

# **IDS11**

Eleventh International Dendrimer  
Symposium

## **Abstract Book**

14<sup>th</sup> – 18<sup>th</sup> July 2019

Funchal, Madeira Island – PORTUGAL

**Abstract Book**

IDS11 –11<sup>th</sup> International Dendrimer Symposium

**Editor**

Centro de Química da Madeira

Address:

Centro de Química da Madeira

Universidade da Madeira

Campus da Penteada

9020-105 Funchal (Portugal)

**IDS11 website & e-mail**

<http://cqm.uma.pt/ids11>

[ids11@mail.uma.pt](mailto:ids11@mail.uma.pt)

**Edited by**

João Rodrigues

Helena Tomás

Mara Gonçalves

Énio Freitas

**ISBN**

978-989-54090-3-7

**Disclaimer:** Reproduction is authorised provided the source and authors are acknowledged. Responsibility for the information and views expressed in this publication lies entirely with the author(s).

© **IDS11 - 2019** Content updated on 07 of July.

# INDEX

---

INDEX.....	i
WELCOME MESSAGE.....	1
PROGRAM .....	5
HONOR COMMITTEE.....	17
INTERNATIONAL ADVISORY COMMITTEE .....	19
SYMPOSIUM CHAIRPERSON .....	20
ORGANIZING COMMITTEE.....	21
IDS11 KN: KEYNOTE LECTURES .....	23
<i>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)</i>	
Donald A. Tomalia .....	25
<i>From the Discovery of Self-Assembling Dendrimers to the Emergence of New Research Fields</i>	
Virgil Percec.....	27
<i>Fluorescent Dendrimers for Biology. How Two-Photon Absorption Properties Can Help?</i>	
Anne-Marie Caminade, Jean-Pierre Majoral, Aurélien Hameau, Artem Zibarov, Mireille Blanchard-Desce, Jean-Baptiste Verlhac, Justin Teissié & Muriel Golzio .....	29
<i>Phosphorus Dendrimers. Design and Applications. Past, Present and Future</i>	
Jean-Pierre Majoral.....	31
<i>Novel Hybrid Dendrimers Harboring Sugar Triads at the Periphery</i>	
René Roy & Rahul S. Bagul .....	33
<i>Nanotechnology Therapeutics: Moving Towards the Clinic</i>	
James R. Baker Jr.....	35

<b><i>Supramolecular Dendrimers for Nanomedicine</i></b>	
Ling Peng .....	37
<b><i>Construction of Dendrimer/Carbon Dot Nanohybrid Platform for Ultrasound-Assisted Enhanced Theranostics of Tumors</i></b>	
Dan Li, Lizhou Lin, Yu Fan, Lianfang Du & Xiangyang Shi.....	39
<b><i>Simplifying the Assembly of Dendritic and Fractal Constructs</i></b>	
George R. Newkome & Charles N. Moorefield .....	41
<b>IDS11 IOC: INVITED ORAL COMMUNICATIONS.....</b>	<b>43</b>
<b><i>Voltage Initiated Tissue Adhesive Dendrimers</i></b>	
Terry W.J. Steele, Manisha Singh & Nigel Tan .....	45
<b><i>Dendritic Micelles as a Versatile Platform for Drug Delivery</i></b>	
Rana Sanyal.....	46
<b><i>Polyurea Dendrimers: Carriers, Killers and Cell Kickers</i></b>	
Vasco D. B. Bonifácio .....	47
<b><i>DENDrimicelles:</i></b>	
<b><i>Dendrimer-Encapsulated-Nanoparticle Coacervate-core Micelles</i></b>	
Jan Bart ten Hove, Fijs van Leeuwen & Aldrik Velders.....	48
<b><i>G2-S16 in Innate and Adaptive Immune System, Microbiome and Human Vaginal Tissue</i></b>	
Alba Martinez, Rafael Ceña-Diez, M <sup>a</sup> Jesús Serramía-Lobera , Rafael Gómez, F. Javier de la Mata, Carlos Guerrero-Beltrán, Manuel Leal & M <sup>a</sup> Ángeles Muñoz-Fernández .....	49
<b><i>Lymph Node Delivery Using Anionic Dendrimers</i></b>	
Chie Kojima.....	50
<b><i>Self-Assembly of Amphiphilic Dendrimers: From Dendromicelles to Dendrimersomes</i></b>	
Oleg V. Borisov, Inna O. Lebedeva & Ekaterina B. Zhulina.....	51
<b><i>Dendrimers for Multimetallic Nanomaterials</i></b>	
Kimihisa Yamamoto.....	52
<b><i>A Self-Assembling Amphiphilic Dendrimer as Effective Targeted Delivery Platform for siRNA Therapeutics</i></b>	
Xiaoxuan Liu & Ling Peng.....	53
<b><i>Cationic Carbosilane Dendrimers Designed for Applications</i></b>	

<i>Tomáš Strašák, Monika Müllerová, Wahid Tatan, Alena Krupková, Lucie Červenková Šťastná, Petra Cuřínová, Dominika Wróbel, Regina Herma, Jan Čermák &amp; Jan Malý.....</i>	<i>54</i>
<b><i>From Peripheral to Central Nervous System: A Journey Towards Targeted Neuronal Delivery</i></b>	
<i>Victoria Leiro, Sofia Santos, Ana Spencer, Marília Torrado, Beatriz Custódio, Natália Magalhães, Pedro Costa, Sara Reis &amp; Ana Paula Pêgo..</i>	<i>55</i>
<b><i>Rotaxane-branched Dendrimers</i></b>	
<i>Hai-Bo Yang.....</i>	<i>56</i>
<b><i>Radical Dendrimers: Biomedical Applications</i></b>	
<i>José Vidal-Gancedo, Vega Lloveras, Luiz F. Pinto &amp; Flonja Liko .....</i>	<i>57</i>
<b><i>Protective Effect of Neutral Phosphodendrimers on Experimental Autoimmune Encephalitis in Mice</i></b>	
<i>Inmaculada Posadas, Laura Romero Castillo, Alberto Rábano, Serge Mignani, Jean-Pierre Majoral &amp; Valentín Ceña.....</i>	<i>58</i>
<b><i>Efficient Solid-Phase Synthesis of Peptide Dendrimers via On-Resin Ligation</i></b>	
<i>Anard Salvaraj &amp; Chai-Lin Kao .....</i>	<i>59</i>
<b><i>Functionalized Nanoparticles to Target and Image Cancer Cells In Vivo</i></b>	
<i>Suhe Wang, Jesse Chen, Somnath Bhattacharjee, Zhengyi Cao, Scott Swanson &amp; James R. Baker Jr.....</i>	<i>60</i>
<b><i>Topology, Amphiphilicity and Dendronization of Carbosilane Dendritic Systems in Biomedical Applications</i></b>	
<i>Rafael Gómez &amp; F. Javier de la Mata.....</i>	<i>61</i>
<b><i>Dendrimeric Microsponge Based Topical Gel of Dithranol</i></b>	
<i>Pushpendra Tripathi &amp; Shalini Tripathi .....</i>	<i>62</i>
<b><i>Tumor Microenvironment-Responsive Dendritic Polymer-Drugs as Nanoscale Systems for Drug Delivery</i></b>	
<i>Kui Luo.....</i>	<i>63</i>
<b><i>Biohybrid Structures and Their Targeting Properties: Considering the Potential Use of Mono- and Polyassociation Steps</i></b>	
<i>Dietmar Appelhans, Johannes Fingernagel, Susanne Boye, Alben Lederer &amp; Brigitte Voit.....</i>	<i>64</i>

<b><i>Multifunctional Hybrid Dendrimer With Dual-Ligands: A Next Generation Dendritic Platform for Drug Delivery</i></b>	
Mayank Kumar Singh, Akella V. Subrahmanya Sarma, M. Jerald Mahesh Kumar, Ramakrishna Sistla & Abhay Singh Chauhan .....	65
<b><i>Molecular Characteristics, Membrane Affinity, Transport Properties and In Vitro Cytotoxicity of Bola-Type Peptide Dendrimers</i></b>	
Maciej Cieślak, Magdalena Stolarska, Katarzyna Trzeciak & Zofia Urbanczyk-Lipkowska .....	66
<b><i>Synthesis and Properties of Antimicrobial Dendrons</i></b>	
Jørn B. Christensen & Rikke Heidemann Olsen .....	67
<b><i>Comparison of Carboxy-methylated G5_PAMAM Dendrimer and Carboxy-methylated Polyethyleneimine Metal Complexes</i></b>	
Tamás S. Miklósi, Levente Novák, Virág Kiss & István Bányai .....	68
<b>IDS11 OC: ORAL COMMUNICATIONS .....</b>	<b>69</b>
<b><i>The Study of Polyamidoamine Dendrimer as Essential Oil Carrier</i></b>	
Hui-Ting Chen, Yi-Ju Lu, Yi-Chin Lo, Po-Chu Wu & Horng-Huey Ko .....	71
<b><i>Exploiting ESI-TOF Mass Spectrometry for Detailed Characterization of Polycationic Carbosilane Dendrimers</i></b>	
Alena Krupková, Petra Cuřinová, Monika Müllerová, Jan Čermák & Tomáš Strašák .....	72
<b><i>Pt(II)-dendrimers as Bio-Imaging Marker for Bacteria in Two-Photon Excitation Microscopy</i></b>	
Noemi Molina, Marvin Cnudde, Juan A. Guadix, Jose M. Perez-Pomares, Cristian A. Strassert, Ezequiel Perez-Inestrosa & Yolanda Vida .....	73
<b><i>Dendrimers Carrying Multiple Redox Units – Is it Good or Bad for Cell Survival</i></b>	
Zofia Urbanczyk-Lipkowska, Maja Morawiak, Marta Sowińska, Maciej Cieślak, Elżbieta Zieminska & Barbara Zabłocka .....	74
<b><i>Covered By Neuroligin-2-derived Peptide Polyamidoamine-Based (PAMAM) Dendrimers Enhances Pancreatic B-Cells' Proliferation and Function</i></b>	
Anna Munder & Arie Gruzman .....	75
<b><i>Mass Spectroscopy for Detailed and Precise Analysis of Dendrimers</i></b>	
Aura Tintaru, Ling Peng & Laurence Charles .....	76

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

Moshe Portnoy, Natali Ashush, Reut Fallek, Amit Fallek, & Mor Weiss-Shtofman.....77

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

Julien Rossignol, Melissa Andrews, Melissa Resk, Clayton Malkowski, Thomas Fagan, John Gallien, Grant Raymor, Sydney Climie, Nikolas Munro, Sindhuja Koneru, Alexa Toth, Nora Fettingner, Bethany MacDonald, Eric Kuhn, Joseph Hellrung, Justin Stadler, Bhairavi Srinageshwar, Balachandar Kathirvelu, Douglas Swanson, Gary Dunbar & Ajit Sharma.....78

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

Evgeny Apartsin, Valeria Arkhipova, Javier Sánchez-Nieves, F. Javier de la Mata & Rafael Gómez.....79

***Dialytic Separation of Anions from DMSO Solution Facilitated by Dendritic Receptors***

Petra Cuřínová, Maximilian Winkler, Jan Budka, Chang Nga Wun, Vratislav Blechta, Lucie Červenková Šťastná, Alena Krupková, Jan Sýkora & Tomáš Strašák .....80

***Fighting Resistant Cancer with Carbosilane Metallodendrimers***

Sandra García-Gallego, Natalia Sanz del Olmo, Marta Maroto-Díaz, Ana M. Bajo, Paula Ortega López, Rafael Gómez & F. Javier de la Mata.....81

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

Marijana Petković, Duarte Fernandes, Pedro Pires & João Rodrigues .....82

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

Victoria Leiro, Ana Patrícia Spencer, Natália Magalhães & Ana Paula Pêgo.....83

**IDS11 YSC: YOUNG SCIENTISTS COMMUNICATIONS ..... 85**

***Antibacterial Activity of Conjugates Between Antimicrobial Peptides and Cationic Carbosilane Dendrons***

<i>Jael Fernández, G. Acosta, D. Pulido, J. L. Copa-Patiño, J. Soliveri de Carranza, M. Royo, Rafael Gómez, F. Albericio, Paula Ortega López &amp; F. Javier de la Mata.....</i>	<i>87</i>
<b><i>PAMAM Dendrimers as Nanocarriers for Platinum Anticancer Complexes</i></b>	
<i>Cláudia Camacho, Helena Tomás &amp; João Rodrigues.....</i>	<i>88</i>
<b><i>New Anionic Poly(Alkylidenamine) Dendrimers as a Potential Microbicide: the Behavior Against HIV-1 Infection</i></b>	
<i>Dina Maciel, Carlos Guerrero-Beltrán, Rafael Ceña-Diez, Helena Tomás, M<sup>a</sup> Ángeles Muñoz-Fernández &amp; João Rodrigues.....</i>	<i>89</i>
<b><i>Dendrimers Incorporating Lanthanide Cations as Near-Infrared Imaging Agents</i></b>	
<i>Kamal Jouad, Guillaume Collet, Marie-Aude Hiebel, Nabil El Brahmi, Mohamed Akssira, Svetlana V. Eliseeva, Stéphane Petoud, Saïd El Kazzouli &amp; Franck Suzenet .....</i>	<i>90</i>
<b><i>Cinnamic Acid-Functionalized PAMAM Dendrimer Generation 4: Drug Delivery and Cytotoxicity</i></b>	
<i>Ana Olival, Helena Tomás &amp; João Rodrigues .....</i>	<i>91</i>
<b><i>A Self-Assembling Amphiphilic Peptide Dendrimer as Anticancer Drug Delivery Platform</i></b>	
<i>Dandan Zhu, Ling Peng &amp; Xiaoxuan Liu.....</i>	<i>92</i>
<b><i>Design and Synthesis of Bioconjugates for Personalized Medicine</i></b>	
<i>Jennifer Daeg, Xiaoying Xu, Brigitte Voit, Achim Temme, Xiangyang Shi &amp; Dietmar Appelhans.....</i>	<i>93</i>
<b><i>[Ru(<math>\eta^5</math>-C<sub>5</sub>H<sub>5</sub>)(PPh<sub>3</sub>)<sub>2</sub>]-PAMAM Metallodendrimers as Promising Anticancer Drugs</i></b>	
<i>Nádia Nunes, Dina Maciel, Helena Tomás &amp; João Rodrigues.....</i>	<i>94</i>
<b><i>Synthesis, Self-Assembling Properties, and Biomedical Applications of Amphiphilic Janus Glycodendrimers</i></b>	
<i>Leila Mousavifar, R. Rej, Rahul S. Bagul, A. Tapenard &amp; René Roy.....</i>	<i>95</i>
<b><i>Synthesis, Characterization and Biological Evaluation of Homo- and Heterofunctionalized Polyamide Dendrimers for Application in Inflammatory Diseases</i></b>	
<i>Ana M. Garzón P., Diego L. Bertuzzi, Kurt Lucas &amp; Cátia Ornelas.....</i>	<i>96</i>



<b><i>Self-Assembling Hybrids of Fluorescent Carbon Dots and PAMAM Dendrimers for DNA Delivery Applications</i></b>	
Ivo J. Martins, Helena Tomás & João Rodrigues .....	97
<b>IDS11 PC: POSTER COMMUNICATIONS .....</b>	<b>99</b>
<b><i>Oxidation-Sensitive Core-Multishell Nanocarrier Systems</i></b>	
Keerthana Rajes, K. A. Walker, Fiorenza Rancan, Elisa Quaas, Annika Vogt & Rainer Haag.....	101
<b><i>Design and Synthesis of Succinylated PAMAM-Isoniazid Sendrimer Prodrug</i></b>	
Renan Vinicius de Araújo & Jeanine Giarolla Renan Vinicius de Araújo & Jeanine Giarolla.....	102
<b><i>Green Dendritic Polymer: Synthesis of Star-Shaped 4arms-PLLA<sub>n</sub>-b-DL<sub>m</sub> Dendritic Peptides with “Core-Shell” Structure</i></b>	
Ruilong Sheng, Zhao Wang & Lin Jia .....	103
<b><i>Cycloaddition of CO<sub>2</sub> Catalyzed by Phosphonium and Amonium Carbosilane dendrimers</i></b>	
Lucie Červenková Šťastná, Monika Müllerová, Roman Petříčkoví, Petra Cuřínová, Martin Košťejn, Stanislav Šabata & Tomáš Strašák.....	104
<b><i>DNA/PAMAM Dendrimer Films: a Highly Stable Platform for DNA-Intercalating Anticancer Drugs</i></b>	
Rita Castro, Pedro Granja, Ana Paula Pêgo, João Rodrigues & Helena Tomás .....	105
<b><i>Ruthenium (II) Carbosilane Metallodendrons as Promising Anticancer Agents</i></b>	
Natalia Sanz del Olmo, Sara Quintana Sánchez, Marta Maroto-Díaz, Sandra García-Gallego, Rafael Gómez, Paula Ortega López & F. Javier de la Mata.....	106
<b><i>Copper(II)-conjugated Metallodendrimers: EPR Study</i></b>	
Riccardo Carloni, Michela Cangiotti, Sandra García-Gallego, F. Javier de la Mata & Maria Francesca Ottaviani.....	107
<b><i>UCST-Type Thermosensitive Dendrimers</i></b>	
Chie Kojima & Mamiko Tamaki .....	108
<b><i>Ruthenium-based Metallodendrimers: Synthesis, Cytotoxicity and Hematotoxicity Studies</i></b>	

<i>Dina Maciel, Francisco Santos, M<sup>a</sup> Ángeles Muñoz-Fernández, Helena Tomás &amp; João Rodrigues</i> .....	109
<b><i>Study of the Biological Activity of Dendrimers Functionalized with Imidazolium Salts</i></b>	
<i>Tamara Rodríguez, José Luis Copa-Patiño, Juan Soliveri, F. Javier de la Mata, Jesús Cano &amp; Rafael Gómez</i> .....	110
<b><i>Microbiological Activity of Dendrimers Modified with 1,8-Naphthalimides</i></b>	
<i>Ivo Grabchev, Desislava Staneva &amp; Evgenia Vasileva-Tonkova</i> .....	111
<b><i>Tuning Spin-Spin Interactions in Radical Dendrimers</i></b>	
<i>Vega Lloveras, F. Liko, L.F. Pinto &amp; José. Vidal-Gancedo</i> .....	112
<b><i>Novel Polyamidoamine Dendrimers for Skin Delivery</i></b>	
<i>Georgios Paraskevopoulos, Anna Nováčková, Martina Langerová, Pavlína Chladová, Denisa Houšková &amp; Kateřina Vavrova</i> .....	113
<b><i>Donor–Acceptor PIMAM Dendrimer Photodiodes</i></b>	
<i>Rita F. Pires, Ana Charas, Jorge Morgado, Teresa Casimiro &amp; Vasco D. B. Bonifácio</i> .....	114
<b><i>Antibacterial Properties of Cotton Fabrics Modified with Fluorescent Dendrimers and Metallodendrimers</i></b>	
<i>Desislava Staneva, Miglena Irikova &amp; Ivo Grabchev</i> .....	115
<b><i>4-Carboxyphenylboronic Acid Modified Poly(amidoamine) Dendrimers Used as Carbohydrates Selector</i></b>	
<i>Yuan-Ting Chan, Ching-Hua Tsai &amp; Chai-Lin Kao</i> .....	116
<b><i>Synthesis and Characterization of Stable Cu-DENPs Using Ascorbic Acid as a Reducing Agent</i></b>	
<i>Duarte Fernandes, Manuel Algarra, Carla S. Alves &amp; Pedro Pires</i> .....	117
<b><i>A New Strategy for Amphiphilic Peptide Dendrimer on Solid Phase</i></b>	
<i>Yung Liao, M. Vijaya Simha &amp; Chai-Lin Kao</i> .....	118
<b><i>RGD-dendritic Structures on Titanium Alloy. Influence in the Relationship Between Bone Cells and the Metal Surface</i></b>	
<i>Noemi Molina, Ana M. Gonzalez-Luque, José Becerra, Leonor Santos-Ruiz, Yolanda Vida &amp; Ezequiel Perez-Inestrosa</i> .....	119
<b><i>Hyaluronic Acid-Modified Dendrimer Entrapped Gold Nanoparticles</i></b>	

<i>Nilsa Abreu, Carla S. Alves, Helena Tomás, Xiangyang Shi &amp; João Rodrigues.....</i>	<i>120</i>
<b><i><sup>99m</sup>Tc-Labelled Polyurea (PURE) Dendrimers for Ovarian Cancer Theranostics</i></b>	
<i>Adriana Cruz, Rita F. Pires, Célia Fernandes, Paula Raposinho, António Paulo &amp; Vasco D. B. Bonifácio .....</i>	<i>121</i>
<b><i>One-pot Accelerated Synthesis to bis-MPA Dendrimers</i></b>	
<i>Sandra García-Gallego, Oliver Andrén &amp; Michael Malkoch .....</i>	<i>122</i>
<b><i>Synthesis of Niclosamide Dendron of Intracellular Release</i></b>	
<i>Rodrigo Vieira Gonzaga, Lucas Adriano do Nascimento &amp; Elizabeth Igne Ferreira .....</i>	<i>123</i>
<b><i>Phosphorus Dendrimers as Rose Bengal Carriers in Photodynamic Therapy</i></b>	
<i>Krzysztof Sztandera, Magdalena Milczarek, Marta Majkowska, Joanna Wietrzyk &amp; Barbara Klajnert-Maculewicz.....</i>	<i>124</i>
<b><i>Topology-Driven Effects of Carbosilane Dendrimers and Dendrons on Immune Cells</i></b>	
<i>Nadezhda Knauer, Ekaterina Pashkina, Evgeny Apartsin, Elena Fuentes, Carlos E. Gutierrez-Ulloa, Marina Buyanova, F. Javier de la Mata &amp; Rafael Gómez .....</i>	<i>125</i>
<b><i>In silico Characterization of PURE Dendrimers-Small Molecules Interactions</i></b>	
<i>Nuno Martinho, Rita F. Pires, Mire Zloh.....</i>	<i>126</i>
<b><i>Carbosilane Glucose Glycodendrimers: Synthesis and Toxicological Analyses</i></b>	
<i>Monika Müllerová, Lucie Červenková Šťastná, Jan Malý, Dominika Wróbel, Liegertová Michaela &amp; Tomáš Strašák .....</i>	<i>127</i>
<b><i>Nanoparticles Act as Adjuvant with Latency Reversal Agents for HIV Treatment and Inhibit HSV-1 in an In Vitro Neuronal Model</i></b>	
<i>Ignacio Rodriguez-Izquierdo, Ignacion Relaño-Rodriguez, M<sup>a</sup> Jesús Serramía-Lobera , Raquel Juárez-Sánchez, Rafael Gómez, F. Javier de la Mata, M<sup>a</sup> Jesús Bullido &amp; M<sup>a</sup> Ángeles Muñoz-Fernández.....</i>	<i>128</i>
<b><i>Fractionation and Degradative Stability of 5<sup>th</sup> Generation PAMAM Dendrimer</i></b>	
<i>Levente Novák, Tímea Szabó &amp; István Bányai.....</i>	<i>129</i>

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

Francisco Santos, Dina Maciel & João Rodrigues .....130

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

Ana Patrícia Spencer, Natália Magalhães, Victoria Leiro & Ana Paula Pêgo.....131

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

Wei Huang, Xiangyang Shi & Pedro Pires.....132

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

Yu Zou & Xiangyang Shi .....133

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

Lydia dos Orfãos, Cláudia Camacho, Helena Tomás & João Rodrigues ...134

***Characterization of Photoluminescent PAMAM Dendrimers for Biomedical Applications***

Cláudia Camacho, Marta Urgellés, Helena Tomás, Fernando Lahoz & João Rodrigues.....135

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

Julien Rossignol, Nikolas Munro, Micheal Fana M., Bhairavi Srinageshwar, Clayton Malkowski, Sydney Climie, Stephanie Baiyasi, Douglas Swanson, Ajit Sharma & Gary Dunbar.....136

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

Mayank Kumar Singh, Akella V. Subrahmanya Sarma, M. Jerald Mahesh Kumar, Ramakrishna Sistla & Abhay Singh Chauhan .....137

***Electrode Modification with G5 PAMAM-NH<sub>2</sub> Dendrimers***

Gina Tavares, José Mesquita & João Rodrigues .....138

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

Ibrahim Althobait & Lance Twymen .....139

<b><i>Stability and Degradation Studies of bis-MPA Based Dendrimers at Different pH and Temperature Conditions by <sup>1</sup>H NMR</i></b>	
<i>Ana Rute Neves, Miguel Faria, Filipe Olim, João Rodrigues &amp; Helena Tomás .....</i>	<i>140</i>
<b><i>Inclusion of Dendrimers in Exosomes</i></b>	
<i>Filipe Olim, João Rodrigues &amp; Helena Tomás .....</i>	<i>141</i>
<b><i>Synthesis of Novel Surface Modified Dendrimers for Dengue and Zika Viral Entry Inhibition</i></b>	
<i>Carla S. Alves, Natacha Antunes, Helena Tomás, Miguel A. R. B. Castanho &amp; João Rodrigues.....</i>	<i>142</i>
<b><i>Synthesis and Characterization of Molecularly Precise Lauric Acid – Dendrimer Conjugates for Gene/Drug Delivery</i></b>	
<i>Helena Chá-Chá, Filipe Olim, Helena Tomás, João Rodrigues &amp; Ruilong Sheng .....</i>	<i>143</i>
<b>AUTHORS INDEX.....</b>	<b>145</b>
<b>PARTICIPANTS LIST.....</b>	<b>151</b>



# WELCOME MESSAGE

---

Dear Participants,

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

Being held every two years since 1999, the IDS is the most important worldwide conference 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 more 88 oral talks, including 24 invited lectures and 11 oral communications from young scientists. Also, we will have 43 poster presentations, and a final poster awards session is programmed too. Globally, this edition of IDS has around 120 participants representing 23 countries.

