



# V-lab 10 years!!



**Juan L. Vivero-Escoto**  
Associate Professor  
Department of Chemistry  
The University of North Carolina at Charlotte

# Vision



Our vision is that by combining **basic science understanding with material science**, some of the most relevant problems of our time will be addressed. In particular, we will focus our initial efforts toward developing nanoparticle-based technologies for biomedical applications.

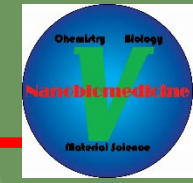
# Mission



The goal of our laboratory is to develop **creative solutions** to overcome some of the main issues in the application of nanotechnology to biomedicine. By its **diverse nature** our laboratory will provide an excellent and friendly environment for undergraduates, graduate students and postdoctoral research fellows. As a participant to the formation of the next generation of scientists, we will ask for **the best individual performance** (safety, ethics, research and education).

# The V-lab TEAM

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- ▶ Postdocs = 3
- ▶ Graduate students = 13 (Ph.D. = 7; M.S. = 6)
- ▶ Undergraduate students = 60
- ▶ Visiting scholars = 3
- ▶ Undergraduate students (Summer research) = 18
- ▶ High school students = 11

# Our NAMES



- ▶ Dr. Hemapriyadarshini (Priya) Vadarevu
- ▶ Dr. Paula Loman-Cortes
- ▶ Dr. Mubin Tarannum
- ▶ Dr. Ridhima Juneja
- ▶ Dr. Merlis Alvarez-Berrios
- ▶ Dr. Zachary Lyles
- ▶ M.S. Alexis Johnston
- ▶ M.S. Paolo Siano
- ▶ M.S. Alexandra Hurst
- ▶ M.S. Eric Fink
- ▶ M.S. Daniel Vega
- ▶ M.S. William Walker
- ▶ Abbe Eliasof, B.S. Chemistry
- ▶ Ashvini Dandapani, B.S. Biology/B.A. Chemistry
- ▶ Kira Marsh, B.S. Chemistry
- ▶ Anh Nguyen, B.A. Chemistry
- ▶ Alejandra Villa, B.A. Chemistry
- ▶ Emma Anderson, B.A. Chemistry
- ▶ Madi Pareja, B.S. Chemistry
- ▶ Zaneta Zhin, B.S. Chemistry
- ▶ Aliyah Aguila, B.S. Chemistry
- ▶ Karina Benitez, B.S. Biology
- ▶ Janay Clegg, B.A. Chemistry
- ▶ Joshua Mikombo, B.S. Biology
- ▶ Jacob Dobbs, B.S. Chemistry
- ▶ Amanda Derby, B.S. Biology
- ▶ Christina Payne, B.S. Biology
- ▶ Ishaq Ibrahim, B.S. Chemistry
- ▶ Taraneh Barjesteh, B.S. Chemical Engineering
- ▶ Vir Kalaria, B.S. Chemistry
- ▶ Samuel McManama, Post-Bac
- ▶ McKinley Kerns, B.S. Chemistry
- ▶ Taylor Walls, B.S. Biology Honors
- ▶ Meredith Collins, B.S. Biology
- ▶ Ricky Son, B.S. Biology (UNC-CH)/B.A. Chemistry
- ▶ Jose Marquez, B.S. Biochemistry
- ▶ Jonathan Duhon, B.S. Chemistry
- ▶ Brandon Black, B.S. Biology Honors
- ▶ Cayli Mena, B.S. Biochemistry
- ▶ Roa Saleh, B.S. Chemistry
- ▶ Jessica Hovey, B.S. Chemistry
- ▶ Caroline Rawlings, B.S. Biology
- ▶ Kebba Mba, B.S. Bioinformatics
- ▶ Sebin Yang, B.A. Chemistry
- ▶ Dmitriy Yermakovich, B.S. Biology
- ▶ Trang Tran, B.S. Biology
- ▶ Rachel Jones, B.S. Biology
- ▶ Cameron Woodall, B.S. Exercise Science
- ▶ Christian Sangio, B.S. Biology/B.A. Chemistry
- ▶ Julius Koomson, B.S. Biology
- ▶ Kristen Armstrong, B.S. Biology

