BOOK OF ABSTRACTS

STANDING AT THE CROSSROADS : 40 YEARS OF MR CONTRAST AGENTS

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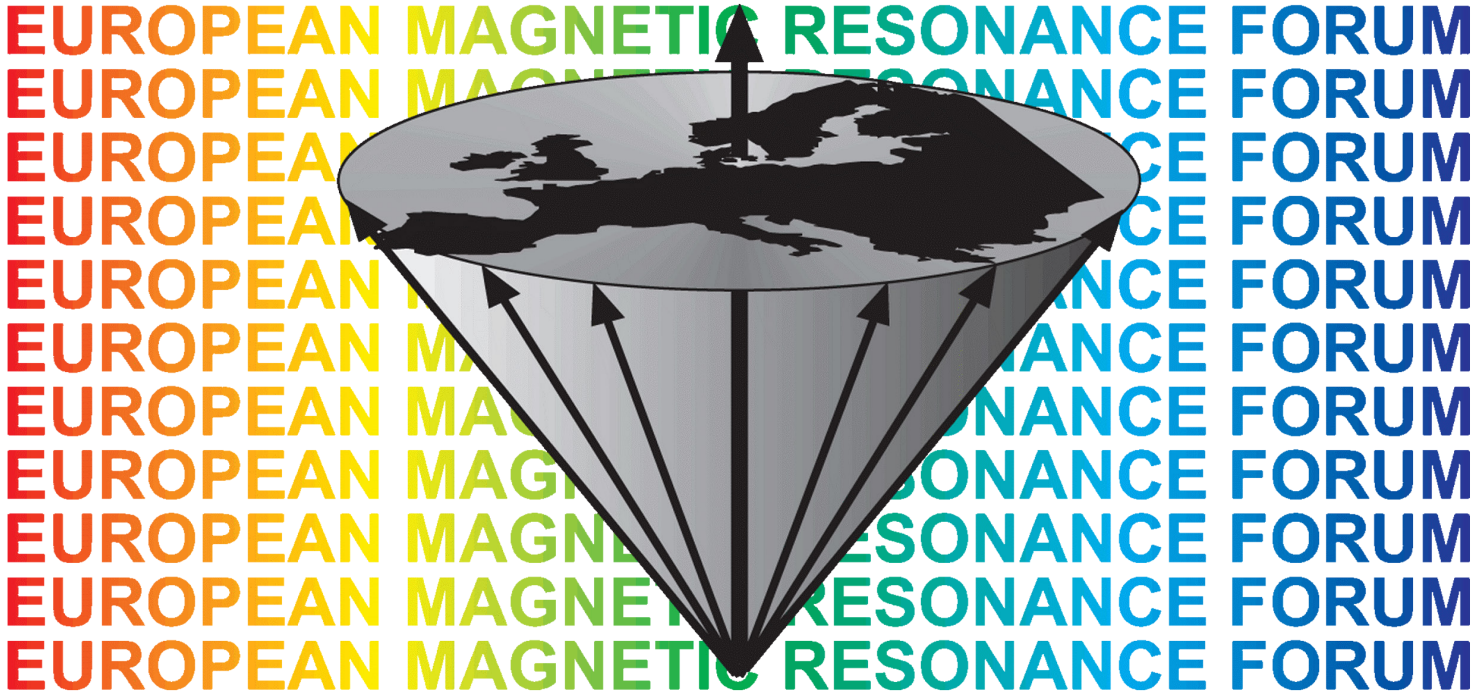

1988 – 2018 :
30 YEARS OF THE
EUROPEAN CONFERENCE
ON CONTRAST AGENT
SCIENCES

Contrast-Enhanced
Biomedical Imaging
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Abstracts

in alphabetical order by first author

Design and Testing of Frequency-Encoding MRI Reporters

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MRI suffers from an intrinsic insensitivity for which the in vivo detection of specific molecules has to be overcome by designing suitable amplification procedures. One possibility relies on the the use of CEST agents (CEST= Chemical Exchange Saturation Transfer). Upon applying a second rf field at the absorption frequency of an exchangeable protons pool, a net saturation effect is detected on the 1H-water signal. These are frequency encoding systems that allow multiple agents detection in the same anatomical region as well as they offer the possibility of designing innovative responsive probes that report on specific parameters (e.g. pH) of the microenvironment in which they distribute. To overcome sensitivity issues, the use of Liposomes (LipoCEST) and RBCs (ErythroCEST) appear to offer valuable solutions.

Another approach deals with the access to hyperpolarized (HP) molecules. The use of HP molecules has opened new horizons providing the possibility of investigating in vivo metabolic processes. It will be shown how a level of hyperpolarization sufficient for in vivo studies can be obtained for pyruvate and lactate through the application of a procedure based on the use of para-Hydrogen and magnetic field cycling.

The Proton Exchange as an Additional Route to Enhance the Relaxivity of Paramagnetic MRI Contrast Agents

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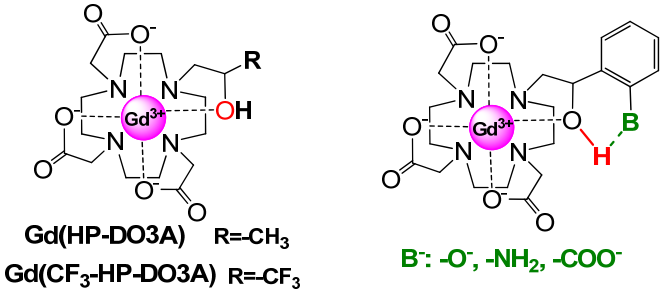
In principle Gd^{III} complexes enhance the nuclear relaxation rate of solvent water protons through the modulation of the dipolar interaction between the unpaired electrons of the metal ion and the nuclear spins of protons *via* three processes: i) the diffusion of water molecules in the proximity of the paramagnetic complex (*outer-sphere* term – r_1^{os}); ii) the exchange of water from the coordination site(s) to the "bulk" (*inner-sphere* term – r_1^{is}); iii) the proton exchange involving the mobile protons in the complex (r_1^{pr}). Among others, proton exchange reactions between functionalities coordinated to the metal center and the bulk water molecules may contribute to enhance the relaxivity. Thus, a thorough mechanistic interpretation of such processes is of outmost importance.

Actually, Gd(HP-DO3A) (ProHance®, Scheme 1) contains a coordinated –O**H** moiety that acts as a source of proton exchange enhanced relaxivity, however at pH values higher than the patho-physiological ones. The relaxivity of Gd(HP-DO3A) was studied as a function of pH and buffer composition in order to identify the main factors of the observed relaxation enhancement due to the exchange of the coordinated hydroxyl proton. It was established that the paramagnetic relaxation time, T_{1M}, of the coordinated hydroxyl proton is ca. 50% shorter than that of the protons in the coordinated water molecule. The control of the pK of the coordinated alcoholic –O**H** moiety in the ligand is fundamental to utilize the proton exchange enhanced relaxivity under physio-pathological conditions. A new derivative of Gd(HP-DO3A) was synthesized by replacing the $–CH_3$ group with a $–CF_3$ moiety (Scheme 1), in this complex the –O**H** group becomes more acidic. Consequently, the maximum contribution of the proton exchange to the relaxivity is shifted to a lower pH region with the trifluoromethyl analog ligand. The proton exchange of the hydroxyl proton is base-catalyzed and, upon comparing different buffer compositions, it was concluded that the proton exchange increases with the decrease of the difference between the protonation constants ($\log K_i^H$) of the coordinated -O**H** moiety and the base-component present in the buffer.

On the other hand, the exchange of the labile –O**H** proton might be also catalyzed by an appropriate basic group attached to the Gd(HP-DO3A) complex in the vicinity of the -O**H** moiety. With this aim we investigated the three Gd(HP-DO3A) derivatives possessing phenol, aniline and benzoic acid pendants (Scheme 1). It was found that the phenol, amine and carboxylate functionalities display an intramolecular H-bonding with the coordinated alcoholic -O**H** moiety that affects either the pK values of the involved functionalities and the rate of the proton exchange process. The establishment of the H-bonding interactions affects the relaxation enhancement properties widening the pH range of their applications.



Scheme 1. Structure of Gd(HP-DO3A) derivatives

Optimizing the Rotational Dynamics of Gd(III)-Based Contrast agents: a 30 Years Long Journey

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In a very recent review, P. Caravan and coworkers observe that: "…*the relaxivity for simple Gd^{III} chelates is limited by fast rotation at all accessible field strengths above 0.1 T. Slowing down the rotational motion of the complex is an effective way to increase relaxivity. This can be achieved by increasing the molecular weight of the contrast agent. This in turn can be achieved by making the complex larger or by the covalent or noncovalent binding of the contrast agent to a macromolecule...*" [*Chem. Rev*. **2019**, *119*, 957]

However, it is well known that relaxivity decreases with increasing at high fields. Similarly, the efficacy of the strategies developed to control molecular motion change with the applied magnetic field. In this contribution, we will examine how these strategies have changed over the past 30 years, following the evolution of imaging field strengths. The optimization of the rotational correlation time (τ_R) of Gd(III)-based contrast agents, at any value of field strength, can be analyzed in detail through a systematic study on the relaxometric properties of multimeric systems. This allows to: a) explore in detail the dependence of r_1 at high fields from the rotational dynamics in a well-defined range of values; b) understand the effect of the different degree of rotational flexibility of the chelate compared to the global tumbling motion of the multimers. We have carried out this study using as a building block a stable and inert bishydrated complex, GdAAZTA. We have prepared and investigated polynuclear complexes containing from 2 to 32 monomeric units that cover a range of molecular masses from 1 to 25 kDa. Taken together, the polynuclear complexes allow exploring τ_R values from about 0.1 to 2 ns. These experimental results, while confirming some theoretical predictions and simulations, offer useful indications to optimize the performance of metal-based MR agents at high fields.

