



# MAD-Nano18

MADEIRA INTERNATIONAL CONFERENCE

**Emerging Trends and Future of  
Nanomaterials for Human Health**

30 NOVEMBER - 02 DECEMBER 2018

MADEIRA ISLAND | PORTUGAL

<https://cqm.uma.pt/madnano18>

## ABSTRACTS BOOK



# **MAD-Nano18**

Madeira International Conference on  
Emerging Trends and Future of  
Nanomaterials for Human Health

## **Abstracts Book**

30<sup>th</sup> of November to 02<sup>nd</sup> of December 2018  
Funchal, Madeira Island – PORTUGAL

# MAD-Nano18

Abstracts Book

MAD-Nano18: Madeira International Conference on Emerging Trends and Future of Nanomaterials for Human Health

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## WELCOME MESSAGE

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Dear Participants,

The International Advisory Committee and the Organizing Committee have the great privilege to welcome you to the MAD-Nano18: Madeira International Conference on Emerging Trends and Future of Nanomaterials for Human Health, in Funchal, Madeira Island, an event hosted by Centro de Química da Madeira (CQM) - University of Madeira (UMa).

The use of nanomaterials for the improvement of human being's health and quality of life is an emerging and very important topic of research that, due to its transversal nature, is attracting the interest of researchers, clinicians, companies and financial supporting agencies all over the world. As in the first edition of this conference, our objective is to create an alternative and informal forum to share the current state of the art in this field among senior and junior scientists. The meeting aims at creating new networks and collaborations, presenting the most innovative nanomaterials and discussing approaches that can be used, now or in the near future, for the diagnosis and treatment of the different diseases that affect humankind, particularly the groups with less access to health care.

With more than 60 participants (from 13 countries) and 45 communications (25 are oral communications), the MAD-Nano18 conference evolved since the last edition in the number of participants and countries represented. In this sense, our objective is to continue to grow, making Madeira Island a lighthouse regarding the present and the future of nanomaterials for human health.

On the occasion of the celebrations of the 600 years of the discovery of Madeira (1419) and Porto Santo Island (1418), "The Island of White Gold", Madeira Island, is the perfect place to organize this conference. Indeed, historically, it may be considered not only as a bridge between the past and the future but also as a geographic key point for the scientific and technological globalization movement that started a few centuries ago. Presently, with the contribution of the Centro de Química da Madeira and the University of Madeira, the Region is now also a gateway from Europe to Asia, Africa, Central and South America, fulfilling the mission of bringing people of different cultures together to share knowledge and innovation in the field of nanomaterials for human health applications.

Finally, this event could not be carried out without the support of FCT - Fundação para a Ciência e a Tecnologia (project UID/QUI/00674/2013 & FACC), ARDITI-Agência Regional para o

## MAD-Nano18

Desenvolvimento da Investigação, Tecnologia e Inovação (project M1420-01-0145-FEDER-000005 – Operação CQM+, Madeira 14-20 Program), the INTERREG MAC2014-2020 (project MAC/4.6d/040) and our Platinum Sponsor, the Bruker Company. We are deeply grateful to all these entities for the given support which was fundamental to build up this Conference.


On behalf of the International Advisory Committee and the Organizing Committee, I wish you all a very fruitful Conference and pleasant stay at Madeira Island.

Funchal 29<sup>th</sup> of November 2018


João Rodrigues  
Chairman of MAD-Nano18

MAD-Nano18

## Thursday, 29<sup>th</sup> November 2018

Time	Activity
17:00 - 20:00	 Participants Registration

## Friday, 30<sup>th</sup> November 2018

Time	Activity	Presenting Author
08:30 - 09:30	 Participants Registration	
09:30 - 10:00	 Opening Session	
10:00 - 10:45	KN1 Nanotechnology's Potential for Agrochemistry	Alexander Schaetz
10:45 - 11:15	 Coffee Break	
11:15 - 11:50	IOC1 Mesoporous Hybrid Nanocontainers for Controlled Release	José Paulo Farinha
11:50 - 12:15	OC1 DNA/PAMAM Dendrimer Films: a Promising Doxorubicin Delivery Platform for Anticancer Therapy	Rita Castro
12:15 - 12:35	OC2 DNA Delivery Using a Self-assembling Nanohybrid of Fluorescent Carbon Dots and PAMAM dendrimers	Ivo Martins
12:35 - 13:10	IOC2 From Medical Probes to Phototherapy Drugs: The Development of Fluorescent Tamoxifen Derivatives	Alicia Boto
13:10 - 15:00	 Lunch	
15:00 - 15:45	KN2 New Advances in Hybrid Plasmonic Nanoparticles for Biomedical Applications	Claire Mangeney
15:45 - 16:10	OC3 Green Nanobiomaterials: Natural (I)-lysine-based Functional Macromolecules/Polymers for Gene Delivery Application	Ruilong Sheng
16:10 - 16:30	OC4 Novel Low-generation Ruthenium (II)-based PAMAM Dendrimers: Synthesis and Cytotoxicity Studies	Nádia Nunes
16:30 - 16:40	 MAD-NANO18 Group Photo	
16:40 - 17:10	 Coffee Break + Poster Session	

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Time		Activity	Presenting Author
17:10	17:45	IOC3 Antifouling Dendrimer-entrapped Gold Nanoparticles Loaded With Gadolinium for CT/MR Imaging of Lung Cancer Metastasis	Xiangyang Shi
17:45	18:10	OC5 Multifaceted Applications on Carbon Nanomaterials	Manuel Algarra
18:10	18:35	OC6 Extracellular Nanofibres and Cancer	Annica K. B. Gad
18:35	19:00	OC7 Marine-based Nanomaterials for Tissue Engineering	Ana Rute Neves

20:00





Conference Dinner

## Saturday, 01<sup>st</sup> December 2018

Time		Activity	Presenting Author
09:00	09:45	KN3 Multilayered 3D- structures From Nano-assembled Multilayers for Biomedicine	João F. Mano
09:45	10:20	IOC4 Polymersomes and Hollow Capsules as Versatile Tools for Mimicking Simple Cell Functions	Dietmar Appelhans
10:20	10:55	IOC5 Nanoparticles and siRNA: a New Glioblastoma Therapy?	Valentin Ceña
10:55	11:15	 Coffee Break	
11:15	11:50	IOC6 A Dendrimer Journey to the Clinical Setting	M. A. Muñoz-Fernández
11:50	12:10	OC8 Platinated Low-generation of PAMAM Dendrimers as Drug Delivery Vehicles for Cancer Treatment	Cláudia S. Camacho
12:10	12:30	OC9 Evaluation of the nanotoxicity of PAMAM dendrimers by <sup>1</sup> H NMR Metabolomics in different cell lines	Ana Olival
12:30	12:50	OC10 Low-generation of Ruthenium Metallodendrimers: a Promising Metallodrug to Fight Cancer	Dina Maciel
12:50	14:25	 Lunch	
14:45	18:00	 Free afternoon or Excursion (Madeira sightseeing tour)	

## Sunday, 02<sup>nd</sup> December 2018

Time	Activity	Presenting Author
09:00 09:45	KN4 Fully Biodegradable PEG-dendrimers for Nucleic Acid Delivery	Ana Pego
09:45 10:20	IOC7 Design of Multifunctional Nanomaterials for Drug Delivery Applications	Cátia Ornelas
10:20 10:55	IOC8 Development of Photonic Crystals for Coating Sensing Design	Joaquim C.G. Esteves da Silva
10:55 11:25	 <b>Coffee Break</b>	
11:25 12:00	IOC9 Analysis of the Putative Ligand Binding to CARF Domain of Csx1 Protein Using Molecular Docking and Molecular Dynamics Simulations	Visvaldas Kairys
12:00 12:45	KN5 Mix-charged Bionanointerface: From Smart to Self-adaptive	Jian Ji
12:45 13:00	 <b>Closing Session</b>	



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# KEYNOTE LECTURES

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# MAD-Nano18



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& IBMC-INEB Associated Laboratory  
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**Jian Ji**, Ph.D  
Zhejiang University  
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## Nanotechnology's Potential for Agrochemistry

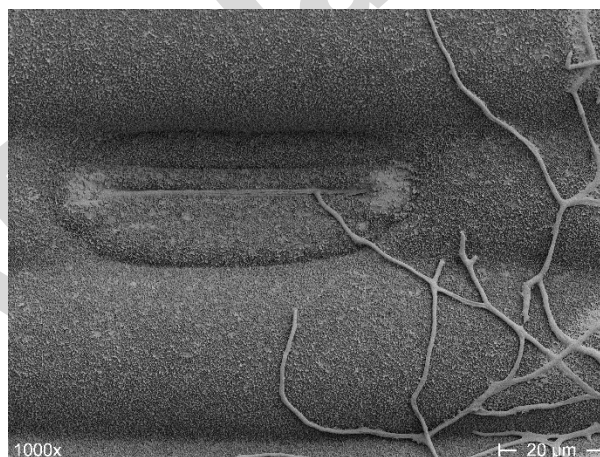
Alexander Schaetz<sup>1</sup>, Alex Heming<sup>1</sup>, Martine de Heer<sup>1</sup>, Kathryn Grayling<sup>2</sup>, Sacha Mooney<sup>2</sup>, Scott Young<sup>2</sup> & Clive Roberts<sup>2</sup>

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<sup>2</sup>The University of Nottingham, Division of Agricultural and Environmental Sciences, Sutton Bonington Campus, Leicestershire LE12 5RD, United Kingdom.

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There is an increasing interest in the use of nano-technology in the field of agrochemistry, either as an improvement to, or an alternative for, crop protection chemicals. Especially the formulation development of agrochemicals (i.e. actives) took advantage of the many promises that nanotechnology held for pharmaceutical drug delivery. However, it is still not clear in how far these concepts can provide benefits that outweigh potential disadvantages in agrochemical products that aim to deliver active ingredients to very different target organisms and environments. The theoretical benefits of nano-formulations (phase domains below one micron) will be discussed and compared to literature results and the performance of experimental samples with Syngenta's active ingredients at nano-scale. In the first part, possible improvements to foliar applied products (e.g. fungicides, Figure 1) will be considered and, in the second, to soil or seed applied compounds.



