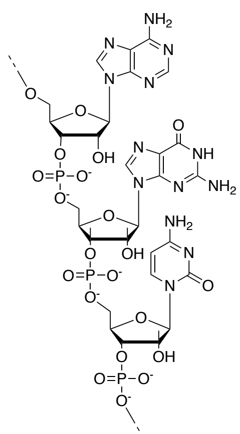
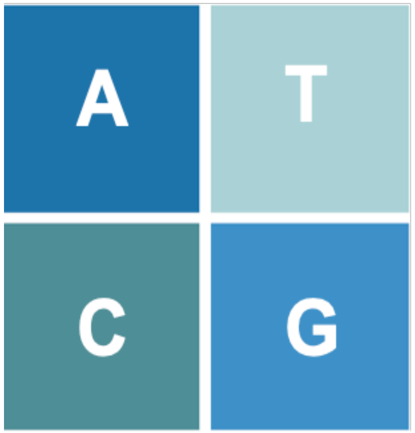
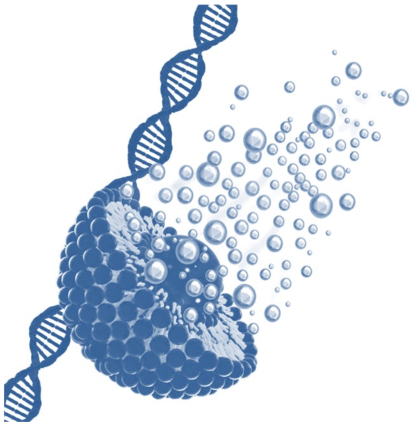
January 22-27, 2023
Les Houches (Haute-Savoie, France)

NUCLEIC ACID BASED BIOCONJUGATES

FOR BIOMEDICAL APPLICATIONS







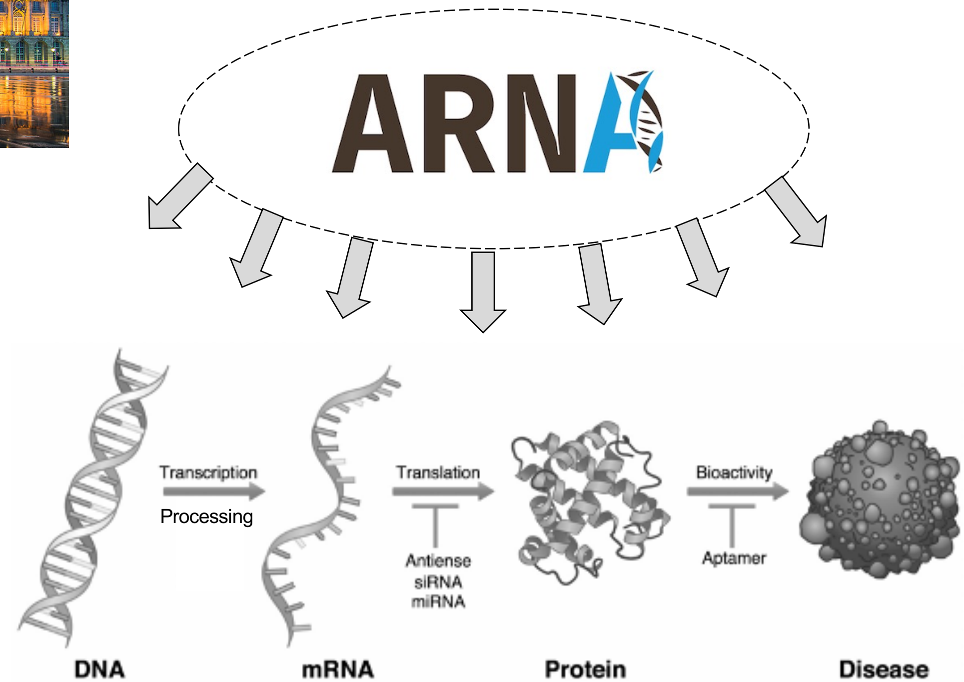
ARNA, INSERM U1212 / UMR CNRS 5320
ChemBioPharm

Prof. Philippe Barthélémy
philippe.barthelemy@inserm.fr

ARNA Laboratory

Nucleic Acids: Natural and Artificial Regulations

INSERM U1212, UMR CNRS 5320



- ✓ Understand key processes involved in gene expression (Transcription, Processing, Translation)
- ✓ Interfere with these processes using oligonucleotide derivatives
- ✓ Construct novel synthetic nucleic acid based bioconjugates

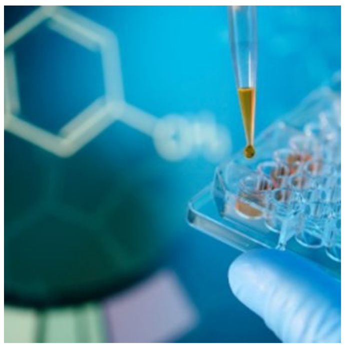
https://arna.cnrs.fr

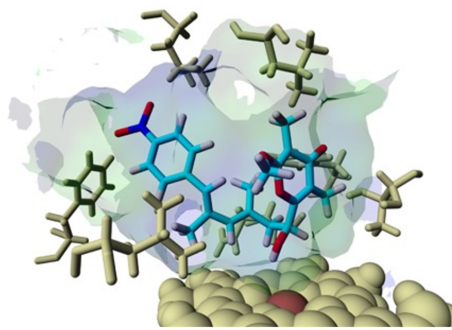
NUCLEIC ACID BASED BIOCONJUGATES

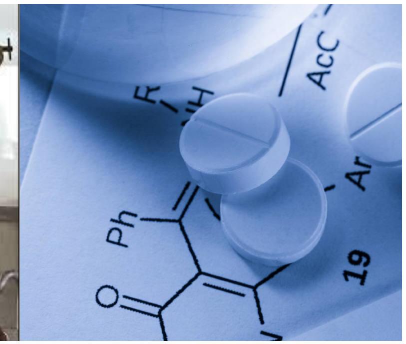
FOR BIOMEDICAL APPLICATIONS

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

Molecular and supramolecular chemistry of nucleic acid for health





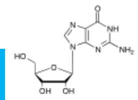


Interdiciplinarity for biomedical Sciences

CHEMBIOPHARM

ChemBioPharm, http://chembiopharm.fr ARNA, INSERM U1212 / UMR CNRS 5320

Nucleic acid chemistry, the context



Nucleoside based medicinal chemistry

1990's. Numerous nucleoside drugs

1970. Acyclovir

1969. ARAc (Cytarabine)

1964. AZT (Zidovudine)

1959. Idoxuridine first antiviral

1953. DNA double helical structure J. Watson, F. Crick and Rosalind Franklin

New biological targets

1990's. miRNA, RNAi…

2019. Remdesivir HVI, SarsCov-2

Miescher Isolation of nuclein

1869

1980

2000

2015

2019 2020

mRNA vaccine

1990's. Antisenses

Nucleic acid-based drugs

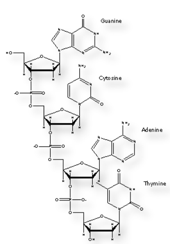
Antisense Ribozymes, DNAzymes, oligonucleotides, decoy oligonucleotides, aptamers, siRNAs and miRNAs

Oligonucleotide based medicinal chemistry

1960. Phosphodiester method

1970. Solid phase synthesis

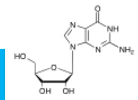
1980. Phosphite and phosphoramidite synthesis



The chemistry of oligonucleotide (LNA, PTO, 2'OMe etc) has been developed to address stability issues and enhance the affinity for the complementary strand

Nucleic acid chemistry, the context

Nucleoside based medicinal chemistry



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Miescher Isolation of nuclein

1869

1980

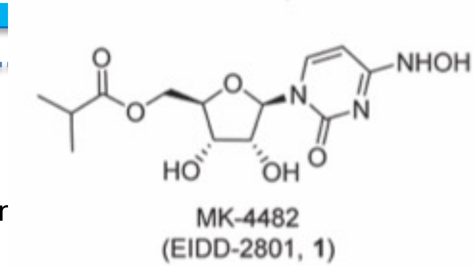
New biological targets


nature microbiology LETTERS
https://doi.org/10.1038/s41564-020-00835-2

Check for updates

Therapeutically administered ribonucleoside analogue MK-4482/EIDD-2801 blocks SARS-CoV-2 transmission in ferrets

Robert M. Cox[1,2], Josef D. Wolf[1,2] and Richard K. Plemper[1]



MK-4482 (EIDD-2801, 1)

0

RNA vaccine

1990's. Ar

d drugs

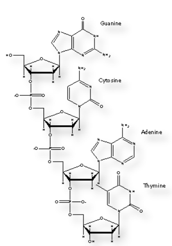
Oligonucleotide based medicinal chemistry

1960. Phosphodiester method

1970. Solid phase synthesis

1980. Phosphite and phosphoramidite synthesis

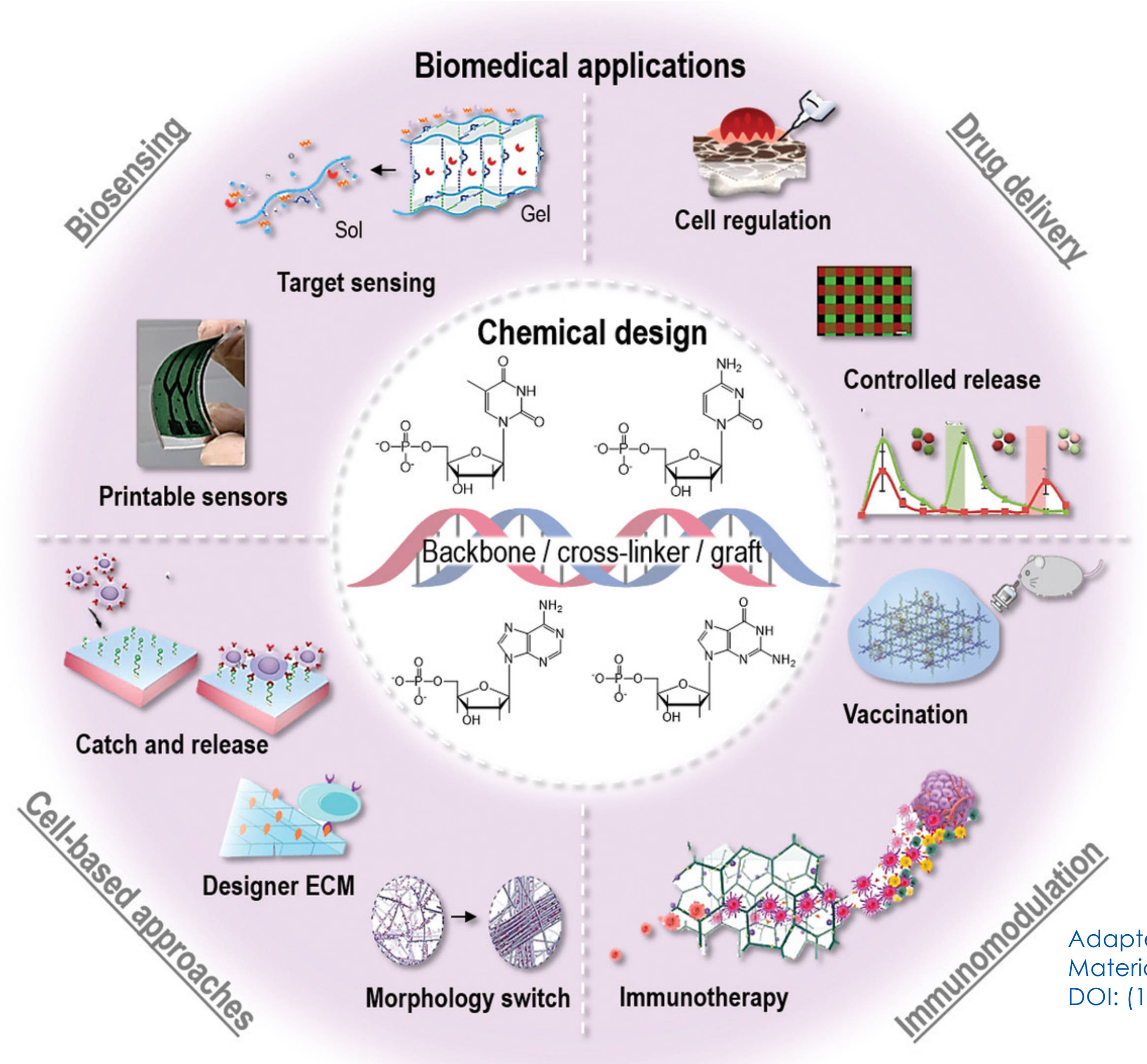
Antisense Ribozymes, DNAzymes, oligonucleotides, decoy oligonucleotides, aptamers, siRNAs and miRNAs



The chemistry of oligonucleotide (LNA, PTO, 2'OMe etc) has been developed to address stability issues and enhance the affinity for the complementary strand

Biomaterials, the context

"There is a critical need for non-polymeric soft materials for biomedical applications"

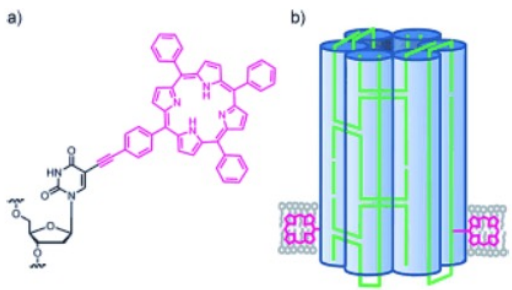


Adapted from Advanced Functional Materials, Volume: 30, Issue: 4, 2019, DOI: (10.1002/adfm.201906253)

bioinspired materials ?

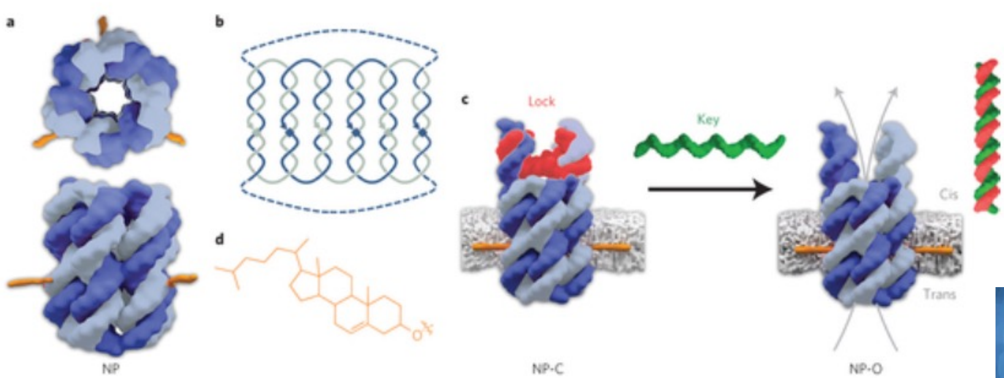
- ✓ Hydrogen bonding
- ✓ π−π stacking
- ✓ Van der Waals forces
- ✓ Hydrofobic effect

→ **MIMICKING NATURE**



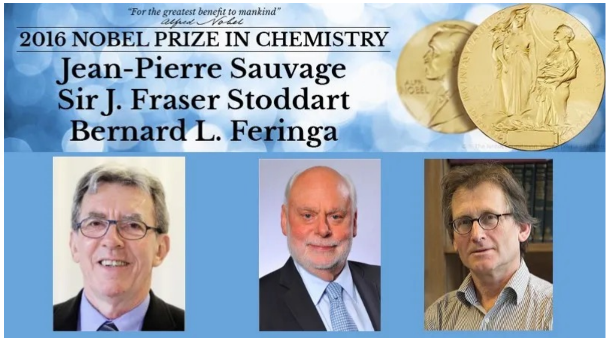
biomimetic DNA-based channel

Jonathan R. Burns et al. Angewandte Chemie (2013)



Jonathan R. Burns et al. Nature Nanotechnology 11, 152–156 (2016)

Molecular machines



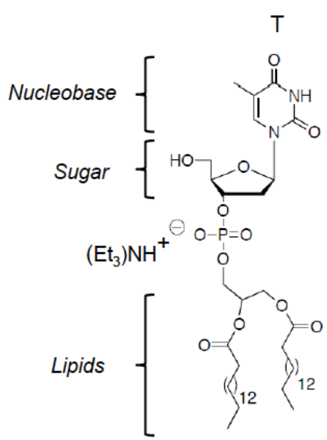
STRATEGY

- Open new therapeutic landscapes
- Explore new advanced materials

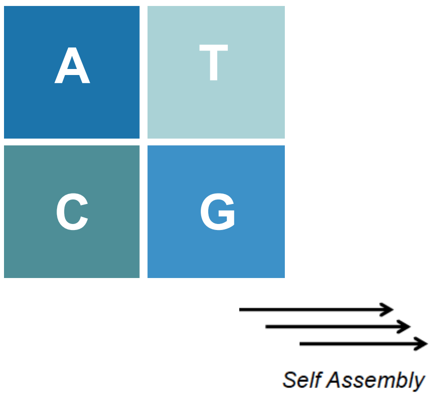
Nucleic acid conjugates at the biological interface

HOW

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

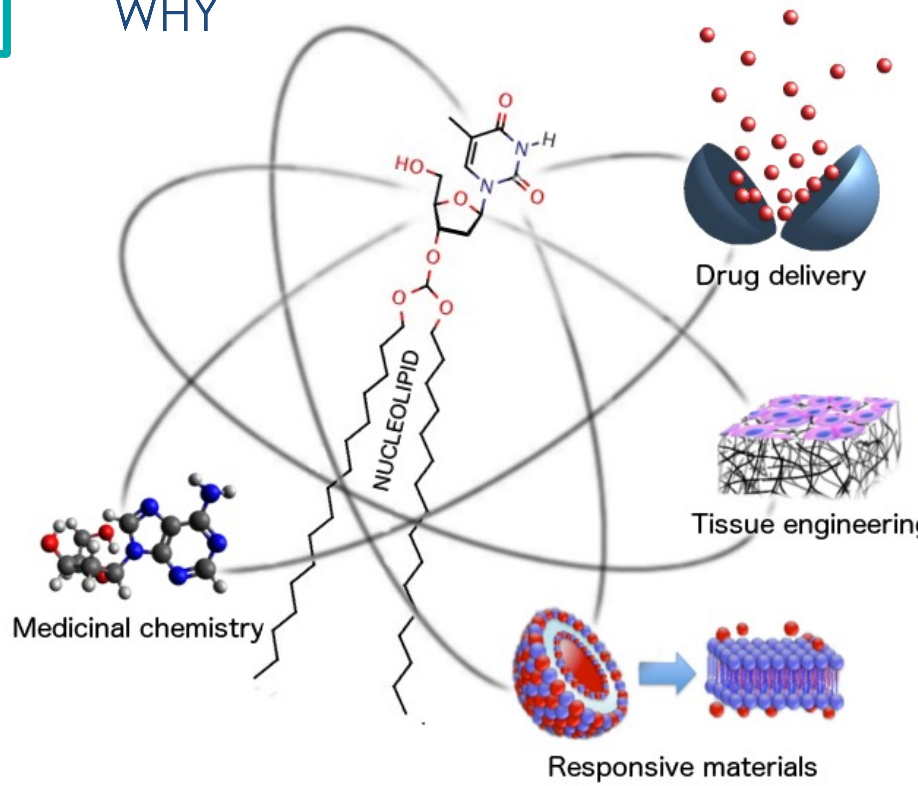


diC_{16}-dT



Nucleolipids
or
Lipid-oligonucleotides

WHY

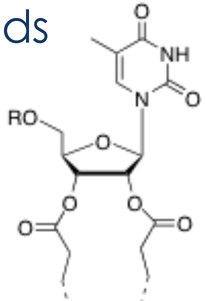


CHEMBIOPHARM

Supramolecular properties

Impact of molecular structure on
the supramolecular properties ?

Nucleolipids

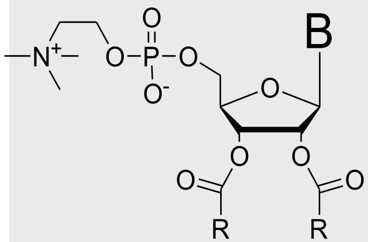


Diacyl nucleolipids

- *J. Am. Chem. Soc.* 126; 7533, (**2004**)

Supramolecular properties

Hybrid bio-mimetic molecular structures => **supramolecular diversity**



B: Uracile or Adenine

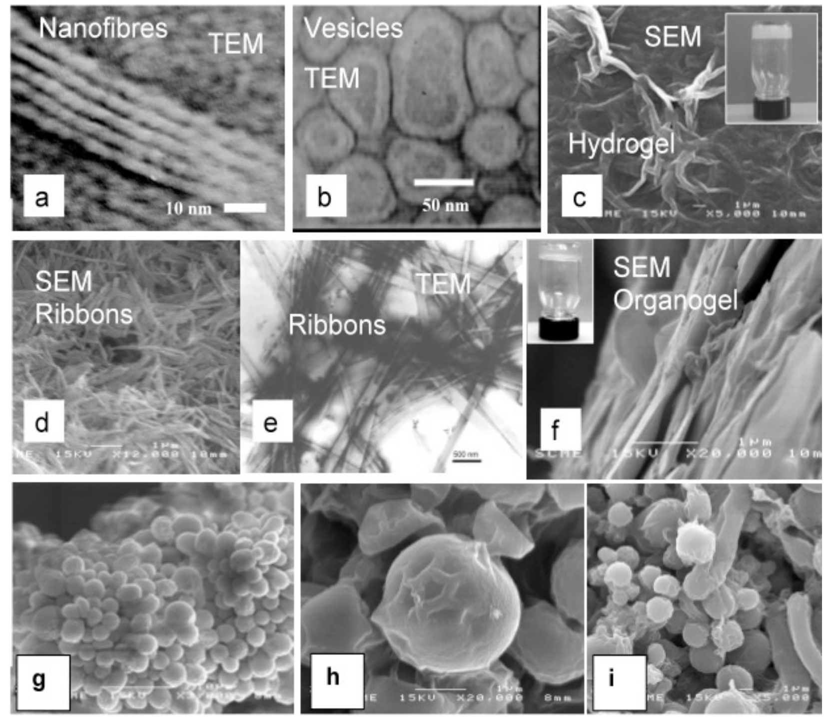
R= myristoyl
R= palmitoyl
R= stearyl
R= arachidonoyl
R= oleyl

phosphocholine derivatives

- *Chem Commun.*, 1661, (**2006**)

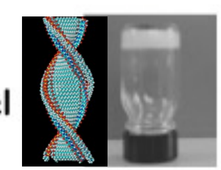
- *Tetrahedron Letters*, 46, 1593, (**2005**)

- *J. Am. Chem. Soc.* 126; 7533, (**2004**)

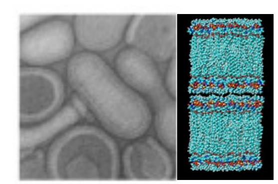


Thermo responsive

Hydrogel



Tm

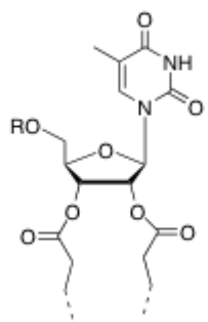


Helical structures below Tm

Lamellar systems above Tm

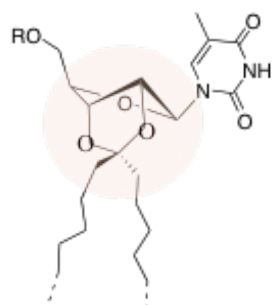
Supramolecular properties

Impact of molecular structure on
the supramolecular properties ?



