Toward Clinical Transfer of Tumor-Targeted Ultrasmall Inorganic Nanoparticles

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Ultrasmall nanoparticles (USNs) (nanoparticles with hydrodynamic diameter <10 nm) are being widely developed pre-clinically and started to emerge in clinical trials over the last decade. Most of these USNs display the same features including short retention time in the blood, rapid renal clearance, and relie on passive targeting strategy to reach the tumor. Through this review, the development of AGuIX USNs is focused on because of their clinical usages as passively targeted USN but also because of their possible biofunctionalizations with peptides and monoclonal antibodies which are validated in various pre-clinical tumor models. As a result, the authors reviewed all the current biofunctionalization strategies that can be employed and confirmed based on a meta-analysis of the literature that biofunctionalized USNs pharmacokinetic and biodistribution profiles are dictated by the USNs and not the active targeting moiety. Additionally, it is demonstrated that such active targeting strategy improves the tumor targeting efficiency of the AGuIX USN but also increases their tumor retention time in comparison to the passively targeted AGuIX USNs, which may lead to an opportunity to reduce the number of injections/expend the therapeutic benefit of the drug product.

1. Introduction

Originally developed to improve the pharmacokinetic (PK) profile and to reduce the off-target toxicity of small molecules such as chemotherapies, nanoparticles (NPs) have been optimized over the last decades to enhance their ability to reach specific targets in the body (i.e., tumor cells, tumor microenvironment, specific organ, or cell types) through various surface chemistry methods.[1–8] In parallel to these developments, new types of NPs called theranostics NPs displaying intrinsic imaging and therapeutic properties have been proposed.[9–14] Interestingly, independent of the type, size, or charge of the NPs, their functionalization enhanced the targeting of tumors-associated antigens (TAAs)[15,16] versus non-targeted NPs in preclinic mouse models.[6,17,18] Nevertheless, the functionalization complexity, the difficulty to scale-up laboratory production, and the increased costs limit the translation to the clinic of such actively targeted products.

Among NPs, ultrasmall nanoparticles (USNs) displaying size (hydrodynamic diameter) <10 nm have been widely developed pre-clinically but also successfully transferred to the clinic as passively targeted NPs (**Table 1**). Functionalization of those USNs with peptides, monoclonal antibodies (mAbs), or fragment of mAbs usually results in the increase of the overall size of the nanoconjugate beyond the 10 nm hydrodynamic size (e.g., mAbs—150 kDa, fragments of antibodies—10–100 kDa).[19–22] Hence, the increase in the size of these final functionalized USN

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Table 1. Recapitulative survey of the ultrasmall nanoparticles (USNs) and close to ultrasmall currently investigated in clinical trials.

