WG1 meeting – July 12-13, 2019

Universidade da Madeira, Funchal, Portugal

AGENDA

Saturday, July,13

10.00-10.15	Introduction and welcome	Barbara Klajnert & Sabrina Pricl
10.15-11.30	SESSION I (chair: Ling Peng)	PRESENTATIONS
10.15-10.30		Sabrina Pricl
10.30-10.45		David Duday
10.45-11.00		Nina Kostevsek
11.00-11.15		Francisco Silva
11.15-11.30		Agnieszka Majkowska-Pilip
11.30-11.45	Coffee break	
11.45-13.30	SESSION II (chair: Sabrina Pricl)	PRESENTATIONS
11.45-12.00		Serge Mignani
12.15-12.30		Daniel Ruiz
12.30-12.45		Martin Hruby
12.45-13.00		Wafa Al-Jamal
13.00-13.15		Dietmar Appelhans
13.15-13.30		Marta Maria Natile
13.30-14.30	Lunch	
14.30-14.45	Introduction to Rounds of discussions at tables	
14.45-15.15	TABLES (Round I)	chairs + approx. 5 participants
15.15-15.45	TABLES (Round II)	chairs + approx. 5 participants

Sunday, July,14

	SESSION III (chair: Barbara Klajnert)	PRESENTATIONS
9.00-9.30		Jean Pierre Majoral
9.30-9.45		Ling Peng
9.45-10.00		Evgeny Apartsin
10.00-10.15		Vasco D.B. Bonifacio
10.15-10.30		Jorn B. Christensen
10.30-10.45		Joao Rodrigues
10.45-11.00	Coffee break	
11.00-11.30	TABLES (Round III)	chairs + approx. 5 participants
11.30-12.00	TABLES (Round IV)	chairs + approx. 5 participants
12.00-13.00	FINAL SESSION (chair: Jean Pierre Majoral)	Presenting results of working groups, discussion
12.00-12.15	table 1	Sabrina Pricl & Kostas Karatasos
12.15-12.30	table 2	Ling Peng
12.30-12.45	table 3	Rana Sanyal
12.45-13.00	table 4	Nazende Gunday-Tureli
13.00-13.15	closing the meeting	Barbara Klajnert & Sabrina Pricl
13.15-14.15	Lunch	

Session I

MIX AND MATCH: COMPUTERS AND TEST TUBES IN DECIPHERING SOME PECULIAR ASPECTS OF CANCER NANOMEDICINES

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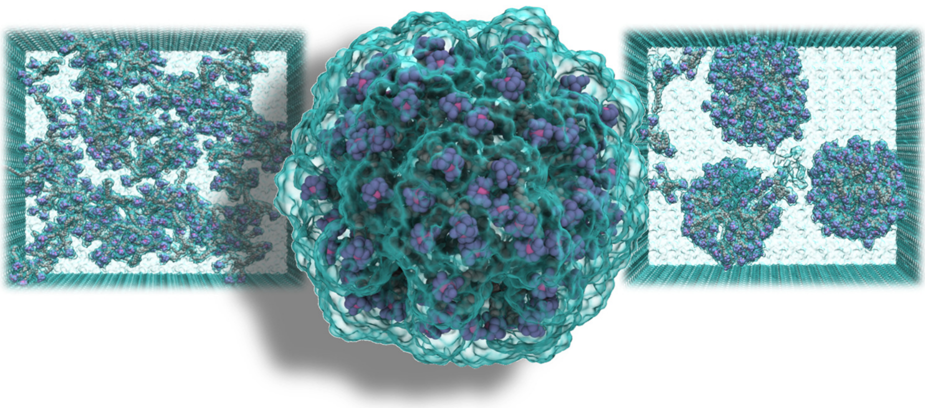
This presentation will provide an overview of collaborative work performed to probe and understand some fundamental yet poorly understood aspects of cancer nanomedicines. Since some *in vivo* and *in vitro* aspects will be covered by other presentations, this contribution will primarily focus on how our combined computational and experimental approach has led to new insights into peculiar facets of these nanomaterials.



Key Words: self-assembling, multivalency, gene delivery, cancer nanomedicine, computer simulations

Acknowledgements: This work receives several funding from different agencies, including the European Commission, the Italian Ministry for University and Scientific Research, the Italian Association for Cancer Research, and the Autonomous Region Friuli Venezia Giulia.

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References: *Nature Communications* **2019**, 10, *Article number 1690*; *Proceedings of the National Academy of Science USA* **2018**, 115, *11454-11459; Journal of the American Chemical Society* ***2018***, 140, *16264-16274; Angewandte Chemie* **2018**, 57, *8530-8534.; Chemical Communications* **2017**, 53, *6335-6338; Chemistry-A European Journal* **2017**, 23, *6391-6397*; *ACS Nano.* ***2016***, 10, *9316-9325*; *Chemical Science* **2016**, 7, *4653-4659*; *Small* **2016**, 12, *3667-3676*; *Proceedings of the National Academy of Science USA* **2015**, 112, *2978-2983*; *Nanoscale* **2015**, 7, *3876-3878*; *Angewandte Chemie* **2014**, 53, *11822-11827*.

NOVEL MESOPOROUS SILICA-BASED NANOPARTICLES FOR MEDICAL APPLICATIONS

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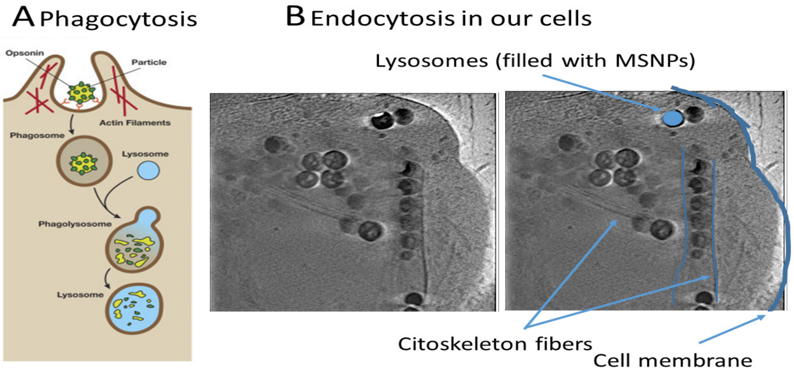
Recent development on amorphous mesoporous silica based nanoparticles (MSNPs) make these nanovectors more versatile and biodegradable for applications involving long duration drug delivery. In general, MSNPs exhibit high payloads, high stability, low toxicity (if highly mesoporous and amorphous) and is easily functionalized with organic or inorganic shells. The MSNPs can easily encapsulated active ingredients, metal or oxide core for medical imaging. Biodegradability of MSNPs can be increased by doping with Ca. Pore size can be tuned to encapsulate small or large molecules. In this communication, we will present the different approaches explored to make MSNPs more suitable for medical applications.



