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Elimination study of intact lipid nanocapsules after intravenous rat administration

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1 **PLEASE DO NOT INCLUDE ANY IDENTIFYING INFORMATION IN THE MAIN BODY OF THE MANUSCRIPT**

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▪ **Abstract:**

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Aim: The present study investigated the renal elimination after intravenous administration of four different formulations of LNCs containing dyes adapted to Förster resonance energy transfer (FRET-LNCs). **Materials and**

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Methods: FRET-LNCs of 85nm or 50nm with a pegylated surface or not were injected and collected in blood or urine of rats at different time points. Quantitative analysis was performed to measure intact FRET-LNCs. **Results/**

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Conclusion: None intact LNCs were found in urine (0 particles/mL) for all formulations. Pegylated 50 nm LNCs were eliminated faster from blood whereas 85 nm pegylated LNCS were eliminated slower than not pegylated LNCs. Elimination of FRET-LNCs was mainly due to liver tissue interaction and not to renal elimination.

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▪ **Tweetable abstract:**

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“This study confirmed that the elimination of FRET LNC is probably mainly due to liver tissue interaction and not to renal elimination” #Nanomedicines#lipidnanocapsules #FRET#pharmacokinetic#Biodistribution

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▪ **Keywords:** Pharmacokinetics, Lipid nanocapsules; Renal elimination; FRET; drug delivery

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▪ **Main body of text:**

1. Introduction

Nanomedicine is one of the most promising invention of the 20st century in the field of health [1]. Formulations in the nanosize range called “nanomedicines” are nowadays widely developed as new drug delivery systems (DDS) in cancer therapy for the diagnosis, or for the targeted delivery of therapeutics. Nanoformulations permit to overcome poor solubility or low bioavailability of active pharmaceutical ingredients (API) [2,3]. The development of these new DDS is rapidly growing with an increasing trend of nanoparticles (NP) based therapies being approved by governmental authorities. However, *in vivo* experimentation in animal models, and the first phase of clinical trials [4–6], are rarely confirmed by large scale clinical research because of biological, technological and clinical limitations to achieve consistent clinical impact [7]. Indeed, after intravenous administration, the first interactions start with serum proteins circulating in blood which become attached onto the surface of the NPs to form a protein corona. This results in a transformation from a physico-chemical identity to a biological identity of NPs [8,9]. After this first step, interactions continue with organs and can be categorized such as NP-liver, NP-kidney or NP-tumor interactions in case of cancer [10–13]. These interactions, particularly with liver and kidney, are responsible for nanoparticle clearance from the body. Efficiency of NPs seems to be linked to their clearance rate from the body and most of the published data reported a rapid liver elimination after injection in the bloodstream [14,15]. As largely described by numerous publications, the liver represents one of the major barriers for drug delivery of NPs [14]. Indeed, it has been recently published that NPs were metabolized using specific hepatic pathways [16], because liver-NP interactions were a consequence of the opsonization phenomenon [8,9]. The protein corona that covers NPs allows a recognition by the mononuclear phagocyte system (MPS) that leads to cellular uptake [9,10]. However, if the majority of NP pharmacokinetic studies have demonstrated liver elimination of NPs [16], the kidneys are the second major organs responsible for their clearance by blood filtration. Compared to the liver elimination pathway, the renal excretion permits to quickly reduce the potential toxicity of some NPs such as inorganic NPs composed by heavy and noble metals or quantum dots [17–19] especially if their size is below 10 nm [20].

The pore size limit of the glomerular filtration membrane (GFM) in kidneys leads to a size threshold for NP renal clearance [13,15]. Despite this threshold, there is growing evidence that NPs larger than filtration cut-off GFM architecture are excreted in urine [21 **Recently, Naumenko et al, demonstrated renal elimination of iron oxide NP by transcytosis mechanism on kidney proximal convoluted tube. Other study from Choi et al., on PEGylated gold (Au-PEG) NPs described diffusion into the mesangium to reach urine instead of filtration within GFM. A recent review by Adhipandito et al. summarize mechanisms of NPS elimination [21-23].** These data seem to indicate that NPs can avoid the degradation and cross throughout the GFM. In this regard, one of our recent *in vivo* experimentation has found a faster clearance of one type of NPs, namely lipid nanoapsules (LNCs) of 50 nm diameter with PolyEthylene Glycol (PEG) coating (LNC-50-PEG) compared to other LNCs after IV injection on rats [24].