# Our NAMES

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- ▶ Amir Hashemi, B.A. Chemistry
- ▶ Alexandra Hurst, B.S. Psychology/B.A. Chemistry
- ▶ Sheram Serrano-Camacho, B.S. Biology
- ▶ Ashutosh Patel, B.S. Biology
- ▶ Patrick Lodge, B.S. Chemistry/Biochemistry
- ▶ Austin Gibbs, B.S. Chemistry
- ▶ Shayan Shaghayeq Nazari B.S. Chemistry and Biochemistry
- ▶ Daniel DeCillis B.A. Biology
- ▶ Alisa D. Geier, Post-Baccalaureate
- ▶ Ankit Amin, B.A. Chemistry
- ▶ Sydney Kent, B.A. Chemistry
- ▶ Edward Lynch, B.S. Chemistry and B.A. Biology
- ▶ Erin Danielle Ross, B.S. Chemistry/Biochemistry
- ▶ Daniel Vega, B.A. Chemistry and B.S. Biology
- ▶ Laura Fritts, B.S. Biochemistry
- ▶ Breyinn Loftin, B.S. Chemistry
- ▶ Preston Pope, B.S. Chemistry/Biochemistry
- ▶ Cesar Roque-Alfaro B.S. Chemistry/Biochemistry
- ▶ Vivero-lab internship and NC-MSEN Pre-College Program program
- ▶ Camila Vallejo
- ▶ Maram Elnagheeb
- ▶ Charles Hood
- ▶ Jaquan Dozier
- ▶ Jared Johnson
- ▶ Nithin Ragunathan
- ▶ Faheem Diaab
- ▶ Brenda Dominguez
- ▶ Aarthi Saravanan
- ▶ Kailey Spicer



# Our FACES



Fall 2012



Fall 2015



Fall 2014



Fall 2013



Summer 2016



Summer 2017



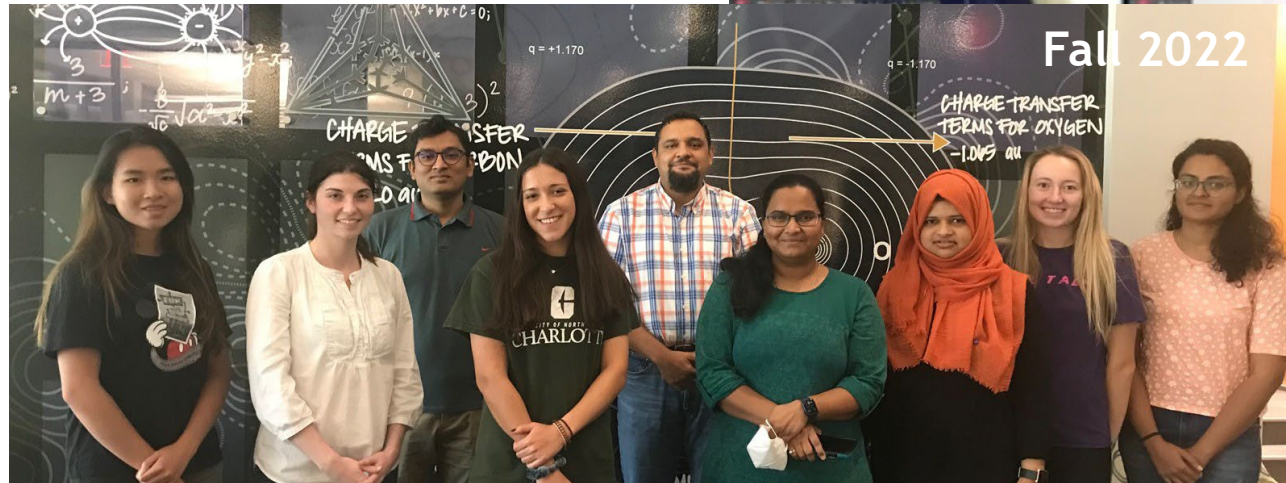
Fall 2018



Fall 2019



# Our FACES





# Publications and Funding



- ▶ Publications = 35 (Papers = 26; Reviews = 2; Book chapters = 3; Proceedings = 4)
- ▶ Funding = ORAU, NIH 1R15CA192160, NSF-EAGER (#1835688), UNC ROI, NIH 1R01CA263897, NIH 1R16GM145434



## Multimodal Polysilsesquioxane Nanoparticles for Combinatorial Therapy and Gene Delivery in Triple-Negative Breast Cancer

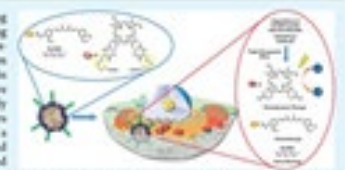
Ridhima Juneja,<sup>1,2</sup> Zachary Lyles,<sup>1,2</sup> Hemapriyadarshini Vadarevu,<sup>1,2</sup> Kamil A. Afonso,<sup>1,2</sup> and Juan L. Vivero-Escoto<sup>1,2,3,\*</sup>