Physicochemical Properties of a New Contrast Agent for Neurodegenerative Disease Diagnosis

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In the last decades, molecular imaging technologies began to attract increased interest for the targeting of diseases. In particular, neurodegenerative disease diagnosis is nowadays investigated through the design of tailor-made contrast agents able to cross over the blood-brain barrier (BBB). Conventional contrast agents are composed of three parts: contrast agent, spacer and vector. Over the last three decades, gadolinium complex of DOTA macrocycle has exhibited enhanced stability properties as compared to other first generation contrast agents. In addition, the versatility of the complexes confers to DOTA-based contrast agents the ability to be used in a large range of imaging modalities, including magnetic resonance (MR), positron emission tomography (PET), single photon emission computed tomography (SPECT) and fluorescence imaging.[1] Variations on the arms of the DOTA macrocycle appears as the way towards the generation of highly stable responsive and selective probes.[2] In this context, the specific targeting of diseases has been drastically enhanced by the incorporation of peptides as vectors. In the present study, the design of L-DOPA functionalized Gd-DOTA complex as a building block for further modifications is under consideration. The synthetic strategy involves the following steps: (i) the selective three-arms protection of cyclen by *tert*-butyl acetate moieties; (ii) the incorporation of a fourth arm exhibiting a primary amine moiety; (iii) amidation reaction on the fourth arm with Boc-L-DOPA; (iv) BOC deprotection; (v) Gd^{3+} complexation by the modified DOTA macrocycle. Both NMR and ESI-MS characterization techniques were used to follow the progress of the reactions.

The physicochemical properties of the complex are investigated by proton relaxometry at various magnetic fields, temperatures and media (pure water, zinc (II)-containing aqueous solutions and HSA-containing solutions)[2]. Here is the presentation of the preliminary results.

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Engineering of Magnetic-based Nanoplatforms for Theranostic

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The rational design of superparamagnetic iron oxide nanoparticles (SPIONs) as contrast agents (CAs) for MRI and heating agent by magnetic hyperthermia (MH) is of key importance to target the actual needs on the development of better performing systems for nanomedecine. In the case of T_2-CAs for MRI, magnetic iron oxide based NPs must be designed to have the highest relaxivity r2 value along with a high r2/r1 ratio. Intrinsic parameters such as saturation magnetisation, NPs size, chemical composition and shape or the aggregation state have a direct effect on relaxivity. However, besides the design of the NP core, the organic coating is also a key component as it allows to control water diffusion and residence time close to the magnetic core. Similarly for the design of SPIONs as heating mediators in MH, intrinsic parameters such as nanoparticle size, nanoparticle anisotropy or collective magnetic behaviour were shown to directly affect heat loss.

In that challenging context, we propose a concept combining a dendritic coating with magnetic IONPs designed for MRI and magnetic hyperthermia. Grafting of dendritic molecules on the surface of 10 nm spherical SPIONs using a phosphonate group as coupling agent has led to a new generation of contrast agents for *in vivo* MRI. The appeal of such strategy is due to the unique properties of the dendritic structures which can be chemically tuned to reach ideal biodistribution or efficient targeting efficacies. They display a good colloidal stability in isoosmolar media and MRI contrast enhancement properties higher than those of commercial products. No evident adverse effect was observed in rat after intraveneous injection, even at high concentrations and a long time after injection. Their biodistribution study showed a fast hepatobiliary with a low urinary eliminations without RES uptake. Besides, we showed that, after i.v. injection in melanoma mice model, NPs coupled with a melanin targeting ligand were specifically uptaken by melanoma tumor cells with very favorable biodistribution and biokinetic properties. A start-up “Superbranche” is under construction for 2019.

Therapeutic functions were added by designing the magnetic core and tuning its shape and compositions. The same investigations and in particular their *in vivo* biodistribution as well as their protein corona study and *in vivo* magnetic hyperthermia experiments, demonstrated again a clear dendron effect and that these dendronized NPs are promising theranostic agents.

Parametric Study of Flow Processes for the Synthesis of Iron Oxide Nanoparticles in Polyol Media

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In the last decades, the synthesis of inorganic nanoparticles has been intensively studied because of their many technological possibilities. Indeed, the reduction of the size to the nanometer scale has led to the discovery of novel and extraordinary properties which found many applications in various technological fields. Among existing inorganic nanosystems, magnetic iron oxide nanoparticles (i.e., magnetite and maghemite) have emerged as a very promising tool, especially in the biomedical field. Because of their great potential, numerous synthetic methods were developed to produce iron oxide nanoparticles, with good control over shape, composition, size and size distribution.

Given to most recent studies, thermal decomposition of organometallic precursors appears as a reference for the synthesis of crystalline magnetic nanoparticles with a good control over the size, the shape and the composition. However, even if the technique arouse a great interest from the scientific community, it is important to note that most of the studies imply the production of hundred milligram-scale. The transposition to industrial production requires the development of scale-up challenges ensuring reproducibility and cost-effectiveness, as well as the use of innocuous reagents. Since then, we propose a scale-up approach based on the continuous flow process technology. The influence of the different synthesis parameters over the particle's physico-chemical properties is reported.

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Synthesis of a Manganese Magnetic Resonance Imaging Contrast Agent Based on Pyclen Structure

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In medicine, medical imaging has a leading place in the diagnosis setting. This is why some researches are continually carried out to improve the available techniques. One of the most used techniques to obtain anatomical informations is magnetic resonance imaging (MRI). The commercially available contrast agents are based on gadolinium complexes. Recently, it has been shown that gadolinium can lead, mainly for patients with renal disfunctions, to a pathology named NSF (nephrogenic systemic fibrosis). Thus it is interesting to develop an efficacy contrast agent based on another paramagnetic ion such as manganese. The macrocycle used in this work is a pyclen derivative which is functionalized to respect protection and deprotection steps. Three different derivatives which differ by the arm present on the pyridine will be synthesized in order to evaluate their efficacy once complexed with manganese. (Figure 1) The products are for the moment under synthesis and relaxometric tests will be performed to evaluate the relaxivity of the different derivatives.

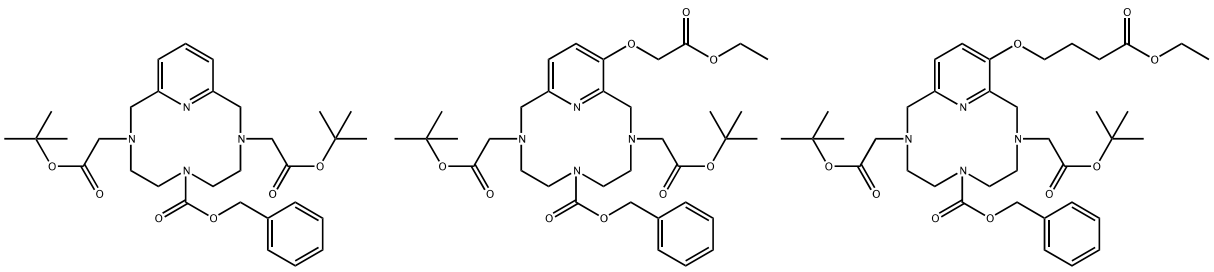

Figure 1. 3 pyclen derivatives used in this work

Development of a paraCEST and Fluorine MRI Contrast Agent

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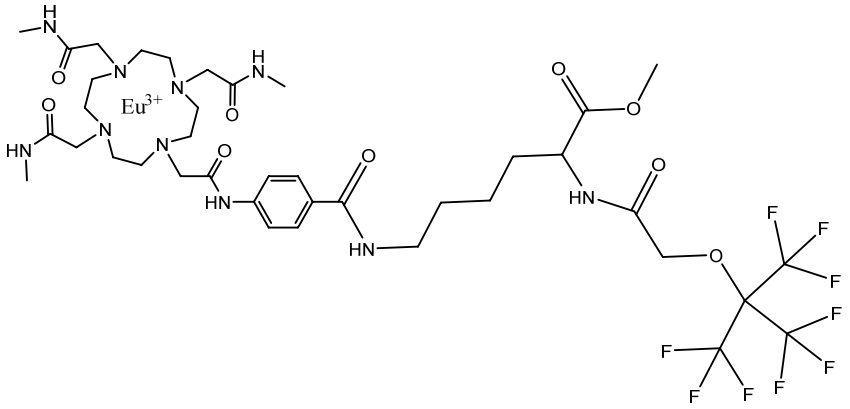
Magnetic Resonance Imaging is a useful imaging technique that allows the detection of different pathologies. To improve the sensitivity of this technique, a lot of researches are performed on the development of contrast agents.

A new kind of contrast agents was developed more recently: the CEST agents. They are based on the presence of exchangeable protons, of which the saturation can be transferred to water and detected as a decrease of the water signal. Among those agents, the paraCEST ones are very interesting because a paramagnetic ion will allow to highly shift the exchangeable protons from water, facilitating their use.
Another kind of contrast agent shows a great interest: the fluorine MRI contrast agents, which can be visualized precisely by ^{19}F MRI. Their drawback is that fluorine has long relaxation times, increasing thus the analyses times. To avoid this problem, it has already been shown that the presence of a paramagnetic ion reduces those relaxation times.