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1 In line with these data, the aim of this study was to investigate the elimination pathway of intact LNCs after IV
2 administration in rats using fluorescence resonance and energy transfer (FRET) which is a method of quantification
3 of intact LNCs already developed for previous PK studies [24–26]. In this context, the in vivo fate of four different
4 LNC formulations containing specific dyes for FRET has been studied. Those formulations will be called FRET-LNCs
5 along this paper. Firstly, a stability study in rat urine has been performed after adaptation of our blood extraction
6 and quantification method to achieve an efficient FRET signal [24]. Then, elimination of intact LNCs was studied to
7 better understand the pharmacokinetic properties of LNCs depending on their size and coating.

8

9 2. Materials and methods

10 2.1. Materials

11 Lipoid®S75-3 (phosphatidylcholine and phosphatidylethanolamine mixture) was purchased from Lipoid GmbH
12 (Steinhausen, Switzerland). Kolliphor®HS-15 (PEG 660 and polyethylene glycol 660hydroxystearate mixture) and
13 DSPE-mPEG(2000)(1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-
14 2000](ammonium salt)) were respectively purchased from BASF (Ludwigshafen, Germany) and Avanti Polar Lipids
15 (Alabaster, AL, USA). Captex® 8000 (glyceryl tricaprilate) was a gift from Abitec Corporation (Columbus, OH, USA).
16 Dil (1,10-dioctadecyl-3,3,30,30-tetramethyl-indocarbocyanine perchlorate) and DiD (1,1'-dioctadecyl-3,3,3',3'-
17 tetramethylindo-dicarbocyanine perchlorate) and Histopaque-1083 were purchased from Thermofisher (Villebon-
18 sur-Yvette, France). Phosphate-buffered saline (PBS) was purchased from PAA Laboratories (Toronto, ON, Canada)
19 and sodium chloride was purchased from Sigma-Aldrich (Saint-Quentin Fallavier, France). Ultrapure water was
20 obtained from a Milli-Q® Advantage A10 System (Merck Millipore, Darmstadt, Germany). Polycarbonate centrifuge
21 tube size 7 × 20 mm (reference 343775) was purchased from Beckman Coulter (Villepinte, France). Heparin sodium
22 5000 UI/mL was purchased from Panpharma (Luitré, France).

23 2.2. Methods

24 2.2.1. Preparation and characterization of LNCs co-loaded with Dil- and DiD-TPB (FRET-LNCs)

25 Firstly, fluorophore probes (Dil and DiD-tetraphenylborate (TPB)) were synthesized using one method previously
26 described [26,27]. Four formulations of FRET-LNCs, containing both fluorophores ,with different targer sizes: 50 nm
27 (LNC-50) and 85 nm (LNC-85) and surface modifications DSPE-mPEG-2000 (PEG) (LNC-50-PEG; LNC-85-PEG) were
28 prepared according to the original phase inversion process described by Heurtault *et al.*[29]. Briefly, premixed
29 Captex®8000 with Dil and DiD, and Lipoid®S75-3 were mixed and heated at 85°C. Kolliphor®HS-15, NaCl and water
30 were then added and homogenized under magnetic stirring. Three cycles of progressive heating and cooling
31 between 70 and 90°C were then carried out and followed by an irreversible shock induced by dilution with 2°C
32 purified water added to the mixture at 78°C. Slow magnetic stirring was then applied to the suspension of LNCs for
33 5 min at room temperature. Formulation details are on **Table 1**.

34 *Table 1 here*

35 Then, FRET-LNCs were characterized for size, zeta potential (ZP), and proximity ratio (PR). First, the mean size (nm)
36 and particle concentration (particle/mL) measurement were performed with nanoparticle tracking analysis (NTA)
37 using a NanoSight® NS300 (Malvern Instrument, Worcestershire, UK). After dilution in ultrapure water (5×10^5 to 1