<sup>1</sup>Department of Chemistry, <sup>2</sup>The Center for Biomedical Engineering and Science, and <sup>3</sup>Nanoscale Science Program, University of North Carolina at Charlotte, Charlotte, North Carolina 28223, United States

Supporting Information

**ABSTRACT:** Multifunctional hybrid nanoparticles are being developed to carry a wide variety of therapeutic and imaging agents for multiple biomedical applications. Polysilsesquioxane (PSiQ) nanoparticles are a promising hybrid platform with numerous advantages to be used as a delivery system. In this report, we demonstrate the ability of a stimuli-responsive PSiQ-based platform to transport and deliver simultaneously protoporphyrin IX, curcumin, and RNA interference inducers inside human cells. This multimodal delivery system shows a synergistic performance for the combined phototherapy and chemotherapy of triple-negative breast cancer and can be used for efficient transfection of therapeutic nucleic acids. The current work represents the first report of using the PSiQ platform for the combined phototherapy and chemotherapy and gene delivery.

**KEYWORDS:** Polysilsesquioxane nanoparticles, Combination therapy, Photodynamic therapy, Stimuli-responsive systems, Gene delivery, Triple-negative breast cancer



Review

## Use of Polyhedral Oligomeric Silsesquioxane (POSS) in Drug Delivery, Photodynamic Therapy and Bioimaging

Paula Loman-Cortes<sup>1,2</sup>, Tamanna Binte Huq<sup>1,2</sup> and Juan L. Vivero-Escoto<sup>1,2,3,\*</sup>

- <sup>1</sup> Department of Chemistry, The University of North Carolina at Charlotte, Charlotte, NC 28223, USA; plomanco@unc.edu (P.L.-C.); thb@unc.edu (T.B.H.)
  - <sup>2</sup> Nanoscale Science Program, The University of North Carolina at Charlotte, Charlotte, NC 28223, USA
  - <sup>3</sup> The Center for Biomedical Engineering and Science, The University of North Carolina at Charlotte, Charlotte, NC 28223, USA
- \* Correspondence: Juan.Vivero-Escoto@unc.edu; Tel.: +1-704-687-5239

**Abstract:** Polyhedral oligomeric silsesquioxanes (POSS) have attracted considerable attention in the design of novel organic-inorganic hybrid materials with high performance capabilities. Features such as their well-defined nanoscale structure, chemical tunability, and biocompatibility make POSS an ideal building block to fabricate hybrid materials for biomedical applications. This review highlights recent advances in the application of POSS-based hybrid materials, with particular emphasis on drug delivery, photodynamic therapy and bioimaging. The design and synthesis of POSS-based materials is described, along with the current methods for controlling their chemical functionalization for biomedical applications. We summarize the advantages of using POSS for several drug delivery applications. We also describe the current progress on using POSS-based materials to improve photodynamic therapies. The use of POSS for delivery of contrast agents or as a passivating agent for nanoparticles is also summarized. We envision that POSS-based hybrid materials have great potential for a variety of biomedical applications including drug delivery, photodynamic therapy and bioimaging.

**Keywords:** polyhedral oligomeric silsesquioxane (POSS); drug delivery systems (DDS); photodynamic therapy (PDT); biomedical applications; imaging



Citation: Loman-Cortes, P.; Binte Huq, T.; Vivero-Escoto, J.L. Use of Polyhedral Oligomeric Silsesquioxane (POSS) in Drug Delivery, Photodynamic Therapy and Bioimaging. *Molecules* **2021**, *26*, 6453. <https://doi.org/10.3390/molecules2616453>



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## Nanoparticle combination for precise stroma modulation and improved delivery for pancreatic cancer

Mubin Tarannum<sup>a,b,1</sup>, Katherine Holtzman<sup>c</sup>, Didier Dreaud<sup>c,d</sup>, Pinku Mukherjee<sup>c,d</sup>, Juan L. Vivero-Escoto<sup>a,b,d,\*</sup>

- <sup>a</sup> Department of Chemistry, University of North Carolina Charlotte, Charlotte, NC 28223, USA
- <sup>b</sup> Nanoscale Science Program, University of North Carolina Charlotte, Charlotte, NC 28223, USA
- <sup>c</sup> Department of Biological Sciences, University of North Carolina Charlotte, Charlotte, NC 28223, USA
- <sup>d</sup> Center for Biomedical Engineering and Science, University of North Carolina Charlotte, Charlotte, NC 28223, USA