Diacyl nucleolipids

- *J. Am. Chem. Soc.* 126; 7533, (**2004**)

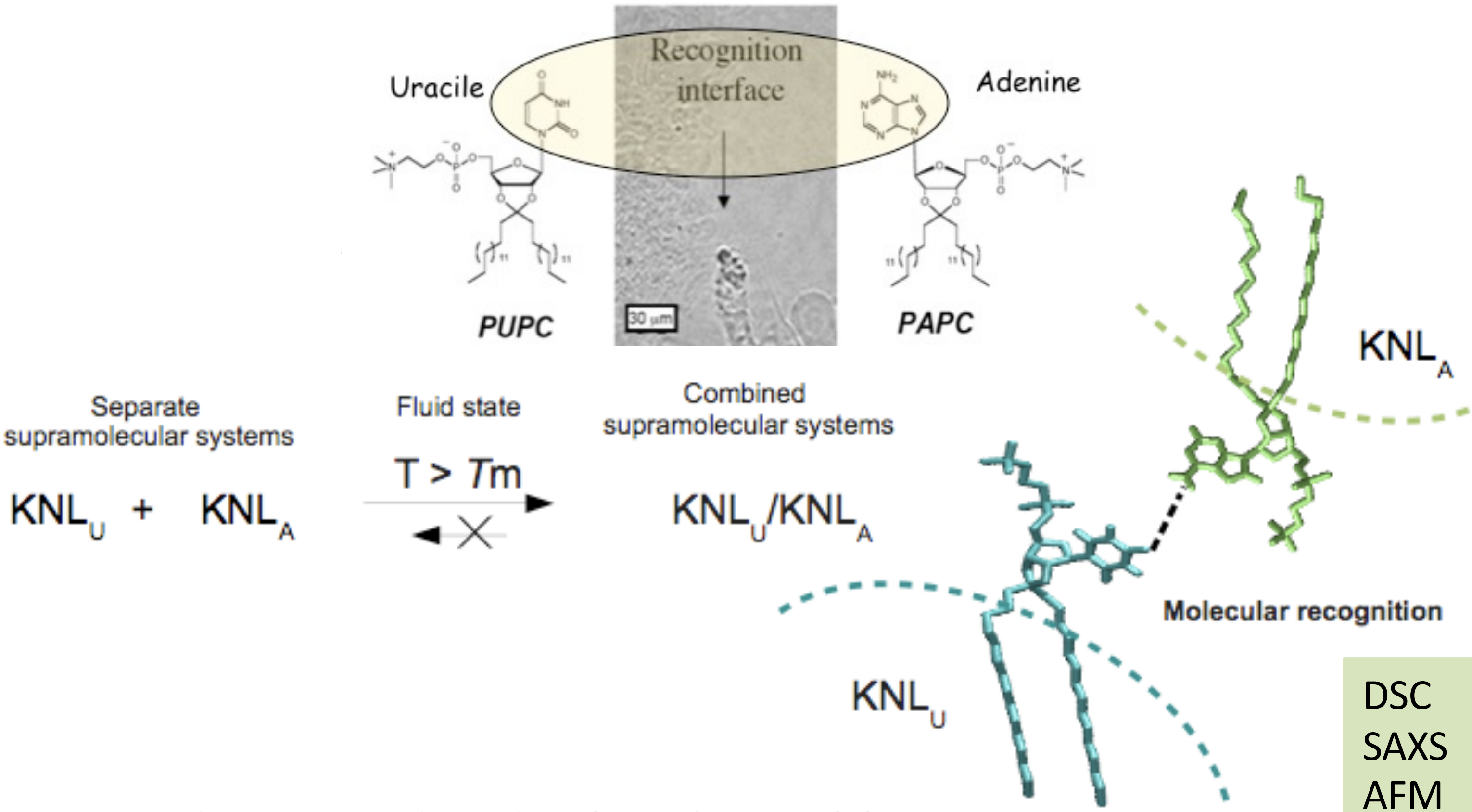


Ketal nucleolipids

- *J. Am. Chem. Soc.* 130; 14454, (**2008**)

Supramolecular properties

Combined Supra Systems directed *via* **nucleobases interactions**

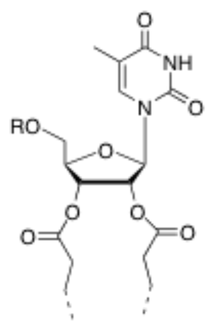


N. Taib *et al.*, *J. Colloid Interface Sci.* (2012) 1;377(1):122-30.
L. Moreau *et al.*, *J. Am. Chem. Soc.*, 130, (2008) (44), 14454-5.

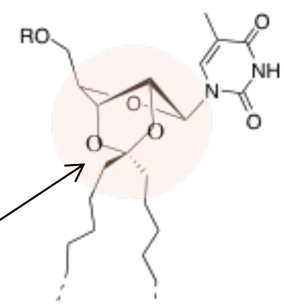
DSC
SAXS
AFM
Langmuir film
IR
..

Supramolecular properties

Impact of molecular structure on the supramolecular properties ?



2'-endo (South)



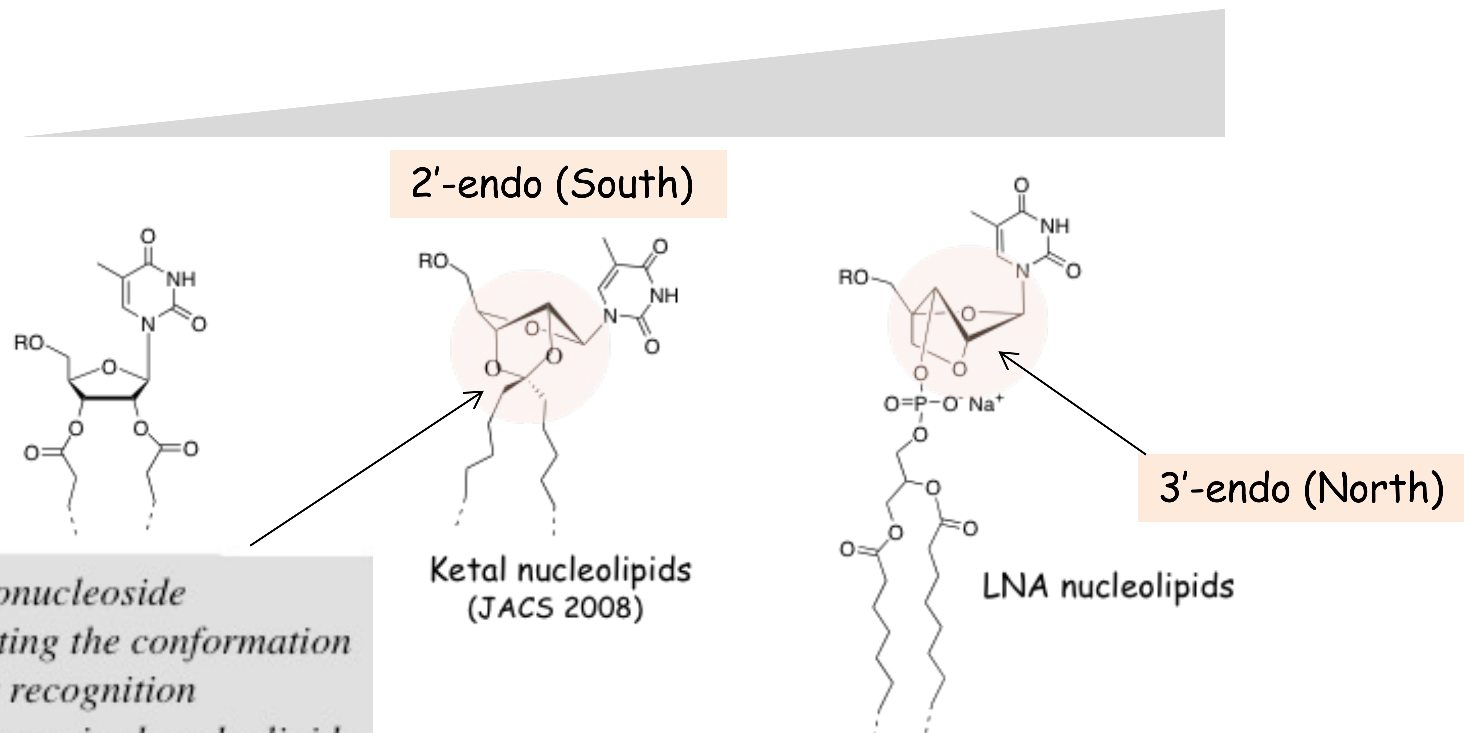
Ketal bicyclic ribonucleoside (C2' endo) restricting the conformation to favor base pair recognition between the self-organized nucleolipids

Ketal nucleolipids

- *J. Am. Chem. Soc.* 130; 14454, (**2008**)

Supramolecular properties

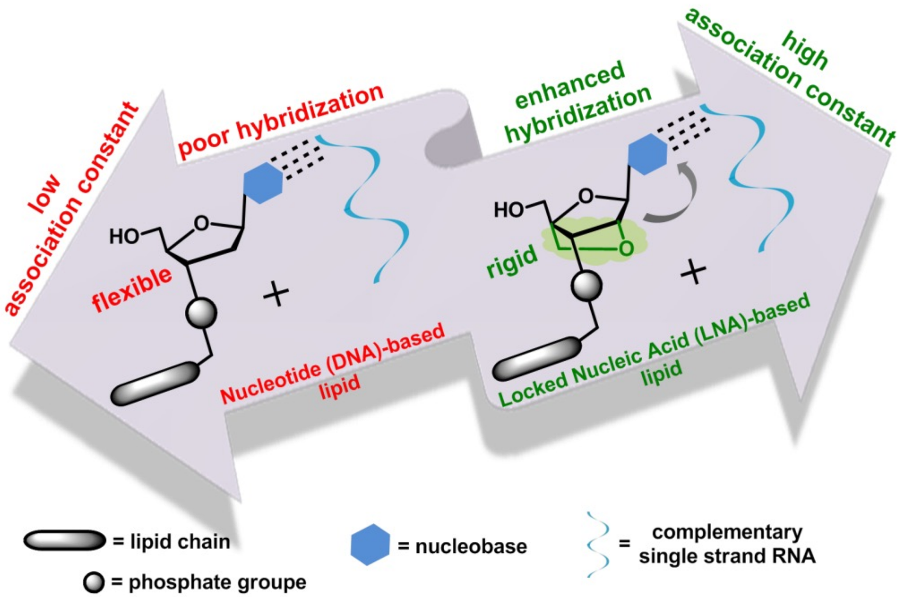
Impact of molecular structure on
the supramolecular properties ?

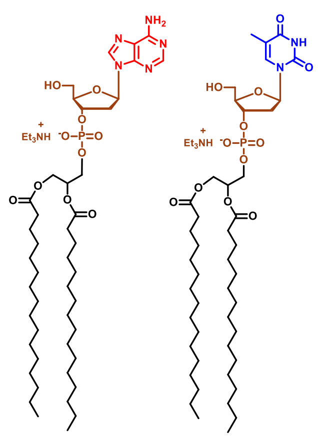


Ketal bicyclic ribonucleoside (C2' endo) restricting the conformation to favor base pair recognition between the self-organized nucleolipids

Supramolecular properties

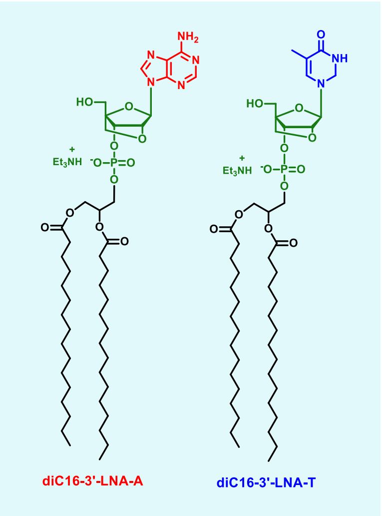
Tuning supramolecular interactions





Nucleotide-lipid

	PolyA[b]		PolyU[b]	
	diC16-3'-dT **2a**[c]	diC16-3'-LNA-T **1a**[c]	diC16-3'-dA **2b**[c]	diC16-3'-LNA-A **1b**[c]
K_d[a] (M^{-1})	2.63×10^{-3} (K_{d3})	3.09×10^{-4} (K_{d3}*)	5.78×10^{-4} (K_d)	4.31×10^{-6} (K_{d1}*) 1.64×10^{-5} (K_{d2}*)
	endothermic		exothermic	



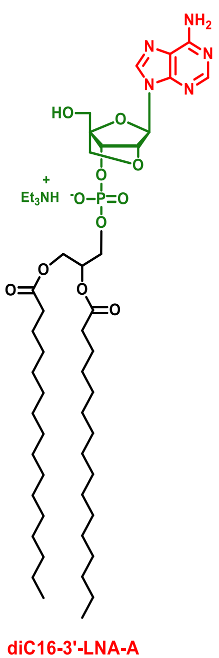
LNA-lipid

A.Patwa, G. Salgado, F. Dole, L. Navailles, and P. Barthélémy, Org. Biomol. Chem., **2013**,11, 7108-7112

Supramolecular properties

Tuning supramolecular interactions

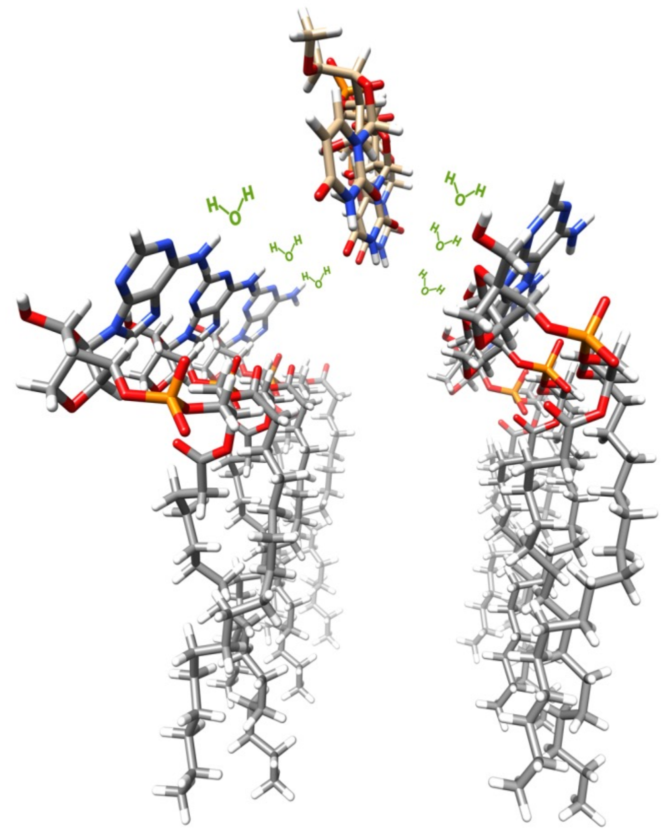
Kd = 43 nM !!



LNA-lipid

LNA conformation **enhances hybridization performance** of nucleolipids

Formation of complex with single strand RNA is **entropically driven**

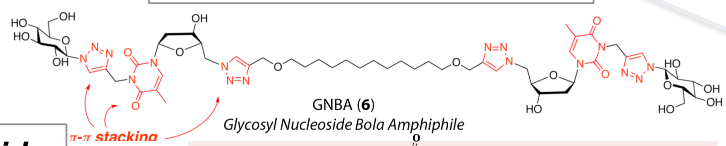


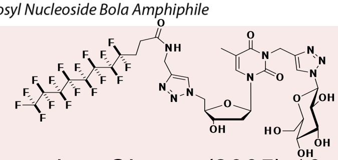
Drawing from NMR experiments

A.Patwa, G. Salgado, F. Dole, L. Navailles, and P. Barthélémy, Org. Biomol. Chem., **2013**,11, 7108-7112

▪ Hybrid amphiphiles

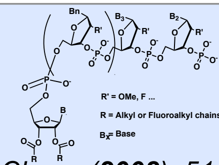
GlycoNucleoLipids (GNLs)





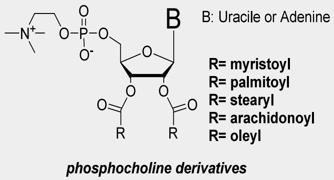
- *Bioconjug. Chem., (**2005**) 16, 864,*
- *Langmuir, (**2009**) 25, 8447*
- *Chem. Commun., (**2009**)* 5127,
- *Tetrahedron letters* (***2010***)
- Chem. Commun., (**2011**) 47, 12598
- Molecules, (**2013**) 18, 12241
- *Angewandte Chemie, (**2015**)* 54, 4517
- *Gels, (**2016**) 2, 25*
- *Chem. Commun., (**2016**), 52, 5860*
- *New J Chem (**2016**) 40, 9903*
- *ACS Appl. Mater. Interfaces, (**2017**) 9, 1093*
- *Biomaterials, (**2017**)*

Lipid Oligonucleotides (LONs)



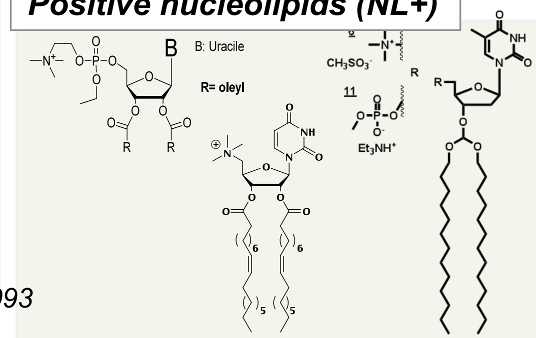
- *J. Med. Chem.,(**2008**) 51, 4374.*
- *Chem. Soc. Reviews, (**2011**) 40, 5844*
- *J. Mater. Chem. B*, (**2013**)
- Bioconjugate Chem., (**2013**) 24,1345
- *New J. Chem.*, (**2014**) 38, 5129
- *Chem. Commun.* (**2017**)

Zwitterionic nucleolipids



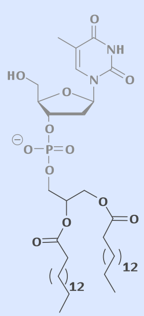
- *J. Am. Chem. Soc. 126; 7533, (**2004**)*
- *Tetrahedron Letters*, 46, 1593, (**2005**)
- Chem Commun., 1661, (**2006**)
- *J. Am. Chem. Soc.* 130; 14454, (**2008**)
- *J. Colloid Interface Science* (**2012**)

Positive nucleolipids (NL+)



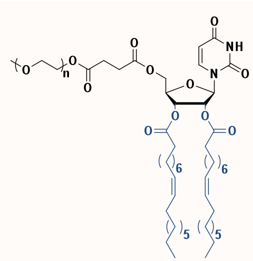
- *Molecular BioSystems, 1, 260, (**2005**)*
- *Bioconjug. Chem., 17, 466, (**2006**)*
- *Bioconjug. Chem.*, 20, 193, (**2009**)
- Accounts of Chemical Research (**2012**)
- *J. Control. Release*, 172, 954–961 (**2013**)
- *New J. Chem.*, 38, 5240-5246 (**2014**)
- *ChemMedChem*, 10, 1797-1801 (**2015**)
- Bioconjugate Chemistry, (**2016**) 2, 569

Negative nucleolipids (NL-)