Commercial name	Particle type	Size (diameter)	Approved application/indication	Status	Ref.
Therapy					
Inorganic					
AGuIX	Hybrid nanoparticle Composition: Polysiloxane-based gadolinium-chelated nanoparticles	5 nm	Therapy and diagnostic: MRI, radiotherapy (RT)	2017: NCT03308604 (Ph I): Gynecologic Cancer 2019: NCT02820454 (Ph I): Brain metastasis – completed (2019) 2021: NCT04789486 (Ph I/II): Non-small cell lung and pancreatic cancer NCT04881032 (Ph I/II): Glioblastoma NCT03818386 (Ph II): Brain metastasis NCT04899908 (Ph II): Brain cancer and metastasis, melanoma, lung, breast, colorectal, gastrointestinal cancer NCT04784221 (Ph II): Recurrent cancer	[14, 25, 35]
Cornell dots	Hybrid Si nanoparticle Composition: Silica (SiO_2) nanoparticles with a Cy5.5 fluorescent dye, a PEG coating, and a ^{124}I radiolabeled Targeting strategy: c(RGDyC) targeting peptide	<10 nm	Therapy and diagnostic: PET, CAT, and MRI scans, drug delivery, radionuclide therapy	2014: NCT02106598 (Ph I/II): Head and neck melanoma 2016: NCT01266096 (Ph I/II): Malignant brain and recurrent metastatic melanoma 2018: NCT03465618 (Ph I): Brain cancer 2019: NCT04167969 (Ph I): Prostate cancer	[36–39]
NanoTherm (magForce)	Composition: iron oxide nanoparticles coated with aminosoloxane	15 nm	Therapy: magnetic hyperthermia	Approved in Europe (2011): Brain tumor, Glioblastoma	[36, 40–42]
NU-0129	Composition: spherical nucleic acid (SNA) gold nanoparticle formulation composed of small interfering RNAs (siRNAs) Targeting strategy: Bcl-2-like protein 12 (BCL2L12)	13 nm	Therapy: Immunotherapy, Targeted molecular therapy, chemo, or radiation therapy	2017: NCT03020017 (Ph I): Glioblastoma multiform and gliosarcoma—completed (2020)	[36, 43, 44]
SPIONS/SMF	Composition: Superparamagnetic iron oxide (SPIONs) nanoparticles with spinning magnetic field (SMF)	12-21 nm	Therapy: Chemotherapy	2020: NCT04316091 (Ph I): Osteosarcoma	[45]
Diagnostic					
Inorganic					
FerroTrace	Composition: super-paramagnetic iron-oxide nanoparticle (SPION) polymer coated Used in combination with indocyanine green dye (ICG),	13 nm	Diagnostic: MRI, NIR surgical camera, and magnetometer	2021: NCT05038098 (Ph I): Gastric adenocarcinoma NCT05092750 (Ph II): Colorectal cancer	[46, 47]

complexes remains an important question, as the minimal size threshold for renal clearance is known to be <10 nm. However, some recent studies suggest the possibility of a renal clearance even with larger NP sizes.[23,24]

Through this review, we sought to specify the biological impact resulting of the functionalization of the USNs on the PK, the biodistribution (BD), and the tumor targeting efficiency. A total of 72 peer reviewed publications assessing full targeting NPs were identified and used in this study (Figure S1, Supporting Information). We selected AGuIX USNs as USN model (a sub-10 nm polysiloxane-based gadolinium-chelated USNs) for this review based on the large amount of pre-clinical studies and their successful translation to the clinic.[25,26] In addition, AGuIX USN is the only one providing both passive and active-targeted reports[22,27–30] enabling direct comparison on the impact of this strategy in term of the abovementioned parameters.

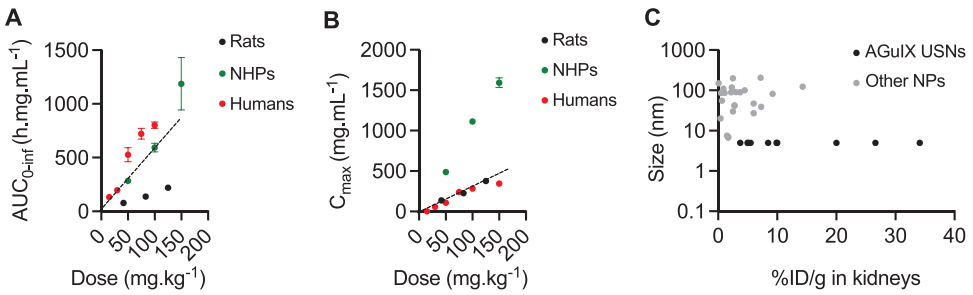

Figure 1. Pharmacokinetic profile and clearance of AGuIX USNs. A) Area under the curves ($AUC_{0\text{-inf}}$) and B) concentration max (C_{max}) for AGuIX USNs in different species (rats, non-human primates (NHPs) and humans). C) Pre-clinical renal clearance of AGuIX USNs in comparison to other NPs (inorganic and organic NPs) in function of the size of the NPs at 24 h. Data presented refer to Tables S1, S2, S4, and S6, Supporting Information.

