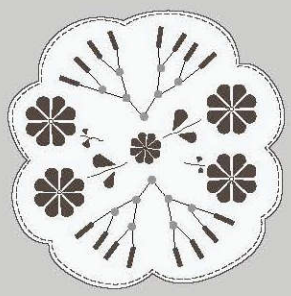

IDS11

11th INTERNATIONAL DENDRIMER SYMPOSIUM

FUNCHAL, MADEIRA - PORTUGAL

14-18 JULY 2019

BOOK OF ABTRACTS

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IDS11

Eleventh International Dendrimer Symposium

Abstract Book

14th – 18th July 2019

Funchal, Madeira Island – PORTUGAL

Abstract Book
IDS11 –11th International Dendrimer Symposium

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WELCOME MESSAGE

Dear Participants,

On behalf of the Advisory Committee, it is my pleasure to welcome you all to the IDS11 - 11th International Dendrimer Symposium in Funchal, Madeira Island. Organized for the first time in Portugal by the Centro de Química da Madeira and hosted by the University of Madeira, our IDS11 Symposium honours science, the pioneers of dendrimers and local tradition by having a logo inspired by dendrimers and by the world famous Madeira embroidery.

Being held every two years since 1999, the IDS is the most important conference worldwide devoted to the latest developments concerning design, synthesis, applications and future directions of dendrimers and dendritic polymers.

Thanks to the work of the Advisory Committee and of all participants, this IDS edition has an excellent Scientific Program involving 9 keynote lectures given by the most prominent and leading scientists in the field. Furthermore, it includes over 57 oral talks of which 24 are invited lectures and 11 are oral communications from young scientists. In addition, we will have 43 poster presentations with a final award session programmed for the best poster. Globally, this edition of IDS has around 120 participants representing 23 countries.

To maximize the opportunities to share new ideas and points of view, we decided to organize interdisciplinary sessions. To this end, we have reduced the number of parallel sessions and shortened the period of time for presentation. As such, we expect participants to focus on the presentation and discussion of new results instead of a parade of work that has already been published. As such, please do not forget to actively participate during the discussion periods and to use the free time provided for networking.

Although we have a very intense scientific program, participants will have the opportunity to visit and taste a bit of Madeira's natural heritage and traditions.

Discovered 600 years ago by the Portuguese navigators Tristão Vaz Teixeira, Bartolomeu Perestrelo and João Gonçalves Zarco, the Islands of Madeira and Porto Santo are considered to be the first territorial encounters in the "Portuguese Age of Discovery". With a subtropical Mediterranean climate, the "Laurisilva" forest of Madeira Island was recognized by UNESCO as a natural World Heritage Site. This, combined with the over 2000 km of "levadas" (aqueducts that carry water from the north coast of the Island to the agricultural regions in the south), have proven to be key factors in attracting tourists from all over the world throughout the year. Funchal, the capital and principal city of Madeira Island, displays a beautiful and natural amphitheatre of houses over the sea. The six centuries of history have transformed the town into a very charming place to visit, also remaining very open to modernity. Together with the most typical building that survives from the early period of Madeira colonization (the Gothic Cathedral from the late fifteenth century), this town is surrounded by views of white villas, tropical gardens, modern buildings and a stunning sea view with modern cruise ships and old boats.

Finally, I would like to express my gratitude for the strong support received from UMa - *University of Madeira*, FCT - *Fundação para a Ciência e a Tecnologia*, ARDITI – *Agência Regional para o Desenvolvimento da Investigação, Tecnologia e Inovação*, the *Regional Secretariat for Tourism and Culture of Madeira* and, of course, the companies BRUKER, DENDRITECH and CYD. Special thanks are also due to all members of the Organizing Committee for helping me in the organization of this IDS edition.

Believing that IDS11 will be a very productive meeting and that you will fall in love with Madeira Island, we expect to receive you again soon. Thank you for coming, enjoy our IDS11 and enjoy life!

João Rodrigues

IDS11 Chairperson

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DENDRIMER

SYMPOSIUM

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14-18 JULY 2019

Sunday, 14th July 2019 – ROOM A

Time			Title
15:00	18:00		Participant Registration
18:00	18:45		Opening Session
18:45	19:30	**KN1**	**Dendrimers and a Nanoperiodic Table: Engineering CNDPs of Soft Superatoms Leading to New Emerging Properties Such as Terahertz Radiation Generators and Non-traditional Intrinsic Luminescence (NTIL)** *Donald Tomalia* Chairperson: George Newkome
19:30	21:00		Welcome Reception

Monday, 15th July 2019 – ROOM A

Time			Title
8:30	9:00		Participant Registration
9:00	9:45	**KN2**	**From the Discovery of Self-Assembling Dendrimers to the Emergence of New Research Fields** *Virgil Percec* Chairperson: Ling Peng
			Session 1 Chairperson: Kimihisa Yamamoto
9:45	10:10	**IOC1**	**Voltage Initiated Tissue Adhesive Dendrimers** *Terry Steele*
10:10	10:30	**OC1**	**The Study of Polyamidoamine Dendrimer as Essential Oil Carrier** *Hui-Ting Chen*
10:30	11:00		Coffee Break
			Session 2 Chairperson: Helena Tomás
11:00	11:25	**IOC2**	**Dendritic Micelles as a Versatile Platform for Drug Delivery** *Rana Sanyal*
11:25	11:45	**OC2**	**Exploiting ESI-TOF Mass Spectrometry for Detailed Characterization of Polycationic Carbosilane Dendrimers** *Alena Krupková*

11:45	12:00	**YS1**	**Antibacterial Activity of Conjugates Between Antimicrobial Peptides and Cationic Carbosilane Dendrons** *Jael Fernández*
12:00	12:20	**OC3**	**Pt(II)-dendrimers as Bio-imaging Marker for Bacteria in Two-photon Excitation Microscopy** *Yolanda Vida*
12:20	12:45	**IOC3**	**Polyurea Dendrimers: Carriers, Killers and Cell Kickers** *Vasco Bonifácio*
12:45	14:45		Lunch
14:45	15:30	**KN3**	**Fluorescent Dendrimers for Biology. How Two-photon Absorption Properties Can Help?** *Anne-Marie Caminade* Chairperson: Virgil Percec
			Session 3 Chairperson: Rana Sanyal
15:30	15:55	**IOC4**	**Dendrimer-Encapsulated-Nanoparticle Coacervate-core Micelles** *Aldrik Velders*
15:55	16:15	**OC4**	**Dendrimers Carrying Multiple Redox Units – Is it Good or Bad For Cell Survival** *Zofia Urbanczyk-Lipkowska*
16:15	16:30	**YS2**	**PAMAM Dendrimers as Nanocarriers for Platinum Anticancer Complexes** *Cláudia Camacho*

16:30	16:55	**IOC5**	**G2-S16 in Innate and Adaptive Immune System, Microbiome and Human Vaginal Tissue** *Mª Angeles Muñoz-Fernández*
16:55	17:25		Coffee Break
			Session 4 Chairperson: Valentin Ceña
17:25	17:50	**IOC6**	**Lymph Node Delivery using Anionic Dendrimers** *Chie Kojima*
17:50	18:10	**OC5**	**Covered by Neuroligin-2-derived Peptide Polyamidoamine-based (PAMAM) Dendrimers Enhances Pancreatic *β*-cells' Proliferation and Function** *Arie-Lev Gruzman*
18:10	18:35	**IOC7**	**Self-assembly of Amphiphilic Dendrimers: from Dendromicelles to Dendrimersomes** *Oleg Borisov*

Tuesday, 16th July 2019 – ROOM A

Time			Title
8:30	9:15	**KN4**	**Phosphorus Dendrimers. Design and Applications. Past, Present and Future** *Jean-Pierre Majoral* Chairperson: Donald Tomalia
			Session 5 Chairperson: Chai-Lin Kao

9:15	9:40	**IOC8**	**Dendrimers for Multimetallic Nanomaterials** *Kimihisa Yamamoto*
9:40	10:00	**OC6**	**Mass Spectroscopy for Detailed and Precise Analysis of Dendrimers** *Aura Tintaru*
10:00	10:15	**YS3**	**New Anionic Poly(alkylidenamine) Dendrimers as a Potential Microbicide: the Behavior Against HIV-1 Infection** *Dina Maciel*
10:15	10:30		Group Photo
10:30	11:00		Coffee Break
			Session 6 Chairperson: Jørn Christensen
11:00	11:25	**IOC10**	**Cationic Carbosilane Dendrimers Designed for Applications** *Tomáš Strašák*
11:25	11:40	**YS5**	**Cinnamic Acid-functionalized PAMAM Dendrimer Generation 4: Drug Delivery and Cytotoxicity** *Ana Olival*
11:40	12:25	**KN5**	**Novel Hybrid Dendrimers Harbouring Sugar Triads at the Periphery** *René Roy* Chairperson: Jean-Pierre Majoral
12:25	14:00		Lunch

14:15	19:00		**Social Program**
20:00			**Conference Dinner**

Tuesday, 16th July 2019 – ROOM C (Parallel session)

Time			Title
			Session 7 Chairperson: Rafael Gómez
9:15	9:40	**IOC9**	**A Self-assembling Amphiphilic Dendrimer as Effective Targeted Delivery Platform for siRNA Therapeutics** *Liu Xiaoxuan*
9:40	10:00	**OC7**	**In Quest for Better Selectivity and Activity: Nucleophilic Organocatalysts Based on Branched/dendritic Design** *Moshe Portnoy*
10:00	10:15	**YS4**	**Dendrimers Incorporating Lanthanide Cations as Near-Infrared Imaging Agents** *Kamal Jouad*
10:15	10:30		***Group Photo***
10:30	11:00		***Coffee Break***
			Session 8 Chairperson: Mª Angeles Muñoz-Fernández

11:00	11:25	**IOC11**	**From Peripheral to Central Nervous System: A Journey Towards Targeted Neuronal Delivery** *Ana Paula Pêgo*
11:25	11:40	**YS6**	**A Self-Assembling Amphiphilic Peptide Dendrimer as Anticancer Drug Delivery Platform** *Dandan Zhu*

Wednesday, 17th July 2019 – ROOM A

Time			Title
9:00	9:45	**KN6**	**Nanotechnology Therapeutics: Moving Towards the Clinic** *James R. Baker Jr.* Chairperson: René Roy
			Session 9 Chairperson: Ana Pêgo
9:45	10:10	**IOC12**	**Rotaxane-branched Dendrimers** *Hai-Bo Yang*
10:10	10:30	**OC8**	**Uptake, Anti-Inflammatory, and Migratory Properties of Mixed-Surface PAMAM Dendrimers in Ischemic Stroke Rats** *Julien Rossignol*
10:30	10:55	**IOC13**	**Radical Dendrimers: Biomedical Applications** *José Vidal-Gancedo*
10:55	11:25		Coffee Break

			Session 10 Chairperson: Xiaoxuan Liu
11:25	11:50	**IOC14**	**Protective Effect of Neutral Phosphodendrimers on Experimental Autoimmune Encephalitis in Mice** *Valentín Ceña*
11:50	12:10	**OC9**	**Amphiphilic Hybrid Triazine-Carbosilane Dendrons: Synthesis and Self-Organization** *Evgeny Apartsin*
12:10	12:25	**YS7**	**Design and Synthesis of Bioconjugates for Personalized Medicine** *Jennifer Daeg*
12:25	12:50	**IOC15**	**Efficient Solid-Phase Synthesis of Peptide Dendrimers** *Chai-Lin Kao*
12:50	14:50		Lunch
14:50	15:35	**KN7**	**Supramolecular Dendrimers for Nanomedicine** *Ling Peng* Chairperson: James R. Baker Jr.
			Session 11 Chairperson: Dietmar Appelhans
15:35	16:00	**IOC16**	**Functionalized Nanoparticles to Target and Image Cancer Cells *In Vivo*** *Suhe Wang*

16:00	16:20	**OC10**	**Dialytic Separation of Anions from DMSO Solution Facilitated by Dendritic Receptors** *Petra Cuřínová*
16:20	16:35	**YS8**	**[Ru(η^5-C_5H_5)(PPh_3)$_2$]-PAMAM Metallodendrimers as Promising Anticancer Drugs** *Nádia Nunes*
16:35	17:20		Coffee Break & Poster Session Exhibition Area – Room B
			Session 12 Chairperson: Barbara Klajnert-Maculewicz
17:20	17:45	**IOC17**	**Topology, Amphiphilicity and Dendronization of Carbosilane Dendritic Systems in Biomedical Applications** *Rafael Gómez*
17:45	18:05	**OC11**	**Fighting Resistant Cancer with Carbosilane Metallodendrimers** *Sandra García-Gallego*
18:05	18:20	**YS9**	**Synthesis, Self-Assembling Properties, and Biomedical Applications of Amphiphilic Janus Glycodendrimers** *Leila Mousavifar*
18:20	18:45	**IOC18**	**Dendrimeric Microsponge Based Topical Gel of Dithranol** *Pushpendra Tripathi*

Thursday, 18th July 2019 – ROOM A

Time			Title
9:00	9:45	**KN8**	**Construction of Dendrimer/Carbon Dot Nanohybrid Platform for Ultrasound-Assisted Enhanced Theranostics of Tumors** *Xiangyang Shi* Chairperson João Rodrigues
			Session 13 Chairperson: Carla Alves
9:45	10:10	**IOC19**	**Tumor Microenvironment-Responsive Dendritic Polymer-Drugs as Nanoscale Systems for Drug Delivery** *Kui Luo*
10:10	10:30	**OC12**	**Fragmentation Pattern of Copper-metallated and Non-metallated OH-Terminated PAMAM Dendrimers Generation 4** *Marijana Petković*
10:30	10:55	**IOC21**	**Multifunctional Hybrid Dendrimer with Dual-Ligands: A Next Generation Dendritic Platform For Drug Delivery** *Mayank Singh*
10:55	11:10	**YS10**	**Synthesis, Characterization and Biological Evaluation of Homo- and Heterofunctionalizated Polyamide Dendrimers for Application in Inflammatory Diseases** *Ana Garzón*
11:10	11:35	**IOC23**	**Synthesis and Properties of Antimicrobial Dendrons** *Jørn Christensen*

11:35	12:05		Coffee Break
12:05	12:50	**KN9**	**Simplifying the Assembly of Dendritic and Fractal Constructs** *George Newkome* Chairperson: Anne-Marie Caminade
12:50	13:35		**Closing session & Poster Awards**

Thursday, 18th July 2019 – ROOM C (Parallel session)

Time		Title	
			Session 14 Chairperson: José Vidal-Gancedo
9:45	10:10	**IOC20**	**Biohybrid Structures and Their Targeting Properties: Considering the Potential Use of Mono- and Polyassociation Steps** *Dietmar Appelhans*
10:10	10:30	**OC13**	**New Fully Biodegradable PEG-Dendritic Block Copolymers: From Synthesis to Application as Efficient Nanocarriers of siRNA** *Victoria Leiro*
10:30	10:55	**IOC22**	**Molecular Characteristics, Membrane Affinity, Transport Properties and *In Vitro* Cytotoxicity of Bola-Type Peptide Dendrimers** *Maciej Cieślak*

10:55	11:10	**YS11**	**Self-Assembling Hybrids of Fluorescent Carbon Dots and PAMAM Dendrimers for DNA Delivery Applications** *Ivo Martins*
11:10	11:35	**IOC24**	**Comparison of Carboxy-Methylated G5_PAMAM Dendrimer and Carboxy-Methylated Polyethyleneimine Metal Complexes** *István Bányai*
11:35	12:05		Coffee Break

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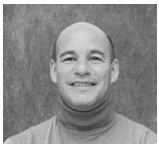

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IDS11 KN: KEYNOTE LECTURES

Dr. Tomalia is the CEO/Founder of NanoSynthons LLC and the National Dendrimer & Nanotechnology Center, Adjunct Professor (Chemistry) University of Pennsylvania, PA and Affiliate Professor (Physics) Virginia Commonwealth University, VA. He received his B.A. in Chemistry from the University of Michigan and Ph.D. in Physical-Organic Chemistry from Michigan State University while working at The Dow Chemical Company. He has founded three dendrimer-based nanotechnology companies; namely, NanoSynthons LLC (2010-present), Dendritic Nanotechnologies, Inc. (2001-2006) (acquired by Starpharma, Melbourne AU) and Dendritech, Inc. (1992-98) (acquired by Dow Chemical, Midland MI). Other positions currently held by Tomalia include: Advisory Board CLINAM, European Foundation for Clinical Nanomedicine; Faculty Member, Faculty 1000 Biology; Associate Editor, Journal of Nanoparticle Research (Nature/Springer); Editorial Advisory Board, Nanomedicine (Elsevier) and Biomolecules (MPDI).

Tomalia is the pioneering scientist/inventor credited with the discovery of living cationic polymerizations of 2-oxazolines leading to poly(oxazolines) (Industrial Research-100 Awards in 1978 & 1986) and the first synthesis of dendrimers. His 1979 discovery of poly(amidoamine) (PAMAM) dendrimers (dendritic polymer architecture) led to a third R&D-100 Award in 1991 and the Leonardo da Vinci Award (Paris, France) in 1996. He received the International Award of The Society of Polymer Science Japan (SPSJ) (2003) which recognized his discovery of the fourth major macromolecular architectural class; namely, dendritic polymers.

Tomalia has been granted >135 U.S. patents, authored over 270 peer-reviewed publications with more than >44,610 citations and an h-index=92 (Google Scholar, 5-10-19). Over 170 papers are focused in the dendrimer/dendritic polymer field. His original dendrimer paper entitled: “A New Class of Polymers: Starburst Dendritic Macromolecules,” Polym. J., 17(1), 117 (1985) has received >4100 citations. Tomalia was inducted into the Thomson Reuters Hall of Citation Laureates in Chemistry (2011) (i.e., top 40 most highly cited scientists in the field of chemistry).

[KN1]

Dendrimers and a Nanoperiodic Table: Engineering CNDPs of Soft Superatoms Leading to New Emerging Properties Such as Terahertz Radiation Generators and Non-traditional Intrinsic Luminescence (NTIL)

Donald A. Tomalia[1,2,3]

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[3]Affiliate Professor (Physics), Virginia Commonwealth University, Richmond VA USA.

Staudinger's *macromolecular hypothesis* clearly demonstrated that large covalent assemblies of monomers may produce a wide range of new emerging properties defined by by their *sizes, shapes, surface chemistries, rigidity/flexibility and elemental compositions.* Beginning with Staudinger's introduction of linear polymers in 1922, a total of four major polymer architectures have emerged and *architecture* is now recognized for the dramatic role it may play in defining new emerging properties. These six parameters above are referred to as *critical nanoscale design parameters* (CNDPs) and are analogous to *critical atomic design parameters* (CADPs) that define the horizontal/vertical ordering of the atomic elements in Mendeleev's periodic table.[1-2] Based on extraordinary CNDP control, atom mimicry and nanoperiodic property patterns observed for *dendrimers, proteins, DNA/RNA, viral capsids and polymeric micelles*, these entities are accepted as quantized nanoscale building blocks now referred to as *soft superatoms.*[1] An abundance of evidence has validated a "systematic nanoperiodic concept" based on hard and soft superatoms. Most compelling are predictive Mendeleev-like nanoperiodic tables for amphiphilic dendrons and dendrimers reported by Percec, et al. [1-3], as well as recently published nanoperiodic tables for proteins.[4] This lecture will overview dendrimer based atom mimicry, nanoperiodic features and the application of CNDP engineering principles to PAMAM dendrimers for creating PAMAM terahertz generators currently used in commercial THz spectrometers.[5] Finally, recent CNDP engineering of certain soft superatoms (i.e., dendrimers, proteins, etc.) leading to new *non-traditional intrinsic luminescence* (NTIL) emission properties [6] will be described.

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[1] Tomalia, D.A.; Khanna, S.N. *Chem. Rev.*, **2016**, *116*, 2705.
[2] Tomalia, D.A.; Khanna, S.N. *Mod. Phys. Lett. B*, **2014**, *28*, 1430002.
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Dr. Virgil Percec received his education in organic and macromolecular chemistry at the Polytechnic Institute (Jassy, Romania) and his PhD in macromolecular chemistry at "P. Poni" Institute of Macromolecular Chemistry, Romania. After postdoctoral stays at the Institute of Macromolecular Chemistry, Hermann Staudinger House of the University of Freiburg, Germany and Institute of Polymer Science of University of Akron, USA, he joined the Department of Macromolecular Science of Case Western Reserve University, Cleveland, USA becoming a full professor in 1986 and Leonard Case Jr. Chair Professor in 1993. In 1999, he joined the Department of Chemistry at the University of Pennsylvania, Philadelphia as the inaugural P. Roy Vagelos Chair and Professor of Chemistry where he is leading a group of undergraduate, graduate and postdoctoral students. Percec's current science activities cover organic and macromolecular synthesis, supramolecular chemistry, self-assembly, biological mimics, complex systems, biological membranes, origins, amplification and transfer of chirality, supramolecular chirality, liquid crystals, supramolecular electronics, nanoscience and other cross-disciplinary research fields, where he contributed over 760 refereed publications, 80 patents and 20 books. Percec pioneered the fields of stereoisomers of substituted polyacetylenes, the transplant of phase transfer catalysis from organic to polymer chemistry, and he is known for the discovery and development of molecular and supramolecular liquid crystals with complex architecture, Nickel-catalyzed cross-coupling, SET-LRP, supramolecular dendrimers, and of complex functional systems by using Nature as a model and biological principles. Percec presented over 1200 endowed, plenary and invited lectures.

He has been Editor of Journal of Polymer Science: Part A: Polymer Chemistry, Advances in Polymer Science and Book Series "Liquid Crystals". He serves on Editorial and Advisory Scientific Boards of 22 International Journals, and of Academic and Industrial Institutions. Percec is a member of foreign Academies, received US and international awards, organized numerous International Symposia and educated over 250 PhD and postdoctoral students.

From the Discovery of Self-Assembling Dendrimers to the Emergence of New Research Fields

Virgil Percec

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This lecture will discuss the discovery of self-assembling dendrons and dendrimers [1a,b] and how a large diversity of discoveries and new research fields were mediated by questions related to their synthesis and the mechanisms of their self-assembly and self-organization. Selected examples are: liquid quasicrystals and their approximants also known as Frank-Kasper phases [1c, d, e] that were subsequently found in block copolymers, surfactants, phospholipids and in numerous other areas of soft matter generating one of the most active recent new field of research. Quasicrystal approximants also led to the discovery of a new concept in living radical polymerization, SIP and SILP, that is not based on reversible activation as ATRP, SET-LRP and all other conventional living radical polymerizations are [1f]. The replacement of Pd with the much less expensive but more reactive Ni in quantitative borylation and Suzuki cross-coupling reactions including the most reactive but air-stable sigma Ni catalysts [1g,h], the supramolecular orientational memory [1i,j], the deracemization in crystal state as a mechanism for the origins of biological homochirality and of isotactic supramolecular polymers from atactic polymers [1k,l], as well as the discovery that sequence-defined monodisperse self-assembling Janus dendrimers and glycodendrimers and their hybrids with bacterial and human cells are efficient biological membrane mimics that encode functions, are just few additional examples that will be discussed [2,3].

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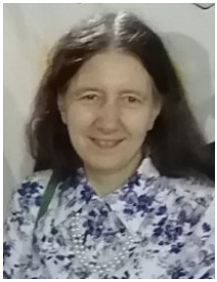

Dr. Anne-Marie Caminade is Director of Research, Exceptional Class CNRS in Toulouse, and the head of the “Dendrimers and Heterochemistry” team in the Laboratoire de Chimie de Coordination (LCC). Her current research interest is on dendrimers and hyperbranched polymers, especially on phosphorus dendrimers, and on their uses, in particular for catalysis, fluorescence, nanomaterials, and biology/nanomedicine. She is co-author of about 470 publications, 54 book chapters (and editor of 2 books), 30 patents, h index 65, about 13,800 citations.

[KN3]

Fluorescent Dendrimers for Biology. How Two-Photon Absorption Properties Can Help?

