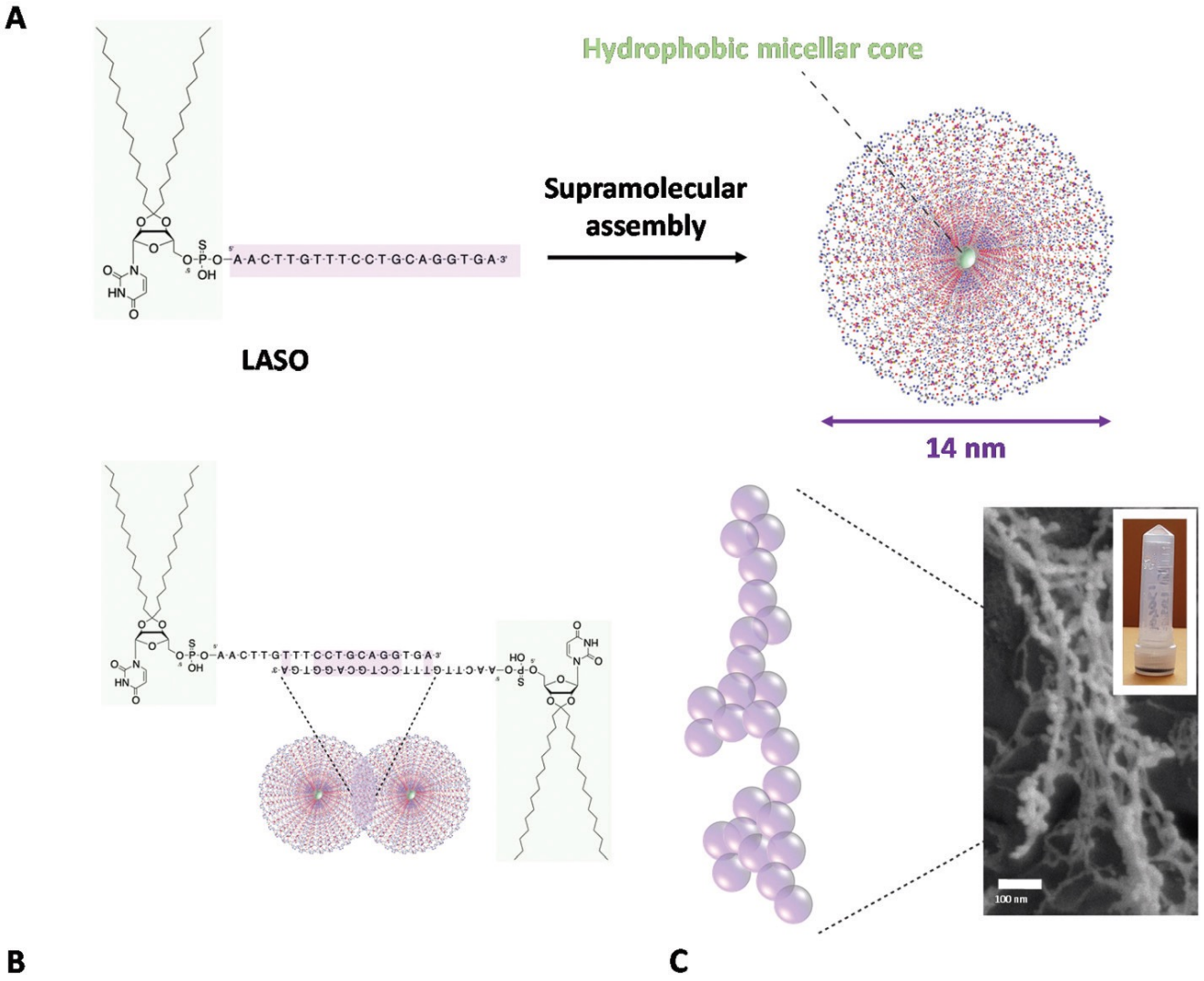


LASOα and $LASO_{TCTP}$ – based gels exhibited dense supramolecular networks with fibers of 10–20 nm in diameter.