**Figure 1.** Electron microscopy image of fungi-hyphae (*Septoria tritici*) infesting winter wheat (*Triticum aestivum*) through stomata (gas exchange pore in leaves). Can nano-formulated fungicides treat the disease more effectively?

[KN2]

## New Advances in Hybrid Plasmonic Nanoparticles for Biomedical Applications

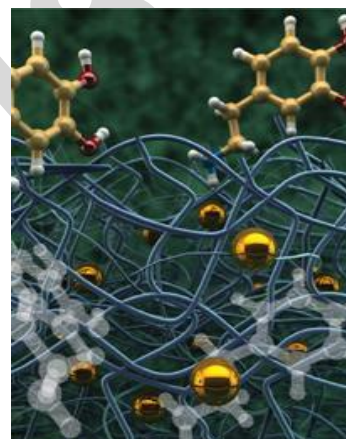
Issam Kherbouche<sup>1,2</sup>, Mai Nguyen<sup>2</sup>, Aazdine Lamouri<sup>2</sup>, Georges Lévi<sup>2</sup>, Jean Aubard<sup>2</sup>, Alexandre Chevillot-Biraud<sup>2</sup>, Stéphanie Lau-Truong<sup>2</sup>, Nordin Felidj<sup>2</sup> & Claire Mangeney<sup>1</sup>

<sup>1</sup>Lab Chim & Biochim Pharmacolog & Toxicol, University Paris Descartes, 75006 Paris, France.

<sup>2</sup>Lab ITODYS, University Paris Diderot, 75013 Paris, France.

In this talk, we present the design of hybrid plasmonic nanostructures, combining gold nanoparticles and functional polymers (smart, reactive and molecularly imprinted polymers) for applications in biosensors and nanomedicine. We will first describe an original strategy for the regioselective functionalization of gold nanoparticles, based on a combination of photo-induced plasmon excitation and aryl diazonium salt chemistry [1-3]. This strategy allows the grafting of the chemoreceptors in specific areas of maximum near field enhancement, resulting in highly sensitive biosensing platforms for the detection of biomarkers by Surface-Enhanced Raman Spectroscopy. The grafting of molecularly imprinted polymer shells is also shown to provide optical nanosensors enabling the direct, label-free detection of various kinds of molecules, such as folic acid and paracetamol [4]. The combination of plasmonic nanostructures and polymers therefore offers promising outlook to merge multiple functions at the nanometer scale, which is of particular interest for biomedicine.

**Figure 1.** Illustration of hybrid plasmonic nanostructures combining gold nanoparticles and functional polymers



### References:

[1] Nguyen M.; Lamouri, A.; Salameh, C.; Levi, G.; Grand, J.; Boubekeur-Lecaque, L.; Mangeney, C.; Felidj, N. *Nanoscale*, 2016, 8, 8633; [2] Nguyen M.; Kherbouche, I.; Gam-Derouich, S.; Ragheb, I.; Lau-Truong, S.; Lamouri, A.; Levi, G.; Aubard, J.; Decorse, P.; Felidj, N.; Mangeney, C. *Chem. Comm.*, 2017, 53, 11364; [3] Tijunelyte, I.; Kherbouche, I.; Gam-Derouich, S.; Nguyen, M.; Lidgi-Guigui, N.; Lamy de la Chapelle, M.; Lamouri, A.; Lévi, G.; Aubard, J.; Chevillot-Biraud, A.; Mangeney, C.; Felidj, N., *Nanoscale Horizon*, 2018, 3, 53; [4] Ahmad, R.; Félidj, N.; Boubekeur-Lecaque, L.; Lau-Truong, S.; Gam-Derouich, S.; Decorse, P.; Lamouri, A.; Mangeney, C., *Chem. Comm.*, 2015, 51, 9678.

## Multilayered 3D-structures from Nano-assembled Multilayers for Biomedicine

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The development of implantable hybrid devices in a variety of biomedical applications are often inspired by the composition and complexity of native tissues. At the lowest level of such organization, one should select the adequate biomaterials to be used as the building block of the structure that will support cells and control their behaviour towards the production of new tissue. We have been proposing the use of multilayered based arrangements prepared by the layer-by-layer technique (LbL) that could be then integrated in more complex porous macroscopic devices, often exhibiting a multi-scale organization. Using adequate templates, non-flat coatings can be fabricated with tuned compositions along the build-up assembly, including porous devices. This enables the production of very well controlled multifunctional and structural devices using mild processing conditions that could be useful in biomedicine, including in tissue engineering. In particular, we have been interested in developing more complex/hierarchical porous structures using natural-based polymers that could fulfil specific requirements in such kind of applications. Often multiple cell types should be integrated in such hybrid devices to recapitulate relevant biological features necessary to trigger the regeneration process. Methodologies developed in our group will be exemplified, permitting the production of: (i) Membrane-like devices able to support the attachment and organization of cells; (ii) 3-dimensional (open) porous nanostructured scaffolds for tissue engineering, enabling the support of cells, by combining LbL and rapid prototyping technology; and (iii) multi-scale spherical objects to encapsulate cells, acting as “living” injectable or (closed porous) implantable devices.

[KN4]

## Fully Biodegradable PEG-dendrimers for Nucleic Acid Delivery

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Dendrimers are attractive carriers for several bioactives [1] due to their unique structural features: globular, well-defined, very branched and controllable nanostructure, low polydispersity and multivalency. Among such bioactives nucleic acids (NAs) are readily compacted into nanostructures named “dendriplexes”, when complexed with positively charged dendrimers that are able to protect them from enzymatic degradation and rapid renal clearance after i.v. administration [2]. However, one important disadvantage of the most commonly used dendrimers is their non-degradability under physiological conditions, that can lead to toxicity by bioaccumulation. Moreover, in the gene therapy field, vector stability can further hinder the intracellular release of the NA, consequently leading to low transfection efficiencies (TE). Therefore, recent interest has focused on the development of biodegradable dendrimers, but only few works report their biomedical applications [3].

We have recently reported a new family of partially/hybrid biodegradable PEG-dendritic block copolymers for siRNA delivery [4,5]. Our systems showed a great ability to mediate siRNA cellular internalization [5], yet a low transfection efficiency (TE) was observed due to the partial vector stability. Here, we present new fully biodegradable and biocompatible PEG-dendritic block copolymers [4], as well as their function as siRNA vectors. Interestingly, the fully degradable character was crucial for a better nucleic acid release from the dendriplexes, contributing to an amazing improvement of the TE compared to their hybrid biodegradable counterparts.

**Acknowledgments:** This is supported by the grants PTDC/CTM-NAN/3547/2014 (FCT, Portugal); FIS-FIS-2015-01\_CCV\_20150630-88 (INFARMED); projects NORTE-01-0145-FEDER-000008 and NORTE-01-0145-FEDER-000012 (Norte Portugal Regional Operational Programme, NORTE 2020, under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (ERDF) and FEDER - Fundo Europeu de Desenvolvimento Regional funds through the COMPETE 2020 - Operacional Programme for Competitiveness and Internationalisation (POCI), Portugal 2020), and by Portuguese funds through FCT/MCTES in the framework of the project "Institute for Research and Innovation in Health Sciences" (POCI-01-0145-FEDER-007274).

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## Mix-charged Bionanointerface: From Smart to Self-adaptive

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The virus, which is made up of a mixed opposite charge of the different types of the amino acid, provide the best example to achieve the specific target in the complex in vivo system. In following the biological inspiration, we demonstrated that the mixed-charged of gold nanoparticle present better “stealth” properties and higher accumulation in tumor than PEG-2000 modified nanoparticles. Combing with the pH-responsive properties of weak electrolytes, the mixed charge bionanointerface can be explored as a robust method to control the aggregation of NPs sensitive to enhance the retention and cellular uptake of inorganic NPs in tumors, which has perfect stealth properties and pH-sensitivity for tumor targeting and photothermal treatment. We further demonstrate that the mixed charge gold nanoparticles present a temperature depending aggregation or dispersion behaviors, which can be further explored as a self-adaptive system to give out a constant output of temperature under near-infrared light irradiation. The output temperature is in accordance with the thermal-sensitivity difference between cancer cells and normal cells. The in vitro cell assessment confirms that the MC-GNP system could selectively kill cancer cells by forming negative feedback thermo-loop.



# **INVITED ORAL COMMUNICATIONS**

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## Mesoporous Hybrid Nanocontainers for Controlled Release

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Mesoporous silica nanoparticles (MSNs) are excellent nanocarriers, featuring good mechanical resistance and high cargo capacity due of their large surface area and pore volume. MSNs can be prepared with well controlled size [1] and allow versatile independent functionalization of the internal and external surfaces. The internal inorganic network can be modified, for example, to incorporate fluorescent beacons for imaging or sensing [2], while the external particle surface can be selectively decorated with biomolecules for targeting [3] and stimuli-responsive polymers for delivery control [4]. Due to their versatility, MSNs can combine therapeutic and diagnostic (theranostic) functionalities, providing an excellent platform for drug delivery on demand [5].