To maximize the opportunities to share new ideas and point of views, we decided to organize interdisciplinary sessions and have a reduced number of parallel sessions. In this scope, having a short time for presentation, we expect participants to focus on new results presentation and discussion instead on a parade of work already published. As so, do not forget to actively participate during the discussion periods and to use the provided free time for networking.

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

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 the first territorial discovery of the "Portuguese Age of Discovery". With subtropical-Mediterranean climate, Madeira Island has their "Laurisilva" forest recognized by UNESCO as a natural World Heritage Site and more than 2000 km of "levadas" (aqueducts that carry water from the north coast of the Island to the agricultural regions in the south), 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 *Madeira's Regional Secretariat for Tourism and Culture* and, of course, the companies BRUKER, DENDRITECH and CYD. A special thanks are also due to all members of the Organizing Committee for helping me to assemble this IDS edition.

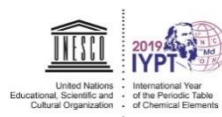
Believing that IDS11 will be a very productive meeting and that you will fall in love with Madeira island, we expect to receive you again soon. Thank you for coming, enjoy our IDS11 and enjoy life!

João Rodrigues

IDS11 Chairperson

Hosts





Organized by



Sponsors



Support



Cofinanciado por:





# PROGRAM



**IDS11**

11<sup>th</sup> INTERNATIONAL




**DENDRIMER**

SYMPOSIUM

FUNCHAL, MADEIRA - PORTUGAL


**14-18 JULY 2019**


**Sunday, 14<sup>th</sup> July 2019 – ROOM A**

Time		Title	
15:00	18:00		Participants Registration
18:00	18:45		Opening Session
18:45	19:30	<b>KN1</b>	<p><b>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)</b></p> <p><i>Donald Tomalia</i></p> <p>Chairman: George Newkome</p>
19:30	21:00		Welcome Reception

**Monday, 15<sup>th</sup> July 2019 – ROOM A**



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

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

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

***Tuesday, 16<sup>th</sup> July 2019 – ROOM A***

Time		Title	
8:30	9:15	KN4	<b>Phosphorus Dendrimers. Design and Applications. Past, Present and Future</b> <i>Jean-Pierre Majoral</i> Chairman: Donald Tomalia
			<b>Session 5</b>

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

12:25	14:00		Lunch
14:15	19:00		Social Program
20:00			Conference Dinner

***Tuesday, 16<sup>th</sup> July 2019 – ROOM C (Parallel session)***



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




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

**Wednesday, 17<sup>th</sup> July 2019 – ROOM A**



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

10:55	11:25		Coffee Break
			<b>Session 10</b> Chairwoman: Xiaoxuan Liu
11:25	11:50	IOC14	<b>Protective Effect of Neutral Phosphodendrimers on Experimental Autoimmune Encephalitis in Mice</b> <i>Valentín Ceña</i>
11:50	12:10	OC9	<b>Amphiphilic Hybrid Triazine-Carbosilane Dendrons: Synthesis and Self-Organization</b> <i>Evgeny Apartsin</i>
12:10	12:25	YS7	<b>Design and Synthesis of Bioconjugates for Personalized Medicine</b> <i>Jennifer Daeg</i>
12:25	12:50	IOC15	<b>Efficient Solid-Phase Synthesis of Peptide Dendrimers</b> <i>Chai-Lin Kao</i>
12:50	14:50		Lunch
14:50	15:35	KN7	<b>Supramolecular Dendrimers for Nanomedicine</b> <i>Ling Peng</i> Chairman: James R. Baker Jr.
			<b>Session 11</b> Chairman: Dietmar Appelhans
15:35	16:00	IOC16	<b>Functionalized Nanoparticles to Target and Image Cancer Cells <i>In Vivo</i></b> <i>Suhe Wang</i>

16:00	16:20	OC10	<b>Dialytic Separation of Anions from DMSO Solution Facilitated by Dendritic Receptors</b> <i>Petra Cuřínová</i>
16:20	16:35	YS8	<b>[Ru(<math>\eta^5</math>-C<sub>5</sub>H<sub>5</sub>)(PPh<sub>3</sub>)<sub>2</sub>]-PAMAM Metallo dendrimers as Promising Anticancer Drugs</b> <i>Nádia Nunes</i>
16:35	17:20		<b>Coffee Break &amp; Poster Session</b> <b>Exhibition Area – Room B</b>
			<b>Session 12</b> Chairman: Barbara Klajnert-Maculewicz
17:20	17:45	IOC17	<b>Topology, Amphiphilicity and Dendronization of Carbosilane Dendritic Systems in Biomedical Applications</b> <i>Rafael Gómez</i>
17:45	18:05	OC11	<b>Fighting Resistant Cancer with Carbosilane Metallo dendrimers</b> <i>Sandra García-Gallego</i>
18:05	18:20	YS9	<b>Synthesis, Self-Assembling Properties, and Biomedical Applications of Amphiphilic Janus Glyco dendrimers</b> <i>Leila Mousavifar</i>
18:20	18:45	IOC18	<b>Dendrimeric Microsponge Based Topical Gel of Dithranol</b> <i>Pushpendra Tripathi</i>


**Thursday, 18<sup>th</sup> July 2019 – ROOM A**

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

11:35	12:05		Coffee Break
12:05	12:50	KN9	<b>Simplifying the Assembly of Dendritic and Fractal Constructs</b> <i>George Newkome</i> Chairman: Anne-Marie Caminade
12:50	13:35		Closing session & Poster Awards

**Thursday, 18<sup>th</sup> July 2019 – ROOM C (Parallel session)**

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

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

# HONOR COMMITTEE

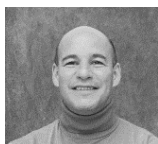
---



Dr. Jorge Carvalho (Regional Secretary for Education)



Professor José Carmo (Rector of the University of Madeira)



Professor Nuno Nunes (Head of ARDITI)



Dr. Carlos Lopes (Startup Madeira CEO)





# INTERNATIONAL ADVISORY COMMITTEE

---

**Ana Paula Pêgo**, Ph.D.

i3S - Instituto de Investigação e Inovação em Saúde, University of Porto, Portugal

**Anne-Marie Caminade**, Ph.D.

CNRS Toulouse, France

**Ashok Kakkar**, Ph.D.

McGill University, Montréal, Canada

**Barbara Klajnert-Maculewicz**,  
Ph.D.

University of Lodz, Poland

**Dietmar Appelhans**, Ph.D.

Leibniz Institute of Polymer Research Dresden, Germany

**Donald Tomalia**, Ph.D.

NanoSynthons LLC, National Dendrimer & Nanotechnology Center, USA

**George R. Newkome**, Ph.D.

Center for Molecular Biology and Biotechnology at Florida Atlantic University (FAU), USA

**Helena Tomás**, Ph.D.

CQM - Centro de Química da Madeira, University of Madeira, Funchal, Portugal

**Jean-Pierre Majoral**, Ph.D.

CNRS Toulouse, France

**João Rodrigues**, Ph.D.

CQM - Centro de Química da Madeira, University of Madeira, Funchal, Portugal & Northwestern Polytechnical University, Xi'an, China

**Jørn B. Christensen**, Ph.D.

University of Copenhagen, Denmark

**Klaus Müllen**, Ph.D.

Max Planck Institute for Polymer Research, Mainz, Germany

**Ling Peng**, Ph.D.

CNRS Marseille, France

**M<sup>a</sup> Ángeles Muñoz**, Ph.D.

Hospital Universitario Gregorio Marañon, Madrid, Spain

**Michael Malkoch**, Ph.D.

KTH Royal Institute of Technology, Stockholm, Sweden

**René Roy**, Ph.D.

University of Québec, Montréal, Canada

**Serge Mignani**, Ph.D.

Université Paris Descartes, France & University of Madeira, Funchal, Portugal

**Xiangyang Shi, Ph.D.**

Donghua University, Shanghai, China  
& University of Madeira, Funchal,  
Portugal

**Chai-Lin Kao, Ph.D.**

Kaohsiung Medical University,  
Taiwan, China

**Maria Francesca Ottaviani, Ph.D.**

University of Urbino, Italy

**Deyue Yan, Ph.D.**

Shanghai Jiaotong University, China

**Xuesi Chen, Ph.D.**

Chinese Academy of Sciences, China

**Xinyuan Zhu, Ph.D.**

Shanghai Jiaotong University, China

**Youqing Shen, Ph.D.**

Zhejiang University, China

**Xiqun Jiang, Ph.D.**

Nanjing University, China

**Zhongwei Gu, Ph.D.**

Nanjing Tech University, China

## SYMPOSIUM CHAIRPERSON

---

**João Rodrigues, CQM** - Centro de Química da Madeira, University of Madeira, Funchal, Portugal & Northwestern Polytechnical University, Xi'an, China.

# ORGANIZING COMMITTEE

---

**Helena Tomás, Ph.D.**

Director of the Organizing  
Committee

University of Madeira/CQM  
Portugal

**Mara Gonçalves, Ph.D.**

Vice-Director of the Organizing  
Committee, University of  
Madeira/CQM  
Portugal

**Carla Alves, Ph.D.**

University of Madeira/CQM  
Portugal

**Dina Maciel, Ph.D. Student**

University of Madeira/CQM  
Portugal

**Cláudia Camacho, Ph.D. Student**

University of Madeira/CQM  
Portugal

**Ana Olival, Ph.D. Student**

University of Madeira/CQM  
Portugal

**Nádia Nunes, M.Sc.**

University of Madeira/CQM  
Portugal

**Filipe Olim, M.Sc.**

University of Madeira/CQM  
Portugal

**Ivo Martins, M.Sc.**

University of Madeira/CQM  
Portugal

**Ana Neves, Ph.D.**

University of Madeira/CQM  
Portugal

**Rosa Perestrelo, Ph.D.**

University of Madeira/CQM Portugal

**Rita Castro, Ph.D.**

University of Madeira/CQM  
Portugal

**Mariana Vieira, Ph.D.**

University of Madeira/CQM  
Portugal

**Lydia dos Orfãos, M.Sc. Student**

University of Madeira/CQM  
Portugal

**Francisco Santos, Underg.**

Student  
University of Madeira/CQM  
Portugal

**Carolina Rodrigues, Underg.**

Student  
University of Lisbon/IST  
Portugal

**Énio Freitas, B.Sc.**

University of Madeira staff  
Portugal

**Bruna Pereira, M.Sc.**

CQM staff

Portugal

**João Serina, M.Sc.**

CQM staff

Portugal

**Débora Reis, M.Sc.**

CQM staff

Portugal

**Sara Bettencourt, M.Sc.**

CQM staff

Portugal

**David Quintal, B.Sc**

CQM staff

Portugal

# 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).

# 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<sup>1,2,3</sup>

<sup>1</sup>NanoSynthons LLC, National Dendrimer & Nanotechnology Center, Mt. Pleasant, MI USA.

E-mail: donald.tomalia@gmail.com

<sup>2</sup>Adjunct Professor (Chemistry), University of Pennsylvania, Philadelphia, PA USA.

<sup>3</sup>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 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.

## References

- [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.
- [3] Rosen, B. M. et al. *J. Am. Chem. Soc.*, **2009**, *131*, 17500.
- [4] Ahnert, S. E. et al. *Science*, **2015**, *350*, 6266.
- [5] Rahman, A.; Rahman, A.K.; Tomalia, D.A. *Nanoscale Horiz.*, **2017**, *2*, 127.
- [6] a) Tomalia, D. A. et al. *Prog. Polym. Sci.*, **2019**, *90*, 35. b) Konopka, M. et al. *J. Nanopart. Res.*, **2018**, *20*, 220.



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

Roy & Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104-6323. E-mail: percec@sas.upenn.edu

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].

### References

- [1] a) Rosen, B. M. et al. *Chem. Rev.*, **2009**, *109*, 6275. b) Shermann, S. E.; Xiao, Q.; Percec, V. *Chem. Rev.*, **2017**, *117*, 6538. c) Zeng, X. B. et al. *Nature*, **2004**, *428*, 157. d) Ungar, G. et al. *Science*, **2003**, *299*, 1208. e) Hudson, S.D. et al. *Science*, **1997**, *278*, 449. f) Percec, V. et al. *Nature*, **1998**, *391*, 161. g) Rosen, B. M. et al. *Chem. Rev.*, **2011**, *111*, 1346. h) Jezorek, R. L. et al. *Org. Lett.*, **2014**, *16*, 6326. i) Peterca, M. et al. *ACS Nano*, **2016**, *10*, 10480. j) Sahoo, D. et al. *ACS Nano*, **2017**, *11*, 983. k) Roche, C. et al. *J. Am. Chem. Soc.*, **2014**, *136*, 7169. l) Roche, C. et al. *Nature Chem.*, **2016**, *8*, 80.
- [2] a) Percec, V. et al. *J. Science*, **2010**, *328*, 1009. b) Percec, V. et al. *Nature*, **2012**, *419*, 384. c) Percec, V. et al. *Nature*, **2004**, *430*, 764.
- [3] a) Yadavalli, S. S. et al. *Proc. Natl. Acad. Sci. U.S.A.* **2019**, *116*, 744. b) Rodriguez-Emmenegger, C. et al. *Proc. Natl. Acad. Sci. U.S.A.* **2019**, *116*, 5376.



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.

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

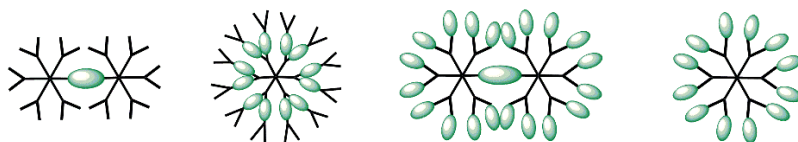
Anne-Marie Caminade<sup>1</sup>, Jean-Pierre Majoral<sup>1</sup>, Aurélien Hameau<sup>1</sup>, Artem Zibarov<sup>1</sup>, Mireille Blanchard-Desce<sup>2</sup>, Jean-Baptiste Verlhac,<sup>2</sup> Justin Teissié<sup>3</sup> & Muriel Golzio<sup>3</sup>

<sup>1</sup>Laboratoire de Chimie de Coordination (LCC), CNRS, 205 Route de Narbonne, BP 44099, 31077 Toulouse Cedex 4, France. E-mail: anne-marie.caminade@lcc-toulouse.fr

<sup>2</sup>Institut des Sciences Moléculaires, Université de Bordeaux, Bat A12, 351 Cours de la Libération, 33400 Talence, France.

<sup>3</sup>Institut de Biologie et de Pharmacologie Structurale (IPBS), 205 Route de Narbonne, BP 64182, 31077 Toulouse Cedex 4, France.

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.

### References

- [1] Caminade, A. M.; Hameau, A.; Majoral, J. P. *Chem. Eur. J.*, **2009**, *15*, 9270.
- [2] Krishna, T. R. et al. *Angew. Chem. Int. Ed.*, **2006**, *45*, 4645.
- [3] Mignani, S. et al. *Eur. J. Med. Chem.*, **2017**, *132*, 142.
- [4] Sourdon, A. et al. *Chem. Eur. J.*, **2019**, *25*, 3637.



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).

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

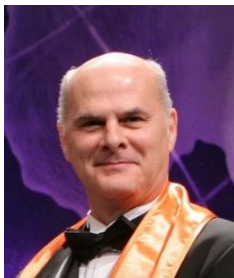
Jean-Pierre Majoral

Laboratoire Chimie de Coordination CNRS 205 route de Narbonne, 31077 Toulouse cedex 4.  
E-mail: jean-pierre.majoral@lcc-toulouse.fr

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 his 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 he 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.

## Novel Hybrid Dendrimers Harboursing Sugar Triads at the Periphery

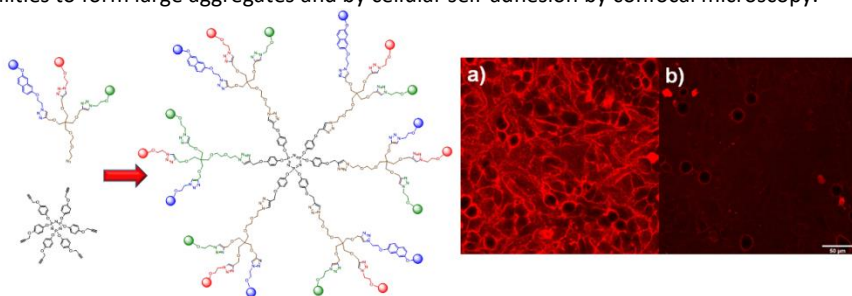
René Roy<sup>1,2,3\*</sup> & Rahul S. Bagul<sup>1</sup>

<sup>1</sup>Department of Chemistry, Université du Québec à Montréal, P.O. Box 8888, Succ. Centre-Ville, Montréal, Québec H3C 3P8, Canada. E-mail: roy.rene@uqam.ca

<sup>2</sup>INRS-Institut Armand-Frappier, Université du Québec, 531 boul. des Prairies, Laval, Québec, H7V 1B7, Canada.

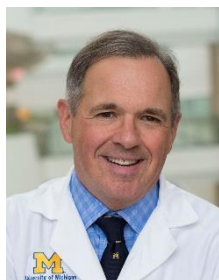
<sup>3</sup>Glycovax Pharma Inc., 424 Guy, Suite 202, Montreal, Quebec, Canada, H3J 1S6.

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.



### References

- [1] Chabre, Y. M.; Roy, R. *Chem. Soc. Rev.*, **2013**, 42, 4657.
- [2] Imbert, A.; Chabre, Y. M.; Roy, R. *Chem. Eur. J.*, **2008**, 14, 7490.
- [3] Chabre, Y. M.; Roy, R. *Curr. Top. Med. Chem.*, **2008**, 14, 1237.
- [4] Roy, R.; Shiao, T. C.; Rittenhouse-Olson, K. B. *J. Pharm. Sci.*, **2013**, 49, 85.
- [5] Roy, R.; Shiao, T. C. *Chem Soc. Rev.*, **2015**, 44, 3924.
- [6] Sharma, R. et al. *Polym. Chem.*, **2014**, 5, 4321.
- [7] Sharma, R. et al. *Polym. Chem.*, **2015**, 6, 1436.



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.



## Nanotechnology Therapeutics: Moving Towards the Clinic

James R. Baker Jr.

Michigan Nanotechnology Institute for Medicine and Biological Sciences, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan 48109, USA.

E-mail: jrbakerjr@umich.edu

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 combinatorial 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.

## Supramolecular Dendrimers for Nanomedicine

Ling Peng

Centre Interdisciplinaire de Nanoscience de Marseille, Aix-Marseille University, CNRS, 163 Avenue de Luminy, 13288 Marseille, France. E-mail: ling.peng@univ-amu.fr

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<sup>1</sup> 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.

### References

- [1] a) Wei, T. et al. *Proc. Natl. Acad. Sci. U.S.A.*, **2015**, *112*, 2978. b) Zhou, Z. et al. *Chem. Comm.*, **2018**, 54, 5956.
- [2] a) Liu, X. et al. *Angew. Chem. Int. Ed.*, **2014**, *53*, 11822. b) Chen, C. et al. *Small*, **2016**, *12*, 3667. c) Liu, X. et al. *Adv. Funct. Mater.*, **2016**, *26*, 8594. d) Dong, Y. et al. *J. Am. Chem. Soc.*, **2018**, *140*, 16264.
- [3] Garrigue, P. et al. *Proc. Natl. Acad. Sci. U.S.A.*, **2018**, *115*, 11454.



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.

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

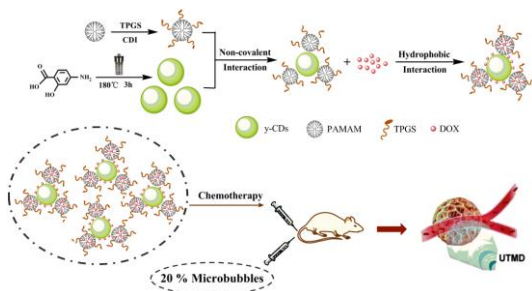
Dan Li<sup>1</sup>, Lizhou Lin<sup>2</sup>, Yu Fan<sup>1</sup>, Lianfang Du<sup>2\*</sup> & Xiangyang Shi<sup>1\*</sup>

<sup>1</sup>College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, Shanghai 201620, China. E-mail: xshi@dhu.edu.cn

<sup>2</sup>Department of Ultrasound, Shanghai General Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200080, China. E-mail: dulf\_sh@163.com

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- $\alpha$ -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 became 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.

## Simplifying the Assembly of Dendritic and Fractal Constructs

George R. Newkome<sup>1</sup> & Charles N. Moorefield<sup>2</sup>

<sup>1</sup>Center for Molecular Biology and Biotechnology, Florida Atlantic University, Jupiter, Florida 33458.  
E-mail: newkome@fau.edu

<sup>2</sup>Dendronex LLC, 109 Runway Drive, Reese Technology Center, Lubbock, Texas 79416 USA.

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-metallo dendrimers 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.

**Acknowledgements:** The authors gratefully acknowledge funding from the National Science Foundation (CHE-11511991) for the initial phases of this work and the James and Vanita Oelschlager support via The University of Akron.

### References

- [1] Newkome, G. R.; Moorefield, C. N. *Chem. Soc. Rev.*, **2015**, *44*, 3954.
- [2] Newkome, G. R.; Moorefield, C. N.; Chakraborty, S. J. *Inorg. Organomet. Polym. Mater.*, **2018**, *28*, 360.
- [3] Chakraborty, S.; Newkome, G. R. *Chem. Soc. Rev.*, **2018**, *47*, 3991.
- [4] Chakraborty, S. et al. *Dalton Trans.*, **2018**, *47*, 14189.
- [5] Newkome, G. R.; Moorefield, C. N.; Xie, T.; Lu, X. *U. S. Pat.* 10,208,069 (2/19/2019).