Key Words: drug delivery, imaging, mesoporous amorphous silica, nanoparticles

Acknowledgements: This work was supported by Luxembourg Institute of Luxembourg, University of Paris 13 and Fonds National de la Recherche Luxembourg (FNR) through projects INTER/MERA/16/11454672 and PRIDE/15/10935404.

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References: *Nano Lett.* **2017** 17 (5), 2747-2756**;** *Sci. Technol. Adv. Mater.* **2013** 14, 055009; *J Nanobiotechnol* **2016** 14, 15*; Adv. Funct. Mater.* **2007** 17, 605–612*; Nanoscale.* **2017** 9 (1), 402-411*; Nanoscale* **2018** 10 (14), 6402-6408; *J. of Colloid and Interface Science* **2016** 469, 213-223; *RSC Adv.* **2016** 6, 95101; *Wiley Interdiscip Rev Nanomed Nanobiotechnol.* **2019** 11 (1), e1515; *Curr Med Chem.* **2013** 20 (17), 2195–2211

PHOTO-THERMAL CANCER TRETMENT AND MRI WITH MAGNETO-PLASMONIC THERANOSTIC NANOPARTICLES

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With combining the magnetic (FePt) and plasmonic (Au) entity in a single nanoparticle (NP) we are able to produce multifunctional NPs enabling both the diagnostic (MRI) and the therapeutic (photo-termal therapy) action. In this work we have combined the advanced synthesis procedures to synthesise the hybrid FePt/SiO_2/Au NPs. The step from “single-core” FePt nanoparticles towards the larger, “multi-core” FePt nanoparticles (>20 nm), led to an increase in the magnetization m(1.5T) from 8 to 19.5 emu/g, without exceeding the superparamagnetic limit, and was attributed to the exchange interactions within one “multi-core” FePt nanoparticle. The MRI investigation showed that such NP_S can used as T_2 contrast agents for MRI as high r_2 values of 87 ± 4 (mM^{-1} s^{-1}), with a suitable r_2/r_1 ratios of 12.9 were obtained. To implement the multi-functionality of photo-termia FePt NPs were firstly covered with SiO_2 layer. Furthermore, a new synthesis approach, i.e., Au double seeding, for the preparation of the Au nanoshells around the FePt/SiO_2 cores, is proposed. The photo-thermal and the MRI response were first demonstrated on an aqueous suspension of hybrid FePt/SiO_2/Au NPs. The cytotoxicity together with the internalization mechanism and the intracellular fate of the hybrid NPs were evaluated in vitro on normal (NPU) and a half-differentiated cancerous cell line (RT4). The control samples as well as the normal cell line incubated with the NPs showed no significant temperature increase during the in vitro photo-thermal treatment ($\Delta T < 0.8$ °C) and thus the cell viability remained high (~90%). On the contrary, due to the high NPs uptake by the cancerous RT4 cell line, significant heating of the sample was observed ($\Delta T =$ 4 °C) and, consequently, after the laser irradiation cell viability dropped significantly to ~60%. These results further confirm that the hybrid FePt/SiO_2/Au NPs developed in the scope of this work were not only efficient but also highly selective photo-thermal agents. Furthermore, the improvement in the contrast and the easier distinction between the healthy and the cancerous tissues were clearly demonstrated with the in vitro MRI experiments, proving that hybrid NPs have an excellent potential to be used as the contrast agent.

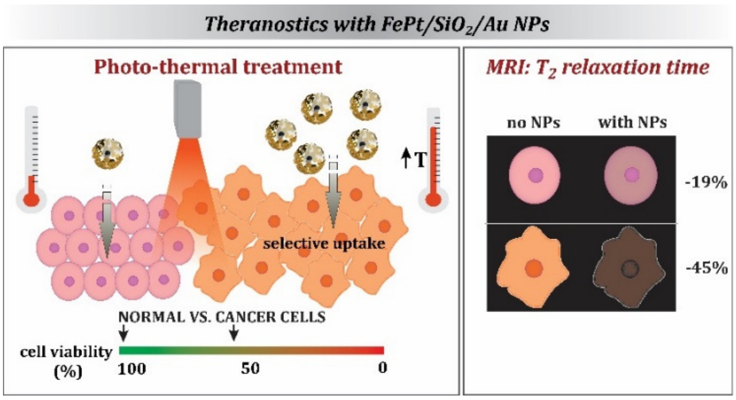

Figure 1: Innovative hybrid FePt/SiO_2/Au NPs as both, highly efficient and selective photo-thermal therapy agent and MRI contrast agent.

Key Words: photo-thermal treatment, magnetic resonance imaging, nanoparticles

Acknowledgements: The study was supported by the Slovenian Research Agency ARRS (project numbers P3-0108 and J2-6760).