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[IOC2]

## From Medical Probes to Phototherapy Drugs: The Development of Fluorescent Tamoxifen Derivatives

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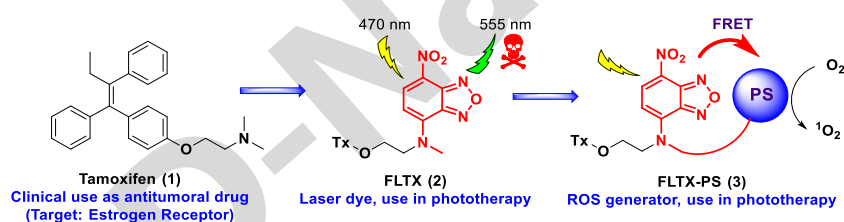
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The antitumoral drug tamoxifen (**1**) is a selective modulator of estrogen receptors (ER), and is used as a preventive treatment and therapy against breast cancer. However, the drug presents important side-effects, such as uterotrophic action leading to an increase in uterine cancer risk, intestinal alterations etc. We were able to identify different interactions with non-pharmacological receptors that explained these side-effects, by designing fluorescent probes [1].

In these studies, it was shown that a NBD-tamoxifen derivative, FLTX, retained tamoxifen action as selective ER modulator while the uterotrophic effects almost disappeared [1]. Surprisingly, this molecule was able to act as a laser pigment (and emit laser light) when irradiated with visible light. Moreover, in combination with a photosensitizer, the molecule was able to generate highly reactive species such as <sup>1</sup>O (ROS) when irradiated at 425 nm, and thus is a promising candidate for photodynamic therapy [2]. The attachment of FLTX to nanoparticles can also increase its potential as phototherapy drug.



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## Antifouling Dendrimer-entrapped Gold Nanoparticles Loaded with Gadolinium for CT/MR Imaging of Lung Cancer Metastasis

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To improve the accuracy and sensitivity of early diagnosis of diseases, it's essential to make full use of the strengths of all kinds of imaging modalities. One ideal solution is to combine two or more imaging elements in one platform for dual mode or multimode imaging applications. In addition, nanoparticles (NPs) often suffer quick clearance by reticuloendothelial system (RES) once they are injected to the body. Therefore, it's critical to render the NPs with good antifouling properties. Herein, we describe the synthesis of three antifouling agents modified generation 5 (G5) polyamidoamine (PAMAM) dendrimers entrapped with gold nanoparticles (Au DENPs). Through protein resistance, macrophage cellular uptake and pharmacokinetics assays, we show that Au DENPs modified with 1,3-propane sultone (1,3-PS) exhibit the best antifouling property. We then prepared G5 PAMAM dendrimer platform modified with Gd (III) chelator DOTA, targeting agent arginine-glycine-aspartic acid (RGD) peptide, 1,3-PS and used them as templates to synthesize Au DENPs, followed by Gd (III) chelation. In particular, the formed multifunctional Au DENPs displayed enhanced X-ray attenuation property, high  $r_1$  relaxivity ( $13.3 \text{ mM s}^{-1}$ ), good cytocompatibility, targeting specificity, and enabled effective dual mode CT/MR imaging of a lung cancer metastasis model in vivo. The developed multifunctional zwitterion-functionalized Au DENPs may be potentially used as an efficient nanoprobe for enhanced dual-modal CT/MR imaging of other cancer types.

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[IOC4]

## Polymersomes and Hollow Capsules as Versatile Tools for Mimicking Simple Cell Functions

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Engineering of multifunctional vesicular (multi)compartments for mimicking specific cellular functions [1] is one promising approach for overcoming protein lack in organ tissues and human diseases. These vesicular compartments have to fulfil various key characteristics (e.g. tuneable by external stimuli, controlling membrane functions for exchanging biomolecules, controlled release of biomolecules, retaining cargo inside of vesicular cavity), while multicompartments should also possess orthogonal-responsive membrane properties to control spatiotemporal and spatially separated biological pathways for establishing protocells [2]. Overall, this would result in the establishment of next-generation therapeutics.

This talk will present the use of pH-responsive and crosslinked polymersomes and hollow capsules as versatile supramolecular tool for mimicking cell functions. In line with this there is a requirement to understand following key characteristics of crosslinked polymersomes and hollow capsules: (i) the pH-dependent molecular switch of membrane properties, (ii) the membrane permeability against cargo (macro)molecules from outside to inside and vice versa, (iii) membrane integration of proteins, and (iv) (un)docking processes on polymersomes surface. From this various functional principles [3-5] are shown to being adaptable for mimicking cell functions and protocells [1,2].

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## Nanoparticles and siRNA: A New Glioblastoma Therapy?

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Glioblastomas (GBMs), are the most common type of primary brain tumor, causing about 4% of death cases associated to cancer [1]. Glioblastoma cells are genetically unstable leading to a highly infiltrative, angiogenic and resistant to chemotherapy neoplasms. This, along with the fact that chemotherapy is not effective in the long term, leads to a poor prognosis with a median survival of only about 14 months from diagnosis, and a 2-year-survival rate as low as 3-5% [2]. This poor prognosis even when GBM patients are treated according to standard care makes essential to search for novel therapeutic approaches.

Interference RNA (RNAi) technology is a very effective gene silencing mechanism that is also a very promising therapeutic tool since it can knockdown proteins involved in the pathogenesis of different diseases by targeting their mRNA [3]. Nanoparticles are generally used as delivery agents for drugs and/or siRNA [4]. Although NPs have the same limitations as other xenocompounds to cross the BBB, several strategies have been devised to improve BBB crossing to increase delivery to the central nervous system, so increasing the efficiency of different therapeutic compounds aimed to treat glioblastoma.

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[IOC6]

## A Dendrimer Journey to the Clinical Setting

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G2-S16 and G1-S4 dendrimers are one of the most promising candidates to develop a topical microbicide against HIV-1 and HSV-2. Heterosexual transmission across genital tissue is the primary route by which women acquire HIV infection. The first cells in the genital tract that HIV encounters during sexual transmission are genital epithelial cells. Cells specialized to recognize and respond to incoming pathogens, resulting in *initiation the innate immune responses*. Several assays were performed to evaluate the modulation of TLR2 and TLR4 expression in iDC, MØ and CD4 T-cells exposed various time with G2-S16. Although G2-S16 inhibits >90% HIV infection, this dendrimer did not stimulate the expression of TLR2 and TLR4 and consequently did not activate inflammatory cytokines. G2-S16 did not affect the production of TNF- $\alpha$  and IL-6 in MØ and did not modified the functional capacity of MØ, increasing its value as microbicide due to the fact that in presence of pathogens, for example HIV, G2-S16 decreases the expression of TNF- $\alpha$  in vaginal mucosa and reduce or block the infection. Thereby, G2-S16 did not affect the production of CCL3 and CCL4 chemokines in MØ, suggesting that treatment with G2-S16 did not induce infiltration of cells or inflamed tissue mediated by CCL3 and CCL4 in *in vivo* models. This dendrimer did not affect the genes expression pattern associated at MØ by using GeneCard (Q-PCR). We showed that mice treated with G2-S16 maintained a normal vaginal microbiota. G2-S16 exerts anti-HIV-1 activity at an early stage of viral replication blocking gp120/CD4/CCR5 and providing a barrier to infection. G2-S16 was stable at different pHs and in presence of seminal fluids, mantained the anti-HIV R5 and X4 activity overtime, did not generate G2-S16 resistance, retained the anti-HIV effect when exposed to semen enhanced viral infection (SEVI), and did not modify vaginal microbiota neither *in vitro* or *in vivo* in mice. The histopathological examination did not show vaginal irritation, inflammation or damage after administration of G2-S16 in female rabbits and mice. G2-S16 prevented 84% vaginal HIV-1 transmission in h-BLT mice and 100% HSV-2 vaginal infection in BALB/c mice. Interestingly, G1-S4 prevente 90% HSV-2 rectal infection. These new innovative and promising microbicides are very close to clinical trial and can contribute to the development of multi-purpose interventions to prevent HIV infection in women and men.

## Design of Multifunctional Nanomaterials for Drug Delivery Applications

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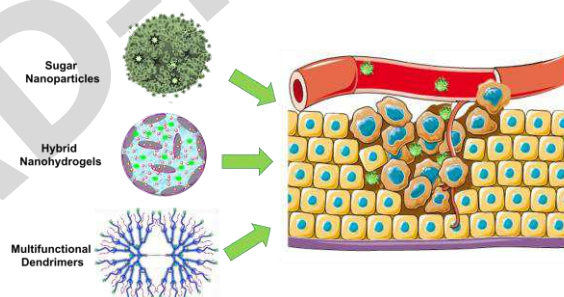
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The concept of nanomedicine has induced a paradigm shift in medicinal chemistry, in which many scientists are shifting their focus toward the development of new nanosystems to deliver drugs rather than developing new drug candidates. Nanomaterials bring important benefits into the drug delivery field due to its nanoscale size and multivalency [1].

Our research group is developing innovative biomaterials based on well-defined multifunctional dendrimers, polymer nanoparticles and biodegradable hydrogels. So far, our materials have showed high biocompatibility and promising results for drug delivery applications.

Stimuli-responsive sugar nanoparticles have been loaded with anti-neoplastic drugs and have showed an increase of efficiency and selectivity against prostate cancer cells [2].

A new nanohydrogel drug delivery platform based on Laponite nanodiscs was developed described. *In vitro* and *in vivo* studies demonstrate that the new nanohydrogels are biocompatible, biodegradable, nonswellable, pH-responsive, non-cytotoxic, and able to deliver antineoplastic drugs into cancer cells. These nanohydrogels are a versatile platform that enables the simultaneous encapsulation of several cancer drugs, yielding an efficient drug cocktail delivery system, which for instance, presents a positive synergistic effect against MCF-7 cells [3].



