Nanoformulation des analogues nucléosidiques et acides nucléiques

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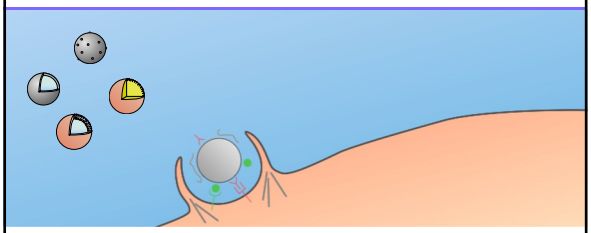

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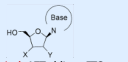
Challenges in the cellular delivery of nucleoside derivatives

Nucleoside analogues (NA)



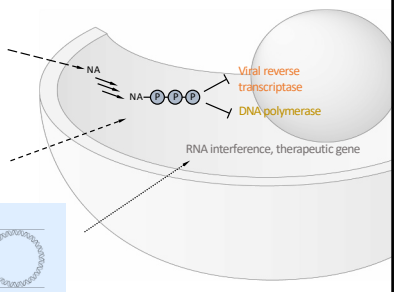
Antiviral: AZT, ddI, ..., FTC
Anticancer: dFdC (Gemcitabine)

Nucleotide analogues

Cidofovir (CDV) NA–P
AZT-TP NA–P–P–P

Nucleic acids

siRNA (~ 20 bp) pDNA (~ 3500 bp)



- Poor stability
- Low or no cellular uptake
- Insufficient phophorylation (NA)

→

- Low half life
- Side effects
- Emergence of resistances

→ **Objectives of nanocarriers:**

- **Protection**
- **Enhance cellular uptake**

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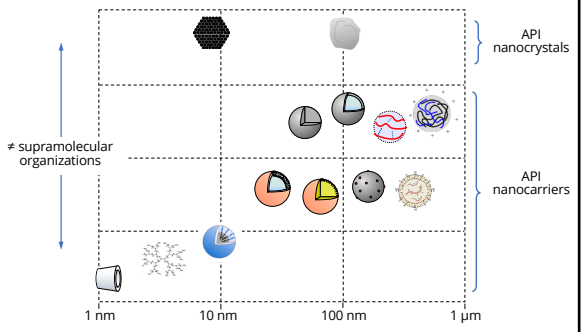
Various types of 'nano-drugs'



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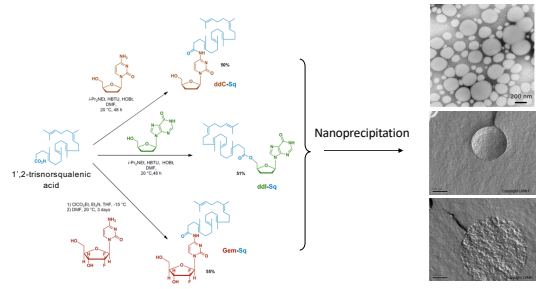
1. Squalenated nucleoside analogues



Prodrug	AZT-Sq	ddI-Sq	ddC-Sq	T-Sq	Gem-Sq
Sq anchorage	5'-OH	5'-OH	Base (N)	5'-OH	Base (N)

100-200 nm nanoparticles with:

- high drug loading (~30% w/w)
- no 'burst release' effect

Couvreur *et al., Nano Letters* **2006**, 6, 2544

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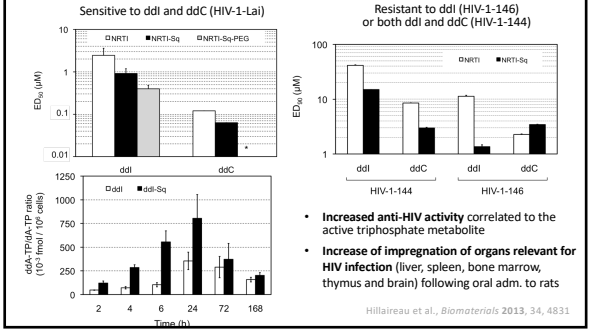
1. Squalenated nucleoside analogues – *antiviral NAs*