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1 $\times 10^6$ factor), FRET-LNCs were injected into the sample chamber using a 1 mL syringe pump with a flow rate of 3-4
2 μL per second. The final measure was given after video sequences capture over 60 seconds (5 replicates) and
3 analyzed by NTA analytical software version 3.2. Then, ZP of the FRET-LNCs was determined by laser Doppler
4 electrophoresis using Zetasizer[®] Nano series DTS 1060 (Malvern Instruments SA, Worcestershire, the UK) diluted by
5 factor 1×10^2 . Finally, the PR of each formulation was determined using fluorescence analysis, it permitted to
6 demonstrate integrity of NPs. With the FluoroMax[®] 4 spectrophotometer (Horiba Jobin Yvon Inc., Piscataway, NJ,
7 USA), the fluorescence emission spectra of FRET-LNCs were recorded. The FRET-LNCs nanoformulations were diluted
8 by a factor 3×10^3 . The emission spectra were collected after excitation (548 nm) from 530 to 720 nm, with an
9 incrementation of 1 nm. The data were recorded for the maximum intensity of FRET donor and acceptor at 569 ± 5
10 nm and 675 ± 5 nm, respectively. To calculate the PR the following equation has been applied $PR = A/(A+D)$, where
11 A and D are the maximum fluorescence intensity of the aforementioned FRET acceptor and donor signals,
12 respectively.

13

14 **2.2.2. Quantification FRET-LNCs in urine**

15 ***Extraction from rat urine***

16 As previously published, the intact FRET-LNCs were firstly extracted from the biological media with the same sucrose
17 density gradient centrifugation technique [24]. For this in vivo experimentation, 100 μL of urine sample were
18 collected and immediately mixed with 100 μL of Histopaque[®]-1083 in the polycarbonate centrifuge tube and kept
19 in ice. Then, the tube was put in Optima MAX-UP Ultracentrifuge (Beckman Coulter, Villepinte, France) with the
20 fixed-angle rotor TLA-100 (Beckmann Coulter, Villepinte, France) during 2 hours with a relative centrifugal force of
21 4×10^5 G at 25 °C. A fixed volume of supernatant (75 μL) was collected and mixed with ultrapure water (225 μL). The
22 FRET signal of each sample was measured, and the PR was calculated. Finally, using the equation derived from the
23 calibration curve the particle concentration was calculated.

24 ***Particle Integrity Analysis***

25 For each kind of FRET-LNCs at each time point, the mean PR was calculated. In a previous study, the PR where the
26 FRET-LNCs displayed full integrity has been statistically determined using equivalent test [24]. If the mean PR at a
27 time point was ≥ 0.80 , the FRET-LNCs were considered intact [24]. In this case, they can be quantified as urine particle
28 concentration by the calibration curve.

29 ***Quantitative Calibration Curve***

30 For the standard solutions, seven dilutions of FRET-LNCs were prepared with the dilution factors ranging from 1×10^3
31 to 5×10^4 and then spiked into urine or PBS. The initial particle concentration of the formulation had been measured
32 in the characterization step by NTA. Maximum FRET acceptor emission intensities of the spiked standard were
33 measured (675 ± 5 nm) and plotted as a function of particle concentration. The linearity of the fitting curve was
34 estimated by the coefficient of determination (R^2) with acceptance criteria of $R^2 \geq 0.980$. Due to the interference
35 from background fluorescent noise at low concentration, the standard concentration with $PR < 0.80$ was excluded
36 from the calibration curve.

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1 All calibration curves were prepared in urine (or PBS for the in vitro experiment). It has been decided to use the same
2 biological matrix to exclude matrix effect in accordance with the ICH and FDA guidelines [30,31].

3 **Lower limit of quantification (LLOQ)**

4 The LLOQ of each FRET-LNCs formulation was defined as the mean of the lowest in vivo particle concentration in the
5 full-integrity phase.

6 **2.2.3. In vitro stability study of FRET-LNCs**

7 FRET-LNCs were diluted at a fixed final concentration of 28.5 Teraparticles/mL (Teraparticles or $T_p = 10^{12}$ particles)
8 in fresh rat urine which was obtained after putting naïve rat in metabolic cage (Techniplast S.p.A, Buguggiate, Italia).
9 The mixture was incubated at 37°C with gentle stirring. Samples of 100 μ L were collected at times 5, 30, 60, 90, 120,
10 180, 240, 360, 1440 min and added to 100 μ L of Histopaque®-1083 in centrifuge polycarbonate tubes (Beckman-
11 coulter, Brea, California, USA). Then, samples have been centrifuged for 2 hours at 400 000 g at 25°C. At the end, 75
12 μ L of the supernatant were immediately collected and mixed with 225 μ L of ultrapure water. Particle concentration
13 of intact FRET-LNCs was quantified as explained below (2.2.5). A control group in PBS was performed with the same
14 experimental conditions.