For non-gelator molecules (LON_{Ctrl}), cryo-SEM images showed simple micellar systems of 10–20 nm in size

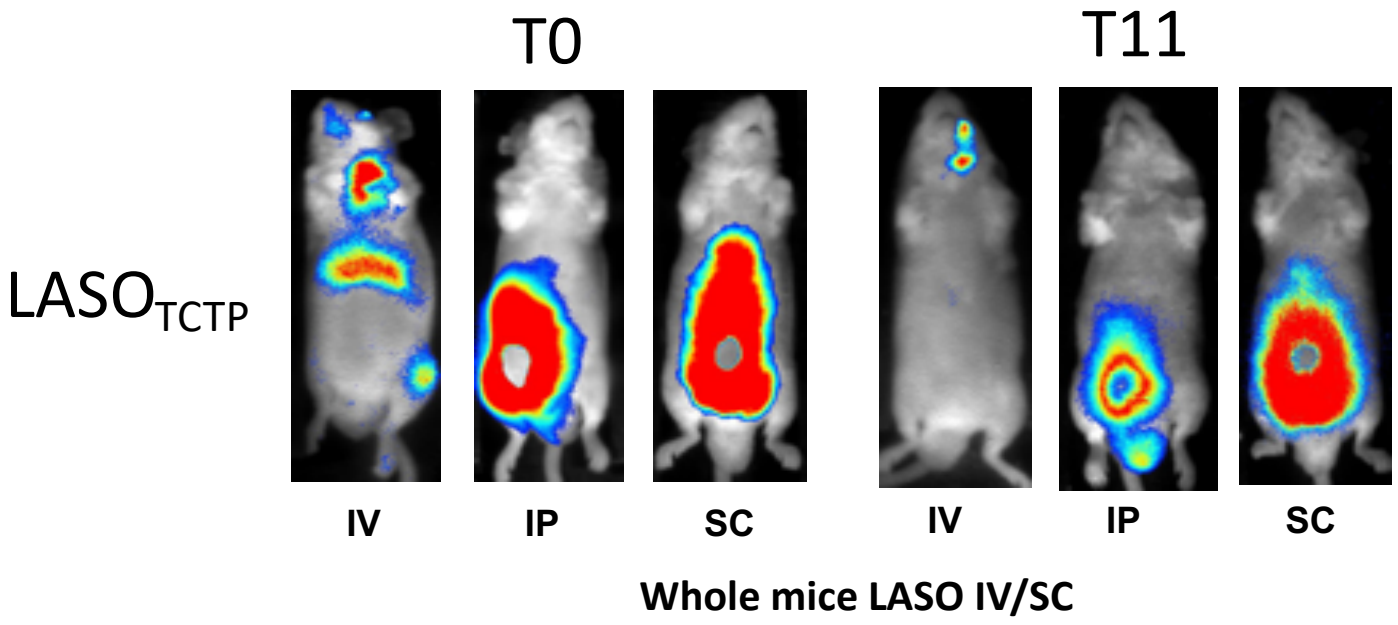
Cryo-SEM images of (A) LASOα, (B) LASOTCTP at 13.9 mM in PBS 1× (scale bar 100 nm)

