SURFACE CONJUGATION OF UPCONVERSION NANOPARTICLES VIA SUPRAMOLECULAR HOST-GUEST SELF-ASSEMBLY

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This dissertation is submitted for the degree of Doctor of Philosophy

December 2018

In loving memory of my grandfather, Mr. Jingzhi Fu (1937-2017)

To my grandmother, my mother, my father, and all of friends

CERTIFICATE OF ORIGINAL AUTHORSHIP

I, Yulong Sun declare that this thesis, is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the School of Life Sciences, Faculty of Science at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise reference or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

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Date: 30 August 2018

ABSTRACT

Surface Conjugation of Upconversion Nanoparticles *via* Supramolecular Host-Guest Self-Assembly

Yulong Sun

Surface functionalization and conjugation hold the key to driving many purpose-synthesized nanoparticles into real-world applications. Lanthanide (Ln) ions doped upconversion nanoparticle (UCNP) is a good example: while it delivers a great promise as molecular probes, sensors, drug carriers and light transducers for a library of application in the area of biological and physical science. However, the hydrophobic surface of UCNPs, sometimes, is one of the main challenges for further applications, especially in natural science. It remains a bottleneck for the community to explore practical strategies to functionalize the UCNPs surfaces for hydrophilicity conversion and further bioconjugation to meet many cellular and molecular specific needs.

Supramolecular self-assembly is one of the leading topics in supramolecular chemistry. It is a process in which disordered molecular building blocks are specifically re-ordered and also a phenomenon where the components of a system assemble themselves spontaneously *via* interaction to form a larger functional unit. In the view of thermodynamics, self-assembly is an equilibrium process where the assembled components are in equilibrium with the individual components. In other words, it is driven by the minimization of Gibbs free energy. Compared with molecular chemistry, self-assembly, as the most critical component of the assembled method, was formed by intermolecular forces.

This thesis shows a new surface conjugation approach for UCNP modification *via* supramolecular host-guest interactions leading as-made oleic acid (OA) stabilized UCNPs (OA-UCNPs) from hydrophobic into hydrophilic. At the same time, the modified

host molecules on the surface of UCNPs can provide a considerable number of cavities, which can form the host-guest interaction with a series of molecules, such as anti-cancer drugs, biomolecules, and inorganic materials. The advantage of the modification approach is no further reaction formed for conjugation, which hugely increases the binding amounts and also shows the excellent binding behaviour by using the different binding systems.

This thesis is aiming to conduct studies of:

(i) the investigation of the surface of OA-UCNPs (in **Chapter 3**)

To convert UCNPs with high efficiency and yield, the original cover needs to be investigated. We predict and proof the binding strength and binding mode between an OA and two ß-$NaYF_4$ crystal surfaces of UCNPs.

(ii) the binding behaviours of different organically functional groups (**Chapter 4**)

Compared with the original of OA from the surface of UCNPs, we also choose several organic molecules which hold different functional groups. We discuss the effect of different functional groups and, most importantly, the binding mode and binding behaviour on the surface of UCNPs.

(iii) the investigation of binding behaviours of macrocycles on the surface of UCNPs and their applications in binding with organic molecules, biomolecules, and inorganic materials (**Chapter 4 ~ Chapter 6**).

We raise and design a new approach to convert the surface of UCNPs with different kinds of macrocycles. Then, we provide three applications in the areas of drug delivery, cell targeting, and energy transfer.

The thesis is organized as follows:

There are four main parts of the thesis, which includes:

- **Part I** Background

In this part, I introduce some basic information about supramolecular chemistry and UCNPs. The section of supramolecular chemistry consists of the concepts of supramolecular chemistry, supramolecular interactions, the selectivity of supramolecular chemistry, host-guest chemistry, self-assembly, and the current development of supramolecular chemistry. In the section of UCNPs, I start from the mechanism of upconversion to show the advantage of the upconversion materials, then display the synthetic methods of UCNPs for the further discussion on the surface modifications.

- **Part II** Literature Review: the surface modification and conjugation of UCNPs.