### ARTICLE INFO

**Keywords:** Pancreatic cancer, Tumor stroma, Mesoporous silica nanoparticles, Combination therapy, SiH inhibitor

### ABSTRACT

Therapeutic success in the treatment of pancreatic ductal adenocarcinoma (PDAC) is hindered by the extensive stroma associated to this disease. Stroma is composed of cellular and non-cellular components supporting and evolving with the tumor. One of the most studied mediators of cancer cell-stroma crosstalk is sonic hedgehog (SHH) pathway leading to the intense desmoplasia induced in PDAC tumors. Herein, we demonstrate that the use of mesoporous silica nanoparticles (MSNs) containing an SHH inhibitor, cyclopamine (CpP), and the combination of chemotherapeutic drugs (Gemcitabine (Gem)/cisplatin (cisP)) as the main delivery system for the sequential treatment led to the reduction in tumor stroma along with an improvement in the treatment of PDAC. We synthesized two versions of the MSN-based platform containing the SHH inhibitor (CpP-MSNs) and the drug combination (PEG-Gem-cisP-MSNs). In vitro and in vivo protein analysis show that CpP-MSNs effectively inhibited the SHH pathway. In addition, the sequential combination of CpP-MSNs followed by PEG-Gem-cisP-MSNs led to effective stromal modulation, increased access of secondary PEG-Gem-cisP-MSNs at the tumor site, and improved therapeutic performance in HPAF II xenograft mice. Taken together, our findings support the potential of drug delivery using MSNs for stroma modulation and to prevent pancreatic cancer progression.

## Biodegradable Silica-Based Nanoparticles with Improved and Safe Delivery of Protoporphyrin IX for the In Vivo Photodynamic Therapy of Breast Cancer

Zachary K. Lyles, Mubin Tarannum, Cayli Mena, Natalia M. Inada, Vanderlei S. Bognato, and Juan L. Vivero-Escoto\*

**Silica-based nanoplateforms are highly versatile and attractive delivery systems for cancer treatment. These platforms have been used for the effective delivery of pharmacological agents in preclinical settings. Though silicon oxide is found naturally in the human body, a major limitation associated with silica-based nanoparticles is their slow biodegradability. Therefore, the potential risks related to the longer bioaccumulation of these materials can be significant. In this work, the synthesis and application of a novel silica-based nanoplateform, polysilsesquioxane nanoparticles (PSiQ NPs) is reported. The developed PSiQ material contains stimuli-responsive properties, and improves biodegradability for the efficient delivery of a clinically relevant photosensitizer, protoporphyrin IX. Herein, it is demonstrated that the PSiQ nanoplateform is biocompatible and exhibits enhanced biodegradability in an immune-competent mouse model. In addition, PSiQ NPs show phototherapeutic efficiency for reducing the tumor burden in an orthotopic model of triple-negative breast cancer. These results may pave the way for the future clinical evaluation of this silica-based nanoplateform.**

biomedical applications. The wide variety of existing silica-based nanomaterials, including solid, mesoporous, hollow, and hybrid, presents several advantages for drug delivery (e.g., ease of synthesis and scale-up, high surface area, tunable porosity, size distribution, and composition) along with the access to versatile surface functionalization.<sup>[1,2]</sup> Some of these nanoparticles have been used to encapsulate molecules and/or metallic nanoparticles.<sup>[3,4]</sup> Despite these advantages, there is no reported clinical use of silica-based nanoparticles for systemic delivery of therapeutic agents. Silica is "generally regarded as a safe (GRAS)" ingredient by the U.S. Food and Drug Administration<sup>[5,7]</sup> nevertheless, a crucial challenge that needs to be addressed, in order to advance this platform for future clinical applications, is to enhance its rate of biodegradability in



Article

## Influence of Cationic meso-Substituted Porphyrins on the Antimicrobial Photodynamic Efficacy and Cell Membrane Interaction in *Escherichia coli*

Alexandra N. Hurst<sup>1,2,3</sup>, Beth Scarbrough<sup>1,2,3</sup>, Roa Saleh<sup>1</sup>, Jessica Hovey<sup>1</sup>, Farideh Ari<sup>1</sup>, Shreya Goyal<sup>2,4</sup>, Richard J. Chi<sup>2,4</sup>, Jerry M. Troutman<sup>1,2,3,\*</sup> and Juan L. Vivero-Escoto<sup>1,2,3,\*</sup>