1.1. Translation of AGuIX USNs

Non-conjugated USNs are mostly developed as inorganic NPs for imaging purposes due to their known short half-life and their ability to be used as contrast agents. Amongst the inorganic USNs transferred to the clinic (Table 1), AGuIX USNs, first described in 2011, are theranostic USNs made of a polysiloxane matrix grafted at their surface with gadolinium cyclic chelates.[31,32,48] The presence of the paramagnetic gadolinium ions (Gd^{3+}) enables T_1 MRI positive contrast properties in addition to radio-enhancing properties due to the high atomic number of the Gd ($Z = 64$) (Figure S2, Supporting Information).[14,33] Over exposure to external radiation therapy (RT), high atomic number species undergo inner-shell ionization inducing a localized physic-based radiation dose enhancement induced by the deposition of electron energy, which subsequently increases the amount of reactive oxygen species (ROS) resulting in an improvement of the radiation therapeutic efficacy.[49] Based on the various positive pre-clinical results,[34] AGuIX USNs were transferred to the clinic in five trials worldwide (Table 1). The successful clinical translation of AGuIX can be explained by different factors including i) the scale-up method to produce kilograms of clinical grade batches, ii) the controlled hydrodynamic diameter close to 5 nm ensuring renal elimination, and iii) their biodegradability in diluted medium that facilitate elimination.

The preliminary reported PK data confirmed the short half-life of AGuIX USNs in rats ($t_{1/2} = 0.31 \pm 0.034$ h)[50] (Table S1, Supporting Information), as well as in cynomolgus monkeys, and in humans ($t_{1/2} = 1.29 \pm 0.27$ h).[25,51] When converted in equivalence dose for a human of 60 kg (based on the FDA conversion charts—FDA report "Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, 2005"), we observed that most of the area under the curves ($AUC_{0\text{-inf}}$) and concentration max (C_{max}) are within the same range despite some slight differences. Such minor change in PK parameters could be due to the nature of the pre-clinical trials aiming to determine the highest safe concentration to be injected and the non-specificity of the translation charts from one species to another which have not been optimized for NPs (**Figure 1**A,B).

As expected, the BD of AGuIX USNs confirmed their propension to accumulate mostly in the kidneys 24 h after systemic injection with 12.84 ± 10.47% of injected dose per gram (% ID/g) (Figure 1C). The major advantage of this short circulation time and the fast renal clearance is the ability to inject higher concentrations of NPs, which is usually difficult to achieve with larger NPs mostly used for drug delivery (such as liposomes) which will accumulate in the spleen/livers.[52–55] This adapted PK parameter has permitted to reach high injected dose levels in regulatory studies; a no observable adverse effect dose level of 120 mg kg^{-1} (in human equivalent dose) has been reached in rodents and 450 mg kg^{-1} dose in cynomolgus monkeys. These results dictated the doses used in the Phase I escalation dose clinical trial NanoRad.[56]

Clinically, AGuIX USNs are injected either once[25] or multiple times[57,58] over the course of the treatment. The results of NanoRad Phase I clinical trial have demonstrated the feasibility and safety of administration of unique injection at doses ≤ 100 mg kg^{-1}.[56] The need to perform multiple reinjections confirms the pre-clinical studies were a decrease of the MRI contrast in the tumor were observed and were performed following NanoRad trial.[14] Such decrease of imaging signal has also been observed clinically despite a longer retention time in brain metastasis over one week (NCT03818386).[25] This loss of signal is proportional to the leak of the USNs from the tumor; for this reason, but also to increase the tumor uptake, mAb-targeted, and peptide-targeted AGuIX USNs were developed to improve the specificity of the USNs to bind specifically to a cell type within the tumor microenvironment (TME). Both approaches reached an improved pre-clinical therapeutic benefit in the context of fractionated radiation therapy.[22,27,29,30,59]