**Figure 1.** Schematic representation of the nanomaterials developed in our research group.

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[IOC8]

## Development of Photonic Crystals for Coating Sensing Design

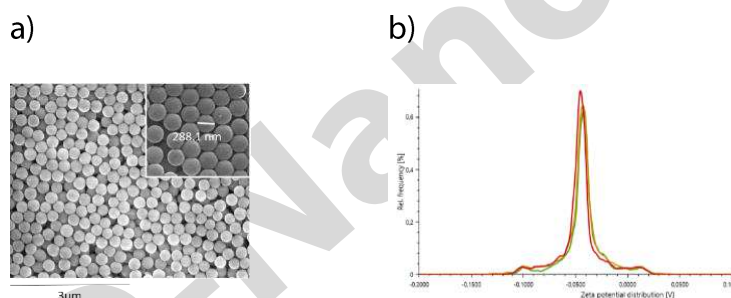
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Photonic crystals (PCs) are self-assembled highly monodispersed structures with periodic variations in the dielectric permittivity and a photonic band gap (PBG) [1,2]. The presence of this PGB determines their ability to control the propagation of light, allowing them to be an ideal platform for novel coatings development and biosensing applications. As a colloid-based porous material, PCs are promising structures since their geometry and cavities are tunable [3].

Taking into account a societal demand to develop simple, reliable and inexpensive devices as diagnosis tools, we are exploring, in an ongoing project, PC-based coatings/biosensors to transduce a physical change in their structure to optical properties. A series of PCs have been designed, synthesised and characterized (Figure 1). This communication will present and discussed the last results of this project.



**Figure 1.** a) SEM image of a PC ordered structure, and b) Zeta potential of a PC solution.

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## Analysis of the Putative Ligand Binding to CARF Domain of Csx1 Protein Using Molecular Docking and Molecular Dynamics Simulations

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Csx1 and Csm6 proteins are encoded by the genes linked to the type III CRISPR-Cas systems. Cyclic RNA oligonucleotides (but not their deoxyribose variants) were shown to be activators of Csx1 ribonuclease activity in Csx1 and related Csm6 proteins [1,2]. However, the binding mode and the mechanism of the allosteric action of the ligand binding is not known. We explored possible locations of the cyclic (AMP)<sub>4</sub> ligand binding on CARF domain surface by docking ligand fragments to the experimentally solved structures. The best fit between the putative c-(AMP)<sub>4</sub> ligand and the protein was found for the Csx1 proteins. After the geometries of c-(AMP)<sub>4</sub> and c-(dAMP)<sub>4</sub> bound to the Csx1 protein were constructed, the resulting structures were subjected to 200 ns GROMACS [3] Molecular Dynamics (MD) simulations. Analogous simulations were also performed without the bound ligand. Principal Component Analysis and Correlation Network Analysis of the liganded and unliganded Csx1 MD trajectories revealed striking differences in the protein dynamics between apo- and liganded proteins, yielding clues to the effect of the ligand.

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# **ORAL COMMUNICATIONS**

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## DNA/PAMAM Dendrimer Films: A Promising Doxorubicin Delivery Platform for Anticancer Therapy

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In several scientific fields, from Materials to Biomedicine, the interactions between nucleic acids and polymers have been studied and used for a broad range of applications. Deoxyribonucleic acid (DNA) and poly(amidoamine) (PAMAM) dendrimers can establish electrostatic interactions due to their opposite charges, by self-assembly, forming dendriplexes [1]. These structures, which are influenced by environmental conditions and PAMAM's physical and chemical properties, have been studied and used as models of DNA-histone interactions in nucleosomes [2]. PAMAM dendrimers have been used as drug delivery systems by transporting drugs adsorbed/conjugated at their surface or by encapsulating them in their interior [3]. On the other hand, DNA materials may also be regarded as good systems for drug delivery due to their affinity for several drugs, especially anticancer drugs [4]. Here, we report the multivariable-dependent preparation of DNA/PAMAM films, solely based on the electrostatic interactions of both components, for sustainable anticancer drug delivery. The obtained films showed a high DNA content, a positive surface zeta-potential, a unique morphology and gelation-induced supramolecular chirality. Stability studies revealed a highly stable and water-insoluble film, with negligible degradation/DNA release along time. Anticancer drug loading was possible for DNA-intercalating/binding drugs such as doxorubicin (DOX) and cisplatin (cisPt), but controlled drug release was only observed for DOX which establishes non-covalent interactions with DNA. Accordingly, *in vitro* cell studies showed that DOX-loaded films were as cytotoxic as DOX+cisPt-loaded ones. The results show that these new DNA/PAMAM dendrimer films may have a great potential as anticancer drug delivery platforms.

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[OC2]

## DNA Delivery Using a Self-assembling Nanohybrid of Fluorescent Carbon Dots and PAMAM Dendrimers

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Carbon Dots (CDs) are a class of zero-dimensional nanomaterials that were discovered in 2004 by Xu *et al.* [1]. CDs are spherical, have a size-range between 1-10 nm, and very interesting properties such as low cytotoxicity, fluorescence, surface functionality, water solubility, and photostability.

Polyamidoamine (PAMAM) is a class of dendrimers which are made of repetitively branched subunits of amide and amine functionality. PAMAM dendrimers have a spherical shape and a size range between 2-10 nm and possess varied properties like as uniform size, controlled molecular weight, and surface functionality [2].

CDs and PAMAM dendrimers carry unique properties that can be used for biomedical applications, and especially for gene delivery [3,4]. Both were already used individually for that purpose but were never combined to deliver DNA. The CDs/PAMAM dendrimer conjugation is not so extensively studied, and only a few groups reported the conjugation either for metal detection or drug delivery, therefore the conjugation between the two constitutes a new research opportunity [5,6].

Herein, we report the synthesis of a self-assembling nanohybrid between CDs and PAMAM dendrimers for DNA delivery purposes. The synthesis of CDs/PAMAM nanohybrid was made by combining CDs and PAMAM dendrimer at room temperature for 24 hours. The fluorescence quenching results confirmed the interaction between CDs and PAMAM dendrimer indicating the formation of a conjugate. Further techniques such as UV-Vis, and FT-IR were also used for characterization. Biological studies namely DNA condensation and cytotoxicity were also made, and the results confirm the potential use of the CDs/PAMAM conjugates for gene delivery applications.

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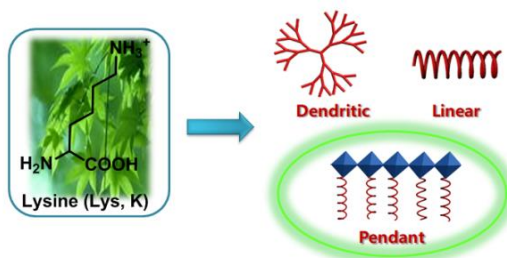
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## Green Nanobiomaterials: Natural (l)-lysine-based Functional Macromolecules/Polymers for Gene Delivery Application

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For sustainable R&D, using renewable and biocompatible natural product resources to construct functional biomaterials towards therapeutic/diagnostic application has been attracted great attentions [1]. In the past 7 years, we developed series of new natural (l)-lysine-based amphiphilic functional macromolecules/polymers [2-4]; they were able to self-assemble into controllable nano-assemblies as functional biomaterials for gene (pDNA) delivery. The results demonstrated that these (l)-lysine-based functional nano-biomaterials possess good biocompatibility and high *in vitro* gene delivery efficiency. Furthermore, the related structure-function relationships and cell biological mechanisms were deeply investigated. In the forthcoming works, we will continue design and prepare natural-based functional nano-biomaterials with the merit of controllable/adjustable/responsible manners towards multi-modality theranostic biomedical applications.



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[OC4]

## Novel Low Generation Ruthenium (II)-based PAMAM Dendrimers: Synthesis and Cytotoxicity Studies

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In recent years, ruthenium compounds have emerged as promising anticancer drugs and are regarded as an alternative for cisplatin and its derivatives. Being transported by albumin or transferrin to tumour cells and internalized by endocytosis, they can inhibit the DNA replication, reduce the RNA synthesis and/or induce cell apoptosis [1]. Furthermore, when functionalized into the periphery of dendrimers, producing metallodendrimers, their anticancer activity is enhanced, and they can selectively target tumours through the EPR effect [2].

Our goal was to prepare novel ruthenium(II)-based PAMAM dendrimers – G0 to G3-(CNRuCp(PPh<sub>3</sub>)<sub>2</sub>)<sub>x</sub>(CF<sub>3</sub>SO<sub>3</sub>)<sub>x</sub> (where  $x = 4, 8, 16$  and  $32$  for G0, G1, G2 and G3, respectively) – to evaluate their antitumor activity against human cancer cell lines. They were prepared via coordination of the Ru( $\eta^5$ -C<sub>5</sub>H<sub>5</sub>)(PPh<sub>3</sub>)<sub>2</sub>]<sup>+</sup> moiety on the periphery of G0 to G3-PAMAM dendrimers through nitrile terminal groups. This synthetic strategy was adapted from the reported methodology previously developed by our group [3], using as structural characterization techniques the 1D/2D-NMR (<sup>1</sup>H, <sup>13</sup>C, <sup>31</sup>P, COSY, and HSQC), FTIR, EA and MS. The cytotoxicity of the metallodendrimers and their precursors (G0 to G3-(CN)<sub>x</sub> and [Ru( $\eta^5$ -C<sub>5</sub>H<sub>5</sub>)(PPh<sub>3</sub>)<sub>2</sub>Cl]) was evaluated against A2780, A2780cisR and MCF-7 human tumor cell lines and against a non-tumorigenic HEK-293T human embryonic kidney cell line. They present distinguished *in vitro* cytotoxicity against the cisPt resistant human ovarian carcinoma cell line (A2780cisR) and against the others tumor cell lines at a nanomolar range, which suggests the superior anticancer activity of the ruthenium(II)-based metallodendrimers vs. platinum-based systems.

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## Multifaceted Applications on Carbon Nanomaterials

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Carbon dots (CDs) are luminescent nanomaterials having good biocompatibility and low toxicity. Being a nanoparticle, it exhibits additional features arising from their dimension over other fluorescent probes. The photo-luminescence property of CDs and their size distribution in the nanorange made them a research point in various fields, along with their synthesis, surface passivation, doping, and toxicity profile [1].