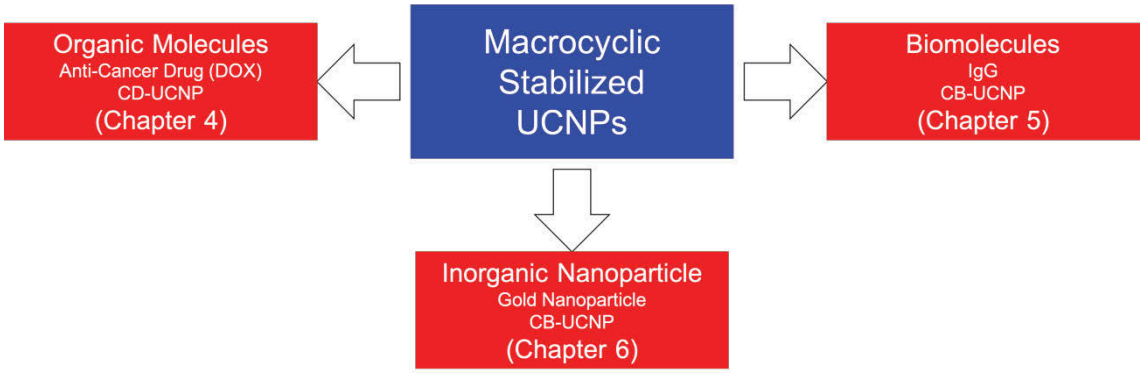
In this part, the surface modified approaches are sorted by the different supramolecular interactions. Except for the surface modification criteria, this review also gives a summary of surface conjugation of UCNP *via* supramolecular interactions with organic molecules and inorganic nanoparticles.

- **Part III** The original surface of OA-UCNPs

This part shows the synthesis and characterization of OA-UCNPs, and also the binding behaviour of OA on two kind crystal surfaces of UCNPs. This part also provides significant evidence to increase the efficiency of ligand exchange and surface binding.

- **Part IV** The applications of macrocycles modified UCNPs

This part includes three kinds of applications: molecular conjugation, biomolecular conjugation, and inorganic nanoparticle conjugation. All of these designs are based on the supramolecular host-guest interactions. In these chapters, we use two kinds of macrocycle to modify the surface of UCNPs for conjugating different types of organic molecules or inorganic materials, which showed in the following figure.



In **Chapter 4**, we conjugate anti-cancer drug, Doxorubicin Hydrochlorate (DOX), on the surface of UCNPs to test the bioavailability of DOX-loaded cyclodextrin-stabilized UCNPs (CD-UCNP). **Chapter 5** shows the binding properties of cucurbit[7]uril-stabilized UCNPs (CB-UCNP) with biomolecules, Immunoglobulin G, for cell targeting. The physical effect of UCNPs with AuNPs is investigated by the same binding approach, which explained in **Chapter 6**.

ACKNOWLEDGEMENTS

First of all, I would like to thank my great family: My grandfather, Mr Jingzhi Fu (1937-2017), for always setting an example for me and telling me how to be a good person. I still keep the letters he wrote to me over the years. These letters are not only encouragement but also a kind of care for me; My grandmother, Mrs Huang, for giving me all her love and parenting. She is the most important person in my life; My mother for her understanding and support. In those days, when I had to face difficult choices, she was the only one who had always supported and encouraged me; and My father for his silently guarding. Thank you so much for their support and encouragement over the past 30 years. They give me all their love but never ask for anything.

In my hometown, I spent 18 years finishing all my educations from elementary school to high school. Thanks all my teachers, who include Mrs Liu, Mr Li, Mrs Zhang, for not only teaching me knowledge but also telling us how to get along with others.

In Harbin, my second hometown, I spent four years getting my bachelor's degrees in engineering and management. I really appreciate all the faculty and staff from Department of Pharmaceutical Engineering for giving the knowledge and taking me into the world of science. Especially, I would like to offer my special thanks to Prof Hongrui Ji and Prof Miao Sun for giving me the great support on my Ph.D. application; Mrs Xizhi Zhao for taking me to the world of organic synthesis. Also, I would like to thank all of my friends in my University, Fujing Liu, Yong Zhao, Shikan Yang for the great support in that four years.

At Jilin University, I would like to thank Prof Yingwei Yang and Prof Sean Zhang for their professional guidance and valuable suggestion in science. I would also like to extend my thanks to these people for the collaboration and contribution to my research: Prof Minjie Li, Dr Bingjie Yang, Guojie Liu, Dr Yue Zhou, Dr Qinglan Li, Dr Yanqiu Wang,

Daxiong Chen, and Yuanchao Lv. Also, I would like to thank Dr Guan Wang, Dr Chu Wang, and Dr Gong Xin from College of Life Sciences for the great collaboration of my project. Special thanks to Ms Yanfang Sun for the unforgettable and enjoyable cooperation on the polymer project. I would also like to extend my thanks to the technicians of the laboratory for their help in offering me the resources in running the program.

At Northwestern University, I would like to give my highest respect to Sir Fraser Stoddart for giving me a chance for joining his group and also for the patient guidance and enthusiastic encouragement. Besides, I would like to thank Dr Dennis Cao for giving me a great help when I arrived Evanston, and Dr Alyssa Avestro for helping me polish my writing and teaching me how to prepare my presentation slides. Then I want to thank my office mate, Dr Yuping Wang for introducing many friends to me, by the way, he is also my lunch mate at that time. Dr Yilei Wu for taking me to the city of Chicago and introducing me to many Italian cultures.