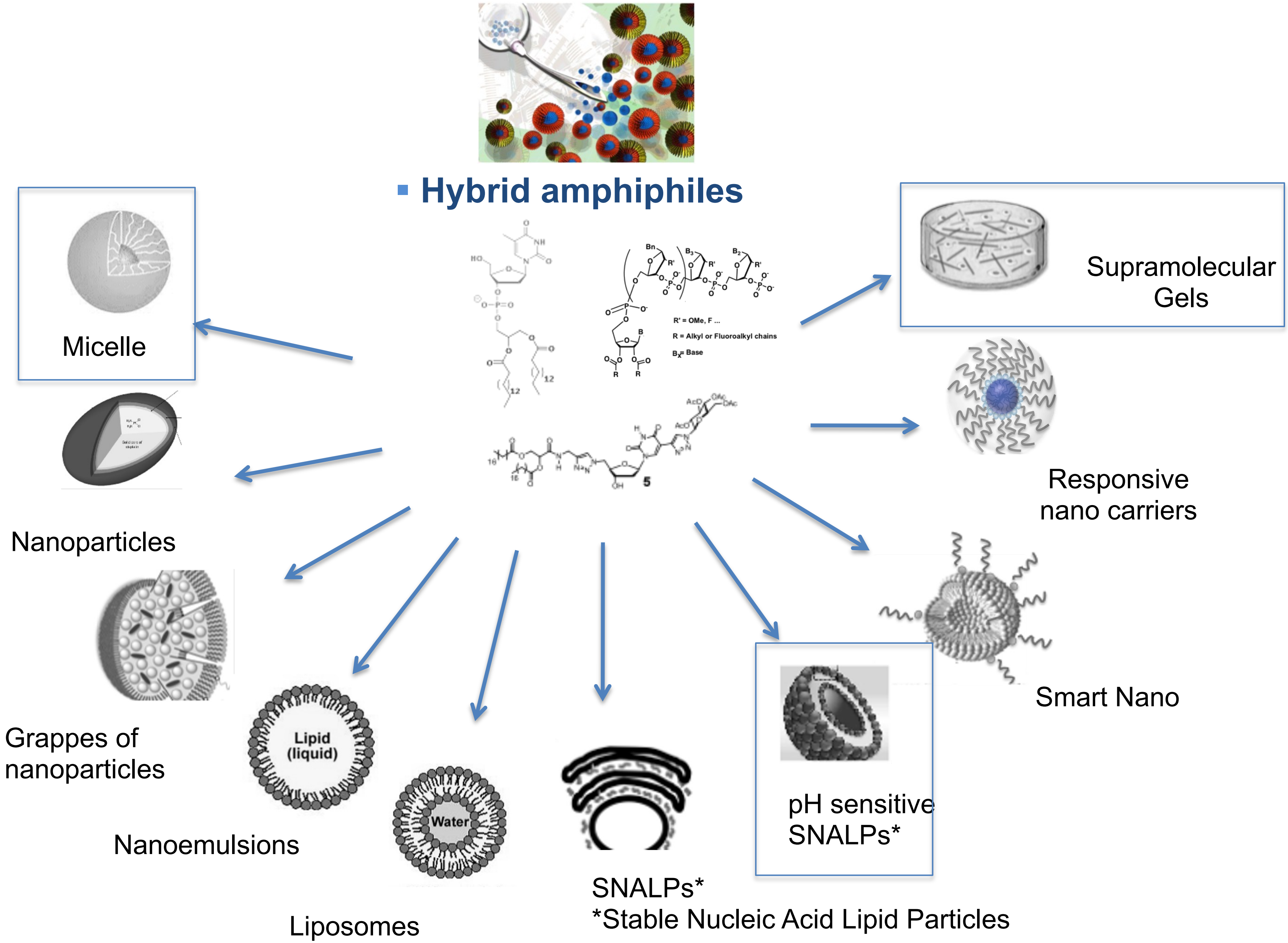


- *New J. Chem (**2007**) 31, 1928,*
- *Bioconjug. Chem., (**2009**)*
- *ACS Nano* (**2011**) 5, 8649
- *J. Nanosci. Lett., (**2012**) 2, 20*
- *Org. Biomol. Chem. (**2013**) 11, 7108*
- *Langmuir, (**2013**) 29 , 5547*
- *New J. Chem., Volume (**2014**) 38, 5240*
- *Bioconjugate Chemistry* (**2016**) 2, 569
- *Advanced Materials* (**2017**) *1605227*
- *Advanced Materials* (**2018**)

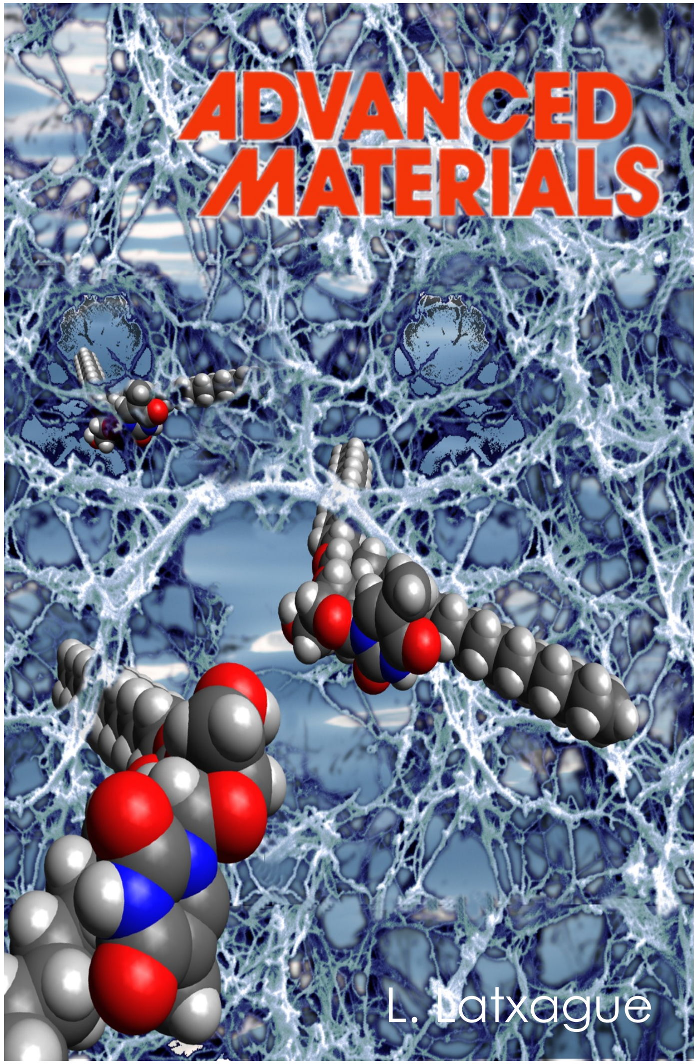
Neutral nucleolipids (NL)



- *Chem Commun.*, (***2005***) 1261
- *Oumzil et al. J. Control. Release, **(2011)***



Hybrid amphiphiles
Micelle
Nanoparticles
Grappes of nanoparticles
Lipid (liquid)
Nanoemulsions
Water
Liposomes
SNALPs*
*Stable Nucleic Acid Lipid Particles
pH sensitive SNALPs*
Smart Nano
Responsive nano carriers
Supramolecular Gels
R' = OMe, F ...
R = Alkyl or Fluoroalkyl chains
Bx= Base



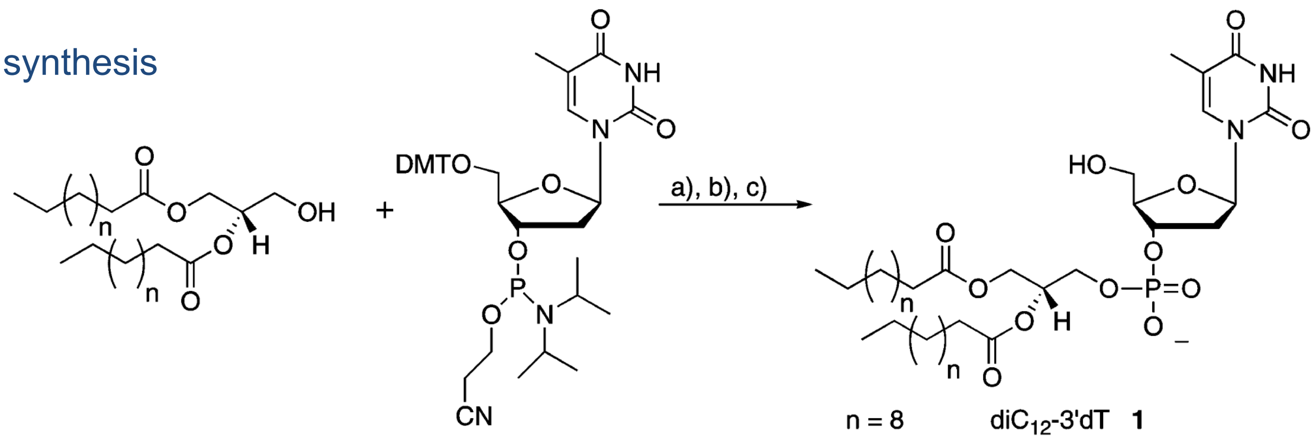
Part 1.

NUCLEOLIPIDS

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

NUCLEOTIDE LIPIDS

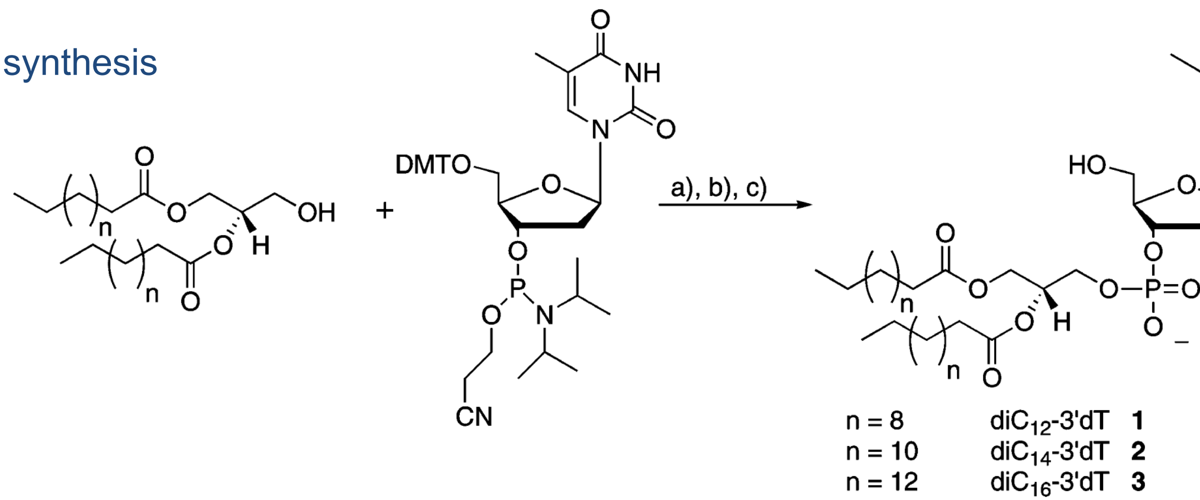
Example of synthesis

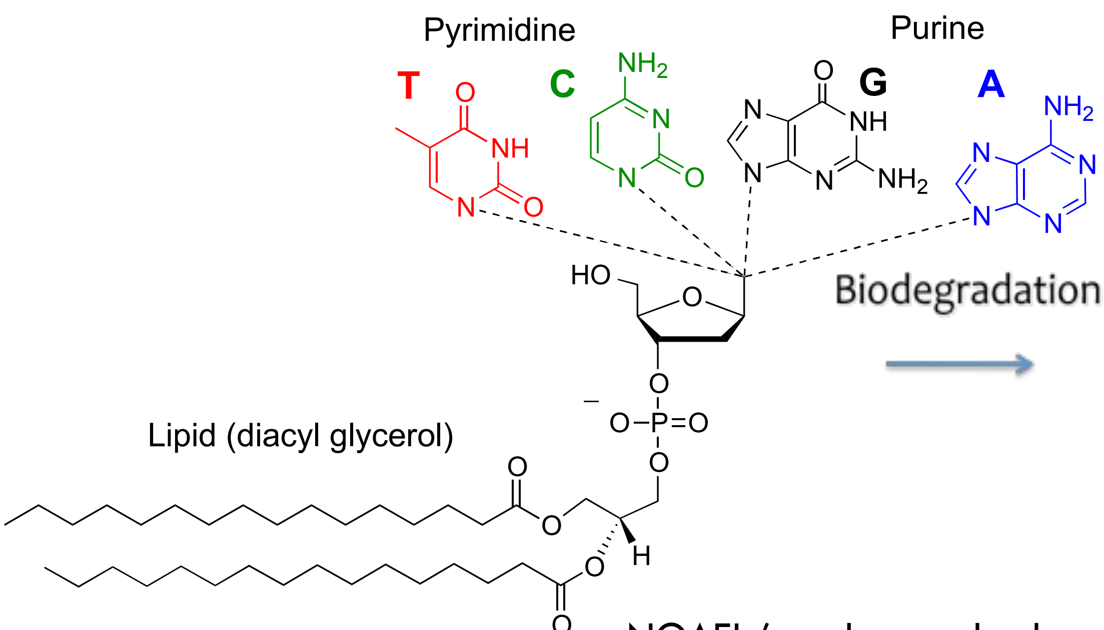


n = 8	diC$_{12}$-3'dT	**1**
n = 10	diC$_{14}$-3'dT	**2**
n = 12	diC$_{16}$-3'dT	**3**

NUCLEOTIDE LIPIDS

Example of synthesis



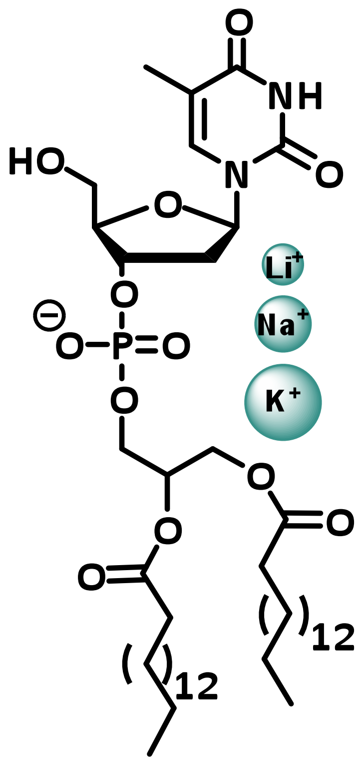


sn 1,2 diacylglycerol
+
Phosphate
+
Nucleoside

Natural non-toxic products

NOAEL (no observed adverse effect level) > 30 mg/Kg/Day

Impact of counter ions on the supramolecular assemblies?



Supramolecular

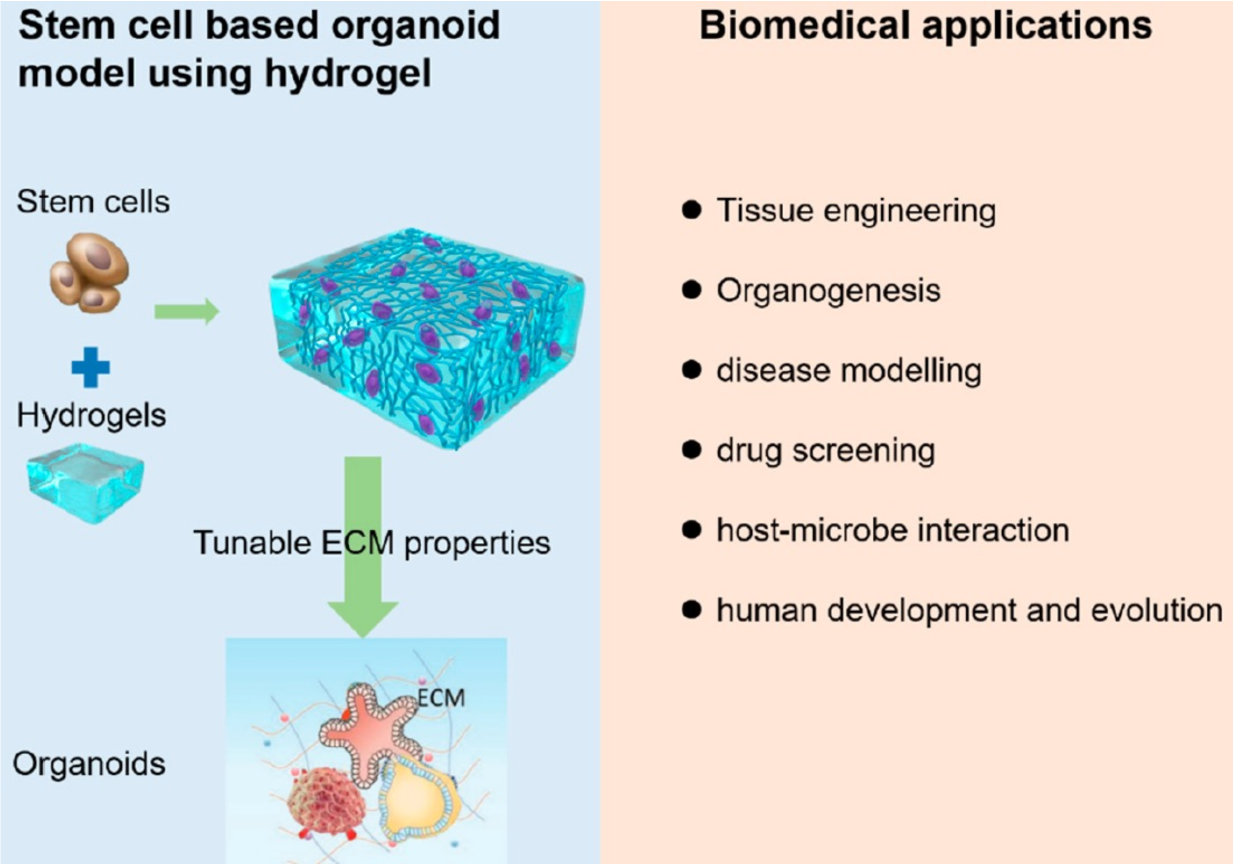
?

Hydrogels?

Ramin M. et al. Cation Tuning of Supramolecular Gel Properties: A New Paradigm for Sustained Drug Delivery ***Advanced Materials*** **(2017)**

Gels are useful materials for biomedical applications

- ✓ Drug delivery
- ✓ Wound healing
- ✓ Tissue engineering
- ✓ Gene delivery
- ✓ Organoids =>



Gels are useful materials for biomedical applications

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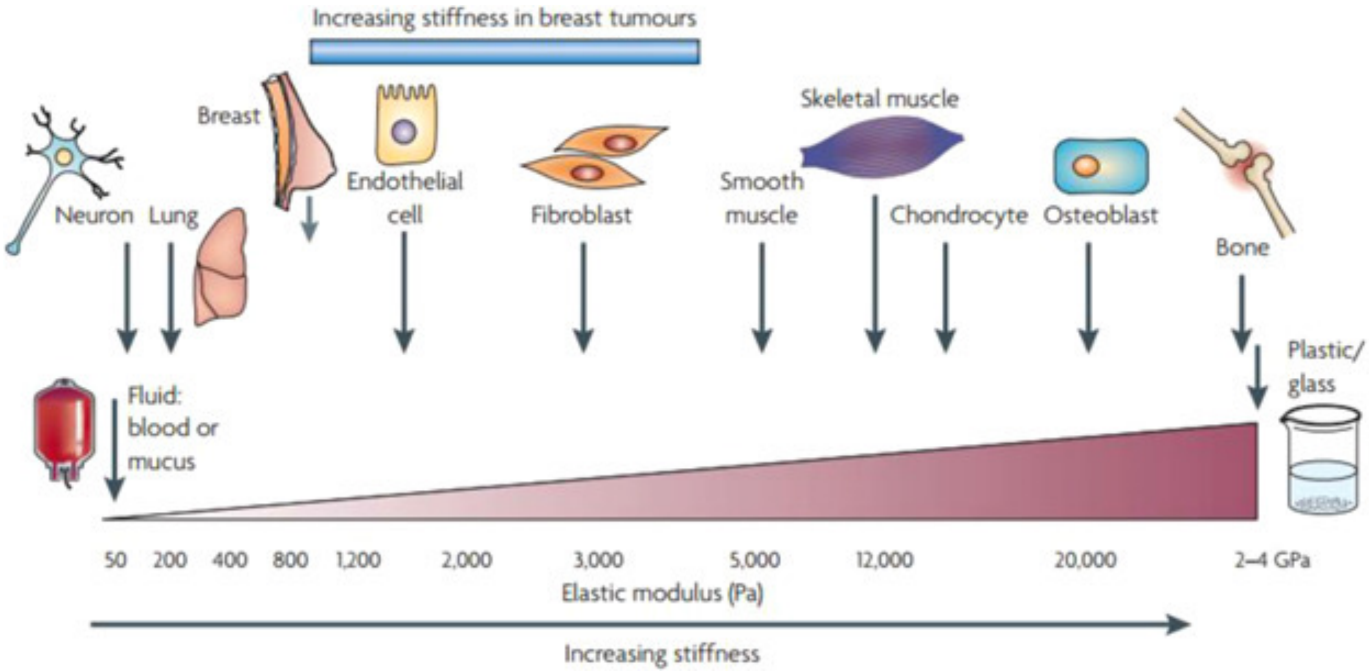
- ✓ Organoids =>



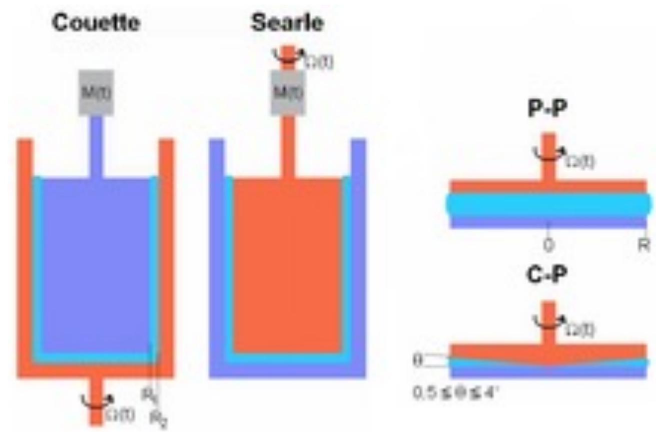
Prince, E.; Kumacheva, E. Design and applications of man-made biomimetic fibrillar hydrogels. *Nat. Rev. Mater.* **2019**, 4, 99–115.

