COST ACTION CA 17140
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CANCER NANOMEDICINE - FROM THE BENCH TO THE BEDSIDE

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Cancer Nanomedicine – from the Bench to the Bedside

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BOOK OF ABSTRACTS

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Nanoactuators for therapy and diagnosis

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In the last decades, inorganic nanoparticles have been steadily gaining more attention from scientists from a wide variety of fields such as material science, engineering, physics, or chemistry. The very different properties compared to that of the respective bulk, and thus intriguing characteristics of materials in the nanometer scale, have driven nanoscience to be the centre of many basic and applied research topics. Moreover, a wide variety of recently developed methodologies for their surface functionalization provide these materials with very specific properties such as drug delivery and circulating cancer biomarkers detection. In this talk we describe the synthesis and functionalization of magnetic and gold nanoparticles as therapeutic and diagnosis tools against cancer.

Gold nanoprisms (NPRs) have been functionalized with PEG, glucose, cell penetrating peptides, antibodies and/or fluorescent dyes, aiming to enhance NPRs stability, cellular uptake, and imaging capabilities, respectively. Cellular uptake and impact were assayed by a multiparametric investigation on the impact of surface modified NPRs on mice and human primary and transform cell lines. Under NIR illumination, these nanoprobes can cause apoptosis. Moreover, these nanoparticles have also been used for optoacoustic imaging, as well as for tumoral marker detection using a novel type of thermal ELISA and LFIA nanobiosensor using a thermosensitive support.

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Unlocking the potential of antibody-drug conjugates in oncology: a focus on HER2 signaling pathway

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Among the variety of scaffolds developed to improve drug delivery to tumors, Antibody Drug Conjugates (ADCs) present unique features taken both from nanomedicine such as cargoing payloads to cancer cells while sparing healthy tissues; and from biologics because the vehicle is a monoclonal antibody. The concept of developing ADCs is decade old, but it is only recently that those novel conjugates have been widely used at bedside, with meaningful efficacy in oncology. In particular, a new generation of linkers have enabled much more stable scaffolds to be designed, *i.e.*, with limited early release of the payload in the blood flow, but with a highly specific release in target cancer cells. Today, several ADCs now a mainstay in some settings while dozens of other candidates are currently entering clinical development stages. Among the variety of target antigen, Her2 is a protein frequently overexpressed in epithelial cancers, especially in some subtypes of breast cancer. Trastuzumab-emtansine has been the first-in-class ADC approved in her2+ breast cancer and showing clinical benefit, despite limitations due to first-generation linker and occurrence of acquired resistance. Next generation ADCs targeting Her2+ such as fam-trastuzumab deruxtecan offers optimized drug-antibody-ratio, smart cleavable linker plus a payload less likely to be affected by acquired resistance. This presentation will present the expectations with ADCs in terms of pharmacokinetics and biodistribution, the main specifications and requirements to develop a successful ADC, from determining the right target, choosing the payload, the vehicle and the linker, and will finally make a focus on targeting Her2 with ADCs in breast cancer.

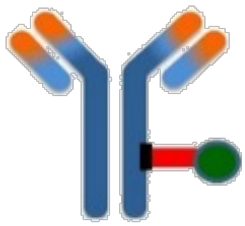

Figure 1. Antibody-drug conjugate (ADC).

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A phthalocyanine-cored dendrimer for photodynamic therapy

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Photodynamic Therapy (PDT) is the treatment of diseases by using light as a therapeutic agent and is a special case of radiotherapy. Classical photodynamic therapy has the limitation that the penetration depth of UV-Visible light is very small, so only the upper layer of the skin is accessible. This can be changed by going to the near infrared region (NIR, 650 -1350 nm), where human tissue is relatively transparent. However, in this case, a molecular antenna needs to present in the tissue that can absorb some of the light and transfer the energy to the surroundings. A molecule with these properties is a photosensitizer and the energy it absorbs can end up as heat in the local environment or the energy transferred to other molecules in the tissue such as oxygen creating singlet oxygen ($^1O_2$). Singlet oxygen is a very reactive form of oxygen that reacts with other molecules locally creating reactive oxygen species (ROS) organic molecules. Either of the processes, local heating or formation of ROS can eventually damage cells causing apoptosis.

Photodynamic therapy (PDT) is very interesting for the treatment of certain types of cancer like skin-, head & neck- and brain-cancer. The advantage is that spatial control of the cell killing is possible by focusing the light source on the cancer tissue or by using an optical fiber for reaching a tumor sitting deeper in the body via the blood vessels. Before treatment, the photosensitizer is administered either by injection or by topical application (as in the case of skin cancer), but increased photosensitivity is a common side effect, where the patient has to avoid exposure to sunlight until the photosensitizer has been cleared from the body. The majority of approved photosensitizers are polycyclic aromatic compounds like porphyrins and phthalocyanines that are highly lipophilic. Solubility in water is possible by conjugation to water-soluble carriers, which can be proteins, polymers, liposomes or nanoparticles. In the present work we repot the synthesis and initial PDT-properties of a polyester-amine dendrimer synthesized by a protective group free approach based on the previous observations by Tomalia and coworkers on nanoscale induced stoichiometry (NCIS)[1] having a Silicon Phthalocyanine core. The compounds show good water solubility as well as PDT-properties.

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Evaluation of carbosilane and bis-MPA based dendrimers as anticancer agents

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Dendrimers are highly branched monodisperse macromolecules that have shown to be very promising candidates in biomedical applications such as drug delivery and gene carriers. Polyamidoamine (PAMAM) dendrimers were the first commercially available family and therefore have dominated the biomedical research field. However, their toxicity towards several cell lines compromises their biocompatibility and encourages the search for new alternatives.
Carbosilane dendrimers are interesting due to their hydrophobic nature that improves their interaction with biological membranes. The inclusion of Schiff-base ligands in the periphery allows the coordination of metal complexes through "chelate" chemical bonds that provides a high level of stability to the final systems. The coordination of metal complexes based on ruthenium (II) and copper (II) has resulted in a new generation of metallodendrimers with not only promising per se anticancer activity but also with the ability to act as non-viral vectors of siRNA[1,2,3]. Additionally, dendrimers based on 2,2-bis(methylol)propionic acid (bis-MPA) are in the spotlight as a consequence of their synthetic versatility, high biocompatibility and biodegradability powered by the internal ester bonds. The inclusion of positive charges in the periphery is inspired by the generation of promising non-viral vectors of genetic material due to its nanoscale size as well as high load capacity[4]. Currently, efforts are dedicated into fine-tuning important characteristics such as the topology and the hydrolytical stability of these systems to transfect glioblastoma cells and neurons. The work in both groups regarding carbosilane dendrimers, with Prof. Javier de la Mata, and bis-MPA dendritic polymers with Prof. Michael Malkoch, has been possible due to an extensive international collaboration between groups belonging to COST Action.