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GOLD NANOPARTCLES FOR IMAGE-GUIDED DELIVERY OF Pt(IV) PRODRUGS

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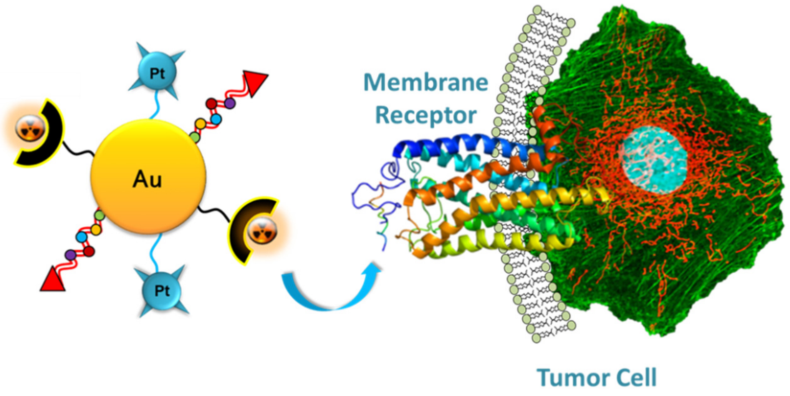
The rapid advance of nanotechnology plays a pivotal role in the design of new strategies for cancer diagnosis and treatment. In this field, gold nanoparticles (AuNPs) have emerged as attractive tools due to their appealing physico-chemical properties. Additionally, AuNPs can also be explored as multifunctional platforms for targeted-delivery of radionuclides and chemotherapeutic drugs for theranostic applications. Herein, we will report on the synthesis, characterization and biological evaluation of AuNPs stabilized with a DOTA-based chelator for coordination of medically relevant trivalent radiometals (e.g. ^{67}Ga, ^{111}In, ^{177}Lu)[1], decorated with a bioactive peptide (bombesin (BBN) analog or substance P (SP) derivative) recognizing the gastrin releasing peptide receptor (GRPr) or the NK1 receptor overexpressed in GBM cells, and carrying Pt(IV) prodrugs. Some of the SP-containing AuNPs were also labeled with ^{125}I profiting from the presence of a Tyr residue in the peptide sequence. The studies included the assessment of cellular uptakes and cytotoxic activity in GBM U87, T98G or U373 cells for the designed multifunctional nanoparticles, aiming to assess their suitability for targeted chemoradiotherapy of glioblastoma.



Key Words: theranostics, nanomedicine, chemoradiotherapy, glioblastoma

Acknowledgements: This work is supported by Fundação para a Ciência e Tecnologia (projects PTDC/MED-QUI/29649/2017 and UID/Multi/04349/2019).

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References: F. Silva, A. Zambre, M. P. C. Campello, L. Gano, I. Santos, A. M. Ferraria, M. J. Ferreira, A. Singh, A. Upendran, A. Paulo and R. Kannan, *Bioconjugate Chemistry*, 2016, **27**, 1153-1164 (1).

GOLD NANOCLUSTERS AS AT-211 CARRIERS FOR ALPHA RADIOIMMUNOTHERAPY

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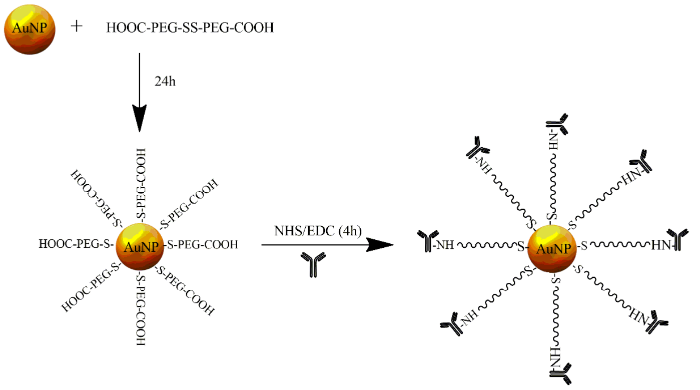
Among various α emitters, ^{211}At ($T_{1/2}$=7.2 h, E_α=5.9 MeV) exhibits very attractive nuclear properties for its application in radionuclide therapy, especially for the treatment of small tumours and cancer metastasis. However, many astatine synthesized compounds exhibited instability *in vivo*, providing inspiration for seeking new ^{211}At labeling strategies. Therefore, in our work we propose to use 5-nm diameter gold nanoparticles (AuNPs) labelled with ^{211}At, modified with polyethylene glycol (PEG) and attached to trastuzumab - HER2-specific monoclonal antibody.

To achieve the 5 nm size of AuNPs, the method elaborated by Soliwoda *et al*. [1] was applied. The nanoparticles were characterized by TEM and DLS techniques. They were modified by PEG chain and conjugated to trastuzumab. Finally, the syntesized bioconjugates were successfully labelled with ^{211}At (the labelling yield higher that 99%), obtained by α irradiation of bismuth target. The ^{211}At-AuNP-PEG-trastuzumab exhibited high stability in human serum. Additionally, *in vitro* biological studies of the radiobioconjugate revealed its high affinity and cytotoxicity towards the HER2-overexpressing human ovarian SKOV-3 cell line. Confocal and dark field microscopy studies indicated that ^{211}At-AuNP-PEG-trastuzumab was effectively internalized and deposited near the nucleus.

These findings show that gold nanoparticles labelled with ^{211}At and functionalized with trastuzumab present a prospective solution for the treatment of unresectable solid cancers expressing HER2 receptors.



Schematic diagram of the synthesis of ^{211}At-AuNP-PEG-trastuzumab radiobioconjugate.

Key Words: gold nanoparticles, targeted tumour therapy, ^{211}At radionuclide, nanobrachytherapy

Acknowledgements: This work was supported by grant 2013/11/B/ST4/00516 from the National Science Centre of Poland

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References: [1] *Langmuir* **2014**, 30, *6684-6693.*

Session II

BENCH-TO-BEDSIDE TRANSLATION OF DENDRIMERS: REALITY OR UTOPIA?

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Nanomedicine, which is an application of nanotechnologies in healthcare is developed to improve the treatments and lives of patients suffering from a range of disorders and to increase the successes of drug candidates. Within the nanotechnology universe, the remarkable unique and tunable properties of dendrimers have made them promising tools for diverse biomedical applications such as drug delivery, gene therapy, diagnostic, and as drug *per se*. Up-todate, very few dendrimers has yet gained regulatory approval for systemic administration, why? In this critical analysis, we briefly focus on the list of desired basic dendrimer requirements for decision-making purpose by the scientists (go/no-go decision), in early development stages, to become clinical candidates, and to move towards Investigational New Drugs (IND) application submission. In addition, the successful translation between research and clinic should be performed by the implementation of a simple roadmap to jump the 'valley of death' successfully.