Gels « the basics »

Gels properties

Dynamic mechanical analysis (DMA)

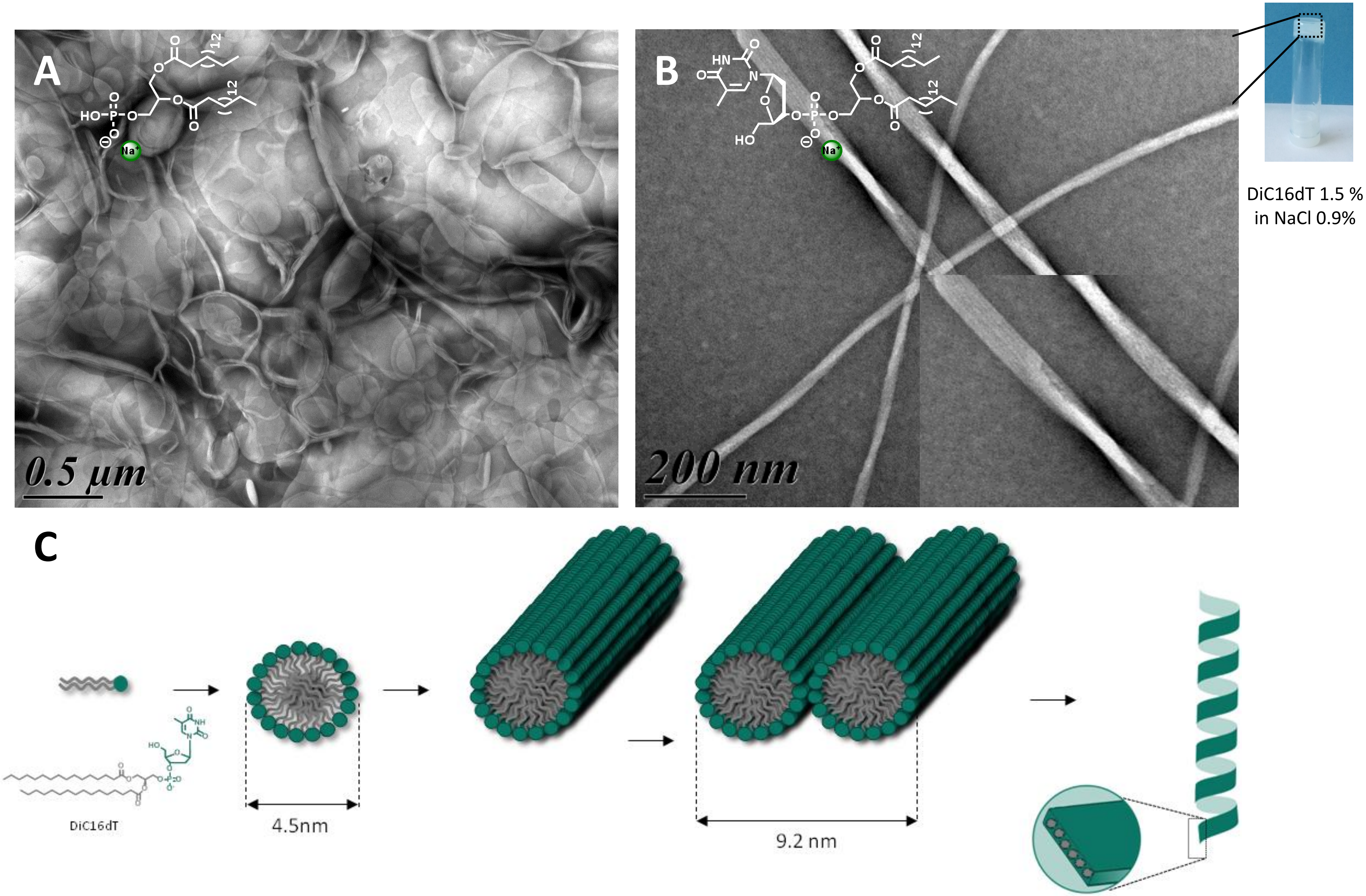
Gels are both solid (G') and liquid (G")



$$\sigma = \gamma\,(G' + iG'')$$

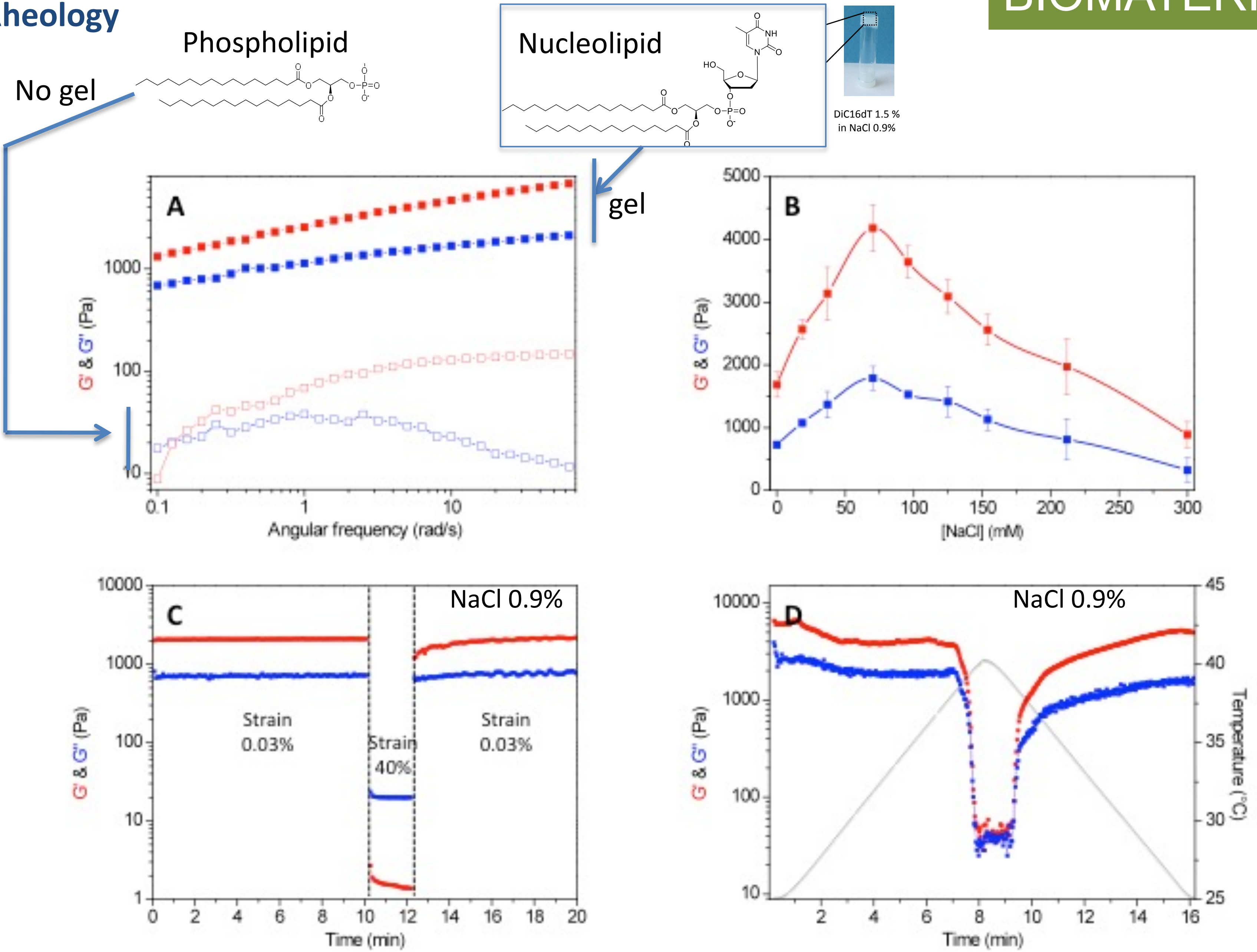
- σ : contrainte
- γ : déformation
- G' : Elastic modulus
- G'' : Viscosity modulus

Self-assemblies



BIOMATERIALS

Rheology

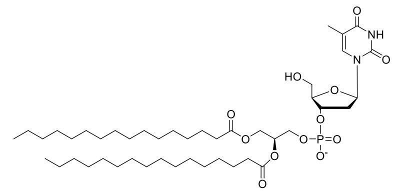


Thixothropy

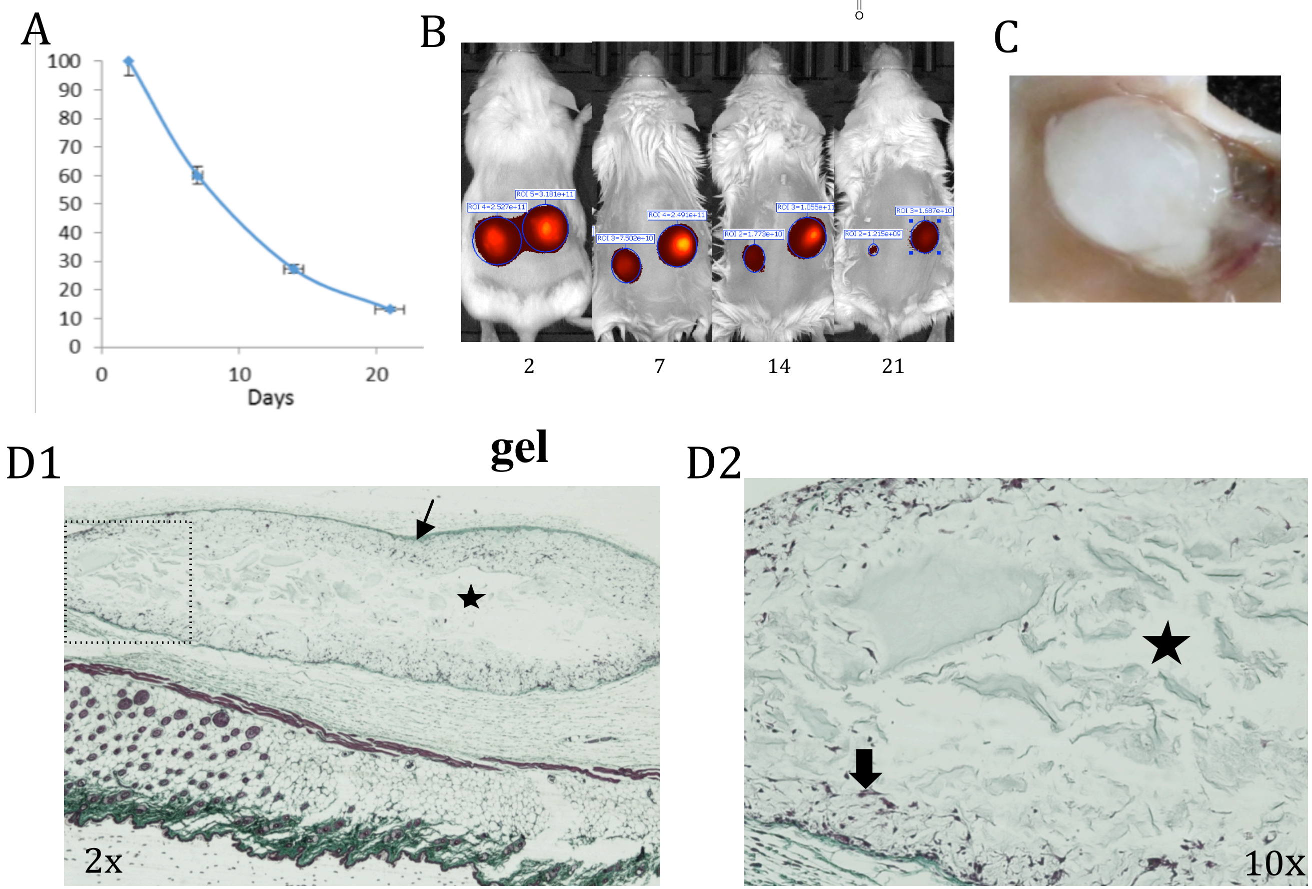
Viscoelastic moduli versus temperature

$diC_{16}dT$ 6% (w/w)

In vivo experiments



DiC16dT Gel was loaded with Cyanine 5.5 as drug mimick

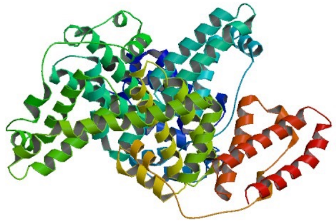


-The ionic supramolecular gel was preserved in physiological conditions even after *in vivo* injection.
- Non immunogenic (no fibrosis)
- No toxicity. NOAEL (no observed adverse effect level) > 30 mg/Kg/Day

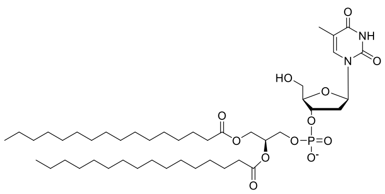
Ramin M. *et al.* ***Adv. Mater. 2017***, *DOI: 10.1002/adma.201605227*

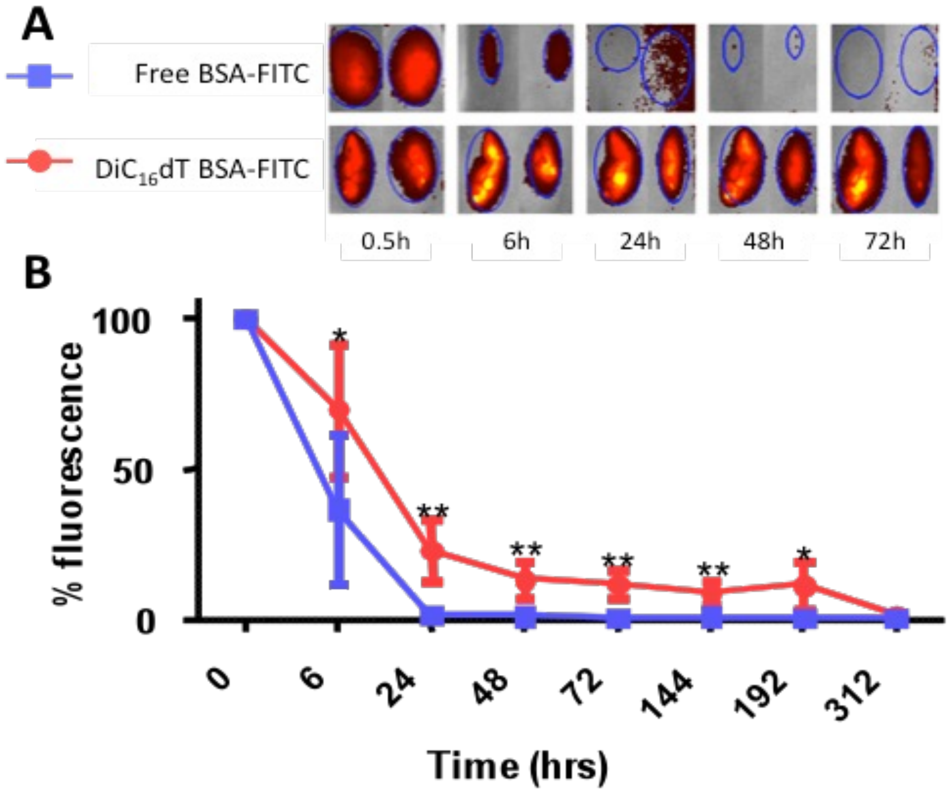
In Vivo Drug Delivery

FITC-tagged -BSA



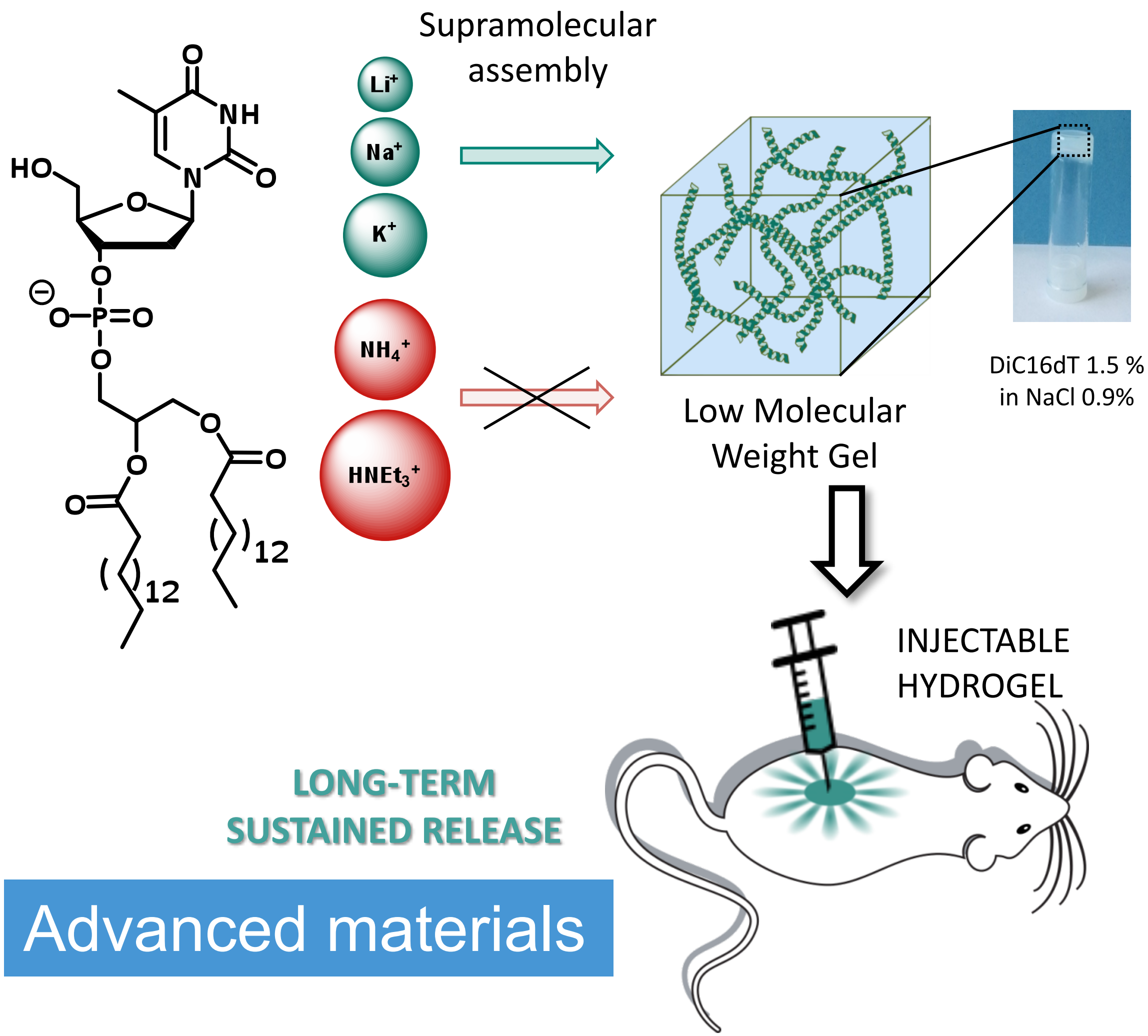
+





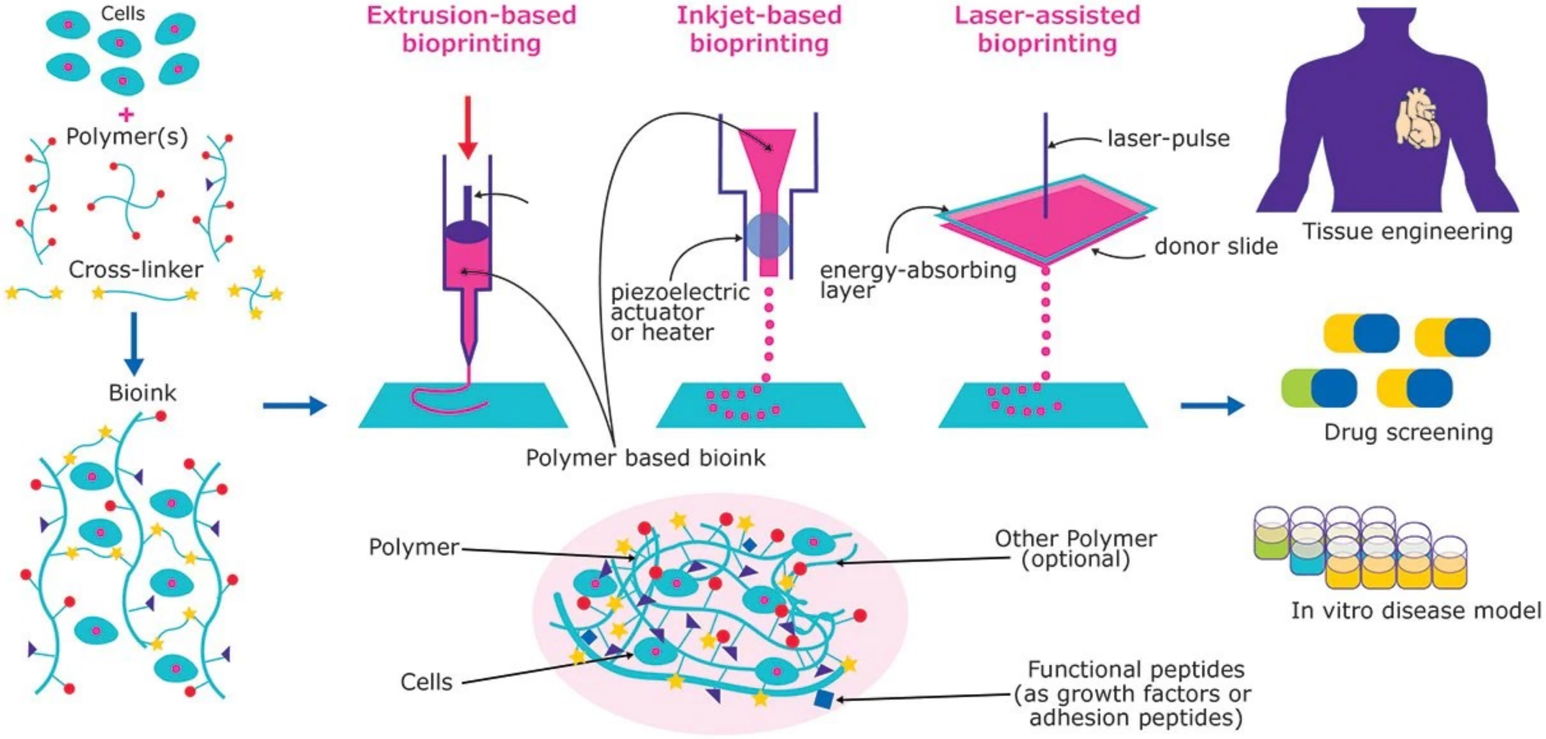
Gel was able to prevent rapid diffusion of BSA and provided a reservoir of molecules, which could be gradually released into the tissues.