15 The concentrations were normalized with the first time point and reported as following calculation
16 $\%C_N = (C_t/C_5) \times 100\%$ where $\%C_N$ is the percentage normalized particle concentration, C_t is the particle concentration
17 at each time point, and C_5 is the initial particle concentration at the time 5 minutes. The integrity of extracted LNCs
18 has been monitored for each sample. Finally, the mean PR of the sample from each time point ($n = 3$) has been
19 statistically compared.

20 **2.2.4. Animal studies**

21 Sprague-Dawley male rats ($n = 16$) were purchased from Janvier Labs (Le Genest-Saint-Isle, France). The rats were
22 aged 9 ± 0.5 weeks, weighted 467 ± 57 g and received a standard laboratory diet and water *ad libitum*. Protocol on
23 animals was designed according to the EU Directive 2010/63/EU and was approved by the Committee on the Ethics
24 of Animal Experiment of the Pays de la Loire, France (APAFIS #2020092411444021). All rats were housed with
25 controlled room temperature (22°C) and dark-light cycle (12h). The rat urine was collected at times 60, 120, 240,
26 360, 480, 600 and 1440 min using metabolic cage (Techniplast S.p.A, Buguggiate, Italia). The urine samples were
27 measured and kept in ice prior to FRET analysis.

28 **2.2.5. IV administration of FRET-LNCs**

29 Four FRET-LNCs formulations were injected intravenously via dorsal penile vein with a fixed dose of 2×10^{14}
30 particles/100 g rat. Four samples of 150 μ L of blood were collected in tail vein at 5, 30, 120 and 1440 min after
31 administration. Thirty minutes after IV injection of FRET-LNCs and just after the 30 min blood time collection point,
32 rats have been put on metabolic cage for urine collection from 60 to 1440 min. Particle concentration of intact FRET-
33 LNCs was quantified in blood and urine sampling as explained previously.

34 **2.3. Statistical analyses**

35 All statistical analyses were performed using the software Prism GraphPad (version 9.3.1, GraphPad Software, San
36 Diego, CA, USA). The statistical significance was assessed for a p-value under 0.05.

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1 *In vitro* Particle Stability

2 The particle concentration as %CN from each time point was statistically compared to the initial %CN at 5 minutes
3 (time factor) and between blood vs PBS (media factor) by repeated measures using two-way ANOVA.

4 **3. Results and discussion**

5 **3.1 Characterization of LNCs formulations**

6 As shown on **Table 2**, the obtained formulations displayed a hydrodynamic diameter close to their target size. Zeta
7 potential of PEG formulations was found negative in contrast to non-modified LNCs. For all formulations, the PR was
8 close to 0.9 demonstrating the full integrity of FRET-LNCs [32].

9 Finally, the particle concentration ranged around 3×10^2 Tp/mL, except for LNC-50-PEG. Indeed, LNC-50-PEG had
10 higher particle concentration (10.1×10^2 Tp/mL), than all the other formulations. For the following *in vitro* stability
11 study and *in vivo* experiment, this difference has been considered.

12 *Table 2 here*

13 **3.2 In vitro stability study of LNCs in urine of rats**

14 To make sure that FRET-LNCs were stable in urine during *in vivo* elimination study in the bladder and in backer with
15 metabolic cage collection, it has been decided to perform an *in vitro* stability study for 24 hours. The final particle
16 concentration in urine has been adjusted to 28.5 Tp/mL supposing that all LNCs were eliminated by kidney filtration.
17 This particle concentration was equivalent to the peak time zero concentration of the *in vivo* study when it is
18 considered that a rat has a theoretical total blood volume of 7.0 mL/100 g rat [33].

19 Results are shown on Figure 1. All formulations were stable during 24 hours in urine at 25°C, no statistical difference
20 has been observed between normalized particle concentration and initial particle concentration. The normalized
21 particle concentration was not statistically different to particle concentration PBS media.