1.2. AGuIX USNs Demonstrate Optimal Tumor Targeting in Various Cancer Models

Despite the short circulation time of the AGuIX USNs in the body (vide supra), at 24 h post-injection, a moderate fraction (1.19 ± 0.87% ID g^{-1}) remains passively targeted to the tumor during their first passage (**Figure 2**A,B). Importantly, this amount is non-significantly different to what can be achieved with larger passively targeted organic NPs developed for drug delivery purposes (3.31 ± 2,82% ID g^{-1}) and inorganic NPs (3.16 ± 2.48% ID g^{-1}) (data extracted from Mittelheisser et al.,[18] p-value = 0.113 and 0.075, respectively, one-way ANOVA) (Figure 2A).

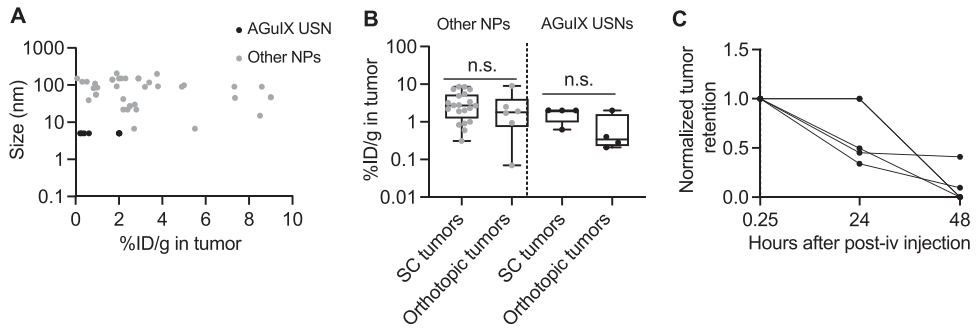

Figure 2. Passive tumor uptake after intravenous injection of AGuIX USNs in mice. A) Tumor uptake comparison based on the size of the NPs at 24 h. B) Comparison at 24 h of the tumor uptake based on the tumor implantation mode. SC—subcutaneous. C) Normalized tumor retention of AGuIX USNs normalized to 15 min after intravenous injection. Data presented refer to Tables S2, S4, and S6, Supporting Information.

Owing to their single passage in the body before renal clearance, the tumor neovascularization dictates the AGuIX USNs passive tumor uptake. This was validated when we compared their propension to target passively tumors, where AGuIX NPs tend to accumulate better in subcutaneous (SC) tumor mouse models than in orthotopic tumor mouse models (p-value = 0.139, Mann Whitney test) (Figure 2B). This can, in part, be attributed to the increase amount of tumor vasculature usually observed with SC tumor models but also owing to the larger overall tumor size. Importantly, in most of these pre-clinical studies, the retention of the AGuIX USNs decrease over time with a usual peak observed around 15 min post-iv injection and, in some models, NPs are still observed 3 days after administration (Figure 2C).[60] This retention is however more stable in orthotopic tumor models than in SC models (Tables S2–S7, Supporting Information).

1.3. Bioconjugation Strategies to Generate Active NPs for Better Tumor Targeting with Favorable PK/BD Features

The tumor accumulation of USNs is mainly mediated by the enhanced permeability and retention (EPR-) effect which is dependent on the heterogeneity of the TME but can vary from one tumor type to another, but also from one animal to the other, or from one tumor to the other on the small animals.[61,62] The surface modification of passively targeted-NPs with peptides and larger proteins such as mAbs have pave the way for novel and more precise targeting strategies.[63–67]

The most common covalent conjugation strategy employed to functionalize the NPs to targeting moieties rely on the use of the nucleophilic site of various amino acid residues. This includes, among other, the amine groups (arginine, histidine, lysine, tryptophan), thiol and thioether groups (cysteine, methionine), hydroxyl and phenol groups (serine, threonine, tyrosine), or the carboxyl groups (glutamic and aspartic acids) (**Figure 3**). While easier in term of synthesis, these approaches remain unspecific and can generate batch-to-batch variations. However, no differences in term of tumor targeting specificity were observed with more site-specific conjugation strategies (**Table 2**).[68,69]