Ramin M. *et al.* ***Adv. Mater. 2017***, *DOI: 10.1002/adma.201605227*



Advanced materials

Ramin M. *et al.* ***Adv. Mater. 2017***, *DOI: 10.1002/adma.201605227*

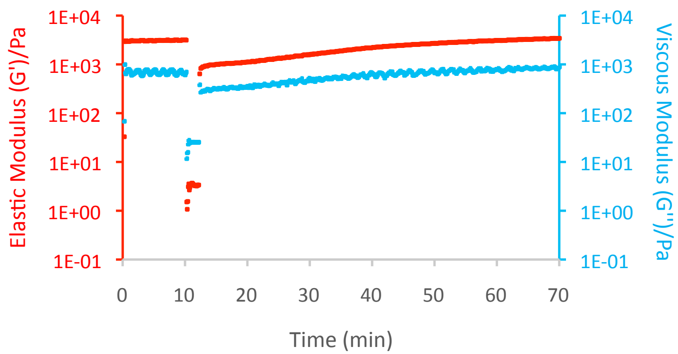


WHAT ARE BIOINKS?

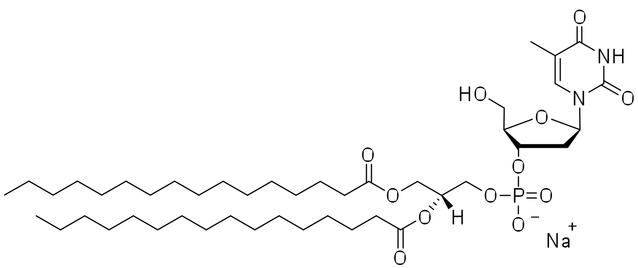
Bioinks contain living cells and biomaterials that mimic the extracellular matrix environment, supporting cell adhesion, proliferation, and differentiation after printing. In contrast to tradtional 3D printing materials, bioinks must have:

•Print temperatures that do not exceed physiological temperatures
•Mild cross-linking or gelation conditions
•Bioative components that are non-toxic and able to be modified by the cells after printing

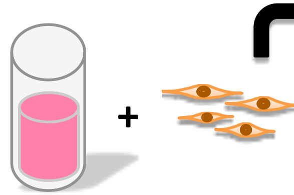
Hydrogels



Thixotropy properties toward printability

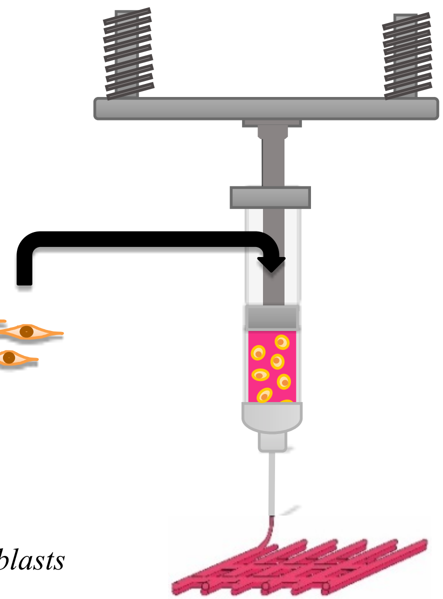


Thymidine based nucleotide lipid DiC$_{16}$DT (III)



3% (w/v) hydrogel
*in **culture medium***
& human gingival fibroblasts

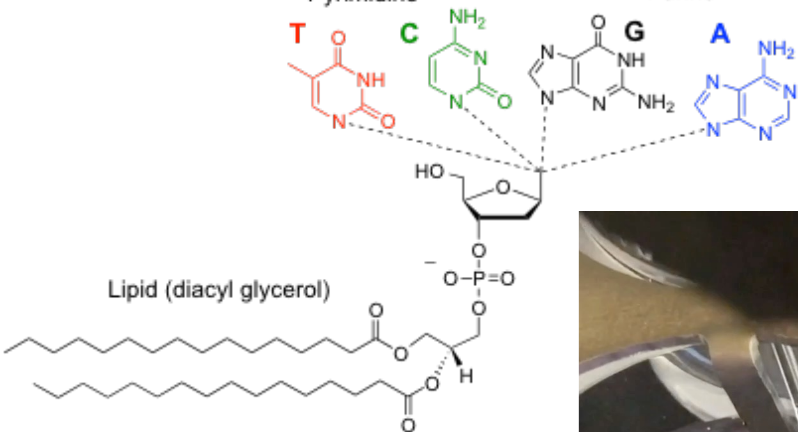
Extrusion-based bioprinting

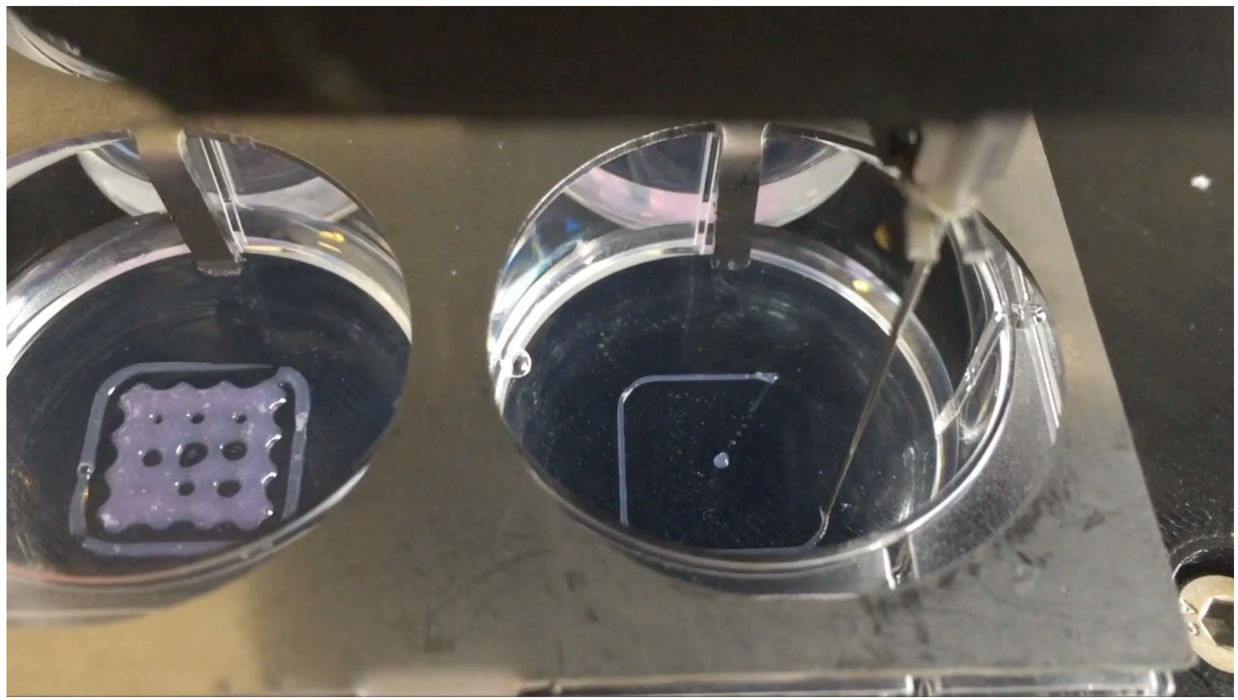


- ✓No crosslinking needed for gel stabilization
- ✓Biocompatible
- ✓G' can be modulated depending on the cell type
- ✓NLs are good candidates for bioinks

Hydrogels

BIOINK FOR 3D BIOPRINTING





2x2mm^2 pores

Dessane, B.*et al. Nature Scientific Reports* **2020**, 10 (1), 2850

BxCRM Bordeaux Consortium for Regenerative Medicine

BIOTIS U1026

Route of administration

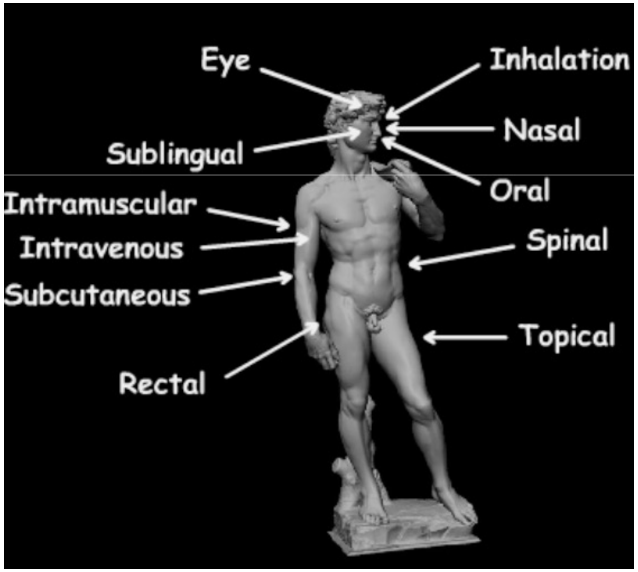
Distribution of drugs depends on the route of administration:

- Oral (gastric…)

- Injections and implants (IV, sub cutaneous, intramuscular, etc)

- Transdermic
(Eyes, nasal, vaginal, anal…)

- Inhalation



Problems :
final amount of the drug reaching the target is generally low relative to the administered dose. Undesirable side effects.

Solution : application of drugs directly to the site of action by local administration (sprays, inhalers, creams nasal solutions, ocular etc.)

=> New strategies of drug delivery

Administartion

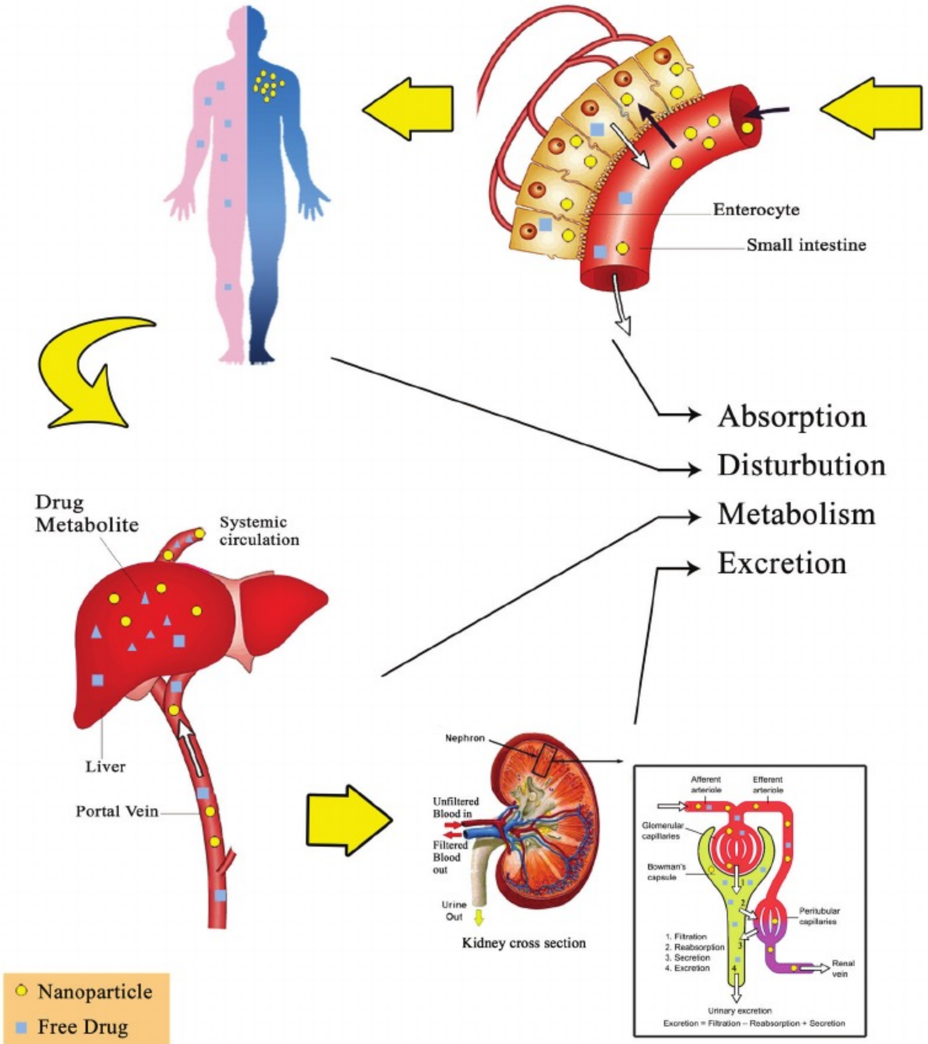
Definitions

Pharmacokinetics: study of the absorption, distribution, biotransformation (metabolism) and excretion of drugs (ADME).

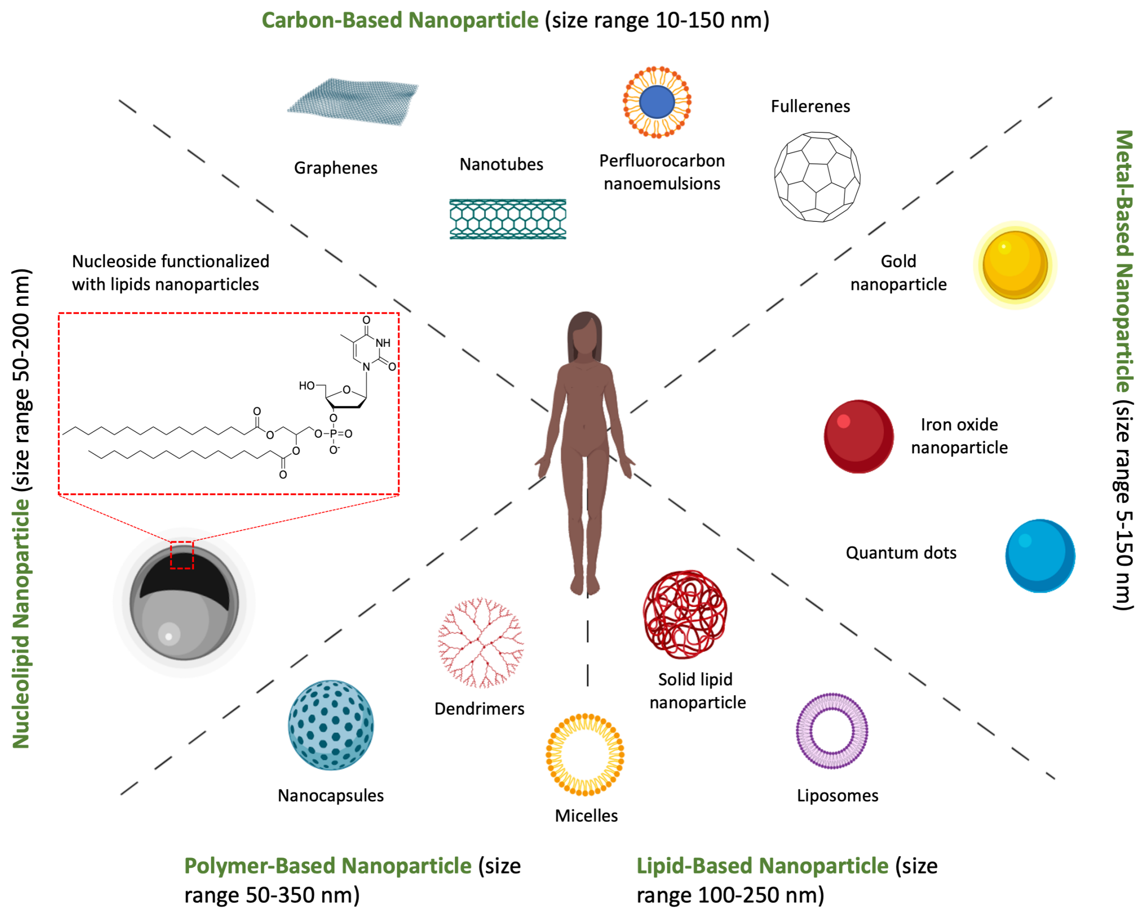
Pharmacodynamics: study of biochemical and physiological effects of drugs and study of mechanisms of drug action in living organisms.

Pharmacotherapeutics (clinical pharmacology): study the use of drugs to prevent and treat diseases.

Toxicology: the study of poisons, including the adverse effects of drugs on living organisms.



Classification



- Drug delivery
  - Lipid-based
  - Polymer-based
  - Inorganic Nanoparticles
  - Magnetic Particles
  - Nucleic Acid/ Peptide-based
  - Cell-based

Adapted by Wicki WD et al 2015

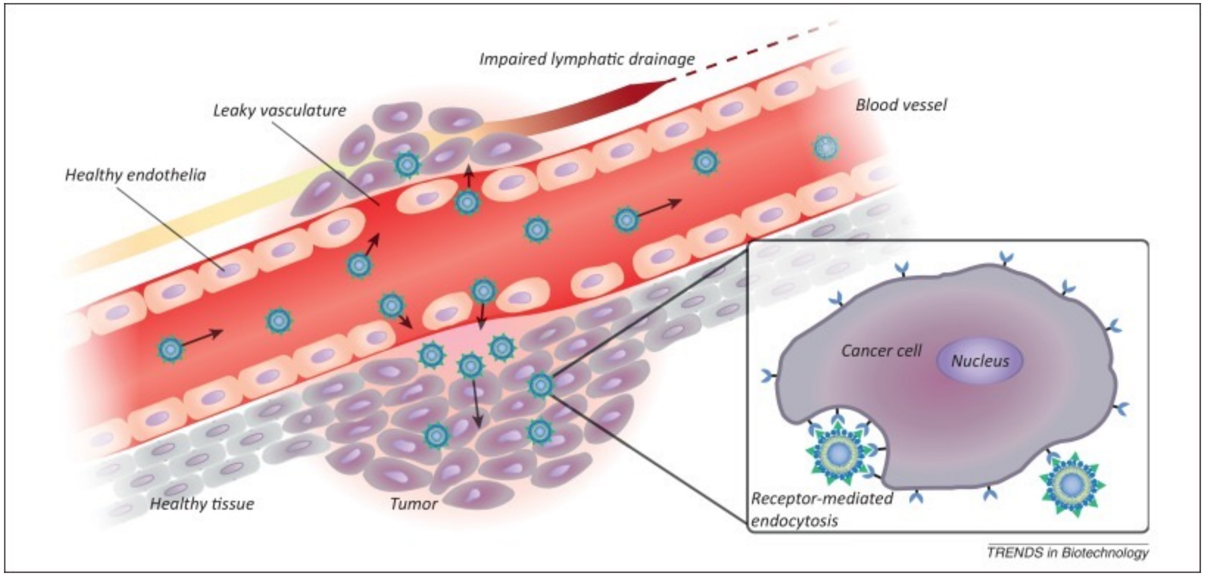
Tools

Major discoveries have stimulated the activity in the field of DDS:

-> EPR Effect
-> PEGylation Stealth Liposome
-> Active targetting

The EPR Effect

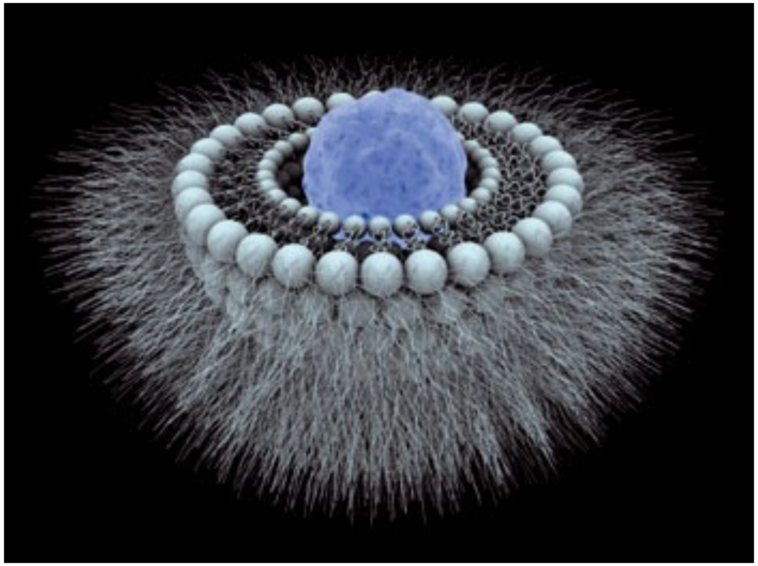
The **enhanced permeability and retention** (EPR) effect is a controversial concept] by which molecules of certain sizes (typically liposomes, nanoparticles, and macromolecular drugs) tend to accumulate in tumor tissue much more than they do in normal tissues



https://www.youtube.com/watch?v=RRLf9-xvAeg

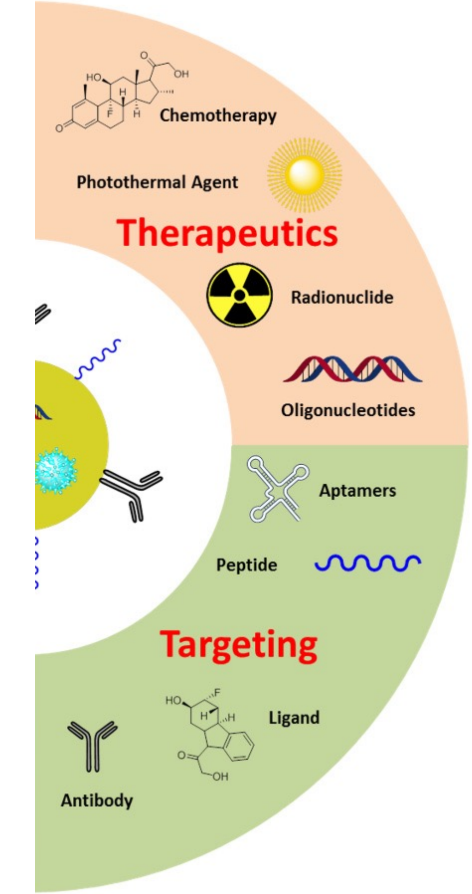
2: PEGylation Stealth Liposome

It was determined that polyethylene glycol CAN be used as a coating on the liposome. Polyethylene glycol was chosen to be used as a coating for its ability to deter the immune system. Thus the ethylene glycol will prevent any reaction from the immune system while the liposome is traveling. Since the liposome cannot be detected by the immune system, it is also known as a stealth liposome.