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Triggerable nanomedicines for targeted cancer therapy

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Most cancer chemotherapeutics lack tissue specificity, resulting in many undesirable side effects. Selective drug delivery to tumour tissues could ultimately increase local drug concentrations at the tumour without the need to escalate the administered doses in patients. A wide range of drug delivery systems has been developed to alter the pharmacokinetics of drug molecules and enhance their tumour targeting. Furthermore, several approaches have been explored to increase drug bioavailability at the site of action, utilising either the unique characteristics of the tumour microenvironment, such as overexpressed enzymes, acidic pH, and hypoxia. Furthermore, external triggers, such as heat, ultrasound, and light, have been used to control drug release better. Our group focuses on developing smart nanocarriers for targeted delivery and cancer therapy. In the present work, we will discuss a few examples of our targeted cancer nanomedicines against prostate cancer using doxorubicin-PSA activatable prodrug and photothermal therapy.

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Ruthenium and copper carbosilane metallodendrimers as anticancer agents

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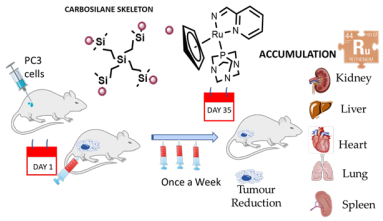
Cancer is a set of diseases that, according to recent studies, cause around 10 million deaths annually worldwide, despite the enormous efforts of thousands of researchers who focus their studies on this area of interest from multidisciplinary approaches and with a huge economic inversion. Our research group is carrying out one of these approaches through the development of metallodendrimers, based on metals such as ruthenium or copper fundamentally. They have shown high antitumor activity in the cell lines in which they have been tested, particularly against prostate and breast cancer lines. With the design of these metallodendrimers we seek to take advantage of the properties offered by these novel systems to improve the activity of drugs developed to date, particularly trying to find cooperative and synergistic effects between the nanoscopic size of dendritic systems and the therapeutic properties of metal complexes[1-3], particularly accepted since the discovery of cisplatin by Barnett Rosenberg. In this work, the most relevant results of our group in this field will be shown, which will reveal a multidisciplinary work, where the collaboration with other COST action groups has been decisive.



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Nanomechanical Phenotype – novel, fast and clinically validated physical biomarker for characterisation of cellular and extracellular structures

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Nanomechanical phenotype is measured by the ARTIDIS platform which harnesses the power of nanotechnology and advanced analytics. It consists of the Atomic Force Microscope based device for nanomechanical measurements and the digital data platform ARTIDISNET. Both enable precise measurements of materials, biomaterials, cell and extracellular matrix stiffness up to molecular level, which can be applied to any material or living tissue providing a broad range of R&D and clinical applications.

Figure 1. ARTIDIS Platform Applications

In oncology, ARTIDIS focuses on breast, lung and pancreatic cancer. Mechanical properties of cancer cells and their microenvironment play a critical role in cancer invasion, progression and immune cell infiltration. ARTIDIS can measure the alterations on the (sub-)cellular level and identify cancerous tissue materials based on the cellular stiffness. The measurement provides a nanomechanical phenotype that is based on more than 5 million nano-palpations per tissue type, 10'000 measurements per patient`s specimen. Nanomechanical information can contribute in further prognostic profiling of malignant lesions and indirectly drive increased choice of treatment plans. Profile changes during treatment are believed to be early indicators of treatment resistance and are envisioned as future tools in personalizing neoadjuvant therapy for breast cancer.

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Thiolated liposomes as mucoadhesive oral delivery system

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The development of polymer coated liposomes as an oral delivery system is projected to improve the transport of degradation sensitive and poorly absorbed drugs through the intestinal membrane in the gastrointestinal tract. To achieve this objective, we have designed liposomes covalently conjugated to thiolated polymers, termed thiomers. Thiomers are well-known for their mucoadhesive as well as permeation enhancing and efflux-pump inhibitory properties [1]. Thiolated liposomes were synthesized either by thin lipid film rehydration or by a single step microfluidics assisted assembling process. The thiolated liposomes were characterised by DLS, zeta potential, TEM and freeze-fracture EM, among other techniques. Efficient coupling of thiomers to the liposomal surface was observed as an increase in the particle size of approximately 150 nm and a positive zeta potential. Particle stability and release behaviour were studied in simulated digestion fluids. A co-culture system (Caco-2:HT29-MTX) that integrates mucus secreting and enterocyte-like cell types was used as a model of the human intestinal epithelium to determine adsorption, mucus penetration, release and transport properties of thiolated SeNP containing liposomes. We found that thiolated liposomes tightly adhered to the mucus layer without penetrating the enterocytes. This finding was consistent with *ex vivo* adsorption studies using freshly excised porcine small intestinal tissues. To assess the potential of thiolated liposomes for oral peptide delivery *in vivo*, salmon calcitonin (sCT) loaded liposomes were orally administered to rats, and the blood calcium level was monitored over 24 hours showing a remarkable reduction of the blood calcium level when compared to free sCT administered orally in the same amount. Thus, our data indicate that thiolated liposomes possess a high potential for oral delivery of different substances.

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Optimization of tyrosine kinase inhibitor-loaded gold nanoparticles for triggered antileukemic drug release and cytotoxic evaluation

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Clinical management of leukemic patients greatly improved due to the identification of possible key molecular targets linked to the development and progression of the disease as is the most frequent FLT3 mutation in AML or the BCR-ABL mutation in ALL. Various tyrosine kinase inhibitors that can function for both specific targeting and necrosis promotion through the patients' own complement-dependent cytotoxicity system were proved successful, and novel and improved formulations are under continuous development. As such, nano-based delivery compounds can offer multiple advantages over conventional drug delivery systems by enhancing the solubility, biocompatibility, bioavailability and the targetability of the drugs. Since loading and delivery of the encapsulated drugs are strongly affected by the physicochemical characteristics of the nanocompound, the optimization of the size, shape, surface charge, and chemical formulation is a prerequisite.