For those reasons, this work has been dedicated to the synthesis of the following bimodal agent, active in paraCEST and in ^{19}F MRI:



The europium complex has been synthesized and its CEST effect has been studied using Z-Spectra. Different saturation power pulses have been used and those tests were performed at 25°C and 37°C, to evidence the importance of the exchange rate constant, which should not be too high. The CEST effect was still present at 37°C despite the higher water exchange rate.

In the next months, the fluorinated part will be grafted on the europium complex and the fluorine relaxation times of the agent before and after complexation with europium will be determined and compared.

Functionalized Silica Nanoplatform Containing Gd(III) Complexes as Contrast Agent for ^{1}H MRI

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Introduction. The inherent low sensitivity of magnetic resonance imaging (MRI) can be overcome by the use of paramagnetic contrast agents (CAs), typically gadolinium complexes. It is known that the effect of a Gd chelate on the longitudinal relaxation rate of water molecules depends on both the inner-sphere and outer-sphere mechanisms. The goal of this project is to develop a nanoplatform dedicated to ^{1}H MRI as potential T_1 CAs. In order to improve the relaxation process, we decided to perform a non-covalent confinement of small gadolinium Gd^{III} based CAs (GdBCAs) in a semi-permeable nanosystem. Thanks to their exceptional properties (i.e. biocompatibility, chemical stability, low toxicity) mesoporous silica nanoparticles (SiO_2 NPs) have been chosen as a matrix.

Experimental section: methodology. The general procedure to achieve to the synthesis of the desired nanosystem can be divided in two steps. The first one consists in the inorganic synthesis of spherical silica nanoparticles by the reverse micro-emulsion procedure[2,3] in the presence of a hydrosoluble paramagnetic CAs*:* the commercially available ProHance®. Then, the particle surface is modified by silanol-PEG chains to ensure aqueous stability and to enable further derivatizations. The systems were characterized by Dynamic Light Scattering (DLS); Nuclear Magnetic Resonance (NMR) spectroscopy; relaxometry measurements; UV-Vis and IR spectroscopies; Transmission electron microscopy (TEM).

Results. Narrow size distribution silica particles were obtained (D_H : 80 nm). Relaxometric measurements of the as-synthetized nanoplatform have proven its efficiency to decrease $T_{1,2}$ of endogenous water protons molecules.

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MRI and CEST: From ParaCEST to DiaCEST

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In this presentation, the development of CEST agents for MRI will be reviewed, with examples from the literature and one from our own work. We will start with examples of the early use of magnetization transfer experiments in high resolution NMR, such as saturation and inversion transfer and STD. The basic principles and the mechanisms of action of these agents will be discussed, both in the spectroscopic and MRI modes, including the main factors affecting the efficiency of CEST agents. The operational classification of these agents, from various endogenous and exogenous diaCEST examples to paraCEST systems, with be illustrated with relevant applications. Sensitivity optimization with supra-, nano- lipo- and hyperCEST systems, as well as multifrequency detection in solution, *in cellulo* and *in vivo* are important milestones. Responsive agents, with selected examples from redox, pH, metal ions and enzyme activity, will be illustrated, mainly with *in vivo* examples, including the strategies to make the CEST information quantitative.

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Chemical Insights into the Issues of Gd-retention in Brain and other Tissues upon the Administration of Gd-based MRI Contrast Agents

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Gadolinium based contrast agents (GBCAs) are commonly used at clinical settings as they add relevant physiological information to the superb anatomical resolution of the MR images. Recently it has been found that an increased signal intensity (SI) in non-contrasted T1-weighted MR images is observed in brain structures (Dentate Nucleus and Globus Pallidus) of patients that received several GBCA administrations. [1] Following this seminal work, it was shown that the observed hyperintensity can be associated to the occurrence of tiny amounts of Gd retained in brain (and other tissues) also in the presence of normal renal function. Whereas these findings were not accompanied by any clinical consequence or by histopathological change, they opened the way to a number of investigations aimed at understanding how and why Gd is retained in the brain (and other) structures.
Herein we want to depict how the fulfilment of this task represents a complex bio-inorganic chemistry problem. In particular, issues will be presented concerning the in vivo stability of GBCAs (combination of equilibrium, kinetic and pharmacokinetic properties), the way how Gd-containing species cross biological barriers, the chemical form (intact GBCA, soluble and insoluble Gd-containing species) of the retained Gd(III)-containing species and the relationship between Gd-speciation and MRI hyper-intensity.[2]

These studies bring new knowledge that goes beyond the field of the potential toxicity of the used Gd-complexes as they allow to get more insight into the complex domain of the thermodynamics and kinetics involving metal containing species in living systems.

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Tracers for Imaging, some Like them Hot

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Quite early in the course of MR imaging development, scientists realised that the physical and chemical properties on which MR imaging was grounded allowed information "enhancement" thanks to artificial addition of well-chosen molecules within the tissue of interest. By naming these molecules "contrast agents" — a denomination that holds 40 years later —, the MR community implicitly positioned MR imaging as a modality used "to see how things are" as opposed to medical imaging used "to see what things do". In order to orient MR towards the opposite arm of medical imaging, the agents that modify MR signals to provide new dimensions to the data should have been termed "tracers". In other words, instead of considering that injected molecules better *contrast* tissues in order to help in their differentiation, the stress could have been put on the fact that those molecules actually *trace* functional or biochemical properties within the organism. Interestingly, most of the current research in the field of MR "contrast agents" actually aims at tracing changes in biochemical or functional properties and not to improve morphological precision.

The "how it looks" versus "how it works" dichotomy stem from the origins of two branches of medical imaging, radiography and nuclear medicine. The affiliation of MR imaging to the radiography camp has major consequences on the way contrast agents are developed, considered and applied. These molecules do not follow the mode of invention, selection and validation of tracers used in nuclear medicine — the so-called radiotracers. In fact, radiotracers are derivatives of molecules that emerge from basic biological or pharmacological research. They have been selected following systematised methodological steps applied in these basic sciences, with a specific attention paid to the quantification of the processes. When a new radiotracer is proposed, primary questions arise. Does it exactly reflect the biochemical process targeted? Does it faithfully translate into medical images what can be probed in vitro with equivalent molecules? Does it quantify the process in the same way and the same units as in vitro analyses? Since most of the cellular processes that deserve imaging analyses are specific and precise, the biochemical constants that characterise them are such that minute amounts of a molecule may exert a substantial and definite effect. This again ties tracer development and pharmacological research. Also, for the same biochemical reasons, minute amounts of a detectable tracer may evidence small quantities of a cellular target. So, we need probes to trace processes that rely on small amounts of targeted molecules and high affinity rates. In addition, in order to keep the system unchanged after the introduction of the tracer, it is crucial to maintain its mass amount at the lowest levels. Even when metabolic processes that involve large amounts of substrates are probed (e.g. energetic pathways), to offer high sensitivity for the detection of a target — sometimes present in a limited number of cells —, it is essential that infinitesimal quantities of the tracer produce an accessible signal. Therefore, considering the exquisite sensitivity of radioactivity detection, isotopic tracers are the ultimate tools to produce medical images that reflect specific metabolic processes of interest, and this is now the case for more than 75 years.

So, if *some like them hot,* it is because the tracers that really matter are targeting precise and meaningful processes identified along the successful story of modern biological research. Good tracers do not just *contrast* tissues with various degrees of a physical characteristic; they reliably pinpoint if a precise biochemical process occurs. They also quantitatively inform us on the evolution of this process, either naturally or after a therapeutic intervention.

NMR Relaxometry for the Study of Paramagnetic Ions Adsorption on Different Substrates

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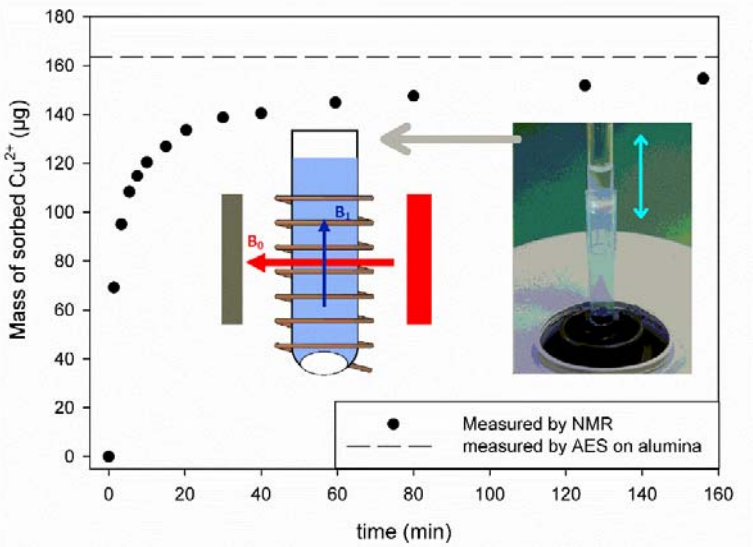
Water pollution by heavy metal is a major environmental problem. Adsorption and ion-exchange are among the most used heavy metal removal techniques. The development and evaluation of new adsorbents and resins is thus an important topic. Some heavy metal ions - like Cu^{2+}, Mn^{2+}, Cr^{3+}, Ni^{2+}… - are paramagnetic and known to affect the Nuclear Magnetic Resonance (NMR) relaxation times T_1 and T_2 of water protons in aqueous solutions. These relaxation times can be used to evaluate the concentration of paramagnetic ion in water. For the adsorption of Cu^{2+} on activated alumina and the capture of Cr^{3+} by an ion-exchange resin, we show - after a comparison with conventional methods - that NMR T_2 relaxometry can be used to perform kinetics study and obtain an adsorption isotherm. The T_2 relaxometric experiment is performed at 0.47 T directly in an NMR tube with 350 µl of solution and 45 mg of adsorbent. For the kinetics study, a single tube is used since the measurement is nondestructive. The NMR experiments allow to determine, for Cu^{2+} adsorption on alumina, a maximum of capacity q_{max} = 4.32 mg(Cu)/g(Al2O3) and an equilibrium adsorption constant K = 0.61 mM^{-1}. For the removal of Cr^{3+} by the ion exchange resin, the maximum capacity is q_{max} = 10.1 mg(Cr)/g(resin) and the equilibrium adsorption constant K = 0.611 mM^{-1}.