However, several challenges remain to perform an efficient bio-functionalization: i) the first relies on the selection of the appropriate medium able to maintain the structure and the properties of the targeting unit. Among those tumor targeting moieties, peptides are more robust than others to various environments (acidic to basic, organic, or aqueous)[70–73] whereas proteins, such as mAbs, are more sensitive and require the conjugation to be performed in physiological environment to avoid their aggregation or denaturation.[73,74] Therefore, the stability and the robustness of the reactive chemical functions are major parameters that facilitates the conjugation reaction while preserving the targeting specificity of the tumor targeting moiety.[75] ii) The second relies on the appropriate synthesis protocol selection; the simpler and the faster the reaction is, the less the tumor targeting moiety will be exposed to a particular environment or will undergo purification cycles initiating its degradation and loss of specificity. For this reason, coupling reactions occurring with limited steps is preferred. For example, one of the most common direct reactions used for functionalization with fluorophores is the reaction of the primary amine with an isothiocyanate group (NCS) to form a thiourea bond (Table 2).[76] However, some reactions such as the C-termination reaction require the addition of a catalyst or crosslinking agent (removed or not) to activate the target function to improve the reactivity of a specific group enabling higher specificity and flexibility of solvents. For those reasons, appropriate compromises must be made to select the most suitable reaction for each coupling reaction.

Here, we recapitulated the pros and cons of each conjugation strategies based on six criteria (Table 2) including i) the function stability in a physiological medium, ii) the reaction specificity with the target function, iii) the number of reaction steps, iv) the formed bond stability in physiological solution, v) the reaction conversion rate, and vi) the reaction robustness/reversibility. Overall, each of these reactions has many advantages and are already widely employed pre-clinically. The main recurrent issue remains the hydrolysis of the reactive functions or the lack of high specificity of the functions.[53,77,78] Currently, biofunctionalization is commonly performed using cross-linking agents (crosslinkers) that are either homo- or hetero-bifunctional.

To overcome the problem of batch-to-batch reproducibility,[15,79,80] optimized conjugation strategies such as bio-orthogonal click-chemistry or enzymatic reactions have been developed to achieve higher conversion yields, specificities, and minimizing the sensitivity to physiological hydrolysis or oxidation.[81,82] However, these approaches also suffer from