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Fluorescent dendrimers are used in many fields, but essentially in biology, to try to understand biological events at the molecular level, and for bio-imaging [1]. Compared to classical fluorescence, two-photon excited (TPE) fluorescence has many advantages, such as a highly spatially confined excitation and intrinsic 3D resolution, and the ability to image at an increased penetration depth in tissue with reduced photo-damages. Incorporating TPE-fluorophores inside the structure of phosphorus dendrimers has been carried out for *in vivo* imaging blood vessels [2], for deciphering the mechanism of action of anti-cancer dendrimers [3], and also for simultaneous two-photon photodynamic therapy and imaging [4].

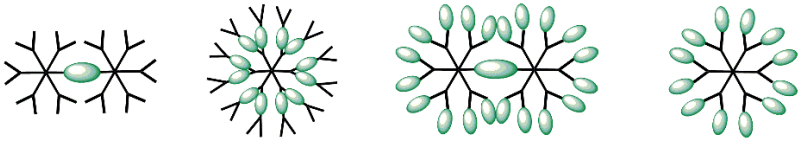

Figure: Schematized localization of TPE-fluorophores in phosphorus dendrimers.

Acknowledgements: Thanks are due to the ANR 2017 SLOW2 for financial support.

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Dr. Jean-Pierre Majoral is Emeritus Director of Research, Exceptional Class at the CNRS in Toulouse. His research interest is focused on the design and the properties of macromolecules, such as phosphorus dendrimers and hyperbranched polymers. Main efforts are directed at the use of dendrimers in medicinal chemistry, material sciences and catalysis. He is co-founder and scientific director of the start-up Dendris. He is a member of several Academies of sciences worldwide, got a dozen of international awards (Germany, Poland, Spain, UK, China, France) and was recently nominated as consulting professor of the University Donghua at Shanghai He is an author of over 665 publications, 7 books, 38 book chapters, and 48 patents (h index 66, over 17,000 citations).

[KN4]

Phosphorus Dendrimers. Design and Applications. Past, Present and Future

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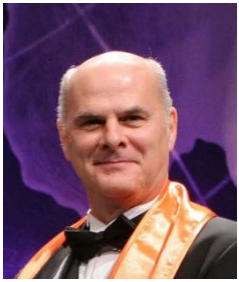
A far-reaching evolution of the dendrimer field of research occurred since the pioneering work of D. Tomalia, G. Newkome, F. Vogtle, and J. Frechet concerning the design of organic dendritic structures. A stone to build this house was the first preparation of phosphorus dendrimers started and developed in the Toulouse group since 1992.

Many efforts allowing us to propose to the scientific community the synthesis of a variety of phosphorus dendrimers, dendrons, bis-dendrons, onion peel dendritic species, macromolecular asterisks etc, have been done. In a parallel time, investigations and analysis of their properties and applications in different area including biology, nanomedicine, catalysis, material science, diagnostic, imaging have been undertaken.

As an illustration, this lecture will point out some of the phosphorus dendrimer contribution in the domain of nanotechnologies with the presentation of selected examples belonging to a recent past and present, spearheads for the development of original applications and exciting extension in the near future in fundamental and applied nanomedicine such as treatment of several diseases, diagnostic, theranostic, or for the formation and the use of dendritic nanohybrid materials.



Dr. René Roy was born in Québec (Canada). He holds a Canadian Research Chair in Therapeutic Chemistry in the Department of Chemistry of the Université du Québec à Montréal (Qc, Canada) since 2004. He has more than 40 years of experience in carbohydrate chemistry. After is Ph. D., obtained in 1980 from the Université de Montréal in medicinal chemistry under the expert guidance of Prof. Stephen Hanessian, he joined the National Research Council of Canada in Ottawa (Canada) from 1980-1985 where is was acquainted with carbohydrate-based vaccines. He was then professor in the Department of Chemistry at the University of Ottawa from 1985-2002. He has been the recipient of the 2003 Melville L. Wolfrom Award from the ACS Division of Carbohydrate Chemistry for his contributions in the design of vaccines and glycodendrimers. He has published over 370 publications and has contributed to the development of two commercial carbohydrate-based vaccines against bacterial meningitis. His actual interests are in multivalent carbohydrate protein interactions, medicinal chemistry, and in bionanomaterials and dendrimers in particular.

[KN5]

Novel Hybrid Dendrimers Harbouring Sugar Triads at the Periphery

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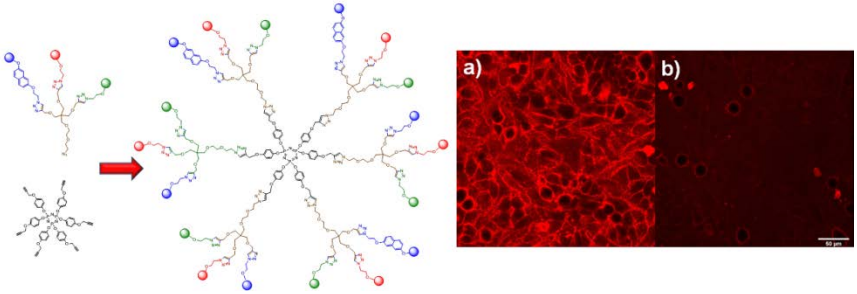
Glycodendrimers have shown great promises as bacterial anti-adhesion therapeutics [1,2]. Hence, they constitute important tools for biomedical applications including diagnostics, drug delivery systems, and vaccines [3,4]. The design of chemical entities possessing the multivalent features of dendrimers is therefore of prime interest [5]. We described herein the first syntheses of hybrid dendrimers harbouring three different sugars ("sugar triads"). They were design to simultaneously target three different bacterial lectines that are involved in lung infections of cystic fibrosis patients. The chemical strategy consisted in the sequential modifications of an AB3 system using "click chemistry". The G2 dendrimer generation was built using our "onion peel" approach [6,7]. The complex glyco-architectures were fully characterized by NMR, MS, FT-IR, DLS, TEM, and confocal microscopy. Their binding properties with lectines were demonstrated by their cross-linking abilities to form large aggregates and by cellular self-adhesion by confocal microscopy.



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Dr. James R. Baker, Jr., MD was the founder of the Mary H. Weiser Food Allergy Center and the Ruth Dow Doan Professor at Michigan Medicine. Most part of his background was done as an allergist and teaching allergy and immunology at the University of Michigan. For nearly 20 years, Dr. Baker was the chief of the Division of Allergy and Clinical Immunology at the University of Michigan. He is a Professor Emeritus at the Department of Internal Medicine, Division of Allergy in the University of Michigan Medical Center. He is also Director, of the University Food Allergy Center and Michigan Nanotechnology Institute for Medicine and the Biological Sciences. Dr. Baker serves as Chairman of the Nanotechnology for Medicine and Biology study section at the National Institutes of Health (NIH). Dr. Baker founded NanoBio Corporation in 1999 and served as its Chief Executive Officer and Managing Director until October 2012. Dr. Baker served as Chief Scientific Officer of NanoBio Corporation. He founded Avidimer Therapeutics, Inc. in 2003 and serves as a its Chief Scientific Officer. He invented the NanoStat technology at the University of Michigan. Dr. Baker is one of three editors of the National Nanotechnology Initiative's Research Directives. His main research is in immunology and host defense field using nanomaterials and their applications in therapeutics. He contributed for the development of new approaches to vaccines by using synthetic lipids and polymeric nanostructures. For nearly 5 years he was the CEO and CMO of Food Allergy Research and Education (FARE). His expertise has contributed for more than 300 scientific publications.

[KN6]

Nanotechnology Therapeutics: Moving Towards the Clinic

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Our group has developed a number of dendrimer-based targeted therapeutics for epithelial, lung and ovarian cancers. These macromolecules are actively targeted to tumors that over-express receptors for a number of receptors for small molecule ligands including folate, riboflavin, RGD and EGF. Our first generation therapeutics used a dendrimer scaffold combined with linking multiple targeting and therapeutic molecules to produce multifunctional combinatory therapeutics. Unfortunately, the complexity of these molecules prevented their entry into clinical trials. We have re-designed the platform using a simplified approach; polyvalent small molecule therapeutics which also act as ligands to target the nanoparticle and kill cancer cells. The revised scaffold still uses a dendritic polymer that is uniquely suited to biomedical applications in that it can be uniformly produced and yet has a diameter less than 10 nanometers. The goal of this work is to develop several polyvalent therapeutics and imaging agents and advance these materials through preclinical animal efficacy and toxicity trials. If this approach is successful *in vivo*, it can facilitate the concept of targeting many small molecule drugs on nanoparticles to address varied tumor types with different genetic or enzymatic alterations associated with individual cancers.

Dr. Ling Peng is a research director at the French National Scientific Research Center (CNRS) and a group leader in the Interdisciplinary Center on Nanoscience in Marseille (CINaM) at Aix-Marseille University in France. She carried her undergraduate study in polymer chemistry at Nanjing University, China, her PhD in organic chemistry at Swiss Federal Institute of Technology in Zurich, Switzerland, and her postdoctoral research in Pharmacy at Strasbourg University in France. She was recruited as a research scientist in CNRS in 1997, promoted as a CNRS research director in 2008.

Dr. Ling Peng has been working actively at the interface of chemistry and biology, and in particular, developing functional dendrimers for biomedical applications, molecular probes for exploring biological events and nucleoside derivatives for drug discovery. She has established bio-inspired structurally flexible dendrimers for nucleic acid delivery, which outperform the current commercially available nonviral vectors. Recently, she has inaugurated the concept of innovative supramolecular systems based on self-assembling amphiphilic dendrimer nanosystems and applied this concept to deliver various natural product anticancer drugs, biopharmaceutics and imaging agents for cancer treatment and imaging. One of these self-assembling dendrimer systems has been scheduled for clinical study. Dr. Ling PENG has co-authored more than 100 scientific papers, 7 patents and 14 book chapters. She has also coordinated and participated in various European projects and networks. She was awarded with the Prize of Dr & Mme Henri Labbé of the French Academy of Sciences and her research team has been labelled by La Ligue Contre Le Cancer in France.

[KN7]

Supramolecular Dendrimers for Nanomedicine

Ling Peng

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Nanomedicine has received great interest for treating various diseases as well as for the non-invasive diagnosis through different imaging modalities. Dendrimers with smart functions are ideal systems for nanomedicine by virtue of their uniquely well-defined structure and multivalent cooperativity confined within a nanosize per se. We will report our recent efforts to establish innovative self-assembling supramolecular dendrimers as drug carriers, gene vectors and bioimaging probes in nanomedicine [1-3]. Starting with small amphiphilic dendrimers, we have constructed various adaptive, modular and responsive supramolecular dendrimers, which are able to carry either hydrophobic drug molecules[1] or hydrophilic nucleic acid therapeutics [2] for effective anticancer activity to combat drug resistance. Also these nanosystems are able to deliver the imaging agents for better and higher imaging quality through combination of the multivalent feature of dendrimer and the EPR effect of the supramolecular nanosystem [3]. The self-assembling supramolecular dendrimers are expected to offer new perspectives in nanotechnology based biomedical applications for treating various diseases.

Acknowledgements: Financial support from La Ligue Nationale Contre le Cancer (EL2016.LNCC/LPP), the French National Research Agency under the frame of EuroNanoMed II (ANR-15-ENM2-0006-02, ANR-16-ENM2-0004-02) is gratefully acknowledged.

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Prof. Xiangyang Shi graduated with Ph.D. (organic chemistry, Institute of Photographic Chemistry, the Chinese Academy of Sciences, Beijing) in 1998, worked as a Research Fellow, Research Associate II, Research Investigator, and Research Assistant Professor at the University of Michigan, Ann Arbor from 2002-2008, then became a professor of special appointment both in Donghua University and in Shanghai Institutions of High Learning (Eastern Scholar) since 2008, and since 2010 he has also been appointed as an “Invited Chair in Nanotechnology” at University of Madeira, Portugal.

[KN8]

Construction of Dendrimer/Carbon Dot Nanohybrid Platform for Ultrasound-Assisted Enhanced Theranostics of Tumors

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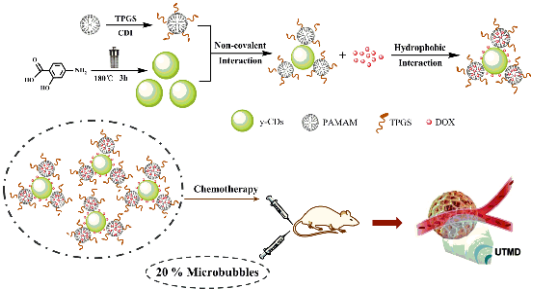
Construction of multifunctional nanosystems to overcome multidrug resistance (MDR) and implement theranostics of tumors is crucial. Herein, we report the construction of dual drug-loaded dendrimer/carbon dot nanohybrid platform for ultrasound-promoted enhanced tumor theranostics to overcome MDR. Firstly, yellow-fluorescent nitrogen-doped carbon dots (y-CDs) were synthesized *via* one-step hydrothermal treatment. In parallel, poly(amidoamine) dendrimers of generation 5 (G5) were covalently modified by the drug efflux inhibitor D-a-tocopheryl polyethylene glycol 1000 succinate (TPGS) to form G5-TPGS. Then, G5-TPGS dendrimers were complexed with y-CDs through electrostatic interaction. Eventually, the G5-TPGS@y-CDs complexes were used to load an anticancer drug doxorubicin (DOX) *via* non-covalent interaction to form (G5-TPGS@y-CDs)-DOX complexes. The complexes were well characterized. We showed that (G5-TPGS@y-CDs)-DOX possessed a high drug loading efficiency (40.68%), excellent fluorescence emission due to the CDs, and pH-dependent release behavior of DOX with a higher release rate at an acidic pH. The *in vitro* and *in vivo* results indicated that (G5-TPGS@y-CDs)-DOX complexes were able to inhibit the growth of drug-resistant cell MCF-7/ADR or xenografted MCF-7/ADR tumor model by overcoming MDR, and be used for fluorescence imaging of tumors. In addition, the inhibition of MCF-7/ADR or xenografted tumor model was able to be further enhanced by the ultrasound-targeted microbubble destruction (UTMD) technology. The developed dendrimer/CD nanohybrids may be used as a platform for UTMD-promoted theranostics of other tumor types.

Figure 1. Illustration of the formation of the dual drug delivery system for theranostics of tumors.



Acknowledgements: This research was financially supported by the National Natural Science Foundation of China (81761148028 and 21773026), the Science and Technology Commission of Shanghai Municipality (17540712000 and 18520750400).

Dr. George R. Newkome received his B.S. and PhD. in Chemistry from Kent State University. His academic and administrative career started at LSU where later on he become a Full Professor and executive director of the LSU Center for Energy Studies. In 1986, he moved to the University of South Florida as Vice President for Research and also as a faculty member in the chemistry department. From 2001-2014, he was Vice President for Research as well as Dean of the Graduate School at the University of Akron and currently the James and Vanita Oelschlager Professor of Science and Technology and Professor in the Departments of Polymer Science and Chemistry, as well as, President of the Ohio Research Foundation and Northeast Ohio Student Venture Fund. In 2015, he was distinguished with the Docteur Honoris Causa de L'Université de Bordeaux and in 2016, the Alumnus of the Year by Kent State University. Over the years he has been part of the panel of numerous corporations and editorial boards, as well as, author of over 515 scientific articles, 55 patents and has edited/written about 20 scientific books. He is also a Fellow of the AAAS, Royal Society of Chemistry, Ohio Academy of Sciences, and the National Academy of Inventors.

[KN9]

Simplifying the Assembly of Dendritic and Fractal Constructs

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Research highlights from the "early days" of dendritic architectures of simple metallocycles and finally to complex, fractal-based, metallosupramacromolecular materials will be presented. Introduction of the first terpyridine-modified dendritic scaffold was followed by the synthesis and self-assembly of polyterpyridine linkers into discrete architectures. Precise control over the shape, size, and transformations of these assemblies is challenging due to the inherent dynamic nature of the non-covalent interactions. Introduction of tailored multiplanar, directed polyterpyridine vertices in conjugation with a series of metal ions (Ru, Os, Fe, Zn, and/or Cd) gave rise to metallosupramolecular cages with tunable conformations responding to specific stimuli such as: concentration, temperature, and counter ions. Extending the dendritic fractal design to a new family of hybrid 3D-metallodendrimers with cuboctahedron cores has been realized, which creates access to new, precise, unimolecular micelles. Moreover, secondary hierarchical self-assembly beyond the discrete macromolecule will be discussed. Utilizing shape-tuned monomers possessing diverse functionality has opened the door to the one-step direct construction of a series of supramacromolecules possessing rigid triangular frameworks opening the door to the assemble of shape-complementary, highly ordered nanostructures. This opens new avenues to smart, designer dendritic and fractal materials.

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IDS11 IOC: INVITED ORAL COMMUNICATIONS

[IOC1]

Voltage Initiated Tissue Adhesive Dendrimers

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Implantable tissue adhesives typically fall within two categories, being activated by either two-part mixing or photo-initiated designs. These curing strategies limit applications to superficial sites and prevent incorporation into minimally invasive surgeries. An unmet clinical need exists for adhesives that allow for manipulation and subsequent adhesive activation towards electroceutical plasters (Figure 1). in wet or inaccessible locations. Herein, the latest developments towards an instant curing adhesive through PAMAM dendrimers and on-demand activation is presented. The PAMAM adhesives are synthesized by grafting donor/acceptor ionic internal additives on dendrimers to form conductive one-pot adhesives that crosslink upon energetic activation [1-5]. AC and DC voltages allow tunable material properties, which are evaluated in real-time with electro-rheology. The novel PAMAM adhesive dendrimers aim to mimic anisotropic tissue moduli while retaining antimicrobial properties. Crosslinking initiation and propagation are observed to be ampere dependent, enabling tuning of both elasticity and adhesive strength. Adhesion bond strengths on a variety of natural and synthetic substrates will be presented to showcase cosmetic and clinical applications.

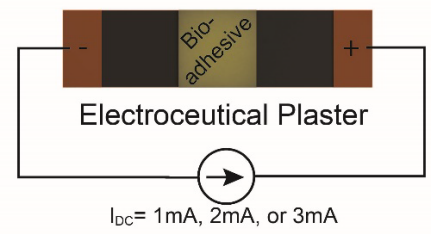

Figure 1. Electroceutical plaster with a current activated bioadhesive.

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[IOC2]

Dendritic Micelles as a Versatile Platform for Drug Delivery

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Most of the cytotoxic chemotherapy agents aim to harm the fast reproducing cells, with the hope to affect tumor. Unfortunately, along with the positive effect they provide, majority of these agents are too toxic to the rest of the body, causing highly undesirable side effects. Targeting cytotoxics directly tumor, is a common solution idea, which has its unique problems to address. There is a wide range of carrier options for targeting purposes, many of which involve nanomedicines. In this presentation, micellar carriers composed of dendritic structures will be discussed. Three different micellar constructs will be shown with comparisons to each other, with the aim to choose appropriate carriers for different applications. The dendritic scaffold is a polyester dendron, providing the inner section of micelle, aiding the loading capacity of the micelle. The hydrophilic portion is provided by polyethylene glycol [1]. Higher concentration of this amphiphilic copolymer in aqueous media results in hydrogels [2,3]. A library of constructs have been prepared with different generations of the dendrons, where the dendron generation is directly proportional to the size of hydrophobic section and also the number of drug molecules that can be conjugated to the dendritic ends [4,5]. Core cross-linked and non-core-linked versions of these micelles were also prepared to compare them for a variety of their propoerties such as drug release [6]. The copolymers have been characterized via NMR and SEC. The micellar assemblies were compared with dynamic light scattering for their critical micelle concentrations. Their stabilities and drug release profiles were investigated. *In vitro* evaluations for cytotoxicity and cell internalization have also been undertaken.

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Polyurea Dendrimers: Carriers, Killers and Cell Kickers

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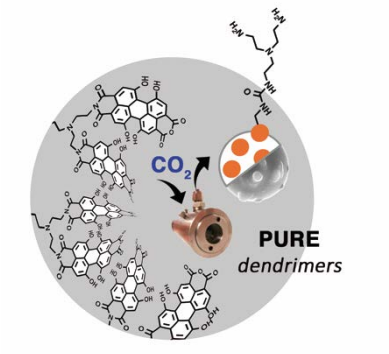
The reaction of amines with carbon dioxide, usually viewed as an undesirable side reaction, was the basis for development of the isocyanate-free one-pot divergent-iterative synthesis of polyurea (PURE) dendrimers [1]. These water-soluble dendrimers are biocompatible, show a pH-dependent intrinsic blue fluorescence, and are fully biodegradable [2]. Since its discovery in 2012, we have demonstrated their potential both in nanomedicine [3-6] and sensing applications [7].

More recently, core and shell modifications enabled the use of PURE dendrimers in novel applications, expanding its scope beyond typical functions. These include their outstanding performance as synthetic mimics of antimicrobial peptides (PURE-SMAMPs), antimalarial agents or triggers of humam stem cells differentiation.



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[IOC4]

DENdrimicelles: Dendrimer-Encapsulated-Nanoparticle Coacervate-core Micelles

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Coacervate-core micelles constitute an important class of nanoaggregates, typically in the range of 50 – 100 nanometer, that are of interest for their application in material and biomedical sciences. We have developed a strategy to obtain insight in the formation, stability and properties of micelles, exploiting PAMAM Dendrimer-Encapsulated Nanoparticles (DENs) as the core-building block, hence coined DENdrimicelles [1]. The electron-dense nanoparticles allow for straightforward analysis by cryo-TEM of these hierarchical nanostructures over multiple length scales (Figure 1) [2]. Cryo-TEM of the DENdrimicelles provides insight in the periodicity of different generations of used dendrimers, the aggregation number of the corresponding micelles, insight in the core-properties [3], details on mesoscale organization, and surprising aspects on stability of thin-layers [4].

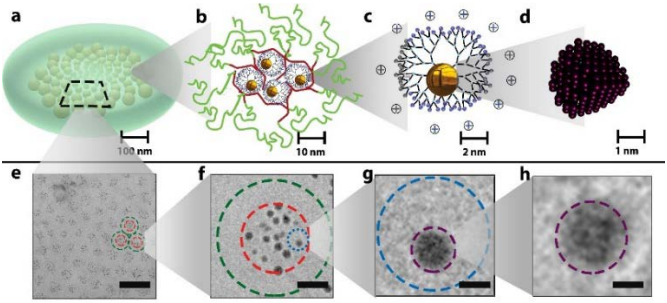

Figure 1. Mesoscale organization of gold-based DENdrimicelles [2].

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[IOC5]

G2-S16 in Innate and Adaptive Immune System, Microbiome and Human Vaginal Tissue

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The use of dendrimers as vaginal microbicides is a promising prevention strategy against sexually transmitted infections. It is essential that prophylactic drugs do not interfere with the normal function of the immune system. We essay the effects of G2-S16, second generation carbosilane dendrimer with sulfonate groups in the periphery, on the immune barrier of the female reproductive tract. The expression of differentiation, maturation and activation markers has been measured in epithelial cells, dendritic cells, M and GM macrophages, and T cells using RT-qPCR and flow cytometry. Our results show that G2-S16 does not alter the natural immunity of the vagina, strongly supporting the biosafety of its for clinical use. On the other hand, the vaginal microbiota comprised a wide variety of bacterial species that aids to maintain a healthy microenvironment with the host cells. Alterations in the composition of this ecosystem could lead to a higher risk to acquire sexually transmitted infections (STI). Our results prove that G2-S16 prevents the alteration of this microenvironment in the presence of HSV-2 or HIV-1. Finally, we are assessing the effectiveness of G2-S16 to prevent infection by HIV-1 or HSV-2 in explants of human vaginal tissue obtained after its expansion from samples from ectocervix and endocervix from healthy women aged between 18 and 50 years of age from a scheduled hysterectomy for prolapse and/or uterine myoma. Viability of the cervico-vaginal tissues was determined using MTT assay. The most effective method for infection by viruses in cervico-vaginal tissue is immersion in viral suspension. We are working with HIV-1, HSV-2 and co-infection HIV-1/HSV-2 with very good expected preliminary results.

Acknowledgements. We acknowledge the Spanish HIV HGM BioBank integrated in the Spanish AIDS Research Network and the National Network BioBank and supported by the Instituto Salud Carlos III for helping to isolate the PBMCs.