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NOVEL (COORDINATION) POLYMER NANOPARTICLES FOR ADVANCED THERANOSTICS

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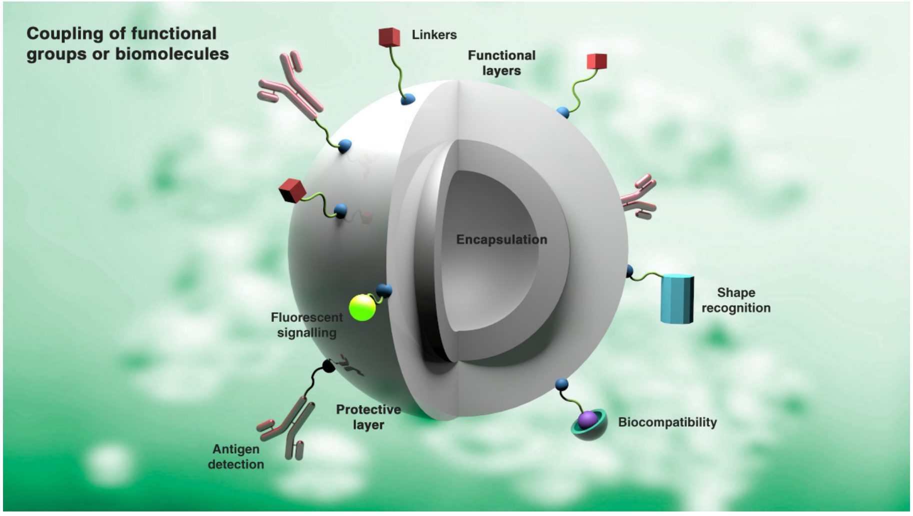
Recently, nanoscale coordination polymer particles (CPPs) have emerged as an alternative platform to provide new opportunities for engineering multifunctional systems with applications in drug delivery and/or biomedical imaging. In general, CPPs exhibit high metal ion payloads content, high biocompatibility, low toxicity and offer the possibility to harbour additional functions. The pre-synthetic design strategies like judicious choice of metal ions and ligands can address the challenges of synthesizing such functional materials. Moreover, the ability to incorporate diverse metals useful for MRI nd/or fluorescence allows constructing novel contrast agents for biomedical imaging. In this communication we will revise the different approaches developed in the group with this aim.



Key Words: drug delivery, imaging, coordination polymer, nanoparticles

Acknowledgements: This work was supported by project RTI2018-098027-B-C21 from the Spanish Government and FEDER funds. ICN2 acknowledges support from the Severo Ochoa Program (MINECO, Grant SEV-2017-0706).

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References: *Biomaterials science* **2019**, 7 (1), *178-186; ACS applied materials & interfaces* **2018**, 10 (45), *38819-38832; Chemical Engineering Journal* **2018**, 340, *94-102; ChemNanoMat* **2018**, 4 (2), *183-193; Chemistry-A European Journal* **2014**, *20* (47), 15443-15450; *Chemical Communications* **2014**, *50* (93), 14570-14572; *Chemistry-A European Journal* **2013**, *19* (51), 17508-17516; *Coordination Chemistry Reviews* **2013**, 257 (19), 2839-2847; *Chemical communications* **2010**, *46* (26), 4737-4739; *Angewandte Chemie International Edition* **2009**, *48* (13), 2325-2329.

POLYMER CONTRAST AGENTS FOR MAGNETIC RESONANCE IMAGING (MRI) - QUO VADIS?

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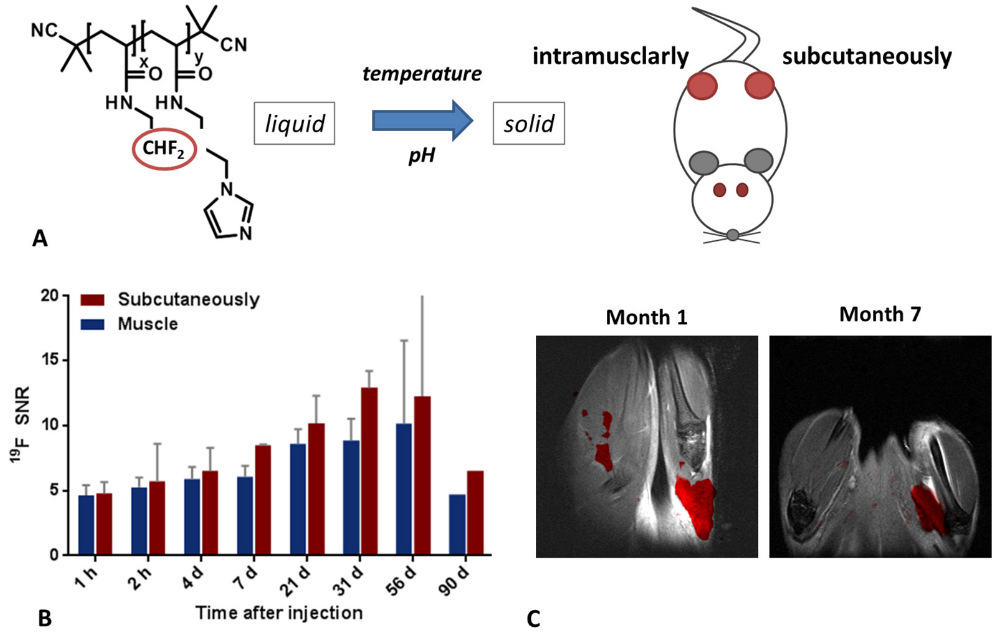
Magnetic resonance imaging is one of the key noninvasive imaging techniques in modern medicine. It is mostly used to provide anatomic information, but in advanced setups, also functional imaging is possible. The MRI is in overwhelming majority of cases used to image ^{1}H nuclei as water is contained in high concentration within the whole organism and ^{1}H nucleus has superior physical properties for MRI imaging. However, also imaging of other naturally abundant nuclei, especially of ^{19}F and ^{31}P, may bring specific benefits in number of cases.

Biocompatible polymers, especially those responding to external stimuli such as pH- or temperature change, bring crucial advantages as contrast agents enhancing possibilities of MRI. The presented contribution will summarize our contribution to polymer-based supramolecular ^{1}H, ^{19}F and ^{31}P MRI contrast agents.



Key Words: polymer, nanoparticle, magnetic resonance imaging

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References: *Magnetic Resonance Materials in Physics Biology and Medicine* **2019**, 32(1), *173-185*, *Drug Delivery and Translational Research* **2018**, 8(1), *73-82*, *Journal of Materials Chemistry B* **2018**, 6(17), *2584-2596*, *Biomacromolecules* **2018**, 19(8), *3515-3524*, *Chemistry of Materials* **2018**, 30(15), *4892-4896*.