In this study we investigated the effect of such parameters for the efficient loading of Midostaurin and Dasatinib tyrosine kinase inhibitors onto polymer-coated gold nanoparticles of various morphologies (spherical, ellipsoidal, hollow, star-like). Stimuli-responsive polymers (Pluronic, poly-2 dimethylamino-ethyl methacrylate and poly-vinyl-pyrrolidone) were used for the encapsulation of the drugs, chemical stabilization and biocompatibilization. The drug nanoconjugates showed a burst release behavior in the presence of glutathione thiol-reducing agent and under the variation of pH. The cytotoxic evaluation on MV4-11 acute myeloid leukemia, SUP-B15 acute lymphoblastic leukemia and CCRF-SB acute lymphoblastic leukemia cells showed increased effect of the drug-nanocomplexes as compared to the free drug by inhibiting cell proliferation in a dose-dependent manner and excellent biocompatibility for polymer-coated nanoparticles.

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Surface modifying PLGA nanoparticles for GBM specific targeting

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Nanoparticles (NPs) are becoming major players in the novel research to treat Glioblastoma Multiforme (GBM). This is because they offer the possibility to deliver therapeutics to the brain which normally would not enter; however, even after crossing the blood-brain barrier, the therapeutic success of NPs against GBM is directly correlated to the ability to selectively accumulate in the cancerous cells without causing toxic effects to healthy cells nearby. In this study, NPs based on the FDA approved polymer poly(lactic-co-glycolic) acid were surface modified with 4 ligands that have receptors that could potentially be upregulated in GBM cells: Adeno associated coat peptide AAVF[1], the glycopeptide g7[2], and two monoclonal antibodies against Cell Surface Vimentin (M08 and M08J)[3]. NP formulations were optimized based on several formulative parameters and a full chemico-physical and morphological characterization was performed. Then, the uptake and toxicity of the NPs at different concentrations and incubation times were analysed *in vitro* on GBM cells. To further demonstrate the GBM specificity, co-culture assays with GBM (C6) and healthy astrocytes (DITNC1) were performed. Specifically, co-culture assays showed not only a significantly higher uptake by GBM cells over healthy astrocytes for NPs conjugated with M08, but also a reduction of GBM cell growth with increased growth of healthy astrocytes. Finally, MO8 conjugated NPs were tested for their ability to selectively transport the anti-cancer drug Paclitaxel with improved effects. These results demonstrate the ability of optimized NPs to enhance specific targeting not only to the brain but specifically to the GBM cells which will help increase the pharmaceutical effectiveness while limiting off-target effects.

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Synthesis and in vitro proof-of-concept studies on nanoparticles (iron oxide/gold) targeting PSMA (Prostate Specific Membrane Antigen) and GRP (Gastrin Releasing Peptide) receptors for PET/MR and SPECT imaging of prostate cancer

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Prostate cancer (PCa) is the most common malignancy worldwide in men. The purpose of the study was to synthesize, label with PET (^{68}Ga) or SPECT (^{99m}Tc) radionuclides and evaluate in cancer models several different types of nanoparticles (NPs) i.e., magnetic iron oxide (mNPs), gold (AuNPs), as potential probes for PET/MR or SPECT imaging of PCa. Before labelling, the NPs were functionalized with the pharmacophore Glu-Urea-Lys and the Bombesin (BN) peptide, which act as substrates for PSMA and the GRPR, both highly expressed on the surface of PCa cells.[1] Two pharmacophores targeting the PSMA (**1**) and GRPR (**2**) were coupled to mNPs carrying -SH (mNP-S1/2) or -NH_2 (mNP-N1/2) groups. The functionalized nanoparticles were characterized for their size, zeta potential, structure, and efficiency of functionalization using DLS, FT-IR and RP-HPLC. A direct labelling procedure of mNP was followed for ^{68}Ga and ^{99m}Tc, which were further evaluated *in vitro* with RBC for their toxicity and with cancer cell lines (PC-3 and LNCaP) for their specificity, internalization and time depended binding.[2,3] The synthesis and characterization of mNPs was accomplished by the group of Prof. Efthimiadou, while the present work was based on previous recent results from our collaboration with Dr. Vranjes-Djuric (Republic of Serbia). A slightly different approach was followed for the AuNPs where the PSMA pharmacophore and the universal DOTA chelator were both modified with an -SH (Glu-Urea-Lys-Cys and DOTA -Cys, respectively) in order to be linked to the AuNP surface. The synthesis of the functionalized AuNPs is currently under way within the framework of a cost group collaboration with Dr. Bilewicz (Poland). Regarding radiolabelling efficiency, the mNP-N proved superior for ^{68}Ga, while the mNP-S for ^{99m}Tc. *In vitro* assays in cells expressing PSMA (LNCaP), and GRPR (PC-3), showed specific time-dependent binding (< 40 min to plateau), high avidity (*e.g.*, PC-3: K_d = 28.27 nM, LNCaP: K_d = 11.49 nM for ^{68}Ga-mNP-N1/2) and high internalization rates for both cell lines. Toxicity studies in these cells showed low toxicity, and minimal haemolysis of red blood cells.

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Day 2, October 26, 2022

Iron oxide nanoflowers as excellent heating agents for magnetic hyperthermia cancer therapy

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The optimisation of IONP properties for magnetically induced hyperthermia (MIH) for cancer treatment is still a very active research area. The heating ability is considered a critical factor in MIH and is usually prioritised when developing synthesis of IONPs destined for this application. However, there is a bottle neck for wide acceptance of MIH therapy due to the quality limitations of commercial iron oxide nanoparticles (IONPs), which display sub-optimal heating efficiency and are associated with high preparation costs. We recently overcame these limitations with our novel synthetic procedure for iron oxide nanoflowers (IONFs) exhibiting heating rates that are 3 times higher than those of any commercially available nanoparticle alternative[1]. The experimental scheme is shown in the Figure 1(a). Polyol process yielded biocompatible single core nanoparticles and nanoflowers (Figure 1(b)). The effect of parameters such as the precursor concentration, polyol molecular weight as well as reaction time was studied, aiming to isolate NPs with the highest possible heating efficiency. Adding polyacrylic acid (PAA) facilitated the formation of excellent nanoheating agents IONFs within 30 min. The progressive increase of the size of the IONFs through applying seeded growth approach resulted in outstanding enhancement of their heating ability with intrinsic loss parameter (ILP) up to 8.49 nH m^2 kg_{Fe}^{-1}. Apart from their exceptional heating efficiency, our IONFs feature exceptional colloidal stability (more than 3 months) and can be synthesised reproducibly via simple protocols in short time, hence, they have good potential for production at large-scale at significantly reduced costs.