- <sup>1</sup> Department of Chemistry, The University of North Carolina at Charlotte, Charlotte, NC 28223, USA; ahurst10@unc.edu (A.N.H.); bscarbro@unc.edu (B.S.); roasaleh@email.unc.edu (R.S.); jhovey@wayne.edu (J.H.); fari@unc.edu (F.A.)
  - <sup>2</sup> The Center for Biomedical Engineering and Science, The University of North Carolina at Charlotte, Charlotte, NC 28223, USA; sgoyal2@unc.edu (S.G.); rchi1@unc.edu (R.J.C.)
  - <sup>3</sup> Nanoscale Science Program, Department of Chemistry, The University of North Carolina at Charlotte, Charlotte, NC 28223, USA
  - <sup>4</sup> Department of Biological Sciences, The University of North Carolina at Charlotte, Charlotte, NC 28223, USA
- \* Correspondence: [juan.vivero-escoto@unc.edu](mailto:juan.vivero-escoto@unc.edu) (J.L.V.-E.); [tel:+1-704-687-5239](mailto:tel:+1-704-687-5239) (J.L.V.-E.)

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Article

## Light-Activated Protoporphyrin IX-Based Polysilsesquioxane Nanoparticles Induce Ferroptosis in Melanoma Cells

Hemapriyadarshini Vadarevu<sup>1,2</sup>, Ridhima Juneja<sup>1</sup>, Zachary Lyles<sup>1,2</sup> and Juan L. Vivero-Escoto<sup>1,2,3,\*</sup>

- <sup>1</sup> Department of Chemistry, The University of North Carolina at Charlotte, Charlotte, NC 28223, USA; hvadarev@unc.edu (H.V.); ridhima.juneja@gmail.com (R.J.); zklyes@gmail.com (Z.L.)
  - <sup>2</sup> Nanoscale Science Program, The University of North Carolina at Charlotte, Charlotte, NC 28223, USA
  - <sup>3</sup> The Center for Biomedical Engineering and Science, The University of North Carolina at Charlotte, Charlotte, NC 28223, USA
- \* Correspondence: [Juan.Vivero-Escoto@unc.edu](mailto:Juan.Vivero-Escoto@unc.edu); Tel.: +1-704-687-5239

**Abstract:** The use of nanoparticle-based materials to improve the efficacy of photodynamic therapy (PDT) to treat cancer has been a burgeoning field of research in recent years. Polysilsesquioxane (PSiQ) nanoparticles with remarkable features, such as high loading of photosensitizers, biodegradability, surface tunability, and biocompatibility, have been used for the treatment of cancer in vitro and in vivo using PDT. The PSiQ platform typically shows an enhanced PDT performance following a cell death mechanism similar to the parent photosensitizer. Ferroptosis is a new cell death mechanism recently associated with PDT that has not been investigated using PSiQ nanoparticles. Herein, we synthesized a protoporphyrin IX (PpIX)-based PSiQ platform (PpIX-PSiQ NPs) to study the cell death pathways, with special focus on ferroptosis, during PDT in vitro. Our data obtained from different assays that analyzed Annexin V binding, glutathione peroxidase activity, and lipid peroxidation demonstrate that the cell death in PDT using PpIX-PSiQ NPs is regulated by apoptosis and ferroptosis. These results can provide alternative approaches in designing PDT strategies to enhance therapeutic response in conditions stymied by apoptosis resistance.

**Keywords:** photodynamic therapy; cancer treatment; cell death mechanisms; melanoma; nanomedicine



Citation: Vadarevu, H.; Juneja, R.; Lyles, Z.; Vivero-Escoto, J.L. Light-Activated Protoporphyrin IX-Based Polysilsesquioxane Nanoparticles Induce Ferroptosis in Melanoma Cells. *Nanomaterials* **2021**, *11*, 2324. <https://doi.org/10.3390/nanomaterials11112324>

# Publications



## RESEARCH ARTICLE



### Advanced Nanoengineering Approach for Target-Specific, Spatiotemporal, and Ratiometric Delivery of Gemcitabine–Cisplatin Combination for Improved Therapeutic Outcome in Pancreatic Cancer

Mubin Tarannum, Md Akram Hossain, Bryce Holmes, Shan Yan, Pinku Mukherjee, and Juan L. Vivero-Escoto\*