NOVEL THERANOSTICS FOR CANCER THERAPY

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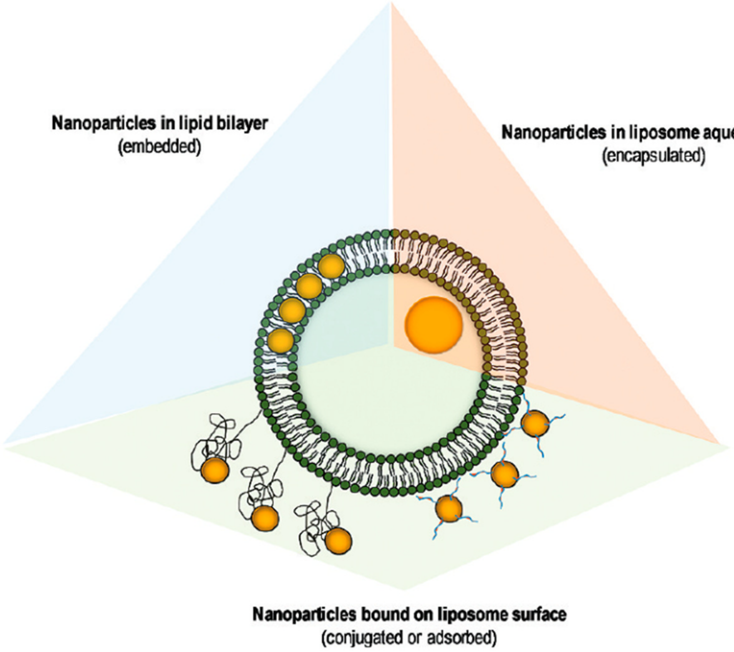
Liposomes are nano-sized, phospholipid-based delivery systems, that have been clinically approved to treat a wide range of diseased conditions. It has been mainly used to deliver a wide range of hydrophilic or hydrophobic therapeutics. Lipid nanoparticles have altered the pharmacokinetics of loaded molecules, and enhance their targeting capabilities. Liposomes also can be used to encapsulate imaging agents, such as magnetic nanoparticles and NIR fluorescent dyes for imaging and theranostic applications. This communication will give an overview of the latest nanoparticles that we have developed in our laboratory for imaging and therapeutic applications.



Key Words: drug delivery, imaging, liposomes, nanoparticles

Acknowledgements: This work was supported by Prostate Cancer UK (CDF-12-02), he Engineering and Physical Sciences Research Council (EPSRC)(EP/M008657/1), Rosetrees Trust and Queen's University Belfast.

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References: Acc Chem Res. **2011**, 44(10), 1094-104; Biomaterials **2011**, 32(11), 3085-93; ACS Nano.**2008**, 2 (3), 408-418;. *Small **2008**, 4(9), 1406-15.* Nanomedicine (Lond). **2007**, 2(1), 85-98.

VARIOUS (SUPRAMOLECULAR) STRUCTURES FOR DISEASE APPLICATIONS

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Our working group is interested in the design and fabrication of next generation delivery systems, diagnostics and therapeutics, which can have dimensions ranging from several nanometers to sub-micrometers. Besides well-established glycoarchitectures for their use as delivery and polymeric therapeutics, polymersomes, hollow capsules and their multicompartments have been established for mimicking cell functions. Most attentions are directed to integrate enzymes on/in polymersomes for fabricating biologically-active hybrid structures within/outside of cells. Moreover, one other goal of our study is to validate the storage and stability of those biologically-active hybrid materials under freeze-drying and frozen conditions. In this communication we will present different aspects for the fabrication of cell mimics.

Key Words: polymersomes, cell mimics, enzymes

Acknowledgements: This work was supported by CSC fellowships and German/Saxon government. Silvia Moreno has been supported by a grant from Fundación Alfonso Martín Escudero (Spain government).

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References: *Adv. Sci.* **2019**, DOI: 10.1002/advs.201801299*; RSC Adv.* **2018**, 8, 25436-25443*; J. Am. Chem. Soc.* **2018**, *140*, 16106-16114; *Angew. Chem. Int. Ed.* **2017**, *56*, 16233-16238; *Angew. Chem. Int. Ed.* **2012**, *51*, 4448-4451.

ENGINEERING THE SURFACE OF UPCONVERTING NANOPARTICLES FOR CANCER TREATMENT

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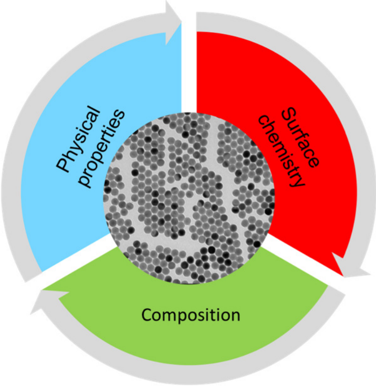
Recently, lanthanoid-doped upconverting nanoparticles able to absorb low-energy near-infrared (NIR) photons and emit visible or ultraviolet light are attracting a significant attention. Their unique optical properties enable luminescent detection without autofluorescence from biological samples that is crucial for bioimaging and diagnostics. Moreover, NIR irradiation allows delivering light deep into the tissue, which can be used for drug or gene delivery and NIR-induced photodynamic therapy (PDT) or photoactivation chemotherapy of tumours.[1] Despite the huge efforts devoted over the last 10 years to the upconversion nanoparticle synthesis and their surface engineering, preparation of nanoparticles suitable for biomedical applications still remains a big challenge. This communication is focused on synthesis of the upconversion nanoparticles with controllable morphology, size, distribution, crystallinity, and high upconversion efficiency, as well as on desirable surface modification for their application as carrier and photo-trigger for the NIR photo-activation of anticancer metallo-prodrugs.[2] Conveniently, the higher energy photons emitted by UCNPs upon NIR-light excitation can activate a light-sensitive prodrug attached to the UCNPs, leading to the release of an active anticancer agent.



Key Words: Upconversion, nanoparticles, surface coating, metallo-prodrug, photodynamic therapy, photoactivated chemotherapy

Acknowledgements: COST project CM1403: The European Upconversion Network is thanked for stimulating scientific discussion. The European Research Council is acknowledged for a Starting grant to S.B. The Holland Research School for Molecular Chemistry (HRSMC) is thanked for a Fellowship to M.M.N. The National Research Council (Italy, CNR) is thanked for an STM-Fellowship to M.M.N.

