MEDICIN
MEdication for Diabetes with Insulin Contained In Nanogels

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Journées Nationales Nanosciences et Nanotechnologies 2012

New strategy for treating diabetes ?

Self-control of glycemia

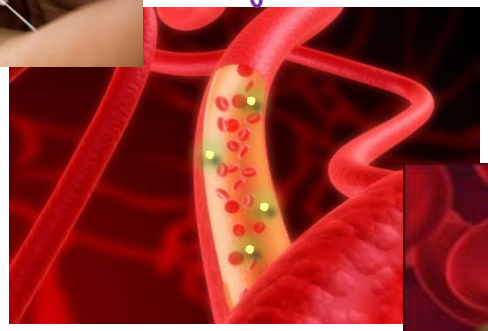
Self administration of insulin

Advantages :

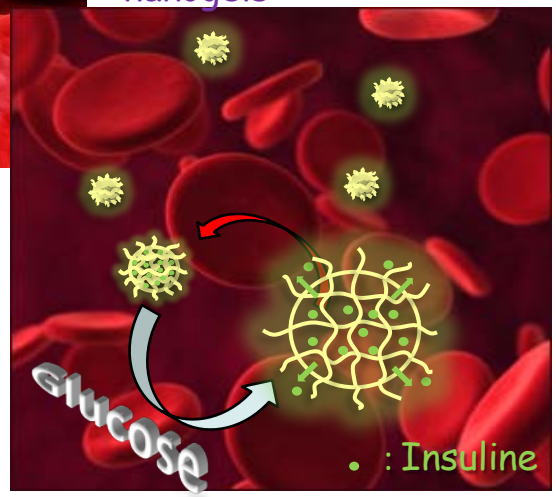
- Decrease the frequency of controls and injections
- Regulation of glycemia around the normoglycemia

New strategy for treating diabetes ?

Weekly subcut injection

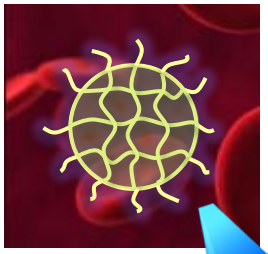


Circulating nanogels

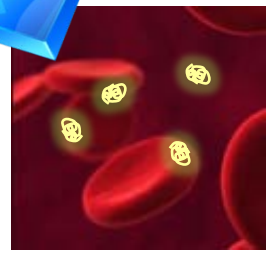


Repeated delivery of controlled amounts of insulin
Using glycemia as a control

After several cycles, the nanogels are empty.



Degradation



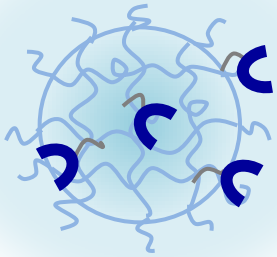
Non toxic residues
Rapid clearance

Design of self-regulated insulin delivery systems

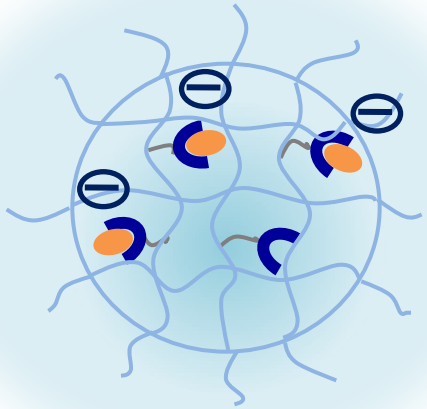
Specifications for nanogels

- Biocompatibility**,** without eliciting any undesirable systemic effects;
- Biodegradable over long term, without toxic by-products;
- Fast, consistent and reversible glucose-responses;
- Size below 400 nm, in order to enter blood circulation, to have a prolonged circulation time and to provide a liquid formulation for subcutaneous administration.
- Insulin delivery with the good pharmacokinetics, i.e. mimicking the pancreatic response to glucose bolus.

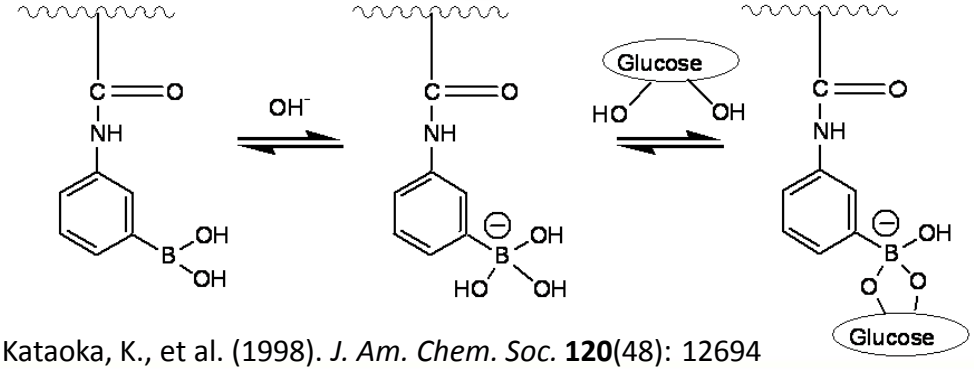
Design of self-regulated insulin delivery systems