# IDS11 IOC: INVITED ORAL COMMUNICATIONS

---

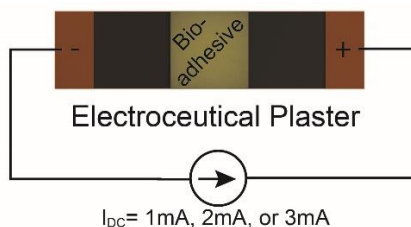


## Voltage Initiated Tissue Adhesive Dendrimers

Terry W. J. Steele, Manisha Singh & Nigel Tan

School of Materials Science & Engineering Nanyang Technological University N4.1-01-29,  
50 Nanyang Avenue, Singapore 639798. E-mail: wjsteele@ntu.edu.sg

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.

### References

- [1] Singh, S. et al. *Adv Healthcare Mater.*, **2018**, 7, 1800538.
- [2] Gan, L. et al. *Macromolecules*, **2018**, 51, 6661.
- [3] Gao, F. et al. *Molecules*, **2018**, 23, 796.
- [4] Nanda, H. S. et al. *Biomacromolecules*, **2018**, 19, 1425
- [5] Feng, G. et al. *Macromol. Biosci.*, **2016**, 16, 1072.

## Dendritic Micelles as a Versatile Platform for Drug Delivery

Rana Sanyal<sup>1,2</sup>

<sup>1</sup>Bogazici University, Department of Chemistry, Bebek, 34342, Istanbul, Turkey.

<sup>2</sup>Bogazici University, Center for Life Sciences and Technologies, Istanbul, Turkey.

E-mail: rana.sanyal@boun.edu.tr

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 properties 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.

**Acknowledgements:** TUBITAK, Scientific and Technological Research Council of Turkey (Project 107T623) is for providing the funding that made this work possible. Presidency of Republic of Turkey Directorate of Strategy and Budget (Project 2009K120520) is acknowledged for their contribution to the infrastructure.

### References

- [1] Altin, H.; Kosif, I.; Sanyal, R. *Macromolecules*, **2010**, *43*, 3801.
- [2] Kaga, S.; Yapar, S.; Gecici, E. M.; Sanyal, R. *Macromolecules*, **2015**, *48*, 5106.
- [3] Kaga, S.; Gevrek, T. N.; Sanyal, A.; Sanyal, R. *J. Polym. Sci. Part A: Polym. Chem.*, **2016**, *54*, 926.
- [4] Bolu, B. S.; Gecici, E. M.; Sanyal, R. *Mol. Pharmaceutics*, **2016**, *13*, 1482.
- [5] Bolu, B. S. et al. *Bioconjugate Chem.*, **2017**, *28*, 2962.
- [6] Calik, F. et al. *Bioconjugate Chem.*, **2019**, *30*, 1087.

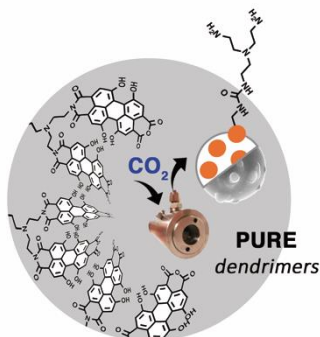
## Polyurea Dendrimers: Carriers, Killers and Cell Kickers

Vasco D. B. Bonifácio

CQFM-IN and IBB-Institute for Bioengineering and Biosciences, Instituto Superior Técnico, Universidade de Lisboa, Lisboa, Portugal. E-mail: [vasco.bonifacio@tecnico.ulisboa.pt](mailto:vasco.bonifacio@tecnico.ulisboa.pt)

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 human stem cells differentiation.



**Acknowledgements:** We thank Fundação para a Ciência e a Tecnologia (FC&T, Lisbon) for financial support through project PTDC/MEC-ONC/29327/2017.

### References

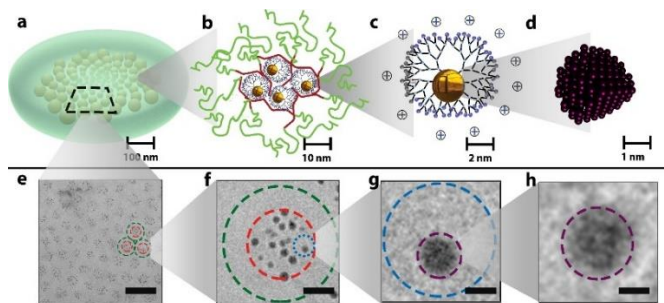
- [1] Restani, R. B. et al. *Angew. Chem. Int. Ed.*, **2012**, 51, 5162.
- [2] Pires, R. F. et al. *ChemistrySelect.*, **2016**, 1, 6818.
- [3] Restani, R. B. et al. *Macromol. Biosci.*, **2015**, 15, 1045.
- [4] Restani, R. B. et al. *RSC Adv.*, **2014**, 4, 54872.
- [5] Restani, R. B. et al. *Part. Part. Syst. Charact.*, **2016**, 33, 851.
- [6] Restani, R. B. et al. *ChemistryOpen*, **2018**, 7, 772.
- [7] Bragança, A. et al. *Part. Part. Syst. Charact.*, **2015**, 32, 98.

## DENdrimicelles: Dendrimer-Encapsulated-Nanoparticle Coacervate-core Micelles

Jan Bart ten Hove<sup>1</sup>, Fijs van Leeuwen<sup>2</sup> & Aldrik Velders<sup>3</sup>

<sup>1,2,3</sup>Laboratory of BioNanoTechnology, Wageningen University, Wageningen, The Netherlands.  
Leiden University Medical Centre, Leiden, The Netherlands. E-mail: aldrik.velders@wur.nl

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].

### References

- [1] ten Hove, J. B.; Wang, J.; van Leeuwen, F. W. B.; Velders, A. H. *Nanoscale*, **2017**, 11, 18619.
- [2] ten Hove, J. B.; Wang, J.; van Oosterom, M.; van Leeuwen, F. W. B.; Velders, A. H. *ACS Nano*, **2017**, 11, 11225.
- [3] ten Hove, J. B.; van Oosterom, M. N.; van Leeuwen, F. W. B.; Velders, A. H. *Sci. Rep.*, **2018**, 13820.
- [4] ten Hove, J. B.; van Leeuwen, F. W. B.; Velders, A. H. *Nat. Commun.*, **2018**, 5207.

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

Alba Martinez<sup>1</sup>, Rafael Ceña-Diez<sup>1</sup>, M<sup>a</sup> Jesús Serramía-Lobera<sup>1</sup>, Rafael Gómez<sup>2</sup>, F. Javier de la Mata<sup>2</sup>, Carlos Guerrero-Beltrán<sup>1</sup>, Manuel Leal<sup>3</sup> & M<sup>a</sup> Ángeles Muñoz-Fernández<sup>1</sup>

<sup>1</sup>Section Immunology, ImmunoMolecular Laboratory. Hospital General Universitario Gregorio Marañón, CIBER BBN, Spanish HIV HGM BioBank. Madrid, Spain.

E-mail: mmunoz.hgugm@gmail.com

<sup>2</sup>Universidad Alcalá de Henares. Madrid, Spain.

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.

### References

- [1] Cena-Diez, R. et al. *Int. J. Nanomedicine*, **2016**, *11*, 2147.
- [2] Chonco, L. et al. *J. Control Release*, **2012**, *161*, 949.
- [3] Briz, V. et al. *Nanoscale*, **2015**, *7*, 14669.
- [4] Sepulveda-Crespo, D. et al. *Nanomedicine*, **2015**, *11*, 1299.

## Lymph Node Delivery Using Anionic Dendrimers

Chie Kojima

Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University. 1-2 Gakuen-cho, Naka-ku, Sakai, Osaka 599-8570, Japan. E-mail: kojima@chem.osakafu-u.ac.jp.

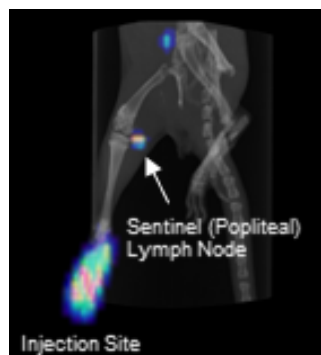
The sentinel lymph node (SLN), the first lymph node draining tumor cells, is a key tissue in cancer diagnosis and therapy. We have prepared dendrimeric imaging agents for the delivery into SLN. Previously, 12 types of dendrimer of different generations (G2, G4, G6, and G8) and different terminal groups (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 dendrimers (P-den), were prepared and compared to the accumulation into lymph node.

These anionic dendrimers were prepared using G5 PAMAM dendrimer, and labeled with a green-fluorescent dye or a radioactive  $^{111}\text{In}$  chelate. These dendrimers were intradermally administrated to the footpads of mice. 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 fluorescence 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).

### References

[1] Niki, Y. et al. *Nanomedicine*, **2015**, *11*, 2119.



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



## Self-Assembly of Amphiphilic Dendrimers: From Dendromicelles to Dendrimersomes

Oleg V. Borisov<sup>1</sup>, Inna O. Lebedeva<sup>1,2</sup> & Ekaterina B. Zhulina<sup>3</sup>

<sup>1</sup>Institut des Sciences Analytiques et de Physico-Chimie pour l'Environnement et les Matériaux, UMR 5254 CNRS UPPA. 2 av. P.Angot, 64053 Pau, France. E-mail: oleg.borisov@univ-pau.fr

<sup>2</sup>Peter the Great St.Petersburg State Polytechnic University. Polytekhnicheskaya 29, 195251, St.Petersburg, Russia. E-mail: innale92@gmail.com

<sup>3</sup>Institute of Macromolecular Compounds of the Russian Academy of Sciences, Bolshoy pr.31, 199004, St.Petersburg, Russia. E-mail: kzhulina@hotmail.com

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 functionalizable 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.

### References

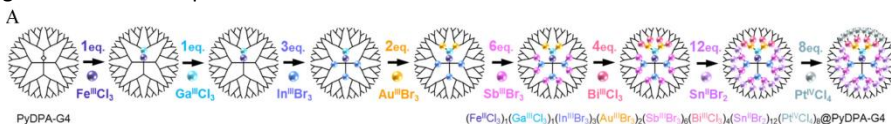
[1] Lebedeva, I. O.; Zhulina, E. B.; Borisov, O.V. *ACS Macro Letters*, **2018**, 7, 811.

## Dendrimers for Multimetallic Nanomaterials

Kimihisa Yamamoto

Tokyo Institute of Technology, 4259 Nagatsuta, Yokohama 226-8503, Japan.  
E-mail: yamamoto@res.titech.ac.jp

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 metalhalides more than 50 as a Lewis acid such as  $\text{SnCl}_2$  and  $\text{FeCl}_3$ , 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 metalhalides 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 dendrimer with a pyridine unit at the core. Lewis acidity of metal salts:  $\text{FeCl}_3 > \text{GaCl}_3 > \text{InBr}_3 > \text{AuBr}_3 > \text{SbBr}_3 > \text{BiCl}_3 > \text{SnBr}_2 > \text{PtCl}_4$ . Layer-by-layer stepwise complexation.

### References

Yamamoto, K. et al. *Nature. Commun.* **2018**, 9, 3758; **2018**, 9, 3873; **2017**, 8, 688; **2017**, 8, 749; **2017**, 8, 2046; **2013**, 4, 2581, *Science Adv.* **2017**, 3, e1700101; **2016**, 2, e1601414, *Acc. Chem. Res.*, **2014**, 47, 1127.

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

Xiaoxuan Liu<sup>1</sup> & Ling Peng<sup>2</sup>

<sup>1</sup>State Key Laboratory of Natural Medicines and Jiangsu Key Laboratory of Drug Discovery for Metabolic Diseases, Center of Advanced Pharmaceuticals and Biomaterials, China Pharmaceutical University, 210009 Nanjing, P. R. China. Email: xiaoxuanliucpu@163.com

<sup>2</sup>Aix-Marseille Université, CINaM, CNRS UMR 7325, Equipe Labellisé par La Ligue, Campus Scientifique de Luminy, Case 913, 13288 Marseille Cedex 9, France.

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.

### References

- [1] Stewart, M. P. et al. *Nature*, **2016**, 538, 183.
- [2] Wittrup, A.; Lieberman, J. *Nat. Rev. Genet.*, **2015**, 16, 543.
- [3] Yu, T. et al. *Angew. Chem. Int. Ed.*, **2012**, 51, 8478.
- [4] Liu, X. et al. *Angew. Chem. Int. Ed.*, **2014**, 53, 11822.
- [5] Liu, X. et al. *Adv. Funct. Mater.*, **2016**, 25, 8594.
- [6] Dong, Y. et al. *J. Am. Chem. Soc.*, **2018**, 140, 16264.

## Cationic Carbosilane Dendrimers Designed for Applications

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

<sup>1</sup>Institute of the Chemical Process Fundamentals of the CAS, v.v.i., Rozvojová 135, 165 02 Prague 6, Czech Republic. E-mail: krupkova@icpf.cas.cz

<sup>2</sup>Jan Evangelista Purkyně University in Ústí nad Labem, Pasteurova 1, 400 96 Ústí nad Labem, Czech Republic.

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<sub>2</sub> 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.

**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).

### References

- [1] Herma, R. et al. *J. Int. J. Pharm.*, **2019**, 562, 51.
- [2] Müllerová, M. et al. *New J. Chem.*, **2018**, 42, 1187.

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

Victoria Leiro<sup>1,2</sup>, Sofia Santos<sup>1,2</sup>, Ana Spencer<sup>1,2,3</sup>, Marília Torrado<sup>1,2,4</sup>, Beatriz Custódio<sup>1,2</sup>, Natália Magalhães<sup>1,2</sup>, Pedro Costa<sup>1,2</sup>, Sara Reis<sup>1,2</sup> & Ana Paula Pêgo<sup>1,2,3,4</sup>

<sup>1</sup>i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Rua Alfredo Allen, 208, 4200-135 Porto, Portugal; E-mail: apegop@i3s.up.pt

<sup>2</sup>INEB – Instituto de Engenharia Biomédica.

<sup>3</sup>Faculdade de Engenharia da Universidade do Porto (FEUP).

<sup>4</sup>Instituto de Ciências Biomédicas Abel Salazar (ICBAS), Universidade do Porto, Porto, Portugal.

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, 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 deliver nucleic acids to the brain in the aftermath of a stroke event. The application of novel nanotechnological 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).

### References

[1] Pêgo, A.P., Leiro, V. et al, inventors; Biodegradable Dendritic Structure, Methods and Uses Thereof 2017 PP 2017. WO/2017/203437 A1.

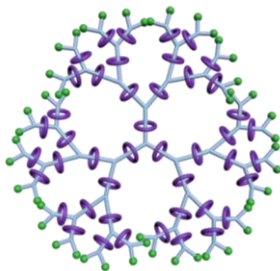
## Rotaxane-branched Dendrimers

Hai-Bo Yang

East China Normal University, 3663 N. Zhongshan Road, Shanghai, 200062, China.

E-mail: hbyang@chem.ecnu.edu.cn

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.

### References

- [1] a) Lee, J. K.; Kim, K. *Top Curr. Chem.*, **2003**, 228, 111. b) Leung, K. C.-F.; Lau, K.-N. *Poly. Chem.*, **2010**, 1, 988.
- [2] Wang, W. et al. *PNAS*, **2015**, 112, 5597.
- [3] Wang, X.-Q. et al. *Nat. Commun.*, **2018**, 9, 3190.

## Radical Dendrimers: Biomedical Applications

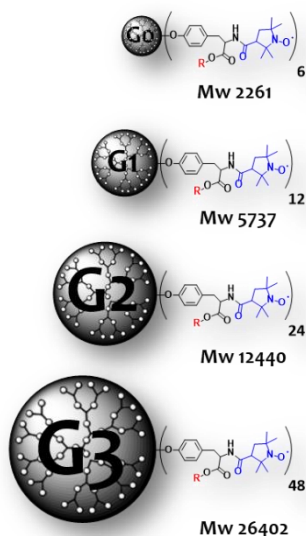
José Vidal-Gancedo, Vega Lloveras, Luiz F. Pinto & Flonja Liko

Instituto de Ciencia de Materiales de Barcelona – CSIC. Campus UAB, 08193 Bellaterra, Barcelona, Spain and CIBER – BBN, Barcelona, Spain. E-mail: j.vidal@icmab.es

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.



### References

[1] a) Badetti, E. et al. *Org. Lett.*, **2013**, 15, 3490. b) Badetti, E. et al. *Macromolecules*, **2014**, 47, 7717. c) Lloveras, V.; Badetti, E.; Wurst, K.; Vidal-Gancedo, J. *Chem. Phys. Chem.*, **2015**, 16, 3302. d) Lloveras, V.; Badetti, E.; Veciana, J.; Vidal-Gancedo, J. *Nanoscale*, **2016**, 8, 5049. e) Lloveras, V. et al. *Chem. Phys. Chem.*, **2018**, 19, 1895. f) Vidal-Gancedo, J. et al. *J. Am. Chem. Soc.*, **2019** submitted.

## Protective Effect of Neutral Phosphodendrimers on Experimental Autoimmune Encephalitis in Mice

Inmaculada Posadas<sup>1</sup>, Laura Romero Castillo<sup>1</sup>, Alberto Rábano<sup>2</sup>, Serge Mignani<sup>3,4</sup>, Jean-Pierre Majoral<sup>5</sup> & Valentín Ceña<sup>1,2</sup>

<sup>1</sup>Unidad Asociada Neurodeath, Universidad de Castilla-La Mancha. Albacete, Spain.  
E-mail: valentin.cena@gmail.com

<sup>2</sup>CIBERNED, Madrid, Spain. E-mail. arabano@fundacioncien.es

<sup>3</sup>Université Paris Descartes, Sorbonne Paris Cité, France. E-mail: serge\_mignani@orange.fr

<sup>4</sup>CQM - Centro de Química da Madeira, Universidade da Madeira, Funchal, Portugal.

<sup>5</sup>Laboratoire de Chimie de Coordination, CNRS, Toulouse Cedex 4, France.  
E-mail: jean-pierre.majoral@lcc-toulouse.fr

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 lymphocytic infiltration involving white matter at various levels of the CNS. When samples from the phosphodendrimer-treated animals were analyzed the inflammatory and demyelination 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.

### References

- [1] Kobelt, G.; Berg, J.; Atherly, D.; Hadjimichael, O. *Neurology*, **2006**, *66*, 1696.
- [2] Posadas, I. et al. *Proc. Natl. Acad. Sci. U. S. A.*, **2017**, *114*, E7660.
- [3] Stromnes, I. M. et al. *Nat. Med.*, **2008**, *14*, 337.

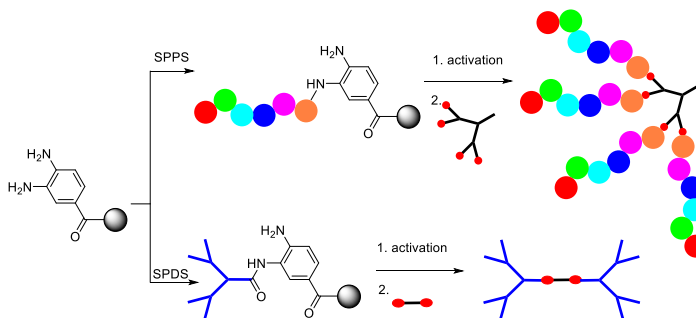


## Efficient Solid-Phase Synthesis of Peptide Dendrimers via On-Resin Ligation

Anard Salvaraj & Chai-Lin Kao

Department of Medicinal and Applied Chemistry, Kaohsiung Medical University. 100, Shiquan 1st Rd., Sanmin Dist., Kaohsiung City, Taiwan. E-mail: clkao@kmu.edu.tw

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 dendrimers *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.



### References

- [1] Huang, A. Y.-T. et al. *Chem. Commun.*, **2013**, 49, 5784.
- [2] Huang, A. Y.-T. et al. *Asian J. Org. Chem.*, **2016**, 5, 860.
- [3] Kao, C.-L.; Huang, Adela Y.-T.; Chen, H.-T. *Macromole. Rapid Commun.*, **2017**, 38, 1700062.
- [4] Selvaraj, A.; Chen, H.-T.; Huang, A. Y.-T.; Kao, C.-L. *Chem. Sci.*, **2018**, 9, 345.

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

Suhe Wang<sup>1</sup>, Jesse Chen<sup>1</sup>, Somnath Bhattacharjee<sup>1</sup>, Zhengyi Cao<sup>1</sup>, Scott Swanson<sup>2</sup> & James R. Baker Jr.<sup>1</sup>

<sup>1</sup>Michigan Nanotechnology Institute for Medicine and Biological Sciences, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan 48109, USA. E-mail: shidasui@umich.edu

<sup>2</sup>Department of Radiology, University of Michigan, Ann Arbor.

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  $21.3 \pm 6.04\%$  compared to G5-Gd enhancement of  $0.56 \pm 5.24\%$  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.

**Acknowledgements:** The authors gratefully acknowledge the financial support of UM-SJTU Seed Project Award. Also acknowledged for their contributions are Drs. Hong Zong and Han Wang.

### References

- [1] Rexer, B. N.; Arteaga, C. L. *Crit. Rev. Oncog.*, **2012**, 17,1.
- [2] Shukla, R. et al. *Bioconjugate Chem.*, **2006**, 17, 1109.
- [3] Mullen, D. G. et al. *ACS Nano.*, **2010**, 4, 657.

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

Rafael Gómez<sup>1,2,3</sup> & F. Javier de la Mata<sup>1,2,3</sup>

<sup>1</sup>Department of Organic and Inorganic Chemistry, Pharmacy Faculty, University of Alcalá de Henares. Ctra. Madrid-Barcelona km.33600, Spain. Institute of Chemical Research "Andrés M. del Río" (IQAR)  
E-mail: rafael.gomez@uah.es; javier.delamata@uah.es

<sup>2</sup>Networking Research Center on Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN) <sup>3</sup>Instituto Ramón y Cajal de Investigación Sanitaria, IRYCIS.

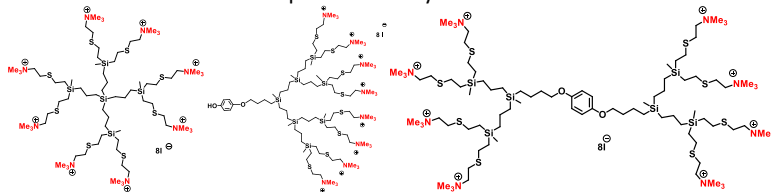
Dendrons have emerged as new dendritic topology and attracted much intention due to the different synthetic possibilities that can afford respecting to conventional spherical dendrimers [1]. Using dendrons as building blocks, several situations can be analysed:

(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) Amphiphilicity: 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 dendronized nanostructured 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.



**Acknowledgements:** This work was supported by grants from PIE14/00061 (INTERCIBER), CTQ2017-86224-P (MINECO), Consortiums NANODENDMED II-CM ref. B2017/BMD-3703 and IMMUNOTHERCAN-CM ref. B2017/BMD-3733 (CAM).

### References

- [1] Caminade, A. M.; Majoral, J.-P. *Molecules*, **2016**, *21*, 538.
- [2] Percec, V. et al. *ACS Nano*, **2014**, *8*, 1554

## Dendrimeric Microsponge Based Topical Gel of Dithranol

Pushpendra Tripathi & Shalini Tripathi

Dept. of Pharmacy, RITM, DR APJ Abdul Kalam Technical University, Lucknow, U.P, India 226031.  
E-mail: tripathi.pushpendra@rediffmail.com

Psoriasis, a chronic and even multisystem inflammatory disorder of skin or joints, is captured as a global concern by the World Health Organisation, and it has been estimated that more than 125 million patients are suffering with psoriasis worldwide [1]. Dithranol (1, 8-dihydroxy-9-anthrone) is a potential topical agent for psoriasis where Application of this agent relieves the patients for prolonged time with a low rate of recurrence [2]. The degradation of dithranol in the presence of oxygen, light, basic pH, and heavy metals, generates free radicals to cause harm to the biological tissues irritate deeply, staining on the patients' skin and clothes without producing any efficacy on psoriatic skin [3].