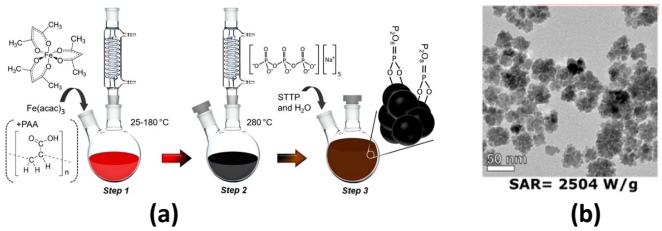

Figure 1. a) Schematic of simple one-pot thermal decomposition of $Fe(acac)_3$ polyol synthesis yielding single core IONPs (without PAA) and IONFs (with PAA) in Step 1 and Step 2. (b) TEM images of the IONFs synthesized with PAA via seeded growth: 2nd feeding step.

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Cancer therapy using porous silicon nanocarriers with stimulus-cleavable linkers

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Porous silicon nanoparticles (pSiNPs) have been widely utilized as drug carriers due to their excellent biocompatibility, large surface area and versatile surface chemistry. However, the dispersion in pore size and biodegradability of pSiNPs arguably have hindered the application of pSiNPs for controlled drug release. Here we describe a step-changing solution to this problem involving the design, synthesis and application of three different linker-drug conjugates comprising anticancer drug doxorubicin (DOX) and different stimulus-cleavable linkers (SCLs) including the photo-cleavable linker (*ortho*-nitrobenzyl), pH-cleavable linker (hydrazone) and enzyme-cleavable linker (β-glucuronide). These SCL-DOX conjugates are covalently attached to the surface of pSiNP *via* copper (I)-catalyzed alkyne-azide cycloaddition (CuAAC, *i.e.* click reaction) to afford pSiNP-SCL-DOXs. The mass loading of the covalent conjugation approach for pSiNP-SCL-DOX reaches over 250 μg of DOX per mg of pSiNPs, which is notably twice the mass loading achieved by non-covalent loading. Moreover, the covalent conjugation between SCL-DOX and pSiNPs endows the pSiNPs with excellent stability and highly controlled release behavior. When tested in both *in vitro* and *in vivo* tumor models, the pSiNP-SCL-DOXs induces excellent tumor growth inhibition.

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Biosensors for cancer diagnostics and targeted drug delivery based on DNA aptamers

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Nucleic acid aptamers are single stranded DNA or RNA that in a solution form binding site specific for certain molecules, cells, viruses or bacteria. The aptamers are characterized by high specificity, which is comparable and even higher than those of antibodies. In contrast with antibodies the aptamers are more stable. They are developed *in vitro* by combinatorial chemistry using SELEX (Systematic Evolution of Ligands by EXponential enrichment). Using the CELL SELEX, it has been possible to develop aptamers specific to cancer markers at the surface of the cells. The aptamers can be chemically modified by various ligands which increase their stability and allowing their immobilization at various surfaces, where serve as receptors in biosensors. This contribution represents overview of recent achievements in application of aptamers in development of biosensors for cancer diagnostics[1]. DNA aptamers can be also used as receptors for modification of the nanocarriers for targeted drug delivery. The examples of applications of nanostructures for targeted drug delivery will be presented.

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Synthetic glycoconjugates - galectin ligands with a therapeutic potential

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Galectins belong to the family of human lectins. By binding terminal galactose units of cell surface glycans, they moderate biological and pathological processes such as cell signaling, cell adhesion, apoptosis, fibrosis, cancerogenesis, and metabolic disorders. The binding of monovalent glycans to galectins is usually relatively weak. Therefore, the presentation of carbohydrate ligands on multivalent scaffolds is exploited to increase and/or steer the affinity of glycoconjugates to galectins[1]. A library of glycoclusters and glycodendrimers with various structural presentations of the functionalized *N*-acetyllactosamine ligand was prepared to evaluate how the mode of presentation affects the affinity and selectivity to the two most abundant galectins, galectin-1 (Gal-1) and galectin-3 (Gal-3)[2]. In addition, the effect of a one- to two-unit carbohydrate spacer on the affinity of glycoconjugates was determined. A new design of the biolayer interferometry (BLI) method with specific AVI-tagged constructs was used to determine the affinity to galectins[3], and compared with the gold-standard method of isothermal titration calorimetry (ITC). This study reveals new routes to high-affinity glycoconjugate inhibitors of galectins of interest for biomedical research.

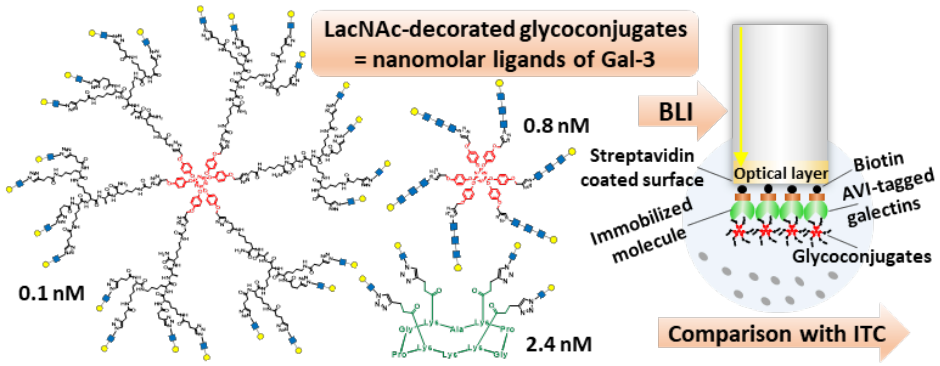

Figure 1. Synthetic glycoconjugates with high affinity to Gal-3 as determined by ITC and BLI

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Self-assembling ionizable dendrimers for biomedical applications

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Dendrimers are of particular interest for biomedical applications thanks to their uniquely controlled structure and multivalent cooperativity. We have recently developed modular supramolecular dendrimers for drug delivery on the basis of self-assembling of small amphiphilic dendrimers[1]. Here, we will report our design, synthesis and evaluation of new ionizable amphiphilic dendrimers for drug and nucleic acid delivery with better safety profile. These amphiphilic dendrimers harbour a hydrophobic alkyl chain and a hydrophilic poly(amidoamine) dendrons with ionizable tertiary amine terminals[2]. They readily self-assembled into nanomicelles with large hydrophobic interior for drug encapsulation while having positively charged surface at physiological pH to interact, protect and transport the negatively charged nucleic acids. Importantly, these dendrimers are less toxic and more biocompatible when compared with the amine-terminating dendrimers. They constitute therefore safe and promising nanovectors for drug delivery.