Glucose



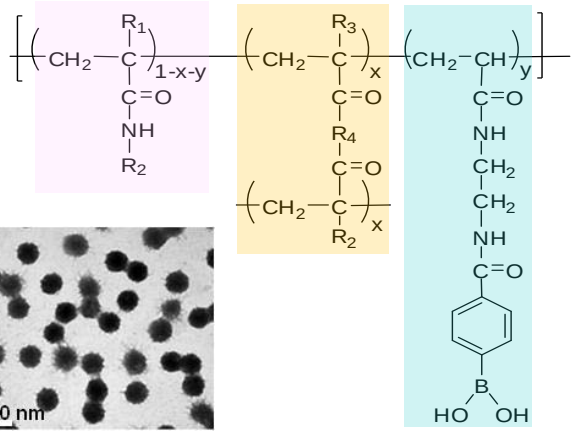
- Glucose oxidase
- Lectin (Concanavalin A)
- **Phenylboronic Acids**
- Glucose Binding protein



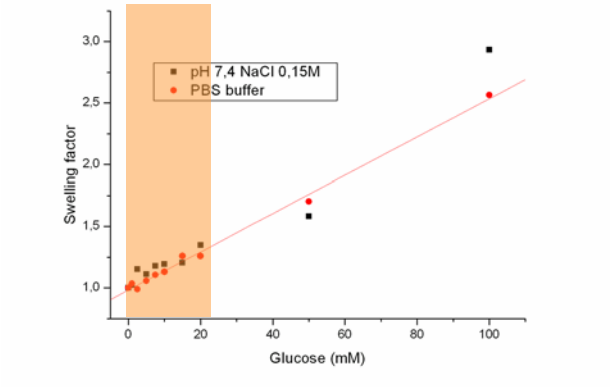
Kataoka, K., et al. (1998). *J. Am. Chem. Soc.* **120**(48): 12694

State of the art

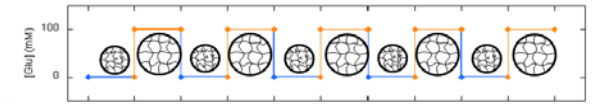
Microgels made of acrylamide derivatives

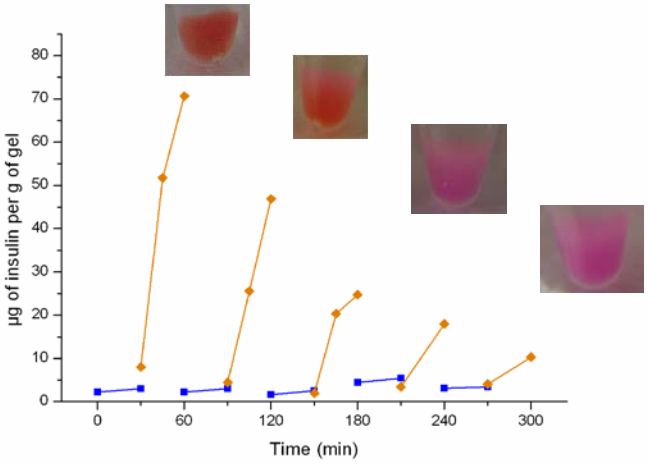


Conditions: pH=7.4, T=37°C, NEMAM-EGDMA-DDOPBA 10%



Cyclic release of insulin doses



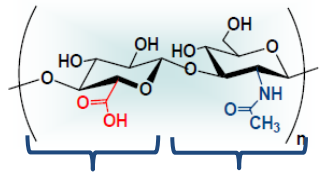


V. Lapeyre et al Biomacromolecules **2006**, *7*, 3356

V. Ravaine et al, *JCR* **2008**, *132*, 2

C. Ancla et al., *Langmuir*, **2011**, 27, 12693

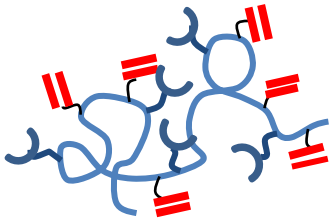
General strategy



D-glucuronic acid D-N-acetylglucosamine

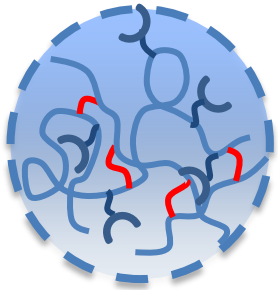
Hyaluronic acid (HA)