22 *Figure 1 here*

23 **3.3 Blood concentrations and renal elimination of LNCs**

24 **Once the preliminary *in vitro* study ensured that FRET-LNCs were stable in urine, an *in vivo* experiment of renal**
25 **elimination was performed after intravenous administration of a weight-adjusted dose (2×10^{14} particles/100 g rat).**
26 **As it was explained in our previous study the particle were considered on the full-integrity phase if measured PR was**
27 **higher than 0.80. This mean value was statically determined from multiple samples using equivalence test namely**
28 **Two one-sided t test (TOST). Thus, concentration of FRET-LNCs was quantified only if PR was higher than this**
29 **threshold value [24]. In the urine samples, it was not possible to measure the particle concentration of intact**
30 **nanoparticles, so it is possible to assume that if there were any particles, they were below the LLOQ.**

31 Thus, in contrast to blood elimination, particle concentrations in rat urine on sampling 30 to 1440 min after
32 intravenous administration were null for each tested formulation. Results of blood sampling are presented on **Figure**
33 **2. The particle concentration vs time profiles were close to what we found in a previous study [24].**

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1 *Figure 2 here*

2 **4. Discussion**

3 In contrast to our previous in vitro experiment in blood, the LNC-50 PEG remained stable in urine. Indeed, as it has
4 been recently described, all formulations were stable in blood during 10 hours of incubation excepted for LNC-50-
5 PEG, for which a surprising significant decrease of particle concentration has been observed after 3 hours [24]. These
6 results obtained in urine seem more logical because the PEGylation concept permit to theoretically enhance the
7 residence time even if the mechanism seems always totally unknown and is not obviously linked to stability of NP
8 [34]. Indeed, as we can confirmed with our previous work, the LNC-50 PEG were associated to a difference in the
9 protein corona formation, which could explain blood instability and increased clearance observed in vivo [23, 35].

10 For in vivo results in urine, it has not been possible to fully quantify intact FRET-LNCs because each calculated PR
11 were under the limit of 0.80. These results mean that FRET-LNCs were not intact and thus no quantifiable by our
12 calibration curves, which were performed with standard PR > 0.80. The faster blood elimination of intact LNC-PEG-
13 50 nm is thus not explained by renal excretion. These results showed that FRET-LNCs would certainly respect the
14 classical way of liver elimination. Although renal nanomedicine elimination is less studied than liver elimination,
15 threshold of renal filtration is thought to be around 10 nm, supposing that larger NPs cannot be cleared by the
16 glomerulus membrane [17,22]. Nevertheless, it has been demonstrated that NPs could reach urine with bypass of
17 glomerulus membrane and cross the proximal convoluted tubules by transcytosis mechanism [21,36]. This was
18 however not observed with our FRET-LNCs, confirming that neither renal filtration nor secretion occurred with LNCs.
19 As it has been reported by Adhipandito *et al.*, the molecular mechanisms of renal elimination remain unknown for
20 larger NPs. Also, as it has been reported by Du et al. that NPs with hydrodynamic diameter > 6 nm passed through
21 endothelium and stayed blocked and accumulated in the mesangium where they were degraded into small
22 fragments, resulting in a renal clearance [13]. Moreover, these large NPs can also be endocytosed by endothelial
23 cells of the peritubular capillaries, and accumulate in this compartment to finally be released in urine [13,17].
24 Regarding these data, even if LNCs where not eliminated under intact formulation in urine, we cannot exclude that
25 these formulations might be degraded in kidneys.

26 The stability of LNCs in blood is certainly involved to explain the faster blood elimination in the case of LNC-50-PEG
27 formulations, in contrast to others LNCs [24], but the liver elimination pathway should also be explored. As it has
28 been described in most previous work, after administration NPs usually accumulate in the liver tissue [10,14,37,38].
29 Even if the transport mechanism is not totally understood, the affinity for this organ seems directly linked to the
30 physico-chemical characteristics of the nanoparticles namely size, shape or surface functionalization [14,20,39]. The
31 liver endothelium has fenestration pore size between 50 to 100 nm which allows clearance of NPs within this size
32 range or lower [40]. In addition, almost all NPs are not directly metabolized by liver tissue but can be eliminated by
33 the reticuloendothelial system (RES) [41]. Indeed, NPs in the blood compartment immediately cause an opsonization
34 phenomenon by circulating proteins. These were recognized by specific cells of MPS, representing by the K upffer
35 cells in the liver to eliminate NPs and would explain, in part, the faster blood elimination of LNC-50-PEG [10,16].

36 Additionally, it has been described that the surface functionalization such as PEG addition can modify the blood
37 clearance [42,43]. The properties of NPs surface modify the corona protein formation and thus the elimination of
38 NPs [44,45]. It is clear that NPs bio-interactions and therefore their biodistribution are affected by their protein
39 corona [46]. In addition, the protein-corona formation may be different for LNC-50-PEG formulations than for others.
40 Pegylation and surface curvature are known to modify the protein adsorption on NPs surface [44,47]. As we

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1 previously observed in another study, it may be possible that LNC-50-PEG induce a specific corona protein which
2 increases opsonisation [47]. This mechanism could be responsible for uptake and sequestration of NPs by the MPS.