Microsponges are a unique delivery system for the controlled release of topical agents, which shows chemical affinity towards oil glands of the skin, thus resides on the skin for longer period. To avoid formation of oxidative inert products of dithranol, to improve solubility of the drug and permeability through skin, the present study envisaged formulation development and evaluation of microsponge based gel of dendrimer entrapped dithranol for topical delivery to bring new generation topical application. Dendrimers, one of the leading nanocarrier, are widely explored, highly branched, multifunctional, nano-sized, monodisperse polymer with special physicochemical properties and exterior functional surface groups.

Percentage yield of the formulation was found to be 66.28%, whereas encapsulation efficiency was ranged between 71.33% to 49.21%, and an average particle size was ranged between  $28 \pm 1.12 \mu\text{m}$  to  $130 \pm 1.01 \mu\text{m}$ . Surface morphology of developed microsponge was confirmed by scanning electron microscopy, revealed micro-porous nature. The optimized microsponge formulation was found to be stable and recorded non-irritant during cutaneous application of the experimental animals. Further, the pharmacokinetic outcomes of study were showed prolong penetration of the drug through the skin, equivalent to the marketed formulation of dithranol. Therefore, it could be conferred that the microsponge formulation of the PAMAM entrapped dithranol can produce prolonged efficacy without producing toxicities to the skin, and thus can effectively be projected in the treatment of diseases like psoriasis. Finally, this report presents topical delivery of microsponges based gel containing dithranol-dendrimer complex to increase the solubility, control oxidation and permeability dithranol through skin with extended release, reduced irritation and improved patient compliance, improved thermal, physical, and chemical stability.

**Acknowledgements:** Authors acknowledge to Dr Vinay Kumar Pathak, Hon' ble, Vice Chancellor, AKTU, Lucknow, for kind support.

### References

- [1] Takeshita, J. et al, *J. Invest. Dermatol.*, **2015**, 135, 2955.
- [2] Savian, A. L. et al., *Mater. Sci. Eng. C.*, **2015**, 46, 69.
- [3] Kemény, L. et al., *Skin Pharmacol. Physiol.* **1990**, 3, 1.

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

Kui Luo

Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital, Sichuan University, Chengdu 610041, China. E-mail: luokui@scu.edu.cn

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.

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

Dietmar Appelhans<sup>1</sup>, Johannes Fingernagel<sup>1</sup>, Susanne Boye<sup>1</sup>, Alben Lederer<sup>1,2</sup> & Brigitte Voit<sup>1,3</sup>

<sup>1</sup>Leibniz Institute of Polymer Research Dresden, Hohe Straße 6, D-01069 Dresden, Germany.

E-mail: applhans@ipfdd.de

<sup>2</sup>Department of Chemistry and Food Chemistry, Technische Universität Dresden, D-01062 Dresden, Germany.

<sup>3</sup>Organic Chemistry of Polymers, Technische Universität Dresden, D-01062 Dresden, Germany, Technische Universität Dresden, 01062 Dresden, Germany.

Over the last  $\geq 10$  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.

### References

- [1] Appelhans, D. et al. *Chem. Soc. Rev.*, **2015**, *44*, 3968.
- [2] Tietze, S. et al. *Small*, **2017**, *13*, 1700072.
- [3] Ennen, F. et al. *ACS Appl. Mater. & Interfaces*, **2016**, *8*, 6261.
- [4] Franiak-Pietryga, I. et al. *Mol. Pharmaceutics*, **2013**, *10*, 2490.

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

Mayank Kumar Singh<sup>1,4</sup>, Akella V. Subrahmanya Sarma<sup>2</sup>, M. Jerald Mahesh Kumar<sup>3</sup>, Ramakrishna Sistla<sup>1\*</sup> & Abhay Singh Chauhan<sup>5\*</sup>

<sup>1</sup>Department of Applied Biology, CSIR-Indian Institute of Chemical Technology, Hyderabad, India.  
E-mail: mayank89singh@gmail.com

<sup>2</sup>Department of Analytical Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad, India.

<sup>3</sup>Animal House Facility, CSIR-Centre for Cellular & Molecular Biology, Hyderabad, India

<sup>4</sup>Academy of Scientific and Innovative Research (AcSIR), New Delhi, India.

<sup>5</sup>Medical College of Wisconsin-School of Pharmacy, Milwaukee, WI, USA.

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.

### References:

- [1] Chauhan, A. S.; Kaul M. J. *Nanoparticle Res.*, **2018**, *20*, 226.
- [2] Chauhan, A. S.; Svenson, S. **2008**, WO2007149500, (A9).

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

Maciej Cieślak<sup>1</sup>, Magdalena Stolarska<sup>1</sup>, Katarzyna Trzeciak<sup>2</sup> & Zofia Urbanczyk-Lipkowska<sup>1</sup>

<sup>1</sup>Institute of Organic Chemistry, PAS, 01-224 Warsaw, Poland. E-mail: mcieslak@icho.edu.pl

<sup>2</sup>Centre of Molecular and Macromolecular Studies PAS, 90-363 Lodz, Poland.

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].

Based 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.

### References

- [1] Gao, Y.-G. et al. *Org. Biomol. Chem.*, **2018**, *16*, 7833.
- [2] Janiszewska, J. et al. *PLoS ONE*, **2016**, *11*.



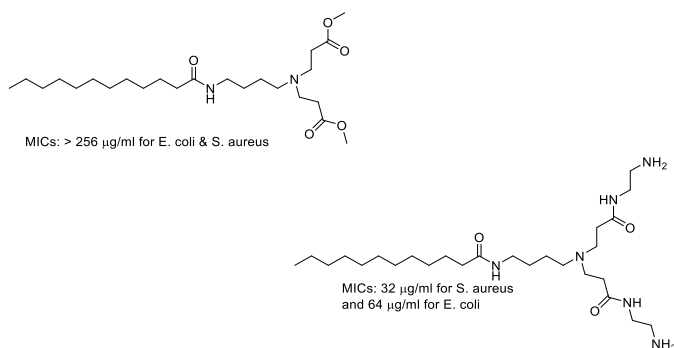
## Synthesis and Properties of Antimicrobial Dendrons

Jørn B. Christensen<sup>1</sup> & Rikke Heidemann Olsen<sup>2</sup>

<sup>1</sup>Department of Chemistry, Faculty of Science, University of Copenhagen. Thorvaldsensvej 40, DK-1871 Frederiksberg C, Denmark. E-mail: jbc@chem.ku.dk

<sup>2</sup>Department of Veterinary and Animal Science, Faculty of Health, Stigbøjlen 4, DK-1870 Frederiksberg C, Denmark.

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.

## Comparison of Carboxy-methylated G5\_PAMAM Dendrimer and Carboxy-methylated Polyethyleneimine Metal Complexes

Tamás S. Miklósi, Levente Novák, Virág Kiss & István Bányai

Department of Physical Chemistry, Faculty of Science and Technology, University of Debrecen, 4032 Debrecen, Egyetem t.1, Hungary. banyai.istvan@science.unideb.hu

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<sub>2</sub>COOH)<sub>2</sub> 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 relaxivities 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.

**Acknowledgements:** The research was supported by the EU and co-financed by the European Regional Development Fund under the projects GINOP-2.3.2-15-2016-00008 and GINOP-2.3.3-15-2016-00004.

### References

- [1] Wöhrle, D. Pomogailo, A.D. (Eds). *Metal Complexes and Metals in Macromolecules* Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2003.
- [2] Merbach, A. Helm, L. Tóth, É. (Eds) *The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging*, John Wiley & Sons, Ltd. 2013, p. 449.

# IDS11 OC: ORAL COMMUNICATIONS

---



## The Study of Polyamidoamine Dendrimer as Essential Oil Carrier

Hui-Ting Chen<sup>1</sup>, Yi-Ju Lu<sup>1</sup>, Yi-Chin Lo<sup>2</sup>, Po-Chu Wu<sup>3</sup> & Horng-Huey Ko<sup>1</sup>

<sup>1</sup>Department of Fragrance and Cosmetic Science. <sup>2</sup> Department, of Medicine. <sup>3</sup>Department of Pharmacy; Kaohsiung Medical University. 100, Shih-Chuan 1<sup>st</sup> Rd, Kaohsiung, Taiwan.

E-mail: htchen@kmu.edu.tw

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<sub>2.0</sub> and G<sub>3.0</sub> 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<sub>2.0</sub> and G<sub>3.0</sub> 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.

**Acknowledgements:** The authors appreciate the financial support from Ministry of Science and Technology, Taiwan. (MOST 107-2632-B-037-001).

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

Alena Krupková<sup>1,2</sup>, Petra Cuřínová<sup>1,2</sup>, Monika Müllerová<sup>1,2</sup>, Jan Čermák<sup>1,2</sup> & Tomáš Strašák<sup>1,2</sup>

<sup>1</sup>Institute of the Chemical Process Fundamentals of the CAS, v.v.i., Rozvojová 135, 165 02 Prague 6, Czech Republic. E-mail: krupkova@icpf.cas.cz

<sup>2</sup>Jan Evangelista Purkyně University in Ústí nad Labem, Pasteurova 1, 400 96 Ústí nad Labem, Czech Republic.

Polyionic synthetic 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 semiquantitative 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).

### References

- [1] Strašák, T. et al. *RSC Adv.*, **2017**, 7, 18724.
- [2] Herma, R. et al. *Int. J. Pharm.*, **2019**, 562, 51.
- [3] Cuřínová, P. et al. *J. Mass Spectrom.*, **2018**, 53, 986.

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

Noemi Molina<sup>1,2</sup>, Marvin Cnudde<sup>3</sup>, Juan A. Guadix<sup>4,2</sup>, Jose M. Perez-Pomares<sup>4,2</sup>, Cristian A. Strassert<sup>3</sup>, Ezequiel Perez-Inestrosa<sup>1,2</sup> & Yolanda Vida<sup>1,2</sup>

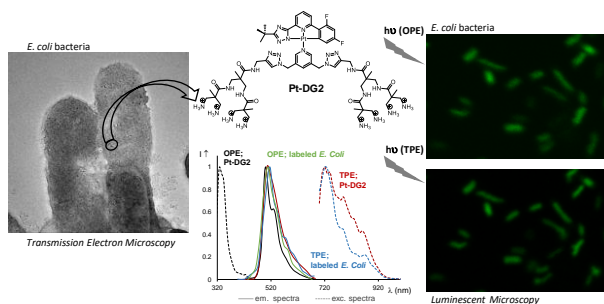
<sup>1</sup>Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Málaga - IBIMA, Campus de Teatinos s/n, 29071 Málaga, Spain. E-mail: nmolina@uma.es; inestrosa@uma.es; yolvida@uma.es

<sup>2</sup>Centro Andaluz de Nanomedicina y Biotecnología (BIONAND), Junta de Andalucía, Universidad de Málaga, C/ Severo Ochoa 35, 29590 Campanillas (Málaga), Spain.

<sup>3</sup>CeNTech – CiMIC - Institut für Anorganische und Analytische Chemie, W. W.-Universität Münster, Heisenbergstr. 11, D-48149 Münster, Germany. E-mail: m\_cnud01@wwu.de; ca.s@wwu.de

<sup>4</sup>Departamento de Biología Animal, Facultad de Ciencias, Universidad de Málaga - IBIMA, Campus de Teatinos s/n, 29071 Málaga, Spain. E-mail: jaguadix@uma.es; jmperezp@uma.es

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.



### References

[1] Ma, D.-L. et al. *Coord. Chem. Rev.*, **2012**, 256, 3087.

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

Zofia Urbanczyk-Lipkowska<sup>1</sup>, Maja Morawiak<sup>1</sup>, Marta Sowińska<sup>1</sup>, Maciej Cieślak<sup>1</sup>, Elżbieta Ziemska<sup>2</sup> & Barbara Zabłocka<sup>2</sup>

<sup>1</sup>Institute of Organic Chemistry, PAS, 01-224 Warsaw, Poland. E-mail: zofia.lipkowska@icho.edu.pl

<sup>2</sup>Mossakowski Medical Research Centre PAS, 02-106 Warsaw, Poland.

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.

### References

[1] Sowinska, M. *Biomolecules*, **2019**, 9, 89.



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

Anna Munder & Arie Gruzman

Department of Chemistry, Faculty of Exact Sciences, Bar-Ilan University, Ramat-Gan, Israel.  
E-mail: Aric-Lev.Gruzman@biu.ac.il

Both pancreatic  $\beta$ -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: neuurexins. These proteins participate in trans-cellular protein-protein interactions across the synaptic cleft. It was shown that  $\beta$ -cells express both neuroligins and neuurexins on their plasma membrane. It was also found that insulin secretion and the proliferation rate of  $\beta$ -cells increased when  $\beta$ -cells were co-cultured with cells overexpressing neuroligins. We propose that neuroligin-derived molecules arranged in clusters can enhance  $\beta$ -cell function and functional maturity, as well as protecting  $\beta$ -cells in stress conditions. To test this hypothesis, several peptides were derived from crystal structures of different neuroligins and neuurexins 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  $\beta$ -cell functions in terms of glucose-stimulated insulin secretion and protects them under stress conditions in vitro and ex vivo. [1]. Recruiting the  $\beta$ -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.

### References

[1] a) Munder, A. et al. *MedChemComm.*, **2019**, *10*, 280. b) Munder, A. et al. *ACS Appl. Mater. Interfaces*, **2017**, *9*, 1189. c) Shtriker, E. et al. *J. Nanoparticle Res.*, **2018**, *20*, 221.

## Mass Spectroscopy for Detailed and Precise Analysis of Dendrimers

Aura Tintaru<sup>1</sup>, Ling Peng<sup>2</sup> & Laurence Charles<sup>1</sup>

<sup>1</sup>Institut of Radical Chemistry - UMR7273, Aix-Marseille University, Campus Saint Jérôme, 13397 Marseille - France. E-mail: [aura.tintaru@univ-amu.fr](mailto:aura.tintaru@univ-amu.fr)

<sup>2</sup>Centre Interdisciplinaire de Nanoscience de Marseille - UMR7325, Aix-Marseille University, Campus Luminy, 13009 Marseille - France.

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.

### References

- [1] Tomalia, D. A.; Christensen, J. B.; Boas, U. Dendrimers, dendrons, and dendritic polymers: discovery, applications, and the future. Cambridge University Press: **2012**.
- [2] Svenson, S. *Chem. Soc. Rev.*, **2015**, *44*, 4131
- [3] Tintaru, A. et al. *Anal. Chim. Acta*, **2014**, *808*, 163.
- [4] Liu, X. et al. *Adv. Funct. Mater.*, **2016**, *26*, 8594.
- [5] Garrigue, P. et al. *PNAS*, **2018**, *115*, 11454.

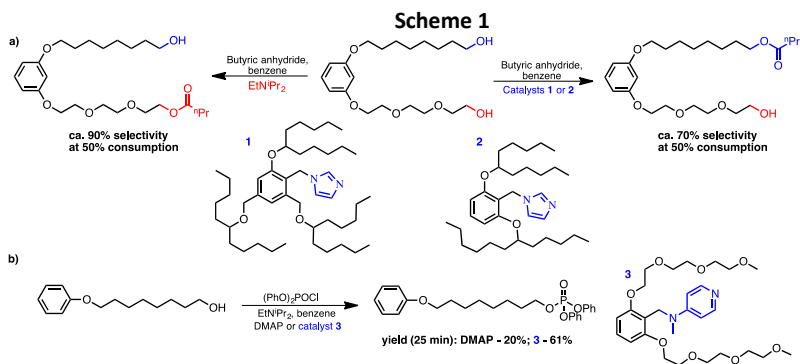
## In Quest for Better Selectivity and Activity: Nucleophilic Organocatalysts Based on Branched/Dendritic Design

Moshe Portnoy, Natali Ashush, Reut Fallek, Amit Fallek, & Mor Weiss-Shtofman

School of Chemistry, Tel Aviv University. Tel Aviv, 6997801, Israel. E-mail: portnoy@tauex.tau.ac.il

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).



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.

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

Julien Rossignol<sup>1,2,3\*</sup>, Melissa Andrews<sup>1,2</sup>, Melissa Resk<sup>1,2,4</sup>, Clayton Malkowski<sup>1,2</sup>, Thomas Fagan<sup>1,3</sup>, John Gallien<sup>1,2,3</sup>, Grant Raymor<sup>1,2</sup>, Sydney Climie<sup>1,2</sup>, Nikolas Munro<sup>1,2,4</sup>, Sindhuja Koneru<sup>1,2,4</sup>, Alexa Toth<sup>1,2</sup>, Nora Fettingner<sup>1,2</sup>, Bethany MacDonald<sup>1,2</sup>, Eric Kuhn<sup>1,3</sup>, Joseph Hellrung<sup>1,3</sup>, Justin Stadler<sup>1,2,3</sup>, Bhairavi Srinageshwar<sup>1,2,3</sup>, Balachandar Kathirvelu<sup>1,2,3</sup>, Douglas Swanson<sup>5</sup>, Gary Dunbar<sup>1,2,4,6</sup> & Ajit Sharma<sup>5</sup>

<sup>1</sup>Field Neurosciences Institute Laboratory for Restorative Neurology; <sup>2</sup>Program in Neuroscience; <sup>3</sup>College of Medicine; <sup>4</sup>Department of Psychology Central Michigan University, Mount Pleasant, MI; <sup>5</sup>Department of Chemistry & Biochemistry, Central Michigan University, Mount Pleasant, MI; <sup>6</sup>Field Neurosciences Inst., 4677 Towne Centre Rd. Suite 101 Saginaw, MI. E-mail: rossi1j@cmich.edu

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<sub>2</sub>) surface dendrimers, which are highly toxic to cells, we have designed and synthesized de novo, mixed-surface dendrimers with 10% -NH<sub>2</sub> 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 (IFN $\gamma$ ) 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.

**Acknowledgments:** Support for this study was provided by the American Heart Association AIREA grant (18AIREA33990094), Neuroscience program, the College of Medicine, the Field Neurosciences Institute, and the John G. Kulhavi Professorship in Neuroscience at CMU.

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

Evgeny Apartsin<sup>1,2</sup>, Valeria Arkhipova<sup>1,2</sup>, Javier Sánchez-Nieves<sup>3,4</sup>, F. Javier de la Mata<sup>3,4</sup> & Rafael Gómez<sup>3,4</sup>

<sup>1</sup>Institute of Chemical Biology and Fundamental Medicine SB RAS. 8, Lavrentiev ave., 630090 Novosibirsk, Russia. E-mail: eka@niboch.nsc.ru

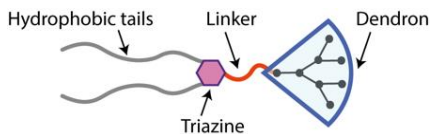
<sup>2</sup>Department of Natural Sciences, Novosibirsk State University. Novosibirsk, Russia.

<sup>3</sup>Departamento de Química Orgánica y Química Inorgánica, Universidad de Alcalá. Alcalá de Henares, Spain.

<sup>4</sup>Networking Research Center on Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN). Madrid, Spain.

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 disassembly 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.

**Acknowledgements:** This study was supported by RFBR grant 18-33-20109, by MINECO grant CTQ-2017-85224-P, by the grant of the President of RF MK-2278.2019.4.

## Dialytic Separation of Anions from DMSO Solution Facilitated by Dendritic Receptors

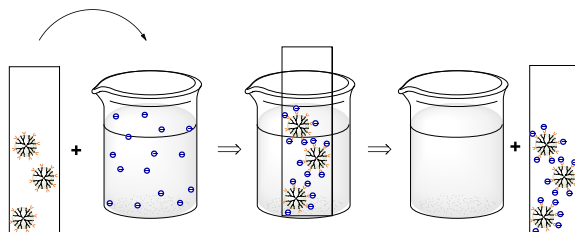
Petra Cuřínová<sup>1,2</sup>, Maximilian Winkler<sup>2</sup>, Jan Budka<sup>3</sup>, Chang Nga Wun<sup>3</sup>, Vratislav Blechta<sup>2</sup>, Lucie Červenková Šťastná<sup>1,2</sup>, Alena Krupková<sup>1,2</sup>, Jan Sýkora<sup>2</sup> & Tomáš Strašák<sup>1,2</sup>

<sup>1</sup>Jan Evangelista Purkyně University. Ústí nad Labem, Czech Republic. E-mail: curinova@icpf.cas.cz.

<sup>2</sup>Institute of Chemical Process Fundamentals of Czech Academy of Sciences, Prague. Czech Republic.

<sup>3</sup>Department of Organic Chemistry, University of Chemistry and Technology Prague, Czech Republic.

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 isophthalamidic 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).

### References

- [1] Busschaert, N.; Caltagirone, C.; Van Rossom, W.; Gale P. *Chem. Rev.*, **2015**, *115*, 8038.
- [2] Navakhun, K.; Sawangsri, R.; Ruangpornvisuti, V. *J. Mol. Struct.*, **2014**, *1061*, 32.
- [3] Strašák, T. et al. *RSC Adv.*, **2017**, *7*, 18724.

## Fighting Resistant Cancer with Carbosilane Metallodendrimers

Sandra García-Gallego<sup>1,3,4</sup>, Natalia Sanz del Olmo<sup>1</sup>, Marta Maroto-Díaz<sup>1</sup>, Ana M. Bajo<sup>2</sup>, Paula Ortega López<sup>1,3,4</sup>, Rafael Gómez<sup>1,3,4</sup> & F. Javier de la Mata<sup>1,3,4</sup>

<sup>1</sup>Department of Organic and Inorganic Chemistry and Research Institute in Chemistry “Andrés M. del Río” (IQAR), Faculty of Pharmacy, University of Alcalá, Madrid, Spain.

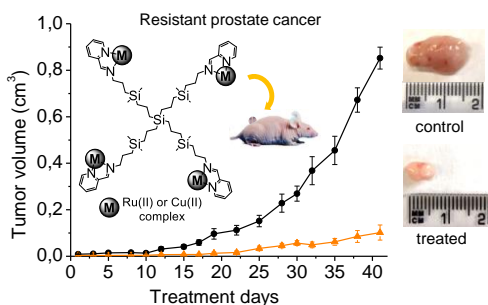
E-mail: sandra.garciagallego@uah.es

<sup>2</sup>Department of Biology of Systems, Biochemistry and Molecular Biology Unit, University of Alcalá.

<sup>3</sup>Network Research Center on Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Spain.

<sup>4</sup>Institute Ramón y Cajal for Health Research (IRYCIS), Spain.

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.

### References

- [1] a) Maroto-Díaz, M. et al. *Eur. Polym. J.*, **2019**, *113*, 229. b) Maroto-Díaz, M. et al. *Dalton Trans.*, **2016**, *45*, 7049.
- [2] a) Carloni, R. et al. *Manuscript in preparation*. **2019**. b) Sanz del Olmo, N. et al. *J. Inorg. Biochem.*, **2017**, *177*, 211.

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

Marijana Petković<sup>1</sup>, Duarte Fernandes<sup>1</sup>, Pedro Pires<sup>1</sup> & João Rodrigues<sup>1, 2</sup>

<sup>1</sup>CQM-Centro de Química da Madeira, Universidade da Madeira, Campus da Penteada, 9020-105 Funchal Portugal. E-mail: marijana.petkovic@staff.uma.pt

<sup>2</sup>School of Materials Science and Engineering/Center for Nano Energy Materials, Northwestern Polytechnical University, Xi'an 710072, China.

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.

### References

- [1] Mignani, S. et al. *Adv. Drug Delivery Rev.*, **2018**, 73, 136.
- [2] Müller, R. and Allmeier, G. *Rapid Commun. Mass Spectrom.*, **2006**, 20, 3803.
- [2] So, H.; Lee, J.; Han, S. Y.; Oh, H. B. *J. Am. Soc. Mass Spectrom.*, **2012**, 23, 1821.



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

Victoria Leiro<sup>1,2</sup>, Ana Patrícia Spencer<sup>1,2,3</sup>, Natália Magalhães<sup>1,2</sup> & Ana Paula Pêgo<sup>1,2,3,4</sup>

<sup>1</sup>INEB – Instituto de Engenharia Biomédica and <sup>2</sup>i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Rua Alfredo Allen, 208, 4200-135 Porto, Portugal.