Grafting of cross-linkable agent and glucose sensor



Chemical cross-linking

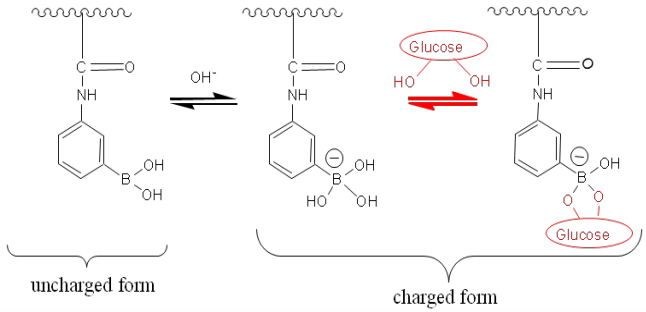
In confined conditions



- Biocompatible
- Bioresorbable
- Stealthy
- Can be covalently modified

- Cross-linkable group:

- Glucose sensor:



Project organization

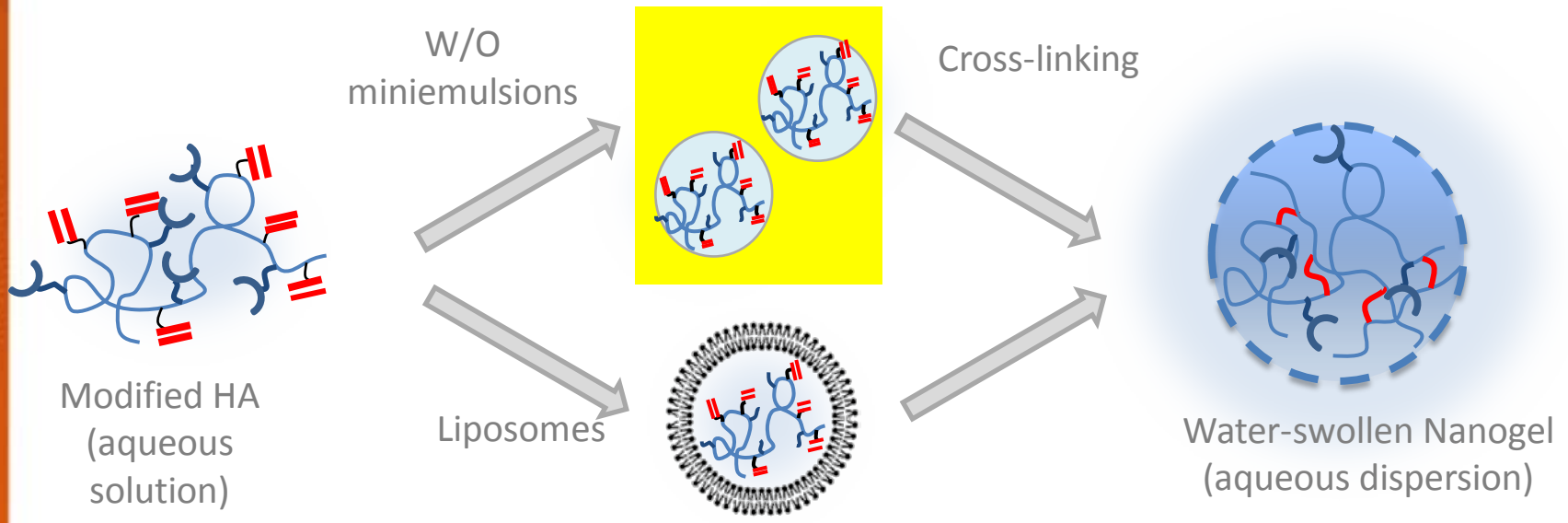
Glucose-responsive nanogels

1) Build up nanogels with controlled size/structure made of water-soluble fragile polymer

2) Design of glucose-responsive gels made of polysaccharides

Part I : Nanogels made of HA

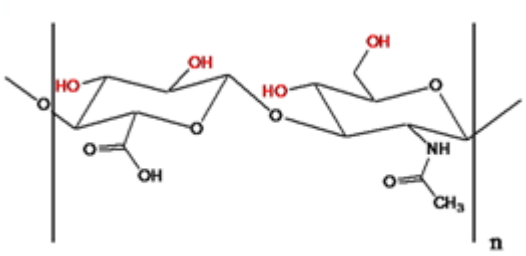
Build up nanogels with controlled size/structure made of water-soluble fragile polymer