3 This uptake rate is strongly dependent on NPs properties and particularly in surface functionalization [14]. Moreover,
4 Wei et al. reported that PEGs or its impurities can induce an unstable formulation in vivo notably because of
5 enzymatic degradation [48]. In addition to the likely difference on the protein corona formation, this impurities-
6 induced degradation would also be responsible for the increased blood clearance of LNC-50-PEG compared to others
7 tested formulation

8 **Conclusion**

9 In summary, no FRET-LNCs formulations were cleared as native structures in urine. The faster blood elimination of
10 LNC 50 nm with PEG addition has not been explained by a renal excretion. Renal elimination mechanisms need to
11 be thoroughly investigated for all new nanomedicine formulations to better characterize their fate in vivo.
12 Fundamental understanding of the physiological challenges of nanomedicines, and notably on their elimination
13 pathways, will advance more effective delivery strategies. That will constitute a milestone to the future
14 pharmacokinetic studies of LNCs in the goal of future success in nanomedicine translation into the clinic.

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17 PROJECT).

18 **Declaration of competing interest**

19 The authors declare that they have no known competing financial interests or personal relationships that could
20 have appeared to influence the work reported in this paper

21
22 **Summary Points (Original Research articles, Systematic Reviews, White Papers & Company profiles):** 8–10 bullet
23 point sentences highlighting the key points of the article.
24

- 25 • In vivo rat pharmacokinetic study after intra venous administration of lipid nanocapsules was
26 performed
- 27 • Two types of formulations differing by size and surface were studied
- 28 • Renal elimination of intact lipid nanocapsules was sought using FRET technique
- 29 • FRET technique was used to quantify intact nanoparticles in blood and urine
- 30 • None intact nanoparticles were found in urine after Intravenous injection
- 31 • Elimination mechanisms of nanoparticles were hepatic and not renal

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Figure/Table legends

Figure 1. Stability of FRET-LNCs in rat urine over 24 hours. The diagram represents % normalized particle concentration (%C_N) in urine and PBS for each FRET-LNCs subtype. The experiment was conducted in triplicate and reported as the arithmetic mean and standard deviation (whisker).

Figure 2. Plasma particle concentration vs. time profile of 50-nm and 85-nm FRET-LNCs following IV bolus. Data is reported as the arithmetic mean and standard deviation (whisker).

Table 1. Composition of FRET-LNCs

Table 2. FRET-LNCs formulations characteristics

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- 27 ■ **Reference annotations:** authors should highlight 6–8 references that are of particular significance to the
28 subject under discussion as “* of interest” or “** of considerable interest”, and provide a brief (1–2 line)
29 synopsis.
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- 31 **Lebreton V, Kaeokhamloed N, Vasylaki A et al. Pharmacokinetics of intact lipid nanocapsules using
32 new quantitative FRET technique. *J. Control. Release* 351, 681–691 (2022).
33 This study was the first pharmacokinetic study which permit a building of population-pharmacokinetic model.
34 The surprising results obtained were the starting point of this specific study of elimination.
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37 epithelium model. *J. Control. Release* 253, 11–18 (2017).
38 This study was the cornerstone of FRET technique development that has made it possible to carry out these
39 pharmacokinetic studies.
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42 intravenous and oral administration on resistant tumor. *Nanomedicine (Lond).* 10 (4), 589-601. (2015)
43 The result of this study were very interesting because it highlighted plasmatic concentration of paclitaxel was
44 higher when it has loaded on nanoparticles although the nanoparticle were destroyed in intestinal mucus. These
45 results have encouraged interest in intact nanoparticles.
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48 This review summarized the behavior of nanoparticles after different routes of administration and gives some
49 interesting hypotheses to improve targeting and pharmacokinetic profiles of nanoparticles.
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1 *Alexis F, Pridgen E, Molnar LK, , et al. Factors affecting the clearance and biodistribution of polymeric
2 nanoparticles. Mol. Pharm. 5 (4), 505–15 (2008).
3 This review discusses the factors influencing the pharmacokinetic profiles and, more specifically, the elimination
4 of the polymeric nanoparticles we have developed and studied in our laboratory.