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References: [1] F. Zhang, Photon Upconversion Nanomaterials, in Nanostructure Science and Technology Series. Edited by Springer 2015. [2] M.S. Meijer, V. Saez Talens, M.F. Hilbers, R. E. Kieltyka, A. M. Brouwer, M.M. Natile S. Bonnet, manuscript submitted.

Session III

HOW TO PLAY WITH PHOSPHOROUS CHEMISTRY FOR THE RATIONAL DESIGN OF DENDRIMERS IN NANOMEDICINE

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Biocompatible phosphorus dendrimers represent a versatile platform in drug delivery (*e.g.,* drugs and gene transfection delivery), and as a drug, *per se* as well as in imaging applications.due to the possible high level of control over their architectural design, allowing for the tunable control of sizes and shapes (cores and interiors). In addition, easy access to tunable surface functionality leading either to neutral or charged (anionic, cationic) phosphorus dendrimers represents a strong advantage. Thus, biocompatible phosphorus dendrimers have been developed for several diverse important therapeutic applications, such as oncology, prevention of neurodegenerative diseases, inflammation, and HIV therapeutic domain, among others. Indeed phosphorus dendrimers have the strong advantage of being biocompatible (*e.g.,* low systemic toxicity, good PK/PD profile, etc.), are generally easy to prepare and importantly, can be prepared under GMP (good manufacturing practices) grade, which is mandatory for entering into clinical phases.

This presentation mainly centered on the design of phosphorus dendrimers will illustrate how the extraordinary versatility of phosphorus chemistry allows to propose the synthesis of a large variety of phosphorus dendrimers of diverse composition and functionalities Remarkably, beside the classic intravenous route, phosphorus dendrimers can also be administered *via* several other routes, such as orally or transdermal, and through inhalation and nasal routes. Selected examples of the applications of these dendrimers in nanomedicine will be briefly presented and discussed.

SELF-ASSEMBLING DENDRIMER NANOSYSTEMS FOR BIOMEDICAL APPLICATIONS

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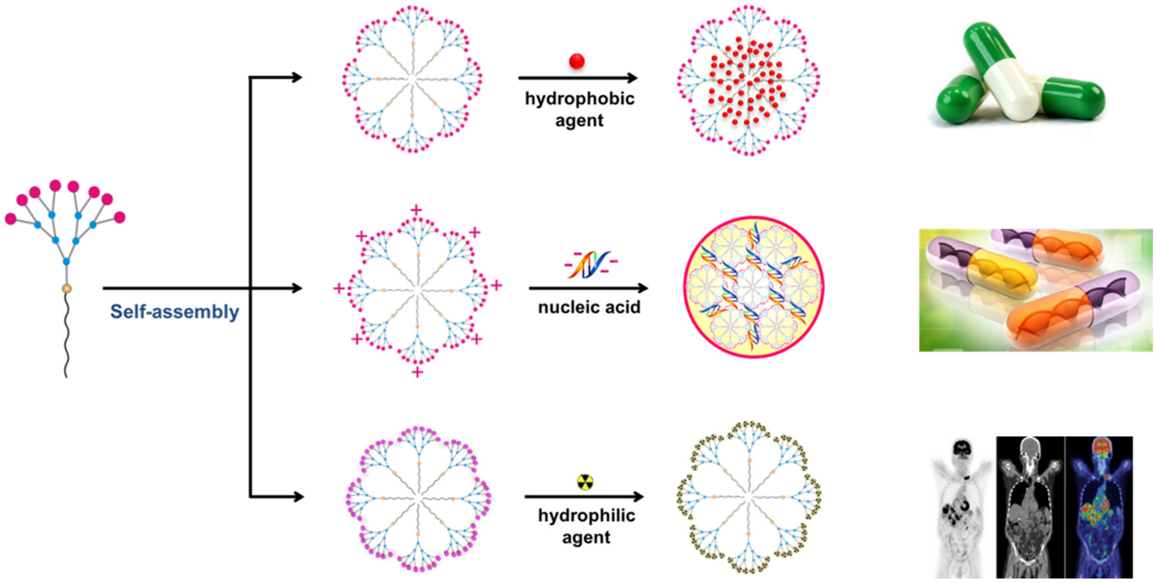
Nanotechnology based drug delivery is widely expected to bring new promise in cancer treatment thanks to the EPR effect of the tumor microenvironment and the possibility to integrate multiple therapeutic and diagnostic platforms into a "theranostic" approach for personalized medicine. Dendrimers are ideal nanomaterials for drug delivery by virtue of their uniquely well-defined structure and multivalent cooperativity confined within a nanosize per se. Recently, self-assembling supramolecular dendrimers have emerged as promising nanosystems for modular, adaptive and responsive delivery. We will present our effort in establishing self-assembling dendrimer nanosystems in this direction for the functional delivery of various chemo- and bio-therapeutics as well as imaging agents [1-3] in the view to offering new perspectives in nanotechnology based biomedical applications.



Key Words: dendrimer, nanovector, drug delivery, gene therapy, bioimaging

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References: [1] Wei et al, *Proc. Natl. Acad. Sci. U.S.A.* **2015**, *112*, 2978; Zhou et al, *Chem. Comm*. **2018**, *54*, 5956–5959. [2] Liu et al, *Angew. Chem. Int. Ed.,* **2014**, *53*, 11822; Liu et al, *Adv. Funct. Mater.* **2016**, *26*, 8594–8603; Dong et al, *J. Am. Chem. Soc.* **2018**, *140*,16264. [3] Garrigue et al, *Proc. Natl. Acad. Sci. U.S.A.* **2018**, *115*,11454.

BIOMATERIALS BASED ON CATIONIC CARBOSILANE DENDRITIC MOLECULES AS NANOCARRIERS FOR ANTI-CANCER NUCLEIC ACIDS

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The delivery of therapeutic nucleic acids (NAs) into cells to modulate the expression of target genes is a promising tool of innovative medicine, in particular, for cancer treatment. However, the features of this technique require the use of carriers to deliver NAs into a cell. Cationic dendritic molecules – dendrimers and dendrons – are good candidates for this purpose [1].