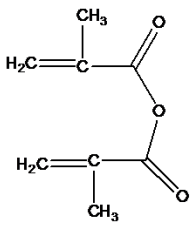
Part I : Nanogels made of HA

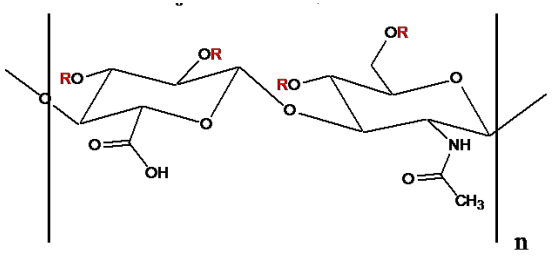
Synthesis of cross-linkable HA chains

Random grafting of methacrylate moities on the hydroxyl groups



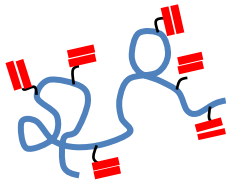
Water/DMF



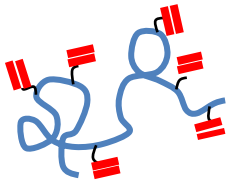


R=H or

HA-MA



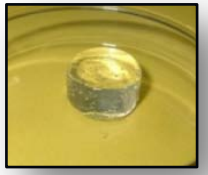
➢DM: from 0.1 to 0.4



Radical polymerization

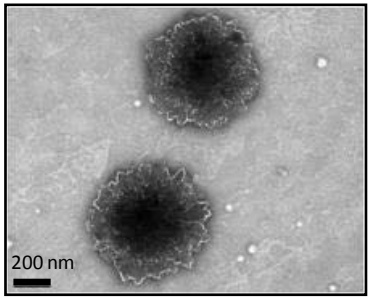
Irgacure 2959

hν



Part I : Nanogels made of HA

Water-in-oil emulsion method



Crosslinking
hν