Human PBMC infected *in vitro* by reference HIV strains

Sensitive to ddI and ddC (HIV-1-Lai)

Resistant to ddI (HIV-1-146) or both ddI and ddC (HIV-1-144)



- **Increased anti-HIV activity** correlated to the active triphosphate metabolite
- **Increase of impregnation of organs relevant for HIV infection** (liver, spleen, bone marrow, thymus and brain) following oral adm. to rats

Hillaireau et al., *Biomaterials* **2013**, 34, 4831

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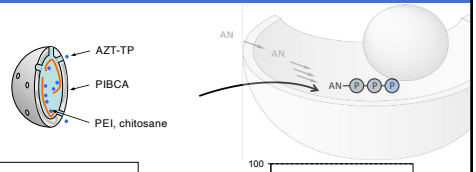
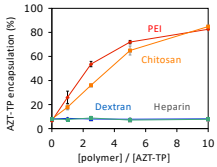
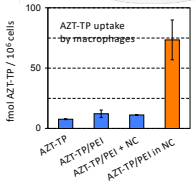
2. Aqueous-core nanocapsules for nucleotide analogues







- **Combination of hydrophobic and cationic polymers** allows efficient entrapment and cellular uptake of AZT-TP
- **Limitation: low drug loading** ~0.1% w/w

Hillaireau *et al., J Control Release* **2006**

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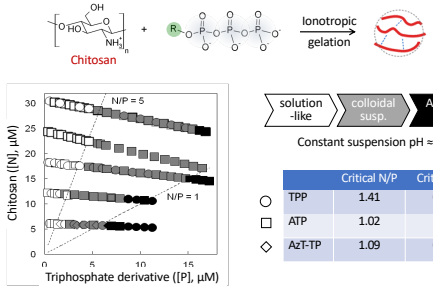
3. Nanogels of nucleotide analogues – *drug-triggered assembly*



	Critical N/P	Critical +/–
TPP	1.41	0.99
ATP	1.02	1.03
AzT-TP	1.09	0.97

➡ **Colloidal suspensions obtained for N/P ≳ 1 can be obtained for triphosphate group-containing drugs**

Giacalone *et al.*, *Biomacromolecules* **2013** 14(3), 737-42

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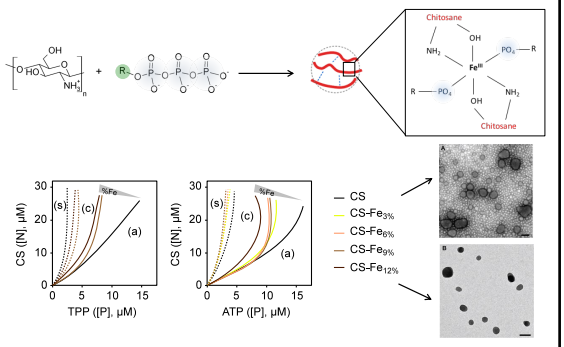
3. Nanogels of nucleotide analogues – *incorporation of Fe^{III}*



➡ **Substitution of CS by CS-Fe does not compromise nanogel formation, modifies critical N/P**

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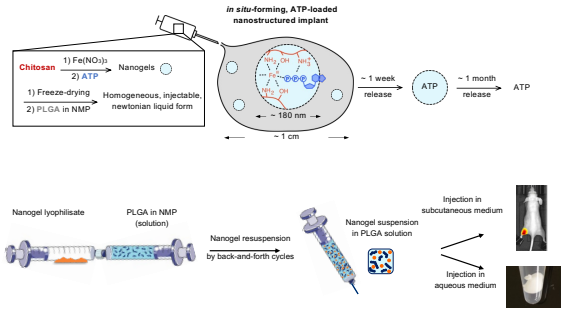
4. An injectable implant of nucleotide-loaded nanogels