At Tsinghua University, I would like to express my great appreciation to my research mentor, Prof Hongyu Zhang. That was the darkest time when I joined his group. He gave me a lot of support and made me regain my confidence. That was also a good experience that I learned a lot of knowledge of tribology from him, which gave me a new direction for future research. Besides, I would like to thank the whole group, Yanfang Sun, Tao Sun, Yi Wang, Yixin Wang, Xiaolong Tan, Yiwei Zheng, Ke Ren, Peng Zhao, Sizhe Liu, Dr Mingrui He, Dr Xiuling Ji, Kuan Zhang, Yaoyu Jiao, Ying Han, and Li Wan.

In 2015, I moved to Sydney and started my new journey in UTS. First of all, I would like to express my great appreciation to my supervisors, Dr Joshua Chou, Dr Helen Xu, and Prof Alison Ung. Thank Josh for the opportunities that he has created for me, as well as his patience and guidance in my darkest time. Thank Helen for bringing me to the world of crystal chemistry, allowing me to comprehend material science from a more

microscopic perspective. And also thank Alison for the great help on organic chemistry. More importantly, every time I chat with Alsion, I have a feeling at home. I am very fortunate to have these three as my supervisors. In these few years, they are more than just my supervisors, more like my best friend.

Much of the work described in this thesis cannot be completed so smoothly without the help of the kind people around me in the lab: Dr Wenjing Zhang for the great support on nanoparticles; Dr Joshua Chou for helping and teaching me on cell study; Baoming Wang for the cell imaging test and warm discussion; Dr Helen Xu for the material analysis and characterization; Yingzhu Zhou for the optical test; and Dr Olga Shimoni for the analysis of protein conjugation. Besides, I would like to thank my lab mates, Jiayan Liao, Bo Shao, Alex Gee, Matthew Cappadona, Christian Clarke, and Iurii Bodachivskyi for the support and encouragement. I also would like to thank all the members from Advanced Tissue Regeneration & Drug Delivery Group and Institute for Biomedical Materials and Devices for their great suggestion and discussion: Prof Dayong Jin, Dr Fan Wang, Dr Jinghua Fang, Dr Lu Liu, Zhiguang Zhou, Ming Guan, Chao Mi, Hao He, Dr Ying Wang, Anantdeep Kaur, Huan Wu, Yuan Liu, Dr Peter Su, Dr Laixu Gao, Guochen Bao, and Dr Joris Goudsmits. I am particularly grateful for the lab and technical assistance given by Dr Linda Xiao, Dr Ronald Shimmon, and Katie McBean.

In addition, I would like to thank my friends when I live in Sydney: Sheran Li, a knowledgeable person, for her warm sharing, great help and useful suggestions; Steven Vasilescu, my first Australian friend, for teaching me many useful English words which we could not learn from textbook; Jen Ming and Shilun Feng, the cute couple, for their positive life style; Jim Li, the non-economically suitable warm man, for his kindness, sharpness, and helpfulness; Wenjing Zhang, the sunflower, for bringing us the joy and special brain circuit; Yingzhu Zhou and Baoming Wang in “3A on the way” group for their help, encouragement and support in those days; Yibin Wei and Xiaoteng Jia in

“Sausage BBQ” group for our unlimited chat and alcohol; Mehran Kianinia, Yan Wang and Xin Xu, the Gold Coast group, for the unforgettable seaside Spring Festival; Penny Fang, the live map of Sydney, for her delicious chicken legs and food recommendations that won’t let you down; Yameng Zheng, an emotional person, for taking in her luxuriously configured office; and Zhengnan Shan, a person who never gets drunk, for his courtesy and humility.

Finally, I would like to thank all the people who appeared or will appear in my life. Thank you so much for telling me how the world is and how to enjoy the life.

Yulong Sun

City Campus, UTS

28 August 2018

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LIST OF ABBREVIATIONS AND ACRONYMS

3D: Three Dimensional

Ad: Amantadine Hydrochloride

ATR: Attenuated Total Reflectance

AuNP: Gold Nanoparticle

BB[n]: Bambus[n]uril

BSA: Bovine Serum Albumin

C[n]A: Calix[n]arene

CB[7]: Cucurbit[7]uril

CB[n]: Cucurbit[n]uril

CB-UCNP: Cucurbit[7]uril Stabilized Upconversion Nanoparticle

CB-UCNP@IgG-ADC: N-1-Adamantanecarboxyl Immunoglobulin G Self-Assembled on the Surface of Cucurbit[7]uril Stabilized Upconversion Nanoparticle