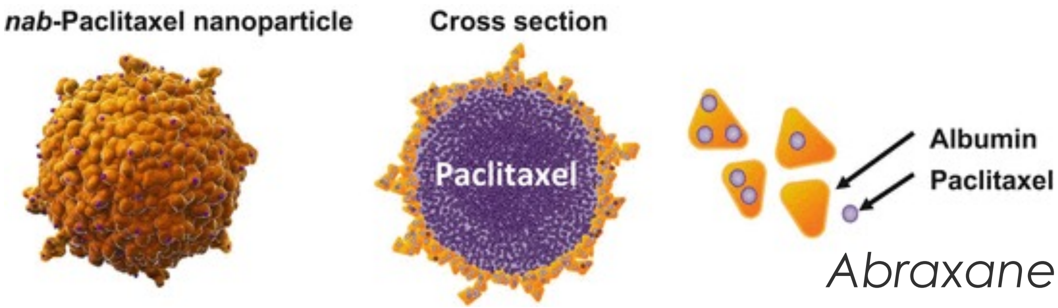


https://www.youtube.com/watch?v=27nxR8M344Q

3: Targeting

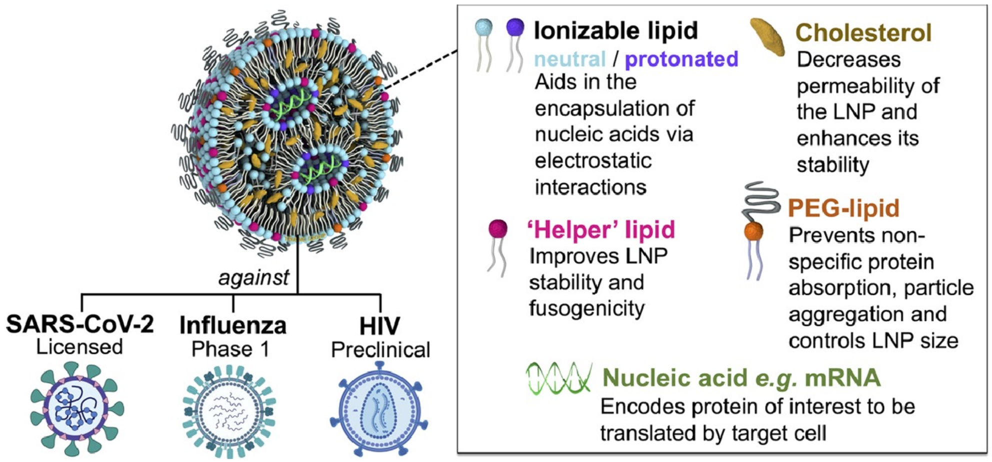


Example

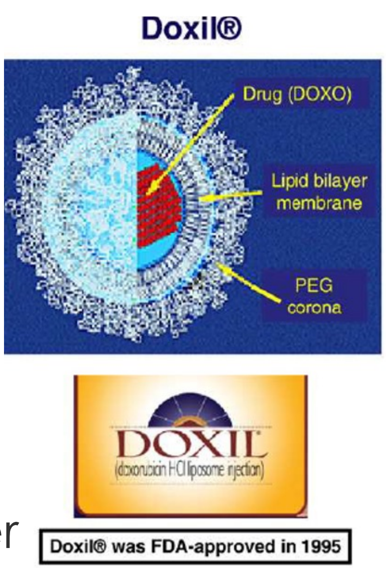


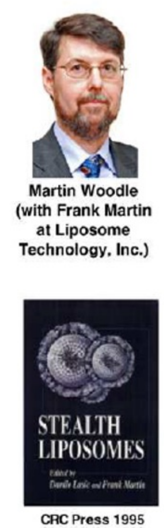
Abraxane
Breast cancer (FDA approved in 2005

Messager RNA Vaccination



Adapted from E.H. Pilkington, E.J.A. Suys, N.L. Trevaskis et al. Acta Biomaterialia 131 (2021) 16

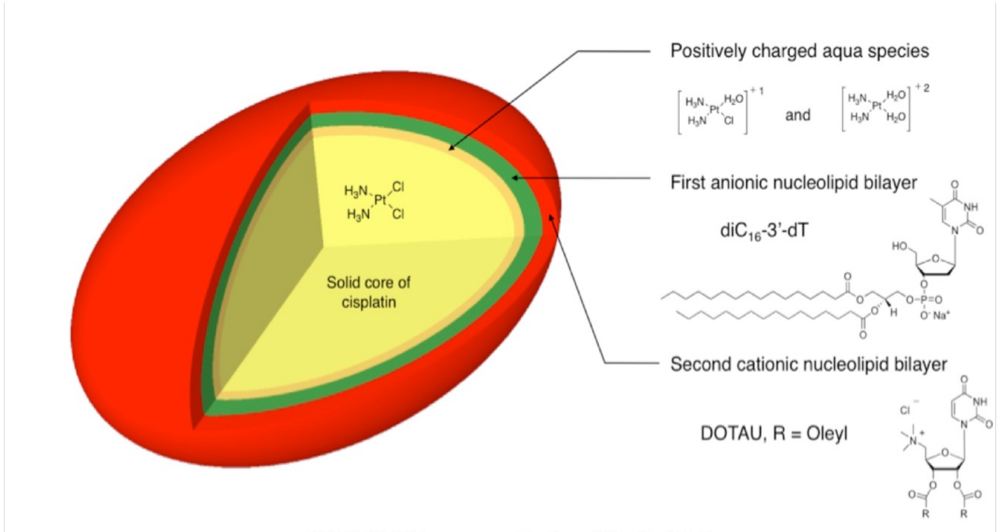




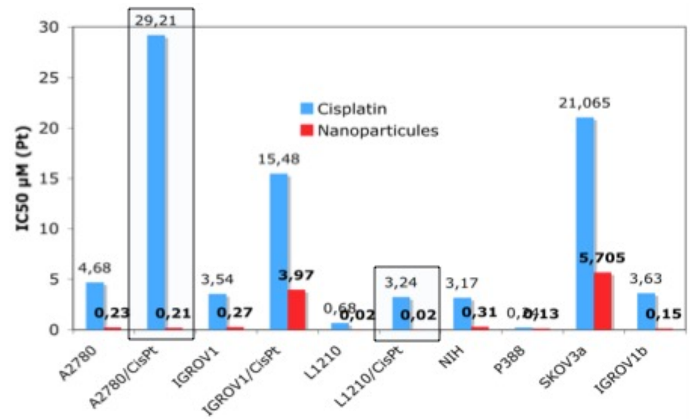
Ovarian cancer

Improvement of chemotherapies?

- Nucleolipids Based Nanoparticles for CisPt delivery

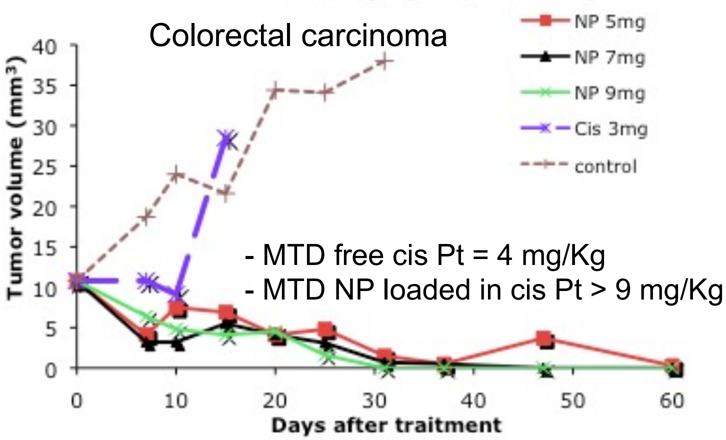


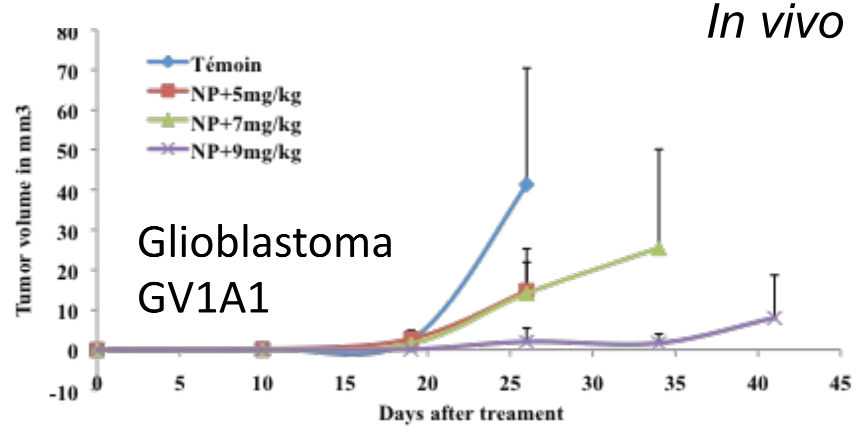
In vitro



IN VIVO **assays (rats, ProB, IV)**

In vivo



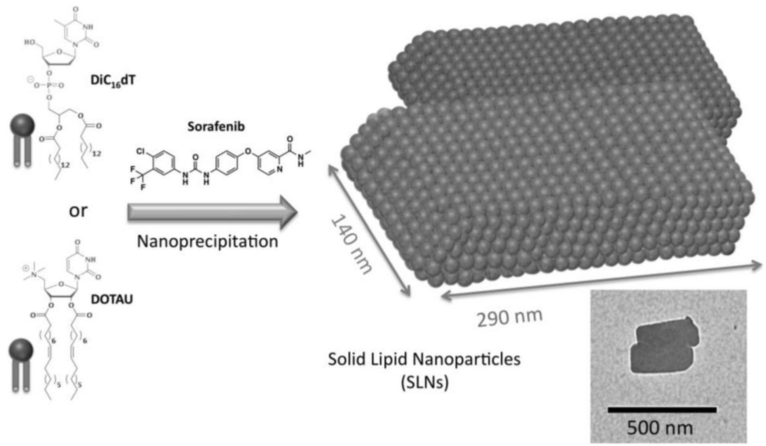


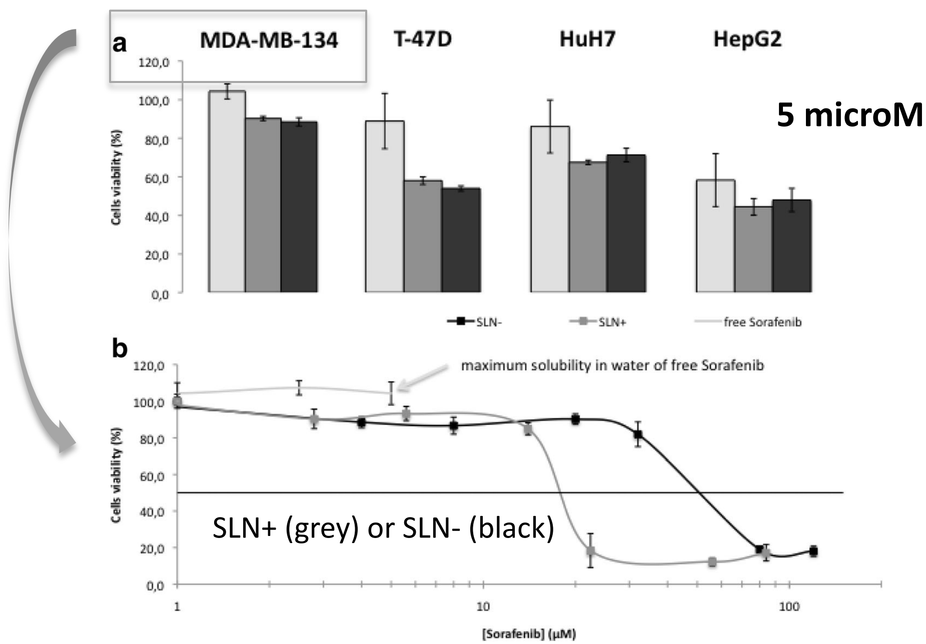
Khiati *et al.* (2011) ACS Nano

Improvement of chemotherapies?

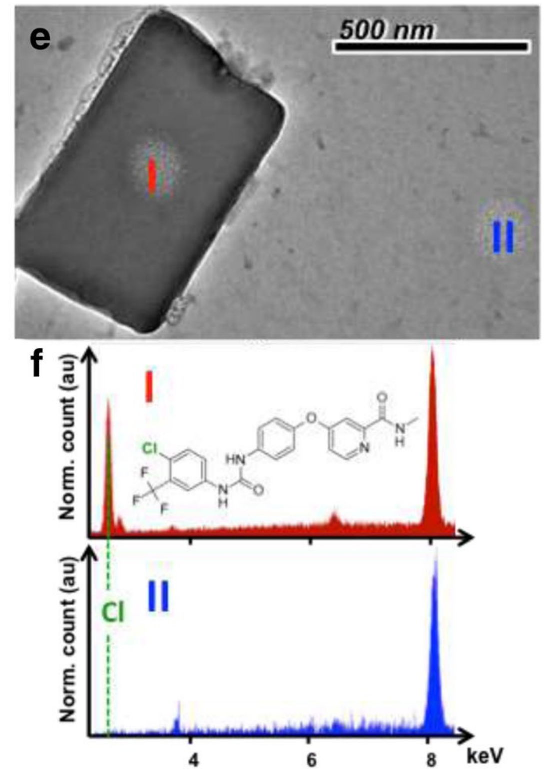
DRUG DELIVERY

SOLID NANOPARTICLES



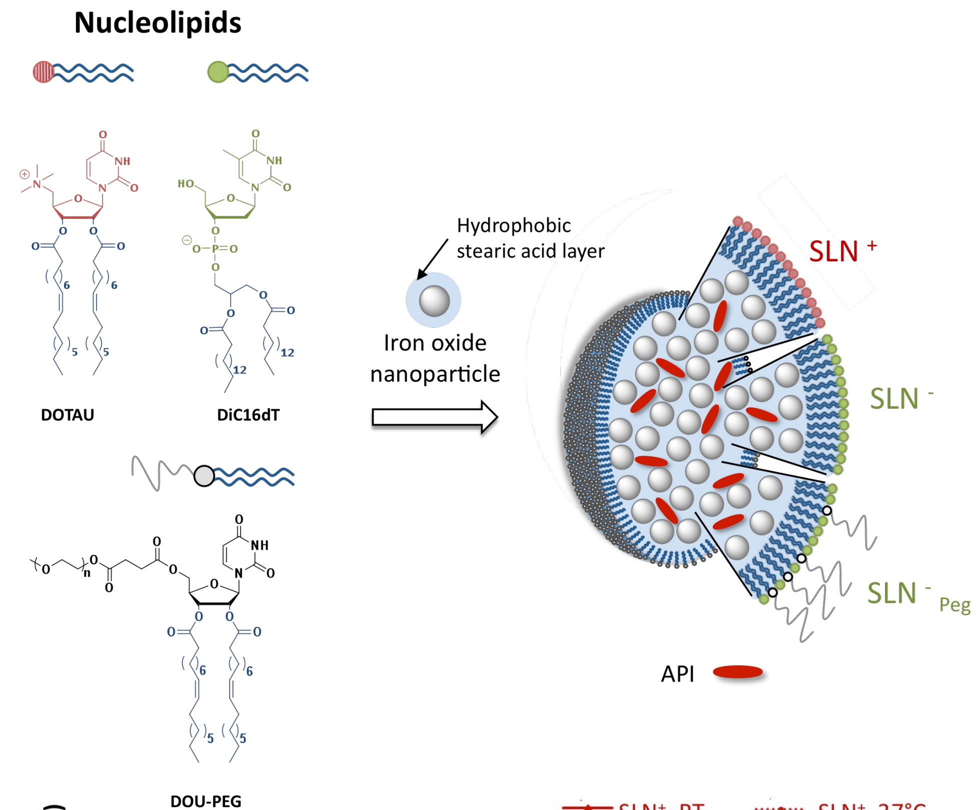


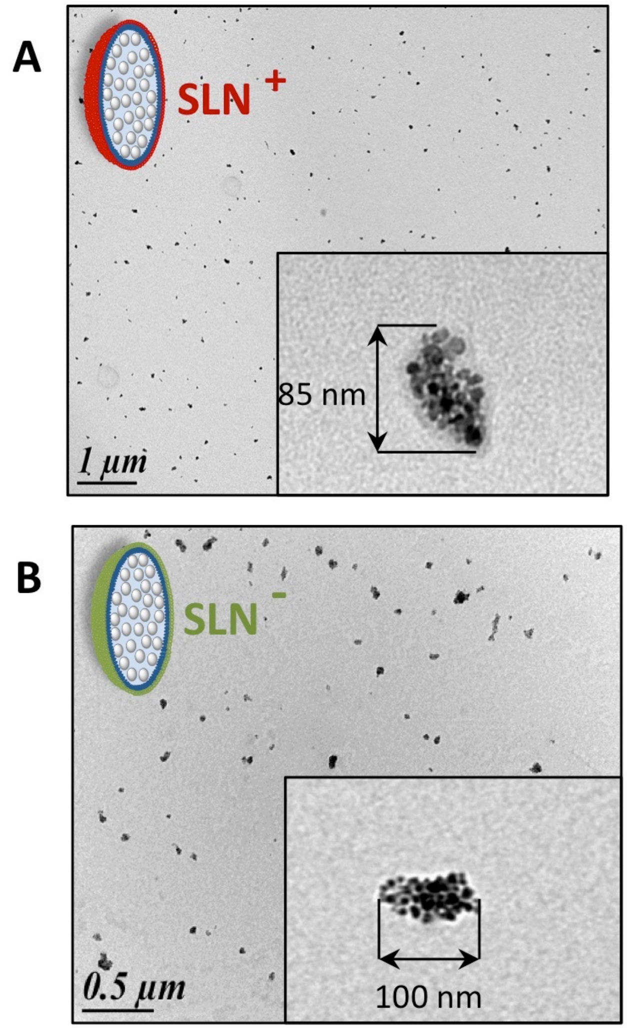
- Sorafenib is a RAF kinase inhibitor which suppresses ERK phosphorylation
- liver cancer (hepatocellular carcinoma)

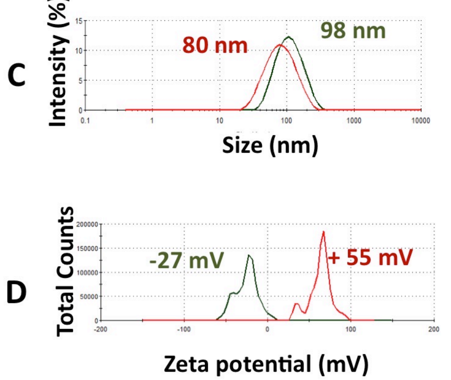


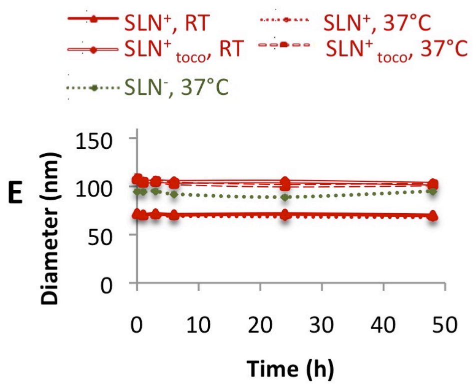
Benizri *et al. Nanoscale Research Letters* **(2018)** 13:17

Nanoparticles (MRI)









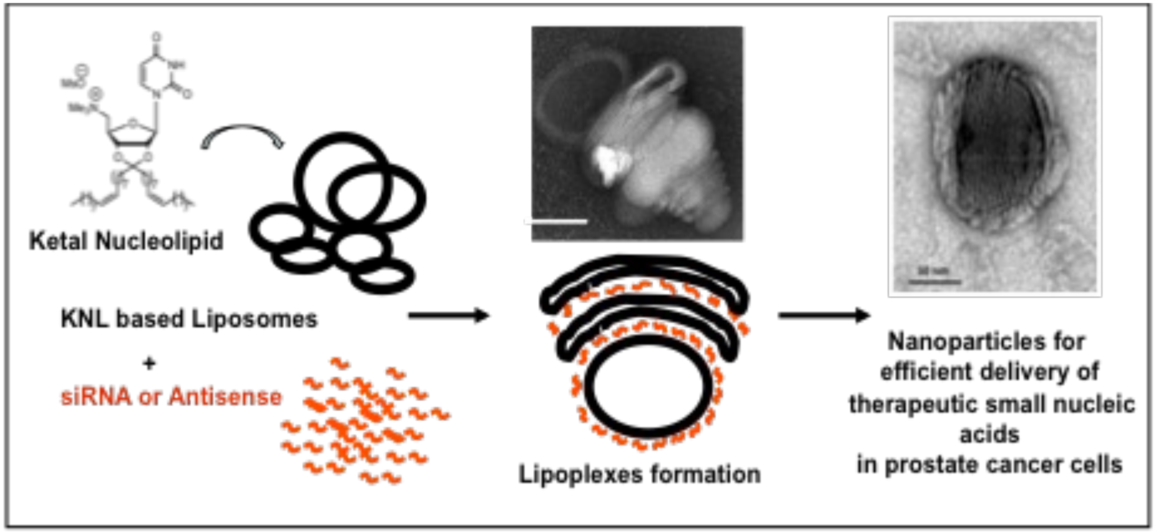
- SLNs have high magnetization properties
- Inhibition of platelet aggregation (PGI2)

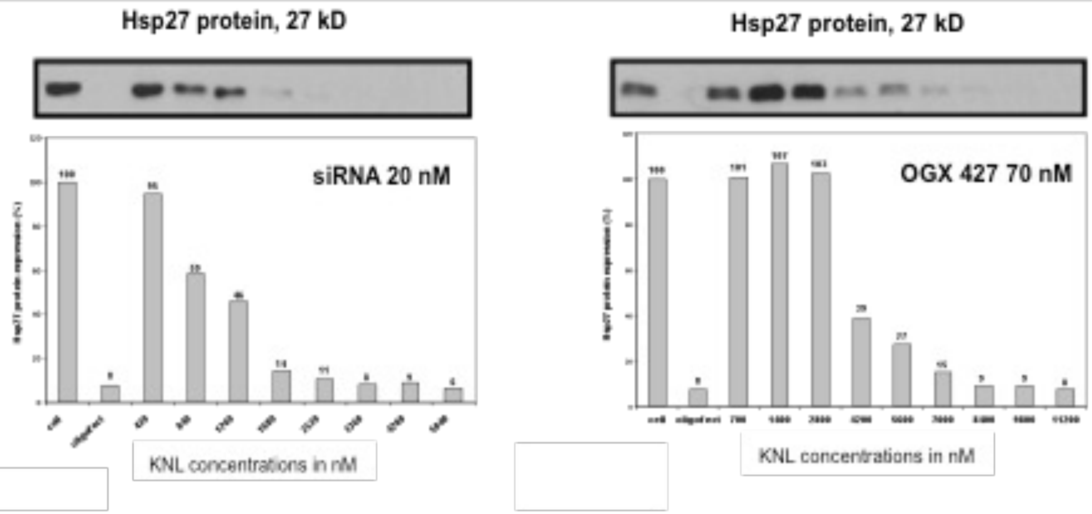
P. Barthélémy *et al.* *PCT,* ***2015***