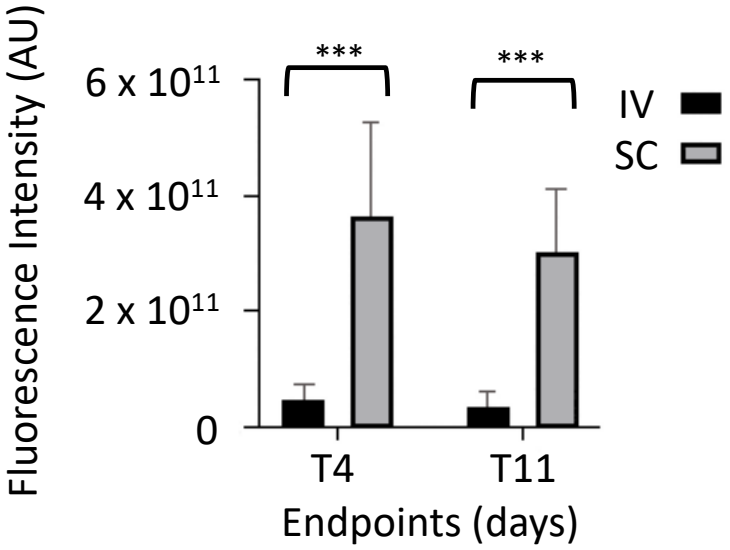
Supramolecular behaviors



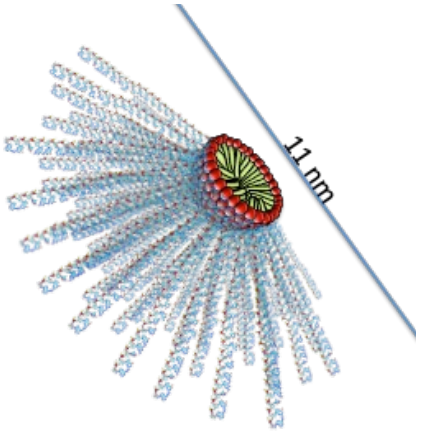
Micelle-micelle supramolecular interactions stabilizing an entangled pearl-necklace network at the nanoscales

In vivo injection





Conclusions LASOs gels



MAIN RESULTS

- ✓ **LASOs supramolecular properties allow the formation of hydrogels** (micelle–micelle interactions stabilized *via* a self-complementarity mechanism).

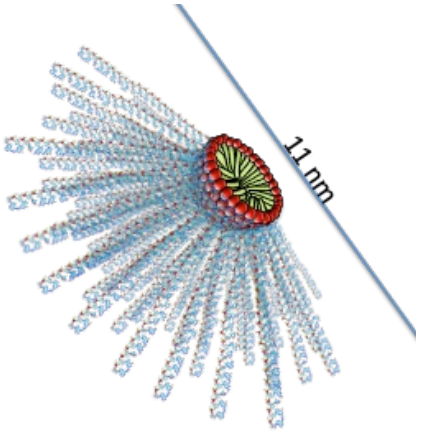
- ✓ **LASO TCTP and LASOa are the first lipid-oligo to be used as hydrogel for SC administration**

- ✓ ***In vivo* studies revealed that the LASOs exhibit a sustained release after SC administration**

- ✓ **Self-delivery" of LASOs both *in vitro* and *in vivo* without transfecting reagents**

S. Benizri, A. Gaubert et al. ***Biomater. Sci.***, 2021,**9**, 3638-3644

Conclusions LASOs gels



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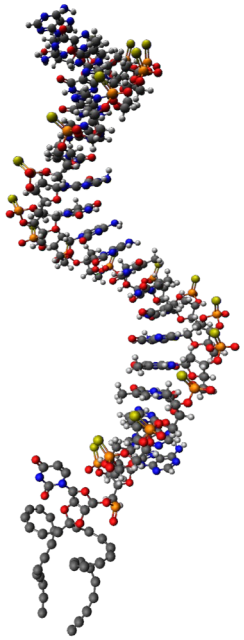
S. Benizri, A. Gaubert et al. ***Biomater. Sci.***, 2021,**9**, 3638-3644

A quick study of the self-complementarity properties achieved on **FDA approved therapeutic oligonucleotides**, including Mipomersen, Inotersen, Eterplirsen, Golodirsen, Nusinersen indicates that **these drugs are good candidates for gelation**

Open questions: - Biodistribution <-> **modifications** <-> Mode of administration (IV, SC)

Crauste-Manciet Sylvie (PU-PH)
Desvergnes Valérie (CR)
Gaubert Alexandra (MCU)
Gissot Arnaud (MCU)
Kauss Tina (MCU)
Latxague Laurent (MCU)
Vacher Gaelle (MCU)
Verget Julien (ITA)
Vialet Brune (ITA)
Recart Agnès (ITA)
Julie Baillet (D)
Sébastien Benizri (D)
Guillaume Bougueon (D)
Aladin Hamoud (D)
Koffi Kowouvi (D)
Geoffrey Prevot (D)
Nitin Bansode (Post Doc)
Naila Mebarek (ATER)
Jessica Labarre-Lainé (Post Doc
…
Aliès Bruno (MCU)
Ba Boubakar (MCU-PH)
Ferey Ludivine (MCU)
Gaudin Karen (Prof.)
Langlois Marie-Hélène (MCU)
Millet Pascal (MCU-PH)
Thu Van Nguyen (ITA)
…

CHEMBIOPHARM



Thanks for your attention

http://chembiopharm.fr

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