Longitudinal relaxation of the loaded substrates can also be used to evaluate the amount of adsorbed paramagnetic ion, directly on the wet sorbent. Even if it is limited to paramagnetic heavy metal ions and necessitates rather high metal concentration, NMR relaxometry could become an interesting additional tool for the study of heavy metal adsorption. Low-resolution NMR could also be used to monitor the removal of paramagnetic ion directly on the column during a column experiment.



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Metallic Bismuth Nanoparticles Synthesis from Batch to Flow Continuous Chemistry Coupled to Sonication

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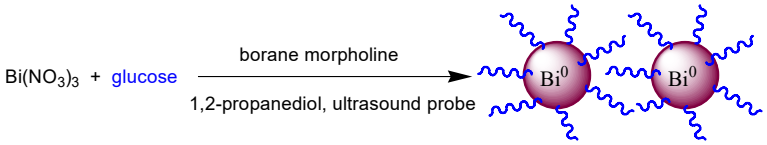
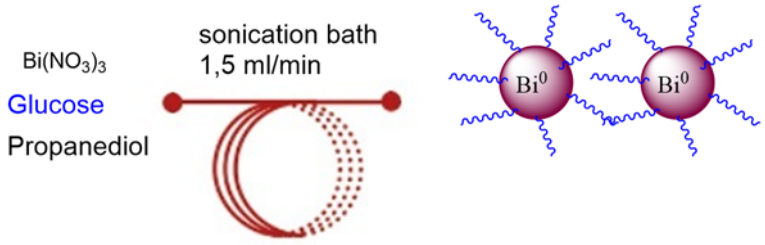
Bismuth nanoparticles (Bi NPs) were poorly described in literature. Though these nanoparticles have probably significant potential in the medical field as a therapeutic and/or diagnostic agent thanks to a high X-ray absorption especially due to their high atomic number (Z= 83). Further bismuth is an eco-friendly element with many advantages: it is abundant, in expensive, and biocompatible. [1]

Different known methods to synthesize Bi NPs have been recently reported in a book chapter "Inorganic frameworks as smart nanocariers for drug delivery". The potential of these syntheses has been highlighted from the point of green chemistry view. [2,3]
Among described syntheses, we were interested to metallic Bi NPs formation from bismuth nitrate reduction with borane morpholine at 80°C by classical heating. The D-glucose produced from renewable feedstock is used as a coating agent and the 1, 2-propanediol as a nontoxic solvent. [4] This synthesis which required a short reaction time (60 seconds) is difficult to control and to reproduce on a large scale.
In this work, we tried to optimize ultrasound assisted synthesis by modifying thermal activation mode, D-glucose amounts, reaction time and purification step. In batch by sonication, a complete bismuth salt reduction is optimized by modifying the pulse mode.



In a second time, these previous batch conditions are transferred to continuous flow coupled to sonication. To our knowledge, this is the first metallic Bi NPs synthesis in a continuous flow process couplet to sonication. All the reagents are introduced *via* a HPLC pump and reduction reaction is actived under sonication.



Several comparisons are done between thermal and ultrasound activation in batch and *via* the flow continuous process. Nanoparticles productivity is discussed and their characterizations performed by infrared spectrum (IR), Transmission Electron Microscopy (TEM), X-Ray Diffraction (XRD) and then are discussed.

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Avoiding Gadolinium Quenching through Photoporation for Enhanced Magnetic Resonance Imaging of Cells

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Cell-based therapies for a variety of applications such as regenerative medicine and cancer immunotherapy are receiving a lot of attention in recent years. Appropriate imaging techniques are required for the *in vivo* imaging of cells so as to better understand the treatment outcome and to optimize treatment conditions. Next to the use of PET, SPECT and CT, magnetic resonance imaging (MRI) is of interest as it does not rely on harmful ionizing radiation, while providing both a higher spatial resolution and excellent soft-tissue contrast. However, one of the disadvantages of MRI is its low sensitivity which requires that cells are labelled with suitable contrast agents. Gadolinium chelates are of particular interest as it is the only MRI contrast agents that has already been clinically approved. However, typically long incubation times are needed to reach detectable intracellular concentrations. Moreover, as these agents are internalized by endocytic processes, the signal becomes quenched at increasing concentrations of gadolinium.

Here, we evaluated the use of a new cell transfection method, known as “photoporation”, to circumvent limited endocytic uptake and endosomal quenching by directly delivering the gadolinium into the cytosol. Photoporation makes use of sensitizing nanoparticles, such as gold nanoparticles, to create transient pores up to 30 nm into the cellular membrane by the induction of vapour nanobubbles (VNBs) after irradiation with a pulsed (nano- or picosecond) laser. The Gadolinium contrast agent that is dissolved in the cell medium can then diffuse into the cell’s cytoplasm, resulting in a high amount of label inside the cells. Here we evaluated this approach on HeLa cells as a model cell line in which we delivered Calcein as an easy to quantify fluorescent cell impermeable dye with a similar molecular weight as Gadolinium chelates. We optimized the photoporation conditions such as the fluence and gold nanoparticle concentration and reached an efficiency up to 96% while retaining a cell viability of more than 80%. Next we photoporated Gadolinium chelates at different concentrations and performed MRI measurements, showing that quenching could effectively be avoided. Next experiments will focus on more relevant cell types, such as dendritic cells or T lymphocytes, and performing in vivo cell tracking.

Acknowledgements. Funding by the Special Research Fund (BOF) of Ghent University is acknowledged. We acknowledge also the financial support of FWO (3G0B281N, 3G006714) and VLAIO (IWT SBO 140061).

Innovative and Strategic Materials against Cancer: Preclinical Researches on IER5/Cdc25B Targeted Multi-type Wide Spectral Novel Low-molecular-weight Phospha Sugar Antitumor Agents and Tumor Accumulative Higher Sensitive Sugar Dendritic Gd-DTPA Complex MRI Contrast Agents to Innovate in Cancer Therapy

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Innovative and strategic materials against tumor to decrease sharply the number of people died of cancer are desired eagerly. To innovate in medical technologies of diagnosis and cure for various kinds of tumors by novel medicinal materials, i.e., IER5/Cdc25B targeted novel phospha sugar molecular targeted antitumor agents (e.g., TBMPP), were prepared and evaluated in vitro and in vivo methods, and then these novel medicinal materials were revealed preclinically to have excellent characters and potentials for cancer treatments.

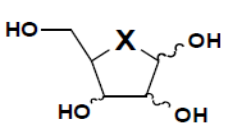


Figure 1. Pseudo sugars (X=CH_2, NH, S, P(O)R, etc.)

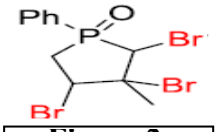


Figure 2. Deoxy-tribromo-phospha sugar

Phospha sugar derivatives are one kind of *pseudo* sugar derivatives (**Figures 1** and **2**). Deoxytribromophospha sugar derivatives such as TBMPP (**Figure 2**) prepared by novel synthetic method starting from phospholenes were first found to exert excellent characters, wide spectral, and high antitumor activities by MTT *in vitro* evaluation as well as microscopic observation against various kinds of leukemia cells such as K562 and U937 cell lines as well as solid cancer cells such as lung cancer.

Mechanistic studies for TBMPP against leukemia cells by Western blotting showed that the phospha sugar enhanced the expression of IER5 and suppressed the expression of Cdc25B, and then the cell cycles of tumor cells stopped at the mitosis stage to induce apoptosis [1]. As the results, tumor cells only die selectively and specifically by phospha sugar derivatives (on the other hand, there are no damages on normal cells.).

In vivo evaluation for phospha sugar TBMPP was successfully performed by using a nude mouse transplanted by K562 cells as shown in **Figure 3**.

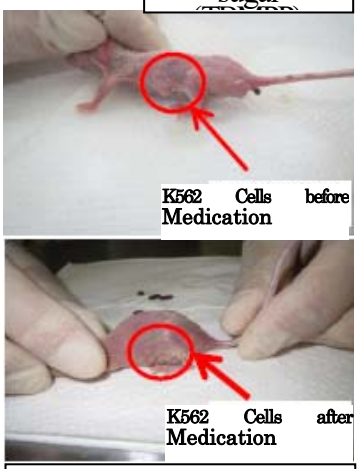
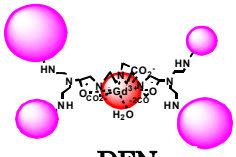


Figure 3. Successful *in vivo* evaluation for TBMPP.