This presentation is focused on the different applications we have obtained for several carbon nanoparticles doped with heteroatoms (N, S, and P) such as chemical sensing, antibacterial [2], and imaging areas [3]. Moreover, hybrid materials based on metal-organic frameworks (MOFs) with S- and N-CDs [1], will be presented and, compared with their antibacterial activity [4].

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[OC6]

## Extracellular Nanofibres and Cancer

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Cancer development is marked by a massive increase of fibres in the extracellular microenvironment. In contrast to the normal microenvironment, the cancer microenvironment promotes growth of cancer cells [1]. In addition, cancer cell migration along extracellular fibres causes tumor-cell invasion and metastasis, the number one cause of human death in cancer. However, how the fibres in the cancer microenvironment control cancer remains to be fully clarified. In order to determine how the stiffness of extracellular fibres controls cancer, we used microengineered nanofibres of different elastic modulus [2], seeded normal human cells on soft and stiff fibres, and analysed the size, shape, cell-fibre-adhesions and the cytoskeleton of the cells. Our preliminary observations suggest that cells on soft fibres are elongated, have well defined F-actin protrusions, large adhesions and/or adhesions that are aligned along the fibres. In contrast, cells on stiff fibres showed less elongation, less organized F-actin and adhesions, with small adhesions at the end of thin filopodia or lamellas. F-actin rich protrusions not linked to fibres were more common in cells on soft fibres.

Taken together with earlier observations of the cytoskeletal and adhesion changes that accompany oncogenic transformation and metastasis in these cells [3], our data suggest that the elastic modulus/stiffness of nanofibres in the extracellular microenvironment controls the transformation of normal cells to cancer cells, and cell invasion.

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## Marine-based Nanomaterials for Tissue Engineering

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The ocean offers an enormous source of natural compounds with wide biomedical applications. They have properties like biocompatibility, biodegradability and malleability as well as anti-inflammatory and antimicrobial actions [1]. Marine-derived biomaterials have been studied for tissue engineering, namely calcium phosphates (such as hydroxyapatite from fish bones), chitosan (from squid endoskeletons and structurally similar to glycosaminoglycans), and collagen type II (from jellyfish and also present in cartilage structure). Hence, additional efforts have been placed on finding ways to use these valuable marine resources more efficiently and in a sustainable way on tissue regeneration [2].

The application of nanotechnology in the field of regenerative medicine has been exploited in our group with promising challenges for future biomedical concerns. Nanomaterials based on marine resources have been developed for application in bone and cartilage tissue engineering. A rational design of nanogels has been devoted concerning the choice of marine-resources composition, their stability and safety. The preliminary results have demonstrated effective outcomes using human mesenchymal stem cells differentiated into osteoblasts.

This project is well aligned with 2030 Agenda, concerning Goal 3 for ensuring the healthy lives and promoting well-being for all at all ages, and also concerning Goal 14 for the conservation and sustainable use of oceans and marine resources, where the ecological exploitation of Madeira Atlantic area is highly encouraged.

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[OC8]

## Platinated Low-generation of PAMAM Dendrimers as Drug Delivery Vehicles for Cancer Treatment

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The use of nanocarriers to delivery anticancer drugs and improve the therapeutics by enhancing the uptake and minimizing the side-effects have been, nowadays, used as a strategy. This behavior is because the selective release increases the drug concentration in a specific site of the body due to enhanced permeability and retention (EPR) effect of the drug in tumour tissues [1,2]. In the current work, low generation of anionic poly(amidoamine) (PAMAM) dendrimers were used as a nanoplatform to improving the efficacy of *cisplatin* by delivering it in tumour cells. Two different approaches were implemented in this study. In the first approach, *cisplatin* was directly conjugated to the anionic PAMAM dendrimer in a *monodentate form*. In the second approach, silver nitrate was used to remove both chloride groups from the *cisplatin* structure before the addition of the anionic PAMAM dendrimer allowing the *bidentate form* conjugation. Moreover, the type of the conjugation will determine the efficacy of the nanosystem. The prepared metallodendrimers were characterized by different techniques, including NMR, Dynamic Light Scattering, Infrared Spectroscopy, Ultraviolet-visible and Fluorescence Spectroscopy. Preliminary results revealed that depending on the generation of the anionic PAMAM dendrimer the monodentate or bidentate form is more effective against the A2780 and A2780cis cell lines.

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## Evaluation of the Nanotoxicity of PAMAM Dendrimers by <sup>1</sup>H NMR Metabolomics in Different Cell Lines

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The rapid growth in the development of nanoparticles for use in a variety of applications, including targeted drug delivery, cancer therapy, imaging, and sensors, has led to concerns related with the potential toxicity of such particles in humans [1]. Dendrimers represent a class of nanomaterials having unique molecular architectures and physicochemical properties that make them good candidates as delivery vehicles in the biomedical field [2]. They are amongst the nanomaterials investigated for cancer diagnostic and treatment applications since they can target solid tumor sites through the enhanced permeability and retention effect and/or by active targeting after adequate chemical functionalization [3]. However, the cellular effects of dendrimers are scarcely explored in the literature. Metabolomic technologies can provide high-throughput screening information regarding the effects of exogenous materials and compounds on cells [4]. The aim of this project is the assessment of the *in vitro* cellular effects of polyamidoamine (PAMAM) dendrimers, generation 4, in different cell lines, by <sup>1</sup>H NMR metabolomics, to understand their mechanism of action and guarantee that their use in the biomedical field is non-dangerous. Experiments were done using extracts of fibroblast (NIH 3T3), human osteosarcoma (CAL-72) and human ovarian carcinoma (A2780) cells (treated and non-treated cells were analysed). Around 35 metabolites were identified in these cell lines and quantified using Chenomx NMR Suite software (evaluation version). The statistical analysis showed that the dendrimer differently affected each cell line. Our results also revealed that it is possible to identify groups of expressed metabolites characteristic of each cell line. This work confirms the effect of PAMAM dendrimers on the three types of studied cell lines and the power of <sup>1</sup>H NMR metabolomics as an easy tool for cellular, molecular profiling and for studying the effects of nanomaterials on cells.

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[OC10]

## Low Generation of Ruthenium Metallodendrimers: a Promising Metallodrug to Fight Cancer

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Cancer is one of the leading causes of death worldwide. Therefore, is essential to discover new treatments to fight against this disease. Metal complexes, such as ruthenium, have been explored as new therapeutics as anticancer drugs for their diversity and characteristics [1,2]. Ruthenium has proved its potential against different types of cancer presenting less toxicity when compared with platinum drugs [2,3].

Here we describe the use of dendrimers combined with ruthenium complexes as a potential anticancer agent. Based on our previous work [4] we present a family of low generation poly(alkylideneamine)-based dendrimers (generation 0, 1 and 2) and their biological studies. Briefly, we designed and characterized a new family of dendrimers with nitrile terminal groups functionalized with the ruthenium moiety  $[\text{Ru}(\eta^5\text{-C}_5\text{H}_5)(\text{PPh}_3)_2]^+$ . The compounds were characterized by NMR (<sup>1</sup>H and <sup>31</sup>P), FTIR, and zeta potential techniques. Their *in vitro* anticancer activity was also evaluated against several cancer cell lines. These metallodendrimers present good anticancer activity at a nanoscale concentration range when compared to the metallodrug cisplatin.

**Acknowledgments:** This research was supported by Fundação para a Ciência e a Tecnologia (FCT) with Portuguese Government funds through the CQM Strategic Project UID/QUI/00674/2013, and the Ph.D. Grant SFRH/BD/102123/2014 (D.M.). The Madeira 14-20 Program, through the project PROEQUIPRAM - Reforço do Investimento em Equipamentos e Infraestruturas Científicas na RAM (M1420-01-0145-FEDER-000008) and ARDITI-Agência Regional para o Desenvolvimento da Investigação Tecnologia e Inovação, through the project M1420-01-0145-FEDER-000005 - Centro de Química da Madeira - CQM<sup>+</sup> (Madeira 14-20 Program) are also acknowledged.

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# POSTER COMMUNICATIONS

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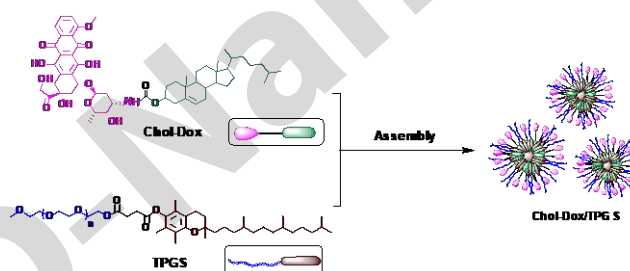


## Self-assembly of Chol-Dox and TPGS into Prodrug-based Nanomaterials for Combinatorial Tumor Chemotherapy

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In this work, we demonstrated a prodrug-based drug delivery nanosystem by self-assembling of Cholesterol Doxorubicin conjugate (**Chol-Dox**) and Tocopheryl polyethylene glycol 1000 succinate (**TPGS**) prodrugs using thin-film hydration method [1]. The **Chol-Dox/TPGS** assemblies (molar ratio 2:1, 1:1 and 1:2) were able to form nanoscaled particles (**Figure 1**) with the average hydrodynamic particle diameter of 100~200 nm, surface zeta potential of -0.4~-20.6 mV, and remarkable solution stability (in 0.1M PBS, 30 days). Notably, the Doxorubicin loading and releasing properties could be adjusted by changing the molar ratio of **Chol-Dox** and **TPGS**, thus leading to controllable tumor inhibition. The results demonstrated that the **Chol-Dox/TPGS** assemblies could be employed as promising candidates for prodrug-based nanomaterials for combinatorial [2] tumor chemotherapy.