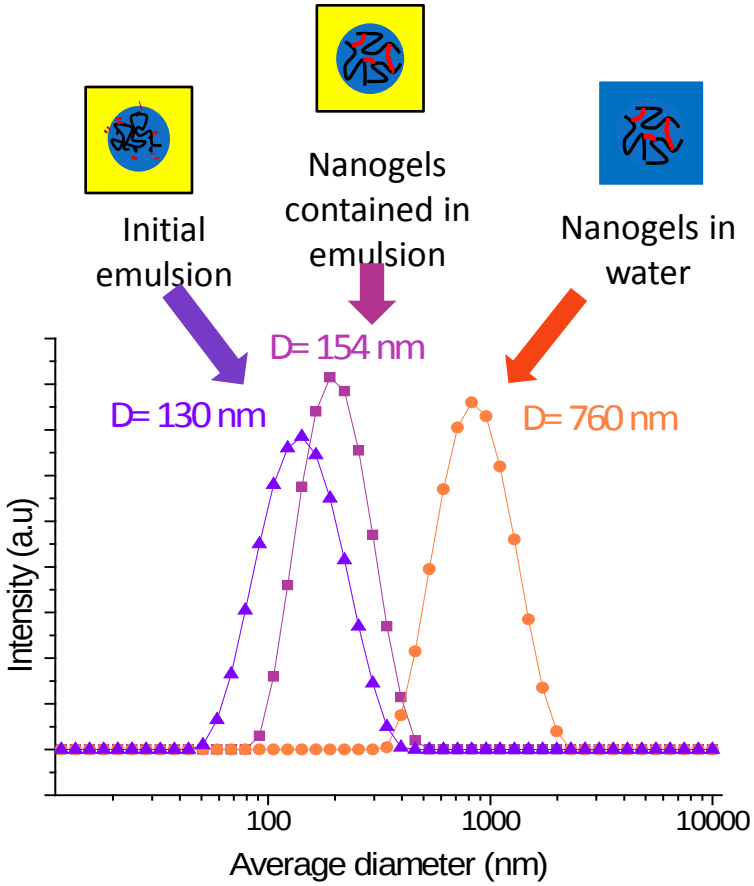
Oil removal and
dispersion in water

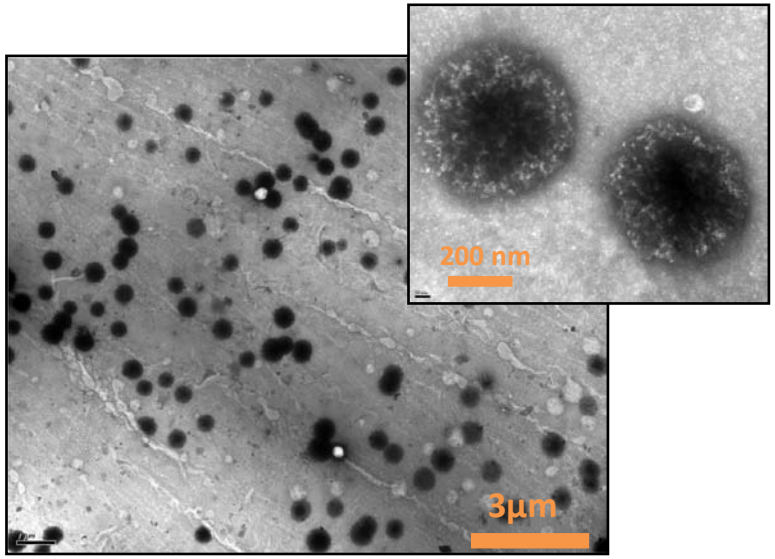
Organic phase
Oil + Emulsifiers

Aqueous phase
Solution of modified HA + photoinitiator

Part I : Nanogels made of HA

Water-in-oil emulsion method

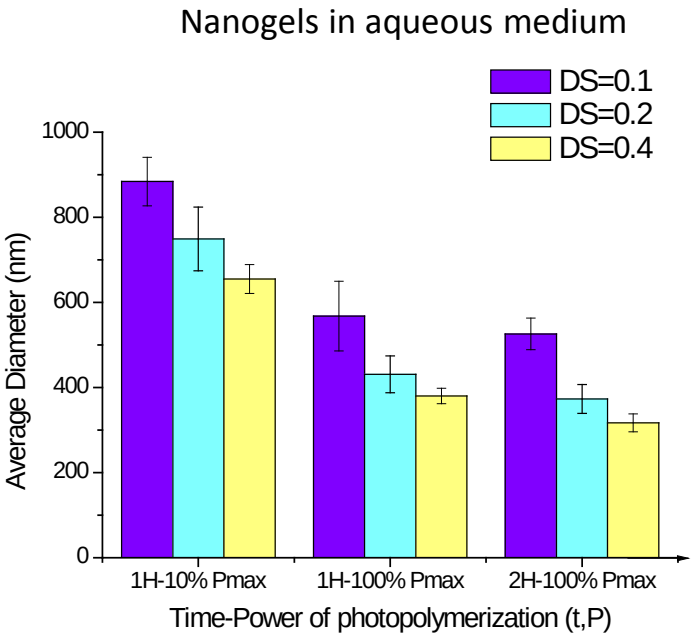


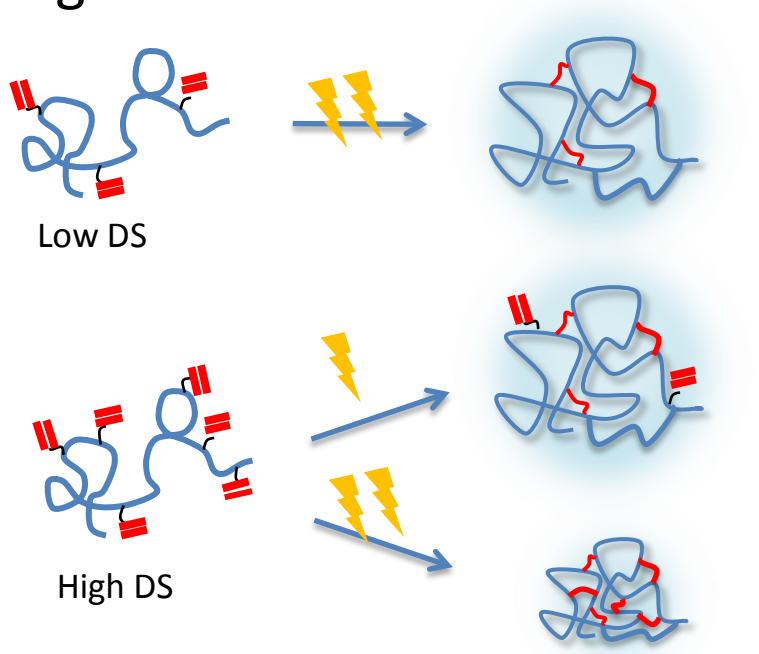


TEM analysis

Part I : Nanogels made of HA

Nanogel with controlled swelling degree





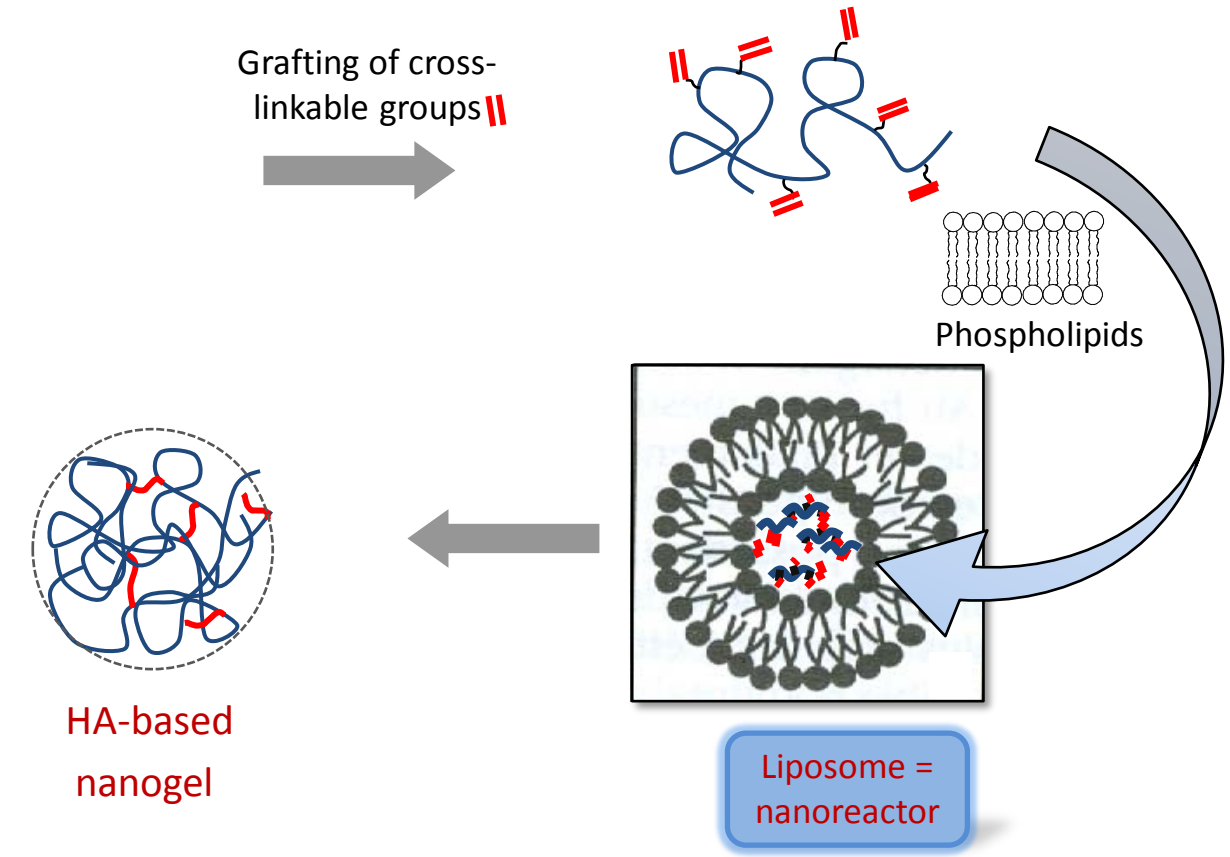
Cross-linking density controlled by :

- **the photopolymerization conditions**
- **the degree of substitution (DS)**