Pancreatic ductal adenocarcinoma (PDAC) is an intractable malignancy with a dismal survival rate. Recent combination therapies have had a major impact on the improvement of PDAC prognosis. Nevertheless, clinically used combination regimens such as FOLFIRINOX and gemcitabine (Gem)/nab-paclitaxel still face major challenges due to lack of the safe and ratiometric delivery of multiple drugs. Here, a rationally designed mesoporous silica nanoparticle (MSN)-based platform is reported for the target-specific, spatiotemporal, ratiometric, and safe co-delivery of Gem and cisplatin (cisPt). It is shown that systemic administration of the nanoparticles results in synergistic therapeutic outcome in a syngeneic and clinically relevant genetically engineered PDAC mouse model that has rarely been used for the therapeutic evaluation of nanomedicine. This synergism is associated with a strategic engineering approach, in which nanoparticles provide ratiometric controlled delivery and in situ differential release of Gem/cisPt drugs with the goal of overcoming resistance to P<sub>0</sub>-based drugs. The platform is also rendered with additional tumor-specificity via a novel tumor-associated mucin1 (TMUC1)-specific antibody, TAB004. Overall, the platform suppresses tumor growth and eliminates the off-target toxicities of a highly toxic chemotherapy combination.

the stages combined; a trend that has not improved significantly over decades.<sup>13–15</sup> Multiple reasons contribute to the ineffectiveness of current PDAC treatments, underscoring the need for developing novel and effective therapeutic options aimed at improving PDAC prognosis.<sup>16,17</sup> Basic as well as clinical research have recently turned toward combination therapies with the FDA's approval of FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin), gemcitabine (Gem) plus nab-paclitaxel, and ONIVYDE (liposomal formulation of irinotecan) used in combination with 5-fluorouracil and leucovorin.<sup>18–20</sup> A number of other combinations, including multidrug chemotherapy and molecular agents, are also currently under investigation.<sup>20,21</sup> Recent insights gained from the characterization of recurrent genetic alterations has revealed that a subset of PDACs, linked to germline-based mutations, can ben-

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journal homepage: [www.elsevier.com/locate/mtcomm](http://www.elsevier.com/locate/mtcomm)



### Molecular dynamic simulation of polyhedral oligomeric silsesquioxane porphyrin molecules: Self-assembly and influence on morphology

Paula Loman-Cortes<sup>a,b</sup>, Donald J. Jacobs<sup>c,d,\*</sup>, Juan L. Vivero-Escoto<sup>a,b,d,\*</sup>

<sup>a</sup> Department of Chemistry, University of North Carolina, Charlotte, NC 28223, USA  
<sup>b</sup> Nanoscale Science Program, University of North Carolina, Charlotte, NC 28223, USA  
<sup>c</sup> Department of Physics and Optical Science, University of North Carolina, Charlotte, NC 28223, USA  
<sup>d</sup> The Center for Biomedical Engineering and Science, University of North Carolina, Charlotte, NC 28223, USA

#### ARTICLE INFO

**Keywords:**  
Polyhedral oligomeric silsesquioxane (POSS)  
Porphyrin  
Self assembly  
Aggregation  
Simulation

#### ABSTRACT

Molecular dynamics was used to study the aggregation in water of three versions of polyhedral oligomeric silsesquioxane porphyrin (POSSP) molecules. The POSSP molecules have different functional groups: POSSP-TB has one hepta-isobutyl POSS unit, POSSP-Pb has one hepta-phenyl POSS molecule, and POSSP-TiB has four hepta-isobutyl POSS units. Three control porphyrins (TPP, ATPP, TATPP) were also simulated in this study. The effects of the different substituents on the POSS aggregation process and final morphology were investigated. It is observed that the isobutyl substituents in the POSS units drives the aggregation mainly through the hydrophobic effect. In the case of the phenyl POSS unit, the self-assembly process is also carried through the hydrophobic effect, but  $\pi$ - $\pi$  and H-bonding interactions play a role too. The final morphology of the aggregates show that the porphyrins associated with POSSP-TB and POSSP-TiB are far apart from each other contrary to POSSP-Pb, which may have a major implication on the optical properties of these aggregates. This study provides valuable insights on the aggregation in water of POSSP molecules, which are a tunable platform to design novel functional materials.



Article

### Imaging and SERS Study of the Au Nanoparticles Interaction with HPV and Carcinogenic Cervical Tissues

Andrea Ceja-Fdez<sup>1</sup>, Ramon Carriles<sup>2</sup>, Ana Lilia González-Yebra<sup>3</sup>, Juan Vivero-Escoto<sup>4</sup>, Elder de la Rosa<sup>5</sup> and Tzazara López-Luke<sup>6,\*</sup>