Sugar dendritic Gd-DTPA complex (DEN-OH) (**Figure 4**) was prepared by introduction of protected sugar dendritic parts around the core part of diethylenetriamine pentaacetic acid (DTPA) and then successive complex formation with gadolinium(III) chloride and hydrolysis. The prepared DEN-OH for MRI contrast agent showed quite clear images of quite early stage of cancer (**Figure 5**).



DEN-

Figure 4. Schematic representation of DEN-OH.

These novel medicinal materials may be able to innovate in cancer treatments. We are looking forward to having partners of alliance and/or collaboration with us.

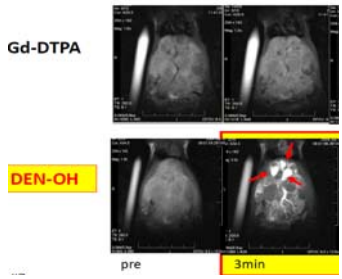


Figure 5. MRI of liver cancer of a Rat with Gd-DTPA (Top) and DEN-OH (Bottom).

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Gadolinium Chelates Incorporated in Nanohydrogels : Characterization by DOSY NMR and Relaxometry

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Magnetic Resonance Imaging (MRI) is one of the most popular imaging techniques used in the clinical field thanks to its non invasiveness and its high spatial resolution. It suffers however from a low sensitivity which can be compensated by the use of contrast agents. The currently used MRI contrast agents being poorly efficient, the development of hypersensitive ones could help to reduce the injected doses and to facilitate the diagnosis of some diseases.

This study describe the development of nanohydrogels based on chitosan and hyaluronic acid incorporating gadolinium chelates in order to enhance their efficacy. More particularly, a focus will be done on the functionalization of either chitosan or hyaluronic acid by different molecules allowing to adress the nanohydrogels to specific tissues (functionalization with PEG or with a small fluorinated molecule to target the lymph nodes) or with a fluorescent probe (such as rhodamine) to allow the detection of the contrast agent by another imaging technique (Optical Imaging in that case). This functionalization has been fully characterized by DOSY NMR which allows to discriminate non grafted and grafted molecules thanks to the measurement of their diffusion coefficient.

A relaxometric study of the different nanohydrogels was also performed in order to evaluate their efficacy.

This work is supported by the “Programme de coopération transfrontalière Interreg France-Wallonie-Vlaanderen” (Nanocardio project).

Fluorinated Paramagnetic Contrast Agents: Synthesis, Physico-chemical Characterizations and Molecular Dynamic Simulations

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Introduction. Medical imaging is a dynamic area of researches whose one of the goal is the elaboration of more efficient contrast agents (CA). Those agents need to be improved to optimize the detection of affected tissues such as cancers or tumours while decreasing the injected quantity of agents. The paramagnetic contrast agents containing fluorine atoms can be used both on proton and fluorine MRI. This research field is therefore promising thanks to the ability to map the anatomy by ^{1}H MRI and locate exactly the agents by ^{19}F MRI.

Methods. One of the challenges in this domain is to synthesize a molecule containing several chemically equivalent fluorine atoms with short relaxation times to allow the record of ^{19}F MR images in good conditions. In that aim, we propose to synthesize a CA containing a paramagnetic ion and nine chemically equivalent fluorine atoms by a cycloaddition reaction between two previously synthesized molecules. Initially, a derivative of DOTA-GA macrocyclic ligand has been synthesized through a multistep synthesis. Diverse lanthanide ions have then been complexed in order to evaluate the more efficient to decrease the fluorine atoms relaxation time T_1. Finally, a nonafluorinated compound has been synthesized and grafted on the DOTAGA derivative in order to obtain the final fluorinated complexes (figure 1).

Results. The structure of the fluorinated paramagnetic contrast agents (Gd^{3+}, Dy^{3+}, Tb^{3+}, Eu^{3+} complexes) were confirmed by mass spectrometry. Those fluorinated contrast agents were then characterized by ^{19}F NMR where differences were observed on the fluorine relaxation times T_1 and T_2 depending on the lanthanide ion: Gd^{3+} induced a strong decrease of the relaxation times T_1 and T_2 whereas Eu^{3+} is nearly inefficient. On the other hand, Tb^{3+} and Dy^{3+} induced a moderate and appropriate decrease of each T_1 and T_2. Moreover, no concentration dependence of relaxation times was observed in this range of concentration for all the tested lanthanide ions, proving that only the internal effect is present.

Molecular dynamic simulations have been performed in order to understand the folding of the molecule. These simulations showed that strong interactions force the molecule to fold, inducing a decrease of the distance between the paramagnetic ion and fluorines.

Conclusions. This study has shown the paramagnetic influence of several lanthanide ions on fluorine atoms situated close to them. Although the gadolinium ion has the highest paramagnetic effect, its influence can sometimes be too strong and decreases the relaxation times in a too significant way. An alternative can then be envisaged by the use of the dysprosium and terbium ions which allow to obtain appropriate relaxation times for clinical use.

Pre-clinical Medical Imaging at the Center for Microscopy and Molecular Imaging

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The Center for Microscopy and Molecular Imaging (CMMI) provides to the scientific community a wide range of high tech equipment for pre-clinical imaging, together with the expertise of senior scientists. The Non-Ionizing Molecular Imaging (NiMI) pole of CMMI owns 4 technologies dedicated to small animal imaging (mice, rats): Magnetic Resonance Imaging (MRI at 1T and 9.4T), Optical Imaging (bioluminescence and fluorescence), and Photoacoustic Tomography. Those different systems were already used in several preclinical studies related to cancer, infection, cardiology, cell therapy and drug discovery.

Magnetic Resonance Imaging provides images based on spatial encoding of radio frequency (RF) signals allowed by hydrogen nucleus resonance after RF excitation in strong external magnetic field. This method is known for its high-resolution images of soft tissues, based on mainly water hydrogen nuclei (and fat). At CMMI, MRI can be performed in 2D or 3D, at 9.4T (Bruker Biospec) for more advanced applications (higher spatial or time resolutions for more detailed, functional, dynamic or molecular aspects), and at 1T (Bruker ICON) for more “routine” applications requiring less resolution (e.g. morphological studies such as tumor growth monitoring). Studies involving paramagnetic or superparamagnetic contrast agent injection can also be performed.

Optical imaging consists in visualizing light emitted through bioluminescence (BLI; luciferin-luciferase reaction) or fluorescence (FLI; after light excitation). The system currently operated at CMMI is a Photon Imager Optima (Biospace). BLI is a senstitive and specific method that allows for detection of in vivo implanted luciferase-expressing cells after luciferin injection. For instance, many cancer cell models can be studied with BLI in pre-clinical imaging. FLI is performed in visible and near-infrared part of the spectrum, and can be used to study injectable fluorescent tracers or to detect cells expressing fluorescent proteins. Up to 10 mice can be observed simultaneously.

Photoacoustic imaging mixes fluorescence and ultrasound imaging aspects. It is based on pulsed laser excitation of chromophores, which absorb light and emit ultrasound after thermoelastic expansion due to local temperature increase. Ultrasounds are collected by the system (InVision 256-TF from iTheraMedical) that reconstructs a 3D (tomography) image looking like echography. Signals in tissues are provided by endogen chromophores wich can be selectively excited (haemoglobin, oxygenated haemoglobin, melanin…) by tuning the laser at a certain wavelength. This technology is thus called Multispectral Optoacoustic Tomography (MSOT). Exogenous chromophores can be injected and detected as well.

Relaxometric Properties of Saponites Bearing Ln^{3+} Ions in the Inorganic Framework

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The introduction of *f*-block elements, as ions or complexes, in synthetic saponite clays may lead to the development of novel lamellar systems with interesting optical and magnetic features.[*Dalton Trans.*, **2018**, *47*, 7896]

In this work, we introduce both Gd^{3+} and Eu^{3+} ions directly into the inorganic framework of a synthetic saponite, thus conferring both paramagnetic and luminescent properties to final material (GdEuSAP). Samples with only Gd^{3+} or Eu^{3+} have been prepared as references (GdSAP, EuSAP). The Gd^{3+} and Eu^{3+} loading in samples resulted to be 0.02 mmol/g. $1/T_1$ ^{1}H-NMRD profiles of aqueous suspensions show the typical shape of slowly tumbling systems, with a broad hump at high magnetic fields and a maximum r_1 relaxivity centered around 30-40 MHz at 310 K (Figure 1). The materials showed improved relaxometric performances at high magnetic fields compared to commercial Gd^{3+}-chelates and comparable to those of zeolite-based materials with Gd^{3+} in structure. The r_1 is influenced by diffusion phenomena through saponite interlayer, as suggested by its increase with temperature. The suspensions were treated with EDTA ligand and no release of paramagnetic ions in solution was observed.

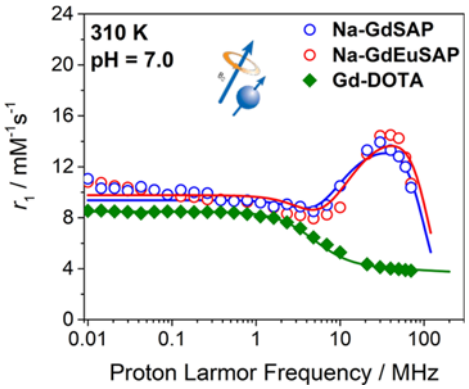

Figure 1. $1/T1$ ^{1}H-NMRD profiles of GdEuSAP (-○-, red), GdSAP (-○-, blue) and Gd-DOTA (-◊-, green) at 310 K, over the frequency range 0.01-70 MHz and neutral pH.