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[IOC6]

Lymph Node Delivery Using Anionic Dendrimers

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The sentinel lymph node (SLN), the first lymph node draining tumor cells, is a key tissue in cancer diagnosis and therapy. We have prepared dendrimeric imaging agents for the delivery into SLN. Previously, 12 types of dendrimer of different generations (G2, G4, G6, and G8) and different terminal groups (amino, carboxyl, and acetyl) were prepared to determine the optimal dendrimer structure for the SLN delivery. Radiolabeled dendrimers were intradermally administrated to the right footpads of rats. All G2 dendrimers were predominantly accumulated in the kidney. Amino-terminal, acetyl-terminal, and carboxyl-terminal dendrimers of greater than G4 were mostly located at the injection site, in the blood, and in the SLN, respectively. SLN was successfully detected by single photon emission computed tomography imaging using carboxyl-terminal dendrimers of greater than G4 [1, Fig. 1]. In this study, three anionic dendrimers, carboxyl (C-den), sulfonyl (S-den) and phosphonyl dednrimers (P-den), were prepared and compared to the accumulation into lymph node.

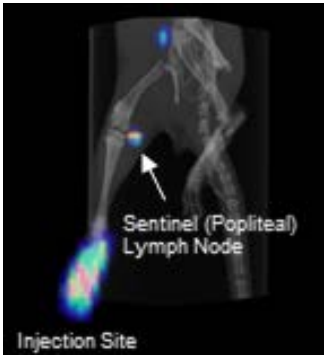

Figure 1. Fused SPECT/CT images of G6-COOH-injected rats.

These anionic dendrimers were prepared using G5 PAMAM dendrimer, and labeled with a green-fluorescent dye or a radioactive ^{111}In chelate. These dendrimers were intradermally administrated to the footpads of mices. After 3 h, all anionic dendrimers were detected at the lymph nodes. P-den was well associated with immune cells such as B cells, dendritic cells and macrophages, but C-den and S-den were not. The lymph node showed high flurescence signal of P-den after 24h but did not that of C-den and S-den. These suggest that anionic dendrimers were efficiently accumulated into the lymph node. However, the association with immune cells and the retention in the lymph node were different among the terminal group of the dendrimer. Our findings are of importance for the development of dendrimer-based lymph node imaging agents and lymph node-targeted drug carriers.

Acknowledgements: This is a collaboration work with Prof. Mikako Ogawa and Prof. Yuji Kuge (Hokkaido Univ,), and Prof. Yasuhiro Magata (Hamamatsu Univ. Sch. Medicine).

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Self-Assembly of Amphiphilic Dendrimers: From Dendromicelles to Dendrimersomes

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Amphiphilic dendrimers comprising linear and dendritically branched (or, in the case of Janus dendrimers, two dendritically branched) hydrophobic and hydrophilic blocks are capable to undergo self-assembly in aqueous solutions giving rise to diverse nanostructures, such as dendromicelles of various morphologies or dendrimersomes. Such nanostructure are promising as nanocarriers for targeted drug and gene delivery since they can incorporate multiple binding sites in the exposed to the environment corona domains. We propose a theoretical approach that enables us to predict how structural properties and morphologies of the nano-assemblies and the number of potentially functionalized terminal groups can be controlled by molecular architecture and, in particular, by dendronization of one or both blocks. We predict that linear-dendritic block copolymers with dendritic hydrophilic blocks form preferentially spherical micelles with dendritic coronae, whereas their linear-linear homologs may form cylindrical micelles of polymersomes. Spherical micelles with dendritic coronae combine relatively small hydrodynamic radii with large number of funcionalizable terminal groups [1]. On the contrary, Janus dendrimers with symmetric dendritically branched hydrophilic and hydrophobic blocks exhibit stronger trend to assembly into worm-like micelles or dendrimersomes. The developed theory is further generalized for description of mesophases formed by linear-dendritic and double-dendritic block copolymers in concentrated solutions.

Acknowledgements: this work was supported by Ministry of Research and Education of the Russian Federation within State Contract 14.W03.31.0022.

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[IOC8]

Dendrimers for Multimetallic Nanomaterials

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Dendrimers are highly branched organic macromolecules with successive layers or generations of branch units surrounding a central core. Organic, inorganic hybrid versions have also been produced by trapping metal ions or metal clusters within the voids of the dendrimers. Their unusual, tree like topology endows these nano meter sized macromolecules with a gradient in branch density from the interior to the exterior, which can be exploited to direct the transfer of charge and energy from the dendrimer periphery to its core. Here, we show that many metalharides more than 50 as a Lewis acid such as $SnCl_2$ and $FeCl_3$, complex to the imines groups of a spherical poly (phenyl azomethine) dendrimer in a stepwise fashion according to an electron gradient with complexation in a more peripheral generation proceeding only after complexation in generations closer to the core has been completed. By attaching an electron withdrawing group to the dendrimer core, we are able to change the complexation pattern, so that the core imines are complexed last. By further extending this strategy, it should be possible to control the number and location of metal ions incorporated into dendrimer structures, which might and uses as tailored catalysts or fine controlled clusters for advanced nano catalysts. We show that, many metalharides complex to the imines groups of a asymmetric poly (phenyl azomethine) dendrimer with pyridine unit at the core in a stepwise fashion according to an electron gradient, which shows 8 changes in isobestic points during the titration complexation (Figure 1). The multi-metal assembly in a discrete molecule can be converted to a size regulated multi-metallic clusters with a size smaller than 1 nm using as a dendrimer molecular reactor. Due to the well-defined number of multi-metallic clusters in the sub nanometer size region as a new substance, we expect that their properties are much different from that of bulk or general metal nanoparticles.

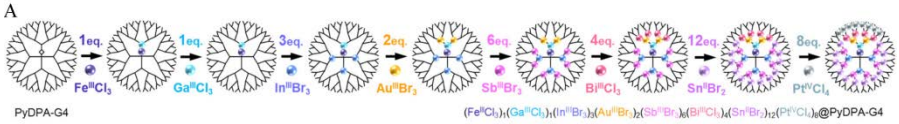

Figure 1. Multimetallic accumulation of eight metals on a Phenyazomethine dedrimer with a pyridine unit at the core. Lewis acidity of metal salts: $FeCl_3$ > $GaCl_3$> $InBr_3$ > $AuBr_3$ > $SbBr_3$ > $BiCl_3$ > $SnBr_2$ > $PtCl_4$. Layer-by-layer stepwise complexation.

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[IOC9]

A Self-Assembling Amphiphilic Dendrimer as Effective Targeted Delivery Platform for siRNA Therapeutics

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RNA interference (RNAi) holds great promise for therapeutic applications. However, safe and successful clinical translation essentially requires further advancement of developing efficient delivery systems [1]. Among myriad nanocarriers, amphiphilic dendrimers, marrying the characteristic of dendrimers, self-assembly performance of amphiphilic molecules and the bio-mimicry of lipids, become particularly appealing as nano-vectors for drug delivery in nanomedicine, in particularly for small interfering RNA (siRNA) therapeutics [2]. Here, we reported a series of amphiphilic dendrimers are able to self-assemble into adaptive supramolecular assemblies upon interaction with siRNA, and effectively delivers siRNAs to various cell lines, including human primary and stem cells, thereby outperforming the currently available non-viral vectors [3-5]. Furthermore, a ballistic approach for targeted siRNA delivery to cancer cells used an amphiphilic dendrimer equipped with a dual targeting peptide bearing a RGDK warhead [6]. The dual targeting RGDK could coat siRNA/dendrimer complexes via electrostatic interactions led to small and stable nanoparticles for targeting cancer cells. Thanks to a RGDK warhead, the targeted system had enhanced siRNA delivery, stronger gene silencing and more potent anticancer activity compared to non-targeted or covalent dendrimer-based systems. Our study demonstrates that the targeted system based on self-assembling amphiphilic dendrimers represent new and versatile perspectives for functional siRNA delivery, heralding a new age of dendrimer-based self-assembled drug delivery in biomedical applications.

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[IOC10]

Cationic Carbosilane Dendrimers Designed for Applications

Tomáš Strašák[1,2], Monika Müllerová[1,2], Wahid Tatan[1], Alena Krupková[1,2], Lucie Červenková Šťastná[1,2], Petra Cuřínová[1,2], Dominika Wróbel[2], Regina Herma[2], Jan Čermák[1,2] & Jan Malý[2]

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Cationic multivalent systems possess complex and unique behavior in solution at surfaces and interfaces as compared to their monovalent counterparts. We have recently synthesized several series of carbosilane dendrimers (CS-DMM) of different generations peripherally functionalized with various quarternary phosphonium groups which exhibit interesting biological properties [1]. Next we extended our methodology on heterocyclic cationic species. CS-DMM decorated by thiazolium (the most distinctive part of coenzyme thiamine) and imidazolium moieties at their periphery were prepared. Azolium units can readily generate N-heterocyclic carbenes - an interesting units with multiple catalytic activity. Thus, here we report synthetic approaches, analytical methods and generation/type dependent properties of cationic CS-DDM as well as their nanocomposites with natural clays. Positive charges on peripheral groups predestinate those compounds for a specific utilization. Their cytotoxicity and use as non-viral gene delivery vectors in the gene therapy applications will be presented. Catalytic activity will be demonstrated on many different chemical transformations. As appealing application for CO_2 utilization - cycloaddition of carbon dioxide into carbonates or series of NHC-catalyzed umpolung reactions will be discussed along with recycling and re-using of organocatalysts from reaction mixture.

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From Peripheral to Central Nervous System: A Journey Towards Targeted Neuronal Delivery

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Nervous system problems are common and encompass a large spectrum of traumatic injuries, diseases or iatrogenic lesions. The poor regenerative capacity, particularly in the case of the central nervous system, cannot be attributed to an intrinsic inability of neurons to sprout and re-grow after injury, as axons are able to regenerate in the presence of a permissive growth environment. One of the challenges facing the neuroscience field is the development of effective therapies that can avoid neuronal cells from dying in the aftermath of a lesion and enhance the regenerative capacity of the nervous system based on the advances achieved in basic research.

We have been exploring cationic systems to serve as nucleic acid delivery systems specifically targeted to neurons, working towards the design of neuroprotective and neuroregenerative therapeutic strategies. In this talk, the we will guide you through the journey that led us to the design of a new family of fully biodegradable dendrimers [1] that we are exploring to delivery nucleic acids to the brain in the aftermath of a stroke event. The application of novel nanothecnological strategies to assess the potential of the developed systems and contribute to the design of more efficient nucleic acid delivery systems will also be discussed.

Acknowledgements: This work was supported by the grants PTDC/CTM-NAN/3547/2014 (FCT, Portugal); FIS-FIS-2015-01_CCV_20150630-88 (INFARMED); NORTE-01-0247-FEDER-033399 (FEDER - Sistema de Incentivos à Investigação e Desenvolvimento Tecnológico, Projetos em Co-promoção do Programa Interface); 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 ERDF and FEDER - Fundo Europeu de Desenvolvimento Regional funds through the COMPETE 2020 - 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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[IOC12]

Rotaxane-branched Dendrimers

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Rotaxane dendrimers, which are defined as "*the dendritic molecules containing rotaxane-like mechanical bonds to link their components*" by Kim, have evolved to be a hot topic within the field of mechanically interlocked molecules (MIMs) and dendrimer chemistry. The alliance between rotaxane and dendrimer endows the resultant rotaxane dendrimers not only intriguing topology but also wide applications in the field of molecular nanoreactors, gene delivery, and light-harvesting system, etc [1]. Over the past few years, the research mainly focused on rotaxane dendrimers with rotaxane cores or (pseudo)rotaxane termini. However, the construction of rotaxane dendrimers with rotaxane branches has been rarely explored due to the intrinsic complexity and steric hindrance with hyperbranched mechanical bonds. Based on our continuous interests on linear neutral platinum-acetylide chemistry, we have successfully realized the construction of type III-A [46]rotaxane dendrimers up to fourth-generation via a divergent strategy [2] (Figure 1). Recently, starting from a switchable [2]rotaxane precursor, the use of a controllable divergent approach allowed for the successful synthesis of rotaxane-branched dendrimers up to the third-generation with 21 switchable rotaxane moieties dispersed on each branch [3]. I will present our recent advances on rotaxane-branched dendrimers in this meeting.

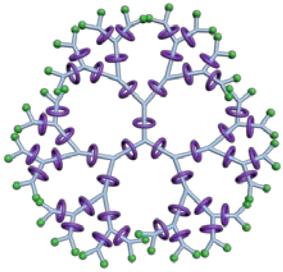

Figure 1: Schematic representation of rotaxane-branched dendrimer.

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Radical Dendrimers: Biomedical Applications

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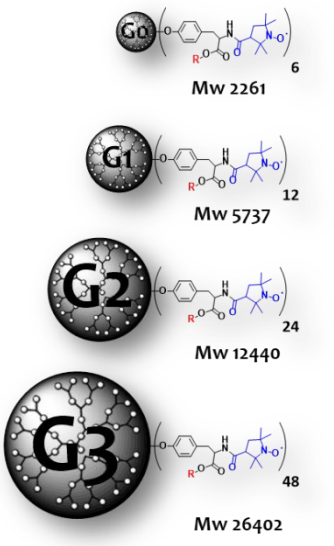
Our interest is focused on the study of molecular materials based on radical dendrimers, their magnetic properties as well as their biomedical applications. [1]

The term "radical dendrimers" has been used in the case of highly functionalized dendrimers with organic radicals. Here we present a series of several generations of dendrimers built with phosphorus as branching points (PPH) and with nitroxyl radicals as end groups. The interaction between pendant stable radicals at the exterior of the dendritic surface and their dynamic behaviour can be studied by Electron Paramagnetic Resonance (EPR) spectroscopy, to understand the magnetic properties of these functionalized dendrimers as well as other related ones like relaxivity. The properties of the radical dendrimers depend on the core dendrimer, the size (generation of the dendrimer), the radical and the linker between the radical and the dendrimer branches.



Molecules with many unpaired electrons, which possess high-spin ground state and stability at room temperature, are particularly challenging and promising targets. For example as contrast agents for Magnetic Resonance Imaging as alternative imaging probes to gadolinium Gd (III) and other metal based contrast agents to overcome their established toxicity.

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[IOC14]

Protective Effect of Neutral Phosphodendrimers on Experimental Autoimmune Encephalitis in Mice

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Multiple sclerosis is a devastating autoimmune disease causing a decrease in life expectation of 10 to 12 years [1]. We have previously shown that neutral high generation phosphorus dendrimers bearing 48 (G3) or 96 (G4) bisphosphonate groups on their surface show impressive anti-inflammatory activity both *in vitro* and *in vivo* in a mouse model of sub-chronic inflammation [2]. We have explored the effect of these neutral phosphodendrimers on the clinical outcome of experimental autoimmune encephalitis (EAE) in mice, an animal model for human multiple sclerosis. After inducing EAE using myelin oligodendrocyte glycoprotein [3], the clinical score of the treated animals rose to 2.5 over a maximum of 5 (animal death). Both G3 and G4 neutral phosphodendrimers decreased the clinical score to the levels achieved by fingolimod (one of the standard treatments for the human disease). Histological analysis of the central nervous system of the animals showed frequent foci of lymphocitic infiltration involving white matter at various levels of the CNS. When samples from the phosphodendrimer-treated animals were analyzed the inflammatory and demyelinitation signs were markedly decreased in line with the observed decrease in clinical score. We have also studied the G3 dendrimer biodistribution and found that, as expected due to its size, the dendrimer accumulates in liver and lungs. Interestingly, there is also an accumulation in the kidneys and the heart. However, no accumulation was observed in the central nervous system suggesting a peripheral action on the immune system.

Acknowledgements: Supported, in part, by project SAF2017-89288-R from MINECO, Spain to V.C.

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Efficient Solid-Phase Synthesis of Peptide Dendrimers *via* On-Resin Ligation

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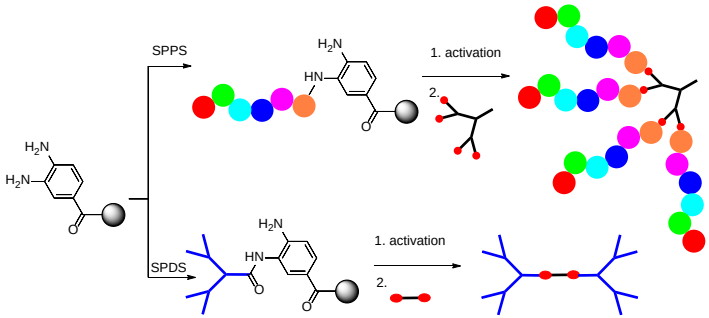
The preparation of pure dendritic compounds is a challenge. In past few years, we developed efficient dendrimer synthesis through solid-phase synthesis. [1-3] Herein, we reported our recent work for the solid-phase dendrimer synthesis of pure peptide dendrmers *via* on-resin ligation. On this newly developing diaminobenzoic acid (Dbz) linker, [4] various length of peptides were prepared through typical SPPS. Thereafter, Dbz moieties were converted to benzotriazole (Bt) moiety which served as a leaving group to introduce various nucleophiles at cleavage step. By using this on-resin ligation method, di, tri, and tetra branched compounds were successfully synthesized with short timeframe and high purity. A cationic rich 13 residue peptide could be implanted to dendritic core by this approach. Furthermore, inverse PAMAM dendrons could also be prepared on the Dbz resin and generated full dendrimers by using diamines as nucleophiles.



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[IOC16]

Functionalized Nanoparticles to Target and Image Cancer Cells *In Vivo*

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Breast cancer is a highly heterogeneous disease. 20-30% of breast cancers are characterized by the overexpression of human epidermal growth factor receptor 2 (HER-2). HER-2 positive breast cancer is usually more aggressive and resistant to medical therapy [1]. Early detection of breast cancer is vital to improving treatment efficacy and patient survival rates. To address this critical problem, we designed and tested novel nano-imaging agents that contain gold nanoparticles (AuNPs) and gadolinium (Gd), conjugated with Herceptin (humanized anti-HER-2 antibody) to target HER-2 positive cancer [2]. In the current study, generation-5 (G5) polyamidoamine (PAMAM) dendrimers were selected as a backbone for the nano-imaging agent due to their unique size, high ratio of surface groups to molecule and bio-functionality [3]. G5-PAMAM dendrimers were first chemically modified to encapsulate AuNPs and Gd, and then Herceptin-azide was conjugated to Au-G5-Gd through click chemistry to synthesize Au-G5-Gd-Herceptin. Here we report the preparation and use of a dendrimer-antibody conjugate to specifically target and image malignant mammary epithelial cells that overexpress HER-2. The targeting specificity of Au-G5-Gd-Ab was first tested against a series of cell lines *in vitro.* The specific binding of Au-G5-Gd-Ab to HER-2 positive breast cancer cells was verified by flow cytometry and confocal microscopy. Most importantly, G5-Gd-Ab significantly enhanced magnetic resonance imaging (MRI) tumor signal intensity ($p < 0.001$) by 21.3 ± 6.04% compared to G5-Gd enhancement of 0.56 ± 5.24% after 24 hours of injection in mice bearing the HER-2 positive tumor. The specificity of this conjugate for cells over-expressing HER-2 suggests that this approach could provide a basis from which to develop nano-diagnostic agents designed for early detection of HER-2 positive cancers by magnetic resonance imaging. In conclusion, our results reveal the novel synthesis of a conjugate that efficiently targets and images breast tumor in HER-2 transgenic mice model. This finding provides a dendrimer platform with both targeting and imaging capabilities that also offer potential opportunities for targeted delivery of other therapeutic and diagnostic agents.

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Topology, Amphiphilicity and Dendronization of Carbosilane Dendritic Systems in Biomedical Applications

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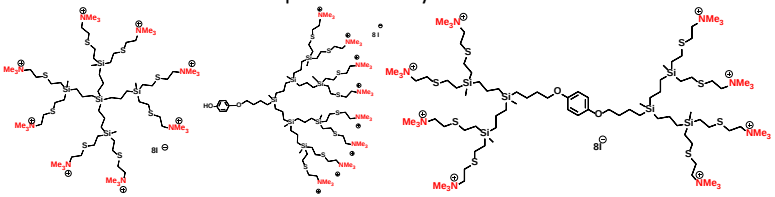
Dendrons have emerged as new dendritic topology and attracted much intention due to the different synthetic possibilities that can afford respecting to conventional spherical dendrimers [1]. Using dendrons as building blocks, several situations can be analysed:

(i) Topology: bow-tie or Janus dendrimers can be designed and on the bases of their different geometry, different behaviours can be expected in the interaction with viral or cell membranes. Examples using carbosilane dendritic systems of different topologies (see Figure 1) as anti-amyloid agents against human islet amyloid polypeptide aggregation or as antiviral agents against HIV will be described.

(ii) Amphililicity: modulation of the dendron substituents both in the periphery and the focal point may influence their supramolecular properties towards the formation of micelles [2]. The aggregation behavior of carbosilane dendrons containing lipophilic groups at the focal point will be shown.

(iii) Dendronization processes: the chemical information programmed within the dendritic architecture of the dendron can be transferred to a more complex situation to generate dendronizated nanostructurated materials with potentially different biomedical behaviours. For that, dendronization of metallic nanoparticle and their biomedical applications will be also explained.

All these possibilities open new and promising perspectives for biomedical applications inconceivable for the spherical and symmetrical dendrimers.



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[IOC18]

~~Dendrimeric Microsponge Based Topical Gel of Dithranol~~

Pushpendra Tripathi & Shalini Tripathi

Lucknow, for kind support.

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Tumor Microenvironment-Responsive Dendritic Polymer-Drugs as Nanoscale Systems for Drug Delivery

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The dendrimers, as a new type of biomedical material, have excellent biocompatibility and multivalent structures which are easy to modify and functionalize for anti-cancer treatment. Tumor microenvironment (TME)-responsive dendrimers-based drug delivery systems that deliver a drug in spatial-, temporal- and dosage-controlled patterns have demonstrated tumor-specific treatment. We moved on to designing a series of biodegradable dendritic polymers for multiple stimuli-responsive drug delivery, including dendrimers, dendronized polymers, branched polymers and linear-dendritic polymers-based prodrugs nanoparticles. These nanoscale systems have shown exhibit good biocompatibility and significant antitumor efficacy. These nano-platforms were conjugated anticancer agents including doxorubicin, gemcitabine, paclitaxel and oxaliplatin through pH-sensitive hydrazone bond, N, O-coordination and enzyme-sensitive GFLG linker, resulting in a series of TME-responsive nanoscale drug delivery systems. Through the systemic delivery of dendronized PEG-platinum (II), 25-fold higher tumor platinum uptake at 36 h post-injection was seen observed due to the enhanced permeability and retention (EPR) effect, which far higher than the reported TME-responsive drug delivery systems.

Recently, we designed a series of TME-responsive linear-dendritic polymers-based nano-platforms via organic chemistry and reversible addition-fragmentation chain transfer (RAFT) polymerization. For example, dendronized and block poly[N-(2-hydroxypropyl) methacrylamide] (polyHPMA)-based copolymer-doxorubicin conjugate were prepared by the two-step RAFT polymerization method. Finally, we explored systematically the relationship between the structure and their behaviors for drug delivery and found that amphiphilic dendronized polymers with a moderate HLB value display enhanced stability and highly efficient tumor retention. These high-performance TME-responsive dendritic polymers based nano-platforms may be employed as a safe and efficient multiple stimuli-responsive drug delivery systems for cancer diagnosis and therapy.

[IOC20]

Biohybrid Structures and Their Targeting Properties: Considering the Potential Use of Mono- and Polyassociation Steps

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Over the last ≥ 10 years we have validated the potential use of dendritic glycoarchitectures as delivery systems, polymeric therapeutics and biohybrids [1-4]. Especially, the previous fabrication of biohybrids, triggered by the conjugation between the binding pockets of (strept)avidin and biotinylated dendritic glycoarchitectures provides some unknown issues (e.g. non-complete conversion of biotinylated dendritic glycoarchitectures through biotin-avidin conjugation or stability of biohybrids after post-modification through biotin-(strept)avidin conjugation).

Here we present recent developments for the design and fabrication of different biohybrids, composed of pentavalent biotinylated dendritic glycopolymers and streptavidin, and their changing targeting properties. The use of different analytical tools (e.g. asymmetrical flow field-flow fractionation coupled with SLS and DLS and in-situ AFM) revealed new insights in the polyassociation process between biotinylated glycopolymers and streptavidin that biotin/streptavidin conjugation in biohybrids is a dynamic binding similar to host-guest interactions, further tuned by displacement events. For example, addition of slightly excess biotinylated components to biohybrids will result in dissociation and reassociation processes, followed by the establishment of new balancing biohybrids. Such sequential binding events offer new possibility in the fabrication of dynamic biohybrid structures for their use in the biomedical field.