- Departamento de Física Médica, División de Ciencias e Ingenierías Campus León, Universidad de Guanajuato, León 37150, Mexico; [a.caja@ugto.mx](mailto:a.caja@ugto.mx)
  - Centro de Investigaciones en Óptica, A.P. 1-948, León 37150, Mexico; [ramonc@ciq.mx](mailto:ramonc@ciq.mx)
  - Departamento de Ciencias Aplicadas al Trabajo, División Ciencias de la Salud, Campus León, Universidad de Guanajuato, León 37670, Mexico; [anallilia@ugto.mx](mailto:anallilia@ugto.mx)
  - Department of Chemistry, The University of North Carolina at Charlotte, 9201 University City Blvd., Charlotte, NC 28223, USA; [juan.vivero-escoto@unc.edu](mailto:juan.vivero-escoto@unc.edu)
  - Facultad de Ingenierías, Campus Escamote, Universidad De La Salle Bajío, León 37150, Mexico; [edelarosa@desalle.edu.mx](mailto:edelarosa@desalle.edu.mx)
  - Instituto de Investigación en Metalurgia y Materiales, Universidad Michoacana de San Nicolás de Hidalgo, Edificio U, Ciudad Universitaria, Morelia 58030, Mexico
- \* Correspondence: [tzazara@umich.mx](mailto:tzazara@umich.mx)

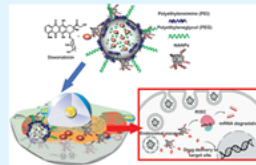
**Abstract:** In this work, gold NPs were prepared by the Turkevich method, and their interaction with HPV and cancerous cervical tissues were studied by scanning electron microscopy, energy-dispersive x-ray spectroscopy, confocal and multiphoton microscopy and SERS. The SEM images confirmed the presence and localization of the gold NPs inside of the two kinds of tissues. The light absorption of the gold NPs was at 520 nm. However, it was possible to obtain two-photon imaging (red emission region) of the gold NPs inside of the tissue, exciting the samples at 900 nm, observing the morphology of the tissues. The infrared absorption was probably due to the aggregation of gold NPs inside the tissues. Therefore, through the interaction of gold nanoparticles with the HPV and cancerous cervical tissues, a surface enhanced Raman spectroscopy (SERS) was obtained. As preliminary studies, having an average of 1000 Raman spectra per tissue, SERS signals showed changes between the HPV-infected and the carcinogenic tissues; these spectral signatures occurred mainly in the DNA bands, potentially offering a tool for the rapid screening of cancer.

**Keywords:** gold nanoparticles; HPV; cervical cancer; two-photon imaging; confocal microscopy; multiphoton microscopy; Raman spectroscopy and SERS

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**ABSTRACT:** Programmable nucleic acid nanoparticles (NANPs) with precisely controlled functional compositions can regulate the conditional activation of various biological pathways and responses in human cells. However, the intracellular delivery of NANPs alone is hindered by their susceptibility to nuclease activity and inefficient crossing of biological membranes. In this work, we optimized the internalization and therapeutic performance of several representative NANPs delivered with mesoporous silica nanoparticles (MSNPs) tailored for efficient electrostatic association with NANPs. We compared the immunostimulatory properties of different NAMS-NP complexes formed with globular, planar, and fibrous NANPs and demonstrated the maximum immunostimulation for globular NANPs. As a proof of concept, we assessed the specific gene silencing by NA-MSN-P complex functionalized with siRNA targeting green fluorescent protein expressed in triple-negative human breast cancer cells. We showed that the fibrous NANPs have the highest silencing efficiency when compared to globular or planar counterparts. Finally, we confirmed the multimodal ability of MSNPs to co-deliver a chemotherapy drug, doxorubicin, and NANPs targeting apoptosis regulator gene *BCL2* in triple-negative breast cancer and melanoma cell lines. Overall, the combination of NANPs and MSNPs may become a new promising approach to efficiently treat cancer and other diseases via the simultaneous targeting of various pathways.

**KEYWORDS:** nucleic acid nanoparticles (NANPs), mesoporous silica nanoparticles (MSNPs), small interfering RNA, combination therapy, triple-negative breast cancer, melanoma, doxorubicin



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### Nanoparticle-based therapeutic strategies targeting major clinical challenges in pancreatic cancer treatment

Mubin Tarannum<sup>a,b,1</sup>, Juan L. Vivero-Escoto<sup>a,b,c,\*</sup>

<sup>a</sup> Department of Chemistry, University of North Carolina Charlotte, Charlotte, NC 28223, USA  
<sup>b</sup> Nanoscale Science Program, University of North Carolina Charlotte, Charlotte, NC 28223, USA  
<sup>c</sup> The Center for Biomedical Engineering and Science, University of North Carolina Charlotte, Charlotte, NC 28223, USA