**Figure 1.** Molecular structures of the Chol-Dox and TPGS and their Chol-Dox/TPGS assemblies in aqueous solution.

**Acknowledgments:** We greatly acknowledge ARDITI-Agência Regional para o Desenvolvimento da Investigação Tecnologia e Inovação (project M1420-01-0145-FEDER-000005-Centro de Química da Madeira-CQM+); FCT-Fundação para a Ciência e a Tecnologia (project PEst-OE/QUI/UI0674/2013, CQM, Portuguese Government funds), and Madeira 14-20 Program PROEQUIPRAM - Reforço do Investimento em Equipamentos e Infraestruturas Científicas na RAM (project M1420-01-0145-FEDER-000008). RS and ARN also acknowledge ARDITI and CQM for their fellowship grants ARDITI-CQM\_2017\_003-ISG and ARDITI-CQM\_2017\_011-PDG, respectively.

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[PC2]

## Synthesis and Characterization of Oligo(phenylene-ethynylene)s Having Triazene Clip Terminal as Anticancer Agents

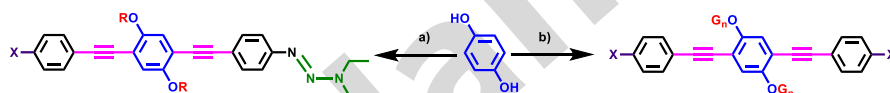
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Oligo(phenylene-ethynylene)s (OPEs) are luminescent linear oligomers with extended conjugated aromatic and ethynylene moieties. They have optical, electronic properties and lately gained an important role in the biological fields [1]. For example, they can be light-activated biocides, inhibitors of bacteria [2], luminescent and fluorescent labeling probes for proteins, liposomes and mammalian cell membranes [1]. Several polymers with triazene moieties were tested for their biological activity (>N=N=N-) and were successfully used in cancer therapy [3]. Ruthenium complexes have attracted much interest as a promising alternative to platinum, showing a remarkable antitumoral and antimetastatic activity, associated with lower toxicity [4]. Following our previous work [5-6], the objective of this project is to synthesize and characterize two families of compounds of non-metalled and metalled  $\pi$ -conjugated OPEs using a triazene clip terminal and evaluate their anticancer activity.



**Scheme 1** – General synthetic strategy. a) Triazene clip terminated; b) dendrons as a protective sheath OPEs derivatives. R= CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>; X= H, CH<sub>3</sub>(CH<sub>2</sub>)<sub>7</sub>, CCSi(CH<sub>3</sub>)<sub>3</sub>, CCH, CCRu; G= Bis-MPA.

The synthetic pathway involves a Pd/Cu-catalyzed coupling reaction between aryl bromides/iodides and terminal alkynes. The OPEs are functionalized with donors and acceptor groups, and with Ru complex. All oxygen-sensitive reactions are performed under an Argon or N<sub>2</sub> atmosphere. The compounds were prepared and structurally characterized using various techniques (NMR, FTIR, and EDX). Afterward, the anticancer activity of these compounds will also be evaluated.

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## Hyaluronic Acid-Modified Dendrimer Entrapped Gold NPs

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For a long period, advances in cancer treatment have only been translated into improvements in patient care but not into the improvement of early-stage diagnosis [1]. Nanomedicine has become a rapidly emerging field, allowing for the use of nanoparticles (NPs) in several biomedical applications. Poly(amidoamine) (PAMAM) dendrimers are considered perfect templates for the synthesis of inorganic NPs due to their nanoscale size, controlled shape, well-defined composition and monodisperse distribution [2]. Moreover, due to their high surface charge, the modification of the terminal groups of PAMAM dendrimers with targeting molecules, imaging agents or drugs is possible. Gold (Au) NPs have been used as imaging agents for X-ray computed tomography (CT) due to their strong X-ray attenuation properties [3]. For this work, regarding the development of a new imaging agent for targeted CT imaging of CD44 overexpressing cancer cells, hyaluronic acid (HA)-modified dendrimer-entrapped gold nanoparticles (Au DENPs) were prepared. For this, HA, which is a naturally occurring glycosaminoglycan frequently used as a drug carrier and a targeted ligand for CD44 receptors [4], was conjugated to amine-terminated generation 5 PAMAM dendrimers (G5.NH<sub>2</sub>). This conjugate served as a template for the synthesis of Au DENPs. Characterization results of the formed HA-modified Au DENPs were obtained by <sup>1</sup>H NMR spectroscopy, dynamic light scattering, zeta potential measurements, UV-Vis spectroscopy and SDS-PAGE. Preliminary cytotoxicity studies on the obtained compounds will also be presented.

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[PC4]

## Ligand Development by Phage Display Technology – Application to Bionanosensors for the Diagnosis of Zika

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Zika is an infectious disease with a recent worldwide outbreak. Current diagnostic tools for this disease is based on serological studies and antigen/genome detection, which are time-consuming and require specialized laboratory equipment [1]. Specificity is also a problem since cross-reactivity with other similar viruses is common and will originate false positive results. Therefore, the main purpose of this work is to overcome these challenges by developing an approach, based on phage display technology, that will allow for an early, rapid and differential routine diagnosis of Zika.

The phage display technique allows for the presentation of randomized peptide sequences on the surface of bacteriophages [2]. Large peptide libraries can be displayed and used for affinity screening of specific target molecules. Phages bound to a specific target go through several repeated cycles in order to produce a phage mixture enriched with the relevant phage-displaying peptides. The target-binded bacteriophages are thus amplified and the correspondent peptides identified and characterized.

In this work, a peptide library is being used towards Zika-specific molecules having in view the identification of peptides which will be further used as components in bionanosensors. This work will provide new insights into the development of robust bionanosensors as diagnostic tools for Zika virus detection with high sensitivity and selectivity. The ideal outcome will be an innovative biosensing method for non-invasive, rapid, and in real time diagnosis.

**Acknowledgments:** This work is supported by FCT-Fundação para a Ciência e a Tecnologia (project PEst-OE/QUI/UI0674/2013, CQM, Portuguese Government funds), and through Madeira 14-20 Program, project PROEQUIPRAM - Reforço do Investimento em Equipamentos e Infraestruturas Científicas na RAM (M1420-01-0145-FEDER-000008) and by ARDITI-Agência Regional para o Desenvolvimento da Investigação Tecnologia e Inovação through the project M1420-01-0145-FEDER-000005 - Centro de Química da Madeira - CQM+ (Madeira 14-20).

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## Sub-Nanomolar and Selective Detection of Dopamine in Human Fluids by N-Doped Carbon Dots

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N-doped carbon dot (N-CD) nanoparticles were obtained by a one-step green approach [1]. Using HR-TEM, spherical, well-dispersed nanodots with a mean average size of 19 nm were visualized. Moreover, this morphological analysis demonstrated ordered, thin-layered nanosheets. XPS, ATR and fluorescence spectra were also acquired supporting the typical surface functionalization with carbonyl ( $-C=O$ ), amine and amide groups, as well as an excitation wavelength dependence. Cytotoxicity evaluation using HEK293T cells finally demonstrated a biocompatible nanomaterial to be applied in the bioanalytical area. To demonstrate their feasibility in the detection area, dopamine was selected to be quantitatively analyzed. The fluorescence technique implemented demonstrated the capacity of the CDs to detect dopamine at 430 nm (excitation at 350 nm), showing a quenching effect. Stern-Volmer plots showed a linear response in the range of 0.5 to 100  $\mu\text{g/L}$ . The developed system/method was applied in human fluids. Relative standard deviations ( $n=3$ ) of 0.2-1% and 0.1-0.8% obtained for urine and human serum respectively comprised between 5-75  $\mu\text{g/L}$  dopamine. The method has an excellent selectivity against other related molecules and ions.

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[PC6]

## Supported Copper-Based Nanoparticles: An Ascorbic Acid Redox Approach

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Nanoparticles (NPs) prepared from earth-abundant metals have attracted significant consideration for their potential as viable replacements for expensive metals used in many commercial chemical processes [1]. In this context, copper NPs are particularly appealing since copper (Cu) is vastly abundant and cheap. Cu also displays good electronic, optical, antimicrobial, and chemical properties. Yet, CuNPs are limited due to their intrinsic instability under atmospheric conditions, making them prone to oxidation. Various efforts have been made to increase the stability of CuNPs, including investigating Cu-based NPs associated with organic structures, such as polymers like polyvinylpyrrolidone (PVP) and dendrimers [2,3].

This project was focused on the preparation and characterization of long-term stable Cu-based NPs, using different synthesis strategies and without employing harmful reagents or solvents. Based on previously reported methods [2,3], the particles were synthesized using the environmentally friendly ascorbic acid (AA) as a reducing agent. PAMAM dendrimers and PVP were used as templates and capping agents, and the reactions were done at 60°C and room temperature. The particles underwent various characterization techniques, including Ultraviolet-Visible Spectroscopy and Scanning Electron Microscopy coupled with Energy-Dispersive X-ray Analysis. The results indicate the presence of diversely shaped Cu<sup>0</sup>, Cu<sup>1+</sup>, and Cu<sup>2+</sup>-based particles (e.g. polyhedral, spherical, and disk-like). Preliminary evaluation of the cytotoxicity using HEK 293T cells show that the particles attained using PAMAM and PVP do not present significant toxicity at concentrations below 500 and 5µg/mL, respectively.

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## Olive Tree Biomass to Produce Nanoparticles

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Olive tree biomass (OTB), a waste product derived from the pruning of olive trees, has a high carbohydrate content that has attracted the biorefinery industry [1]. Nevertheless, these scraps are traditionally and naturally used in heat production [2]. The emergence of nanotechnology, which has made the production of non-toxic, carbon-based nanoparticles possible, provides a compelling opportunity for the treatment of such materials with enormous advantages [3, 4].

In this work, OTB was subjected to a soft one-step treatment in which trifluoroacetic acid (TFA) treatment and different catalysts were used. Fluorescent nanosized (5 nm) particles of interest were obtained that displayed the characteristic behaviour of carbon dots (CDs). After characterization, the CDs showed a fluorescence emission at 520 nm (with excitation at 420 nm) and a noticeable excitation dependence, while XPS analysis revealed the surface functional groups on the surface of the CDs.