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Multifunctional Hybrid Dendrimer With Dual-Ligands: A Next Generation Dendritic Platform for Drug Delivery

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Dendrimers provide unique multifunctional architecture compared to other lipid and polymer-based drug delivery systems. Multiple targeting ligands provide more efficacy for drug targeting and dendrimer is a suitable candidate because of its polyvalent surface. We have developed a novel hybrid dendrimer concept for creating a next generation dendritic platform for drug delivery. We are reporting the synthesis and performance evaluation of multifunctional hybrid dendrimers by multivalent ligand conjugation and physical hybrid dendrimer approach [1, 2] with both folic acid and mannopyranoside, which are proven effective as targeting ligands in penetrating the blood brain barrier (BBB) and targeting glioblastoma multiforme (GBM). The proposed hybrid system (physical) also has an inherent advantage of pH-based targeting by cleaving into the individual dendritic system in tumor microenvironment and stable at physiological environment. The targeting efficiency of proposed system was evaluated in C57BL/6J glioma bearing mice using non-invasive *in-vivo* imaging system followed by its preclinical studies using docetaxel (DTX), which has limited aqueous solubility, severe systemic toxicity, and lack of specificity towards BBB and tumor cells. In addition, its treatment in glioma bearing mice results in a significant reduction of tumor volume by 84.44%, higher tumor cell apoptosis and improved median survival by 4.21 folds. The pharmacokinetics profile showed 2 folds improvement in *in-vivo* compared to intravenous injection of commercially available Taxotere®. Further, histopathology (H&E) and immunohistochemistry investigation (VEGF, Ki-67, COX-II and COX-I) supported the tumor regression and survival studies. These results demonstrate that hybrid dendrimer with dual-ligand technology will serve as a next generation dendritic platform to prepare an advanced multifunctional nanodevice.

Acknowledgements: Council of Scientific and Industrial Research, India (CSIR-INDIA) for Senior Research Fellowship.

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[IOC22]

Molecular Characteristics, Membrane Affinity, Transport Properties and *In Vitro* Cytotoxicity of Bola-Type Peptide Dendrimers

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Treatment of many diseases including cancer represents major therapeutic challenge in modern medicine. In recent years search for nanomolecular drug delivery systems has become a vivid research area with great perspective to improve bioavailability of already known drugs that are toxic or poorly water-soluble. Dimeric bola-type molecules where two bulky fragments are connected with flexible spacer have aroused great attention due to its high potential as a nanocarriers for drugs or genetic material to treat variable diseases [1].

Basing on our previous research we designed novel bola-type dimers containing amphiphilic heads constructed from branched peptides (Lys, Orn - scaffolds) connected by chemically stable or biodegradable spacers [2]. Reliable methodology for the synthesis and purification of amphiphilic cationic dendrons, and bola-type dimers as well further functionalization to obtain high affinity for cell membranes and the ability to form supramolecular complexes with drug or siRNA molecules was derived.

Although bola-type constructions are well characterized in material science, knowledge about their interactions with cell system at molecular level is less advanced. Therefore, we performed HPLC complexation experiments of bola-dimers with known anticancer drugs and characterized them in solution by NMR and DLS methods. Supramolecular interactions at atomic level of dendrimeric bola-dimers embedded in phospholipid bilayers, mimicking healthy and malignant eucariotic cells, were studied by application of solid state NMR techniques, i.e. combination of magic angle spinning (MAS) and the nuclear Overhauser enhancement spectroscopy (NOESY). This allowed to determine the location of bola-dendrimer in phospholipid membranes and correlate it with cytotoxicity.

Acknowledgements: Financial support from the National Science Centre, grant No 2015/19/B/ST5/03547 is acknowledged.

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Synthesis and Properties of Antimicrobial Dendrons

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Antimicrobial resistant bacteria are an increasing problem worldwide. In EU alone more than 25000 people die annually due to Methicillin resistant Staphylococcus aureus (MRSA) and other bacterial infections and there is an urgent need for new antibiotics. Many polyamines are natural products, that have different biological properties; some are neurotransmitters, some are toxins in animals like bees and spiders, while others are transporters of silica in marine organisms or can have antimicrobial activity. Common for all these is, that they are linear polyamines amidated with fatty acids. We are interested in methods for scalable dendrimer and dendron synthesis as well as new antibiotics and therefore it was natural to test some of our new amphiphilic dendrons for antimicrobial activity. One of first two compounds shown in figure 1 had activity both against a gram positive (S. aureus) and a gram negative (E. coli) bacterium. The talk will present data regarding synthesis as well as our results so far on establishing a structure-activity relationship.

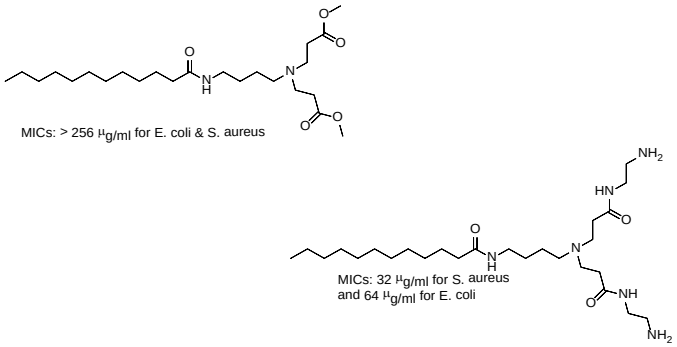

Figure 1: Two amphiphilic dendrons together with their MIC-values against two different strains of bacteria.

[IOC24]

Comparison of Carboxy-methylated G5_PAMAM Dendrimer and Carboxy-methylated Polyethyleneimine Metal Complexes

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Macromolecular ligands complexing metal ions are of importance in medical or environmental applications because of their high stability and nano sizes. These ligands can coordinate toxic transition metal ions from water and the formed nano-sized complexes can easily be removed. In medical applications, beyond the size, the advantage of high stability and kinetic inertness of these complexes attracts remarkable interests [1]. Paramagnetic complexes of Gd(III) and Mn(II) are of great importance as MRI contrast agents [2]. The basic requirement is high relaxivity (capability to enhance the relaxation rate of water protons) through labile water molecules in the first coordination sphere, however this can be the reason also of dissociation and toxicity. We show a new approach to this problem from the basic research side. Organic nanoparticles were prepared containing the important -$N(CH_2COOH)_2$ units in size of about 8 nm from polydisperse branched polyethyleneimine as well as monodisperse highly branched G5_PAMAM dendrimer. The prepared ligands are fully characterized by multinuclear and multidimensional NMR spectroscopy. The structure, formation and stability of the paramagnetic complexes were determined by low-field NMR.

We show that the Gd(III) complexes have 4-5 times higher longitudinal and transverse relaxivites at physiological pH than the commercial Gd-containing contrast agents. In case of manganese the relaxivity of the nanocomplexes is comparable to that of the aqua complex of Mn(II) containing six exchangeable water molecules. The most important feature of the prepared complexes is that neither of them contain water molecules directly coordinating to the metal ions in spite of their high relaxivity, therefore the risk of decomposition and toxicity is very low. The effect of difference in degree of polydispersity is discussed as well.

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IDS11 OC: ORAL COMMUNICATIONS

[OC1]

The Study of Polyamidoamine Dendrimer as Essential Oil Carrier

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The aim of this study was to determine whether dendrimer could be used as an effective delivery system to encapsulate and control the release of volatile essential oil. Essential oils (EOLs) constituents in general are volatile and easy to deteriorate, therefore, these drawbacks made difficulties in its applications and functional abilities. In recent years, dendrimers have been used as delivery systems to increase the stability, prevent the degradation and improve the property of drugs but it has not been apply to EOLs. In this study, the polyamidoamide (PAMAM) dendrimer $G_{2.0}$ and $G_{3.0}$ were used to encapsulate linalool and *L*-limonene, which are our examples of EOLs. The loadings of EO in dendrimers were quantitatively analyzed by high performance liquid chromatography (HPLC); the interaction of host-guest was analyzed by ultraviolet–visible spectroscopy (UV-vis) and nuclear magnetic resonance (NMR); finally, the release profiles was determine by electronic nose. As results, the water solubility of EOLs were all increased. The improvement was dramatical in linalool groups, but was not so significant in *L*-limonene groups. We proposed that linalool possesses hydroxyl group to form the interaction with PAMAM through hydrogen bonding and dipole-dipole interaction. In contrast, *L*-limonene is nonpolar due to the interaction with PAMAM was weak. However, neither linalool nor *L*-limonene had differences between PAMAM $G_{2.0}$ and $G_{3.0}$ treated. The UV-vis spectra showed blue shift effect. It demonstrated the EOLs were trapped into the internal cavity of PAMAM, and the similar findings could also be confirmed by NMR. The volatilization of the EOLs became slower after PAMAM encapsulation, and the folds of release rates decreased two and four more for linalool and *L*-limonene, respectively. In conclusion, PAMAMs are effective carriers for encapsulating EOLs through host-guest interactions to improve water solubilities and provide sustained-releases.

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[OC2]

Exploiting ESI-TOF Mass Spectrometry for Detailed Characterization of Polycationic Carbosilane Dendrimers

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Polyionic syntetic macromolecules are gaining considerable attention due to their unique nature which can be utilised in a variety of applications including medicine, mainly as nanocarriers or vesicles. Among other types, polycationic carbosilane dendrimers exhibit outstanding properties given by large difference in polarity between their interior and periphery and they can be considered as unimolecular micelles. We have recently synthesized several series of carbosilane dendrimers of different generations peripherally functionalized with various quarternary phosphonium groups which exhibit interesting biological properties [1,2]. Detailed characterization of these molecules using ESI-TOF MS exploited their polyionic nature which allowed to analyse these large molecules as multiply charged ions in a relatively narrow range of low *m/z* with the advantage of high resolution [3]. The results disclose the type and origin of defects in their structure as well as some processes taking place in the course of ionization process, and at least semiquantitave interpretation is also possible. LC-MS using GPC column showed partial separation of defective molecules according to the number of defects which proves that these defects are not due to fragmentation. The same methodology was then used for the analysis of several series of carbosilane dendrimers bearing imidazolium and thiazolium moieties at their periphery. Generation- and type-dependent formation of NHC carbenes was observed in the course of measurement; the results are in accordance with known order of acidity of the parent azolium cations and electrochemical study which should support the ESI MS results is currently underway.

Acknowledgements: This work was supported from ERDF/ESF project "UniQSurf - Centre of biointerfaces and hybrid functional materials" (No. CZ.02.1.01/0.0/0.0/17_048/ 0007411).

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Pt(II)-dendrimers as Bio-Imaging Marker for Bacteria in Two-Photon Excitation Microscopy

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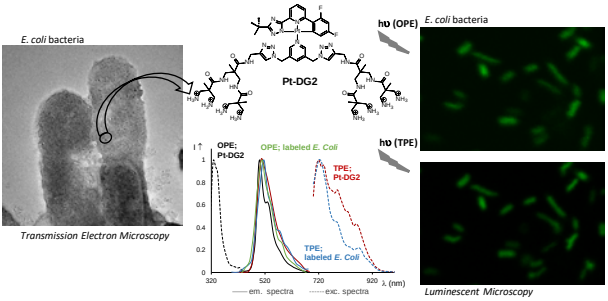
The use of luminescent markers based on metal complexes in two-photon excitation microscopy techniques are of great interest in the field of bioimaging. However, despite the excellent luminescent properties of Pt(II) complexes, their application in this field is still limited, due to their poor solubility and quenching problems in aqueous media [1]. The insertion of a Pt(II) complex into a dendritic structure, gives as a result an unique luminescent marker soluble in biological media. The dendrimer provides excellent properties to the metal complex such as solubility in aqueous media, protection against quenching processes and binding to bacterial surfaces. The new probe can be used as bacteria cells marker in luminescent microscopy, operating under one or two-photon excitation (OPE/TPE) conditions, as well as in electron microscopy, thus providing a powerful tool in the field of bioimaging.



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[OC4]

Dendrimers Carrying Multiple Redox Units – Is it Good or Bad for Cell Survival

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Exposition to ozone level and ultra-violet radiation is one of the major concerns in context of public health. Numerous studies confirmed that abundant free radicals initiate undesired processes, e.g. carcinogenesis, cells degeneration, etc. Therefore, the design of redox-active molecules with novel structures, containing radical quenchers molecules with novel structures, and understanding their chemistry and biology might be one of the prospective solutions.

We designed peptide dendrimers with different structure of dendrimeric scaffolds, carrying multiple copies of polyphenols with antioxidant properties (caffeic, ferulic, etc. acids), *p*-aminobenzoic acid (PABA) or tryptophan (Trp) and evaluated their molecular antioxidant properties in terms of quenching neutral and cationic radicals in DPPH and ABTS tests, respectively. Cytotoxicity against human melanoma and fibroblast cells as well as against primary cerebral granule cells (CGC) alone and challenged by neurotoxic glutamate and production of reactive oxygen species (ROS) in presence of dendrimers were measured.

On molecular level, the designed redox-active residue-functionalized dendrimers expressed high ability to quench neutral and cationic radicals. However, their antioxidant properties and cytotoxicity were not strictly concentration but to a high degree also dendrimeric structure dependent [1].

Acknowledgements Financial support from the National Science Centre, grant No 2015/19/B/ST5/03547 is acknowledged.

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[OC5]

Covered By Neuroligin-2-derived Peptide Polyamidoamine-Based (PAMAM) Dendrimers Enhances Pancreatic B-Cells' Proliferation and Function

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Both pancreatic β-cell membrane and presynaptic active zones of neurons are the assembly sites of similar protein complexes mediating regulated secretion of bioactive molecules. These synapse-inducing proteins include neuroligins and their binding partners: neurexins. These proteins participate in trans-cellular protein-protein interactions across the synaptic cleft. It was shown that β-cells express both neuroligins and neurexins on their plasma membrane. It was also found that insulin secretion and the proliferation rate of β-cells increased when β-cells were co-cultured with cells overexpressing neuroligins. We propose that neuroligin-derived molecules arranged in clusters can enhance β-cell function and functional maturity, as well as protecting β-cells in stress conditions. To test this hypothesis, several peptides were derived from crystal structures of different neuroligins and neurexins using molecular modelling methods. These peptides were conjugated with nanoscale composites; polyamine based dendrimers and others. Covered by NL-2 derived peptide nanocomposites (HSA-28D) enhanced β-cell functions in terms of glucose-stimulated insulin secretion and protects them under stress conditions in vitro and ex vivo. [1]. Recruiting the β-cells' "neuron-like" secretory machinery as a target for diabetes treatment is a novel approach. Such nanoscale composites might therefore provide a unique starting point for designing a novel class of antidiabetic therapeutic agents.

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[OC6]

Mass Spectroscopy for Detailed and Precise Analysis of Dendrimers

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Since their conception, dendrimers have been considered and appreciated as admirable chemical entities and functional materials, holding great promises for a wide range of applications, in particular in biomedical field, by virtue of their unique structural properties and multivalent cooperativity [1]. However, biomedical applications of dendrimers require high quality and reliable structures [2]. As dendrimers contain a large number of repetitive structural units, traditional NMR methods can therefore not offer clear-cut structural characterization. Mass Spectrometry (MS) is able to provide accurate analysis of the elemental composition, structural elucidation as well as conformational information of dendrimers thanks to the different ionization techniques available to ionize all type of compounds without causing any structural alteration.

We will present here our efforts in using–MS, in combination with NMR, to study functional dendrimers on their composition, structure and conformation etc [3-5]. In parallel, an efficient MS protocol has been developed in order to assist the dendrimer synthesis and to help the detection and further removing of impurities.

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In Quest for Better Selectivity and Activity: Nucleophilic Organocatalysts Based on Branched/Dendritic Design

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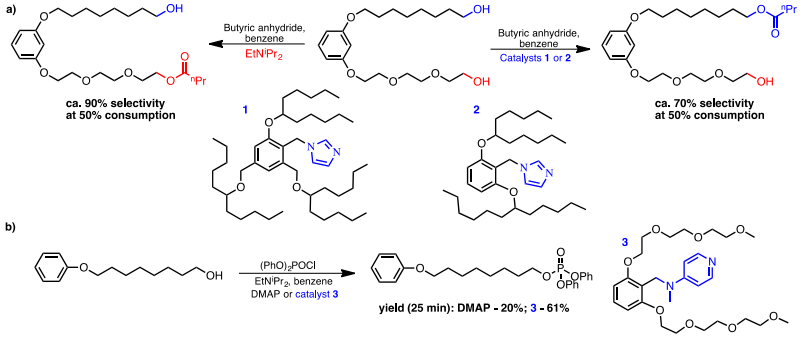
While the field of organocatalysis underwent fast development in the past decades, many organocatalytic systems still suffer from low activity or selectivity. The low activity can be sometimes counterbalanced by increasing the reaction time or the catalyst loading. The impaired selectivity is, however, irreparable.

A new design of organocatalysts, embracing a nucleophilic active site surrounded by long or branched dendritic tails, potentially controlling the access of substrate molecules to the catalytic core, was explored in our group with the aim of achieving site-selectivity in chemical transformations of diol or polyol substrates. Thus, in an acylation of model amphiphilic diol substrates, the use of a nucleophilic catalyst, particularly branched/dendritic catalyst with the imidazole site in the core, enabled a remarkable shift of the site-selectivity from a polar alcohol site, preferred in background non-catalyzed or base-promoted reactions, to an apolar site (Scheme 1a).

Scheme 1



In a related phosphorylation reaction, a similar design of the catalysts, though with long oligoether tails, led to highly active catalytic systems. Remarkably, when the imidazole active center was replaced by an aminopyridine moiety, the activity of the formed systems surpassed that of DMAP, a benchmark phosphorylating catalyst (Scheme 1b).

Expansion of these results to additional catalytic systems and substrates will be presented at the talk.

[OC8]

Uptake, Anti-Inflammatory, and Migratory Properties of Mixed-Surface PAMAM Dendrimers in Ischemic Stroke Rats

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Numerous potential applications of polyamidoamine (PAMAM) dendrimers have been reported in biology and medicine. Our focus is to design dendrimers that provide therapeutic value besides acting simply as carriers of guest chemicals. Towards this end, we have incorporated "ethanol-like" and sulfur moieties into mixed-surface PAMAM dendrimers that would help alleviate inflammation associated with several brain diseases. Instead of the conventional G4 100% amine (-NH_2) surface dendrimers, which are highly toxic to cells, we have designed and synthesized de novo, mixed-surface dendrimers with 10% -NH_2 and 90% neutral amidoethanol (-OH) groups (known as G4-90/10). Our in vitro studies have shown that these dendrimers: (1) can be labelled with fluorescent dye for tracking purposes; (2) are uptaken by different cells types; and (3) are less toxic. Moreover, our G4-90/10 dendrimers have cystamine disulfide (S-S) core, which is advantageous as they can split into dendrons with thiol groups (-SH), which are known to have anti-inflammatory properties. Our in vitro data confirmed that these dendrimers show those properties by reducing the release of interferon gamma (IFNγ) from active B-cells extracted from splenocytes. Moreover, we also found that these dendrimers can cross the blood-brain barrier (BBB) and reach the brain when injected systemically into rodents. Given these properties, we are using our mixed-surface PAMAM dendrimers to reduce inflammation in a rat model of ischemic stroke. As a proof of concept, we injected these fluorescently tagged dendrimers into the rat brain (ipsilateral and contralateral to the infarct area), 7 days following a 90 min ischemic stroke. We found that (1) the dendrimers have a trend towards reducing the inflammation in the stroke brain compared to the controls; (2) the dendrimers were found to migrate near the infarct, irrespective of the injections either to the ipsilateral or contralateral side of the infarct and; (3) the dendrimers were also taken up by the neurons and glial cells. The second phase of this will be to systemically inject the dendrimers into the stroked rats to assess their ability to reduce inflammation. The third phase of the project will be to use these dendrimers to deliver potential drugs or biomolecules to the brain of stroked and assess their ability to reduce neuropathological and behavioral deficits.

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Amphiphilic Hybrid Triazine-Carbosilane Dendrons: Synthesis and Self-Organization

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The use of supramolecular assemblies as drug delivery vehicles draws attention due to the flexibility of their architecture, high loading capacity, biocompatibility and biodegradability, possibility to target them to a given tissue etc. Amphiphilic dendritic molecules are novel and promising precursors for the supramolecular assemblies. By changing the structure and architecture of dendritic molecules, it is possible to drive their self-assembly towards desired supramolecular topologies.

In this work, we report the synthesis of first examples of amphiphilic carbosilane dendrons bearing two hydrophobic moieties and a dendron G1-3 organized around a triazine fragment (fig. 1). Such an architecture drives the self-assembly of dendrons in water medium into bilayer supramolecular constructions – dendrimerosomes. Furthermore, triazine acts as a pH-sensitive block that drives the dendrimerosome disassemblage at slightly acidic pH thus making them stimuli-sensitive.

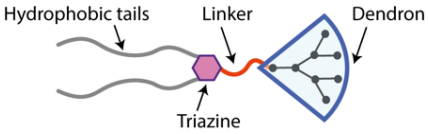

Figure 1. Structure of amphiphilic hybrid triazine-carbosilane dendrons.

The formation of supramolecular dendron associates has been studied, as well as their pH-sensitivity. The binding of nucleic acids to dendrimerosomes has been demonstrated. The results obtained provide a platform for the rational design of supramolecular drug carriers.

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[OC10]

Dialytic Separation of Anions from DMSO Solution Facilitated by Dendritic Receptors

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The impact of anionic species on the environment and human health is well recognised. For complexation of anions via hydrogen bonding, a variety of receptors was proposed, synthesized and tested so far [1]. Nevertheless, the application of these receptors for separation of anions from the solutions is still rare. Attachment of a well explored anion sensing moiety, an isophtalamidic group [2], to dendritic structures of high molecular weight [3] leads to a new class of receptors. These compounds possess the advantage of multiple complexation sites with high affinity towards anions. Moreover, they offer the possibility of separation of the formed complex from the solution by the methods of nanofiltration and subsequent recycling of the receptor.

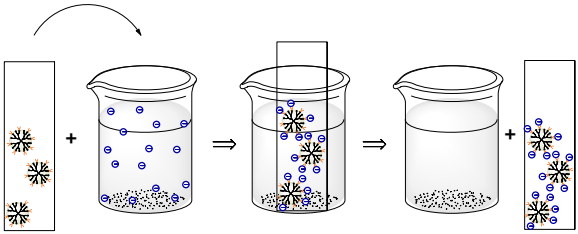

Figure 1: Separation of anions from solution via complexation and subsequent dialysis.

Acknowledgements: This work was supported from ERDF/ESF project "UniQSurf - Centre of biointerfaces and hybrid functional materials" (No. CZ.02.1.01/0.0/0.0/17_048/0007411).

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[OC11]

Fighting Resistant Cancer with Carbosilane Metallodendrimers

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Cancer, the leading cause of death worldwide, is currently facing a major challenge related to tumor cell drug resistance. Resistance to chemotherapy is believed to cause treatment failure in over 90% of patients with metastatic cancer. Precision nanomedicine – and dendrimers in particular- can overcome the limitations of current therapies. In the search of new metallodrugs with different modes of action, improved efficacy and minimum side-effects, we found out the broad possibilities of carbosilane metallodendrimers (Figure 1). These water-soluble metallodrugs bearing ruthenium (II) [1] or copper (II) [2] complexes were wisely designed and characterized, including NMR and EPR assays. As proof-of-concept, we performed the evaluation on prostate and breast resistant tumors. Relevant *in vitro* as well as *in vivo* assays revealed a significant decrease in resistant prostate tumor growth, with long-term survival of the animals and no signs of toxicity.

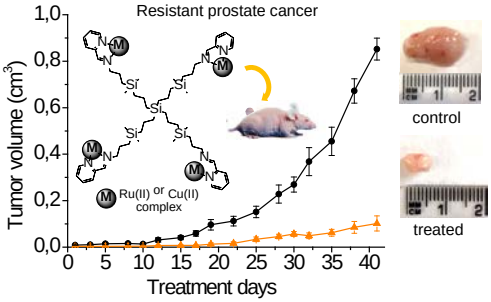

Figure 1. First-generation carbosilane arene Ru(II)-metallodendrimers revealed up to 82% decrease in tumor growth in a mice model of advanced prostate cancer.