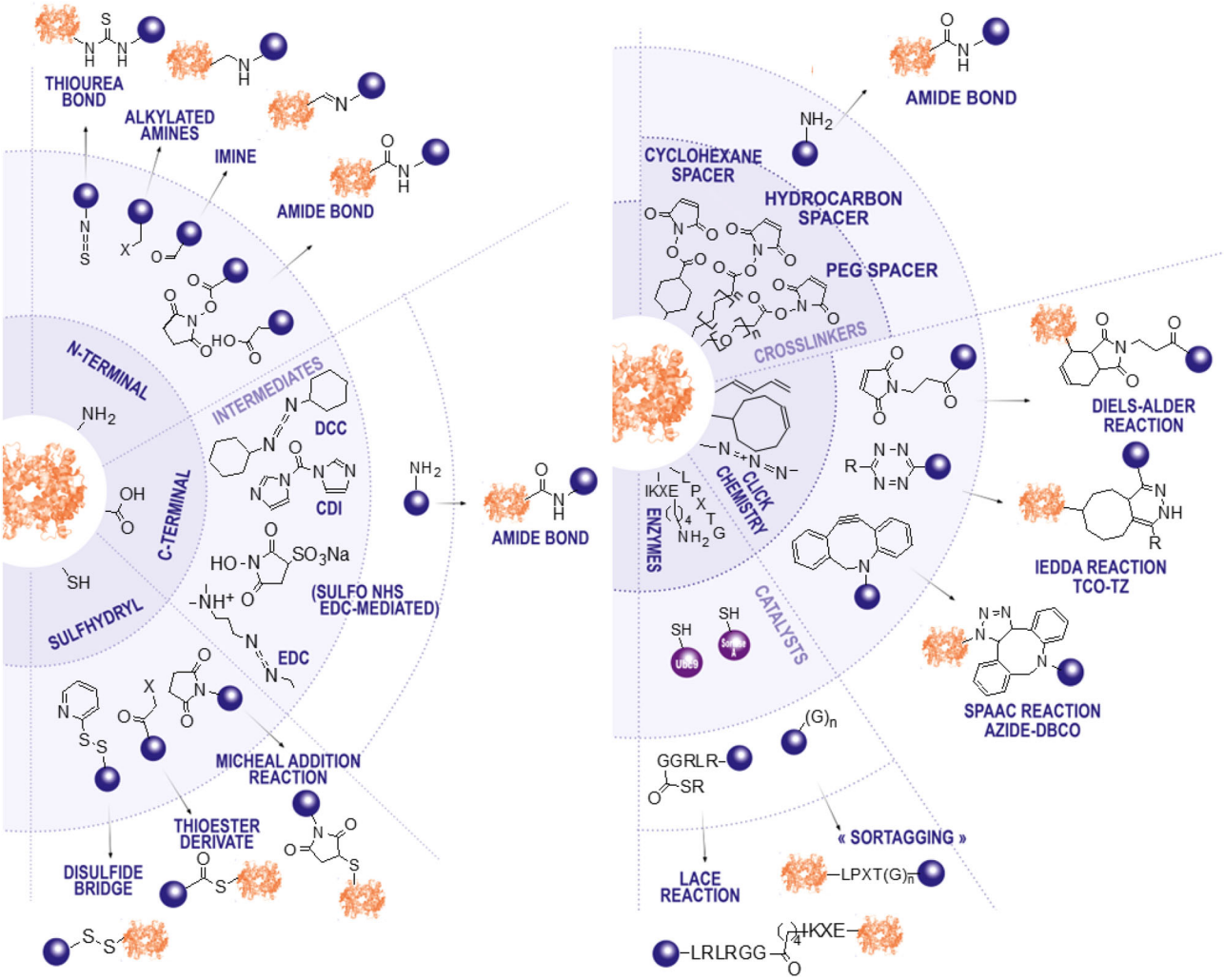

Figure 3. Bioconjugation strategies between the biomolecules and the nanoparticles without protein modification (left) and by direct reaction with protein modification (right). To facilitate the understanding the NHS group is arbitrarily represented at the end of the crosslinker.

several drawbacks including the uncontrolled reaction with the targeted amino acid and hence lead to potential loss of specificity.[83]

1.4. Biofunctionalization Strategies Applied to AGuIX USNs

The primary amine, issued from APTES, localized at the surface of AGuIX USNs has been exploited to develop various conjugates ranging from the grafting small peptides (a few kDa) to the grafting of larger proteins such as mAbs (≈150 kDa) (Table S1, Supporting Information).[22,27,29,30,110,111] The first generation of active-targeted AGuIX USNs was based on the peptide grafting via EDC/NHS reaction to conjugate an anti-NRP1 peptide.[112] To date, the biofunctionalization of AGuIX USNs has been mostly validated pre-clinically based on the functionalization of the amine of the mAbs by either click-chemistry approach or the use of heterobifunctional linkers.[22,29,112] These two approaches were validated in both SC and orthotopic tumor models. In both cases, the active targeting strategy demonstrated a similar tumor targeting efficiency than those achieved with other functionalized NP types (**Figure 4**A). Importantly, this method enabled the improvement of the tumor uptake in comparison to the passive targeting route by 1.43-fold (p-value = 0.058, paired t-test) (Figure 4B). Additionally, the direct targeting of tumor associated antigens increased the overall tumor retention time of the AGuIX USN in comparison to the passive targeting analogues (Figure 4C). The increase of the hydrodynamic size of the mAb-targeted AGuIX USNs in comparison to the non-conjugated AGuIX USNs demonstrated a slight increase of the half-life circulation time in the body (28.7 ± 2.3 min vs 18.2 ± 1.0 min, p-value = 0.0005, paired t-test) (Figure 4D). Importantly, with a half-life <30 min for both approaches, these results confirm that the AGuIX USNs does not recirculate in the body and are processed during their first passage, which is at the opposite of the common expectation when mAbs are employed for drug delivery. This result, in addition to the biodistribution data in the liver, spleen, and kidneys (p-value = 0.243, 0.231, and