Studies evaluating the effects of the nanoparticles on HEK 293T cells were also performed. Here, the nanoparticles were shown to be biocompatible with an ability to be used as (bio)chemical sensors.

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[PC8]

## Exploratory Evaluation of the Potential of Magnetic NPs as Powerful Sorbents for Extraction of Cancer Biomarkers

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Cancer, one of the most deadliest diseases of the world, is characterised by metabolic alterations that cause cells abnormal growth resulting in an uncontrollable proliferation. To reduce the mortality due to the different type of cancer diseases, the early diagnosis is essential to the treatment become more effective [1-6]. One of the most promising areas towards cancer diagnosis is the metabolomics which detects a specific metabolite profile from biological fluid samples. This profile consists of a panel of small molecules derived from a global or target analysis that can be acquired through high-resolution analytical methods, including the nuclear magnetic resonance (NMR) spectroscopy and ultra high-performance liquid chromatography (UHPLC) [1, 2]. In recent years, magnetic nanoparticles (MNPs) have been widely used in oncology for tumour targeting and contrast agent for magnetic resonance image diagnosis (MRI). The most researched MNP are the magnetite ( $\text{Fe}_3\text{O}_4$ ) and maghemite ( $\text{Fe}_2\text{O}_3$ ) due to ease of synthesis, low cost, and biocompatibility. However, their sorption capacity towards cancer biomarkers remains unknown [4-8]. This study aims to evaluate the adsorption capacity of magnetic nanoparticle - magnetite ( $\text{Fe}_3\text{O}_4$ ) and maghemite ( $\text{Fe}_2\text{O}_3$ ) towards the extraction of cancer biomarkers present on urine using the  $^1\text{H}$  nuclear magnetic resonance ( $^1\text{H-NMR}$ ) spectroscopy. To achieve this, the extraction methodology was optimised on fortified synthetic urine regarding MNP quantity, ultrasound stimulation time and temperature, whereas the best optimization results will be applied on a validation with urine samples of breast, colon, and lung cancer patients and healthy volunteers to identify and quantify the biomarkers.

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## Modification of Electrodes with N-and S-doped Carbon dots. Evaluation of the Electrochemical Response

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Nitrogen and sulfur-doped carbons dots (N-CDs and S-CDs) have been synthesized with a hydrothermal method and incorporated as surface electrode modifiers to evaluate their electrochemical properties. In contrast to standard CDs, which can be deposited over carbon electrodes in a stable and durable way, water solubility of the doped carbon dots forced us to test other modification strategies. The procedure finally followed was to incorporate doped CDs in a graphite/polystyrene ink, in a weight ratio of 10%. The first task was to characterize the synthesized materials, for which different spectroscopies, scanning microscopies and elementary analysis were applied. Next, a glassy carbon electrode (GCE) was thus surface-modified with the doped CDs and applied for the effective enhancement of the electrochemical signal of different organic compounds corresponding to different families. This modification needed a first activation using a 10 mM solution of H<sub>2</sub>O<sub>2</sub> to obtain a properly conductive surface. The compounds tested to check electrochemical behavior were tryptophane, cysteine and tyrosin (oxidizable aminoacids), salicylic acid and acetaminophene (pharmaceutical compounds) and ascorbic acid (a natural antioxidant). Modified GCEs exhibit an enhanced sensitivity, probably caused by enlargement of active surface, but in addition, signals of salicylic acid were shifted to lower potentials, what is a proof of the increase of the heterogeneous electron transfer rate and demonstrated an enhanced electrochemical response. The effect of the doping heteroatom on the response is more noticeable for N-CDs than for S-CDs, but both displayed better responses than the unmodified CDs, resulting on an increase of two times the response of the GCE. Moreover, the voltammogram shape for each nanomaterial are different, making it a valuable characteristic for the use of modified CDs in sensor arrays for electronic tongues.

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[PC10]

## A Stunning Intrinsic Blue Florescence From the Exceptional Class of Dendrimers - PAMAM Dendrimers

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The unique class of dendrimers, PAMAM dendrimers, with their innumerable applications in different areas are considered a potential nanocarrier in the biomedical field [1,2]. In this work, we studied different generations of amine-terminated PAMAM dendrimers (3,4 and 5) having in view the enhancement of their intrinsic fluorescence without labelling any dye. For that purpose it was used an oxidative treatment.

Photoluminescence/absorbance studies in solid and liquid state as well the cytotoxicity of the different generations of fluorescent PAMAM dendrimers were performed. In addition, doxorubicin was encapsulated in generation 4 and its release profile in different pH media (PBS 7.4 and 5) where compared with the pristine PAMAM dendrimer.

Our results demonstrate that is possible to increase the intrinsic fluorescence of PAMAM dendrimers and at the same time reduce their toxicity and used these fluorescent dendrimers as drug carriers and as bioimaging systems, making them a promising nanocarrier in the future.

**Acknowledgments:** This research was supported by Fundação para a Ciência e a Tecnologia (FCT) with Portuguese Government funds (CQM Strategic Project PEst-OE/QUI/UI0674/2013) and by IDR through the Project PROEQUIPRAM-Reforço do Investimento em Equipamentos e Infraestruturas Científicas na RAM (M1420-01-0145-FEDER-000008). The support of ARDITI - Agência Regional para o Desenvolvimento da Investigação Tecnologia e Inovação through the project M1420-01-0145-FEDER-000005 - Centro de Química da Madeira - CQM<sup>+</sup> (Madeira 14-20) and through the project M1420 - 09-5369-FSE-000001- PhD Grant is also acknowledged.

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## Poly(alkylidenamine) Dendrimers with Anionic Terminal Groups as a Potential Microbicide Against HIV-1 Infection

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Human immunodeficiency virus (HIV) is an infectious disease responsible for millions of new infections each year. Nanotechnology has progressed in discovering new nanomaterials, such as dendrimers, to be used in the diagnosis, treatment, and prevention of all kind of diseases [1, 2]. Anionic dendrimers, for instance, have exhibited promising outcomes as antiviral agents against HIV-1 infection [2].

In this work, we describe the synthesis and characterization of poly(alkylidenamine) dendrimers, from generation 1 to 3 and their *in vitro* studies. The carboxylate and sulfonate dendrimers were characterized by <sup>1</sup>H- and <sup>13</sup>C-NMR, mass spectrometry (MS) and FTIR techniques. After that, the biocompatibility and antiviral activity were evaluated using the TZM.bl cell line and the R5-HIV-1<sub>NLAD8</sub> and X4-HIV-1<sub>NL4.3</sub> isolates, respectively. The results showed that G1C and G1S dendrimers presented high inhibition against R5-HIV-1<sub>NLAD8</sub> (more than 85%) and X4-HIV-1<sub>NL4.3</sub> isolates by blocking the entry of HIV-1. Moreover, they preserved their antiviral activity even at acidic pH values. Therefore, the prepared dendrimers have potential to be used as microbicide candidates against HIV-1 infection.

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[PC12]

## Exploring PAMAM Dendrimer-DNA Interactions using Coarse Grained Molecular Dynamics Calculations

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The Molecular Dynamics (MD) calculations involving large fragments of DNA are computationally prohibitive due to the sheer size of the system. For this reason, we chose to use a Coarse Grained (CG) MD, in which several heavy atoms were replaced with one specially parametrized particle, dramatically decreasing the system size. We used MARTINI force field [1] and GROMACS software [2] for our simulations. The coarse grained models of 200 bp ssDNA and G3 PAMAM dendrimer were mixed at the ratio used in the wet lab experiments, placed in a simulation box filled with the solvent and ions, and subjected to 400 ns MD simulation. In the presentation, the resulting emerging superstructure consisting of DNA partially wrapped around the dendrimers will be discussed.

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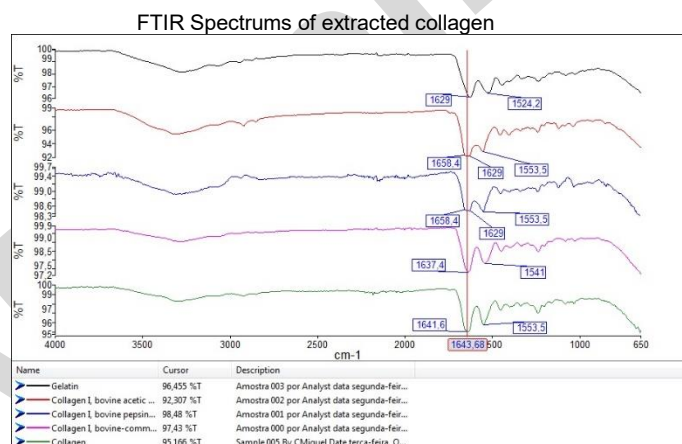


## Extraction and Characterisation of Collagen

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The ECM provides many cellular functions such as spreading, migration, proliferation and differentiation [1]. Therefore, it plays a major role in cancer metastasis. We aim to understand how extracellular nanofibres of collagen influence cell behavior in cancer. Collagen is one of the major constituents of ECM, and increased levels of extracellular collagen promote cancer. In order to purify collagen from Bovine tendon, we first removed non-collagenous proteins washed with NaOH and thereafter washed with acetone to remove fat. After, we used acetic acid and a combined pepsin and sonication treatment to extract collagen. Thereafter, we checked the purity of collagen with Fourier-transform infrared spectroscopy (FTIR) and compared the obtained spectrum with literature. The results show that our collagen is purified and well extracted from other molecules. Now we can use this purified collagen doubtlessly for making nanofibres with electrospinning to growth cancer cells in than analyze their growth and determine how the adhesion of normal *versus* cancer cells differ.