Acknowledgements: This work has been supported by grants from CTQ2017-86224-P (MINECO), Project SBPLY/17/180501/000358 JCCM and CIBER-BBN.

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[OC12]

Fragmentation Pattern of Copper-metallated and Non-metallated OH-Terminated PAMAM Dendrimers Generation 4

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Complex structure and architecture of dendrimers make them suitable as nanocarriers for drug and gene delivery [1], but higher generations of these species are difficult for structural characterization. A soft ionization mass spectrometric method, matrix-assisted laser desorption and ionization mass spectrometry (MALDI MS), might be a method of choice since it is possible to detect the high mass species with multiple ionization sites. However, due to technical limitations, an optimization of the method is required when analyses of higher generations of dendrimers by MALDI MS are in focus [1]. In this study, we have investigated the fragmentation pattern of MALDI mass spectra of polyamidoamine dendrimer with ethylenediamine core with 64 hydroxyl groups on the surface (G4 PAMAM-OH) and compared to the fragmentation pattern of Cu-metallated species. Fragmentation was induced by the In-Source-Decay (ISD) approach, which utilizes increased laser intensities. Three matrices for MALDI were tested, and 2,5-dihydroxybenzoic acid (DHB) was found the most suitable for G4 PAMAM OH dendrimer detection, as it was possible to detect the ion corresponding to the complete analyte. The analysis of parent spectra of non-metallated and Cu-metallated species already revealed higher number of fragments in the m/z region around 2 000, 3 000 and 10 000, even with lower laser powers, along with the singly (m/z around 14 000) and doubly charged ions (signal around m/z 7 000) arising from the non-fragmented species. In contrast to G3 PAMAM OH dendrimer, which was investigated by other authors [2], we were able to detect the lower number of fragments in our spectra, which also correspond to the *S* and *E*-type of fragments. The number of fragments was not significantly higher compared to the parent spectra, but their position was slightly shifted towards lower m/z values.

Acknowledgements: This work was supported by FCT- Fundação para a Ciência e a Tecnologia (Pest-OE/QUI/UI0674/2019, CQM Portuguese Government Funds), by 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 Program) and Grant ARDITI-CQM/2018/005-STMG-MS.

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[OC13]

New Fully Biodegradable PEG-Dendritic Block Copolymers: from Synthesis to Application as Efficient Nanocarriers of siRNA

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Dendrimers represent a powerful class of vehicles for different bioactives [1] due to their globular, well-defined, very branched and controllable nanostructure, low polydispersity and multivalency. Of special relevance is their capacity to complex nucleic acids (NA) in compact nanostructures, named "dendriplexes", protecting them from degradation and rapid renal clearance [2]. However, one hurdle of the most used dendrimers is their non-degradability under physiological conditions that could result in complications induced by their bioaccumulation. Moreover, in the gene therapy field, vector stability can further hinder the NA intracellular release, leading to low transfection efficiencies (TE) [3]. Therefore, recent interest has focused on the development of biodegradable dendrimers, but only few works report their biomedical applications [4]. Because of this, we have recently reported a new family of partially/hybrid biodegradable PEG-dendritic block copolymers for siRNA delivery [5,6]. Our systems showed a great ability to internalize siRNA [5], yet a low transfection efficiency was observed due to the partial vector stability.

Here, we present new fully biodegradable PEG-dendritic block copolymers: their synthesis and successful functionalization with different amine groups [6], as well as their function as siRNA vectors in neuronal cell lines. Our fully biodegradable dendritic nanosystems showed a great ability to complex, protect and mediate the intracellular release of siRNA, leading to excellent TE.

The present study puts forward these fully biodegradable PEG-dendritic block copolymers not only as suitable vectors for nucleic acids, but also opens new avenues for further developments exploring their use in theranostics.

Acknowledgements: FCT (SFRH/BPD/69110/2010, BAITS (PTDC/CTM- NAN/3547/2014); siRNAC (NORTE-01-0247-FEDER-033399); NORTE-01-0145-FEDER-000008 and NORTE-01-0145-FEDER-000012.

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IDS11 YSC: YOUNG SCIENTISTS COMMUNICATIONS

Antibacterial Activity of Conjugates Between Antimicrobial Peptides and Cationic Carbosilane Dendrons

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Although the huge number of antibiotics described since penicillin discovery, we are now going through an antibiotic resistance period due to its overuse and the effort reduction on new antibacterial drugs [1]. Nowadays, the increase effort to explore new antimicrobial agents has opened a huge researching field: the field of antimicrobial peptides (AMPs) [2]. On the other hand, cationic carbosilane dendrons with antibacterial activities could represent a possibility for AMPs transport and protection [3].

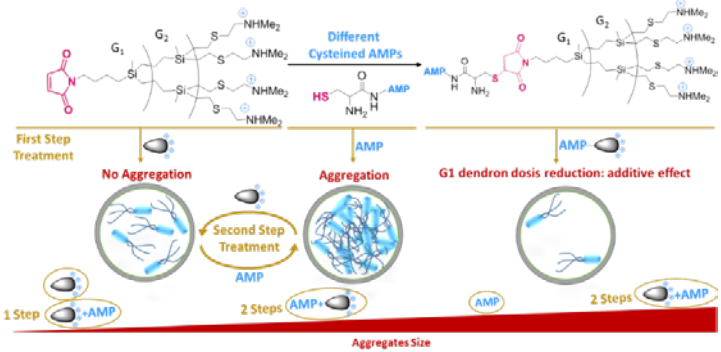

Figure 1. Dendron/AMP treatment and their different treatment combination.

Here, we will present carbosilane dendrons used for AMPs conjugation and details of their antibacterial activity will be given (Figure 1).

Acknowledgements: This work has been supported by grants from CTQ2017-86224-P (MINECO), Consortiums NANODENDMED II-CM ref B2017/BMD-3703 and IMMUNOTHERCAN-CM B2017/BMD-3733 (CAM), Project SBPLY/17/180501/000358 JCCM and CIBER-BBN.

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[YSC2]

PAMAM Dendrimers as Nanocarriers for Platinum Anticancer Complexes

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Metal-based compounds have attracted the interest of the scientific community because of their promising anticancer properties. Among them, *cisplatin* is one of the most used metal complexes for the treatment of various types of cancer [1]. Nevertheless, the undesirable side effects and resistance have been limiting their potency, triggered the search for alternative platinum compounds derivatives, such as *oxaliplatin* [2].

With the aim to enhance the efficacy of the platinum drugs *cisplatin* and *oxaliplatin*, low generation of anionic poly(amidoamine) (PAMAM) dendrimers were used by us as a nanocarrier to delivering it into tumour cells. The prepared metallodendrimers with *cisplatin* were characterized by different technics including NMR, FTIR, UV-Visible/Fluorescence Spectroscopy and Dynamic Light Scattering. Their effectiveness was then studied in A2780 and A2780cis cancer cell lines and its biocompatibility toward to the blood cells by hematoxicity. Currently, the metallodendrimers with *oxaliplatin*, are being synthesized/characterized and further *in vitro* studies will be performed to determine the capability to release the drug and targeting the tumour. Afterwards, the anticancer activity of the different nanosystems will be compared by evaluating the efficacy of our approach regarding resistance to cancer cells.

Acknowledgements: This work was supported by Fundação para a Ciência e a Tecnologia (CQM Project PEst-OE/QUI/UI0674/2019, Portuguese Government funds), 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 Program) and the PhD Grant project M1420-09-5369-FSE-000001 (CC).

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[YSC3]

New Anionic Poly(Alkylidenamine) Dendrimers as a Potential Microbicide: the Behavior Against HIV-1 Infection

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Human immunodeficiency virus (HIV) is responsible for millions of new infections each year. 80% of all infections are from sexual transmission, and about half of the infected cases are women [1]. Therefore, the pursuit for finding new nanomaterials, such as dendrimers, to assist in the diagnosis, treatment and prevention of this kind of diseases is very important [1,2]. Here, we describe the preparation and characterization of anionic poly(alkylidenamine) dendrimers with carboxylate (C) and sulfonate (S) terminal groups, from generations 1 (G1) to 3 (G3), having in view their use as microbicides. The stability of these dendrimers in aqueous solution was confirmed by ^{1}H-NMR. Afterwards, their cytotoxicity and antiviral activity were evaluated using the TZM.bl cell line and R5-HIV-1_{NLAD8} and X4-HIV-$1_{NL4.3}$ isolates. The results showed that G1C and G1S dendrimers present high inhibition against R5-HIV-1_{NLAD8} (more than 85%) and X4-HIV-$1_{NL4.3}$ isolates by blocking the entry of HIV-1. Additionally, their antiviral activity was preserved at different pH values. The *in vivo* studies with the G1C and G1S dendrimers showed that both are biocompatible, with no visible irritation or inflammation seen in the vaginal epithelium. So, these new anionic poly(alkylidenamine) dendrimers have a good potential as microbicide candidates against HIV-1 infection.

Acknowledgements: This research was supported by Fundação para a Ciência e a Tecnologia (FCT) with Portuguese Government funds through the CQM Strategic Project PEst-OE/QUI/UI0674/2019, and the PhD Grant SFRH/BD/102123/2014 (D.M.). The support of the international network CYTED 214RT0482 in the domain of the HIV infection is highly appreciated. The authors also acknowledge the Madeira 14-20 Program and ARDITI-Agência Regional para o Desenvolvimento da Investigação Tecnologia e Inovação, respectively through the project PROEQUIPRAM - Reforço do Investimento em Equipamentos e Infraestruturas Científicas na RAM (M1420-01-0145-FEDER-000008) and the project M1420-01-0145-FEDER-000005 - Centro de Química da Madeira - CQM^{+} (Madeira 14-20).

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[YSC4]

Dendrimers Incorporating Lanthanide Cations as Near-Infrared Imaging Agents

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The creation of efficient imaging tools is crucial for the early-stage diagnostic of a large panel of diseases. For this purpose, fluorescence/luminescence imaging has undeniable advantages such as the availability of inexpensive and portable imaging equipment and the high sensitivity of detection. In order to take advantage of this imaging modality, fluorescent probes are required. Fluorescent probes that exhibit excitation and emission bands in the biological transparency window are of particular interest [1]. Taking advantage of the energy transfer between organic sensitizers and lanthanide cations [2], we have developed highly absorbing probes based on PAMAM dendrimers absorbing and emitting in the near-infrared that possess interesting features for biological imaging.

For this purpose, a particularly useful family of dendrimers are PAMAM (polyamidoamine) dendrimers [3], whose branches contain internal amide groups capable of binding hard Lewis acid lanthanide ions through their oxygen atoms and characterised by their internal cavities. We report the synthesis of a generation 3 (32 end-branches) PAMAM dendrimer that contains a total number of 60 internal amide groups suitable for the coordination of 8 lanthanide ions and based on a Near-Infrared sensitizing core "antenna". Therefore, discussion of the organic synthesis, spectroscopic properties and optic imaging of the dendrimer will be the aim of this communication.

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[YSC5]

Cinnamic Acid-Functionalized PAMAM Dendrimer Generation 4: Drug Delivery and Cytotoxicity

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Emerging evidence support cancer as a metabolic disease as, for example, most cancer cells are able to reprogram their energy metabolism via the "Warburg effect", limiting it largely to glycolysis and leading to a state known by ''aerobic glycolysis'' [1,2]. Studies have described that alpha-cyano-4-hydroxycinnamic acid (ACCA) displays *in vitro* and *in vivo* efficacy against this reprogramming of glucose metabolism by inhibiting monocarboxylate transporters and, thus, the uptake of metabolites used by aerobic glycolysis [1,2]. The goal of this project is to synthesize new cinnamic acid-terminated dendrimers to target the altered glucose metabolism in cancer cells. Furthermore, these dendrimers can also be used for encapsulation of anticancer drugs (like doxorubicin, DOX) to achieve synergistic effects in the treatment. In this study, generation 4 poly(amidoamine) PAMAM dendrimers were functionalized with cinnamic acid via carbodiimide reaction. After their characterization by NMR and MALDI-TOF MS, they were successfully loaded with DOX and studies were done regarding the effect of functionalization on the release of the drug. *In vitro* cytotoxicity assays were also performed using CAL-71 cells. The results concerning to the new cinnamic acid-functionalized dendrimers have been compared to the commercial PAMAM dendrimer. The use of dual-acting molecules, like ACCA, may hold great promise to be used for targeted delivery of different anticancer drugs.

Acknowledgements: This work was supported by Fundação para a Ciência e a Tecnologia (CQM Project PEst-OE/QUI/UI0674/2019, 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 Program) (AO Ph.D. grant M1420-09-5369-FSE-BD-CQM-007).

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[YSC6]

A Self-Assembling Amphiphilic Peptide Dendrimer as Anticancer Drug Delivery Platform

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Cancer is one of the biggest threats to human health. Drug resistance and side effects are main challenges in cancer therapy [1]. Nanomedicine carrying anticancer drug can accumulate at tumor site, which is able to promote anticancer drug internalization, permeate into the depth of tumor tissue, and improve efficacy of cancer treatment [2]. Among myriad nanocarriers, amphiphilic dendrimers, marrying the characteristic of dendrimers, self-assembly performance of amphiphilic molecules and the bio-mimicry of lipids, become particularly appealing as nanovectors for drug delivery in nanomedicine [3]. Here, we report a self-assembling anticancer drug delivery system based on amphiphilic peptide dendrimers (AmPD), which can effectively encapsulate the anticancer drug doxorubicin (DOX). The obtained AmPD/DOX nanoassemblies were able to significantly enhance drug cellular uptake in DOX-resistant cell lines. In addition, the AmPD/DOX nanoassemblies could significantly reduce side effects compared with free DOX. More importantly, they could effectively permeate and distribute in 3D multicellular tumor spheroids model. Collectively, our studies demonstrated that the nanomedicine based on the self-assembling amphiphilic peptide dendrimer constitutes a promising and effective drug delivery platform in cancer therapy.

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[YSC7]

Design and Synthesis of Bioconjugates for Personalized Medicine

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With increasing knowledge in pharmacogenomics, personalized therapy becomes more diverse and applicable. However, the development of suitable delivery systems remains challenging. Here, we present a "tool-kit" of bioconjugates (BCs) (Figure 1) for the functionalization of drug and gene delivery systems for tailored therapy and diagnostic approaches. Based on electrostatic interaction or click chemistry, these BCs can be introduced into various systems like dendriplexes, polymersomes or silica nanoparticles.

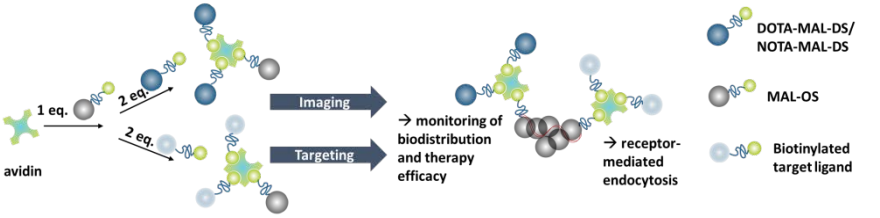

Figure 1: Synthesis of cationic BCs and adsorption on a dendriplex surface by electrostatic interaction.

BCs were synthesized using the interaction of avidin with biotinylated ligands, more precisely with one cationic, maltosylated poly(propylene imine) (PPI) and two functional ligands for imaging or targeting. For imaging, biotinylated PPI was modified with chelators followed by introduction of a dense maltose shell, while targeting ligands were introduced using biotinylated poly(ethylene glycol) (PEG) spacers. Information will be given regarding the synthesis and characterization of the biotinylated compounds as well as the properties of the developed bioconjugates. Biological studies include the cytotoxicity of the compounds, first studies on cell internalization and first *in-vivo* SPECT imaging experiments. Storage conditions and first biological experiments are very promising in respect of the future use of such BCs in the biomedical field.

[YSC8]

[Ru(η^5-C$_5$H$_5$)(PPh$_3$)$_2$]-PAMAM Metallodendrimers as Promising Anticancer Drugs

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Ruthenium compounds have been studied over the last years as anticancer drug candidates, exhibiting a set of interesting characteristics. Some of these features include: their ability to bind to albumin and transferrin (and related high accumulation in cancer cells which overexpress transferrin receptors); their intercalation with DNA; and effectiveness at inducing apoptosis, necrosis and/or autophagy [1]. Furthermore, their therapeutic activity and selectivity can be enhanced when functionalized on the periphery of dendrimers, producing metallodendrimers [2]. We herein present the synthesis and characterization (by NMR, FTIR, EA, MS and DLS techniques) of a new family of ruthenium(II)-metallodendrimers – G0 to G3-[Ru(η^5-C$_5$H$_5$)(PPh$_3$)$_2$]$_x$[CF$_3$SO$_3$]$_x$ (where x = 4, 8, 16 and 32 for each generation, respectively). The evaluation of their *in vitro* cytotoxicity, hemotoxicity, and reactivity towards DNA and human serum albumin (HSA) was also performed. Following our former studies [3], their preparation was accomplished via coordination of the metallofragment [Ru(η^5-C$_5$H$_5$)(PPh$_3$)$_2$]$^+$ on the periphery of polynitrile PAMAM dendrimers. Their anticancer activity was established using A2780, A2780cisR and MCF-7 human tumor cells, as well as human primary fibroblasts (BJ cell line, used as a control). This parameter was found to be distinctly high (IC_{50} are at a nanomolar range), and generation dependent, for all the studied cancer cell lines. The metallodendrimers exhibited strong interactions with DNA and HSA and, regarding the hemotoxicity studies, at the IC_{50} concentrations obtained for the cancer cell lines, they were non-toxic for the healthy human red blood cells. The abovementioned results validate that these novel metallodendrimers are quite promising for anticancer research.

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[YSC9]

Synthesis, Self-Assembling Properties, and Biomedical Applications of Amphiphilic Janus Glycodendrimers

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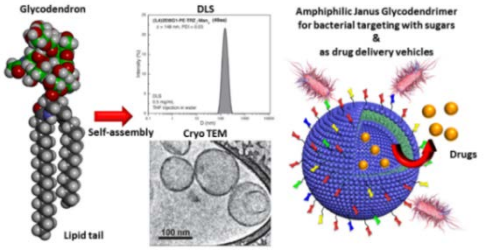
Sugar containing small drug molecules [1] and glycoconjugates [2] constitute important tools for biomedical applications. The design of simplified chemical entities possessing the essential features of dendrimers is essential. Toward this goal, we identified small mannopyranosides that could bind to uropathogenic *E. coli* FimH having high therapeutic promises as bacterial antiadhesion [3]. One of these candidates, a □-D-mannopyranoside incorporating a hydrophobic aglycone had low nM affinity [4]. We constructed amphiphilic Janus dendrimers that self-assembled into liposomes incorporating the optimized ligands [5,6]. Mannosylated dendrons harbouring both a hydrophobic as well as an hydrophilic (peg) linkers were first synthesized using classical Lewis acid-catalyzed glycosidation. Mannodendrons were next elaborated from an azide-ending sugar monomer which was coupled onto an alkyne-ending pentaerythritol scaffold using click chemistry (Copper-catalyzed cycloaddition). The azido dendrons was next coupled by amide linkage to a lipid moiety built from 3,5-dihroxybenzoic acid as before [5,6]. The resulting amphilic Janus glycodendrimers were allowed to self-assemble using the injection method in appropriate buffers. They were characterized using DLS, TEM, and cryo-TEM. Their binding properties with lectines were demonstrated by their cross-linking abilities to form large aggregates.



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[YSC10]

Synthesis, Characterization and Biological Evaluation of Homo- and Heterofunctionalizated Polyamide Dendrimers for Application in Inflammatory Diseases

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Inflammation is a general pathomechanism associated with numerous diseases of great global impact as many cancers, metabolic disorders and infectious, neurodegenerative and autoimmune diseases [1]. Dendrimers appear as a convenient starting point for the design of these drugs. These nano-sized and well-defined branched macromolecules have interesting chemical properties and a wide variety of biological applications [2]. We synthesized G2 and G3 polyamide dendrimers with potential application in the treatment of diseases that are caused by inflammatory processes. These dendrimers were homo- and heterofunctionalizated bearing NO-releaser and/or bile acids BA; compounds with recognized biocompatibility and anti-inflammatory properties (Figure 1). The final dendrimers did not show significant cytotoxicity in THP-1 cells at the concentrations tested. Bifunctional G3 dendrimers exhibited the most interesting anti-inflammatory activities. The best ones presented 54.7%, 65.3% and 70.4% of IL-8 inhibition at 13.3, 8.57 and 10.9 nM, respectively. These results are very promising for the application of dendrimers as innovative drugs against a variety of diseases caused by inflammatory processes.

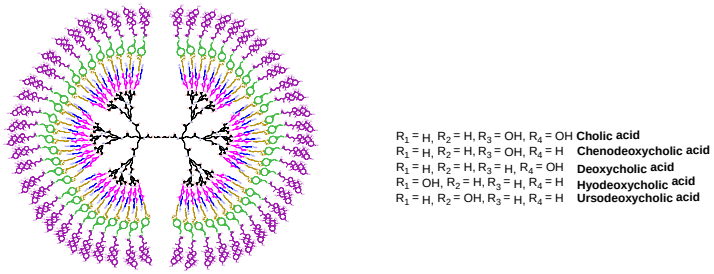

Figure 1: G3 polyamide dendrimer bifunctionalizated with NO-releasing moieties and BAs.

Acknowledgements: UNICAMP, CAPES, FAPESP, DAAD, MPIC.

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Self-Assembling Hybrids of Fluorescent Carbon Dots and PAMAM Dendrimers for DNA Delivery Applications

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Carbon dots (CDs) and PAMAM dendrimers are subject of broad interest due to their fascinating properties for biomedical applications [1,2]. Carbon dots are fluorescent, water-soluble, photostable, and low cytotoxic while PAMAM dendrimers are quickly surface functionalized, have controlled-molecular weight, low polydispersity and ability to carry cargo either on the interior or on the surface of its structure [3]. The combination of carbon dots and PAMAM dendrimers is not so extensively studied, and they were never combined for DNA delivery applications. Therefore, the preparation of a fluorescent hybrid based on carbon dots and PAMAM dendrimers to deliver DNA and study its potential intracellular imaging was explored. For the preparation of a self-assembling hybrid, the surface of carbon dots should be preferentially of anionic nature to assemble with the cationic PAMAM dendrimers by electrostatic interaction. This strategy presents some advantages, *e.g.* lower impact on the fluorescence of carbon dots, possible enhancement of CDs fluorescence by PAMAM dendrimers via the charge-transfer process, and quite ease experimental setup. Moreover, the ability of PAMAM dendrimers to condense DNA is expected to be maintained after conjugation with carbon dots, as well as the observation of cytotoxicity reductions.
In this work, carbon dots with an anionic surface were combined with cationic G4-G6 PAMAM-NH_2 dendrimers at room-temperature to obtain G4-G6 CDs@PAMAM hybrids, and they were characterized by UV-Vis, Fluorescence Spectroscopy, FT-IR, NMR, DLS, and TEM. Photostability studies under different conditions of pH and ionic strength were also performed, as well as biological studies (cytotoxicity and transfection). All these results will be presented and discussed.

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IDS11 PC: POSTER COMMUNICATIONS

[PC1]

Oxidation-Sensitive Core-Multishell Nanocarrier Systems

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Drug delivery into and across the skin has wide applications ranging from conventional dermatological therapy of inflammatory skin diseases, such as atopic dermatitis or psoriasis, and skin tumour therapy, such as topical chemotherapy and photodynamic therapy, to transcutaneous drug delivery and vaccination. While systemic therapy experienced a surge of innovations and new active molecules in the past decade, only few innovative molecules made it into new topical formulations due to poor skin uptake.

Dermal drug delivery can host problems due to various reasons such as a drug's lipophilicity or size affecting its permeability through the skin barrier. Skin is characterised by different redox environments changing over the different skin layers. Those redox environments also vary in healthy and inflamed skin, thus offering the usage of redox dependent drug delivery.