In this work. several libraries of carbosilane dendrimers and dendrons of generations 1-3 bearing various functional moieties on the periphery and in the focal point (in the case of dendrons) were prepared (fig. 1) [2,3]. The dendrons bearing pyrene moieties in focal point were anchored on the surface of functionalized carbon nanotubes (CNTs) [4].

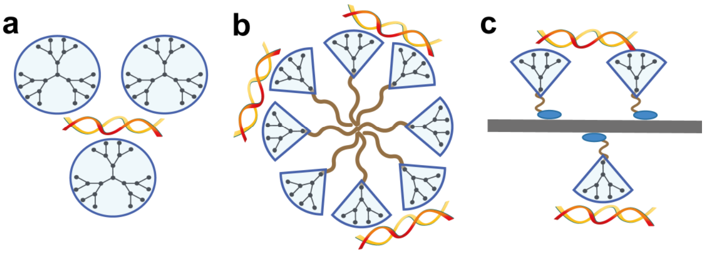

Fig. 1. siRNA complexes with dendrimers (a), dendritic micelles (b) and dendronized carbon nanotubes (c).

The dendrimers behave in water medium as individual molecules, whereas dendrons bearing hydrophobic moieties tend to aggregate to form supramolecular associates. The dendritic species bind anti-cancer NAs efficiently to form soft biomaterials – dendriplexes. The dendronization of functionalized CNTs followed by the NA complexation leads to the multifunctional CNT derivatives. In summary, the structure and geometry of dendritic precursors define the topology and properties of their associates and, in turn, of the corresponding dendriplexes. These constructions can be used for the targeted TNA delivery.

Key Words: dendrons, supramolecular associates, siRNA.

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Correspondence: eka@niboch.nsc.ru

References: *Pharmaceutics* 10 (**2018**) 126, *Pharmaceutics* 11 (**2019**) 25, *Org. Biomol. Chem.* 15 (**2017**) 7352-7364, *ChemNanoMat* 4 (**2018**) 220-230.

POLYUREA DENDRIMERS: LIFE IN A BOX

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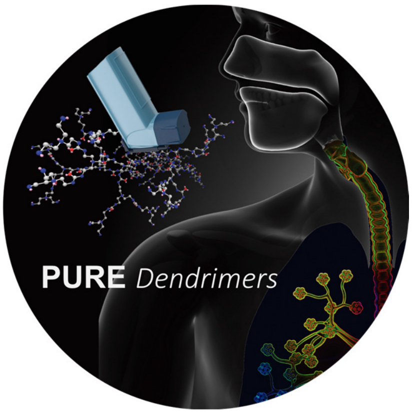
The reaction of amines with carbon dioxide, usually viewed as an undesirable side reaction, was the basis for development of the isocyanate-free one-pot divergent-iterative synthesis of polyurea (PURE) dendrimers. These water-soluble dendrimers are biocompatible, show a pH-dependent intrinsic blue fluorescence, and are fully biodegradable. Since its discovery in 2012, we have demonstrated their potential both in gene and drug delivery.

In the last years, using a supercritical-fluid-assisted spray drying technology (SASD), nano-in-micro dry powder formulations based in polyurea dendrimers have been developed for inhalation chemotherapy. These formulations contain drug loaded polyurea dendrimers and allow an efficient and fast local drug delivery.



Key Words: polyurea dendrimers, fluorescence, drug delivery, inhalation chemotherapy

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References: *ChemistryOpen* **2018**, 7, 772; *ChemistrySelect* **2016**, 1, 6818; *Part. Part. Syst. Charact*. **2016**, 33, 851; *Macromol. Biosci.* **2015**, 15, 1045; *RSC Adv.* **2014**, 4, 54872; *Angew. Chem. Int. Ed.* **2012**, 51(21), 5162.

UPSCALING OF PAMAM-DENDRIMER SYNTHESIS

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The translation of nanodrugs from bench to bedside is a bottleneck, which basically reflects a huge gap between research in academia and industry. The recent (2012-2017) European large-scale project Cosmophos-nano dealt with diagnosis and treatment of atherosclerosis using nanomedicine platforms. One of these platforms were based on dendrimers and the talk will concentrate on how this platform was developed and the problems associated with translation of a nanomaterial like dendrimers from laboratory to bedside.

Key Words: drug delivery, imaging, dendrimer, nanoparticles, theranostica

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References: *http://www.cosmophos-nano.eu; WO 2017/191219 A1 (**2017**; Can. J. Chem.* 95, **2017**, 954 – 964; *J. Cont. Rel. 246, **2017**, 88 – 97; J. Phys. Chem. B 120, **2016**, 9576 – 9580.*

G0-G3 RUTHENIUM(II)-BASED PAMAM METALLODENDRIMERS: ANTICANCER ACTIVITY AND HEMOTOXICITY

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The Molecular Materials Research Group at CQM, in cooperation with other groups all over the world, is developing work in the field of dendrimers for different applications (e.g. electronics and biomedical applications) for over 20 years, exploring diverse dendrimer platforms and synthetical approaches[1]. Probably less known, part of our work aims at exploring the advantages of combining metal complexes with low generation dendrimers for anticancer applications, playing with the metal properties, structural diversity and synergetic effects[2]. In the last decades, organometallic Ru(II) complexes have been explored as anticancer drugs, being considered viable candidates to be used against tumours that are resistant to the widely used *cisplatin* drug[3]. The incorporation of these organometallic complexes in dendritic scaffolds (producing metallodendrimers) can result, for instance, in improved anticancer activity, solubility and PK/PD behaviour[4]. In this communication, we will present the preparation and characterization of four generations of ruthenium(II)-based PAMAM metallodendrimers – G0 to G3 - $[CNRuCp(PPh_3)_2]x[CF_3SO_3]x$ (where x = 4, 8, 16 and 32 for each generation, respectively), and their cytotoxicity and hemolytic activity in healthy human blood. The *in vitro* anticancer activities of the prepared metallodendrimers were studied using A2780, A2780cisR and MCF-7 cancer cells and against human primary fibroblasts (BJ cell line). Our most recent results show that the prepared metallodendrimers are remarkably cytotoxic, at a nanomolar range, for all the tumour cell lines (including the *cisplatin*-resistant human ovarian carcinoma cell line A2780cisR), non-toxic for the non-tumour human cell line, and do not induce hemolysis in blood, demonstrating the benefits of the use of metal complexes combined with dendrimers.