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[PC14]

## Laponite<sup>®</sup>-based Nanogels for Alendronate Delivery

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Osteoporosis is a bone disease that reduces bone mineral density with aging, often leading to fractures. Bisphosphonates (BPs) are the most effective treatment available for osteoporosis, due to their osteoclast inhibiting activity [1]. However serious gastrointestinal side effects are associated with BPs, such as esophagitis and ulcer of esophagus. Moreover, oral bioavailability of BPs is very low due to poor absorption through gastrointestinal tract. Laponite<sup>®</sup> is a synthetic clay with great potencial as a vehicle for drug delivery in nanomedicine since it can serve as a mean for the protection of drugs against degradation in the physiological environment, improve the bioavailability of bioactive compounds and help reducing their side effects in our organism [2]. Furthermore, Laponite<sup>®</sup> by itself has been associated with an osteogenic effect [2]. Therefore, this work proposes Laponite<sup>®</sup>-based nanogels as bone-targeted BPs delivery systems for the treatment of osteoporosis by both diminishing osteoclast activity and simultaneously promoting osteogenesis.

Laponite<sup>®</sup>-based nanogels containing alendronate (a type of bisphosphonate) were prepared and characterized using suitable physical and chemical techniques. The results obtained show that the developed Laponite<sup>®</sup>-based nanogels had a high encapsulation efficiency for alendronate and reduced the *in vitro* cytotoxicity effect of this compound. Also, osteogenic differentiation assays showed positive results, with the nanogels enhancing the process due to the presence of Laponite<sup>®</sup> in the formulation.

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## Biotechnology of Antimicrobial Peptides from Naturally Inspired Templates of Vertebrate Cathelicidins

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Due to the worrying increase in antimicrobial resistance to conventional antibiotics, the search for alternatives is becoming increasingly important. Antimicrobial peptides originating from natural resources are naturally found in a variety of invertebrate, plant and animal species, and they are involved in innate immunity. Antimicrobial peptides neutralize target pathogens through deleterious interactions with membrane components resulting in perturbation and/or lysis, or an ability to replicate or enter target mammalian cells. A further advantage of a membrane-targeted mode of action is that peptide antimicrobials are active against both metabolically active and non-metabolizing microorganisms, whereas most current antimicrobial agents are active only against replicating microbes, because they target key metabolic pathways required for multiplication.

Cathelicidins are found in varying numbers in numerous different vertebrate species. A remarkable degree of molecular diversity has been noted within this gene family. We have applied a bioinformatics approach to the identification of novel cathelicidins from the genome of vertebrates. The aim of this study was to identify novel AMP candidates, such as cathelicidins from organisms living in germ-filled environments by using refined computational methods. Immunological inspiration" attained from domestic and exotic species can likely provide us with superior templates for use in development of new immunomodulating and antimicrobial drugs.

We here illustrate a simple method for the identification of two cathelicidin genes in the genome of lower vertebrates (birds and reptiles) living in different environments, and thus surrounded by different pathogens. We also perform the bioinformatic analysis of the corresponding active peptides to detect possible antimicrobial properties and describe the functional characterisation of the two identified cathelicidins against a panel of reference microorganisms. Finally, we describe our current attempt for the biotechnological production of these peptides in the cyanobacteria *S. elongatus*.

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## Extracellular Nanofibres and Cancer

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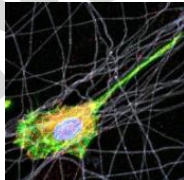
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The interactions between cells and the extracellular matrix influences basic cellular activities which can modify cancer development. To better understand the *in vivo* synergy among normal cells and the microenvironment, we produced nanofibers with different mechanics and architecture. We obtained nanofibers of different stiffness by varying the time that they were exposed to cross-linking UV light [1]. Normal fibroblasts cells were then seeded on these fibrillar microenvironment. To study how the fibres influenced cells, we then analysed the actin filaments, focal adhesions and the nuclei of the cells by confocal microscopy, as shown below. The collected data supports the hypothesis that the fibrous extracellular matrix stiffness regulates different cell properties such as general shape, size, cytoskeleton, cell-matrix-adhesions and the nucleus.

Normal cells on soft fibres



**Figure 1.** Normal cell seeded on nanofibres that were exposed to UV light for 10 seconds, stained for F-actin (green), phosphotyrosine (red), fibres (white) and cell nucleus (blue).

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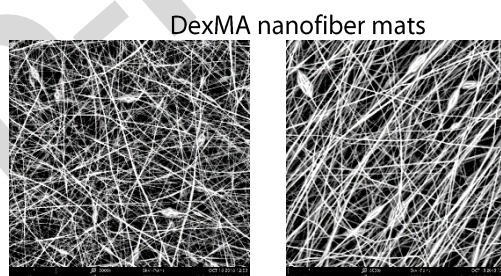
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## Electrospun Methacrylated Dextran Nanofibers for Cell Experiments

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Cells in the human body do not reside in a void. In contrast, cells are either surrounded by, or in contact with an intricate network of diverse nanofibers: the extracellular matrix (ECM). The ECM composition and structure vary between tissues and control cell functioning. ECM alterations are present in many diseases, including cancer, and are also essential for the wound healing process [1]. In order to understand how the ECM controls cell behavior, it is instrumental to perform cell culture experiments using substrates mimicking ECM at, ideally, the 3D level. ECM mimicking substrates are also useful for biomedical applications, e.g. wound dressings [1]. Electrospinning has been used for decades to prepare various types of nano- and microfibers [2], and there is a growing interest to produce nanofiber mats (2D) and meshes (3D) with clearly defined topology, stiffness and degree of functionalization, to determine how ECM controls cells in physiological and pathophysiological conditions. Methacrylated dextran (DexMA) is beneficial to use in electrospinning cell substrates, due to the possibility of fine tuning the fiber parameters as well as protease resistance [3]. We have successfully synthesized and characterized DexMA, and thereafter produced DexMA nanofiber mats and meshes with defined fiber orientation and stiffness, using electrospinning. We characterized the substrates with advanced microscopy techniques, such as scanning electron microscopy (SEM), and will use the substrates to deepen our understanding of tumor cell metastasis.



**Figure 1.** SEM images (5000x magnification) of the electrospun DexMA mats made of randomly oriented (left) or partially aligned (right) nanofibers.

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[PC18]

## Copper (II) Complexes Formed in the Presence of Low Generation Poly(alkylideneamine) Dendrimers: A UV-Vis Study

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Dendrimers are a well-known class of macromolecules, which present promising potential applications in life and materials science, due to their well-defined structure, controllable size and multivalence[1]. An important property of dendrimers is their three-dimensional nature which allows a possible complexation of metal ions in various sites per molecule[2]. Particularly, the interactions with copper ions are interesting to research as copper is an essential biological metal and its ions have shown various biological activity[3].

Following our previous work in the field of dendrimers chemistry[4], we aim to investigate the interaction, and possible complexation, of  $\text{Cu}^{2+}$  with poly(alkylideneamine) dendrimers having a hexanediamine core (HDA) core in aqueous solutions. To accomplish this, aqueous solutions of G0, G1 and G2 amine-terminated dendrimers, as well as, G1 and G2 sulfonate-terminated and G1, G2 and G3 carboxylate-terminated dendrimers, were mixed with an aqueous solution of  $\text{CuSO}_4$  (as a source of  $\text{Cu}^{2+}$ ) and studied using UV-Vis techniques.

Our preliminary results suggest the complexation of the copper with the dendrimers, as the ions move from the periphery to the interior of the dendrimer. Considering the geometry of  $\text{Cu}^{2+}$ , in the case of the carboxylate and sulfonate dendrimers, a  $\text{Cu}^{2+}\text{-N}_2\text{O}_2$  complex, involving two carboxylate/sulfonate groups and two tertiary amine groups, is a possible coordination mode. Although it is proposed that the coordination of the  $\text{Cu}^{2+}$  is stronger to the sulfonate oxygen, due to the higher wavelengths observed. For the interaction of the  $\text{Cu}^{2+}$  with the amine dendrimers, the formation of  $\text{Cu}(\text{NH}_2)_2\text{XY}$  complexes with the periphery primary amine, where X and Y are water and tertiary amine groups from the interior of the dendrimer, is suggested. Further studies are underway to confirm the proposed coordination modes.

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## Polyester Dendrimers as Delivery Vehicles for Doxorubicin

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Nanoparticle-based approaches for cancer therapy are currently on the spotlight due to their contribution to the improvement of drug's therapeutic efficiency and side effects [1]. Dendrimers have gathered special attention, because of their well-defined structure, wide variety of functional groups and high branching degree. However, poly(amidoamine) (PAMAM) dendrimers, which are the most studied family of dendritic structures, possess high cytotoxicity, and low solubility and biodegradability [2].

On the contrary, polyester dendrimers have been described as non-toxic, biocompatible and biodegradable. This class of dendrimers has gained a huge attraction from researchers [3,4] because they are also capable of encapsulation and/or conjugation of/to hydrophobic drugs, increasing their solubility, providing them protection from the surrounding environment, and avoiding their rapid body clearance [3]. Doxorubicin (DOX) is one of the most used anti-cancer drugs, although being associated with high severe, life-threatening cardiotoxicity side effects [5]. Taking into account all that has been previously stated, the goal of this work was to evaluate the possibility of using polyester dendrimers as DOX delivery vehicles. Dendrimers with different surface groups and generations were evaluated - generations 4 and 5 were selected to be studied, as well as dendrimers containing amine and hydroxyl surface groups. This study revealed that polyester dendrimers based on 2,2-bis(hydroxymethyl)propionic acid (bis-MPA) monomer are quite compatible, independently of the surface functional groups. The amine-terminated dendrimers exhibited a higher capacity to retain the drug whereas hydroxyl-terminated dendrimers could offer a more sustained and controlled release profile. These results were confirmed by the cytotoxicity studies performed in different models of cancer cell lines and in human mesenchymal stem cells (hMSCs). In summary, the results demonstrated that it is possible to adjust the drug delivery properties of polyester dendrimers by modifying their surface functional groups.

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