Polymeric drug delivery systems aim at overcoming the solubility issue by entrapping the drug in a solubility-enhancing polymeric environment. Among the vast diversity of polymeric drug delivery systems, dendritic nanocarriers are considered as universal systems, as their defined core-shell architecture offers many benefits.

The skin harbours mainly glutathione (GSH) / glutathione disulphide (GSSG) buffers maintaining the redox systems. Oxidative environments host among increased GSSG levels also reactive oxygen species (ROS). Carrier systems can utilise those redox environments by incorporating oxidation sensitive components. Hydrophobicity changes of thioether moieties upon oxidation can thereby lead to a controlled drug release in the skin [1].

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[PC2]

Design and Synthesis of Succinylated PAMAM-Isoniazid Sendrimer Prodrug

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Tuberculosis registered, in 2017, 10 million new cases, resulting in 1.4 million of deaths, putting the disease in the top ten death causes in worldwide and the most fatal infectious disease in the world [1]. Moreover, it has an extensive issue on treatment regimen, as its long extension leads to low adhesion [2]. Dendrimers, on the other hand, have shown a lot of biological application, especially as drug carriers. The dendrimer prodrug, planned by prodrug design, can be useful to improve the pharmacokinetics/pharmaceutical properties of a prototype [3,4,5]. Considering that, prodrug dendrimer composed of first generation ethylenediamine core polyamidoamine (PAMAM) dendrimers, using succinic acid (spacing group) and isoniazid (drug) was synthesized to obtain potentially tuberculostatic dendrimer prodrugs. For the compound purification, four eluent systems were tested, being the most effective using silica gel with the solvents AcOEt/MeOH (70:30, v/v). The product was obtained as white solid: 1H NMR (300 MHz, Methanol-d4) δ 8.61 (d, J = 5.3 Hz, 1H), 7.71 (d, J = 4.6 Hz, 1H), 6.96 (d, J = 6.1 Hz, 0H), 3.59 (d, J = 2.9 Hz, 1H), 3.38 – 3.13 (m, 4H), 2.79 (s, 0H), 2.58 (td, J = 9.3, 8.2, 4.3 Hz, 2H). 13C NMR (75 MHz, Methanol-d4) δ 173.25, 172.12, 149.65, 128.97, 128.17, 126.86, 121.71, 50.89, 28.18, 26.17, 21.29. It is expected that this novel compound can provide a scaffold for an extended controlled release of isoniazid, improving its pharmacokinetics profile, addressing a well-known problem of tuberculosis treatment adhesion. The compound will be further characterized using HPLC, LC-MS and its efficacy will be tested on biological assays against *Mycobacterium tuberculosis*.

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[PC3]

Green Dendritic Polymer: Synthesis of Star-Shaped 4arms-PLLA$_n$-*b*-DL$_m$ Dendritic Peptides with "Core-Shell" Structure

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Developing green and degradable dendrimers or dendritic polymers have attracted great attentions in recent decades[1]. In earlier study, we prepared series of poly(*l*-lactide) (PLLA)-based dendritic polymers[2] towards biomaterial applications[3]. To expand the molecular topology diversity for achieving high performance, we herein prepared a series of star-shaped 4arms-PLLA$_n$-DPL$_m$ dendritic peptides with "Core-Shell" structures through combination of ring-opening polymerization of (*l-)*-lactide, twice-repeated coupling of Boc-protected-(*l-)*-Lysine and following with TFA-deprotection (Figure 1). The molecular structures have been fully identified by ^{1}H NMR and GPC analysis. The results demonstrated that the star-shaped 4arms-PLLA$_n$-DPL$_m$ could be successfully prepared with controllable molecular weight and comparatively low molecular polydispersity (PDI<1.3).

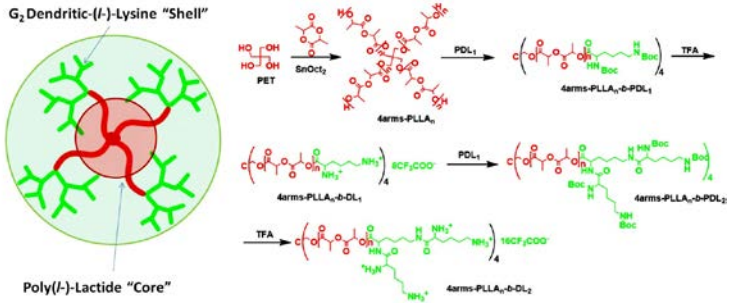

Figure 1. The molecular structure and synthesis routes of the star-shaped dendritic peptide.

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[PC4]

Cycloaddition of CO_2 Catalyzed by Phosphonium and Amonium Carbosilane dendrimers

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Conversion of carbon dioxide (CO_2) into valuable chemicals is used in a wide range of application areas ranging from fuel additives to bulk and commodity chemicals, and to special products with biological activity such as pharmaceuticals. Here we report series of bifunctional organocatalysts (phosphonium/ammonium catalytic centres, hydroxy groups), which are covalently attached to the exterior of carbosilane dendrimers. Prepared catalysts proved to be highly active in the cycloaddition of CO_2 and epoxides producing cyclic carbonates [1]. As we confirmed by Density Functional Theory (DFT) calculations, the hydrogen-bond donating hydroxy group in the side chain of the catalyst leads to a synergistic effect accelerating the catalytic reaction. Moreover, we investigated possibilities of an effective recycling of the catalysts from the reaction mixture. The first approach is a separation of the catalyst by nanofiltration. The second approach is based on an intercalation of the catalysts into the interlayer space of a natural montmorillonite through ion exchange reaction [2]. Resulting solid nanocomposites are easily separable from the reaction mixture with only a slight loss of the catalytic activity.

Acknowledgements: This work was supported from ERDF/ESF project "UniQSurf - Centre of biointerfaces and hybrid functional materials" (No. CZ.02.1.01/0.0/0.0/17_048/0007411).

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DNA/PAMAM Dendrimer Films: a Highly Stable Platform for DNA-Intercalating Anticancer Drugs

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The electrostatic interactions between DNA and polycations, such as PAMAM dendrimers, have been studied using both empirical and *in silico* approaches [1], especially gene therapy [2]. These interactions allow the formation of self-assembled dendriplexes, which have been used, for example, as models for the DNA-histone interactions in nucleosome [3]. Here, instead of nanoparticles, we report the preparation of novel DNA/PAMAM dendrimer films for the sustained release of anticancer drugs. The prepared films revealed very interesting SEM and AFM imaging results. Also, the obtained films are water-insoluble, highly stable in physiological conditions and in pH ≤ 9, and show positive surface charge and supramolecular chirality. Taking advantage of DNA's presence in the film, doxorubicin (DOX), a DNA-intercalating drug [4] was efficiently loaded therein, presenting a controlled and sustained release over time, in physiological conditions, including in serum-containing medium. Loading with cisplatin (cisPt), a drug that covalently binds DNA, resulted in an efficient loading but in a nearly inexistent release. On the other hand, 5-fluorouracil, a DNA synthesis antimetabolite, did not even get loaded into the films. Accordingly, the DOX-loaded DNA films were as cytotoxic as DOX/cisPt loaded ones using ovarian cancer cells (A2780). Concluding, these new DNA/PAMAM films can be selectively used according to the characteristics of the drug and are promising for topical/*in situ* applications. *In vivo* studies using these delivery systems are envisaged to confirm their potential in cancer treatment.

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[PC6]

Ruthenium (II) Carbosilane Metallodendrons as Promising Anticancer Agents

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The discovery by B. Rosenberg of *cisplatin* as an anticancer agent was a starting point in the use of inorganic agents for the treatment of cancer [1]. However, its main disadvantage lies in the large number of side effects that presents. In the search of new more selective drugs, ruthenium (II) complexes turned out to be among the most promising ones [2]. Moreover, the inclusion of this metal ion in nanosystems such as dendrons increases the selectivity towards tumor cells, through EPR effect [3]. With the aim of developing new heterofunctional nanocarriers of Ru(II), we have carry out the synthesis and structural characterization of schiff-base containing carbosilane dendrons, as ruthenium(II) chelating moiety in the focal point. We have synthesized different complexes of ruthenium with different ligands in order to evaluate the effect of the nature of the ligand in the anticancer activity. As proof-of-concept, the metallodendrons were studied as agents against resistant prostate cancer, currently only treated with palliative drugs. Results obtained *in vivo* with the most promising candidate of the different families of ruthenium metallodendrons, has shown an inhibition of 40% in comparison with untreated mice.

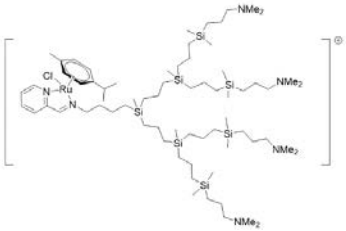

Figure 1. Proposed structure of ruthenium (II) metallodendron with cymene units as a ligand.

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Copper(II)-conjugated Metallodendrimers: EPR Study

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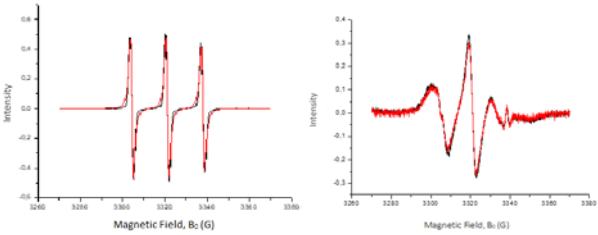
EPR (Electron Paramagnetic Resonance) is a useful technique, which provides structural and dynamical information of systems containing paramagnetic species. In this work we investigated the structural and dynamical properties of copper(II)-conjugated metallodendrimers, aimed to treat various kinds of neoplasms. Copper-carrying dendrimers have already shown the ability to slow down, the tumoral growth [1]. The study was conducted in absence and presence of cetyl-trimethylamonium bromide (CTAB) micelles and egg lecithin liposomes, as cell membrane models. The computer-aided analysis of the EPR spectra allowed us to characterize the interactions occurring between the dendrimers and the membranes [2]. A different interacting behaviour depending on the generation, metal counterion and equilibration time will be shown and discussed, as well as possible future changes in the dendrimer structure or in the metal choice. Fast and slow component simulations, for a dendrimer-liposome sample, selected as example.



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[PC8]

UCST-Type Thermosensitive Dendrimers

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Temperature-responsive polymers are one of smart materials. Temperature-responsive polymers are classified into LCST (lower critical solution temperature)-type which becomes turbid by heating and UCST (upper critical solution temperature)-type which dissolves by heating. Our previous studies have shown that PAMAM dendrimers modified with a hydrophobic amino acid, phenylalanine (Phe), at the amino termini showed LCST-type temperature sensitivity at high pH [1]. In this study, dendrimers showing temperature sensitivity at acidic pH were designed (Figure 1). Carboxyl-terminal Phe-modified dendrimers were synthesized, and the sensitivity of this kind of dendrimer to pH and temperature was evaluated.

The amino-terminal PAMAM dendrimer was reacted with various acid anhydrides such as succinic anhydride (Suc), cyclohexane-dicarboxylic anhydride (CHex), phthalic anhydride (Ph). Then, Phe was reacted at the carboxyl termini. Temperature sensitivity was dependent on both pH and anhydride linker. These dendrimers' solutions were clear at high pH, but turbid at low pH. At the intermediate pH, UCST-type temperature sensitivity was observed (Figure 2). This is the first report of UCST-type temperature-sensitive dendrimers [2].

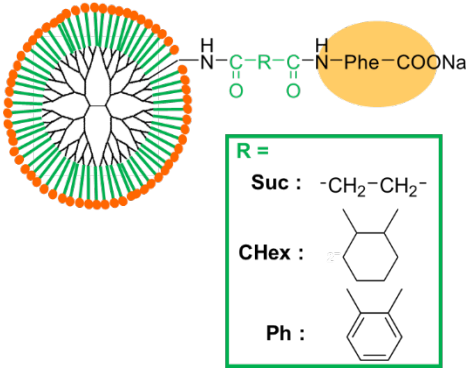

Figure 1. Design of carboxyl-terminal Phe-modified dendrimers.

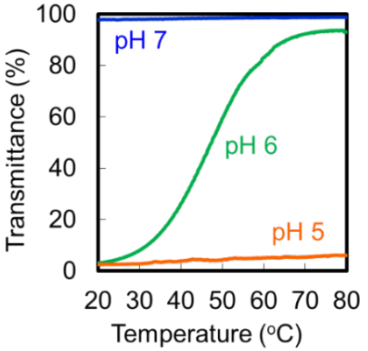

Figure 2. The pH and thermo-sensitivity of G4-Ph-Phe dendrimer.

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Ruthenium-based Metallodendrimers: Synthesis, Cytotoxicity and Hematotoxicity Studies

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Nowadays, the discovery of new treatments to fight against cancer is still the main concern among scientists. Metal compounds, like ruthenium complexes, have proven their potential against several types of tumors presenting less toxicity then platinum drugs [1,2].

Here, based on our previous work [3], we present a family of low generation poly(alkylidenamine)-based dendrimers (generation 0, 1 and 2) and its biological studies. Briefly, we designed and characterized a new family of dendrimers functionalized with the ruthenium moiety $[Ru(\eta^5\text{-}C_5H_5)(PPh_3)_2]^+$. The metallocompounds were characterized by ^{1}H- and ^{31}P-NMR, mass spectrometry (MS) and FTIR techniques. Their stability was also studied by ^{1}H- and ^{31}P-NMR at 25 and 37ºC. The *in vitro* anticancer activity was evaluated against three cancer cell lines and a non-cancerogenic model. Their hematotoxicity was tested using human blood. These metallodendrimers present good anticancer activity at a nanoscale concentration range. For instance, the cytotoxicity of the G2Ru metallodendrimer is 5-fold (A2780), 61-fold (A2780cisR) and 27-fold (CAL-72) higher than that of the well-known metallodrug *cis*platin.

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[PC10]

Study of the Biological Activity of Dendrimers Functionalized with Imidazolium Salts

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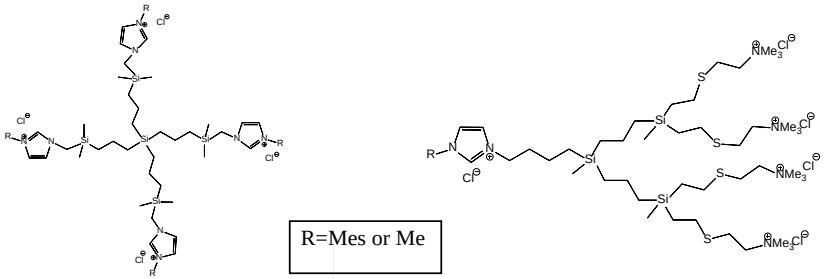
A new family of dendrimers and dendrons functionalized with imidazolium salts have been synthesized, and their biological activity was evaluated. Imidazolium salts show interesting biological properties, above all antimicrobial and antitumor activities [1]. We have selected two types of imidazolium salts, methylimidazolium and mesylimidazolium, with the purpose of demonstrating the structural variation effect, in which amphiphilicity and solubility could be modified in the dendrimers. All of them were tested against Gram-positive (*s. aureus*) and Gram-negative (*e. coli*) bacteria. Furthermore, in order to select the best compound they were evaluated in erythrocytes, as healthy human cell line. Regarding antitumoral activity, this new family of compounds were also tested against PC3 (advanced prostate cancer cell line) and HCC1806 (triple negative breast cancer cell line).

Results suggested a remarkable widespread biological activity acting as promising agents to be used as potential therapeutic systems.



Acknowledgements: This work was supported by grants CTQ2017-86224-P (from MINECO), Consortium NANODENDMED-II-CM (B2017/BMD-3703) and CIBER-BBN.

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Microbiological Activity of Dendrimers Modified with 1,8-Naphtalimides

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Recently the very attractive macromolecules of dendrimers have been studied extensively in different scientific aspects - biological, biomedical, environment protection, photovoltaic and light-emitting devices etc. Their modification with bioactive monomer units yields bioactive dendrimers. That has given rise to a novel field in dendrimer studies focused on metallodendrimers with unique biological and biomedical activities. Incorporation of metal ions into the dendrimer structures opens interesting prospects for dendrimer chemistry and enhances their biological activity. Therefore, currently the application of such compounds in medical chemistry as a new class of metal – containing biomolecules has expanded significantly. The high concentration of surface functional groups in their molecules has provoked thorough investigations, especially on their prospective applications as antibacterial and antifungal agents.

Amongst them derivatives of 1,8-naphthalimide are an interesting class of heterocyclic systems with promising biomedical and pharmacological activity. Many of those derivatives exhibit high antibacterial, antifungal, antiviral anti-inflammatory or anticancer activity or sensor properties. Aiming at enhancing those activities scientists resort to incorporation of a larger number of biologically active 1,8-naphthalimide units into one dendrimer molecule.

This communication reports on the bioactivity of such compounds based on the combination of the effects of dendrimer matrix, 1,8-naphthalimide units and metal complex produced upon a single molecular structure. The microbiological properties of poly(propyleneimine) and polyamidoamine dendrimers modified with 1,8-naphthalimide and their Zn(II) or Cu (II) complexes has been evaluated. The antimicrobial activity of the dendrimers deposited onto the surface of a 100% cotton fabric has also been discussed with regard to potential applications of the modified textiles as antibacterial materials.

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[PC12]

Tuning Spin-Spin Interactions in Radical Dendrimers

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The term "radical dendrimers" has been used in the case of highly functionalized dendrimers with organic radicals [1]. Since radical dendrimers' properties may depend upon the nature and location of pendant radical groups, knowledge of their dynamics and spin-spin interactions is essential. Electron paramagnetic resonance (EPR) is the tool of choice to carry out such studies. The flexibility of the scaffold and the length of the linker between the radical and the dendrimer are expected to determine the extension of the spin exchange coupling between radicals. To discover in what magnitude the spin exchange coupling could be tuned by changing the properties of the linker, two generations (G0, G1) of polyphosphorhydrazone (PPH) dendrimers were synthesized and fully functionalized with pendant TEMPO radicals via acrylamido (Gn-acrylamido-TEMPO) or imino (Gn-imino-TEMPO) group linkers. The EPR and Cyclic Voltammetry studies showed that there existed much higher interactions among pendant group radicals, when bounded to the dendrimer by imino group linkers (Figure 1). Thus, we have been able to drastically change the way that the pendant radicals interacted, by the solely substitution of the dendritic radical linker [2].

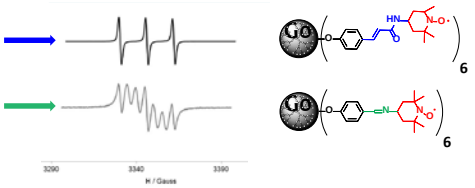

Figure 1. EPR spectra of G_0-acrylamido-TEMPO (up, without interactions) and G_0-imino-TEMPO (down, showing spin-spin interactions).

Acknowledgments: This work was supported by the Intramural CSIC project (201760E080).

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[PC13]

Novel Polyamidoamine Dendrimers for Skin Delivery

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Peptide dendrimers and polyamidoamine (PAMAM) dendrimers have been used to date as effective transdermal or topical drug delivery systems, with the latest in a much greater extent [1]. The structural characteristics of the aforementioned molecules guided us to develop lower generations (up to third, Figure 1) of novel dendritic structures containing amide groups and amino-branching points in their interior. The structure of bis(2-aminoethyl)glycine selected as repeating monomer and expanded from an ethylenodiamine core by the convergent method.

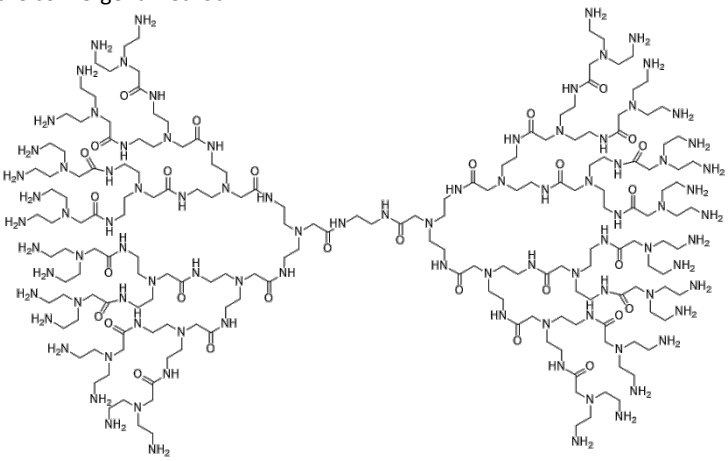

Figure 1*:* The third generation of new dendrimers.

The new poly(amido amine) dendrimers were fully characterized and evaluated for their effect as (trans)dermal drug delivery systems.

Acknowledgements: The study was supported by the Czech Science Foundation (19-09600S) and the Charles University (GAUK 184217 and SVV 260401).

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[PC14]

Donor–Acceptor PIMAM Dendrimer Photodiodes

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New types of hybrid photodiodes (HPD) have been developed in the past few years, especially due their potential in the field of image sensing and biomedicine [1]. The chase for low cost, low temperature response, long lifetime, high response and sensitivity to light, high gain photodiode and low noise lead to development of new organic, inorganic or hybrid semiconductors [2]. The unique properties of the dendrimers scaffold allowed the construction of donor-acceptor semiconductors having both electron donor and electron acceptor units connected with π-bridges [3]. In this work, based on pevious work [4] promising low cost, low current, stable photodiode devices were produced under room temperature, using one single layer of a biocompatible matrix (agarose) incorporating poly(imidazolone amine) (PIMAM) dendrimers (Figure 1) and ruthenium dyes using a stainless steel electrode. These devices achieved nA dark currents along with good detectivities.

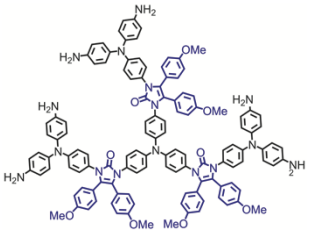

Figure 1. Chemical strusture of a donor-acceptor PIMAM dendrimer.

Acknowledgements. We thank Fundação para a Ciência e a Tecnologia (FC&T, Lisbon) for financial support through projects EXPL/CTM-ENE/1502/2013, UID/EEA/50008/2013 and PhD grant SFRH/BD/109006/2015 (R.F.P). Project Suprasol (LISBOA-01-0145-FEDER-028365, PTDC/QUI-QOR/28365/2017), funded by Fundo Europeu de Desenvolvimento Regional (FEDER), through Programa Operacional Regional LISBOA (LISBOA2020) and national funds (FC&T).

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[PC15]

Antibacterial Properties of Cotton Fabrics Modified with Fluorescent Dendrimers and Metallodendrimers

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[2]Medical Faculty, Sofia University "St. Kliment Ohridski", Sofia, Bulgaria.
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The antibacterial properties of cotton fabrics modified with fluorescent dendrimers, their copper complex and with dendrimers encapsulating copper nanoparticles have been compared. Upon illumination with visible light all the textile samples have enhanced antibacterial activity. The complete inhibition of gram-positive *Bacillus cereus* bacterial growth has been produced by textile modified with fluorescent dendrimers encapsulating nanoparticles. It can be assumed that the largest synergistic impact is attained via the simultaneous effects of fluorophores, nanoparticles and light.

In this study 1,8-naphtalimide fluorophores have been used for modification of first generation PAMAM dendrimers. It has been proven by means of EPR analysis that, eight copper ions coordinate with one fluorescent dendrimer ligand. A new methodology for modifying the textile material with dendrimers containing nanoparticles has been developed. For this purpose, a photochemical reaction with visible light has been run under ambient conditions using a combination of eosin Y and *N*-methyldiethanolamine and has been successfully applied to reduce copper ions in the dendrimer complex. The process of copper ions reduction to nanoparticles has been monitored by colorimetric, fluorescence and EPR analysis.