Key Words: dendrimers, Ruthenium, nanomedicine, anticancer drugs, hemotoxicity

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References: **[1]** see for example: *Molecular Pharmaceutics* **2010**, 7, 763-774; *Journal of Controlled Release* **2010**, 144, 55-64; *Biomacromolecules* **2011**, 12, 472-481; *Current Medicinal Chemistry* **2012**, 19, 4969-4975; *Organometallics* **2013**, 32, 406-414; *Biomacromolecules* **2014**, 15, 492–499; *Colloids and Surfaces B: Biointerfaces* **2015**, 125, 82-89; *Journal of Biomedical Nanotechnology* **2015**, 11, 1370-1384; *RSC Advances* **2016**, 6, 97116-97128; *Current Pharmaceutical Design* **2017**, 23, 3076-3083; *Chemical Society Reviews* **2018**, 47, 514-532; *Science China Materials* **2018**, 61, 1367-1396*; Nanoscale* **2019**, 11, 9679-9690. **[2]** See for example: *Organometallics* **2004**, 23, 4271-4276; *Comptes Rendus Chimie* **2005**, 8, 1789-1797; *European Journal of Inorganic Chemistry* **2006**, 47-50; *European Journal of Inorganic Chemistry* **2010**, 1729-1735; *New Journal of Chemistry* **2011**, 35, 1938-1943; *Molecules* **2018**, 23, 1471. **[3]** *Chemical Society Reviews* **2017**, 46, 5771-5804; **[4]** *Chemical Society Reviews* **2018**, 47, 514-532

Posters

STUDY ON POLY(PROPYLENEIMINE) METALLODENDRIMERS MODIFIED WITH 4-BROMO-1,8-NAPHTHALIMIDE UNITS AS ANTIMICROBIAL AND ANTICANCER AGENTS AND THEIR EPR CHARACTERIZATION

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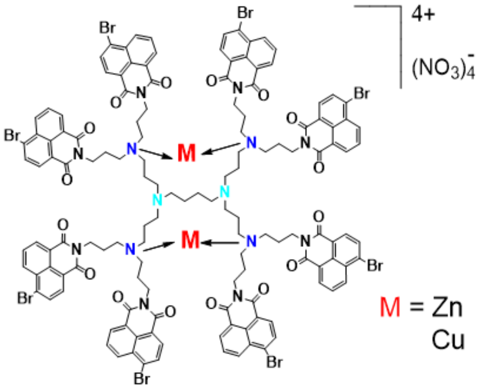
The synthesis, EPR characterisation and biological evaluation of two new metallodendrimers, i.e. a poly(propyleneimine) dendrimer functionalized at the external surface with 4-bromo-1,8-naphthalimide and conjugated with Cu(II) and Zn(II), was performed with the aim to evaluate their antimicrobial and anticancer activity. The antimicrobial activity was investigated in meat-peptone broth against bacteria B. subtilis and P. aeruginosa, and the yeast C. lipolytica. The results showed that the compounds inhibited effectively the tested pathogens even after their deposition on a textile fabric.



Modified PPI Metallodendrimer

Anticancer activity was investigated against three human permanent cell lines from non-small cell lung cancer (A549), triple negative breast cancer (MDA-MB-231) and carcinoma of the uterine cervix (HeLa) in the c = 0.01– 30 µM concentration range. The results suggest that these compounds are promising for application in biomedicine as anticancer drugs in the design of new effective preparations. The antimicrobial and anticancer activity may be related to the peculiar structural and dynamical properties revealed for the Cu(II) complexes, by a computer aided analysis of the electron paramagnetic resonance (EPR) spectra. This analysis indicated the formation, at the lowest Cu(II) concentrations, of a flexible rhombic Cu-N4 coordination with the internal amino groups of the dendrimer, which transformed into a Cu2-N4 coordination already at 0.25 equiv. of Cu(II).

Acknowledgements: This work was supported by project H09/03-2016 from the National Science Fund, Ministry of Education and Science of Bulgaria

SYNTHESIS OF NOVEL BOLA-TYPE AMPHIPHILIC PEPTIDE DENDRIMERS AND THEIR COMPLEXES WITH ANTICANCER DRUGS

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Treatment of major diseases of the human kind including cancer represents major therapeutic challenge in contemporary medicine. Since the discovery in 2006 the Nobel prize-awarded mechanism of RNA interference (RNAi), small interfering RNA (siRNA) has become a promising drug candidate for the treatment of variable diseases. However, to achieve therapeutic success effective and safe carriers that can cross biological barriers and reach the target site to achieve selective delivery of siRNA or drugs are required.[1] Therefore, development of novel delivery tools is one of the necessary steps of contemporary nanomedicine.

Dimeric bola-type molecules where two bulky fragments are connected with flexible spacer are an example of potential drug and/or siRNA carriers. It was discovered that such unique structure improves cargo/carrier complex stability and transfection efficiency.[2]

We synthesized "bola" dimers containing amphiphilic heads constructed from branched peptides connected by chemically stable or biodegradable spacer. The effectiveness of synthetic methods in solution or on solid support, and coupling reactions (active ester method vs. the Schotten-Baumann method) was compared. Structure of the designed dimers was optimized basing on our previous studies on amphiphilic peptide dendrons that delivered siRNA selectively to glioblastoma cells leaving intact neurons and astrocytes.[3]

In conclusion, we have developed a methodology for the synthesis of amphiphilic cationic dendrons based on poly-lysine or poly-ornithine scaffolds, functionalized with various organic residues to obtain high affinity for cell membranes and the ability to form supramolecular complexes with drugs or siRNA molecules. Dendrons were combined with flexible linkers to create dimeric amphiphilic "bola" structures. After purification and characterization, we performed HPLC complexation experiments of bola-dimers with known anticancer drugs.

Key Words: bola-dimers, drug delivery, imaging, coordination polymer, nanoparticles

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References: 1: *Journal of Pharmaceutical Sciences* **2015**, 10, 1; 2: *ACS Central Science* **2015**, 1, 303; *SMALL* **2016**, 12(27), *Advanced Functional Materials* **2016**, 26(47), 8594-8603; 3676; 3: *PLoS ONE* **2016**, 11, 11.