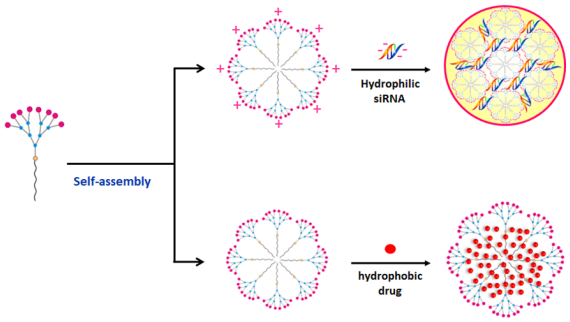

Figure 1. Cartoon illustration of supramolecular dendrimers for drug and nucleic acid delivery.

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Beyond nucleic acids as vaccines: curing ocular diseases with nucleic acids?

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Delivery of – especially biological – drugs into the various compartments of the eye remains an enormous challenge. In this talk I will highlight recent work of our group in which we evaluate the potential of pulsed laser light to cross biological barriers in the eye. The first part of my lecture will introduce photoporation of cell membranes for the delivery of macromolecular drugs, especially nucleic acids. A special emphasis will be on recent findings which show the capacity of photoporation for drug delivery into the corneal epithelium. In the second part I will show how light allows to destroy biological aggregates in the vitreous of the eye. Finally, I will introduce photoporation of the inner limiting membrane and how this might be of interest to improve transport of drugs, including nucleic acid nanomedicines, into the retina. This presentation will discuss date presented in recent publications from our group[1-8].

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Design of novel nanoformulation to decrease cardiotoxicity of doxorubicin

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Doxorubicin (DOX) is a chemotherapeutic agent successfully used for the treatment of various neoplasms, however its use entails risks of side-effects such as irreversible cardiomyopathy[1]. To enhance its pharmaceutic potential, novel nanoformulated poly(lactic-co-glycolic acid) DOX (PLGA) was prepared and their cardiotoxic effects were compared with commercially and clinically approved conventional (CNV) and liposomal (LPS) formulations. Formulations were administrated intraperitoneally to male and female Wistar rats four times, once per week. Then, serum levels of cardiac troponin T (cTnT) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) were quantified with ELISA assays, and expression of inflammation-related genes (IL-6, IL-8, TNFα and IL-1β) in heart tissue of treated and control rats was evaluated using Real-Time PCR. Heart cryosections of treated and control rats were analyzed by imaging mass spectrometry (IMS).

CNV and LPS formulations significantly increased cTNT levels compared to control animals, while PLGA showed no such effect. NT-proBNP was decreased in animals treated with CNV and LPS, while no changes were observed for treatment with PLGA formulation. CNV significantly increased expression of IL-6 and IL-8 in heart tissue, which was not observed in PLGA-treated rats. Results of IMS analysis have shown reduced expression of inflammation markers in PLGA-treated rats compared to CNV- and LPS-treated animals. Therefore, novel PLGA formulation demonstrated lower inflammatory potential compared to clinically approved CNV and LPS, indicating the potential for novel nanoformulations for safer drug delivery in cancer therapy.

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Acknowledgments

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Carbosilane glycodendrimers for anticancer drug delivery

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Natural glycoconjugates, *i.e.*, carbohydrates covalently linked to other biomolecules (peptidoglycans, glycoproteins, glycolipids, and lipopolysaccharides), and also small molecules (glycosides) play a crucial role in normal biochemical processes in living organisms. Forms of glycoconjugates are involved, among others, in cell-to-cell communication and recognition. Carbohydrate recognition is also involved in various pathological conditions comprising cancerous malignancy, and bacterial, viral and parasitic infections. Advances in biomedical research require the development of biocompatible and specific synthetic glycoconjugates[1,2].
Here, we present i) robust synthetic methods to carbosilane (CS) dendritic structures for multivalent presentation of carbohydrate units, and ii) biophysical and biological evaluation of the compounds for their use in biomedical applications. Series of CS glycodendrimers (glyco-DDMs) with glucose and galactose moieties at the periphery were prepared from azide- and propargyl-terminated precursors. *In vitro* cytotoxicity assays revealed exceptional biocompatibility of the glyco-DDMs irrespective of their generation and series. The application potential of the compounds in anticancer therapy was investigated by encapsulating the drug doxorubicin. Testing of the resulting dendrimer-drug complexes on MCF-7 and A2780 cancer cell lines showed their promising generation- and concentration-dependent anticancer activity, as well as pH-dependent drug release. Overall, the CS glyco-DDMs proved to be beneficial glycoconjugates for biomedical applications[3].

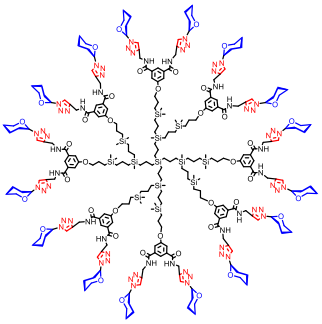

Figure 1. Carbosilane glycodendrimer with glucose units at the periphery.

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Nanoparticles for glioblastoma therapy

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Glioblastomas (GBMs), Grade IV gliomas, are the most common primary brain tumours in adults. Median survival is approximately 14 months since the primary diagnosis, and 2-year survival is about 25 %. Thus, new therapeutic alternatives are indeed needed to further improve GBM patient's survival. Cyclodextrins (CDs) are water-soluble nanostructures comprising a lipophilic interior and a hydrophilic surface. Some CDs have actually reached clinical trials and even clinical use, while other CD-derivatives have been regarded as potential DNA and RNA vectors as well. In this work an amphiphilic β-CD-derivative decorated with 7 oligoethylenimine branches, has been tested as a siRNA transfection vector. This compound has proved to complex siRNA in a reversible fashion and to protect it from RNase-mediated degradation.
Specific siRNAs were designed to be vectorized by AMC6, in order to lower the levels of notorious proteins in GBM, in particular p42-MAPK, p44-MAPK, Rheb, and O^6-methylguanine-DNA-methyltransferase (MGMT). AMC6-mediated siRNA transfection indeed proved to be efficient by extensively knocking-down p42-MAPK, p44-MAPK and Rheb in GL261 and T98G glioma cells, and also MGMT in T98G cells. Only very low toxic effects appeared when any of these siRNAs or SCR siRNA were used at a concentration of 100 nM.
GBM cell lines used herein responded very poorly to TMZ. Only at very high concentrations some significant toxicity was detected. When AMC6:siRNA nanoplexes were used in addition to TMZ, we observed a clear potentiation in toxicity in some cases. In particular, TMZ toxicity was potentiated by knocking-down p42-MAPK alone or combined with p44-MAPK or Rheb, increasing TMZ-induced cell death from 1.5 to 3.3-fold. Altogether, these results suggest that the toxicity exerted by TMZ can be potentiated in GBM cell lines by knocking-down different proteins, thus disturbing different cell pathways involved in GBM cell proliferation and survival.
Preliminary *in vivo* experiments were conducted in mice to characterise biodistribution of AMC6 and AMC6:Cy5.5-SCR siRNA nanoplexes. These experiments showed no toxicity, ubiquitous distribution of both AMC6 and siRNA, and an evident accumulation in the liver, which faded away with time. When a transferrin-decorated version of AMC6 was used instead, a slightly different biodistribution profile was observed, with an increase in its presence in the brain (about +240 %).