Table 2. Summary of the main grafting strategies on N-terminal, C-terminal, and sulfhydryl function commonly present on the biomolecules with their major advantages and drawbacks. The three functions annotated with an asterisk (*) in the second column are the most common reactions used in bioconjugations.

Usual grafting function	Functionalized-NPs and intermediates	Function after reaction	Advantages	Limitations	Ref.
Primary amine ($-NH_2$)	Isothiocyanates/isocyanates	Urea or thiourea	• One step reaction • Stable bond	• Unstable reactive function in aqueous environment (hydrolysis of NHS ester) – associated with low yield • **Lack of specificity** (side reaction with to sulfhydryl or hydroxyl groups)	[84–87]
	Aldehydes/Ketones Intermediate (reducing agent): Sodium cyanoboro-hydride ($NaCNBH_3$)	Imine	• Stable reactive function in aqueous environment • High specificity • Stable bond	• Unstable intermediate (Imine/Schiff base)	[88–90]
	N-hydroxysuccinimide (NHS) ester/ Sulfo-NHS ester*	Amide	• One step reaction • Stable bond	• Unstable reactive function in aqueous environment (hydrolysis of NHS ester) - associated with low yield • Lack of specificity (side reaction with to sulfhydryl or hydroxyl groups)	[91, 92]
Carboxyl (-COOH)	Primary amine Intermediate: *N,N*-Dicyclohexyl carbodiimide (DCC)	Amide	• Intermediate stable in organic medium • High specificity of the intermediate • Stable bond	• Intermediate insoluble in aqueous medium • Unstable activated NPs (Side reaction of the intermediate with another carboxylic acid)	[93, 94]
	Primary amine Intermediate: *N,N′*-Carbonyl diimidazole (CDI)	Amide	• High specificity of the intermediate • Stable bond	• Intermediate unstable in aqueous environment (hydrolysis) • Lack of specificity (side reaction with hydroxyl group)	[94–96]
	Primary amine Intermediate: 1-ethyl-3-[3-(dimethylamino) propyl]carbodiimid (EDC)/NHS*	Amide	• Intermediate soluble in aqueous medium • High specificity of the intermediate • Stable bond	• Intermediate unstable in aqueous environment (hydrolysis) • Unstable activated NPs (side reaction with the aspartate or glutamate residues)	[22, 97–100]
Sulfhydryl (—SH)	Maleimide*	Thioether	• One step reaction • High specificity • Stable bond	• Unstable reactive function in aqueous environment (hydrolysis) – associated with low yield	[101–106]
	Disulfide bridge	Disulfide bridge	• Stable function in aqueous environment • One step reaction • High specificity	• Relatively unstable bond in presence of thiol	[107–109]

0.082, respectively, paired *t*-test) (Figure 4E–G) confirm that the pharmacokinetic properties of AGuIX USNs are more influential than the conjugation moiety in determining the biodistribution of the conjugate, as recently emphasized by Mittelheisser et al.[18] It opens the way to benefit from enhanced tumor uptake while associating rapid elimination. In addition, one more interesting feature that we and others have observed is the absence of protein corona effect for AGuIX.[113,114]