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[PC16]

4-Carboxyphenylboronic Acid Modified Poly(amidoamine) Dendrimers Used as Carbohydrates Selector

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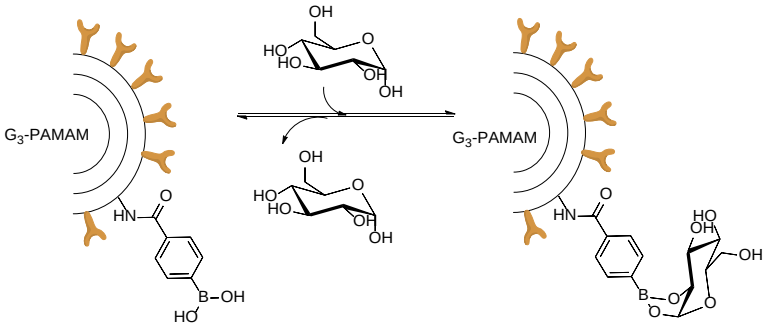
Boronic acid possess unique affinity to *cis*-diol moieties which are widely presented in biomolecules such as saccharides, glycan, nucleosides. Therefore, boronic acid was considered as an excellent model for monitoring their presence. We have prepared second to sixth generation of 4-carboxyphenylboronic acid modified poly(amidoamine) dendrimers (PAMAM-CPBA) which exhibits strong and selective affinity to glucose than other carbohydrates. Among them, the third generation PAMAM-CPBA exhibited the strongest binding affinity to glucose. Herein, G3-PAMAM-CPBA was subjected to the binding experiment in the mixture of carbohydrates under various environment. The result clearly showed selective binding to glucose. The compound is potential used as glucose buffer to maintain the concentration of glucose in solution with littler interference to other carbohydrates.



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[PC17]

Synthesis and Characterization of Stable Cu-DENPs Using Ascorbic Acid as a Reducing Agent

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Copper nanoparticles (CuNPs) are particularly appealing materials for the replacement of less earth-abundant metals like silver and gold. Cu also displays good electronic, antimicrobial, optical, and chemical properties despite its limitations under atmospheric conditions (i.e. the use of CuNPs are limited due to their intrinsic instability making them prone to oxidation). Various efforts have been made to increase the stability of CuNPs, including the association of the CuNPs with organic structures such as polymers [1].

This project was focused on the preparation and characterization of long-term stable Cu-based dendrimer entrapped NPs (Cu-DENPs). The particles were synthesized at a temperature of 60°C using the environmentally friendly ascorbic acid as a reducing agent and antioxidant, while the fourth generation hydroxyl-terminated polyamidoamine (G4·OH PAMAM) dendrimer was used as a template for the controlled growth of the NPs.

The long term stability of the NPs was confirmed by Ultraviolet-Visible (UV-Vis) Spectroscopy and Nuclear Magnetic Resonance (NMR) Spectroscopy. The NPs were also characterized using other techniques such as Photoluminescence (PL) Spectroscopy. Preliminary cytotoxic evaluation studies towards HEK 293T cells using the MTT assay showed that the obtained particles did not present significant toxicity with concentrations up to 500 µg/mL (cell viability >80%).

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[PC18]

A New Strategy for Amphiphilic Peptide Dendrimer on Solid Phase

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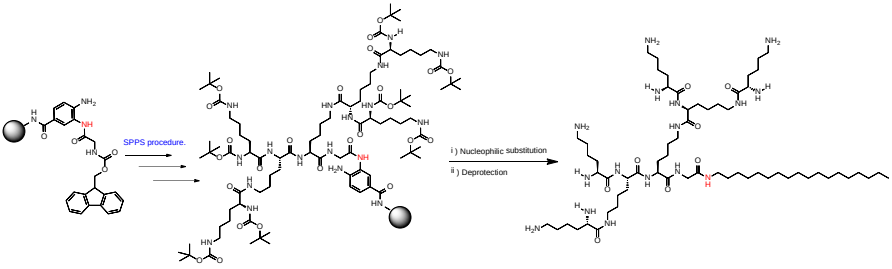
Amphiphilic dendrimers were reported to form a stable vesicle and dendrimersomes which generated excellent affinity to cell membrane and nucleic acid. Because of these characteristic advantages and easy to prepare in compare to the same size of dendrimers, such approach was proposed to be new vehicles for gene and drugs/contrast agents. However, the amphiphilic character can cause the difficulty in the preparation, characterization and purification of macromolecules, which damage the further applications and investigation. Therefore, a new convenient synthesis is needed. Herein, a diaminobenzoic acid linker was applied in the solid-phase dendron synthesis which synthesized lysine branches with various surface groups as hydrophilic region. After the synthesis, the activation of diaminobenzoic acid moiety to benzotriazole which served as a leaving group to introduce various length of hydrocarbon as hydrophobic part at cleavage step. The products could be collected without chromatographic purification. The result clearly exhibits the advantages of this method which is potential for the preparation of complicated amphiphilic compounds.



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RGD-dendritic Structures on Titanium Alloy. Influence in the Relationship Between Bone Cells and the Metal Surface

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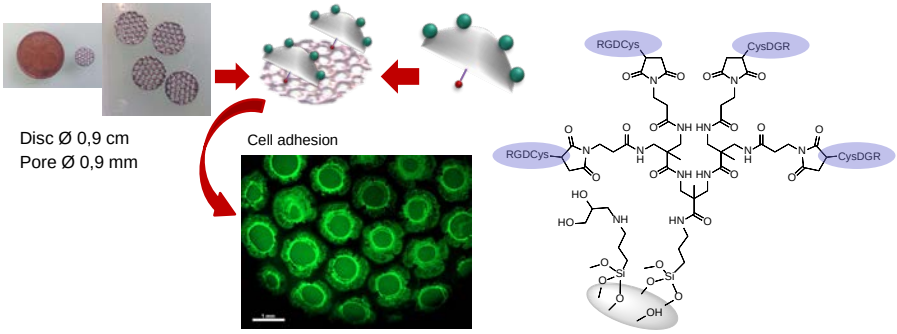
Prosthetic implants are used in surgical procedures to replace a joint (hip or knee) allowing the functional recovery of the patient. Prostheses are usually made of titanium alloys. However, the lack of chemical and structural bond between the metal and the surrounding bone tissue causes a fail in the long term due to poor osseointegration. Titanium surface with RGD domains would positively influence the relationship between bone cells and the metal surface of the prostheses, thus promoting a better osseointegration [1]. Arginine-glycine-aspartic acid tripeptides (RGD) were conjugated to dendritic structures and used to pre-treat titanium disk. We demonstrate that dendrimer-presented tripeptides efficiently improves cell-material interaction.



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[PC20]

Hyaluronic Acid-Modified Dendrimer Entrapped Gold Nanoparticles

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Being the most widely studied dendrimers, poly(amidoamine) (PAMAM) dendrimers are a class of highly branched, monodisperse molecules with a well-defined structure and composition. As such, they are considered perfect templates for the synthesis of inorganic nanoparticles [1]. Nevertheless, due to their abundance of positively charged surface groups, modification of these dendrimers with targeting molecules, imaging agents or drugs is essential.

Aiming at the development of a new vehicle for the targeted X-ray computed tomography (CT) imaging of CD44 overexpressing cancer cells, hyaluronic acid (HA), a naturally occurring glycosaminoglycan often used as a drug carrier and targeting ligand for CD44 receptors [2], was conjugated to amine-terminated generation 5 PAMAM dendrimers ($G5.NH_2$). The previously prepared conjugate served as a template for the synthesis of dendrimer-entrapped gold nanoparticles (Au DENPs). Characterization results of the formed HA-modified Au DENPs were obtained by ^{1}H, ^{13}C and HSQC NMR spectroscopy, FTIR spectroscopy, dynamic light scattering, zeta potential measurements, UV-Vis spectroscopy and SDS-PAGE. Preliminary cytotoxicity studies of the obtained compounds will also be presented.

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^{99m}Tc-Labelled Polyurea (PURE) Dendrimers for Ovarian Cancer Theranostics

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Ovarian cancer is a silent and highly lethal disease, accounting for about 4% of all malignancies diagnosed in women [1]. Actually, only 15% of cases are diagnosed at early stages. It is clinically proven that an early detection increases the 5-year survival rate by about 90%, and new detection methods are urgently needed. Molecular radiotherapy is an anticancer technique based on the use of radiopharmaceuticals, able to emit ionizing radiation (β and α particles or Auger-electrons). Interestingly, the use of radiopharmaceuticals might allow a theranostic approach of cancer, as some radionuclides have physical properties suitable for nuclear medical imaging and also for internal radiotherapy. For example, ^{99m}Tc is the most used radionuclide for SPECT imaging in diagnostic nuclear medicine, but it is also considered to have some potential in Auger therapy [2]. In the present work, polyurea (PURE) dendrimers [3] were functionalized with folic acid (PURE$_{G4}$-FA), thus allowing a molecular recognition strategy to target the folate receptor (FR-α), highly expressed in ovarian cancer. The PURE$_{G4}$-FA dendrimers were directly labelled with technetium-99m (^{99m}Tc-PURE$_{G4}$-FA) without the need of further functionalization of the dendrimers with an extra ^{99m}Tc-ligand (Figure 1). The stability of ^{99m}Tc-PURE$_{G4}$-FA was investigated in different cellular culture media, and cellular uptake studies were performed using ovarian cancer cell lines.

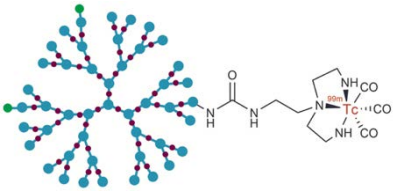

Figure 1. Structural representation of ^{99m}Tc-PURE$_{G4}$-FA.

Acknowledgements: We thank Fundação para a Ciência e a Tecnologia (FC&T, Lisbon) for financial support through projects PTDC/MEC-ONC/29327/2017 and UID/Multi/04349/2019.

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[PC22]

One-pot Accelerated Synthesis to bis-MPA Dendrimers

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The frequently tedious synthetic routes towards dendritic macromolecules are hindering their transfer to real applications. Click Chemistry, multicomponent reactions and one-pot approaches are among the most successful strategies, but still find some limitations. Inspired by the "AB_2-CD_2 approach" [1], we accurately designed orthogonally complementary monomers using bis-MPA and reacted them using a chemoselective toolbox which comprises fluoride-promoted esterification (FPE) with imidazolide-activated compounds, copper-catalyzed azide-alkyne cycloaddition (CuAAC), *N*-hydroxysuccinimide mediated amidation and UV-initiated thiol-ene coupling (TEC) reactions. The heterolayered dendrimers expanded the properties and greatly simplified the synthetic protocol of traditional dendrimers [2].

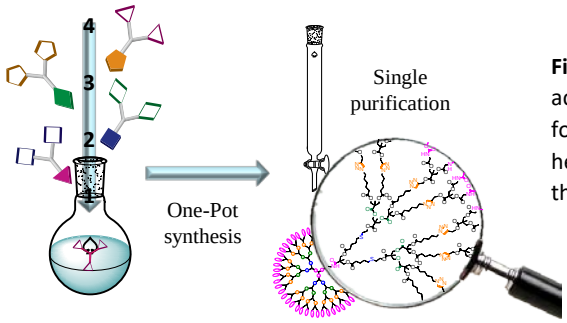

Figure 1. The one-pot accelerated approach delivered a fourth generation bis-MPA heterolayered dendrimer in less than 2.5 h and 67% yield.

Acknowledgements: This work was supported by the Swedish Research Council VR (2011-5358, 2010-435 and 2015-04779); the Knut and Alice Wallenberg Foundation KAW (2012-0196); and the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie Grant Agreement No. 655649.

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[PC23]

Synthesis of Niclosamide Dendron of Intracellular Release

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Nanotechnology is a promising field in the pharmaceutical field and widely used in the design of nanosystems for drug delivery associated with prodrug design strategies [1]. This universe encompasses the stimuli-responsive and self-imolative, intelligent transporters capable of triggering the release of bioactive agents from the carrier [2,3]. Neglected diseases (ND) have great need and urgency of new drugs in the therapy, and then a novel intracellular release system for glutathione reductase/trypanothione reductase (GSH/TR) was designed to deliver niclosamide, a candidate for repositioning for the treatment of Chagas disease and leishmaniasis. An intelligent nanocarrier consisting of a disulphide cross-linker coupled to the drug and dendron by carbamate linkages was planned for their stability to the metabolism. Therefore, the release of the bioactive drug or compound is intended to occur by GSH/TR action on the disulphide spacer, promoting the cascade self-release of the bioactive compound. Figure 1 shows the proposed structure for the dendron.

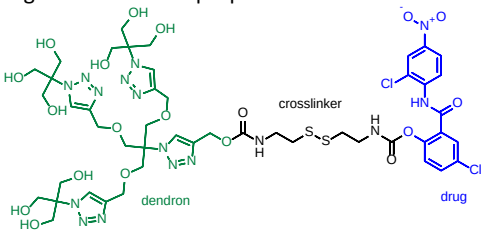

Figure 1 – Structure proposed for niclosamide dendron designed.

The dendron was synthesized from derivatives of trometamol, an *O*-propargyl compound (37% yield) and an azide (90% yield), through cyclization by click chemistry reaction. Niclosamide and propargyl alcohol were functionalized with *p*-nitrophenyl chloroformate to form the respective carbon esters (28% and 35% yield, respectively). The carbon esters will be coupled to cysteamine, by carbamate bonds, and the linkage of the drug will be performed. All intermediates obtained were analysed by ^{1}H and ^{13}C NMR, and infrared.

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[PC24]

Phosphorus Dendrimers as Rose Bengal Carriers in Photodynamic Therapy

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Photodynamic therapy (PDT) is based on application of photosensitizers that after irradiation by light with a specified wavelength produce reactive oxygen species and singlet oxygen [1], which start the cascade of reactions leading to cell death [2]. Unfortunately, most photosensitizers are not without drawbacks, therefore they are subjected to various modifications such as conjugation to dendrimers in order to enhance their delivery to tumor. Dendrimers, due to their shape and nanometric size, may easily penetrate into the tumor and retain in tumor interstitium. This process is described as an enhanced permeability and retention effect [3]. Moreover, their structure allows for the attachment of drugs to functional surface groups and encapsulation of the active compounds inside the dendritic scaffold [4]. Our research focused on the determination of the ability of phosphorous dendrimers to act as rose bengal (RB) carries. Cells (ASZ, BSZ, CSZ, provided by Dr. Ervin Epstein, Children's Hospital Oakland Research) were used in *in vivo* and *in vitro* studies. In *in vitro* studies we examined an ability of the dendrimer-RB conjugate to generate singlet oxygen, as well as its phototoxicity. At the same time tumorigenic potential of murine basal cell lines (ASZ, BSZ, and CSZ) was tested after subcutaneous transplantation of 1, 5 or 10 × 10^6 cells/mouse. Preliminary results show that the dendrimer conjugated with 6 molecules of RB (D0-6RB) causes a two-fold increase of singlet oxygen generation, which translates into an enhancement of its phototoxicity from 20% for free RB to 60% for the conjugate D0-6RB at 1 µM drug concentration. Moreover, the dark toxicity is not observed for this system. The *in vivo* results show that all tested cancer cell lines possess tumorigenic potential. The tumor growth kinetics of ASZ cells is the most advantageous and necrosis of these tumors does not appear, thus this cell line has been chosen for further studies. In the next step, the selected conjugate with the highest therapeutic potential will be tested *in vivo*.

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[PC25]

Topology-Driven Effects of Carbosilane Dendrimers and Dendrons on Immune Cells

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Dendritic molecules – dendrimers and dendrons – gain much attention in nanomedicine as prospective therapeutic agents and drug carriers. In particular, their activity towards immune cells has been shown. Here we explore the influence of the molecular topology of dendritic molecules on their effect on peripheral blood mononuclear cells (PBMCs) obtained from healthy donors and chronic myelogenous leukemia cells (K562 cell line). Dendritic molecules under study were: fully symmetric cationic carbosilane dendrimers G1-3 having 1,3,5-trihydroxybenzene as a core; cationic carbosilane dendrons G1-3 having hexanoate or palmitate moieties in the focal point. The dendrimers behave in water medium as individual molecules; the amphiphilic dendrons self-organize into micelles.

Both PBMCs and K562 cells show dose-response toxicity profiles upon incubation with dendritic molecules, as shown by WST assay. However, the dendrimers have been found to stimulate PBMCs proliferation when taken in small doses (ca. 1 μM; IC_{50} >30 μM). These findings can be explained by the differences in the response of PBMCs subpopulations on the presence of dendrimers. In contrast, dendrons generally do not stimulate cell proliferation (IC_{50} 5-10 μM). These differences can result from the features of the supramolecular behaviour of dendrimers and dendrons. Currently, further studies are being conducted to elucidate the effect of dendritic molecules on PBMCs subpopulations. Unlike PBMCs, K562 cells do not proliferate more actively when incubated with dendrimers or dendrons (IC_{50} ~5 μM).

These results contribute to better understanding of the topology-activity relationships of nanomedicines.

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[PC26]

In silico Characterization of PURE Dendrimers-Small Molecules Interactions

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Dendrimers are versatile molecular carriers with a high potential for biomedical applications. There has also been increasing interest in understanding interactions of dendrimers with small molecules (SM) to aid the design of novel drug carriers (DCs). In particular *in silico* methodologies are used to explore the properties that govern formation of dendrimers-SM complexes. In fact, the use of molecular dynamic (MD) simulations has provided valuable insights into the structural properties that characterize the distribution of SM within the dendrimer and how these correlates with *in vitro* data [1,2].

Herein we describe the use of MD simulation to study the binding of SM to polyurea (PURE) dendrimers [3] of different sizes and protonation states in an effort to rationalize our *in vitro* results as well as evaluate their potential as DCs. To this aim, we generated initial 3D models of PURE dendrimers with different generations (G4 to G6) and different protonation states using our previously described method [4]. The obtained PURE dendrimers models were then equilibrated in a water box and further simulated in fully solvated systems in the presence of different SM to characterize their interactions. The observed interactions in PURE-SM complexes corroborated the effects observed *in vitro* and confirm the potential of PURE to encapsulate drugs that can be further optimized for drug delivery.

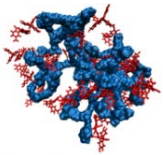

Figure 1. $PURE_{G4}$ (blue) complexes with multiple molecules of 4-carboxyfluorescein (red).

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[PC27]

Carbosilane Glucose Glycodendrimers: Synthesis and Toxicological Analyses

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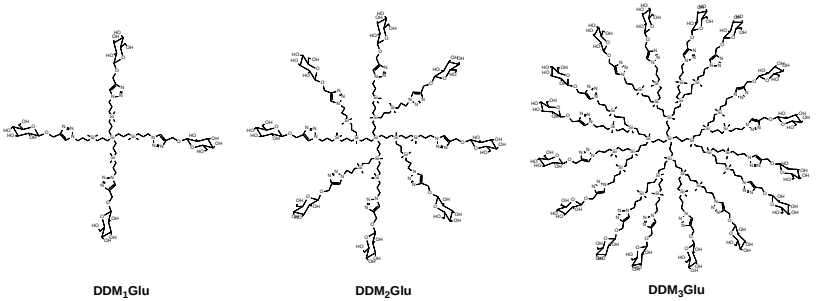
Dendrimers (DDMs) as a class of symmetric nanoparticles are studied for their promising applications in biomedicine [1,2]. Cationic DDMs, mostly investigated in gene delivery due to their ability to form complexes with negatively charged nucleic acids, also exhibit relatively high toxicity [3]. Glycodendrimers (glyco-DDMs) with carbohydrate peripheral moieties proved to be a suitable alternative to positively charged DDMs [2]. Still, the toxicity issues are widely discussed. Here we present the synthesis, analytical characterization and, to our best knowledge, also the first *in vivo* toxicological data (modified FET, Zebrafish embryos) for novel 1-3rd generation glucose glyco-DDMs (DDM_1Glu, DDM_2Glu, DDM_3Glu) and their comparison with the traditional *in vitro* cytotoxicity assays (MTT, 3 types of rodent cell lines). Overall, the modified FET revealed two to three orders of magnitude difference between *in vivo* and *in vitro* toxicity of the tested glyco-DDMs [4].

While, in general, the glyco-DDMs are of great promise as efficient vectors in drug/gene delivery, their developmental toxicity should be further investigated.



DDM_1Glu DDM_2Glu DDM_3Glu

Acknowledgments: This work was supported from ERDF/ESF project "UniQSurf - Centre of biointerfaces and hybrid functional materials" (No. CZ.02.1.01/0.0/0.0/17_048/0007411).

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[PC28]

Nanoparticles Act as Adjuvant with Latency Reversal Agents for HIV Treatment and Inhibit HSV-1 in an *In Vitro* Neuronal Model

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The major obstacle that impedes HIV eradication in ART-treated HIV-1 individuals is the establishment of long-lived latently infected resting CD4+ T cells. Due to the fact that no drug has been effective, the search for new drugs and combinations are a priority in the HIV cure. We studied the role of G1-S4, G2-S16 and G3-S16 polyanionic carbosilane dendrimers in the context of latent HIV persistence. As we did not know how our dendrimers work in combination with latency reversal agents (LRAs) we studied their potential effect in their presence. Our data indicate that the combination treatment of our dendrimers with the PKC agonist does not modify the antilatency activity in J89GFP lymphocyte cell line. Interestingly enough, G3-S16 dendrimer alone and its combination with BRY, RMD or PNB showed a significant increased expression of EGFP in THP89GFP monocyte cell line. We showed for the first time that nanoparticles, in this case, G3-S16 dendrimer played an important role in new treatments against HIV infection. On the other hand, in recent years, infections caused by HSV-1, and their typical outbreaks invading the nervous system have widely been related to Alzheimer´s disease (AD). The HSV-1 infection increases the β-secretase activity, deregulating the balance between the amyloidogenic and non-amyloidogenic pathways, and subsequently, raises the β-Amiloid peptides accumulation, one of the main hallmarkers in the pathology of AD. In that sense, to achieve an effective treatment against both HSV-1 infections in neuronal system and AD, has been a principal goal. The latest studies show that nanotechnology is one of the best approaches and treatments of diverse pathologies against viral infections nowadays. Gold NPs have been studied in immunotherapy, cancer diseases and cellular disruptions with very promising results. Our work shows that a new gold nanoparticle family inhibits the HSV-1 infection in an *in vitro* neuronal model, as well as it recovers the normal levels related to hallmarks in AD. These data make gold NPs a promising treatment against neuronal HSV-1 infections and neuronal disorders related to the βA peptides, becoming potential candidates for further studies in the fight against neuronal disorders.

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[PC29]

Fractionation and Degradative Stability of 5th Generation PAMAM Dendrimer

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Commercial 5th generation PAMAM dendrimer – found to be polydisperse by size-exclusion chromatography – was fractionated by diafiltration using three membranes of different molecular weight cut-off values yielding four sample fractions. Three of them seem to contain dendrimers or dendrimer clusters according to their UV and RI signals, while the fraction under 10000 Da gave very weak signals with these detectors and is probably composed of smaller size degradation products. The samples were monitored on-line during chromatography for fluorescence which is a known property of PAMAM dendrimers [1]. All four fractions were fluorescent to some extent, indicating the presence of smaller and larger PAMAM derivatives in each fraction. Interestingly, specific fluorescence of the smallest molecular weight sample was even higher that of the fractions containing dendrimers. These findings show this dendrimer undergoes degradation upon storage, but it was shown otherwise certain storage conditions allow PAMAM to remain stable for very extended periods [2]. We therefore attempted to artificially degrade PAMAM by using acidic, basic, oxidative, reductive conditions at room temperature for 72 h and 70 °C for 20 h, as well as by exposing the sample to direct sunlight. Basic, oxidative, reductive conditions and direct sunlight all caused different degrees of degradation with the effect of oxidation being the most drastical: the chromatographic peak corresponding to PAMAM completely disappeared, but UV absorbance and fluorescence intensity of the degradation product markedly increased compared to the initial PAMAM sample. This indicates that fluorescence is probably due to certain oxidized derivatives, maybe even in the case of purified PAMAM. Acidic conditions on the other hand had only a very limited effect on stability even at 70 °C, PAMAM remained almost intact in this medium. These findings indicate PAMAM is best stored in acidic medium at low temperature in the dark, these conditions can greatly prolong the lifespan of this dendrimer.

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[PC30]

Synthesis and Characterization of Low Generation of Sulfonated and Carboxylated Poly(Alkylidenamine) Dendrimers

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Dendrimers are a class of hyper-branched polymeric macromolecules, which present a well-defined structure, monodispersity, controllable size and multivalence [1, 2]. Their nanoscale size, as well as, their good biocompatibility makes the study of dendrimers an interesting field of research for biomedical applications [3].