Acknowledgments
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Multifunctional nanomedicines of chemotherapeutic and antiangiogenic effect to target glioblastoma are validated in 3D tumor microtissue-forming unit and in vivo orthotopic model

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Glioblastoma (GBM) is the most common and lethal type of primary brain tumor. The 5-year survival of GBM patients is still limited to a dismal 5%, highlighting the need to advance more effective GBM therapies. GBM tissue presents an abnormal expression of the L-type amino acid transporter 1 (LAT1), for which histidine (His) is an inexpensive and powerful targeting ligand. Although His is expected to provide higher accumulation of drug nanoparticles (NPs) into GBM cells via LAT1 binding, consequently enhancing the anti-tumor response, it has been poorly explored in GBM-targeted therapies. Driven stimuli-responsive NPs for docetaxel (DTX) delivery to GBM are reported, with multifunctional features that circumvent insufficient blood-brain barrier (BBB) trafficking and lack of GBM targeting. NPs are dual-surface tailored with a (i) brain-targeted acid-responsive Angiopep-2 moiety that triggers NP structural rearrangement within BBB endosomal vesicles, and (ii) L-Histidine moiety that provides NP preferential accumulation into GBM cells post-BBB crossing. In tumor invasive margin patient cells, the stimuli-responsive multifunctional NPs target GBM cells, enhance cell uptake by 12-fold, and induce 3-times higher cytotoxicity in 2D and 3D cell models. Innovative 3D glioblastoma microtissue-forming unit containing cancer cells, macrophages and endothelial cells were established to validate the effect of L-Histidine decorated NPs on macrophage polarization and cell metabolic activity. Moreover, the in vitro BBB permeability is increased by 3-fold. A biodistribution in vivo trial confirms a 3-fold enhancement of NP accumulation into the brain. Lastly, the in vivo anti-tumor efficacy is validated in GBM orthotopic models following intratumoral and intravenous administration. Median survival and number of long-term survivors is increased by 50%. Overall, a preclinical proof of concept supports these stimuli-responsive multifunctional NPs as an effective anti-GBM multistage chemotherapeutic strategy to respond to multiple fronts of the GBM microenvironment. Bevacizumab-loaded NPs are currently tested for their antiangiogenic effect using the 3D glioblastoma microtissue-forming unit.

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Co-clinical organoid platform for individualization of cancer chemotherapy

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Surgery is the most frequently applied curative treatment option for malignant tumors. However, the long-term outcome of post-surgical patients with advanced cancer is impaired by residual tumor cells invading the tumor microenvironment, eventually leading to local or distant tumor recurrence and therapeutic resistance. In recent decades, patient-derived organoids have emerged as a valuable technological tool in research on basic cancer biology and translational drug development. Using stem cell culture and fresh tumor resection material, we present an interdisciplinary workflow at a German academic medical center to generate and characterize biological tumor avatars of intestinal or hepatobiliary cancer patients. This methodology, which integrates hospital information system data, ethical considerations, pathological assessment, logistics and in vitro processing in a minimal time window, allows the characterization of chemotherapy resistance of the tumor during post-surgery recovery and before the onset of adjuvant therapy. This workflow allows for rational adjustment of the chemotherapy regimen of individual patients in a clinically relevant time window. We will also discuss the clinical benefits of organoid-instructed treatment programs at other centers. Co-clinical trials support the certification process of clinical oncology centers, thereby impacting hospital management agendas. Given the leading expertise of our center in robotic surgery, the talk will also comment on the relevance of this emerging surgical innovation for personalized disease model generation. Functional test matrices of individual tumor twins may also have an impact beyond personalized medicine, such as identifying and repurposing approved drugs and developing new biomarker-targeted nanodrugs.

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NaDeNo – Unleashing the potential of hard-to-deliver drugs

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NaDeNo is a Norwegian company founded on >10 years of nanomedicine research at SINTEF[1-3]. NaDeNo is developing a platform of proprietary polymeric nanoparticles to overcome drug delivery hurdles, with initial focus on repurposing of effective drugs in areas of high unmet medical need. One such drug is cabazitaxel, a highly potent taxane which therapeutic potential has been limited due to its hydrophobicity, high systemic toxicity and the instability of the commercial preparation, Jevtana®[4]. Our lead candidate PACAB-002 is a proprietary combination of poly(alkyl cyanoacrylate) and cabazitaxel, for which highly encouraging preclinical data have been generated. PACAB-002 is intended for local administration in the peritoneal cavity for the treatment of peritoneal metastasis originating from colorectal and ovarian cancer. This is a cancer indication of high unmet medical need, for which there are currently no effective treatment options. Through encapsulation in nanoparticles, we have shown even drug distribution and long retention time, tumor specific drug accumulation, low systemic toxicity and a significant reduction in tumor weight in mouse models. PACAB-002 hence represents a safer and more efficient treatment option for peritoneal metastasis.

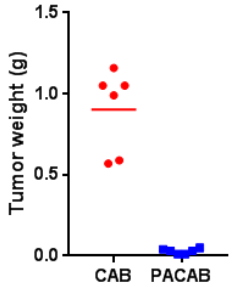

Figure 1. Preclinical proof of concept for lead candidate PACAB-002 in mice bearing B76 xenografts originating from human ovarian cancer. Tumor weight at study end (day 38). CBZ is non-encapsulated cabazitaxel (Jevtana®-like formulation), whereas PACAB is cabazitaxel encapsulated in poly(alkyl cyanoacrylate) nanoparticles, n=6.