2. Conclusion

In conclusion, only a small number of USNs have been translated to the clinic, including the AGuIX USNs. Improving the tumor retention time due to a better specificity of the targeting of the tumor associated antigens remains a challenge that can be achieved with the functionalization of the USNs with mAbs or other proteins/peptides. As such, in the context of AGuIX, a single administration of active-targeted agents could lead to longer exposition time and hence longer enhancement of radiation therapies. However, the cost of such technical developments may hinder such process which is often limited by the batch-to-batch differences and necessitates large scale-up to be accepted by the regulations. Interestingly, when performed, the functionalization of USNs, highlighted here with the case study of AGuIX, confirms that the PK/BD properties of these conjugates are dictated by the NPs and not the mAbs. This result is in line with what has been demonstrated for larger NPs.[18] The next challenge for such development will be their validation through a phase II/III trial confirming or infirming the need of such functionalization to improve the delivery of NPs to the tumors.

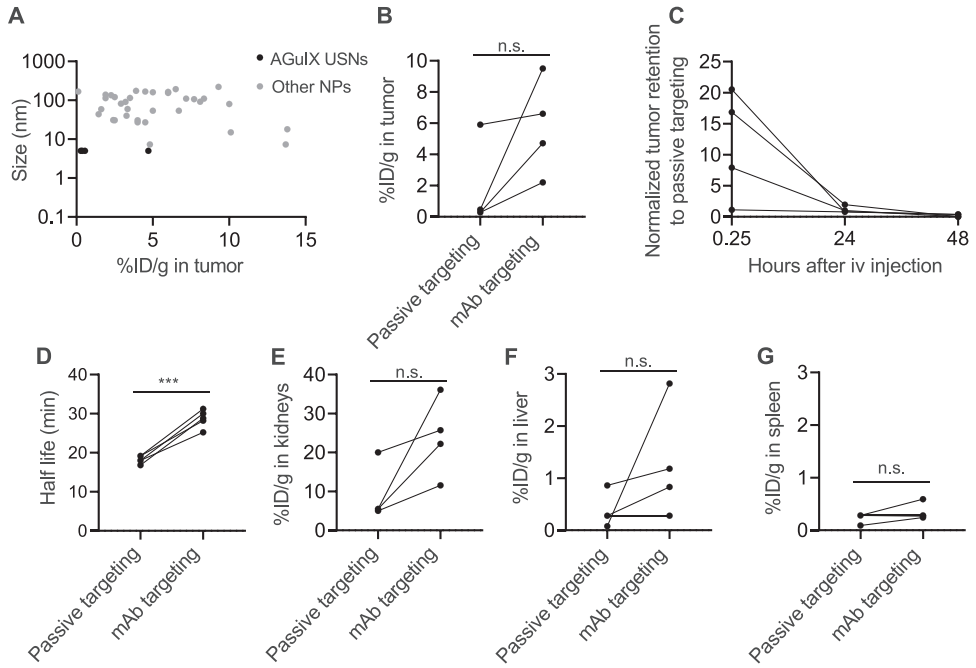

Figure 4. Antibody-targeted AGuIX USNs. A) Comparison at 24 h of the tumor targeting efficiency of monoclonal antibody (mAb)-targeted AGuIX USNs and other organic and inorganic functionalized NPs. The size represents the size of the NPs only. B) The tumor targeting efficiency of AGuIX USNs is improved when functionalized with the mAbs at 1 h in comparison to its counterpart passive targeting route in the same mouse model. C) The tumor retention time at 24 h of mAb-targeted AGuIX USNs is improved when compared to the passive targeting route. D) Half-life comparison between mAb-targeted AGuIX USNs and the passively targeted AGuIX through the same study. E) Kidneys, F) liver, and G) spleen uptake at 24 h compared between the passive and the mAb-targeted AGuIX USNs. Data refer to the Tables S2–S7, Supporting Information.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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L.C. and M.B. contributed equally to this work.

Conflict of Interest

L.C. is employee of NH TherAguix, that develops AGuIX nanoparticles. O.T., F.L. and A.D. are sharholders of NH TherAguix

Keywords

active targeting, bioconjugation, cancer, ultrasmall nanoparticles

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