E-mail: victoria.leiro@ineb.up.pt

<sup>3</sup>Faculdade de Engenharia da Universidade do Porto (FEUP), Porto, Portugal.

<sup>4</sup>Instituto de Ciências Biomédicas Abel Salazar (ICBAS), Universidade do Porto, Porto, Portugal.

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.

### References

- [1] Leiro, V. et al. *Adv. Funct. Mater.* **2018**, *28*, 1700313.
- [2] Leiro, V. et al. *Curr. Gene Ther.* **2017**, *17*, 105.
- [3] He, C. L. et al. *Adv Healthc Mater.* **2012**, *1*, 48.
- [4] Leiro, V. et al. *Bioconjug. Chem.* **2015**, *26*, 1182.
- [5] Leiro, V. et al. *J. Mat. Chem. B.* **2017**, *5*, 4901.
- [6] Pêgo, A.P., Leiro, V. et al, inventors; Biodegradable Dendritic Structure, Methods and Uses Thereof. **2017**, WO/2017/203437.



# IDS11 YSC: YOUNG SCIENTISTS COMMUNICATIONS

---



## Antibacterial Activity of Conjugates Between Antimicrobial Peptides and Cationic Carbosilane Dendrons

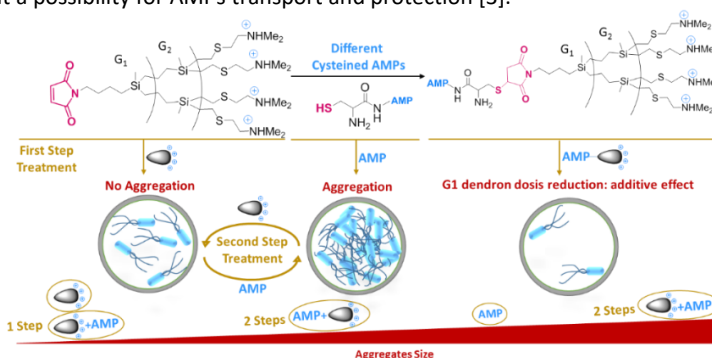
Jael Fernández<sup>1,2</sup>, G. Acosta<sup>2</sup>, D. Pulido<sup>2</sup>, J. L. Copa-Patiño<sup>5</sup>, J. Soliveri de Carranza<sup>5</sup>, M. Royo<sup>2</sup>, Rafael Gómez<sup>1,2</sup>, F. Albericio<sup>2</sup>, Paula Ortega López<sup>1,2\*</sup> & F. Javier de la Mata<sup>1,2</sup>

<sup>1</sup>Departamento Química Orgánica y Química Inorgánica, Universidad de Alcalá, Spain. Instituto de Investigación Química "Andrés M. del Río" (IQAR), Instituto Ramón y Cajal de Investigación Sanitaria, IRYCIS, UAH, Spain. Email: javier.delamata@uah.es

<sup>2</sup>Networking Research Center on Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN)

<sup>8</sup>Departamento Biomedicina y Biotecnología, Universidad de Alcalá, Spain.

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.

### References

- [1] Viswanathan VK. *Gut Microbes*, **2014**, 5, 3.
- [2] Ramesh, S. et al. *J Pept Sci.* **2016**, 22, 438.
- [3] Rasines B, Cuevas N, Ros J, Copa Patiño JL. *Dalton Trans.* **2009**, 40, 8704.

## PAMAM Dendrimers as Nanocarriers for Platinum Anticancer Complexes

Cláudia Camacho<sup>1</sup>, Helena Tomás<sup>1</sup> & João Rodrigues<sup>1,2\*</sup>

<sup>1</sup>CQM - Centro de Química da Madeira, MMRG, Universidade da Madeira. Campus da Penteada, 9020-105 Funchal, Portugal. E-mail: \*joaor@uma.pt

<sup>2</sup>School of Materials Science and Engineering/Center for Nano Energy Materials, Northwestern Polytechnical University, Xi'an 710072, China.

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).

### References

- [1] Ndagi, U., Mhlong, N., Soliman, M.E. *Drug Des. Devel. Ther.*, **2017**, *11*, 599.
- [2] Li, B. et al. *Chem. Sci.*, **2017**, *8*, 4458.

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

Dina Maciel<sup>1</sup>, Carlos Guerrero-Beltrán<sup>2</sup>, Rafael Ceña-Diez<sup>2</sup>, Helena Tomás<sup>1</sup>, M<sup>a</sup> Ángeles Muñoz-Fernández<sup>2</sup> & João Rodrigues<sup>1,3\*</sup>

<sup>1</sup>CQM - Centro de Química da Madeira, MMRG, Campus Universitário da Penteada, 9020-105 Funchal, Portugal. E-mail: \*joaor@uma.pt.

<sup>2</sup>Laboratorio de Inmunobiología Molecular, Hospital General Universitario Gregorio Marañón, Madrid, Spain. Instituto de Investigación Sanitaria Gregorio Marañón and Spanish HIV HGM BioBank, Madrid, Spain. Networking Research Center on Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Madrid, Spain.

<sup>3</sup>School of Materials Science and Engineering/Center for Nano Energy Materials, Northwestern Polytechnical University, Xi'an 710072, China.

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 <sup>1</sup>H-NMR. Afterwards, their cytotoxicity and antiviral activity were evaluated using the TZM.bl cell line and R5-HIV-1<sub>NLAD8</sub> and X4-HIV-1<sub>NL4.3</sub> isolates. The results showed that G1C and G1S dendrimers present high inhibition against R5-HIV-1<sub>NLAD8</sub> (more than 85%) and X4-HIV-1<sub>NL4.3</sub> isolates by blocking the entry of HIV-1. 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).

### References

- [1] Coutinho, C.; Sarmiento, B.; das Neves, J. J. *Controlled Release*, **2017**, 266, 119.
- [2] a) Singh, L. et al. *Ther. Adv Infectious Dis*, **2017**, 4, 105. b) Mignani, S. et al. *Chem. Soc. Rev.*, **2018**, 47, 514.

## Dendrimers Incorporating Lanthanide Cations as Near-Infrared Imaging Agents

Kamal Jouad<sup>1,2</sup>, Guillaume Collet<sup>3</sup>, Marie-Aude Hiebel<sup>1</sup>, Nabil El Brahmi<sup>2</sup>, Mohamed Akssira<sup>4</sup>, Svetlana V. Eliseeva<sup>3</sup>, Stéphane Petoud<sup>3,\*</sup>, Saïd El Kazzouli<sup>2,\*</sup> & Franck Suzenet<sup>1,\*</sup>

<sup>1</sup>Institut de Chimie Organique et Analytique UMR 7311, Université d'Orléans Rue de Chartres BP 6759 45067. Orléans Cedex 2 France. E-mail : \*kamal.jouad@etu.univ-orleans.fr

<sup>2</sup>Centre Euromed de Recherche, Université Euro-Méditerranéenne de Fès, Faculté Euromed de Génie, BP 51, 30000 Fès, Maroc.

<sup>3</sup>Centre de Biophysique Moléculaire UPR 4301 Rue Charles Sadron 45071. Orléans Cedex 2 France.

<sup>4</sup>Université Hassan II Casablanca. Faculté des Sciences et Techniques. Département de Chimie. B.P. 146 Mohammedia 28800 Maroc.

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.

### References

[1] Frangioni, J. V. *Curr. Opin. Chem. Biol.*, **2003**, 7, 626.

[2] Foucault-Collet, A. et al. *Proc. Natl. Acad. Sci.*, **2013**, 110, 17199.

[3] Dewald, J. R.; Tomalia, D. A. Dense Star polymers having core, core branches, terminal groups. 1985. U.S. Patent 4,507,466.



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

Ana Olival<sup>1</sup>, Helena Tomás<sup>1</sup> & João Rodrigues<sup>1,2\*</sup>

<sup>1</sup>CQM - Centro de Química da Madeira, MMRG, Universidade da Madeira, Campus da Penteada, 9020-105 Funchal, Portugal. E-mail: \*joaor@uma.pt

<sup>2</sup>School of Materials Science and Engineering/Center for Nano Energy Materials, Northwestern Polytechnical University, Xi'an 710072, China

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" <sup>[1,2]</sup>. 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 <sup>[1,2]</sup>. 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).

### References

- [1] Hanahan, D.; Weinberg, R. A. *Cell*, **2011**, *144*, 646.
- [2] Gurrapu, S. et al. *ACS Med. Chem. Lett.*, **2015**, *6*, 558.
- [3] Leiro, V.; Garcia, J. P.; Tomás, H.; Pêgo, A. P. *Bioconj. Chem.*, **2015**, *26*, 1182
- [4] Sherje, A.; Jadhav, M.; Dravyakar, B.; Kadam, D. *Int. J. Pharm.*, **2018**, *548*, 707.

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

Dandan Zhu<sup>1</sup>, Ling Peng<sup>2</sup> & Xiaoxuan Liu<sup>1</sup>

<sup>1</sup>State Key Laboratory of Natural Medicines and Jiangsu Key Laboratory of Drug Discovery for Metabolic Diseases, Center of Advanced Pharmaceuticals and Biomaterials, China Pharmaceutical University, 210009 Nanjing, P. R. China. Email: xiaoxuanliucpu@163.com

<sup>2</sup>Aix-Marseille Université, CiNaM, CNRS UMR 7325, Equipe Labellisé par La Ligue, Campus Scientifique de Luminy, Case 913, 13288 Marseille Cedex 9, France.

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.

### References

- [1] Holohan, C.; Van Schaeybroeck, S.; Longley, D. B.; Johnston, P. G. *Nat. Rev. Cancer J.*, **2013**, *13*, 714.
- [2] Davis, M. E.; Chen, Z. G.; Shin, D. M. *Nat. Rev. Drug Discov.*, **2008**, *7*, 771.
- [3] Wei, T. et al. *Proc. Natl. Acad. Sci. USA*, **2015**, *112*, 2978.

## Design and Synthesis of Bioconjugates for Personalized Medicine

Jennifer Daeg<sup>1,2</sup>, Xiaoying Xu<sup>1,2,4</sup>, Brigitte Voit<sup>1,2</sup>, Achim Temme<sup>3</sup>, Xiangyang Shi<sup>4</sup> & Dietmar Appelhans<sup>1</sup>

<sup>1</sup>Leibniz-Institut für Polymerforschung Dresden e.V. Hohe Straße 6, 01069 Dresden, Germany.

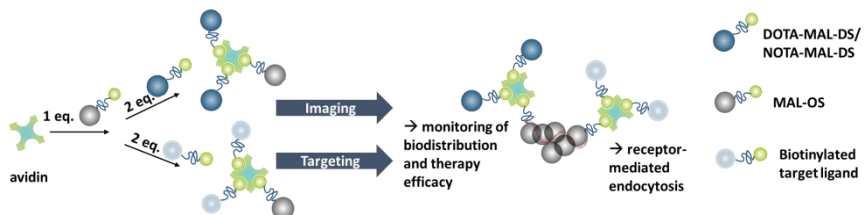
E-mail: daeg@ipfdd.de.

<sup>2</sup>Organic Chemistry of Polymers, Faculty of Chemistry and Food Chemistry, TU Dresden. 01062 Dresden, Germany.

<sup>3</sup>Experimental Neurosurgery and Tumor Immunology, Department of Neurosurgery, University Hospital Carl Gustav Carus, TU Dresden. 01307 Dresden, Germany.

<sup>4</sup>State Key Laboratory for Modification of Chemical Fibers and Polymer Materials, College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, Shanghai 201620, People's Republic of China.

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.

## [Ru( $\eta^5$ -C<sub>5</sub>H<sub>5</sub>)(PPh<sub>3</sub>)<sub>2</sub>]-PAMAM Metallodendrimers as Promising Anticancer Drugs

Nádia Nunes<sup>1</sup>, Dina Maciel<sup>1</sup>, Helena Tomás<sup>1</sup> & João Rodrigues<sup>1,2\*</sup>

<sup>1</sup>CQM – Centro de Química da Madeira, MMRG, Universidade da Madeira, Campus da Penteada, 9000-390 Funchal, Portugal. E-mail: \*joaor@uma.pt

<sup>2</sup>School of Materials Science and Engineering/Center for Nano Energy Materials, Northwestern Polytechnical University, Xi'an 710072, China.

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( $\eta^5$ -C<sub>5</sub>H<sub>5</sub>)(PPh<sub>3</sub>)<sub>2</sub>]<sub>x</sub>[CF<sub>3</sub>SO<sub>3</sub>]<sub>x</sub> (where  $x = 4, 8, 16$  and  $32$  for 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( $\eta^5$ -C<sub>5</sub>H<sub>5</sub>)(PPh<sub>3</sub>)<sub>2</sub>]<sup>+</sup> 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<sub>50</sub> 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<sub>50</sub> 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.

**Acknowledgements:** We acknowledge FCT for funding through the CQM Strategic Project Pest-OE/QUI/UI0674/2019, IDR and Madeira 14-20 Program through the project PROEQUIPRAM – Reforço do Investimento em Equipamentos e Infraestruturas Científicas na RAM – (M1420-01-0145-FEDER-000008) and ARDITI – Agência Regional para o Desenvolvimento da Investigação Tecnologia e Inovação – for the support through the project M1420-01-0145-FEDER-000005 – CQM\* (Madeira 14-20 Program).

### References

- [1] Lenis-Rojas, O. A. et al. *Inorg. Chem.*, **2018**, 57, 13150.
- [2] Govender, P.; Therrien, B.; Smith, G. S.; *Eur. J. Inorg. Chem.*, **2012**, 17, 2853.
- [3] a) Jardim, M. G.; Rissanen, K.; Rodrigues, J. *Eur. J. Inorg. Chem.*, **2010**, 11, 1729.  
b) Gouveia, M. et al. *Molecules*, **2018**, 23, 1471.

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

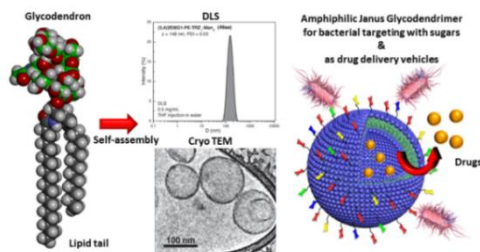
Leila Mousavifar<sup>1,2</sup>, R. Rej<sup>1</sup>, Rahul S. Bagul<sup>1</sup>, A. Tapenard<sup>1</sup> & René Roy<sup>1,2,3\*</sup>

<sup>1</sup>Department of Chemistry, Université du Québec à Montréal, P.O. Box 8888, Succ. Centre-Ville, Montréal, Québec H3C 3P8, Canada. E-mail: mousavifar.seyedeheila@courrier.uqam.ca

<sup>2</sup>INRS-Institut Armand-Frappier, Université du Québec, 531 boul. des Prairies, Laval, Québec, H7V 1B7, Canada.

<sup>3</sup>Glycovax Pharma Inc., 424 Guy, Suite 202, Montreal, Quebec, Canada, H3J 1S6.

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 2-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-dihydroxybenzoic acid as before [5,6]. The resulting amphiphilic 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.



## References

- [1] Mousavifar, L. et al. *Acc. Chem. Res.*, **2018**, 51, 2937.
- [2] Chabre, Y. M.; Roy, R. *Chem. Soc. Rev.*, **2013**, 42, 4657.
- [3] Touaibia, M. et al. *Molecules*, **2017**, 22, 1.
- [4] Mousavifar, L. et al. *Arkivoc.*, **2018**, vii, 384.
- [5] Zhang, S. et al. *Angew. Chem. Int. Ed.*, **2014**, 53, 10899.
- [6] Percec, V. et al. *J. Am. Chem. Soc.*, **2013**, 135, 9055.

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

Ana M. Garzón P.<sup>§1</sup>, Diego L. Bertuzzi<sup>§2</sup>, Kurt Lucas<sup>±3</sup> & Cátia Ornelas<sup>§4\*</sup>

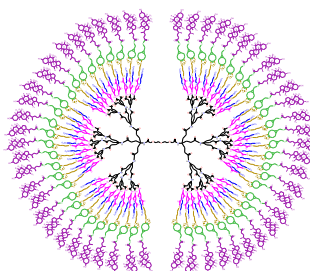
<sup>§</sup>Institute of Chemistry, University of Campinas – UNICAMP. Rua José de Castro, s/n, Cidade Universitária – SP, 13083-970 Campinas, Brazil.

<sup>±</sup>Max Planck Institute for Chemistry, Hahn-Meitner-Weg 1, D-55128 Mainz, Germany.

E-mail: <sup>1</sup>a180768@dac.unicamp.br, <sup>2</sup>diego.bertuzzi@hotmail.com, <sup>3</sup>k.lucas@mpic.de,

<sup>4</sup>catiaornelas@catiaornelaslab.com

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 heterofunctionalized 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.



$R_1 = H, R_2 = H, R_3 = OH, R_4 = OH$  Cholic acid  
 $R_1 = H, R_2 = H, R_3 = OH, R_4 = H$  Chenodeoxycholic acid  
 $R_1 = H, R_2 = H, R_3 = H, R_4 = OH$  Deoxycholic acid  
 $R_1 = OH, R_2 = H, R_3 = H, R_4 = H$  Hyodeoxycholic acid  
 $R_1 = H, R_2 = OH, R_3 = H, R_4 = H$  Ursodeoxycholic acid

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

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

**References** [1] Lucas, K. and Maes, M. *Mol. Neurobiol.*, **2013**, *48*, 190. [2] Ornelas, C. *Macromol. Chem. Phys.*, **2016**, *217*, 149.

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

Ivo J. Martins<sup>1</sup>, Helena Tomás<sup>1</sup> & João Rodrigues<sup>1,2\*</sup>

<sup>1</sup>CQM - Centro de Química da Madeira, MMRG, Universidade da Madeira, Campus da Penteada, 9020-105 Funchal, Portugal. E-mail: \*joaor@uma.pt

<sup>2</sup>School of Materials Science and Engineering/Center for Nano Energy Materials, Northwestern Polytechnical University, Xi'an 710072, China.

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<sub>2</sub> 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.

**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).

### References

- [1] Namdari, P.; Negahdari, B.; Eatemadi, A.; *Biomed Pharmacoter.*, **2017**, *87*, 209.
- [2] Mignani, S. et al. *Chem. Soc. Rev.*, **2018**, *47*, 514.
- [3] Vögtle, F.; Richardt, G.; Werner, N. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. 2009, 354.





# IDS11 PC: POSTER COMMUNICATIONS

---



## Oxidation-Sensitive Core-Multishell Nanocarrier Systems

Keerthana Rajes<sup>1</sup>, K. A. Walker<sup>1\*</sup>, Fiorenza Rancan<sup>2</sup>, Elisa Quaas<sup>1</sup>, Annika Vogt<sup>2</sup> & Rainer Haag<sup>1\*</sup>

<sup>1</sup>Institute of Chemistry and Biochemistry, Freie Universität Berlin. Takustr. 3, 14195 Berlin, Germany. E-mail: haag@chemie.fu-berlin.de.

<sup>2</sup>Clinical Research Center for Hair and Skin Science, Department of Dermatology and Allergy, Charité - Universitätsmedizin Berlin. Charitéplatz 1, 10117 Berlin, Germany.

E-mail: annika.vogt@charite.de

\*Co-authors

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].

### References:

[1] Xiao, C. et al. *Polym. Chem.*, **2015**, 6, 738.

[PC2]

## Design and Synthesis of Succinylated PAMAM-Isoniazid Sendrimer Prodrug

Renan Vinicius de Araújo & Jeanine Giarolla

Department of Pharmacy, Faculty of Pharmaceutical Sciences, University of Sao Paulo, Avenida Professor Lineu Prestes, 580, São Paulo, Brazil. E-mail: renan.arajo@usp.br; jeanineg@usp.br

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:  $^1\text{H}$  NMR (300 MHz, Methanol- $d_4$ )  $\delta$  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).  $^{13}\text{C}$  NMR (75 MHz, Methanol- $d_4$ )  $\delta$  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*.

**Acknowledgements:** The authors are grateful to FAPESP (2017/21154-7) and CNPq (422928/2016-0) for the financial support.

### References

- [1] *World Health Organization*. The top 10 causes of death, available in <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death>, **2017**.
- [2] Reichman, L.B.; Lardizabal, A.; Hayden, C.H. *Am. J. Respir. Crit. Care Med*, **2004**, *170*, 832.
- [3] Tomalia, D.A. et al. *Polym J*, **1985**, *17*, 117.
- [4] Santos, S.S.; Ferreira, E.I.; Giarolla, J. *Molecules*, **2016**, *21*, 686.
- [5] Araújo, R.V.; Santos, S.S.; Ferreira, E.I.; Giarolla, J. *Molecules*, **2018**, *23*, E2849.

# Green Dendritic Polymer: Synthesis of Star-Shaped 4arms-PLLA<sub>n</sub>-b-DL<sub>m</sub> Dendritic Peptides with “Core-Shell” Structure

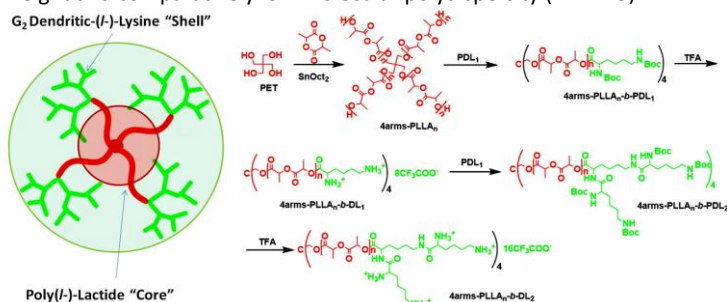
Ruilong Sheng<sup>1\*</sup>, Zhao Wang<sup>2,3</sup> & Lin Jia<sup>3\*</sup>

<sup>1</sup>CQM-Centro de Química da Madeira, Universidade da Madeira, Campus da Penteada, 9020-105, Funchal, Madeira, Portugal. E-mail: ruilong.sheng@staff.uma.pt

<sup>2</sup>Department of Materials, Jinling Technology College, Nanjing, 200444, China.

<sup>3</sup>Department of Polymer Materials, Shanghai University, 99 Shangda Road, Mailbox 152, Shanghai 200444, China.

Developing green and degradable dendrimers or dendritic polymers have attracted great attentions in recent decades<sup>1</sup>. In earlier study, we prepared series of poly(*L*-lactide) (PLLA)-based dendritic polymers<sup>2</sup> towards biomaterial applications<sup>3</sup>. To expand the molecular topology diversity for achieving high performance, we herein prepared a series of star-shaped 4arms-PLLA<sub>n</sub>-DPL<sub>m</sub> 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 <sup>1</sup>H NMR and GPC analysis. The results demonstrated that the star-shaped 4arms-PLLA<sub>n</sub>-DPL<sub>m</sub> 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.

**Acknowledgements:** We greatly acknowledge ARDITI-(project M1420-01-0145-FEDER-000005-Centro de Química da Madeira-CQM<sup>+</sup>) and ARDITI-2017-003-ISG; FCT-(project PEst-OE/QUI/UI0674/2019, CQM), and Madeira 14-20 Program PROEQUIPRAM- (project: M1420-01-0145-FEDER-000008), Shanghai Pujiang Program (no. 15PJ1402400) and Jinling Tech Project (No: jit-b-201828) for the sponsorship.

## References

- [1] Hirao, A.; Goseki, R.; Ishizone, T. *Macromolecules*, **2014**, 47, 1883.
- [2] (a) Li, Y. et al. *Biomacromolecules*, **2009**, 10, 2284. (b) Zhu, Y. et al. *Macromol. Biosci.*, **2011**, 11, 174.
- [3] Sun, J. et al. *J. Biomater. Appl.*, **2016**, 31, 606.