#### ARTICLE INFO

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Nanoparticle-based approaches  
Pancreatic ductal adenocarcinoma  
Combinatorial drug delivery  
Tumor microenvironment  
Cancer immunotherapy  
Stroma modulation

#### ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest cancers due to its aggressiveness and the challenges for early diagnosis and treatment. Recently, nanotechnology has demonstrated relevant strategies to overcome some of the major clinical issues in the treatment of PDAC. This review is focused on the pathological hallmarks of PDAC and the impact of nanotechnology to find solutions. It describes the use of nanoparticle-based systems designed for the delivery of chemotherapeutic agents and combinatorial alternatives that address the chemoresistance associated with PDAC, the development of combination therapies targeting the molecular heterogeneity in PDAC, the investigation of novel therapies dealing with the improvement of immunotherapy and handling the desmoplastic stroma in PDAC by remodeling the tumor microenvironment. A special section is dedicated to the design of nanoparticles for unique non-traditional modalities that could be promising in the future for the improvement in the dismal prognosis of PDAC.

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## FULL PAPER

siRNA Delivery



### RNA Fibers as Optimized Nanoscaffolds for siRNA Coordination and Reduced Immunological Recognition

Lauren Rackley, Jaimie Marie Stewart, Jacqueline Salotti, Andrey Krokhotin, Ankit Shah, Justin R. Halman, Ridhima Juneja, Jaclyn Smollett, Lauren Lee, Kyle Roark, Mathias Viard, Mubin Tarannum, Juan Vivero-Escoto, Peter F. Johnson, Marina A. Dobrovolskaia, Nikolay V. Dokholyan, Elisa Franco, and Kirill A. Afonin\*

RNA is a versatile biomaterial that can be used to engineer nanoassemblies for personalized treatment of various diseases. Despite promising advancements, the design of RNA nanoassemblies with minimal recognition by the immune system remains a major challenge. Here, an approach is reported to engineer RNA fibrous structures to operate as a customizable platform for efficient coordination of siRNAs and for maintaining low immunostimulation. Functional RNA fibers are studied in silico and their formation is confirmed by various experimental techniques and visualized by atomic force microscopy (AFM). It is demonstrated that the RNA fibers offer multiple advantages among which are: i) programmability and modular design that allow for simultaneous controlled delivery of multiple siRNAs and fluorophores, ii) reduced immunostimulation when compared to other programmable RNA nanoassemblies, and iii) simple production protocol for endotoxin-free fibers with the option of their cotranscriptional assembly. Furthermore, it is shown that functional RNA fibers can be efficiently delivered with various organic and inorganic carriers while retaining their structural integrity in cells. Specific gene silencing triggered by RNA fibers is assessed in human breast cancer and melanoma cell lines, with the confirmed ability of functional fibers to selectively target single nucleotide mutations.

#### 1. Introduction

RNA regulates a myriad of biological processes at different levels. RNA interference (RNAi)<sup>1</sup> for instance, is one of the therapeutically relevant pathways that allows the regulation of gene expression using exogenous RNAs. Notably, the very first therapy based on RNAi has just been approved by FDA.<sup>2</sup> Aside from synthetic RNAi inducers, several other promising classes of therapeutic nucleic acids (TNAs) have been developed, such as antisense oligos, aptamers, ribozymes, and mRNAs.<sup>3,4</sup> TNAs are being increasingly considered for the treatment of a wide variety of conditions, including cancers, metabolic disorders, viral infections, cardiovascular disorders, and inflammatory diseases, especially where traditional small molecule drugs fail.<sup>5</sup>

The simultaneous use of multiple TNAs is anticipated to have significant synergistic effects. One example is combinatorial RNAi used for the simultaneous



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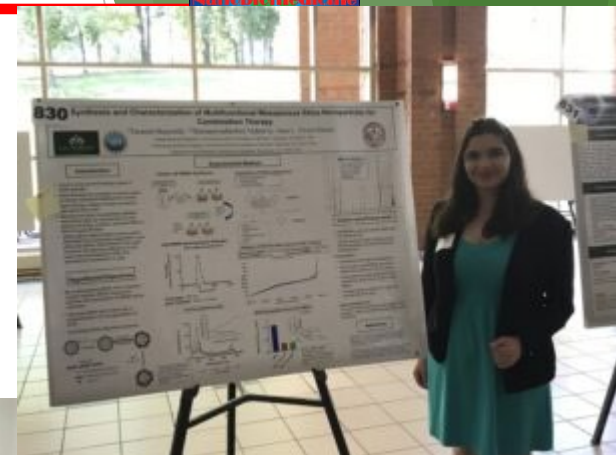
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