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Acknowledgements

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ICG-tagged aptamer as drug delivery system for *in vitro* and *in vivo* malignant melanoma models

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Malignant melanoma accounts for about 1% of all skin malignant tumors and represents the most aggressive and lethal form of skin cancer[1]. Clinically, there exist different therapeutic options for melanoma treatment, such as surgery, chemotherapy, radiotherapy, photodynamic therapy and immunotherapy2,3. However, serious adverse effects usually arise, and survival rates are still low[4]. AS1411 is a G-quadruplex (G4) aptamer capable of tumor-specific recognition, since it binds to nucleolin, a multi-functional protein expressed in many different types of cancer cells[5]. Thus, we synthesized and evaluated a novel drug delivery system composed of AS1411 and indocyanine green (ICG) to track its accumulation in tumoral cells in a melanoma mouse model. Using a simple supramolecular strategy, we conjugated the complex AS1411-ICG with C_8 ligand, an acridine orange derivative with potential anticancer ligand. Then, we performed *in vitro* cytotoxicity experiments using the B16 mouse melanoma cell line, and *in vivo* experiments using a B16 mouse melanoma model to study biodistribution. The circular dichroism data suggest that C_8 does not affect the parallel G4 topology of AS1411-ICG, whereas it increases its thermal stability. Incubation of B16 melanoma cells with the AS1411-ICG complex associated with C_8 increases the cytotoxicity compared with AS1411-ICG alone. From the *in vivo* studies, we conclude that both AS1411-ICG and AS1411-ICG-C_8 presented the potential to accumulate preferentially in tumor tissues. Moreover, these compounds seem to be efficiently removed from the mice's bodies through kidney clearance. In summary, these results suggest that these complexes derived from AS1411 aptamer could act as a delivery system of ligands with antitumoral activity for *in vivo* melanoma therapy.

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Cryo-EM of Drug Delivery Nano Vehicles

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Cryo-EM relates to a family of methods that together prob the structure and morphology of individual particles in solution at multiple length-scales. The traditional and leading technique in this family, cryo-TEM, is particularly powerful for analyzing suspensions and formulations of delivery vehicles: It directly and without image processing illuminates structural details, and it discloses heterogeneity in shape and size as well as complexity that is many times beyond what we could anticipate or imagine [1]. Cryo-TEM is also useful for understanding dynamics and time-dependent processes. All the information, importantly, relates to the native, bulk state, and is at nanometer resolution.

To demonstrate the possibilities offered, the talk will highlight the insight from cryo-EM to a number of recent studies, including the development of a nanovesicles formulation to treat the orphan disease Fabry [2], nanoparticle delivery systems of MicroRNA Therapeutics [3], mRNA vaccine to protect against SARS-CoV-2 infection [4], lipid nanoparticles for RNA delivery [5], solid -lipid nanoparticles [6], and polymeric micelles for co administration of antiretroviral combinations [7].

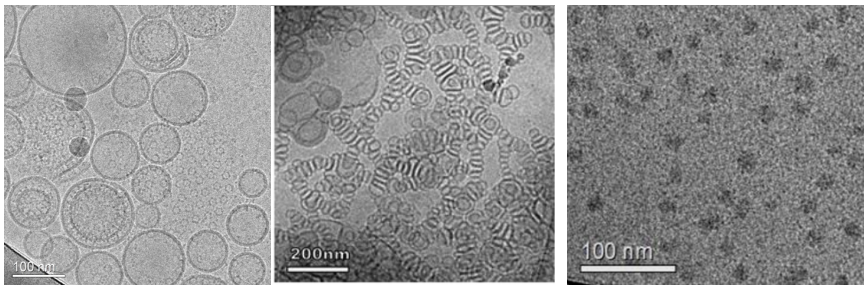

Figure 1. Left: Quatsome/α-galactosidase nanovesicles to treat Fabry [2]. Middle: Quatsomes/MicroRNA conjugates [3]. Right: β-casein micelles encapsulating an antiretroviral combination [7].

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Development of an occupational risk assessment for nanobiomaterials used in advanced therapy medicinal product for cancer treatment

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The assessment of the safety of nano-biomedical products for patients is an essential prerequisite for their market authorization. However, it is also required to ensure the safety of the workers who may be unintentionally exposed to nano-biomaterials (NBMs) in these medical applications along the entire lifecycle of these products, considering not only product manufacturers but also healthcare personnel (*e.g.*, nurses, physicians, technicians) using the products for treating patients.
In this context, three main life cycle stages (*e.g.*, product manufacturing, use and end-of-life) and specific categories of workers for each of them were identified for the description of exposure scenarios of magnetite (Fe3O4) NBMs coated with PLGA-b-PEG-COOH used as contrast agent in magnetic resonance imaging (MRI) for the diagnosis of solid tumours. To collect information about the product manufacturing and end-of-life stages, interviews to product manufacturers and waste disposal personnel were performed, while for the use stage, a questionnaire for healthcare staff was developed and then sent to public and private clinicals and hospitals where different type of contrast agent are administered. Based on information collected, several Contributing Exposure Scenarios were identified and important considerations on workers exposure (e.g., number of people performing every single task, possible routes of exposure, duration of tasks), risk management measures used (e.g., personal protective equipment and local exhaust ventilation system) and characteristic of the room or building (e.g., dimension of the room, type of ventilation) were obtained. Moreover, a monitoring campaign was also performed at the industry where possible release during synthesis of NBMs was assessed. Monitoring measurements revealed a negligible inhalation exposure of workers potentially exposed during the production of magnetite NBMs. The exposure measurements as well as information collected were then used to perform a probabilistic risk characterization for the formulated exposure scenarios, including uncertainty analysis.

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Testing extracellular vesicles as cisplatin carriers in lung cancer on a chip platform

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Lung cancer is the most common cause of cancer related death. Although several treatments are available, they are usually leave the patients struggling with unwanted side-effects. Studies of mesenchymal stem cell (MSC) extracellular vesicles (EV) suggest that they can be used as drug carriers to become modern drug delivery systems to cancer cells. Lung cancer-on-a-chip (LCoC) systems are novel vascularised in vitro model system with liquid flow to mimic drug delivery trough circulation and study cancer tissue response. Currently available LCoC models are developed from PDMS (Polydimethylsiloxane), that is not suitable for drug testing since it absorbs small molecules. Therefore, we developed new LCoC model from thermoplastics to study MSC derived EVs loaded with cisplatin in comparison to EVs without cisplatin and cisplatin alone. LCoC was established by using stable cell line A549 and commercial primary cell line - HPMEC (Human pulmonary microvascular endothelial cells). Cisplatin loaded MSC EVs were produced from immortalized commercial adipocyte derived MSC – ASC52-telo by growing them in media with nontoxic cisplatin concentration. Cisplatin loaded EVs were administrated within endothelial channel of LCoC and compared between MSC EVs without cisplatin, cisplatin without EV and negative control within previously optimized flow. Cell viability, biological barrier integrity and migration was evaluated by different assays. Preliminary results showed that cisplatin loaded EVs do not decrease biological barrier integrity and decreased A549 cell migration to endothelial channel suggesting, that cisplatin loaded EV could potentially decrease chemotherapy effect on endothelial cells.