## Cycloaddition of CO<sub>2</sub> Catalyzed by Phosphonium and Amonium Carbosilane dendrimers

Lucie Červenková Šťastná<sup>1,2</sup>, Monika Müllerová<sup>1,2</sup>, Roman Petříčkovič<sup>1,2</sup>, Petra Cuřínová<sup>1,2</sup>, Martin Košťejn<sup>2</sup>, Stanislav Šabata<sup>1,2</sup> & Tomáš Strašák<sup>1,2</sup>

<sup>1</sup>Jan Evangelista Purkyně University in Ústí nad Labem, Pasteurova 1, 400 96 Ústí nad Labem, Czech Republic. E-mail: stastna@icpf.cas.cz

<sup>2</sup>Institute of the Chemical Process Fundamentals of the CAS, v.v.i., Rozvojová 135, 165 02 Prague 6, Czech Republic.

Conversion of carbon dioxide (CO<sub>2</sub>) 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<sub>2</sub> 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).

### References

- [1] Müllerová M. et al. *New J. Chem.*, **2018**, 42, 1187.
- [2] Strašák, T. et al. *RSC Adv.*, **2017**, 7, 18724.

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

Rita Castro<sup>1</sup>, Pedro Granja<sup>2,3</sup>, Ana Paula Pêgo<sup>2,3</sup>, João Rodrigues<sup>1</sup> & Helena Tomás<sup>1\*</sup>

<sup>1</sup>CQM- Centro de Química da Madeira, MMRG, Universidade da Madeira, Campus Universitário da Penteada, 9020-105 Funchal, Portugal. E-mail: \*lenat@staff.uma.pt

<sup>2</sup>INEB – Instituto de Engenharia Biomédica, Universidade do Porto, Porto, Portugal.

<sup>3</sup>I3S – Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal.

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  $\text{pH} \leq 9$ , 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.

**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). Rita Castro acknowledges ARDITI for the Post-Doc Grant ARDITI-CQM/2018/020-PDG.

### References

- [1] a) Bielinska, A. U.; Kukowska-Latallo, J. F.; Baker, J. R. *Biochim. Biophys. Acta*, **1997**, *1353*, 180. b) Maiti, P.K., Bagchi, B. *Nano Lett.*, **2006**, *6*, 2478.
- [2] Santander-Ortega, M. J.; Lozano, M. V.; Uchegbu, I. F.; Schätzlein, A. G. (2016). *Polymers and Nanomaterials for Gene Therapy*, 113–146. Woodhead Publishing.
- [3] Huang, Y.-C. et al. *Macromolecules*, **2016**, *49*, 4277.
- [4] Pérez-Arnaiz, C.; Busto, N.; Leal, J.M.; García, B. *J. Phys. Chem. B*, **2014**, *118*, 1288.

## Ruthenium (II) Carbosilane Metallodendrons as Promising Anticancer Agents

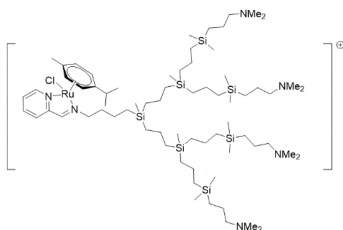
Natalia Sanz del Olmo<sup>1,2,3</sup>, Sara Quintana Sánchez<sup>1,2,3</sup>, Marta Maroto-Díaz<sup>1,2,3</sup>, Sandra García-Gallego<sup>1,2,3</sup>, Rafael Gómez<sup>1,2,3</sup>, Paula Ortega López<sup>1,2,3</sup> & F. Javier de la Mata<sup>1,2,3</sup>

<sup>1</sup>Department of Organic Chemistry and Inorganic Chemistry, University of Alcalá, Spain. Institute of Chemical Research "Andrés M. del Río" (IQAR).

<sup>2</sup>Ramón y Cajal Health Research Institute, IRYCIS, UAH, Spain. Email: javier.delamata@uah.es

<sup>3</sup>Networking Research Center on Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN).

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.

**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.

### References

- [1] Rosenberg, B. et al. *Nature*, **1969**, 222, 385.
- [2] Trondl, R. et al. *Chem. Sci.*, **2014**, 5, 2925.
- [3] Fang, J. et al. *Adv. Drug Deliv. Rev.*, **2011**, 63, 136.



## Copper(II)-conjugated Metallodendrimers: EPR Study

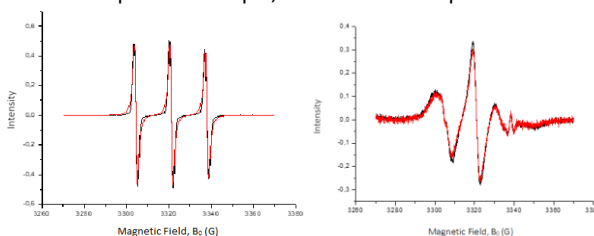
Riccardo Carloni<sup>1</sup>, Michela Cangiotti<sup>1</sup>, Sandra García-Gallego<sup>2</sup>, F. Javier de la Mata<sup>2,3</sup> & Maria Francesca Ottaviani<sup>1</sup>

<sup>1</sup>Department of Pure and Applied Sciences, Università degli studi di Urbino "Carlo Bo". Via Ca' le Suore 2/4, 61029 Urbino PU. E-mail: r.carloni1@campus.uniurb.it

<sup>2</sup>Department of Organic and Inorganic Chemistry, University of Alcalá, Alcalá de Henares, Spain. Chemical Research Institute "Andrés M. del Río" (IQAR), Health Research Institute. Ramón y Cajal, IRYCIS, UAH, Spain.

<sup>3</sup> Networking Research Center on Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN).

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-trimethylammonium 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.



### References

- [1] Ottaviani, M. F. et al, *RSC Adv.*, **2014**, *4*, 36573.
- [2] Carloni, R. et al., *Manuscript in preparation*, **2019**.

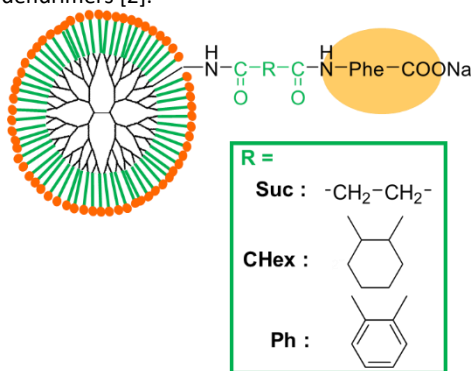
## UCST-Type Thermosensitive Dendrimers

Chie Kojima & Mamiko Tamaki

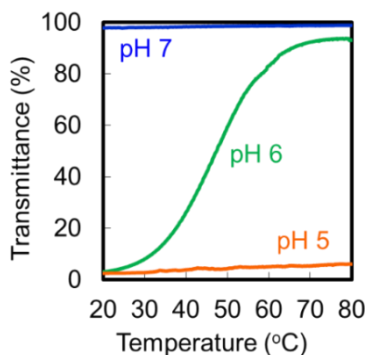
Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University. 1-2 Gakuen-cho, Naka-ku, Sakai, Osaka 599-8570, Japan. E-mail: kojima@chem.osakafu-u.ac.jp

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.

### References

- [1] Tono, Y. et al, *Langmuir*, **2006**, 22, 4920.  
 [2] Tamaki, M.; Fukushima, D.; Kojima, C. *RSC Advances*, **2018**, 8, 28147.

## Ruthenium-based Metallodendrimers: Synthesis, Cytotoxicity and Hematotoxicity Studies

Dina Maciel<sup>1</sup>, Francisco Santos<sup>1</sup>, M<sup>a</sup> Ángeles Muñoz-Fernández<sup>2</sup>, Helena Tomás<sup>1</sup> & João Rodrigues<sup>1,3\*</sup>

<sup>1</sup>CQM - Centro de Química da Madeira, MMRG, Campus Universitário da Penteada, 9020-105 Funchal, Portugal. E-mail: \*joaor@uma.pt.

<sup>2</sup>Laboratorio de Inmunobiología Molecular, Hospital General Universitario Gregorio Marañón, Madrid, Spain. Instituto de Investigación Sanitaria Gregorio Marañón and Spanish HIV HGM BioBank, Madrid, Spain. Networking Research Center on Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Madrid, Spain.

<sup>3</sup>School of Materials Science and Engineering/Center for Nano Energy Materials, Northwestern Polytechnical University, Xi'an 710072, China.

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 than 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  $[\text{Ru}(\eta^5\text{-C}_5\text{H}_5)(\text{PPh}_3)_2]^+$ . The metallocompounds were characterized by <sup>1</sup>H- and <sup>31</sup>P-NMR, mass spectrometry (MS) and FTIR techniques. Their stability was also studied by <sup>1</sup>H- and <sup>31</sup>P-NMR at 25 and 37°C. 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 metalldrug *cisplatin*.

**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/UI0674/2019, and the PhD Grant SFRH/BD/102123/2014 (D.M.). 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).

### References

- [1] Mjos, K. D.; Orvig, C. *Chem. Rev.* **2014**, *114*, 4540.
- [2] Lazarević, T.; Rilak, A.; Bugarčić, Ž. D. *Eur. J. Med. Chem.* **2017**, *142*, 8.
- [3] a) Jardim, M.G.; Rissanen, K.; Rodrigues, J. *Eur. J. Inorg. Chem.* **2010**, 1729; b) Gouveia, M. et al. *Molecules*, **2018**, *23*, 1471.

## Study of the Biological Activity of Dendrimers Functionalized with Imidazolium Salts

Tamara Rodríguez<sup>1,2,3</sup>, José Luis Copa-Patiño<sup>4</sup>, Juan Soliveri<sup>4</sup>, F. Javier de la Mata<sup>1,2,3</sup>, Jesús Cano<sup>1,3</sup> & Rafael Gómez<sup>1,2,3</sup>

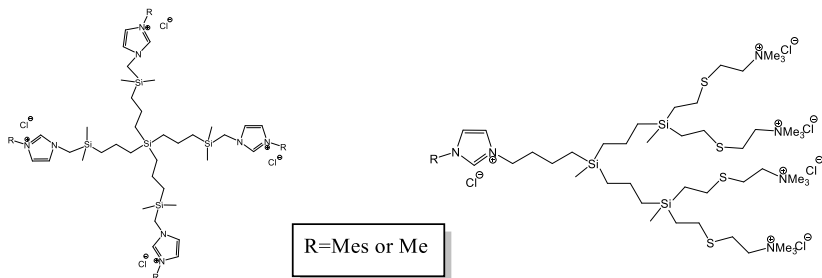
<sup>1</sup>Department of Organic and Inorganic Chemistry, Pharmacy Faculty, University of Alcalá de Henares. Ctra. Madrid-Barcelona km.33600, Spain. Institute of Chemical Research "Andrés M. del Río" (IQAR). E-mail: tamara.rodriguezp@edu.uah.es; jesus.cano@uah.es; rafael.gomez@uah.es

<sup>2</sup>Networking Research Center on Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN) <sup>3</sup>Instituto Ramón y Cajal de Investigación Sanitaria, IRYCIS.

<sup>4</sup>Department of Microbiology, Pharmacy Faculty, University of Alcalá de Henares, Spain.

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.

### References

[1] Nurhanna Riduan, S.; Zhang, Y. *Chem. Soc. Rev.*, **2013**, 42, 9055.

## Microbiological Activity of Dendrimers Modified with 1,8-Naphtalimides

Ivo Grabchev<sup>1</sup>, Desislava Staneva<sup>2</sup> & Evgenia Vasileva-Tonkova<sup>3</sup>

<sup>1</sup>Faculty of Medicine, Sofia University "St. Kliment Ohridski", 1407 Sofia, Bulgaria.

E-mail: i.grabchev@chem.uni-sofia.bg

<sup>2</sup>Faculty of Chemical Technology, University of Chemical Technology and Metallurgy, 1756 Sofia, Bulgaria

<sup>3</sup>The Stephan Angeloff Institute of Microbiology, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria.

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.

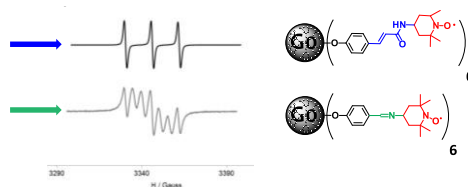
**Acknowledgments:** The authors acknowledge Grant H-09/03-2016, Scientific Research Fund, Ministry of Education and Science of Bulgaria.

## Tuning Spin-Spin Interactions in Radical Dendrimers

Vega Lloveras, F. Liko, L.F. Pinto & José Vidal-Gancedo

Institut de Ciència de Materials de Barcelona ICMA-B-CSIC; Campus UAB, 08193 Bellaterra, Barcelona, Spain and CIBER-BBN, Barcelona, Spain. E-mail: vega@icmab.es

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<sub>0</sub>-acrylamido-TEMPO (up, without interactions) and G<sub>0</sub>-imino-TEMPO (down, showing spin-spin interactions).

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

### References

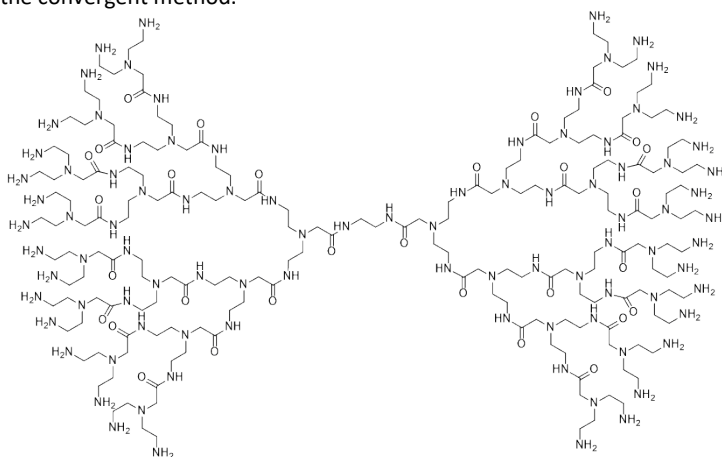
- [1] a) Badetti, E. et al. *Org. Lett.* **2013**, *15*, 3490. b) Badetti, E. et al. *Macromolecules*, **2014**, *47*, 7717. c) Lloveras, V.; Badetti, E.; Wurst, K.; Vidal-Gancedo, J. *Chem. Phys. Chem.*, **2015**, *16*, 3302. d) Lloveras, V.; Badetti, E.; Veciana, J.; Vidal-Gancedo, J. *Nanoscale*, **2016**, *8*, 5049.
- [2] e) Lloveras, V. et al. *Chem. Phys. Chem.*, **2018**, *19*, 1895.

## Novel Polyamidoamine Dendrimers for Skin Delivery

Georgios Paraskevopoulos, Anna Nováčková, Martina Langerová, Pavlína Chladová, Denisa Houšková & Kateřina Vavrova

Skin Barrier Research Group, Faculty of Pharmacy, Charles University. Akademika Heyrovského 1203, 50005, Hradec Králové, Czech Republic. E-mail: paraskeg@faf.cuni.cz

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 ethylenediamine 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).

### References

[1] Dave, K.; Krishna Venuganti, V. V. *Ther. Delivery*, **2017**, *8*, 1077.

## Donor–Acceptor PIMAM Dendrimer Photodiodes

Rita F. Pires<sup>1</sup>, Ana Charas<sup>2</sup>, Jorge Morgado<sup>2,3</sup>, Teresa Casimiro<sup>4</sup> & Vasco D. B. Bonifácio<sup>1</sup>

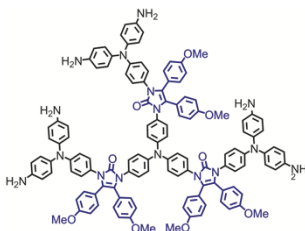
<sup>1</sup>CQFM-IN and IBB-Institute for Bioengineering and Biosciences, Instituto Superior Técnico, Universidade de Lisboa. Lisboa. Portugal. E-mail: ritafpires@tecnico.ulisboa.pt

<sup>2</sup>Instituto de Telecomunicações, Instituto Superior Técnico, Universidade de Lisboa. Lisboa. Portugal.

<sup>3</sup>Department of Bioengineering, Instituto Superior Técnico, Universidade de Lisboa. Lisboa, Portugal.

<sup>4</sup>LAQV-REQUIMTE, Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade NOVA de Lisboa. Caparica. Portugal.

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  $\pi$ -bridges [3]. In this work, based on previous 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 structure 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).

### References

- [1] Agostinelli, T. et al. *J. Appl. Phys. Lett.*, **2008**, 93, 203305.
- [2] Armin, A. et al. *Laser Photonics Rev.*, **2014**, 8, 924.
- [3] Rajavelu, K. and Rajakumar, P. *Org. Electron.*, **2018**, 56, 192.
- [4] Restani, R. B. et al. *Angew. Chem. Int. Ed.*, **2012**, 51, 5162.



## Antibacterial Properties of Cotton Fabrics Modified with Fluorescent Dendrimers and Metallodendrimers

Desislava Staneva<sup>1</sup>, Miglena Irikova<sup>1</sup> & Ivo Grabchev<sup>2</sup>

<sup>1</sup>Faculty of Chemical Technology, University of Chemical Technology and Metallurgy, Sofia, Bulgaria. E-mail: grabcheva@mail.bg

<sup>2</sup>Medical Faculty, Sofia University "St. Kliment Ohridski", Sofia, Bulgaria.  
E-mail: i.grabchev@chem.uni-sofia.bg

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-naphthalimide 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.

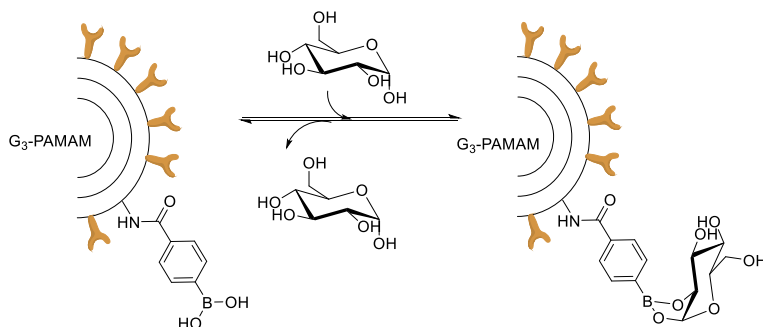
**Acknowledgments:** The authors acknowledge Grant H-09/03-2016, Scientific Research Fund, Ministry of Education and Science of Bulgaria.

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

Yuan-Ting Chan, Ching-Hua Tsai & Chai-Lin Kao

Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 80708, Taiwan. E-mail: judyyund1221@gmail.com

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.



**Acknowledgements:** Thanks for MOST and KMU supports.

### References

- [1] Tsai, C.-H. et al. *Chem. Commun.*, **2018**, 54, 4577.
- [2] Zhao, L et al. *Materials*, **2017**, 10, 170.

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

Duarte Fernandes, Manuel Algarra, Carla S. Alves & Pedro Pires\*

CQM – Centro de Química da Madeira, Universidade da Madeira. Campus Universitário da Penteada, 9020-105 Funchal, Portugal. E-mail: \*pedro.pires@staff.uma.pt

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%).

**Acknowledgements:** This work was supported by the Fundação para a Ciência e a Tecnologia (FCT, Portuguese Government funds) through the CQM Strategic Project PEst-OE/QUI/UI0674/2013, by the Madeira 14-20 Program, project PROEQUIPRAM - Reforço do Investimento em Equipamentos e Infraestruturas Científicas na RAM (M1420-01-0145-FEDER-000008), and by Agência Regional para o Desenvolvimento da Investigação, Tecnologia e Inovação (ARDITI) through project M1420-01-0145-FEDER-000005 - Centro de Química da Madeira - CQM\* (Madeira 14-20 Program). CSA also acknowledges the ARDITI for a Post-doc Grant (002458/2015/132) through the project M1420- 09-5369-FSE-000001).

### References

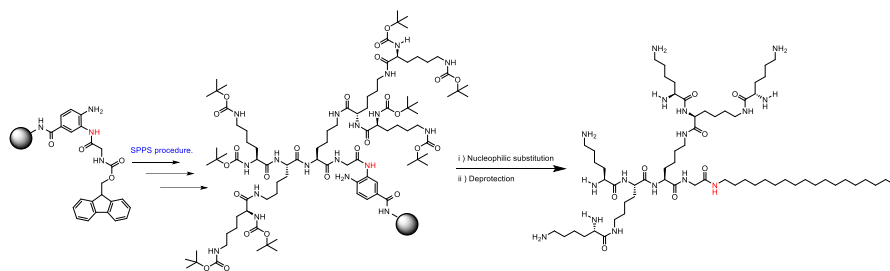
[1] Din, M. I. and Rehan, R. *Anal. Lett.*, **2017**, 50, 50.

## A New Strategy for Amphiphilic Peptide Dendrimer on Solid Phase

Yung Liao, M. Vijaya Simha & Chai-Lin Kao

Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 80708, Taiwan. E-mail: victor851123@gmail.com

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.



**Acknowledgements:** Thanks for MOST and KMU supports.

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

Noemi Molina<sup>1,2</sup>, Ana M. Gonzalez-Luque<sup>3,2</sup>, José Becerra<sup>3,2</sup>, Leonor Santos-Ruiz<sup>4,2</sup>, Yolanda Vida<sup>1,2</sup> & Ezequiel Perez-Inestrosa<sup>1,2</sup>

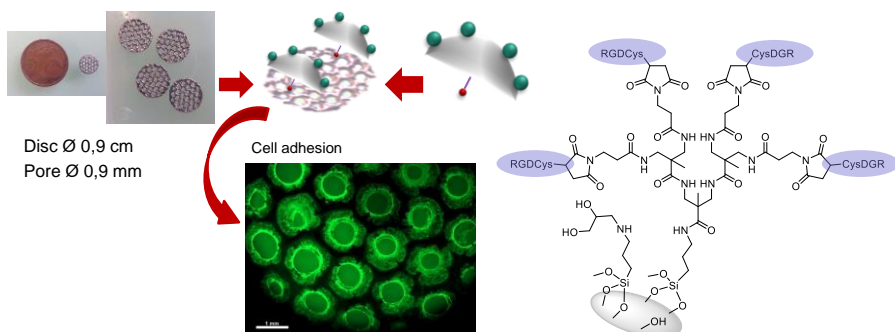
<sup>1</sup>Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Málaga - IBIMA, Campus de Teatinos s/n, 29071 Málaga, Spain. E-mail: nmolina@uma.es; yolvida@uma.es; inestrosa@uma.es

<sup>2</sup>Centro Andaluz de Nanomedicina y Biotecnología (BIONAND), Junta de Andalucía, Universidad de Málaga, C/ Severo Ochoa 35, 29590 Campanillas (Málaga), Spain. E-mail: jbecerra@bionand.es

<sup>3</sup>Departamento de Biología Celular, Genética y Fisiología, Facultad de Ciencias, Universidad de Málaga - IBIMA, Campus de Teatinos s/n, 29071 Málaga, Spain. E-mail: anagonzalu@uma.es

<sup>4</sup>Centro de Investigación Biomédica en Red - Bioingeniería Biomateriales y Nanomedicina (CIBER-BBN), Spain. E-mail: lsantos@uma.es

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.



### References

[1] Hersel, U.; Dahmen C.; Kessler, H. *Biomaterials*, **2003**, 24, 4385.

## Hyaluronic Acid-Modified Dendrimer Entrapped Gold Nanoparticles

Nilsa Abreu<sup>1</sup>, Carla S. Alves<sup>1,\*</sup>, Helena Tomás<sup>1</sup>, Xiangyang Shi<sup>1,2</sup> & João Rodrigues<sup>1,3</sup>

<sup>1</sup>CQM - Centro de Química da Madeira, MMRG, Universidade da Madeira, Campus Universitário da Penteada, 9020-105 Funchal, Portugal. E-mail: \*calves@staff.uma.pt

<sup>2</sup>College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, Shanghai 201620, China.

<sup>3</sup>School of Materials Science and Engineering/Center for Nano Energy Materials, Northwestern Polytechnical University, Xi'an 710072, China.

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<sub>2</sub>). 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 <sup>1</sup>H, <sup>13</sup>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.

**Acknowledgements** This work was supported by FCT-Fundação para a Ciência e a Tecnologia (CQM Project PEstOE/QUI/UI0674/2019, Portuguese Government funds), and through the 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 Post-doc Grant (002458/2015/132) (CSA) through the project M1420-09-5369-FSE-000001. Funds from FCT and Santander Bank for the Invited Chair in Nanotechnology (X. Shi) are also acknowledged.

