

DESIGN and SYNTHESIS of MULTIFUNCTIONAL NANOPARTICLES for MULTI-MODAL IMAGING and THERANOSTICS APPLICATIONS

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CERTIFICATE OF ORIGINAL AUTHORSHIP

I, Du Li, declare that this thesis, submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the School of Mathematical and Physical 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.

I certify that the work in this thesis has not previously been submitted for a degree nor has it been submitted as part of the requirements for a degree at any other academic institution except as fully acknowledged within the text. This thesis is the result of a Collaborative Doctoral Research Degree program with Donghua University.

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ABSTRACT

Tumor imaging can localize neoplastic lesions in the body. Since early detection of tumors will improve early treatment and prognosis, continuing to enhance current multi-modal tumor imaging approaches towards higher sensitivity, resolution, and speed is critically needed in guiding the personalized therapy. Contrast agents are often essential in significantly improving the imaging quality to achieve better limits of detection for cancer cells. Clinically used contrast agents are generally based on small molecules, which suffers from severe disadvantages such as short half-decay time and non-specificity. With the rapid development of nanotechnology, nanoscale contrast agents have been extensively synthesized and applied for early detection of tumors with prolonged residence time in the bloodstream and passive targeting abilities. Nanoparticle-based contrast agents have relatively large surface-to-volume ratios to enhance surface binding and the amount of payloads for nanomedicine delivery. Their compositions, morphology and surface properties are tunable, which renders them with unique properties compensating the drawbacks of molecular contrast agents. Nanoscale contrast agents can incorporate tumor targeting agents to promote the specific targeting abilities with improved imaging contrast and detection sensitivity. Moreover, multifunctional nanoparticles can be made with robust and well-defined surfaces to incorporate multimodal imaging, targeting biomolecules, and drug delivery as both diagnostic agents and theranostic vehicles.

This thesis reports the rational design, synthesis and tumor imaging applications of various nanoscale contrast agents, including gold nanoparticles (AuNPs) for Computed Tomography (CT) imaging, gadolinium ions modified nanoparticles for Magnetic Resonance (MR) imaging, upconversion nanoparticles for optical imaging. Hyperbranched polyethyleneimine (PEI) polymeric carriers have been used as the template for the fabrication of contrast agents, which offers several advantages, including abundant terminal groups for surface modification, improved solubility and stability, biocompatibility, and prolonged circulation. Particularly, I have demonstrated the dual mode CT/MR tumor imaging abilities of Au/gadolinium and Au/Gd₂O₃ nanoparticles-based nanoparticles. Polydopamine-coated Au nanostars have been fabricated for CT imaging and enhanced photothermal therapy of tumors. Furthermore, I have demonstrated the fabrication of photon up-converting nanoparticle probes with improved brightness to realize tumor imaging using low irradiance of near infrared excitation. These findings provide new ideas and directions for the development of new multimodal imaging contrast agents and multifunctional therapeutic agents.

KEY WORDS: Tumor imaging, CT imaging, MR imaging, Polyethyleneimine, gold nanoparticles, gold nanostars, Gd₂O₃, photothermal therapy, upconversion nanoparticles

List of Acronyms (in alphabetic order)

AA	Ascorbic Acid
ASGPR	Asialoglycoprotein Receptor
Au PENPs	PEI-entrapped gold Nanoparticles
Au NPs	gold Nanoparticles
CT	Computed Tomography
DA	Dopamine
DOX	Doxorubicin
DMEM	Dulbecco's Modified Eagle Medium
DLS	Dynamic Light Scattering
EPR	Enhanced Permeation and Retention
EGFR	Epidermal Growth Factor Receptor
FBS	Fetal Bovine Serum
FI	Fluorescein Isothiocyanate
[¹⁸ F]FDG	Fluorodeoxyglucose
FA	Folic Acid
FWHM	Full-Width at Half-Maximum
Gd ₂ O ₃	Gadolinium Oxide
GNR	Gold Nanorod
H&E	Hematoxylin and Eosin
HCC	Hepatocellular Carcinoma
HU	Hounsfield Units
HA	Hyaluronic Acid
ICP-OES	Inductively Coupled Plasma-Optical Emission Spectroscopy
LA	Lactobionic Acid
LSPR	Localized Surface Plasmon Resonance
MA	Mercaptoacetic Acid
MOF	Metal Organic Framework
MPI	Magnetic Resonance Imaging

MR	Magnetic Resonance
MSOT	Multispectral Photoacoustic Tomography
MWCO	Molecular Weight Cut-off
NaBH ₄	Sodium Borohydride
NHS	N-hydroxysuccinimide
NIR	Near Infrared
NPs	Nanoparticles
OA	Oleic Acid
OA ⁻	Oleate Anions
OA ^H	Oleic Acid Molecular
ODE	1-Octadecene
OCT	Optical Coherence Tomography
PBS	Phosphate Buffered Saline
pD	Polydopamine
PEG	Polyethylene Glycol
PEI	Polyethyleneimine
PEI-SH	Thiolated Polyethyleneimine
PDT	Photodynamic Therapy
PET	Positron Emission Tomographic
PTT	Photothermal Therapy
QDs	Quantum Dots
SPECT	Single Photon Emission Computed Tomography
SPR	Surface Plasmon Resonance
TEM	Transition Electron Microscopy
TUNEL	TdT-mediated dUTP Nick-End Labeling
UCNPs	Upconversion Nanoparticles
UV	Ultraviolet
XPS	X-ray Photoelectron Spectroscopy
XRD	X-ray Powder Diffraction