Simulation of the Nuclear Magnetic Relaxation Induced by Superparamagnetic Nanoparticles Trapped in a Biological Tissue

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Service de Physique Biomédicale, UMONS

Superparamagnetic nanoparticles are generally composed of iron oxides and have the property of having a high magnetization when submitted to a high external field, and no remnant magnetization in zero field. There is a variety of theoretical models which try to quantitatively explain the relaxation induced by those types of nanoparticles: this effect can be modeled by the magnetic inhomogeneities produced by the nanoparticles and the diffusion of the water molecules around them [1].

The diffusion coefficient of water molecules is an important parameter in these models. However, they only consider relaxation in a homogeneous medium: in a biological tissue, the diffusion of the water molecules is strongly constrained by the presence of a network of cells in which water diffuses. Moreover, cellular membranes affect the water molecule movement through their permeability. Those constraints on diffusion affect the relaxation times [2].

This work aims at simulating by using Monte Carlo techniques the relaxation of water molecules in a tissue loaded by superparamagnetic nanoparticles. The tissue is modeled as a periodic layout of semi-permeable membranes. It is shown that, when all the cells are identically loaded by the nanoparticles, the simulated relaxation times do no differ from the relaxation in a homogeneous medium and do not depend on the cell permeability. If the tissue cells are not all loaded in the same way, the relaxation can greatly vary and will depend on the cell permeability and the spatial distribution of the nanoparticles. This effect should thus be taken into account for the iron quantification by MRI in vivo.

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Synthesis of Paramagnetic Dendrimers for MRI

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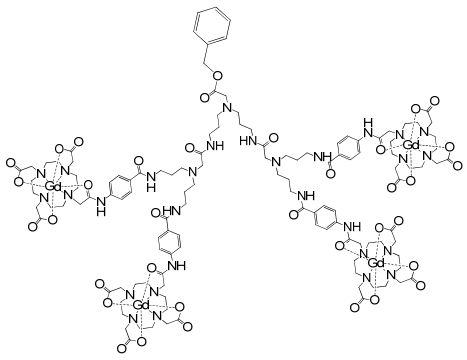
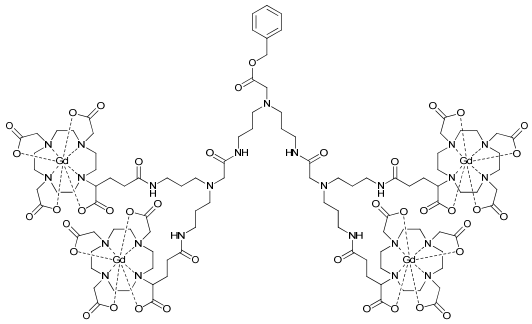
The multivalent character of dendrimers has positioned these well-defined and highly branched macromolecules at the forefront in the development of new contrast agents for magnetic resonance imaging (MRI). In recent years, several research groups have explored the use of dendrimers as a new class of MRI contrast agents[(2,3)]. Indeed, by modifying the periphery of the dendrimer with gadolinium (III) chelates grafting, the relaxivity of the resulting MRI contrast agent is increased considerably compared to low molecular weight Gd(III) chelates[(1)].

The aim of our project is therefore to synthesize a bimodal contrast agent for MRI and optical imaging, specific for the detection of atherosclerotic plaques. In the poster, the dendrimer 1 and 2 (scheme below) syntheses will be described. They correspond to a generation 1 dendrimer, synthesized via 6-step reaction from Bis(3-aminopropyl)amine. They exhibit 4 primary amine functions on the periphery which can be functionalized either with an organic ligand derived from Gd-DO3A (compound 1) and then metalated with Gd-DOTAGA chelate (compound 2). The efficiency of these two structures to improve MRI sensitivity will be compared.



Compound 1



Compound 2

As perspectives, we will optimize the grafting conditions to obtain a tetra gadolinium product in sufficient quantity. After grafting an optical probe and a peptide, *in vitro* and *in vivo* tests will be performed at the Center for Microscopy and Molecular Imaging (CMMI) and toxicity tests on HUVEC cell lines will be done at the University of Ghent.

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Individual Retrospect on Contrast Media Research for Translational Medicine

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Biomedical imaging, especially being enhanced by contrast agents (CAs), has been playing a key role fundamental and clinical medicine. At such anniversary celebrations, it is a precious opportunity for us as active participants to count what we have contributed to the research and applications of CAs over the last three decades. In the mid of 1980's, to help inoperable liver cancer patients, trans-arterial chemo-embolization (TACE) using an oily contrast media Lipiodol was first studied with a rat model [1], which triggered me as a Chinese surgeon to devote to a career in imaging and contrast media research. Nowadays, TACE is still applied in clinic worldwide.

In early 1990's, the above rat model was adapted in KUL Belgium for preclinical research on MRI hepatobiliary contrast agents for liver tumor characterization [2], which was honored by a Stauffer Award in 1993. The findings have been proven by later clinical applications of those new CAs.

Further research has led to a discovery that turned "tumor-seeking" MRI CAs into novel necrosis-avid contrast agents (NACAs) [3], with potential multiple utilities [4], which was honored with the Europe MR AWARD in 2000.

A typical application is for therapeutic assessment using NACA-enhanced MRI in tumor-bearing rats after necrosis -inducing therapies such as radio-frequency ablation (FRA) [5] and tumor vascular disrupting agents (VDAs) [6].

Another potential application is for myocardial viability assessment in acute heart attack by using necrosis-avid MRI CAs [7] or radio-nuclear tracers [8] in animal models simulating clinical patients.

A dual targeting pan-anticancer theragnostic strategy namely OncoCiDia was elicited by combining a tumor VDA and a radio-iodinated necrosis-avid tracer [9], which was honored with a Lasser's Award in 2009 and AOCR Best Exhibit Award in 2010, and is now under early clinical trials [10, 11].

To answer questions emerged in clinical OncoCiDia tests, rats with primary and secondary liver cancers were studied using contrast-enhanced MR imaging [12, 13], which could further derives into a potentially curative approach for micro-cancers [14] (work in progress).

To explore OncoCiDia, quantitative 3D visualization of rodent pancreas was realized by using a multifunctional contrast dye for pancreatitis and pancreatic cancer studies [15-17].

Perfusion and diffusion MRI using CAs has also been studied in rodent stroke models [18].

Clinically, twin-to-twin transfusion syndrome (TTTS) has been investigated by using contrasted angiography and histology, which has consolidated an interventional remedy for this disorder in the fetus stage [19].

Translationally, by using a home-formulated contrast dye, we were able to study intrahepatic microvascular passage of contrast materials in rat livers [20, 21], which may impact our current perspectives and practice for hepatic digital subtraction angiography (DSA) and TACE in clinical practice (work in progress).

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NMR and Structural Study of Lanthanide Complexes of *trans*-DOTA-diamide

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A new DOTA-like ligand (Figure 1) was prepared by five-step procedure. Lanthanide(III) complexes of this ligand were prepared using lanthanide(III) chlorides in aqueous solution. Several XRD structures were obtained and mostly square-antiprismatic (SA) isomers were observed in the solid state. The lanthanide(III) complexes were also studied by NMR spectroscopy. Europium(III) complex in solution was studied more thoroughly. Similarly to Eu(III)-DOTA complex, two diastereoisomers with square-antiprismatic and twisted-square-antiprismatic geometry are present in the solution. The two isomers found in solution are in dynamic equilibrium and these species interconvert by two pathways: arm rotation and ring inversion. These two processes are not equally fast. In order to observe the kinetics of these processes, several 2D ^{1}H EXSY spectra with variable mixing times were obtained. The dependence of integral intensity of the peaks assigned to the macrocyclic protons on mixing time were fitted by Bloch-McConnell equation. As a result, rate constants of arm rotation and ring inversion for each isomer were obtained. So far, such data are available only for two systems.[1] Relaxometric parameters will also be discussed.

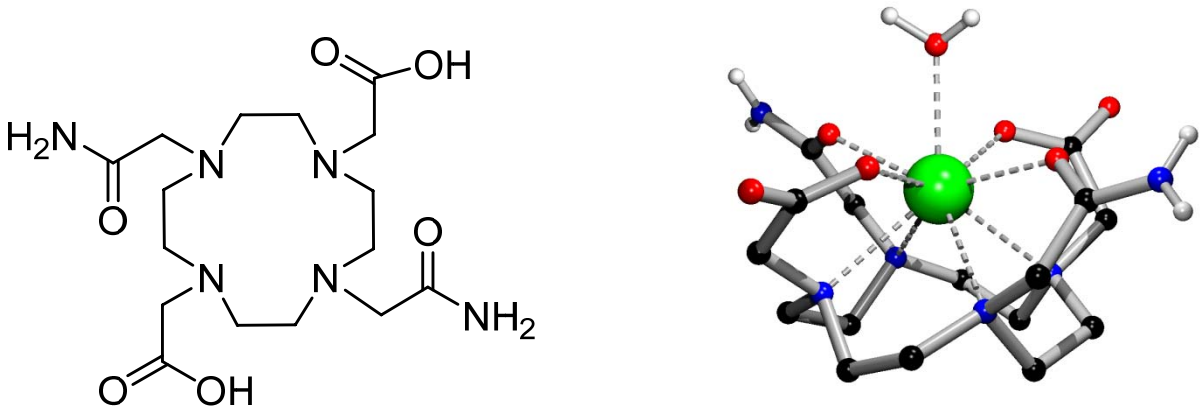

Figure 1. Formula of the studied ligand and the solid-state of europium(III) complex of this ligand. Colour code: black = C, white = H, red = O, blue = N and green = Eu.