Based on our previous work in the field of dendrimer chemistry [4], we aim to synthesize sulfonate and carboxylate poly(alkylidenamine) dendrimers with 1,2-ethylenediamine and 1,6-hexanediamine cores, at generations 1 and 2 as antiviral agents. To accomplish this a Michael-type addition of acrylonitrile to the core was carried out, forming tetranitrile G0 dendrimers, which were then reduced to polyamine dendrimers. The sulfonate and carboxylate G1 dendrimers were then synthesized using Michael-type reactions. The same process was then repeated, parting from the G0 amine dendrimers, affording the pretended G2 polyanionic dendrimers. The prepared compounds were then characterized by NMR and FTIR, and Zeta potential techniques.

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[PC31]

Innovative Fully Biodegradable PEG-dendritic Block Copolymers: Biological Assessment as siRNA Delivery Vectors

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Cationic dendrimers are promising carriers for nucleic acids due to exceptional structural features: globular, highly branched, nanosize, low polydispersity, multivalency, and ability to complex and protect nucleic acids (NA), in compact nanostructures ("dendriplexes") [1]. These attractive characteristics show that dendrimers can be the long-awaited response to a need that limits many approaches in gene therapy [2].

However, the non-degradability under physiological conditions of the most frequently used dendrimers can lead to cytotoxicity due to accumulation of synthetic materials inside cells or tissues. Moreover, for gene therapy purposes, the degradation can contribute to the NA release, consequently leading to higher transfection efficiencies [3].

Therefore, we have recently reported a new family of fully biodegradable PEG-dendritic block copolymers [4]. Here, we present their biological evaluation as siRNA delivery systems. These dendritic structures were able to complex and protect siRNA in small dendriplexes (nanosizes between 42-60 nm), with polydispersity indexes and spherical morphologies very suitable for siRNA intracellular uptake, without causing cytotoxicity. Internalization and transfection efficiencies were assessed by flow cytometry in *U2OS/eGFPLuc* cells, obtaining excellent GFP silencing effects.

The developed fully biodegradable PEG-dendritic block copolymers showed promising capabilities that can make it great candidates as nanocarriers for different biomedical applications.

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[PC32]

Comparison of Cell Behavior on PVDF/MCNTS Electrospun Nanofibers with Random and Aligned Configuration

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Polyvinylidene Fluoride (PVDF)/Multiwalled Carbon Nanotubes (MCNTs) nanofibers were fabricated using a lab-designed conventional electrospinning setup. Later aligned and random nanofibers meshes of PVDF/MCNTs were arrayed on the parallel Au electrodes, which were seeded with NIH3T3 cells.

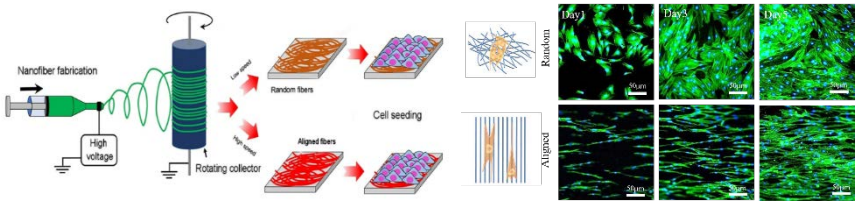

Figure 1 Schematic of PVDF/MCNTs scaffold fabrication and NIH3T3 cell culture Fluorescence merged image of NIH3T3 cells cultivated on random and aligned PVDF/MCNTs meshes for 1, 3 and 5 days.

A system has been designed to explore the behavior of fibroblast cells on aligned and random PVDF/MCNTs nanofibers, which arrayed on parallel electrode, as schematically illustrated in Fig. 1. The outstanding cell viability and proliferation based on PVDF/MCNTs nanofibers arrayed on Au electrode show a great potential for investigating the effect of inverse piezoelectricity on several cells.

Acknowledgements: This study was financially supported by Natural Science Foundation of China (81761148028 and 21773026), and Fundamental Research Funds for the Central Universities, Fundação para a Ciência e a Tecnologia (FCT) with Portuguese Government funds through the CQM Strategic Project PEst-OE/QUI/UI0674/2019, 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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[PC33]

Incorporation of Ultrasmall Iron Oxide Nanoparticle and Doxorubicin Within Polymer Nanogels for Tumor Theranostics

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We here synthesized polyetheylenimine (PEI)-based nanogels (NGs) which loaded both MR contrast agent ultrasmall iron oxide (Fe_3O_4) nanoparticles (NPs) and anticancer drug doxorubicin (DOX) for tumour theranostics. The synthesis of PEI-based nanogels was first carried out by inverse mini-emulsion (water-in-oil, W/O) polymerization strategy [1]. Then the NGs were conjugated with ultrasmall Fe_3O_4 NPs formed *via* hydrothermal method [2] and activated by EDC/NHS. At last, the NGs were acetylated by acetic anhydride and sequentially used to load DOX. The formed PEI-based nanogels possess good dispersibility and cytocompatibility, significantly enhanced r_1 relaxivity (2.29 $mM^{-1}s^{-1}$), excellent drug loading efficiency (51.4%), as well as sustained drug release profile. Strikingly, the NGs present enhanced T1 MR imaging ability and a high therapeutic efficacy of tumour cells.

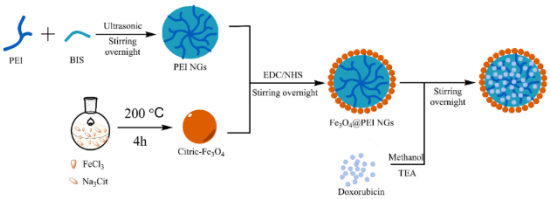

Figure 1. Scheme of the synthesis of the hybrid PEI-based nanogel.

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[PC34]

Fluorinated and Non-fluorinated Generation Four (G4) PAMAM Dendrimers

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Dendrimers are among the most interesting synthetic polymers to be used as delivery vehicles in biological systems due to their unique properties, such as a well-defined 3D structure, monodispersity, void spaces, and low viscosity [2]. Fluorination of dendrimers is reported to improve their affinity to the cell membrane, also increasing their transfection efficiency, endosomal escape, and serum stability [1, 2, 3]. In this study, generation four poly(amidoamine) (PAMAM) dendrimers were functionalized with 2,3,5,6-tetrafluoro-4-hydroxybenzoic acid, resulting from the fluorination of the parent compound 4-hydroxybenzoic acid which shows anti-bacterial, anti-fungal, and anti-nematicidal properties, also having high sigma receptor affinity [4, 5]. Our goal is to evaluate the biological performance of both these types of dendrimers and see if the fluorinated dendrimer presents advantages vis. the non-fluorinated one. For the synthesis, solutions with increasing molar equivalents of the compounds were added to a concentrated PAMAM solution and stirred for two days. This resulted in fluorinated and non-fluorinated dendrimers with different functionalization degrees able to be biologically tested. The successful bonding of the fluorinated and non-fluorinated compounds to the PAMAM dendrimer was confirmed by NMR, FTIR, MALDI-TOF, and UV-visible and Fluorescence spectroscopies. Biological studies, such as the evaluation of cytotoxicity, transfection efficiency, and anti-bacterial and anti-fungal effects, are under way to conclude about the potential advantages on the use of PAMAM dendrimers with 2,3,5,6-tetrafluoro-4-hydroxybenzoic acid.

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[PC35]

Characterization of Photoluminescent PAMAM Dendrimers for Biomedical Applications

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Dendrimers, and especially the family of poly(amidoamine) (PAMAM) dendrimers, have been associated to photoluminescence phenomena which may be interesting to explore in terms of applications [1]. In the current work, the intrinsic fluorescence properties of amine-terminated PAMAM dendrimers, generation 3 to 5, were evaluated having in view potential biomedical applications. For that purpose, PAMAM dendrimers were treated with ammonium persulfate (APS) to enhance their fluorescence intensity without the need to label them with fluorescent probes. The absorbance and photoluminescence properties of APS-treated PAMAM dendrimers were then studied at different pH values and as a function of generation. Additionally, the *in vitro* cytotoxicity of these dendrimers was evaluated, as well as the possibility of using them as drug carriers.

Results showed that the APS-treated PAMAM dendrimers present a higher absorbance and fluorescence intensity when compared with pristine PAMAM dendrimers, being this behaviour generation and pH dependent. Whereas absorbance increases with increasing generation, fluorescence intensity decreases, although always exhibiting an intense blue fluorescence when irradiated at 366nm. Moreover, in acid conditions, the fluorescence of the dendrimers is more intense. The APS-treated PAMAM dendrimers are also less cytotoxic than pristine PAMAM dendrimers. After loading doxorubicin (DOX) in generation 4 APS-treated dendrimers, the blue fluorescence of dendrimers was not considerably affected. Indeed, drug release studies at different pH media (PBS 7.4 and 5) showed that they constitute promising drug delivery systems presenting the advantage of being intrinsically fluorescent.

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[PC36]

Use of Mixed-Surface PAMAM Dendrimer Nanoparticles Carrying Encapsulated Curcumin as a Potential Therapy for Glioblastoma in Mice

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Glioblastoma (GB), a grade-4 astrocytoma, is an aggressive form of brain tumor having high mortality and morbidity rates (12 and 15 months after diagnosis). There is no cure for this cancer and the current chemotherapy and radiation therapy do not eradicate the tumor cells completely increasing the risk of tumor recurrence following radiation-based treatments. The average survival time following radiation-based therapy is 14.6 months. Use of anti-cancer drug is another alternate for GB. However, not all of the anti-cancer drugs cross the blood-brain barrier (BBB) to reach the tumor site. Previous studies found increased expression of pro-inflammatory markers in the GB brain, which results in metastasis, and high inflammation in the tumor brain. Therefore, decreasing pro-inflammatory signals and cell proliferation are potential targets as a therapy for GB. Curcumin (Cur), a natural phytochemical found in plants, is known to have anti-inflammatory, anti-oxidant and anti-carcinogenic properties. Cur can also cross the BBB; however, it is not water-soluble which makes its delivery challenging. Due to its solubility issues, Cur does not reach the brain in therapeutic amounts. Some studies use lipid formulation of Cur. However, they were found to be toxic and further increases inflammation in the tumor brain. We used mixed-surface PAMAM dendrimer G4 (surface modified with 10% amines and 90% ethanolamine hydroxyl surface, known as G4-90/10) to encapsulate and solubilize the curcumin (G4-90/10-ECur). Our results show effective release of Cur from the dendrimers to the cells. The dendrimers and dendrimers encapsulated cur have good safety profiles *in vitro* and *in vivo*. Moreover, G4-90/10 has a cystamine (Cys; S-S) core that can split to give dendrons with thiol groups (-SH) facilitating release of Cur to the cells. We used the G4-90/10-ECur to test the therapeutic effects of Cur and G4-90/10 in mouse-derived glioblastoma cells (Gl261) and in GB mice transplanted with these cells. The GB mice were injected with the Gl261 cells to initiate tumor and the G4-90/10-ECur was intracranially injected into the tumor 1 week later. Our data shows that G4-90/10-ECur dendrimers (1) are water soluble; (2) specifically kill GB cells *in vitro,* sparing the neurons and glial cells (3) reduce inflammation *in vitro* and *in vivo* in GB brain and (4) increase the survival of the GB mice by ~25%. A future aspect of this research involves injecting G4-90/10-ECur systemically to the GB mice as these dendrimers can cross the BBB.

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[PC37]

Hybrid Dendrimer-Based Supramolecular Nanoassembly: a Next Generation Dendrimer Architecture for Drug Delivery

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Dendrimers have proven to be effective for drug delivery and its biodisposition varies with change in its surface, generation and core. In an effort to understand the role of critical nanoscale design parameters (CNDP's), Dr. Chauhan's group has developed a novel hybrid dendrimer approach to harness unique features of individual dendrimers and create a nano-assembly [1, 2]. We report an easy in-situ method of creating supramolecular hybrid dendrimer nano-assembly by mixing G4.0 PAMAM ($–NH_2$) and G3.5 PAMAM (–COONa) dendrimers with a chemotherapeutic drug docetaxel (DTX).

Zeta potential, HR-TEM monographs with SAED pattern and ^{1}H-NMR proved the formation of nano-assembly. In-vitro dissolution, release studies revealed pH dependent dissolution and sustained release profile. Cellular uptake, cytotoxicity, apoptosis and cell cycle analysis in human/mouse glioblastoma cells indicates the effectiveness of hybrid dendrimers.

The comparative preclinical pharmacokinetic profile of proposed system was evaluated in male Sprague-Dawley (SD) rats with commercially available Taxotere®. The oral administration of the hybrid dendrimers showed pharmacokinetic profile equivalence to intravenous injection of Taxotere®. Further, histopathological observation of organs indicated no systemic toxicity in hybrid dendrimer treated animals when compared with control and Taxotere® treated animals.

These results demonstrate that hybrid dendrimer technology can bypass complex chemistry steps to prepare sophisticated dendrimer nanodevice. In brief, hybrid dendrimer can be seen as 'Click' engineering within dendritic platform.

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[PC38]

Electrode Modification with G5 PAMAM-NH_2 Dendrimers

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Lately, dendrimers have been explored for sensing purposes owing to the monodispersity, tuneable size and structure, surface modifiability, multivalency, hydrophilicity and high stability, both mechanical and chemical, of these synthetic polymers [1,2]. As a result of these properties, dendrimers can be a valuable addition to sensor development. Nowadays, dendrimers are widely explored in biosensors as platforms for the immobilization of biomolecules (*e.g.* enzymes, antibodies). Specifically, for poly(amidoamine) dendrimers, a less enticing property for sensing purposes might be its low conductivity, which can be increased by the addition of conductive nanomaterials like metallic nanoparticles. This work focused on the development of a chemical sensor for 4-nitrophenol detection based on poly(amidoamine) (PAMAM) dendrimers and gold nanoparticles (AuNPs).

Firstly, gold and vitreous carbon electrodes were sequentially modified with thiols, G5 PAMAM-NH_2 dendrimers and citrate-stabilized AuNPs, and then characterized by cyclic voltammetry and impedance spectroscopy in a hexacyanoferrate (II)/(III) redox couple system. In the second part, the electrocatalytic activity of the modified electrodes towards the 4-nitrophenol reduction in 0.05 M phosphate buffer solution was assessed by cyclic voltammetry. The modifications were successful, and vitreous carbon-based surfaces modification with G5 PAMAM-NH_2 dendrimer resulted in electrodes with higher stability and sensitivity. The lowest limit of detection was calculated for PAMAM dendrimer and 3-mercaptopropionic acid-modified vitreous carbon electrode, 17 μM, with 4-nitrophenol in linear range of 690 – 37 μM.

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[PC39]

Non-covalently Functionalized Dendrimers and Selective Inhibitors for Protein-Protein Interactions

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The interactions of proteins with each other and with biological macromolecules to form complexes plays an important role in biology [1]. Interactions that are unregulated in some manner give rise to diseases such as Alzheimer's, therefore, it is important to understand the mechanisms of these reactions and how to control them [2].

Protein interactions occur through functional points or "hot spots" located on large interacting surfaces having sizes between 500Å2 and 5000Å2 [3]. Therefore, attempts are being made to design inhibitors of sufficient sizes that can interact fully at the interfacial areas. Another factor that determines selectivity is the number of non-covalent interactions – as a result poly-valency, size, charge, and functionality are important parameters while designing ligands that can bind with the proteins [4]. This paper documents the study of covalently functionalized dendrimers to achieve this purpose. The advantage of these large molecules is that their sizes can be varied in a large range and they can be functionalized with relative ease, so that they can be used for targeted binding of a variety of hot spots [5]. Results indicate that the sizes of the binding area and the size of the dendrimer should be similar for optimal binding to be achieved. Experiments also revealed that functionalization of the dendrimer surface using different amino acids can be used as an effective means to up or down scale the extent of binding. A shortcoming of the study was a lack of understanding of positioning of the target groups in three dimensions – it is difficult to add the groups through proper positioning. New technologies should be developed to develop positioning abilities to develop better therapeutic applications.

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[PC40]

Stability and Degradation Studies of bis-MPA Based Dendrimers at Different pH and Temperature Conditions by ^{1}H NMR

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Dendrimers are a class of synthetic polymers that can be designed for different applications, due to their well-defined structure, multivalency and easy functionalization. These macromolecules consist of branched structures possessing a well-defined core, interior regions and many end groups. Dendrimers have emerged as one of the most promising nanocarriers in the biomedical field, for drug delivery and medical imaging, due to their high-drug loading capacity either by conjugation or encapsulation [1].

Polyester dendrimers have shown to be a promising class of dendrimers due to their biodegradable and biocompatible behaviour. The use of biodegradable dendrimers emerged as a strategy to produce drug carriers with high accumulation and retention in diseased tissues, but at the same time, allowing a rapid and safe elimination of non-toxic dendrimer fragments from the body [2].

Having this in mind, the main objective of this work was to study the stability and degradation of biodegradable polyester dendrimers based on bis-MPA monomers at different conditions (such as temperature, pH and blood serum presence) by ^{1}H NMR spectroscopy technique.

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[PC41]

Inclusion of Dendrimers in Exosomes

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Exosomes are naturally occurring nanoparticles (50 – 150 nm), present in biological fluids, that are released by cells and are key players in intercellular communication processes [1]. Simultaneously to their recognition as potential biotherapeutics due to their molecular content, eliciting desired biological responses, they are also being studied as possible vehicles for exogeneous materials inside the human body. In this scope, human mesenchymal stem cells (hMSCs) that show a large capacity for *ex vivo* expansion and immunosuppressive properties, are the ideal source of exosomes for biomedical applications [2].

The focus of this work was to include dendrimers inside hMSCs-derived exosomes. Dendrimers are nanoscale molecules that may be used as drug/gene delivery vehicles and, so, the underlining idea was that exosomes could help them to cross the body biological barriers and more easily reach their target. The inclusion of exogeneous molecules inside exosomes is, however, challenging. Here, we raised the hypothesis that it would be possible to load the dendrimers into the exosomes by simply exposing the cells to their solutions. That is, supposing that dendrimers could be internalized and then excreted to the cell medium inside exosomes. So, first, generation 4 poly(amidoamine) (PAMAM) dendrimers were labelled with rhodamine and characterized (^{1}H NMR, FTIR, UV/Vis and fluorescence spectroscopies). After, a protocol for exosome isolation was established and the isolated exosomes were characterized by DLS, TEM and acetylcholinesterase activity. hMSCs were then exposed to the labelled dendrimers and the released exosomes were collected to evaluate their content in dendrimers. Surprisingly, the dendrimers were not excreted inside exosomes and, instead, were accumulated in the cellular perinuclear zone as assessed by fluorescence microscopy. These findings may be useful for those involved in the biomedical applications of dendrimers.

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[PC42]

Synthesis of Novel Surface Modified Dendrimers for Dengue and Zika Viral Entry Inhibition

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Dengue and Zika are both considered to be major global problems that must be acted upon with urgency [1]. One strategy for the treatment of these infectious diseases lies in the development of antiviral therapies targeting the initial stages of viral entry into host cells. For both the dengue virus (DENV) and the zika virus (ZIKV), DC-SIGN receptors have been shown to play an important role in viral entry and subsequent infection of host cells [2, 3]. Thus, these receptors are important targets for inhibiting viral transmission.

In this work, a system capable of targeting the DC-SIGN dependent uptake of either DENV or ZIKV was developed. For this, the unique multivalency and conjugation versatility of the poly(amidoamine) (PAMAM) dendrimers was combined with the DC-SIGN targeting glycomimetic ligand, shikimic acid (SA). SA-functionalized generation four and five amine-terminated PAMAM dendrimers were first prepared. Copper was then reduced into the newly formed conjugates. All of the prepared samples underwent physicochemical characterization. Preliminary studies were also performed to test the cytotoxicity of the prepared NPs on HEK 293T cells.

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[PC43]

Synthesis and Characterization of Molecularly Precise Lauric Acid – Dendrimer Conjugates for Gene/Drug Delivery

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There has always been the need of developing carriers for the protection of fragile therapeutic substances (like genes and drugs), to avoid their degradation under *in vivo* circumstances, and for helping them to surpass the biological barriers that may appear until the final target is reached. Ideally, these carriers should be safe, efficient and possess controllable properties – in this sense, dendrimers have been extensively explored.

The functionalization of dendrimers, namely generation 5 poly(amidoamine) (PAMAM) dendrimers, with fatty acids was already shown to result in an improvement of gene transfection efficiency in human mesenchymal stem cells, especially when natural lauric acid (LA) was used [1]. Herein, we want to evaluate the possibility of using low generation PAMAM dendrimers for the same purpose (and also for small drug delivery) as they are simple and have precise (defect-free) molecular structures that allow their quantitative surface functionalization. By now, a LA-PAMAM G0 conjugate was prepared and purified using classical techniques. ^{1}H NMR analysis clearly showed that the full functionalization of the dendrimer was achieved (Figure 1). In the near future, we are going to prepare similar conjugates using G1, G2 and G3 PAMAM dendrimers and to study their physicochemical properties, cytocompatibility, gene/drug delivery efficiency and intracellular mechanisms.

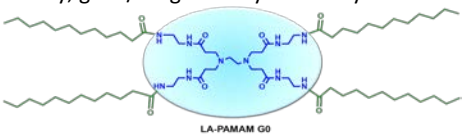

Figure 1. The molecular structure of LA-PAMAM G0.

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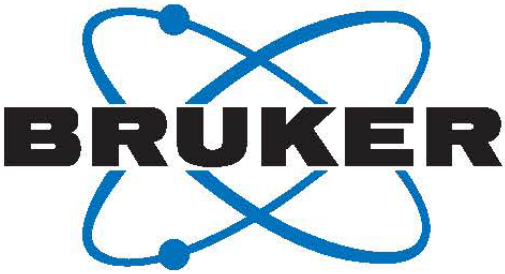
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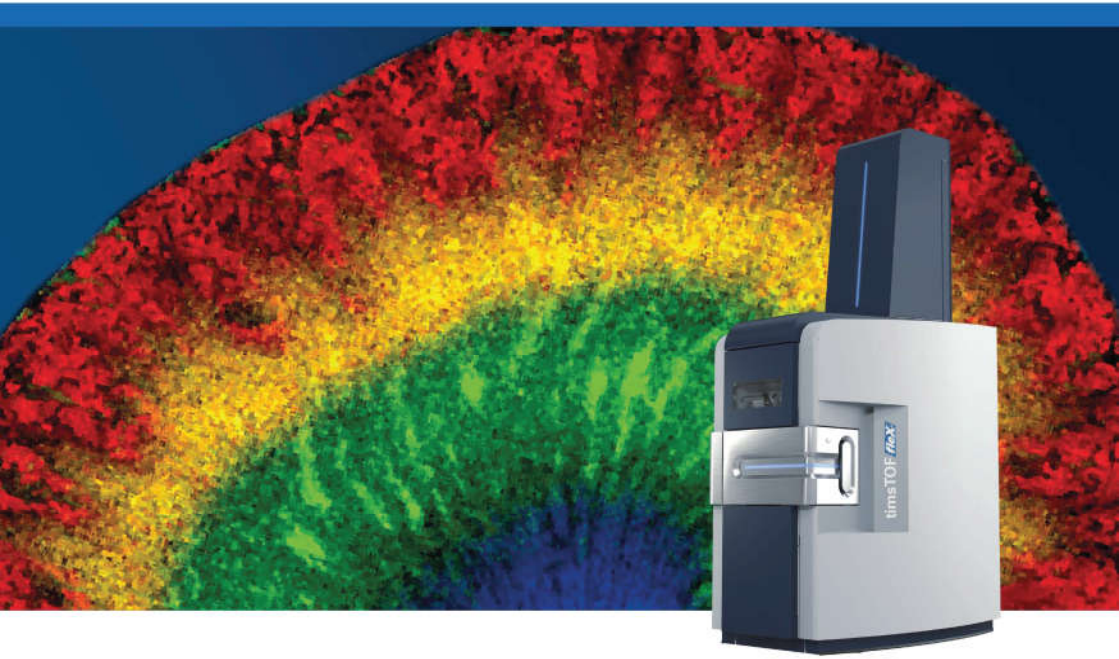

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- Fast mapping of metabolites, lipids, glycans and more to find regions of interest
- Match PASEF powered LC-MS/MS identification with label-free spatial localization
- Dual source design with software controlled switch for uncompromised performance

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