L. Messager et al., in preparation

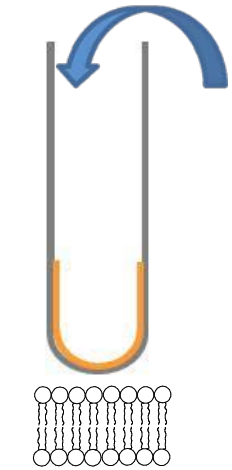
Part I : Nanogels made of HA

Liposome as nanoreactors

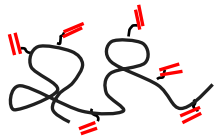


Part I : Nanogels made of HA

Liposome as nanoreactors

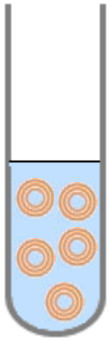


Phospholipids

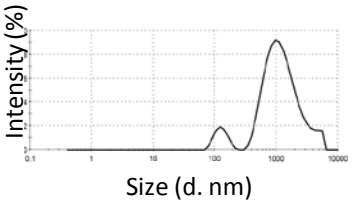


Irgacure
in buffer pH 7.4

stirring



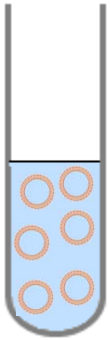
Multilamellar liposomes



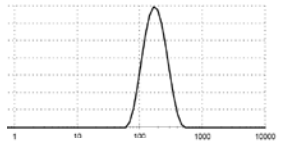
i. Washings

ii. Extrusion

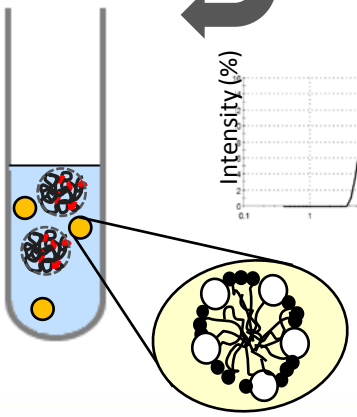
iii. UV (λ=365nm)