### References

- [1] Zhu, J. et al. *Langmuir*, **2018**, 34, 12428.
- [2] Plattt, V. M. and Szoka, F. C. *Mol. Pharm.*, **2008**, 5, 474.

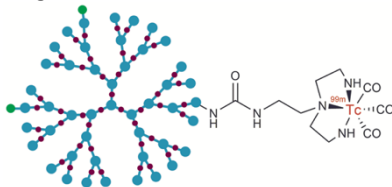
## <sup>99m</sup>Tc-Labelled Polyurea (PURE) Dendrimers for Ovarian Cancer Theranostics

Adriana Cruz<sup>1</sup>, Rita F. Pires<sup>1</sup>, Célia Fernandes<sup>2</sup>, Paula Raposo<sup>2</sup>, António Paulo<sup>2</sup> & Vasco D. B. Bonifácio<sup>1</sup>

<sup>1</sup>CQFM-IN and IBB-Institute for Bioengineering and Biosciences, Instituto Superior Técnico, Universidade de Lisboa. Lisboa. Portugal. E-mail: vasco.bonifacio@tecnico.ulisboa.pt

<sup>2</sup>Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico, Universidade de Lisboa. Lisboa. Portugal. E-mail: apaulo@ctn.tecnico.ulisboa.pt

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 ( $\beta$  and  $\alpha$  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, <sup>99m</sup>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<sub>G4</sub>-FA), thus allowing a molecular recognition strategy to target the folate receptor (FR- $\alpha$ ), highly expressed in ovarian cancer. The PURE<sub>G4</sub>-FA dendrimers were directly labelled with technetium-99m (<sup>99m</sup>Tc-PURE<sub>G4</sub>-FA) without the need of further functionalization of the dendrimers with an extra <sup>99m</sup>Tc-ligand (Figure 1). The stability of <sup>99m</sup>Tc-PURE<sub>G4</sub>-FA was investigated in different cellular culture media, and cellular uptake studies were performed using ovarian cancer cell lines.



**Figure 1.** Structural representation of <sup>99m</sup>Tc-PURE<sub>G4</sub>-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.

### References

- [1] Leung, F. et al. *Adv. Clin. Chem.* **2014**, 66, 25.
- [2] Esteves, T. et al. *Org. Biomol. Chem.* **2010**, 8, 4104.
- [3] Restani, R. B. et al. *Angew. Chem. Int. Ed.*, **2012**, 51, 5162.

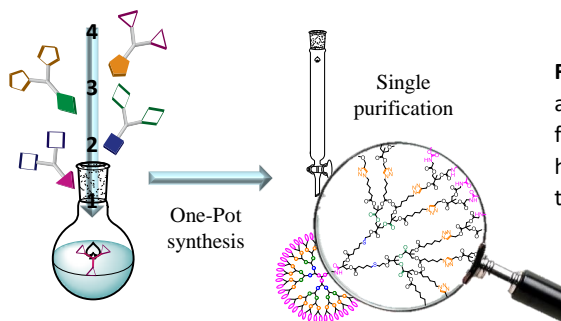
## One-pot Accelerated Synthesis to bis-MPA Dendrimers

Sandra García-Gallego<sup>1,2</sup>, Oliver Andrén<sup>1</sup> & Michael Malkoch<sup>1</sup>

<sup>1</sup>Department of Fiber and Polymer Technology, KTH Royal Institute of Technology, Stockholm, Sweden.

<sup>2</sup>Department of Organic and Inorganic Chemistry and Research Institute in Chemistry “Andrés M. del Río” (IQAR), Faculty of Pharmacy, University of Alcalá, Madrid, Spain. Institute Ramón y Cajal for Health Research (IRYCIS), Spain. E-mail: sandra.garciagallego@uah.es

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<sub>2</sub>-CD<sub>2</sub> 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 imidazolidine-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.

### References

- [1] a) García-Gallego, S.; Hult, D.; Olsson, J.V.; Malkoch, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 2416. b) Antoni, P. et al. *Macromolecules*, **2010**, *43*, 6625.
- [2] García-Gallego, S. et al. *Manuscript in preparation*. **2019**.

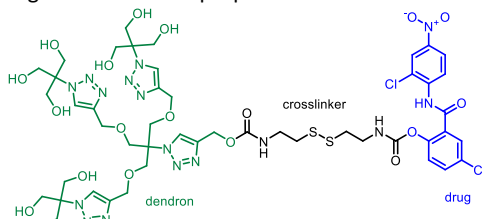


## Synthesis of Niclosamide Dendron of Intracellular Release

Rodrigo Vieira Gonzaga, Lucas Adriano do Nascimento & Elizabeth Igne Ferreira

LAPEN, Faculty of Pharmaceutical Sciences, Department of Pharmacy, University of Sao Paulo (USP), Sao Paulo, Brazil. E-mail: elizabeth.igne@gmail.com

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  $^1\text{H}$  and  $^{13}\text{C}$  NMR, and infrared.

**Acknowledgements:** The authors are grateful to CAPES for a scholarship to RVG, and to CNPq fellowship to EIF.

### References

- [1] Gonzaga, R. V. et al. *Pharmaceutics*, **2018**, *1*, 219.
- [2] Jahangirian, H. et al. *Int. J. Nanomedicine*, **2017**, *12*, 2957;
- [3] Riber, C. F.; Smith, A. A. A.; Zelikin, A. N. *Adv. Health. Mater.*, **2015**, *4*, 1887.

## Phosphorus Dendrimers as Rose Bengal Carriers in Photodynamic Therapy

Krzysztof Sztandera<sup>1</sup>, Magdalena Milczarek<sup>2</sup>, Marta Majkowska<sup>1</sup>, Joanna Wietrzyk<sup>2</sup> & Barbara Klajnert-Maculewicz<sup>1,3</sup>

<sup>1</sup>Department of General Biophysics, Faculty of Biology and Environmental Protection, University of Lodz, 141/143 Pomorska St., 90-236 Lodz, Poland. E-mail: barbara.klajnert@biol.uni.lodz.pl

<sup>2</sup>Hirsfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, 12 Weigla St., 53-114 Wrocław, Poland.

<sup>3</sup>Leibniz Institute of Polymer Research Dresden, 6 Hohe St., 01069 Dresden, Germany.

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<sup>6</sup> 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*.

**Acknowledgements:** This work is sponsored by the National Science Centre, Poland (Project: "Phosphorus dendrimers as a carriers for photosensitizers- *in vivo* studies" UMO-2017/25/B/NZ7/01304).

### References

- [1] Juarranz, Á. et al. *Clin. Transl. Oncol.*, **2008**, 10, 148.
- [2] Robertson, C.A. et al. *J. Photochem. Photobiol. B*. **2009**, 96, 1.
- [3] Agarwal, A.; Gupta, U.; Asthana, A.; Jain, N.K. *Biomaterials*, **2009**, 30, 3588.
- [4] Patri, A.K. et al. *Adv. Drug Delivery Rev.*, **2005**, 57, 2203.

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

Nadezhda Knauer<sup>1</sup>, Ekaterina Pashkina<sup>1</sup>, Evgeny Apartsin<sup>2,3</sup>, Elena Fuentes<sup>4,5</sup>, Carlos E. Gutierrez-Ulloa<sup>4,5</sup>, Marina Buyanova<sup>2</sup>, F. Javier de la Mata<sup>4,5</sup> & Rafael Gómez<sup>4,5</sup>

<sup>1</sup>Research Institute of Fundamental and Clinical Immunology. 14, Yadrintsevskaya str., 630099 Novosibirsk, Russia. E-mail: nuknauer@niikim.ru

<sup>2</sup>Institute of Chemical Biology and Fundamental Medicine SB RAS. Novosibirsk, Russia.

<sup>3</sup>Department of Natural Sciences, Novosibirsk State University. Novosibirsk, Russia.

<sup>4</sup>Departamento de Química Orgánica y Química Inorgánica, Universidad de Alcalá. Alcalá de Henares, Spain.

<sup>5</sup>Networking Research Center on Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Madrid, Spain.

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  $\mu\text{M}$ ;  $\text{IC}_{50} > 30 \mu\text{M}$ ). 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 ( $\text{IC}_{50}$  5-10  $\mu\text{M}$ ). 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 ( $\text{IC}_{50} \sim 5 \mu\text{M}$ ).

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

**Acknowledgements:** This study was supported by RFBR grant 18-33-20109, by MINECO grant CTQ-2017-85224-P, by the grant of the President of RF MK-2278.2019.4.

## *In silico* Characterization of PURE Dendrimers-Small Molecules Interactions

Nuno Martinho<sup>1</sup>, Rita F. Pires<sup>1</sup>, Mire Zloh<sup>2,3</sup>

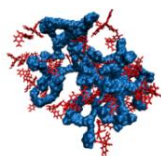
<sup>1</sup>CQFM-IN and IBB-Institute for Bioengineering and Biosciences, Instituto Superior Técnico, Universidade de Lisboa, Lisboa, Portugal. E-mail: nunomartinho@tecnico.ulisboa.pt

<sup>2</sup>School of Life and Medical Sciences, University of Hertfordshire, Hatfield, United Kingdom.

<sup>3</sup>Faculty of Pharmacy, University Business Academy, Novi Sad, Serbia.

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<sub>G4</sub> (blue) complexes with multiple molecules of 4-carboxyfluorescein (red).

**Acknowledgements:** We thank Fundação para a Ciência e a Tecnologia (FCT, Lisbon) for financial support through project PTDC/MEC-ONC/29327/2017.

### References

- [1] Martinho, N. et al. *Molecules*, **2014**, *19*, 20424.
- [2] Jain, V. et al. *Soft Matter*, **2013**, *9*, 6482.
- [3] Restani, R. B. et al. *Angew. Chem. Int. Ed.*, **2012**, *51*, 5162.
- [4] Martinho, N. et. al. *Int. J. Nanomedicine*, **2017**, *12*, 7053.

## Carbosilane Glucose Glycodendrimers: Synthesis and Toxicological Analyses

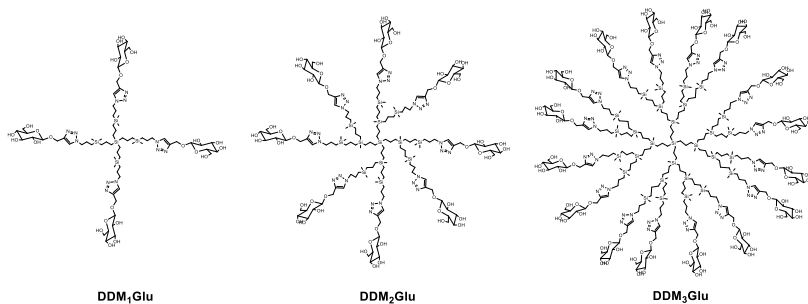
Monika Müllerová<sup>1,2</sup>, Lucie Červenková Šťastná<sup>1,2</sup>, Jan Malý<sup>2</sup>, Dominika Wróbel<sup>2</sup>, Liegertová Michaela<sup>2</sup> & Tomáš Strašák<sup>1,2</sup>

<sup>1</sup>Institute of Chemical Process Fundamentals, Academy of Sciences of the Czech Republic. Prague, Czech Republic. E-mail: mullerovam@icpf.cas.cz

<sup>2</sup>Department of Biology, Faculty of Science, University of J.E. Purkinje. Usti N/L, Czech Republic.

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 1-3<sup>rd</sup> generation glucose glyco-DDMs (DDM<sub>1</sub>Glu, DDM<sub>2</sub>Glu, DDM<sub>3</sub>Glu) 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.



**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).

### References

- [1] Strasak, T. et al. *RSC Adv.*, **2017**, 7, 18724.
- [2] Appelhans, D. et al. *Chem. Soc. Rev.*, **2015**, 44, 3968.
- [3] Jain, K.; Kesharwani, P.; Gupta, U.; Jain, NK. *Int. J. Pharm.*, **2010**, 394, 122.
- [4] Liegertova, M. et al. *Nanotoxicology*, **2018**, 12, 797.

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

Ignacio Rodríguez-Izquierdo<sup>1\*</sup>, Ignacion Relaño-Rodríguez<sup>1\*</sup>, M<sup>a</sup> Jesús Serramía-Lobera<sup>1</sup>, Raquel Juárez-Sánchez<sup>1</sup>, Rafael Gómez<sup>2</sup>, F. Javier de la Mata<sup>2</sup>, M<sup>a</sup> Jesús Bullido<sup>3</sup> & M<sup>a</sup> Ángeles Muñoz-Fernández<sup>1</sup>

<sup>1</sup>Section Immunology, ImmunoMolecular Laboratory. Hospital General Universitario Gregorio Marañón, CIBER BBN, Spanish HIV HGM BioBank. Madrid, Spain.

E-mail: mmunoz.hgugm@gmail.com

<sup>2</sup>Universidad Alcalá de Henares. Madrid. Spain.

The major obstacle that impedes HIV eradication in ART-treated HIV-1 individuals is the establishment of long-lived latently infected resting CD4<sup>+</sup> 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 antil latency 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  $\beta$ -secretase activity, deregulating the balance between the amyloidogenic and non-amyloidogenic pathways, and subsequently, raises the  $\beta$ -Amyloid peptides accumulation, one of the main hallmarks 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  $\beta$ A peptides, becoming potential candidates for further studies in the fight against neuronal disorders.

### References

[1] Gutierrez, C et al. *AIDS*, **2016**, *30*, 1385. [2] Díaz L et al. *Sci. Rep.*, **2015**, *5*, 12444.

## Fractionation and Degradative Stability of 5<sup>th</sup> Generation PAMAM Dendrimer

Levente Novák, Tímea Szabó & István Bányai

Department of Physical Chemistry, Faculty of Sciences and Technology, University of Debrecen. H-4032 Debrecen, Egyetem tér 1., Hungary. E-mail: novak.levente@science.unideb.hu

Commercial 5<sup>th</sup> 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 than 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.

**Acknowledgements:** The research was supported by the EU and co-financed by the European Regional Development Fund under the projects GINOP-2.3.2-15-2016-00008 and GINOP-2.3.3-15-2016-00004.

### References

- [1] Wang, D. and Imae, T. *J. Am. Chem. Soc.*, **2004**, *126*, 13204.
- [2] Kéri, M. et al. *Phys. Chem. Chem. Phys.*, **2017**, *19*, 11540.

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

Francisco Santos<sup>1</sup>, Dina Maciel<sup>1</sup> & João Rodrigues<sup>1,2\*</sup>

<sup>1</sup>CQM—Centro de Química da Madeira, MMRG, Universidade da Madeira, Campus Universitário da Penteada, 9020-105 Funchal, Portugal. E-mail: \*joaor@uma.pt

<sup>2</sup>School of Materials Science and Engineering/Center for Nano Energy Materials, Northwestern Polytechnical University, Xi'an 710072, China.

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.

**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 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).

### References

- [1] García-Gallego, S. et al. *Dalton Trans.*, **2013**, 42, 5874.
- [2] Mignani, S. et al. *Chem. Soc. Rev.*, **2018**, 47, 514.
- [3] Mignani, S. and Majoral, J.P. *New J. Chem.*, **2013**, 37, 3337.
- [4] See for instance: a) Rodrigues, J. et al. *New J. Chem.*, **2011**, 35, 1938; b). Gouveia, M. et al. *Molecules*, **2018**, 23, 1471; c) Maciel, D. et al. *Nanoscale*, **2019**, 11, 9679.



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

Ana Patrícia Spencer<sup>1,2</sup>, Natália Magalhães<sup>1</sup>, Victoria Leiro<sup>1\*</sup> & Ana Paula Pêgo<sup>1,2,3\*</sup>

<sup>1</sup>INEB-Instituto de Engenharia Biomédica and i3S-Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal. E-mail: ana.spencer@i3s.up.pt

<sup>2</sup>Faculdade de Engenharia da Universidade do Porto (FEUP), Universidade do Porto, OPO, Portugal

<sup>3</sup>Instituto de Ciências Biomédicas Abel Salazar (ICBAS) Universidade do Porto), OPO, Portugal.

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/eGFP<sup>Luc</sup>* 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.

**Acknowledgements:** PTDC/CTM-NAN/3547/2014 (BAITS); FIS-FIS-2015-01\_CCV\_20150630-88 (INFARMED); SFRH/BPD/69110/2010 and SFRH/BD/137073/2018 (FCT); NORTE-01-0247-FEDER-033399 (siRNAC), NORTE-01-0247-FEDER-000008 and NORTE-01-0145-FEDER-000012 (N2020).

### References

- [1] Leiro, V. et al. *Curr. Gene Ther.*, **2017**, 17, 105.
- [2] Dufès, C. et al. *Advanc. Drug Del.*, **2005**, 57, 2177.
- [3] Leiro, V. et al. *J. Mat. Chem. B.*, **2017**, 5, 4901.
- [4] Pêgo, A.P., Leiro, V. et al, inventors; Biodegradable Dendritic Structure, Methods and Uses Thereof. **2017**, WO/2017/203437.

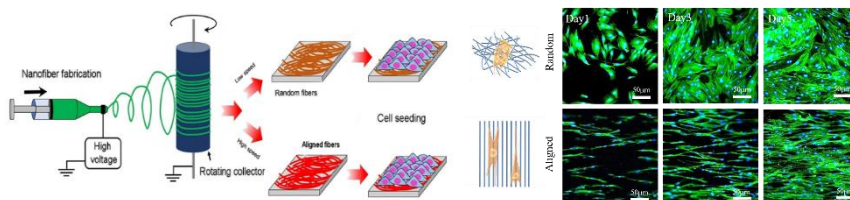
## Comparison of Cell Behavior on PVDF/MCNTs Electrospun Nanofibers with Random and Aligned Configuration

Huang Wei<sup>1,2</sup>, Xiangyang Shi<sup>1,2\*</sup> & Pedro Pires<sup>1\*</sup>

<sup>1</sup>CQM-Centro de Química da Madeira, Universidade da Madeira, Campus da Penteada, 9000-390 Funchal, Portugal. E-mail: weihuang1008@outlook.com, pedro.pires@staff.uma.pt

<sup>2</sup>Key Laboratory of Textile Science and Technology, Ministry of Education, College of Textiles, Donghua University, China. E-mail: xshi@dhu.edu.cn

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).

### References

- [1] Wang, A. et al. *Nano Energy*, **2018**, 43, 63.
- [2] Persano, L. et al. *Adv.Mater.*, **2014**, 26, 7574.

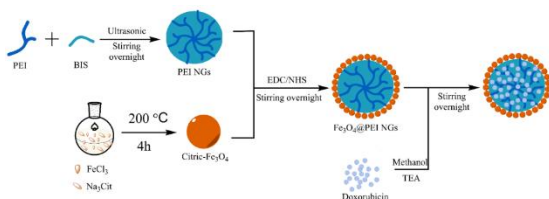
# Incorporation of Ultrasmall Iron Oxide Nanoparticle and Doxorubicin Within Polymer Nanogels for Tumor Theranostics

Yu Zou<sup>1,2</sup> & Xiangyang Shi<sup>1,2\*</sup>

<sup>1</sup>CQM-Centro de Química da Madeira, Universidade da Madeira, Campus da Penteada 9000-390, Funchal, Portugal.

<sup>2</sup>State Key Laboratory for Modification of Chemical Fibers and Polymer Materials, College of Chemistry Chemical Engineering and Biotechnology, Donghua University, Shanghai 201620, P. R. China. E-mail: xshi@dhu.edu.cn

We here synthesized polyethylenimine (PEI)-based nanogels (NGs) which loaded both MR contrast agent ultrasmall iron oxide ( $\text{Fe}_3\text{O}_4$ ) 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  $\text{Fe}_3\text{O}_4$  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 ( $2.29 \text{ mM}^{-1}\text{s}^{-1}$ ), 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.

**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).

## References

- [1] Meurer, R. A. et al. *Angew. Chem. Int. Ed.* **2015**, *56*, 7380.
- [2] Luo Y. et al. *Nanoscale*, **2015**, *7*, 14538.

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

Lydia dos Orfãos<sup>1</sup>, Cláudia Camacho<sup>1</sup>, Helena Tomás<sup>1</sup> & João Rodrigues<sup>1,2\*</sup>

<sup>1</sup>CQM – Centro de Química da Madeira, Universidade da Madeira, Campus da Penteada, 9020-105 Funchal, Portugal. E-mail: joaor@uma.pt

<sup>2</sup>School of Materials Science and Engineering/Center for Nano Energy Materials, Northwestern Polytechnical University, Xi'an 710072, China.

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.

**Acknowledgements:** This work was supported by Fundação para a Ciência e a Tecnologia (CQM Project Pest-OE/QUI/UI674/2019, 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).

### References

- [1] Ghaffari, M. et al. *Eur. J. Pharm. Sci.*, **2018**, 122, 311.
- [2] Wang, M.; Liu, H.; Li, L.; Cheng, Y., *Nat. Commun.*, **2014**, 5, 3053.
- [3] Menaa, F.; Menaa, B.; Sharts, O. N. *J. Mol. Pharm. Pharm. Org. Process Res.*, **2013**, 1, 1.
- [4] Swami, R. et al. *J. Nanoparticle Res.*, **2015**, 17, 264.
- [5] Manuja, R.; Sachdeva, S.; Jain, A.; Chaudhary, J., *Int. J. Pharm. Sci. Rev. Res.* **2013**, 22, 109.

## Characterization of Photoluminescent PAMAM Dendrimers for Biomedical Applications

Cláudia Camacho<sup>1</sup>, Marta Urgellés<sup>2</sup>, Helena Tomás<sup>1</sup>, Fernando Lahoz<sup>2</sup> & João Rodrigues<sup>1,3</sup>

<sup>1</sup>CQM - Centro de Química da Madeira, MMRG, Universidade da Madeira. Campus da Penteada, 9020-105 Funchal, Portugal. E-mail: joaoc@staff.uma.pt

<sup>2</sup>Universidad de La Laguna, Departamento de Física, Apartado 456, 38200 San Cristóbal de La Laguna, Tenerife, Spain. E-mail: flahoz@ull.es

<sup>3</sup> School of Materials Science and Engineering/Center for Nano Energy Materials, Northwestern Polytechnical University, Xi'an 710072, China.

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.

**Acknowledgements:** This work was supported by Fundação para a Ciência e a Tecnologia (CQM Project PEst-OE/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).

### References

[1] Tomalia, D. A. et al. *Prog. Polym. Sci.*, **2019**, *90*, 35.

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

Julien Rossignol<sup>1,2,4\*</sup>, Nikolas Munro<sup>1,2</sup>, Micheal Fana M.<sup>2,4</sup>, Bhairavi Srinageshwar<sup>1,2,4</sup>, Clayton Malkowski<sup>1,2</sup>, Sydney Climie<sup>1,2</sup>, Stephanie Baiyasi<sup>1,2</sup>, Douglas Swanson<sup>5</sup>, Ajit Sharma<sup>5</sup> & Gary Dunbar<sup>1,2,3,6</sup>

<sup>1</sup>Field Neurosciences Institute Laboratory for Restorative Neurology, <sup>2</sup>Program in Neuroscience,

<sup>3</sup>Department of Psychology, <sup>4</sup>College of Medicine, <sup>5</sup>Department of Chemistry & Biochemistry Central Michigan University, Mount Pleasant, MI 48859, USA; <sup>6</sup>Field Neurosciences Inst., 4677 Towne Centre Rd. Suite 101 Saginaw, MI 48604, USA.

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.

**Acknowledgments:** Support for this study was provided by the Neuroscience program, the College of Medicine, the Field Neurosciences Institute, and the John G. Kulhavi Professorship in Neuroscience at CMU.