Oumzil *et al.* *Bioconjugate Chem.* **2016**

Delivery of therapeutic oligonucleotides

- Drugs: siRNA, ASO
- Target: Prostate Cancer



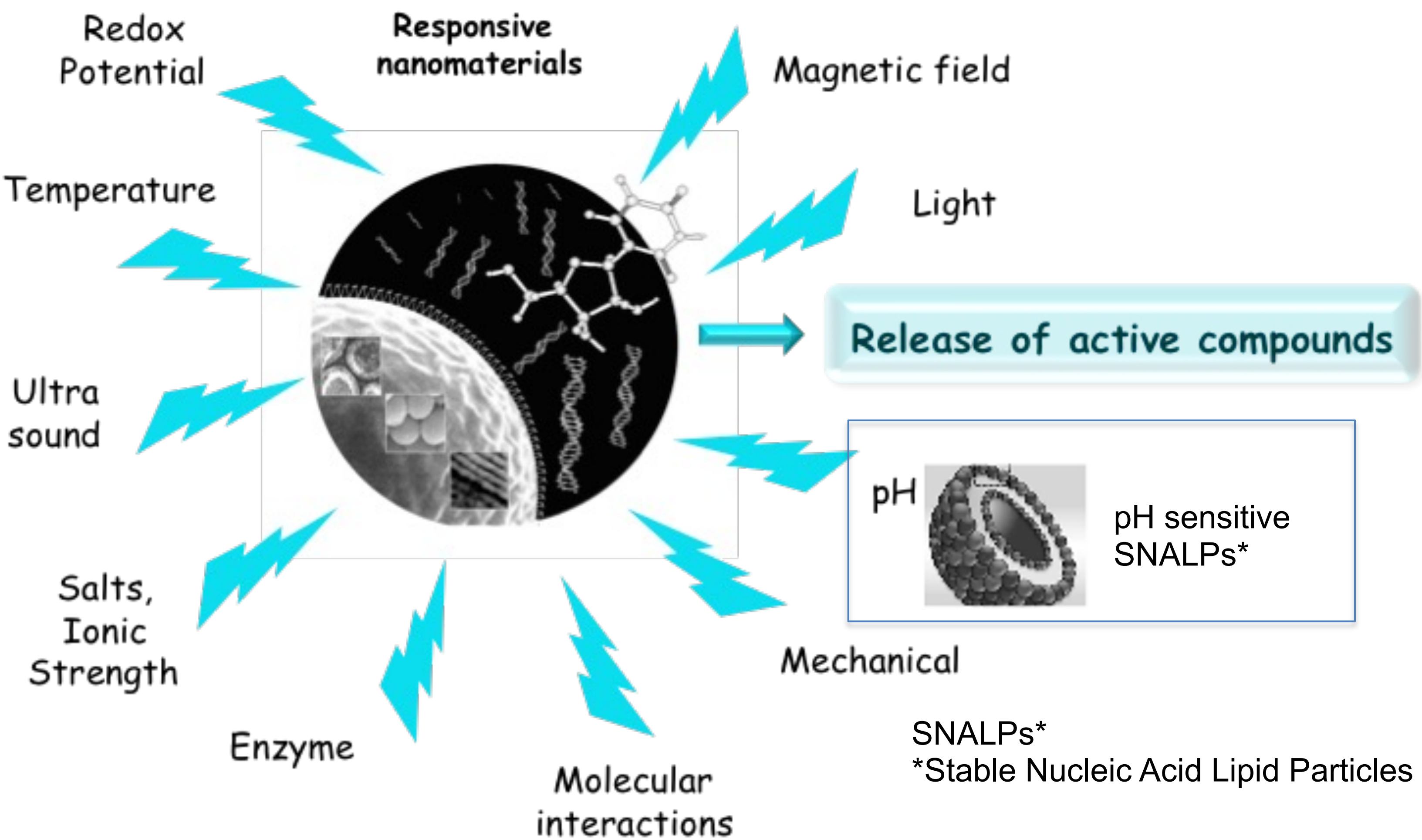


Heat Shock Protein 27 (Hsp27) is overexpressed in Castrate-Resistant Prostate Cancer

High efficacy of Transfection siRNA / ASO for Hsp27 Low toxicity

Luvino et al.
*Journal of Controlled Release 172 (**2013**) 954–961*

- **Delivery of therapeutic oligonucleotides**
  - **Stimuli-responsive DDS?**

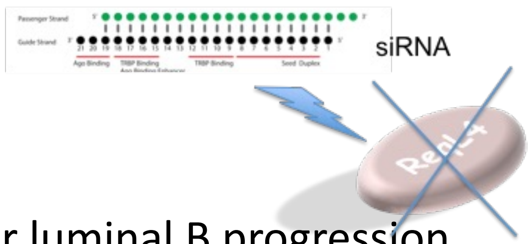


SNALPs*
*Stable Nucleic Acid Lipid Particles

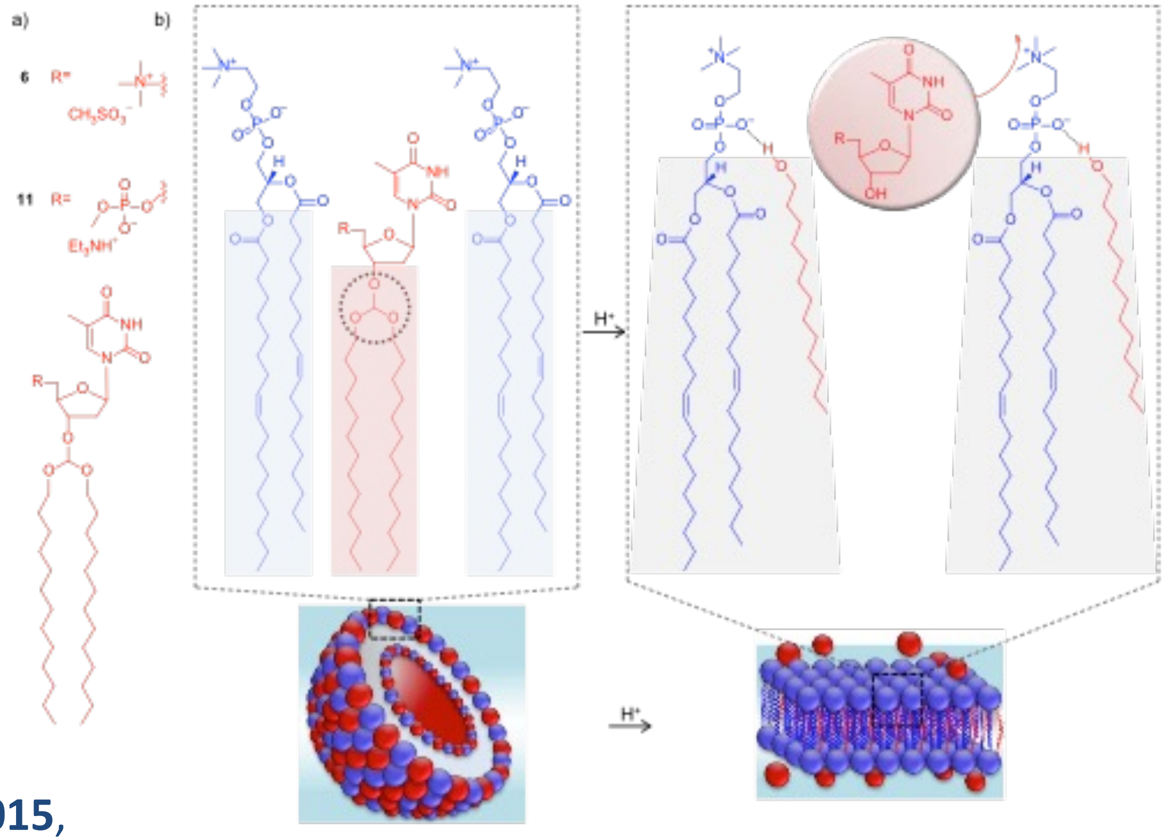
Delivery of therapeutic oligonucleotides

Drug: siRNA

Target: Breast Cancer (luminal B)



RECQL4 is a human RecQ helicase,
which play a critical role in human breast tumor luminal B progression

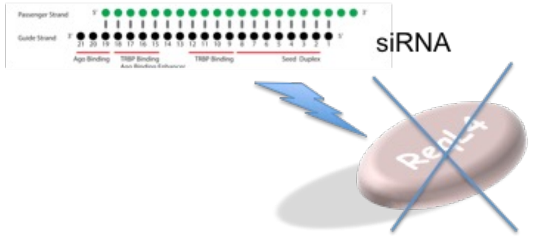


Barthélémy. *et al. PCT* **2015**,
Oumzil *et al. ChemMedChem* **2015**

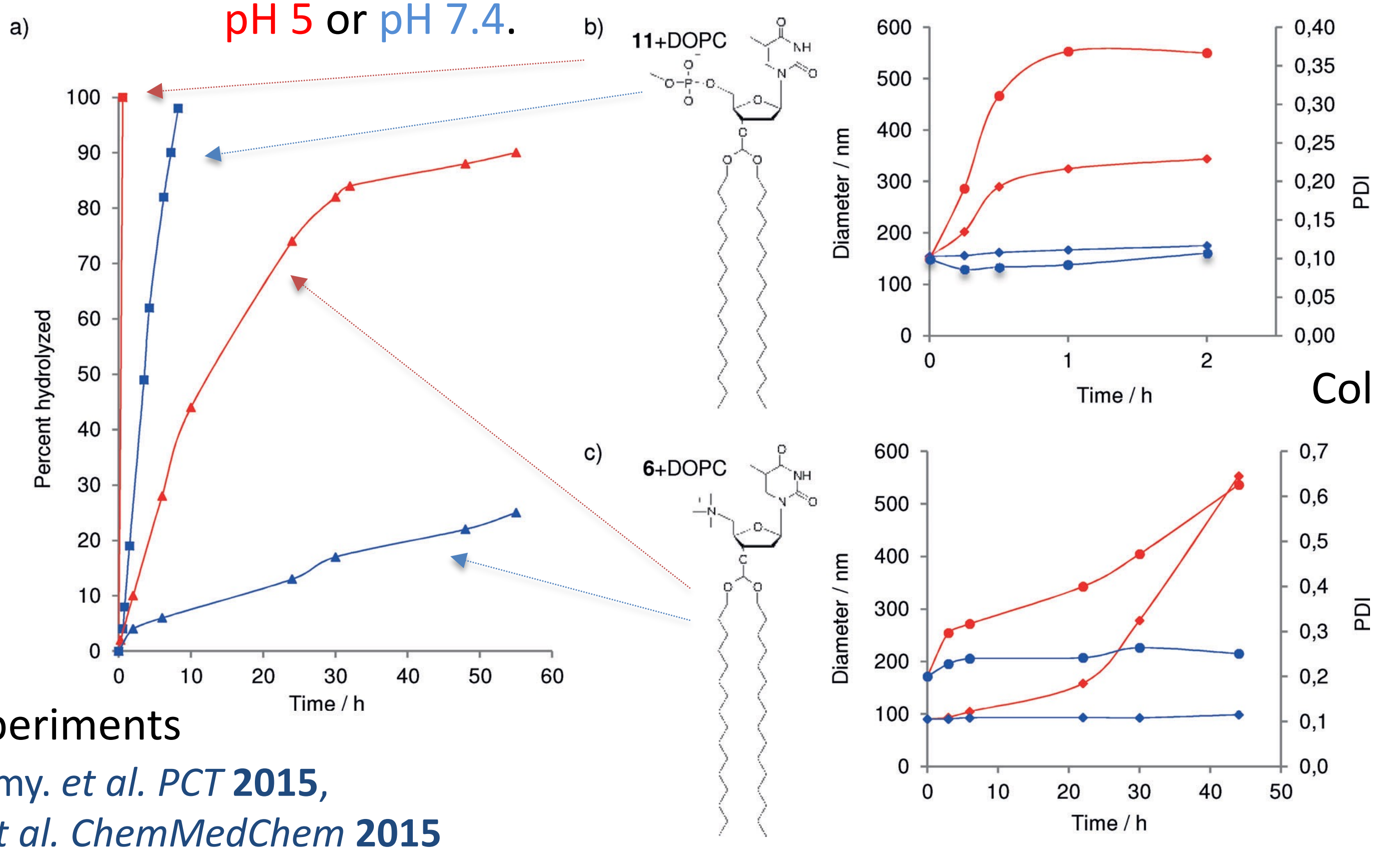
▪ Delivery of therapeutic oligonucleotides

Drug: siRNA

Target: Breast Cancer (luminal B)



pH 5 or pH 7.4.



Colloidal stability

NMR experiments

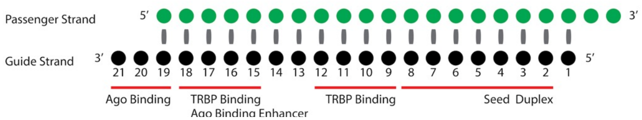
Barthélémy. *et al. PCT* **2015**,

Oumzil *et al. ChemMedChem* **2015**

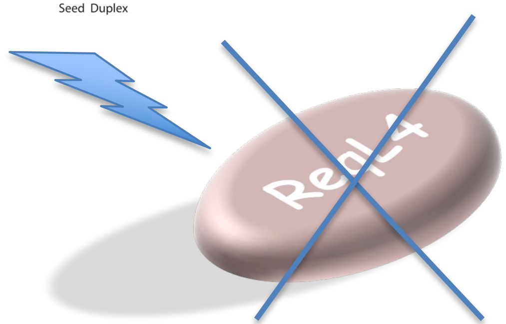
▪ Delivery of therapeutic oligonucleotides

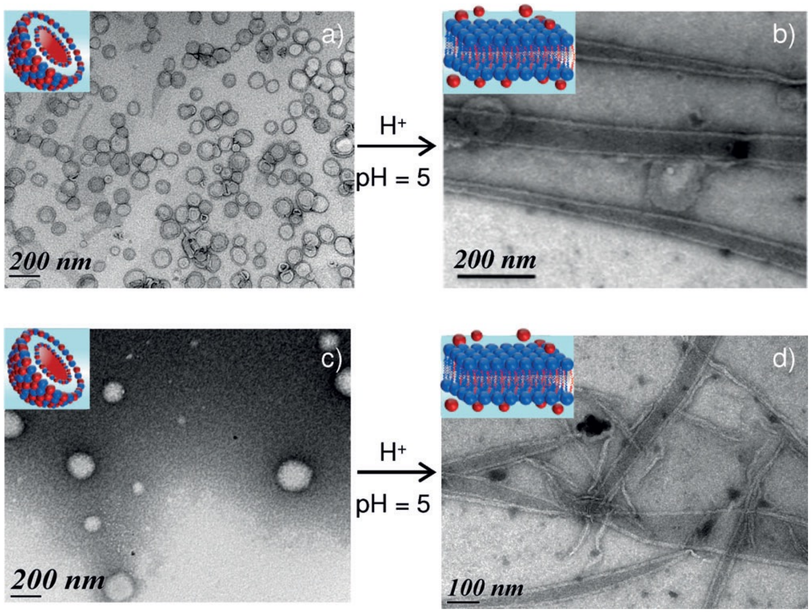
Drug: siRNA

Target: Breast Cancer (luminal B)



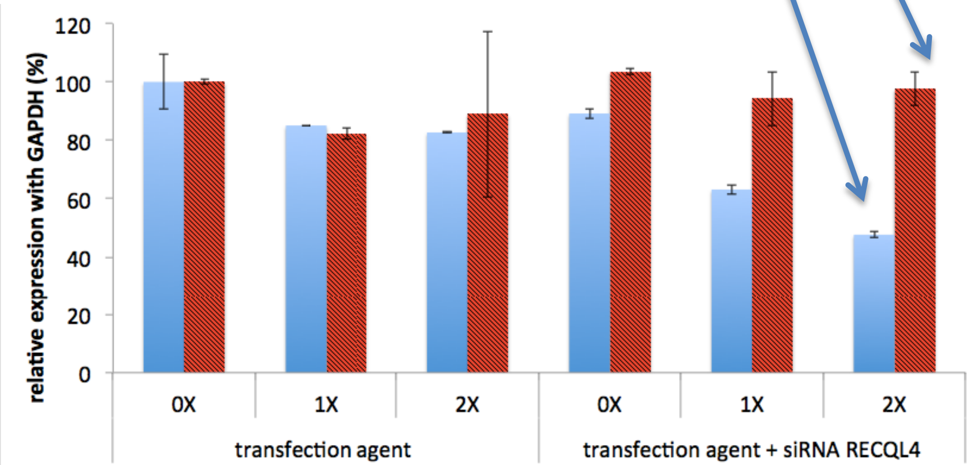
siRNA





DOTAU

ONL$^+$



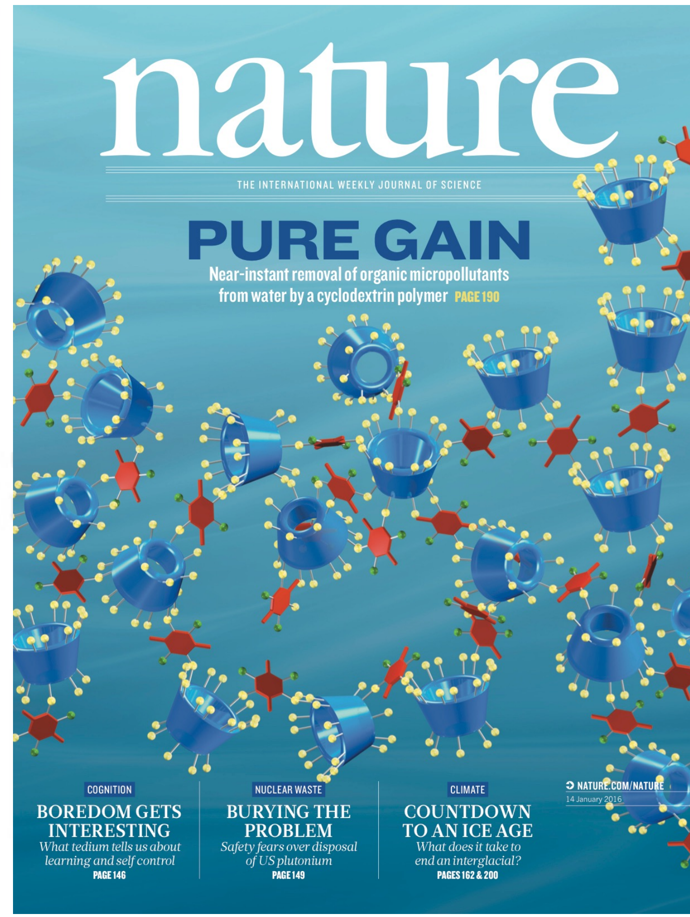
Barthélémy. *et al. PCT* **2015**,

Oumzil *et al. ChemMedChem* **2015**

DECONTAMINATION

POLLUTANTS

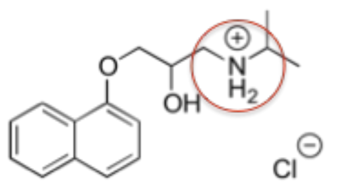
anses
agence nationale de sécurité sanitaire
alimentation, environnement, travail



Alaaeddin Alsbaiee, *et al. Nature*, **2016**, 529, 190-194

NL for drug decontamination

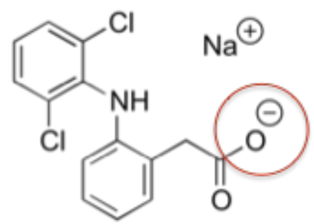
Propranolol



ß-bloquant used for hypertension cases

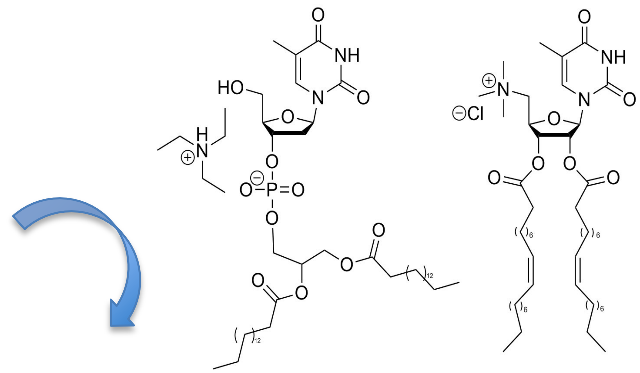
Ranking: 70

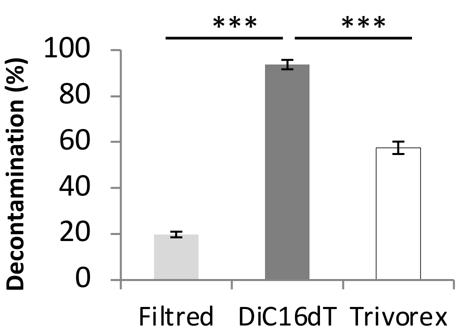
Diclofenac



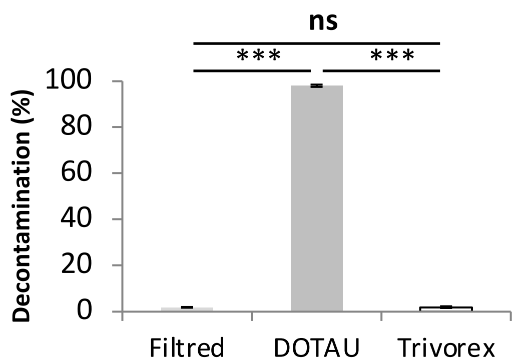
Non steroidal anti-inflammotory used to decrease the joint pains