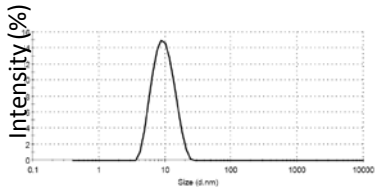


Lipogels

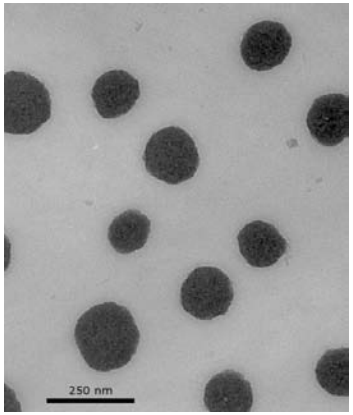


Removal of lipid layer



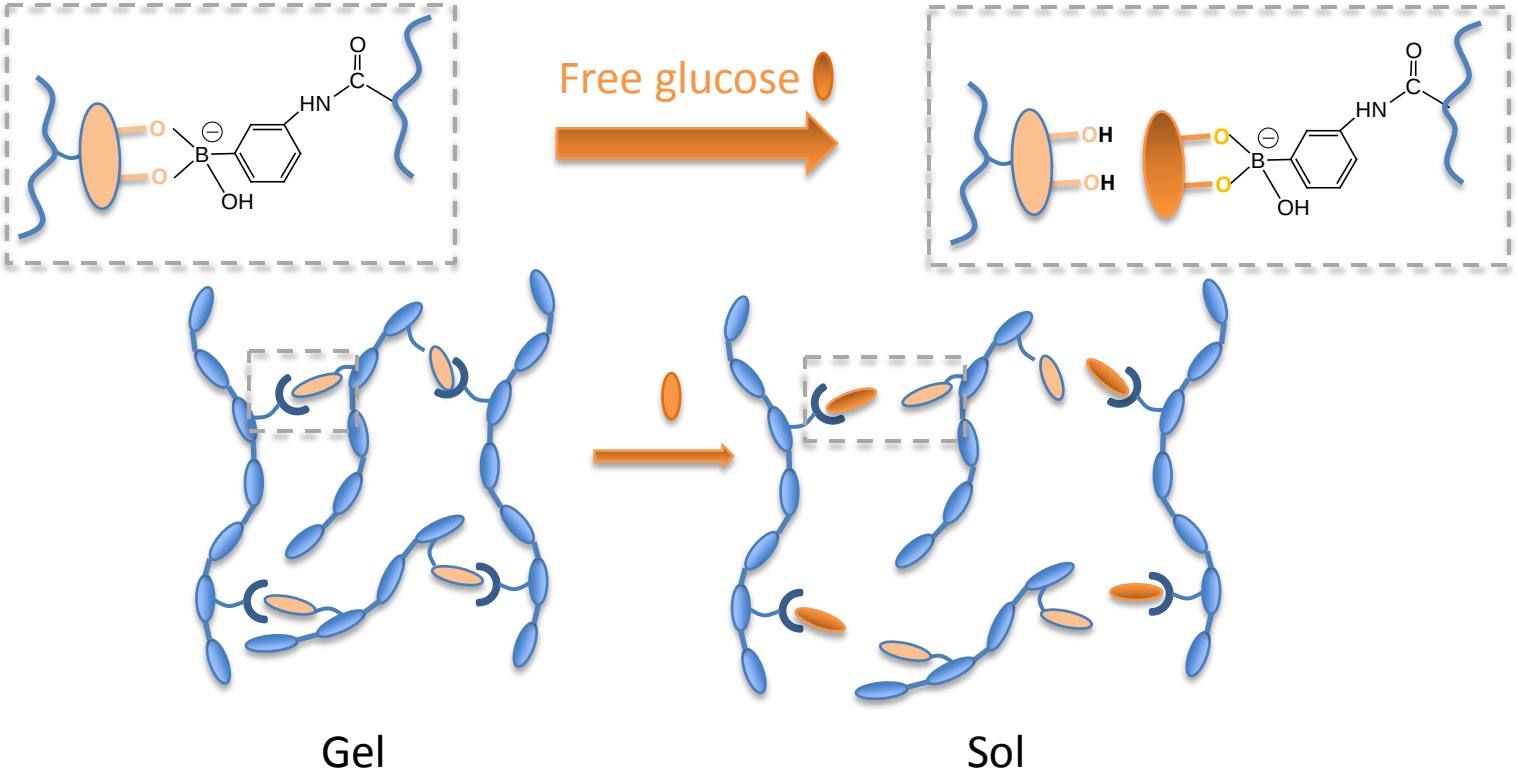


TEM images of naked nanogels negatively stained with uranyl acetate



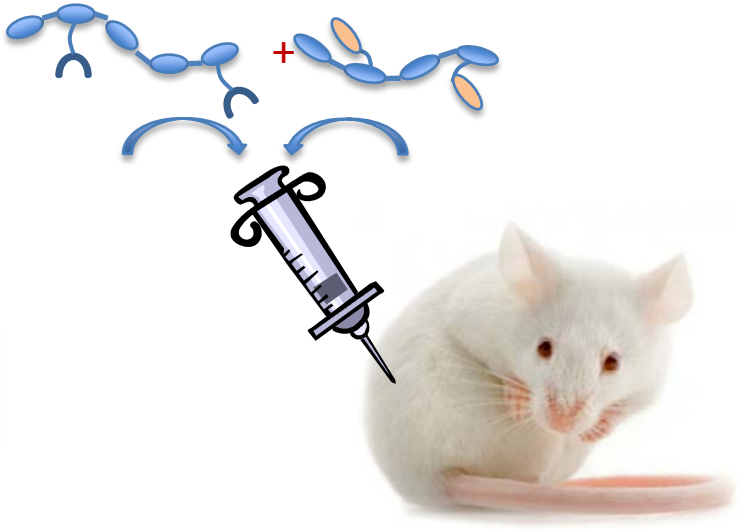
Part II : Glucose-responsive hydrogels

Design of glucose-responsive hydrogels made of polysaccharides



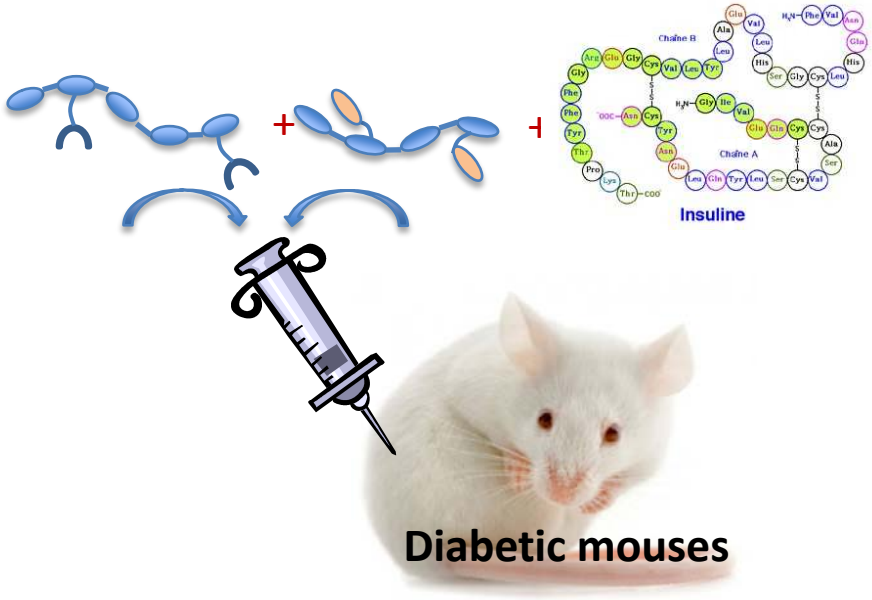
Glucose-responsive hydrogels
In vivo ?

Biocompatibility



Animals alive after 2 weeks
Healthy histological cuts

Diabetes treatment ?



On going studies

Conclusion and outlook

Nanomaterials

Nanogels made of chemically cross-linked HA + Glucose-responsive hydrogels

↓

Biodegradable Glucose-responsive nanogels

Pharmacokinetics/pharmacodynamics

Glucose-responsive hydrogels/nanogels + Insulin

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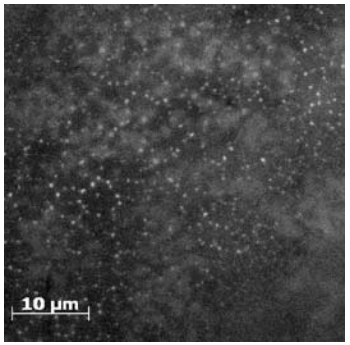
Delivery kinetics as a function of glycemia in vitro/in vivo



Biological studies

- **Nanogel Cytotoxicity**
- **Nanogel hemocompatibility**
- **Nanogel biodistribution (with tagged nanogels)**
- **In vivo hydrogel/nanogel degradation**

Acknowledgements

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