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A new perspective for cancer prevention using magnetic nanoparticles for the therapy of adiposopathy by magneto-mechanical effect

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Recent decades have seen a worrying increase in the incidence and prevalence of obesity and overweight in industrialised countries. In obese patients, the structural and functional alteration of adipose tissue can lead to a state of systemic inflammation and the development of a pathological condition known as adiposopathy. Being overweight is considered the fifth leading risk for global deaths and about 50% of cancers are known to be strongly associated with obesity. Targeting adiposopathy is therefore of crucial importance. In this project, the use of magnetic nanoparticles (MNPs) and the consequent application of magneto-mechanical stress by an external alternating magnetic field were investigated as a potential treatment for adiposopathy. This treatment has shown efficacy as a promising tool for cancer therapy[1,2], however, our project is the first applying the technology to target adiposopathy. 20 nm octahedral magnetite-based MNPs were synthesized and functionalized with chitosan and di-mercapto-succinic acid (DMSA) to increase their stability in the biological environment and to improve their cell interactions. MNPs were incubated with key cells regulating adiposopathy present in adipose tissue (macrophages and adipocytes) and exposed to the alternating magnetic field. In addition, the interaction of the nanoparticles with blood components was also investigated to determine the potential toxicity associated with this therapy[3]. DMSA-MNPs did not affect platelet function or red blood cell integrity, but they induced DNA fragmentation and production of reactive-oxygen species on macrophages and lipolysis, with a fragmentation of lipid droplets on adipocytes following the magneto-mechanical treatment. Therefore, it could be concluded that the nanoparticles developed for this study are blood compatible and that the treatment proposed by our team can lead to morphological and functional recovery of adipose tissue. MNPs may be a promising tool for the treatment of adiposopathy and potentially contribute to the prevention of the development of cancer and other diseases associated to obesity.

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Potential antitumor application of polyphenol-conjugated turnip mosaic virus-derived nanoparticles

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Filamentous plant virus-derived nanoparticles are biodegradable and non-infectious to humans. Their structure is also very amenable to chemical modifications. They constitute an appealing material for biomedical applications including imaging and drug delivery. We had previously used turnip mosaic virus-derived nanoparticles (TuMV NPs) to increase antibody-sensing *in vivo*, to prevent biofilm formation and to build biological nanoscaffolds. Accordingly, we analysed TuMV-NP biodistribution and tumour homing using *in vivo* imaging. We studied *in vitro* the interaction with human cancer cell lines, and the antiproliferative effect of epigallocatechin gallate (EGCG)-functionalised TuMV NPs. We have verified that TuMV NPs are efficiently internalised by human cells and show good tumour homing. The antiproliferative effect of EGCG-TuMV NPs suggests they could be a potential anticancer therapy.

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Fucoidan/dendrimer nanoparticles for glioblastoma treatment: anti-angiogenic behaviour and siRNA delivery studies

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Glioblastoma is a severe type of brain cancer that is difficult to treat due to its localization in the body, as well as the complexity and heterogeneity of its vascularization that favours tumour cell invasion.[1] In this scope, the combination of strategies for angiogenesis inhibition and delivery of therapeutic molecules may help to extend patient's life. Fucoidans are sulfated polysaccharides that can be extracted from brown algae. They have been shown to have biological activity, including anti-angiogenic one, depending on their composition and structural properties.[2] Thus, their inclusion as building blocks in nanoparticles aimed at being used as delivery vehicles for anticancer agents may endow them with intrinsic anti-angiogenic properties. Due to their degradability properties, dendrimers based on 2,2-bis(hydroxymethyl)propionic acid (bis-MPA) are very interesting molecules to be use in nanomedicine too and were already shown to successfully transfect glioblastoma cell lines.[3] The main objective of this work was to prepare and characterize fucoidan/bis-MPA-based dendrimer nanoparticles, and further study their behaviour regarding angiogenesis and siRNA delivery. In a 1st phase, the pro/anti-angiogenic properties of different fucoidans (having different origin, composition, and MW) and of the prepared fucoidan/dendrimer nanoparticles were evaluated (*in vitro* by their effect on the formation of tubular structures formed by endothelial cells and *in vivo* through the CAM assay). In a 2nd phase, a series of experiments to evaluate the possibility of using the nanoparticles to deliver siRNA in glioblastoma cells were performed (capacity to condensate and protect the siRNA, cytotoxicity and knock-down of target proteins).

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Acknowledgments

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Hard road to good manufacturing practices for nanomedicine

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Finding efficient cancer therapies is an urgent and still unresolved problem and, in the fight against this disease, scientists are devoting tremendous efforts towards the utilization of nanomedicines. Nanomedicines have the potential to drive the scientific and technological uplift offering great clinical and socioeconomic benefits to the society in general, industry and interested parties, and key stakeholders. However, only a few nanomedicines have reached the commercial level, most still being in the pre-clinical phase. The establishment of good manufacturing practice (GMP) in nanomedicine manufacturing represents the first prerequisite to transfer and foster the clinical translation of nanomedicine from bench to bedside. The hurdle in the translational process of most nanomedicine - the so-called “innovation valley of death” situation due to lack/deficit of know-how, testing method, technology or facility prior to clinics – can be overcome by guiding technology transfer. Scale-up and GMP manufacturing problems can be encompassed by implementing a “fast-track-to-GMP” strategy. Affordable and advanced testing, manufacturing facilities and services for novel nano-pharmaceuticals are main prerequisites for successful implementation.

This presentation mainly will focus on the early integration of GMP relevant aspects to nanomedicine value chain, already starting from the development phase. Remarkably, beside the classic attempts for harmonisation of compliant methods and approaches to the innovation management strategies to increase GMP compliance, role of Open Innovation Test Beds as Single Entry Point of competent service providers in nanomedicine under one roof will be briefly presented and discussed.

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