Acknowledgments. This work was supported by the CA15209 COST Action (EURELAX) and MŠMT ČR (COST-Inter-excellence No. LTC 17067). We thank Dr. Ivana Císařová and Dr. Jan Kotek for data collection and solving XRD structures, respectively.

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Bismuth metallic nanoparticles: from synthesis to diagnostic and therapeutic and applications

M. Port

Cnam, Paris

In this oral presentation, we will review the different methodologies of syntheses of bismuth metallic nanoparticles and analyze the relevance of these syntheses in terms of green chemistry.

We will also describe the different medical applications described in the literature of metallic nanoparticles of bismuth, in particular, in the antibacterial field and in theranostic applications.

Finally, we will discuss preliminary works done in our laboratory aiming at synthetizing bismuth metallic nanoparticles in reproducible conditions and respecting the principles of green chemistry.

MR Imaging: Quo Vadis?

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Since Röntgen discovered X-rays in 1895, diagnostic imaging has continuously prospered and expanded. Lauterbur's invention of magnetic resonance imaging in 1973 allows imaging diagnoses to cover not only morphology but also function of tissue and/or cell components. #

To foresee the future, it is essential to understand the factors influencing the development of the technique, scientifically, commercially and socially. This includes its instrumentation and accessories; academic and industrial research; fashions and hypes; global cultural differences; changes within societies and human factors; disruptive technologies; the worldwide market for MR contrast agents; and new paradigms. #

The lecture will discuss these topics in detail.#

Further reading and in-depth discussion of the topics mentioned
(www.rinckside.org | ISSN 2364-3889)

1. Rinck PA. MR safety update: Why we may not need a 20-Tesla MRI machine. Rinckside 2016; 27,6: 13-15.
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7. Rinck PA. Debacles mar “Big Science” and fMRI research. Rinckside 2016; 27,7: 17-18.
8. Rinck PA. Some reflections on artificial intelligence in medicine. Rinckside 2018; 29,5: 11-13.
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10. Rinck PA. Paradigm and element shift in MR contrast agent applications. Rinckside 2017; 28,1: 1-2.

See also: Rinck PA: Magnetic Resonance in Medicine. A Critical Introduction. The Basic Textbook of the European Magnetic Resonance Forum. 12th revised and enlarged edition, 2018. ISBN 978-3-7460-9518-9. www.magnetic-resonance.org.#

A New Multimodal Platform to Obtain a Versatile and Targeted MRI and Photoacoustic Contrast Agent

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Medical world is in constant evolution, and the development of the imaging techniques is more and more important. Among these imaging techniques, Magnetic Resonance Imaging (MRI) is widely used thanks to its great advantages: its non-invasiveness, its high spatial resolution and its investigation depth. It possesses however a lack of sensitivity, which could be compensated by the combination with another technique, such as Photoacoustic Imaging.

Photoacoustic imaging (PAI) is a quite new imaging technique based on the detection of acoustic waves produced by the desexcitation of a fluorophore. An analysis is faster than MRI and possesses a better sensitivity. However, the investigation depth is about few centimeters and the absorption is limited by the optical scattering of living tissues.

The development of a bimodal contrast agent, active for both imaging techniques could thus be interesting since it will allow to perform both analyses with only one injection, and it also allows to take benefit of the advantages of both techniques, compensating their weaknesses. This study is thus dedicated to the design of a multimodal platform, able to combine different imaging techniques in one molecule, as well as a targeted biovector, such as a peptide. The synthesis starts with N-Boc-1.3-propanediamine and the main goal is to obtain a trimodal platform, bearing three different functional groups, which can react individually. One functional group will react with a DOTAGA derivative complexed with gadolinium for MRI whereas another extremity will bear a fluorescent probe derivated from Indocyanine Green (ZW800-1) for PAI. The last reaction step will be the grafting of a specific peptide that can target a precise biological disorder like inflammation or Alzheimer disease.

Changing the length, changing the properties: effect of the PEG molecular weight on the pharmacokinetic properties of VSIONs.

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Because of their outstanding magnetic properties, iron oxide nanoparticles have already been the subject of numerous studies in the biomedical field, in particular as negative contrast agent for nuclear magnetic resonance imaging (MRI). Recent studies have shown that below a given size (i.e. 5 nm), iron oxide may exhibit a significant positive (brightening) effect, even at high field (<7T)[1]. When focusing on such application, not only the size of the crystal, but also the control of the coating process is essential to ensure optimal properties. Interestingly, we demonstrated in this work that for a given composition, the thickness of the coating strongly influences the pharmacokinetic properties of the administrated VSIONs. Such behavior has been further confirmed by optical and optoacoustic imaging using a bimodal probe.

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AGuIX® Theranostic Nanoparticles: From the Concepts to First in Man

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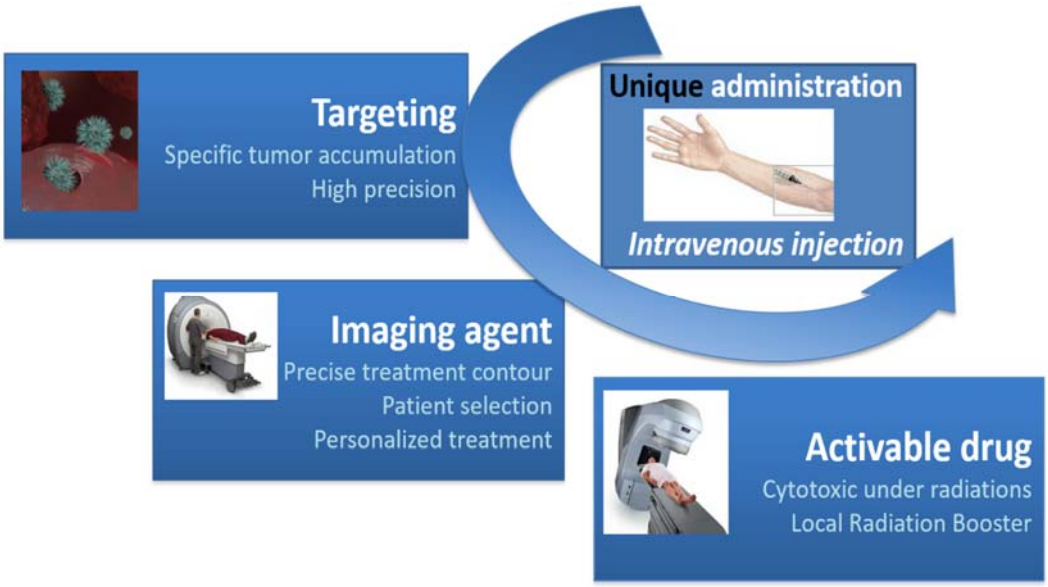
The lecture will take place in the field of nanomedicine and will describe translation to the clinic of first hybrid theranostic nanoparticle injected intravenously: AGuIX®. This nanoparticle has been designed to act as a radiosensitizer to increase locally the effect of the dose in radiotherapy and has been used in two phase Ib clinical trials: Nano-Rad (NCT02820454) for the treatment of multiple brain metastases by whole brain radiotherapy and Nano-Col (NCT03308604) for the treatment of locally advanced cervical cancer by external radiotherapy and Curie-Therapy.

AGuIX nanoparticles are ultrasmall (< 5 nm) nanoparticles made of polysiloxane and gadolinium chelates. These nanoparticles are now synthesized in cGMP conditions and regulatory toxicity tests performed on two different animal species have shown no evidence of toxicity. After intravenous administration, AGuIX nanoparticles accumulate in tumors due to Enhanced Permeability and Retention effect and are eliminated by the renal way. Their bioditribution and the accumulation in the tumor can be followed by MRI due to the presence of gadolinium. Their efficacy as a radiosensitizing agent has been shown on eight different animal models. During Nano-Rad clinical trial, 15 patients have been treated and all the doses (15, 30, 50, 75 and 100 $mg.kg^{-1}$) have been successfully validated. First evidences of the interest of the association between AGuIX and radiotherapy for the treatment of brain metastases have been observed and preliminary results are really encouraging.



Responsive MRI Agents

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Metal complexes, including lanthanide chelates, are widely used as imaging probes in various imaging modalities. One important field in molecular imaging involves the in vivo detection of physico-chemical parameters of tissues, concentration of ions, metabolites, etc. by applying smart, activatable imaging probes that are responsive to the specific parameter to detect [1]. In contrast to nuclear imaging modalities, MRI is particularly well adapted to the design of responsive probes, involving Gd^{3+}-based or PARACEST (Paramagnetic Chemical Exchange Saturation Transfer) agents. The MRI efficacy (relaxivity or CEST properties) of the probe has to be selectively influenced, based on coordination chemistry concepts, by the particular biomarker that we wish to detect. We develop potential smart contrast agents to detect cation or neurotransmitter concentration changes in the extracellular space or to monitor enzyme activity. In this talk, some representative examples will be discussed.