Ranking: 35





Propranolol (50 µg/mL)

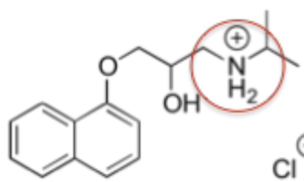


Diclofenac (25 µg/mL)

EP patent 2018: P. Barthélémy, S. Crauste-Manciet, M. Sicard

NL for drug decontamination

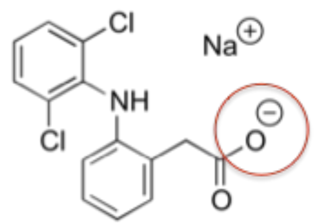
Propranolol



ß-bloquant used for hypertension cases

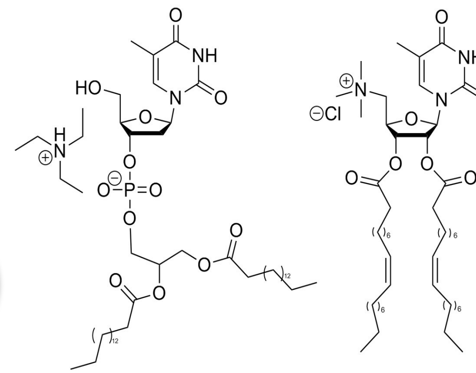
Ranking: 70

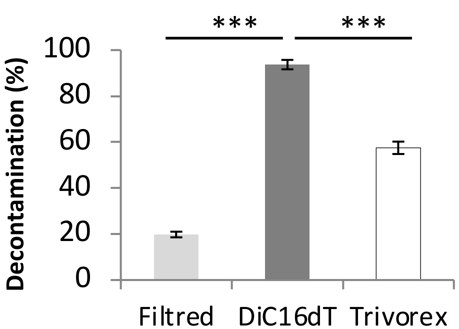
Diclofenac



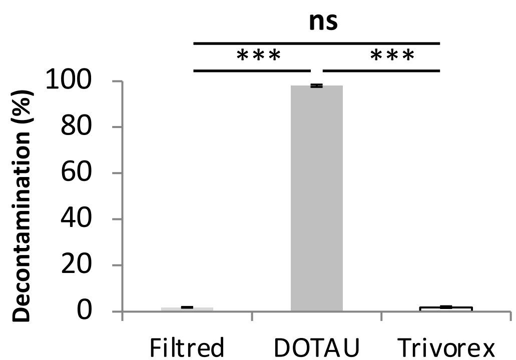
Non steroidal anti-inflammotory used to decrease the joint pains

Ranking: 35





Propranolol (50 µg/mL)



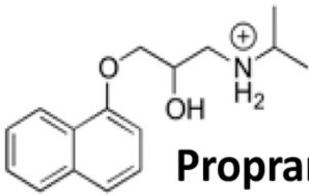
Diclofenac (25 µg/mL)

Issue:
Detection of micropollutants at high dillution C < 100 nM

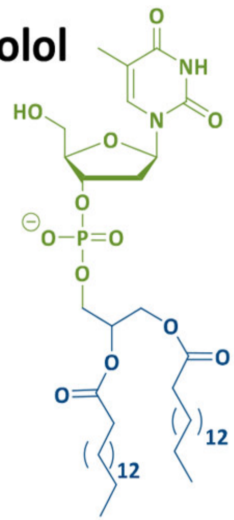
MS spectrometry analyses of 20 micropollutants

EP patent 2018: P. Barthélémy, S. Crauste-Manciet, M. Sicard

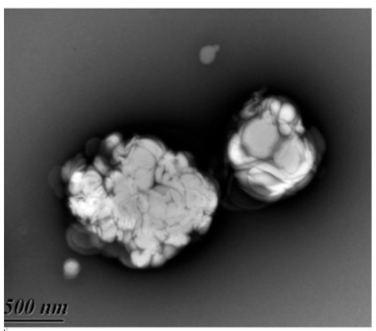
DECONTAMINATION

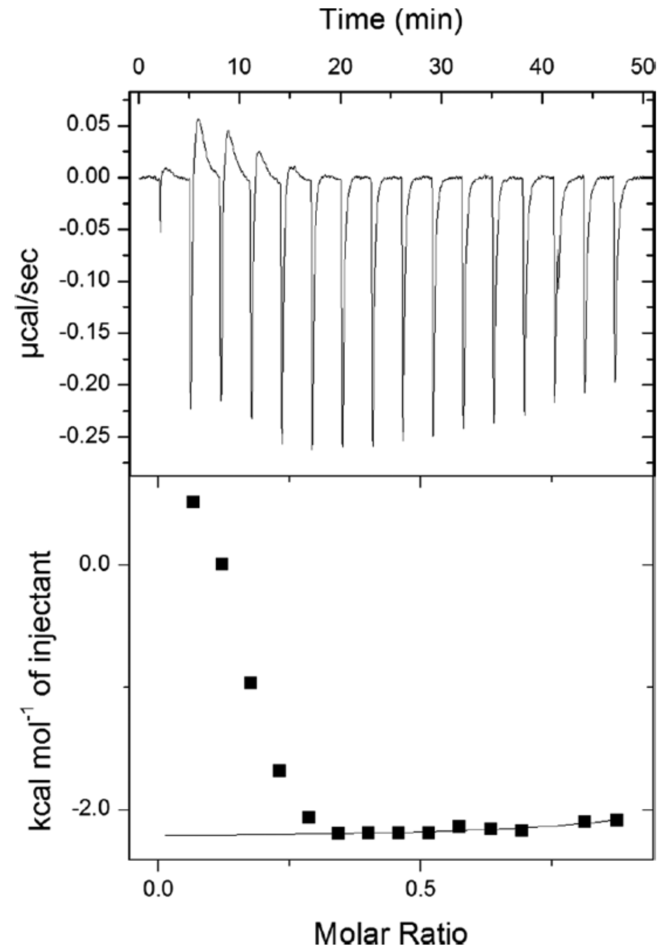


Propranolol



DiC16dT





ITC data for the titration DiC16dT (injectant) to propranolol

Kd = $8 \times 10^{-5}\ M^{-1}$, $\Delta H = -9.27$ kJ/, $\Delta S = 80$ J/mol/deg

Sicard M. et al. ACS Sustainable Chem. Eng. **2020**, 8, 30, 11052–11057

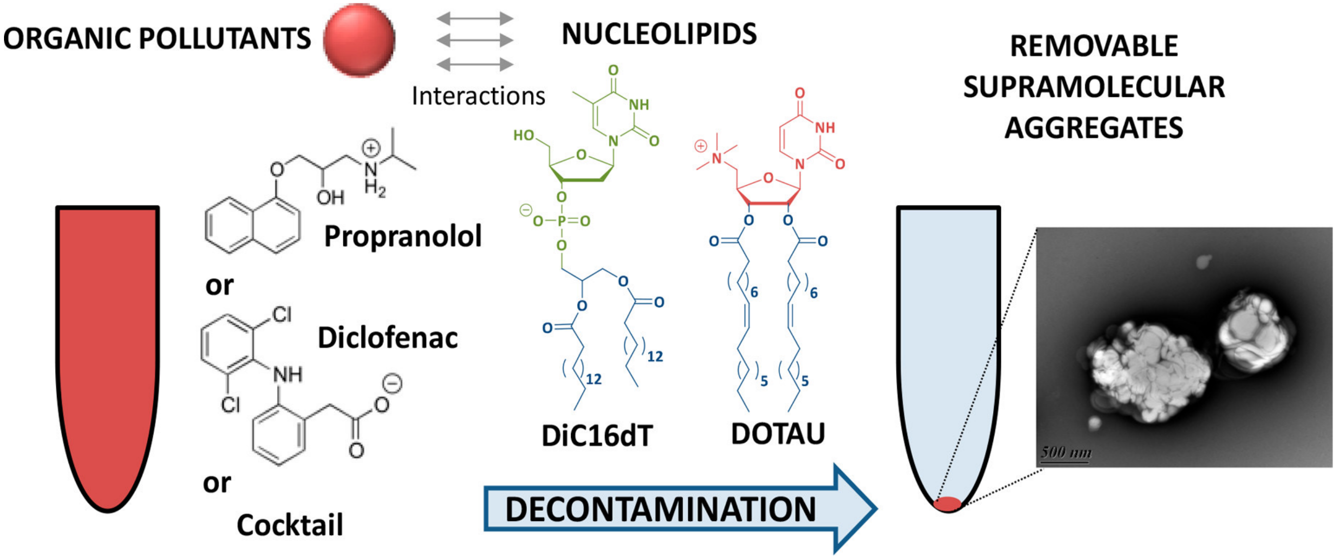
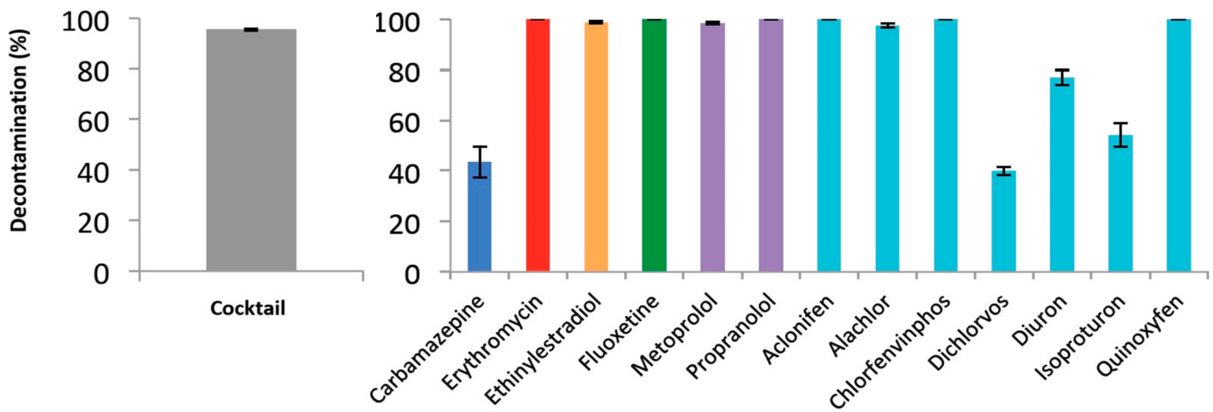


Illustration of the removal of organic pollutants from aqueous samples using nucleolipids (NLs) biomaterials. As a result, the decontamination of the aqueous sample can be achieved.



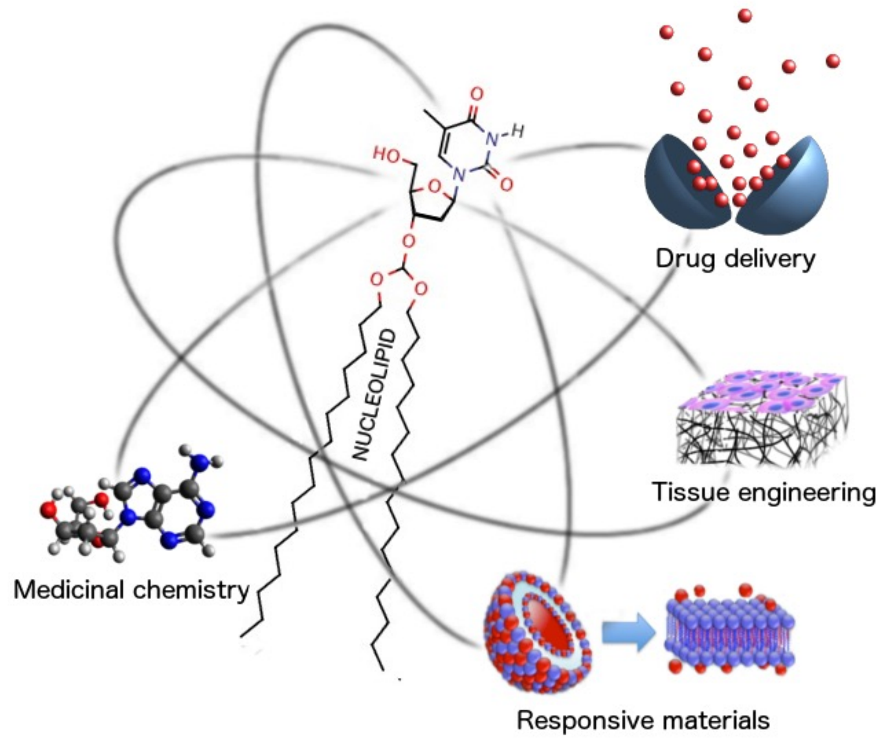
Sicard M. et al. ACS Sustainable Chem. Eng. **2020**, 8, 30, 11052–11057

Conclusion Part 1 Nucleolipids

NUCLEOLIPIDS BASED SUPRAMOLECULAR MATERIALS IN SHORT (POLYMER FREE MATERIALS)

MATERIALS

✓Modulation of the mechanical and rheological properties
✓ Injectable (thixotropy)
✓ Biocompatible materials
✓ No inflammation
✓ In vivo injection



DRUG DELIVERY

✓Controlled/Sustained release of biologics and/or drugs
✓ Bioprinting
✓Drug delivery
✓ Delivery of Oligo
✓Responsive supramolecular Systems

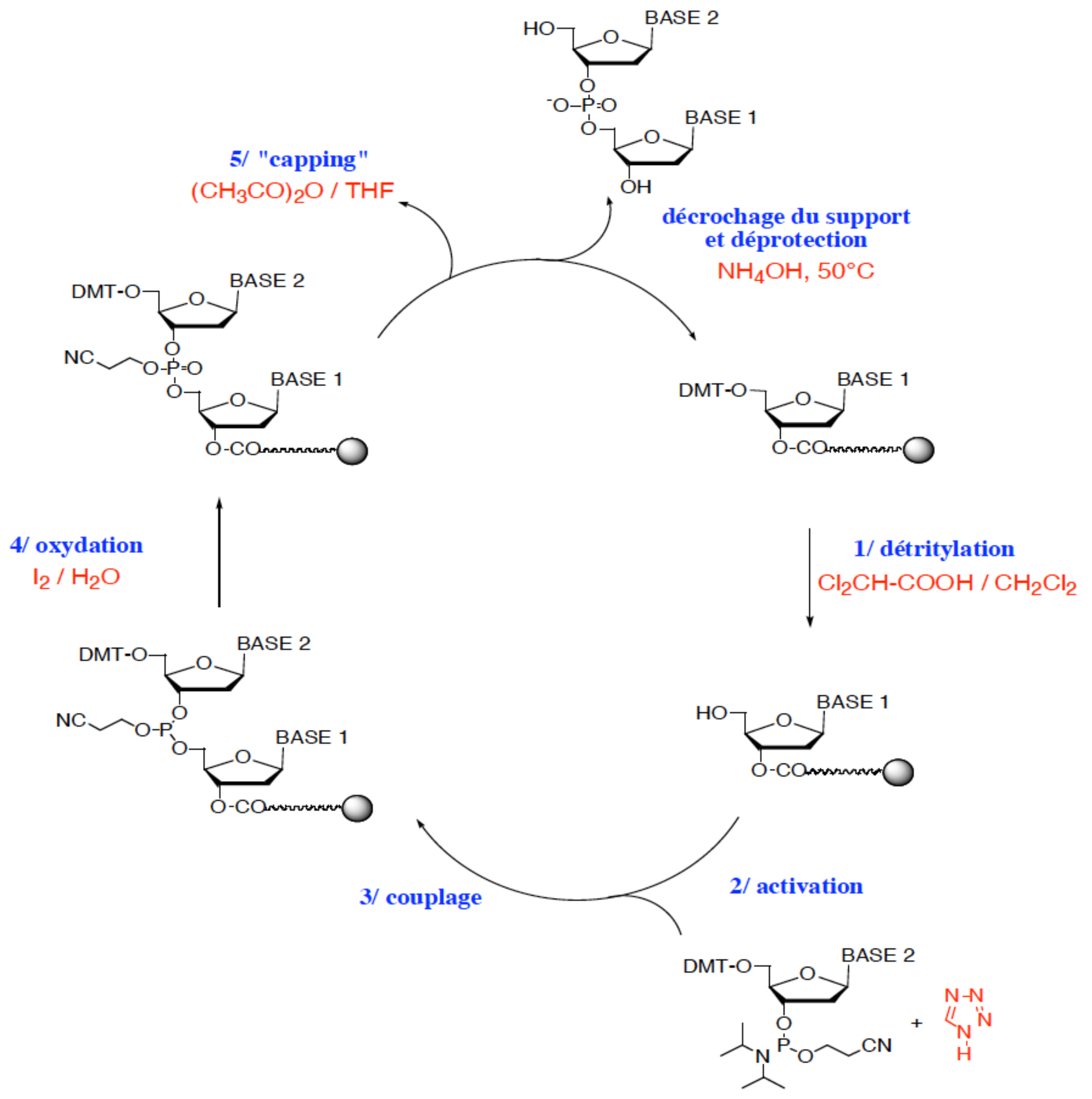
DECONTAMINATION

✓…

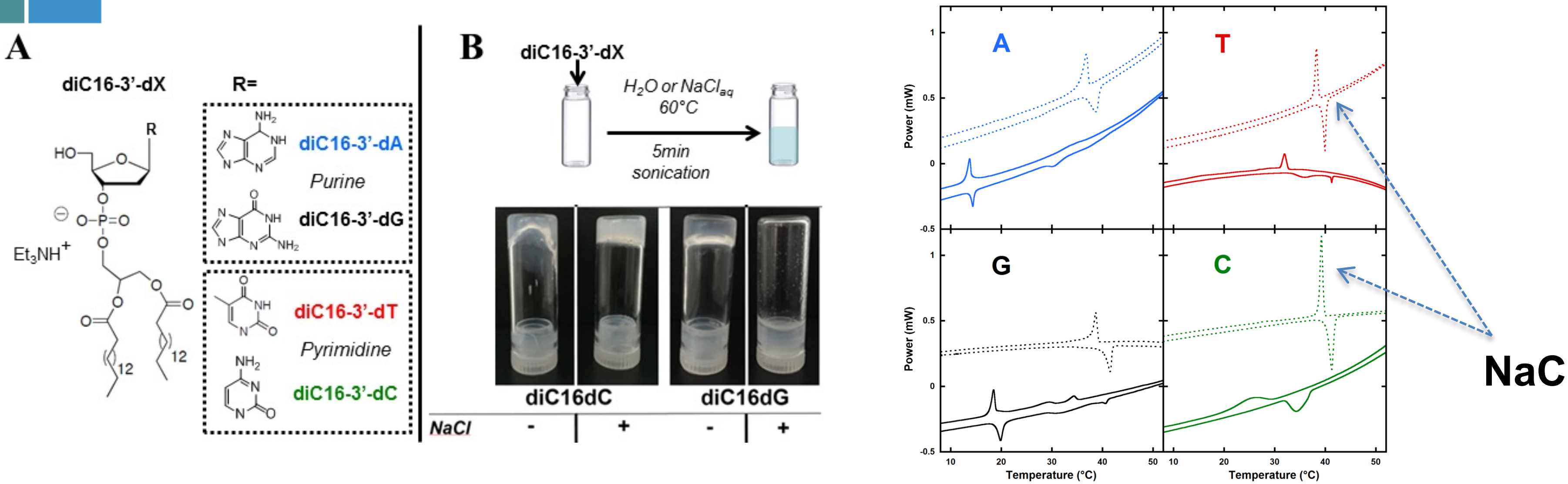
J. Baillet, V. Desvergnes, A. Hamoud, L.Latxague, and P. Barthélémy ***Adv. Mater*. 2018**, 1705078

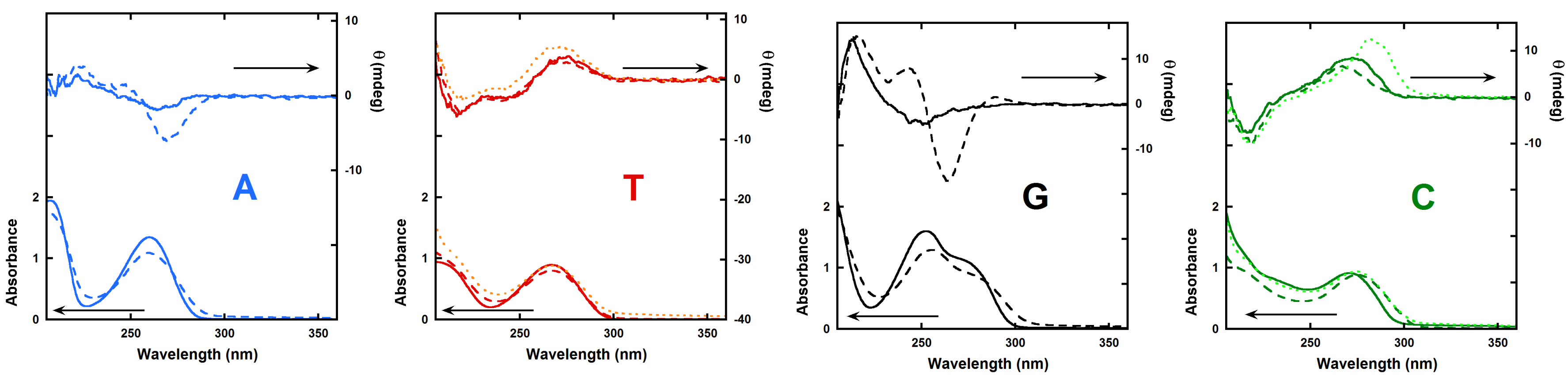
Additional materials

Oligonucleotide synthesis via phosphoramidite



BIOMATERIALS





UV (scale on left axis) and CD (scale on right axis) spectra of NLs prepared in water (dashed line), in NaCl solution (dotted line) with their deoxynucleosides (solid line).

B. Alies, M. A. Ouelhazi , A. Patwa, L. Navailles, V. Desvergnes, P. Barthélémy. *OBC*, (**2018**)