CD: Cyclodextrin

CD-UCNP: Cyclodextrin Stabilized Upconversion Nanoparticle

CD-UCNPs-DOX: Doxorubicin Loaded Cyclodextrin Stabilized Upconversion Nanoparticle

CTAB: Cetyltrimethylammonium Bromide

DAPI: 2-(4-Amidinophenyl)-6-Indolecarbamidine Dihydrochloride

DLS: Dynamic Light Scattering

DMEM: Dulbecco's Modified Eagle's Medium

DMSO: Methyl Sulfoxide

DOX: Doxorubicin Hydrochlorate

DTGA: Differential Thermogravimetric Analysis

EDC: N-(3-Dimethylaminopropyl)-N′-Ethylcarbodiimide Hydrochloride

$ErCl_3 \cdot 6H_2O$: Erbium (III) Chloride Hexahydrate

ESA: Excited State Absorption

EtOH: Ethanol

ETU: Energy Transfer Upconversion

FBS: Fetal Bovine Serum

FRET: Förster Resonance Energy Transfer

FT-IR: Fourier-Transform Infrared

$HAuCl_4$: Chloroauric Acid

IgG: Immunoglobulin G

IgG-ADC: N-1-Adamantanecarboxyl-IgG

ITC: Isothermal Titration Calorimetry

Ln: Lanthanide

Ln-UCNC: Lanthanide Doped Upconversion Nanocrystal

Ln-UCNP: Lanthanide Doped Upconversion Nanoparticle

L-Phe: L-Phenylalanine

L-Phe-AuNP: L-Phenylalanine Reduced Gold Nanoparticle

NH_4F: Ammonium Fluoride

MIM: Mechanically Interlocked Molecules

MTT: Thiazolyl Blue Tetrazolium Bromide

NMR: Nuclear Magnetic Resonance

$NOBF_4$: Nitrosyl Tetrafluoroborate

OA: Oleic Acid

OA-UCNP: Oleic Acid Stabilized Upconversion Nanoparticle

ODE: 1-Octadecene

OM: Oleylamine

PA: Photon Avalanche

P[n]A: Pillar[n]arene

PAH: Poly(Allylamine Hydrochloride)

PEG: Poly(Ethylene Glycol)

Phalloidin-FITC: Phalloidin-Fluorescein Isothiocyanate Labelled

PLNP: Persistent Luminescence Nanoparticle

PMPD: Poly(m-Phenylenediamine)

QD: Quantum Dots

SA: Sodium 1-Adamantanecarboxylate

SDP: Sodium Dodecyl Phosphate

SDS: Sodium Dodecyl Sulphate

TEM: Transmission Electron Microscopy

TGA: Thermogravimetric Analysis

THF: Tetrahydrofuran

UCNP: Upconversion Nanoparticle

UCNP-COOH: Direct Carboxyl-Modified Upconversion Nanoparticle

UV-vis: Ultraviolet Visible

XPS: X-Ray Photoelectron Spectra

XRD: X-Ray Diffraction

$YbCl_3 \cdot 6H_2O$: Ytterbium (III) Chloride Hexahydrate

$YCl_3 \cdot 6H_2O$: Yttrium (III) Chloride Hexahydrate

α-CD: α-Cyclodextrin

α-CD-COONa: Carboxylic α-Cyclodextrin Sodium Salt

α-CD-COOH-UCNP-DOX: Doxorubicin Loaded Carboxylic α-Cyclodextrin Stabilized Upconversion Nanoparticle

β-CD: β-Cyclodextrin

β-CD-COOH: Carboxylic β-Cyclodextrin

β-CD-COONa: Carboxylic β-Cyclodextrin Sodium Salt

β-CD-COOH-UCNP-DOX: Doxorubicin Loaded Carboxylic β-Cyclodextrin Stabilized Upconversion Nanoparticle

β-CD-PO_3Na_2: Phosphoric β-Cyclodextrin Sodium Salt

β-CD-PO_3Na_2-UCNP-DOX: Doxorubicin Loaded Phosphoric β-Cyclodextrin Stabilized Upconversion Nanoparticle

β-CD-SO_3Na: Sulfonic β-Cyclodextrin Sodium Salt

β-CD-SO_3Na-UCNP-DOX: Doxorubicin Loaded Sulfonic β-Cyclodextrin Stabilized Upconversion Nanoparticle

γ-CD: γ-Cyclodextrin

γ-CD-COONa: Carboxylic γ-Cyclodextrin Sodium Salt

γ-CD-COOH-UCNP-DOX: Doxorubicin Loaded Carboxylic γ-Cyclodextrin Stabilized Upconversion Nanoparticle