The Influence of the Aminomethylphosphinic Pendant arm of DO3AP^{R} on Properties of its Lanthanide(III) Complexes

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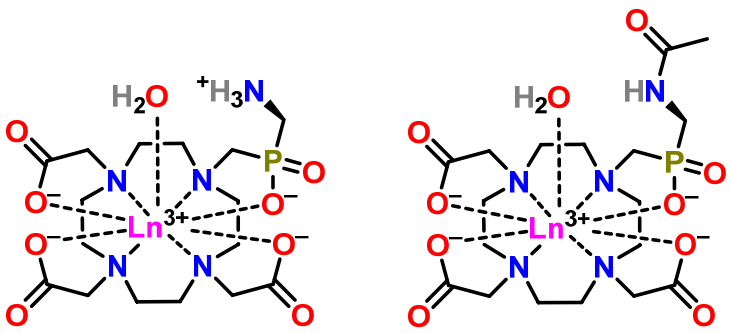
Commonly used non-invasive diagnostic method, Magnetic Resonance Imaging (MRI), has been utilized for dozens of years. To acquire MRI scan with good spatial resolution and enhanced contrast, T_1-contrast agents (CAs) are frequently used. The CAs are paramagnetic complexes mostly containing Gd(III).

Introducing phosphorous atom with closely located protonable group into the ligand can result in pH dependent properties of its complexes. Here, complexes of ligand **L**^{A} with P–CH_2–NH_2 group in the pendant arm were prepared and their relaxometric properties (e.g. water exchange rate, τ_M), ^{31}P NMR chemical shifts (δ_P), or PARACEST effect (paramagnetic chemical exchange saturation transfer) were investigated. Complexes of the amide derivative, **L**^{Ac}, were studied as model compounds without protonable side arm. Water exchange of Gd(III) complex is enhanced as well as overall relaxivity, if compared with Gd(III)–DOTA complex. In lanthanide(III) complexes, LIS (lanthanide induced shift) amplifies differences in δ_P caused by protonation of the pendant amine group. Observation of the PARACEST effect points to defined localization of the amino group even in solution. The pH-sensitive ^{31}P-MRS (magnetic resonance spectroscopy) was studied on some Ln(III) complexes and compared with works on Ln(III) complexes of other phosphorus DOTA derivatives[1–3]. In addition, the solid-state structures of Ln(III) complexes were determined by X-ray diffraction. The observed properties can be explained by changes in hydrogen bond network around the complexes and/or by alternation of properties of the phosphorus atom caused by protonation of the pendant amino group.



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PEGylated Very-Small Iron Oxide Nanoparticles (VSION) : Evidence of their Potential as T_1 Contrast Agents for Magnetic Resonance Imaging

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Introduction: In the biomedical field, IONP are well-known T_2 contrast agents (CAs) for MRI. However, their success as T_2 CAs has been hampered by several disadvantages such as the well-known "blooming-effect" or the intrinsic dark signal of T_2-weighted MRI which can be confusing during diagnosis establishment1. Interestingly, it has been reported recently that a T_1 effect is observable when decreasing the size of the particles below a critical value[2]. This work reports the development of very small iron oxide nanoparticles (VSION) active as potential platforms for high-field (9,4T) T_1 angioMRI applications.

Methods: VSION with a mean diameter of 3,5 ± 0,6 nm (PDI: 1.11) were obtained by thermal decomposition. The transfer of the iron oxide nanoparticles in aqueous media was then performed by means of a ligand exchange protocol with PEG-based ligands (4 PEG chainlength: PEG_{200}, PEG_{400}, PEG_{800} and PEG_{2000}) anchored onto the nanoparticles surface through a biphosphonate moiety.

Results: VSION transferred in aqueous media with PEG_{200} and PEG_{400} biphosphonate derivatives showed poor stability (probably due to a lack of interparticle steric repulsion with these ligands). However, VSION treated with PEG_{800} and PEG_{2000} biphosphonate derivatives demonstrated great stability in physiological media over a period of 3 months. The efficiency of both PEG_{800}-VSION and PEG_{2000}-VSION as T_1 contrast agents was demonstrated through their excellent relaxometric properties (high r_1 values and small r_2/r_1 ratios). Moreover, the demonstration of the T_1 effect observed whether for PEG_{800}-VSION and PEG_{2000}-VSION was performed at 9.4T to confirm the high potential of these platforms for T_1 high-field angio-MRI. Finally, *in vivo* evaluation of these platforms has been performed through i.v. injection on mice. Again, the stability of these systems was evidenced by their long circulation time (>2h) observed on T_1-weighted MRI.

Conclusion: In this work, stable PEGylated VSION have been prepared. The potential of these nanoplatforms for T_1 contrast-enhanced high-field angio-MRI has been evidenced through *in vitro* and *in vivo* experiments showing a remarkable contrast enhancement induced by the probes. However, further studies implying a complementary imaging modality as well as *in vitro* experiments are still to be done to assess the pharmacokinetics and toxicological properties of these nanosystems.

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VDA Induced Necrosis in Micro-Cancers Elicits a Strategy for Early Eradication of Malignancies?

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Background

Previously, our team has developed a pan-anticancer strategy called OncoCiDia, which combines a vascular disrupting agent (VDA) such as CA4P, and a radioactive necrosis-avid compound such as ^{131}I-Hypericin. It is primarily considered to be palliative in late-stage disease [1]. However, its curative potential in early-stage cancers remained unknown.

Methods

A total of 19 rats with 43 induced hepatocellular carcinoma (HCC) of 2.8–20.9 mm in size received CA4P at 10 mg/kg. Tumor-diameter was measured by T2WI. Vascular responses and tissue necrosis were detected by DWI, CE-T1WI and DCE with 3.0 MRI and validated by microangiography and histopathology.

Results

MRI revealed nearly complete necrosis in 5 out of 7 micro-HCCs, but diverse therapeutic necrosis in larger HCCs and necrosis percentage was 36.9% higher in micro-HCC than larger HCCs[2]. Decreased blood supply in both micro-HCCs and liver was validated by perfusion coefficient, with tumor necrosis assessed by apparent diffusion coefficient (ADC) map. DCE revealed lowered tumor blood flow from intravascular into extravascular extracellular space. Microangiography and histopathology revealed hypo- and hypervascularity in 4 and 3 micro-HCCs, massive, partial and minor degrees of tumoral necrosis in 5, 1 and 1 micro-HCCs, respectively. IHC staining with CD34-PAS implicated the presence of endothelia that might be responsible to the superior effect of CA4P in micro-HCCs, which has been proven by implanted tumor models in rats (work in progress).

Conclusions

Based on the nearly complete CA4P-response in both primary and secondary micro-cancers in rats and a mathematical modeling, we proposed a potentially curative strategy on micro-cancers, in which ^{131}I-Hyp may accumulate after induction of necrosis and provide full coverage of radiation to the entire tumor mass.

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Preclinical Researches on Tumor Acumulative and Remarkably Higher Sensitive Novel Sugar Dendritic Gd-DTPA Complex MRI Contrast Agents

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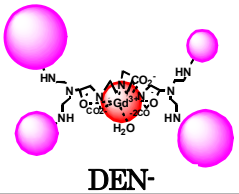

DEN-

Figure 1. Schematic Representation of DEN-OH.

Cancer is one of the most serious diseases. About half number of people in Japan suffered from cancer and 1/3 number of Japanese people actually die of cancer. To decrease the number of people died of cancer remarkably, we have been trying to innovate in pharmaceutical materials for cancer diagnosis and cancer treatment. Among them we focused on the improvement of MRI contrast agents for clearer and higher sencitive cancer diagnostic imaging as well as wider spectral and more effective molecular targeted anti-tumor agents based on biological and chemical properties of sugar derivatives as well as phosphorus deivatives [1].

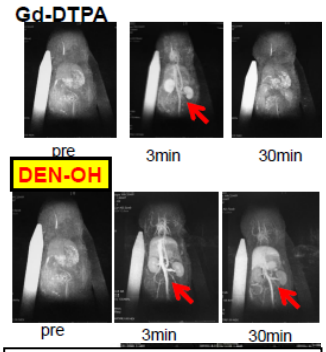

Figure 2. MRA of a Rat with Gd- DTPA (Top) and DEN-OH (Bottom).

Chemical modification of DTPA (diethylenetriaminepentaacetic acid) ligand with protected glucose derivatives gave protected sugar dendritic DTPA ligand, to which Gd^{3+} ion was introduced and succsesively followed by hydrolysis to afford sugar dendritic Gd-DTPA complex (DEN-OH), whose structure consist of Gd-DTPA complex (core part) and sugar dendritic part (outer shell) as shown in Figure 1.

Figure 3. MRI of Liver Cancer of a Rat with Gd- DTPA (Top) and DEN-OH (Bottom).

DEN-OH showed ca. 10 times higher T1 relaxation rate than that of Gd-DTPA complex (Magnevist). DEN-OH showed clearer MR images and longer durability lasting MRA (MR Angiography: Figure 2) than that with Magnevist by using 10% Gd concentration of Magnevist. DEN-OH could draw very small cancer (ca. 2 mm size) remakably clearly (Figure 3). DEN-OH will be able to resolve or may reduce the side effect, NSF. DEN-OH togeter with phospha sugar anti-tumor agent [1] might innovate in cancer therapy dramatically.

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