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

Mayank Kumar Singh<sup>1,4</sup>, Akella V. Subrahmanya Sarma<sup>2</sup>, M. Jerald Mahesh Kumar<sup>3</sup>, Ramakrishna Sistla<sup>1\*</sup> & Abhay Singh Chauhan<sup>5\*</sup>

<sup>1</sup>Department of Applied Biology, CSIR-Indian Institute of Chemical Technology, Hyderabad, India

<sup>2</sup>Department of Analytical Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad, India

<sup>3</sup>Animal House Facility, CSIR-Centre for Cellular & Molecular Biology, Hyderabad, India

<sup>4</sup>Academy of Scientific and Innovative Research (AcSIR), New Delhi, India

<sup>5</sup>Medical College of Wisconsin-School of Pharmacy, Milwaukee, WI, USA

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<sub>2</sub>) and G3.5 PAMAM (–COONa) dendrimers with a chemotherapeutic drug docetaxel (DTX).

Zeta potential, HR-TEM monographs with SAED pattern and <sup>1</sup>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.

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

### References

- [1] Chauhan, A.S. and Kaul M. J. *Nanoparticle Res.*, **2018**, *20*, 226.
- [2] Chauhan, A.S. and Svenson, S., **2008**, WO2007149500,(A9).

## Electrode Modification with G5 PAMAM-NH<sub>2</sub> Dendrimers

Gina Tavares<sup>1</sup>, José Mesquita<sup>1\*</sup> & João Rodrigues<sup>1, 2\*\*</sup>

<sup>1</sup>Centro de Química da Madeira, Universidade da Madeira. Campus da Penteada, Funchal, Portugal.

E-mail: \*jcm@staff.uma.pt \*\*joaor@uma.pt

<sup>2</sup>School of Materials Science and Engineering/Center for Nano Energy Materials, Northwestern Polytechnical University, Xi'an 710072, China.

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<sub>2</sub> 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<sub>2</sub> 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 nM, with 4-nitrophenol in linear range of 690 – 37 μM.

**Acknowledgements:** Fundação para a Ciência e a Tecnologia (FCT) through the CQM Strategic Project PEst-OE/UI0674/2013 and also 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).

### References

- [1] Bahadır, E. B.; Sezgintürk, M. K. *Talanta*, **2016**, *148*, 427.
- [2] Astruc, D.; Boisselier, E.; Ornelas, C. *Chem. Rev.*, **2010**, *110*, 1857.



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

Ibrahim Althobaiti & Lance Twymen

Department of Chemistry, The University of Sheffield, Dainton Building, Brook Hill, Sheffield S3 7HF, United Kingdom. ialthobaiti1@sheffield.ac.uk

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 500Å<sup>2</sup> and 5000Å<sup>2</sup> [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.

### References

- [1] Uversky, V. N., *Protein Sci.*, **2013**, 693.
- [2] Morales, R. et al. *J. Neurosci.*, **2010**, 4528.
- [3] Kozakov, D. et al. *Proc. Natl. Acad. Sci. U. S. A.*, **2011**, 13528.
- [4] Svenson, S., and Tomalia, D. A. *Adv. Drug Delivery Rev.*, **2012**, 102.
- [5] Chen, C. et al. *Small*, **2016**, 3667.

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

Ana Rute Neves<sup>1</sup>, Miguel Faria<sup>1</sup>, Filipe Olim<sup>1</sup>, João Rodrigues<sup>1,2</sup> & Helena Tomás<sup>1</sup>

<sup>1</sup>CQM - Centro de Química da Madeira, Universidade da Madeira, Campus da Penteada, 9020-105 Funchal, Portugal. E-mail: ana.neves@staff.uma.pt

<sup>2</sup>School of Materials Science and Engineering/Center for Nano Energy Materials, Northwestern Polytechnical University, Xi'an 710072, China.

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  $^1\text{H}$  NMR spectroscopy technique.

**Acknowledgements:** This work is supported by FCT (PEst-OE/QUI/UI0674/2019, CQM, Portuguese Government funds), by Madeira 14-20 Program, project PROEQUIPRAM (M1420-01-0145-FEDER-000008) and by ARDITI-Agência Regional para o Desenvolvimento da Investigação Tecnologia e Inovação (M1420-01-0145-FEDER-000005 - CQM\*). ARN also acknowledges ARDITI for her Post-Doc grant (ARDITI-CQM\_2017\_011-PDG) under the project M1420-01-0145-FEDER-000005 - CQM\*.

### References

- [1] Leiro, V.; Garcia, J.P.; Tomás, H.; Pêgo, A.P. *Bioconjug. Chem.*, **2015**, 26, 1185.
- [2] Feliu, N.; Walter, M.V.; Montañez, M.I.; et al. *Biomaterials*. **2012**, 33, 1970.

## Inclusion of Dendrimers in Exosomes

Filipe Olim<sup>1</sup>, João Rodrigues<sup>1,2</sup> & Helena Tomás<sup>1\*</sup>

<sup>1</sup>CQM - Centro de Química da Madeira, Universidade da Madeira, Campus da Penteada, 9020-105 Funchal, Portugal. E-mail: \*lenat@staff.uma.pt

<sup>2</sup>School of Materials Science and Engineering/Center for Nano Energy Materials, Northwestern Polytechnical University, Xi'an 710072, China.

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 exogenous 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 exogenous 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 (<sup>1</sup>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.

**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).

### References

- [1] Liu, C. and Su, C. *Theranostics*, **2019**, *9*, 1015.
- [2] Yu, B.; Zhang, X; Li, X. *Int. J. Mol. Sci.*, **2014**, *15*, 4142.

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

Carla S. Alves<sup>1</sup>, Natacha Antunes<sup>1</sup>, Helena Tomás<sup>1</sup>, Miguel A. R. B. Castanho<sup>2</sup> & João Rodrigues<sup>1,3\*</sup>

<sup>1</sup>CQM - Centro de Química da Madeira, MMRG, Universidade da Madeira, Campus Universitário da Penteada, 9020-105 Funchal, Portugal. \*joaor@staff.uma.pt

<sup>2</sup>Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal

<sup>3</sup>School of Materials Science and Engineering/Center for Nano Energy Materials, Northwestern Polytechnical University, Xi'an 710072, China.

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.

**Acknowledgements:** This work was supported by FCT-Fundação para a Ciência e a Tecnologia (CQM Project PEstOE/UI0674/2019, Portuguese Government funds), and through the 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 Post-doc Grant (002458/2015/132) (CSA) through the project M1420- 09-5369-FSE-000001.

### References

- [1] Oliveira-Cruz, C. et al. T. *FEMS Microbiol. Rev.*, **2015**, 39, 155.
- [2] Alen, M. M. and Schols D. J. *Trop. Med.*, **2012**, 2012, 628475.
- [3] Musso, D. and Gubler, D. J. *Clin. Microbiol. Rev.*, **2016**, 29, 487.

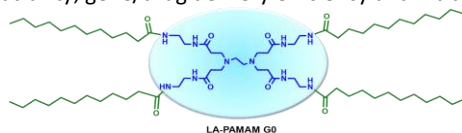
## Synthesis and Characterization of Molecularly Precise Lauric Acid – Dendrimer Conjugates for Gene/Drug Delivery

Helena Chá-Chá, Filipe Olim, Helena Tomás\*, João Rodrigues & Ruilong Sheng\*

CQM - Centro de Química da Madeira, Universidade da Madeira, Campus da Penteada, 9020-105 Funchal, Portugal, \*e-mails: lenat@staff.uma.pt; ruilong.sheng@staff.uma.pt.

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. <sup>1</sup>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.

**Acknowledgements:** This work was supported by FCT - 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). ARDITI-Agência Regional para o Desenvolvimento da Investigação, Tecnologia e Inovação is acknowledged for the project M1420-01-0145-FEDER-000005-Centro de Química da Madeira-CQM\* (Madeira 14-20) and ARDITI-2017-ISG-003 (R. Sheng).

### References

[1] Santos, J.L.; Oliveira, H.; Pandita, D.; Rodrigues, J.; Pêgo, A.P.; Granja, P.L.; Tomás, H. *J. Control. Rel.*, **2010**, *144*, 55.



## AUTHORS INDEX

---





A. Tapenard .....	95
Abhay Singh Chauhan .....	65, 137
Achim Temme .....	93
Adriana Cruz .....	121
Ajit Sharma .....	78, 136
Akella V. Subrahmanya Sarma .....	65, 137
Alba Martinez .....	49
Albena Lederer .....	64
Alberto Rábano .....	58
Aldrik Velders .....	48
Alena Krupková .....	54, 72, 80
Alexa Toth .....	78
Amit Fallek .....	77
Ana Charas .....	114
Ana M. Bajo .....	81
Ana M. Garzón P. ....	96
Ana M. Gonzalez-Luque .....	119
Ana Olival .....	91
Ana Patrícia Spencer .....	83, 131
Ana Paula Pêgo .....	55, 83, 105, 131
Ana Rute Neves .....	140
Ana Spencer .....	55
Anard Salvaraj .....	59
Anna Munder .....	75
Anna Nováčková .....	113
Anne-Marie Caminade .....	29
Annika Vogt .....	101
António Paulo .....	121
Arie Gruzman .....	75
Artem Zibarov .....	29
Aura Tintaru .....	76
Aurélien Hameau .....	29
Balachandar Kathirvelu .....	78
Barbara Klajnert-Maculewicz .....	124
Barbara Zabłocka .....	74
Beatriz Custódio .....	55
Bethany MacDonald .....	78
Bhairavi Srinageshwar .....	78, 136
Brigitte Voit .....	64, 93
Carla S. Alves .....	117, 120, 142
Carlos E. Gutierrez-Ulloa .....	125
Carlos Guerrero-Beltrán .....	49, 89
Cátia Ornelas .....	96
Célia Fernandes .....	121
Chai-Lin Kao .....	59, 116, 118
Chang Nga Wun .....	80
Charles N. Moorefield .....	41
Chie Kojima .....	50, 108
Ching-Hua Tsai .....	116
Cláudia Camacho .....	88, 134, 135

Clayton Malkowski .....	78, 136
Cristian A. Strassert .....	73
D. Pulido .....	87
Dan Li .....	39
Dandan Zhu .....	92
Denisa Houšková .....	113
Desislava Staneva .....	111, 115
Diego L. Bertuzzi .....	96
Dietmar Appelhans .....	64, 93
Dina Maciel .....	89, 94, 109, 130
Dominika Wróbel .....	54, 127
Donald A. Tomalia .....	25
Douglas Swanson .....	78, 136
Duarte Fernandes .....	82, 117
Ekaterina B. Zhulina .....	51
Ekaterina Pashkina .....	125
Elena Fuentes .....	125
Elisa Quaas .....	101
Elizabeth Igne Ferreira .....	123
Elżbieta Zieminska .....	74
Eric Kuhn .....	78
Evgenia Vasileva-Tonkova .....	111
Evgeny Apartsin .....	79, 125
Ezequiel Perez-Inestrosa .....	73, 119
F. Albericio .....	87
F. Javier de la Mata .....	49, 61, 79, 81, 87, 106, 107, 110, 125, 128
F. Liko .....	112
Fernando Lahoz .....	135
Fijs van Leeuwen .....	48
Filipe Olim .....	140, 141, 143
Fiorenza Rancan .....	101
Flonja Liko .....	57
Francisco Santos .....	109, 130
Franck Suzenet .....	90
G. Acosta .....	87
Gary Dunbar .....	78, 136
George R. Newkome .....	41
Georgios Paraskevopoulos .....	113
Gina Tavares .....	138
Grant Raymor .....	78
Guillaume Collet .....	90
Hai-Bo Yang .....	56
Helena Chá-Chá .....	143
Helena Tomás .....	88, 89, 91, 94, 97, 105, 109, 120, 134, 135, 140, 141, 142, 143
Horng-Huey Ko .....	71
Huang Wei .....	132
Hui-Ting Chen .....	71
Ibrahim Althobaiti .....	139

Ignacio Rodríguez-Izquierdo .....	128
Ignacion Relaño-Rodríguez .....	128
Inmaculada Posadas .....	58
Inna O. Lebedeva .....	51
István Bánai .....	68, 129
Ivo Grabchev .....	111, 115
Ivo J. Martins .....	97
J. L. Copa-Patiño .....	87
J. Soliveri de Carranza .....	87
J. Vidal-Gancedo .....	112
Jael Fernández .....	87
James R. Baker Jr. ....	35, 60
Jan Bart ten Hove .....	48
Jan Budka .....	80
Jan Čermák .....	54, 72
Jan Malý .....	54, 127
Jan Sýkora .....	80
Javier Sánchez-Nieves .....	79
Jean-Baptiste Verlhac .....	29
Jeanine Giarolla .....	102
Jean-Pierre Majoral .....	29, 31, 58
Jennifer Daeg .....	93
Jesse Chen .....	60
Jesús Cano .....	110
Joanna Wietrzyk .....	124
João Rodrigues .....	82, 88, 89, 91, 94, 97, 105, 109, 120, 130, 134, 135, 138, 140, 141, 142, 143
Johannes Fingernagel .....	64
John Gallien .....	78
Jorge Morgado .....	114
Jørn B. Christensen .....	67
José Becerra .....	119
José Luis Copa-Patiño .....	110
Jose M. Perez-Pomares .....	73
José Mesquita .....	138
José Vidal-Gancedo .....	57
Joseph Hellrung .....	78
Juan A. Guadix .....	73
Juan Soliveri .....	110
Julien Rossignol .....	78, 136
Justin Stadler .....	78
Justin Teissié .....	29
K. A. Walker .....	101
Kamal Jouad .....	90
Katarzyna Trzeciak .....	66
Kateřina Vavrova .....	113
Keerthana Rajes .....	101
Kimihisa Yamamoto .....	52
Krzysztof Sztandera .....	124
Kui Luo .....	63

Kurt Lucas .....	96
L.F. Pinto .....	112
Lance Twymen .....	139
Laura Romero Castillo .....	58
Laurence Charles .....	76
Leila Mousavifar .....	95
Leonor Santos-Ruiz .....	119
Levente Novák .....	68, 129
Lianfang Du .....	39
Liebertová Michaela .....	127
Lin Jia .....	103
Ling Peng .....	37, 53, 76, 92
Lizhou Lin .....	39
Lucas Adriano do Nascimento .....	123
Lucie Červenková Štastná .....	54, 80, 104, 127
Luiz F. Pinto .....	57
Lydia dos Orfãos .....	134
M. Jerald Mahesh Kumar .....	65, 137
M. Royo .....	87
M. Vijaya Simha .....	118
M <sup>a</sup> Ángeles Muñoz-Fernández .....	49, 89, 109, 128
M <sup>a</sup> Jesús Bullido .....	128
M <sup>a</sup> Jesús Serramía-Lobera .....	49, 128
Maciej Cieřlak .....	66, 74
Magdalena Milczarek .....	124
Magdalena Stolarska .....	66
Maja Morawiak .....	74
Mamiko Tamaki .....	108
Manisha Singh .....	45
Manuel Algarra .....	117
Manuel Leal .....	49
Maria Francesca Ottaviani .....	107
Marie-Aude Hiebel .....	90
Marijana Petković .....	82
Marília Torrado .....	55
Marina Buyanova .....	125
Marta Majkowska .....	124
Marta Maroto-Díaz .....	81, 106
Marta Sowińska .....	74
Marta Urgellés .....	135
Martin Kořtějn .....	104
Martina Langerová .....	113
Marvin Cnudde .....	73
Maximilian Winkler .....	80
Mayank Kumar Singh .....	65, 137
Melissa Andrews .....	78
Melissa Resk .....	78
Michael Malkoch .....	122
Micheal Fana M. ....	136
Michela Cangiotti .....	107

Miglena Irikova .....	115
Miguel A. R. B. Castanho.....	142
Miguel Faria .....	140
Mire Zloh .....	126
Mireille Blanchard-Desce.....	29
Mohamed Akssira .....	90
Monika Müllerová .....	54, 72, 104, 127
Mor Weiss-Shtofman.....	77
Moshe Portnoy .....	77
Muriel Golzio .....	29
Nabil El Brahmi .....	90
Nadezhda Knauer .....	125
Nádia Nunes .....	94
Natacha Antunes .....	142
Natali Ashush.....	77
Natália Magalhães .....	55, 83, 131
Natalia Sanz del Olmo .....	81, 106
Nigel Tan .....	45
Nikolas Munro .....	78, 136
Nilsa Abreu .....	120
Noemi Molina .....	73, 119
Nora Fettingner .....	78
Nuno Martinho .....	126
Oleg V. Borisov.....	51
Oliver Andrén.....	122
Paula Ortega López .....	81, 87, 106
Paula Raposinho .....	121
Pavĺína Chladová.....	113
Pedro Costa .....	55
Pedro Granja.....	105
Pedro Pires.....	82, 117, 132
Petra Cuřínová .....	54, 72, 80, 104
Po-Chu Wu.....	71
Pushpendra Tripathi .....	62
R. Rej.....	95
Rafael Ceña-Diez.....	49, 89
Rafael Gómez.....	49, 61, 79, 81, 87, 106, 110, 125, 128
Rahul S. Bagul .....	33, 95
Rainer Haag .....	101
Ramakrishna Sistla.....	65, 137
Rana Sanyal.....	46
Raquel Juárez-Sánchez.....	128
Regina Herma .....	54
Renan Vinicius de Araújo.....	102
René Roy.....	33, 95
Reut Fallek .....	77
Riccardo Carloni.....	107
Rikke Heidemann Olsen .....	67
Rita Castro .....	105
Rita F. Pires .....	121, 126

Rodrigo Vieira Gonzaga.....	123
Roman Petrićkovič .....	104
Ruilong Sheng .....	143
Saïd El Kazzouli.....	90
Sandra García-Gallego.....	81, 106, 107, 122
Sara Quintana Sánchez .....	106
Sara Reis.....	55
Scott Swanson.....	60
Serge Mignani .....	58
Shalini Tripathi .....	62
Sindhuja Koneru.....	78
Sofia Santos .....	55
Somnath Bhattacharjee .....	60
Stanislav Šabata .....	104
Stéphane Petoud .....	90
Stephanie Baiyasi .....	136
Suhe Wang.....	60
Susanne Boye.....	64
Svetlana V. Eliseeva.....	90
Sydney Climie.....	78, 136
Tamara Rodríguez .....	110
Tamás S. Miklósi.....	68
Teresa Casimiro.....	114
Terry W.J. Steele .....	45
Thomas Fagan .....	78
Tímea Szabó .....	129
Tomáš Strašák.....	54, 72, 80, 104, 127
Valentín Ceña.....	58
Valeria Arkhipova.....	79
Vasco D. B. Bonifácio .....	47, 114, 121
Vega Lloveras .....	57, 112
Victoria Leiro .....	55, 83, 131
Virág Kiss .....	68
Virgil Percec .....	27
Vratislav Blechta .....	80
Wahid Tatan.....	54
Wei Huang .....	132
Xiangyang Shi.....	38, 39, 93, 120, 132, 133
Xiaoxuan Liu .....	53, 92
Xiaoying Xu .....	93
Yi-Chin Lo .....	71
Yi-Ju Lu .....	71
Yolanda Vida .....	73, 119
Yu Fan .....	39
Yu Zou .....	133
Yuan-Ting Chan.....	116
Yung Liao.....	118
Zhao Wang.....	103
Zhengyi Cao.....	60
Zofia Urbanczyk-Lipkowska.....	66, 74



## PARTICIPANTS LIST

---



ADRIANA CRUZ
ALDRIK VELDER
ALENA KRUPKOVÁ
ANA M. GARZÓN
ANA OLIVAL
ANA PAULA PÊGO
ANA RUTE NEVES
ANA SPENCER
ANDREIA LUÍS
ANNE-MARIE CAMINADE
ARIE-LEV GRUZMAN
AURA TINTARU
BARBARA KLAJNERT-MACULEWICZ
BRUNA PEREIRA
CARLA ALVES
CAROLINA RODRIGUES
CHAI-LIN KAO
CHIE KOJIMA
CLÁUDIA CAMACHO
DANDAN ZHU
DÁVID NYUL
DAVID QUINTAL
DÉBORA REIS
DEESY CORREIA
DEISLAVA STANEVA
DIETMAR APPELHANS

DINA MACIEL
DONALD TOMALIA
DUARTE FERNANDES
EMERY SCHEIBERT
EVGENY APARTSIN
F. JAVIER DE LA MATA
FÁTIMA FERREIRA
FELIPE OLIM
FRANCISCA COSTA
FRANCISCO SANTOS
GEORGE R. NEWKOME
GEORGIOS PARASKEVOPOULOS
GINA TAVARES
HAI-BO YANG
HELENA CHÁ-CHÁ
HELENA TOMÁS
HUANG WEI
HUI-TING CHEN
IBRAHIM ALTHOBAITI
ISTVÁN BÁNYAI
IVO GRABCHEV
IVO J. MARTINS
JAEI FERNÁNDEZ
JAMES R. BAKER Jr.
JAN CERMAK
JEAN PIERRE MAJORAL



JEANINE GIAROLLA
JENNIFER DAEG
JOÃO RODRIGUES
JOÃO SERINA
JØRN B. CHRISTENSEN
JOSÉ VIDAL-GANCEDO
JULIEN ROSSIGNOL
KAMAL JOUAD
KEERTHANA RAJES
KIMIHISA YAMAMOTO
KUI LUO
LEILA MOUSAVIFAR
LEVENTE NOVÁK
LING PENG
LUCIE ŠŤASTNÁ
LYDIA DOS ORFÃOS
M <sup>a</sup> ANGELES MUÑOZ-FERNÁNDEZ
MACIEJ CIEŚLAK
MADALENA PEREIRA
MARA GONÇALVES
MARIANA VIEIRA
MARIJANA PETKOVIĆ
MAYANK SINGH
MONIKA MÜLLEROVÁ
MOSHE PORTNOY
NADEZHDA KNAUER

NÁDIA NUNES
NATALIA SANZ DEL OLMO
NILSA ABREU
NOEMI MOLINA
NUNO MARTINHO
OLEG V. BORISOV
PEDRO MOTA
PETRA CUŘÍNOVÁ
PUSHPENDRA TRIPATHI
RAFAEL GÓMEZ
RANA SANYAL
RENÉ ROY
RICCARDO CARLONI
RITA CASTRO
RITA PIRES
RODRIGO GONZAGA
RUI ROCHA
RUILONG SHENG
SANDRA GARCÍA-GALLEGO
SARA BETTENCOURT
SARA REIS
SERGE MIGNANI
SUHE WANG
TAMARA RODRÍGUEZ
TERRY W. J. STEELE
TOMÁŠ STRAŠÁK

---

VALENTÍN CEÑA

---

VASCO D. B. BONIFÁCIO

---

VEGA LLOVERAS

---

VICTORIA LEIRO

---

VIRGIL PERCEC

---

WUSONG LI

---

XIANGYANG SHI

---

XIAOXUAN LIU

---

YOLANDA VIDA

---

YU ZOU

---

YUAN-TING CHAN

---

YUNG LIAO

---

ZOFIA URBANCZYK-LIPKOWSKA

---



Notes:

Notes:

威海晨源分子新材料有限公司

WEIHAI CY DENDRIMER TECHNOLOGY CO., LTD.



# PAMAM DENDRIMERS DENDRITIC POLYMERS

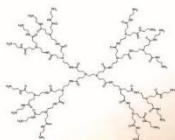
We are the first to realize ton scale dendritic polymers production in Asia.

Diagnostic PAMAM Dendrimers&industrial grade dendritic polymers are offered.  
CYD Products have been widely and largely used in **biomedical field, plastic, coating and ink area.**

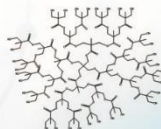
CYD-Professional Manufacturer for low cost dendritic polymers.

CYD is willing to cooperate with each professor or scientist to realize the commercialization of your research findings.

If you are interested in Dendritic Polymers cooperation with us, please send mail to General Manager Will Li by mail **Will.Li@whcyd.com.**



**PAMAM Dendrimers**



**Hyperbranched Polyester**

Weihai CY Dendrimer Technology Co.,Ltd.  
Add: 369-13, Caomiaozhi, Lingang District,  
Weihai City, Shandong, China, 264211  
Tel: 0631-5582236 Mail: [info@dendrimer.com.cn](mailto:info@dendrimer.com.cn)  
Web: [www.dendrimer.com.cn](http://www.dendrimer.com.cn)