Giacalone et al., *Drug Deliv Transl Res* **2024**

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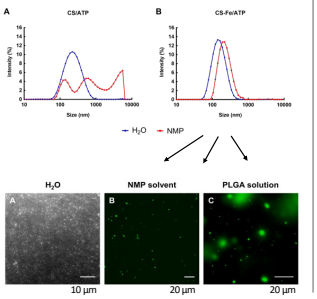
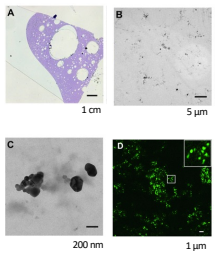
4. An injectable implant of nucleotide-loaded nanogels

Fe^{III} ensures colloidal stability in organic medium



Nanogels identified in formed implant



Giacalone et al., *Drug Deliv Transl Res* **2024**

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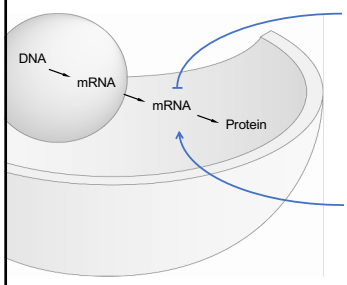
Administration of nucleic acids for therapy



Blockage of gene expression
- Antisense ODN
- RNA interference (*siRNA*)

Production of a protein of interest
→ mRNA

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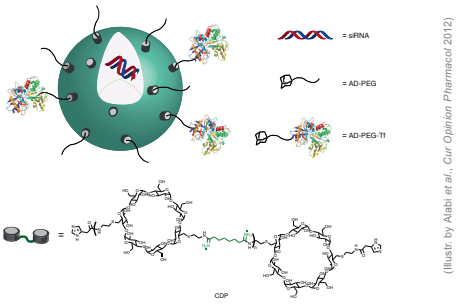
5. siRNA delivery by decorated polyplexes



(Illustr. by Alabi *et al.*, *Cur Opinion Pharmacol* 2012)

"Evidence of RNAi in humans from systemically administered siRNA via targeted NPs"

Davis *et al.*, *Nature* 2010

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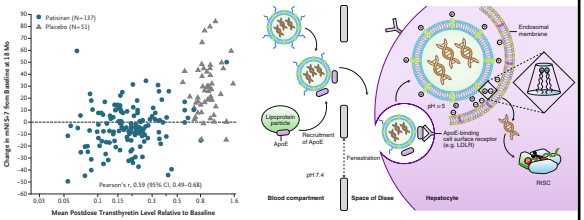
6. The first ARN-based drug: patisiran

- In 2018, an **siRNA has been targeted to the liver** using lipid nanoparticles
- Used in the treatment of polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (hATTR) in adults



Adams *et al. N Engl J Med* **2018**, 379:11-21

Akinc *et al. Nat Nanotechnol* **2019**, 14:1084-1087

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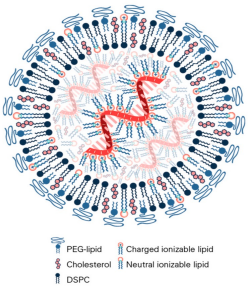
7. Lipid nanoparticle-mRNA – based vaccines



More susceptible to degradation than siRNA (chemical modification is more comlpex)

1-10 mRNA copies/nanoparticle, in central core

Vaccines **2021**, 9, 65. doi.org/10.3390/vaccines9010065

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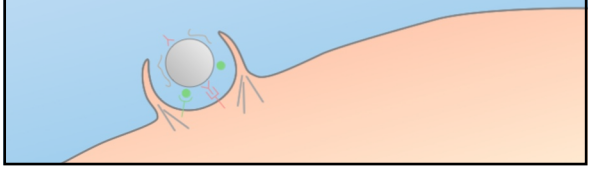
Conclusions on nanomedicine for treatments and vaccines

- Nucleotide analogues and nucleic acids require **specific** formulations
- **Cationic excipients** are key for nano-encapsulation and control of the release
- **Colloidal stability** can determine controlled **release**
- Nanocarriers **enable siRNA and mRNA** administration
  → Future vaccines and new therapeutic approaches



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