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Ravichandran Manisekaran

Design and Evaluation  
of Plasmonic/Magnetic  
Au-MFe<sub>2</sub>O<sub>4</sub> (M-Fe/Co/Mn)  
Core-Shell Nanoparticles  
Functionalized with  
Doxorubicin for Cancer  
Therapeutics

Doctoral Thesis accepted by  
Center for Research and Advanced Studies  
of the National Polytechnic Institute  
(CINVESTAV-IPN), Mexico City

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**CENTER FOR RESEARCH AND  
ADVANCED STUDIES OF THE NATIONAL  
POLYTECHNIC INSTITUTE**

**ZACATENCO UNIT  
DOCTORATE PROGRAM OF  
NANOSCIENCE AND NANOTECHNOLOGY**

**"Design and evaluation of plasmonic/magnetic Au-MFe<sub>2</sub>O<sub>4</sub> (M-  
Fe/Co/Mn) core-shell nanoparticles functionalized with Doxorubicin  
for cancer therapeutics"**

THESIS

Presented by

**RAVICHANDRAN MANISEKARAN**

To obtain the degree of  
**DOCTOR OF SCIENCE**

IN THE SPECIALTY OF  
**Nanoscience and Nanotechnology**

Thesis Directors:

**Dr. VELUMANI SUBRAMANIAM**

**Dr. JOSE TAPIA RAMIREZ**

*To my family, friends, professors,  
and especially to my brother*

*“It doesn’t matter how beautiful your theory is, it doesn’t matter how smart you are. If it doesn’t agree with experiment, it’s wrong”*

—Richard Feynman

*“It ain’t about how hard you hit. It’s about how hard you can get hit and keep moving forward!”*

—Sylvester Stallone

*“The world is your oyster. It’s up to you to find the pearls”*

—Chris Gardner

# Supervisor's Foreword

It's my pleasure to recommend Ravichandran Manisekaran's Doctor of Sciences research work for publication in Springer Theses. This thesis describes the scientific achievements made during his doctoral program at the Centre for Research in Nanoscience and Nanotechnology, and the National Polytechnic Institute (CINVESTAV-IPN), Mexico City. This work was devoted to develop a multifunctional nanoparticle system to enhance the chemotherapeutic efficiency of anticancer drugs.

The field of nanotechnology opens up a new platform for all sciences. In recent years, the functionalization of core-shell nanoparticles has attracted major attention through its applications in biomedicine. Hence, his research work focused on the design, synthesis, and characterization of gold-coated iron oxide core-shell nanoparticles and evaluating its biomedical application for cancer theranostics, i.e., as a pH responsive drug delivery system, MRI contrast agent, and microwave-mediated hyperthermal agent. Magnetic nanoparticle based technology is considered to be one of the most innovative tools, for curing and treating many diseases; it's also considered as next-generation multifunctional nanoparticles involved in probing, monitoring, and treating tissue-devastating disease.

In order to enhance the efficiency of these nanoparticles, gold shell was employed. Apart from this, it also provides a path for various surface functionalization, importantly protecting the core from aggregation, oxidation, etc. The important highlights of this research work is able to control the size, shape, composition, and surface chemistry of nanoparticles.

This system acts as a contrivance encapsulating drugs for synaphic delivery only to the diseased site. This zombie specifically migrates towards the pathological site, thus decreasing the dosage and inimical side effects associated with nonspecific uptake of drugs by normal cells. The designed nanoparticle complex works efficiently as a three-pronged paraphernalia which can be exploited as multimodal imaging particles, synaphic delivery of drugs and on exposure to microwave, the drug released is enhanced along with heat production in the cancerous milieu leading to killing of cancerous cells.

The main target is to treat cancer, because it is considered to spread to every nook and corner of the body fluids and tissues, thus causing difficulty in identifying the mischievous cell. While conventional treatments, such as radiation, surgery, and chemotherapy are successful they come with detrimental side effects affecting the healthy cells as well. Thus, the nanoparticle complex can be used to identify and treat specific cancerous cells without having the same harsh side effects.

The research outputs of different nanoparticles have been published in peer-reviewed journals such as *Nature Scientific Reports*, *International Journal of Pharmaceutics*, and *RSC Advances*. Therefore, the publication of this thesis can extensively encourage more scientific research in the field of nanomedicine.

Mexico City  
June 2017

Velumani Subramaniam

# Preface

Medical scientists in the field of nanomedicine are exploring novel hybrid nanomaterials for efficient designing of multifunctional nanoflotillas [1]. Over the past few years, the combination of magnetic and plasmonic nanoparticles has drawn major interest due to their unique characteristics [2]. Undoubtedly, iron oxide nanoparticles were considered as an efficient flotilla, and the engineering of such a biomedical platform with a biocompatible surface coating, usually gold shell, provides stabilization under various physiological conditions. This modular design enables these nanoparticles to perform multiple functions simultaneously, such as in multimodal imaging, drug delivery, and real-time monitoring, as well as combined therapeutic approaches which serve as one of the most promising candidates for various biological applications [3].

In this thesis we have developed a multifunctional magneto-plasmonic core-shell nanoparticle by single and iterative seeding based methods. This nanocargo consists of an iron oxide nanokernel ( $\text{Fe}_3\text{O}_4$ ,  $\text{CoFe}_2\text{O}_4$ ,  $\text{MnFe}_2\text{O}_4$ ) as a core and multiple layers of gold as a functionalizable active stratum. Gold-coated iron oxide nanokernel helps in augmenting the physiological stability and enhancing surface plasmon resonance property. We have also proposed a novel aspect of site-specific targeting of Doxorubicin using iterative core-shell nanoparticles as a nanopayload and folic acid as a targeting agent for cancerous cells. The gold coating and difference in shell size and shapes, have been well explained using XRD and HRTEM. HAADF-STEM and line mapping confirms the formation of core-shell structure. One single layer of gold offers the capability of binding drugs, but multiple coating further augments the physiological stability and tunes surface plasmon resonance as well as dielectrics for proficient loading of drugs as well as pH-dependent release in specific microenvironment. The functionalization of folic acid and Doxorubicin was confirmed by UV-Visible spectroscopy, FTIR, and TGA which confirmed the formation of noncovalent interactions. SQUID explained the efficacy of iterative method by confirming that even after the gold coating, the core-shell nanoparticles were highly superparamagnetic. The stability of nanoparticles was scrutinized by measuring the zeta potential, which was found to be in the range of  $-5$  to  $-40$  at different pH. The nanoparticle complex was found to be nontoxic for normal cells,

and considerably toxic for Hep2 cells detected by confocal microscopy and MTT assay. The drug loading capacity was found to be more than 80%. The targeted delivery of Doxorubicin using gold-coated iron oxide nanokernel as a nanopayload is demonstrated in this thesis. Drug release was carried out at three different pH like 5.4, 6.8, and 7.4 and found that at pH 5.4 the release is maximum which is favorable for cancer cell treatment. Doxorubicin release kinetics profile has been fit based on Zero-order, First Order, Higuchi, and Hixson-Crowell model. MRI showed that core-shell nanoparticles possess enhanced  $T_2$  contrast for imaging both normal and cancer cells. Microwave-based magnetic hyperthermia studies exhibited an augmentation in the temperature due to the transformation of radiation energy into heat at 2.45 GHz. There was an enhancement in cancer cell cytotoxicity when hyperthermia combined with chemotherapy. Hence, this single nanoplatform can deliver 3-pronged theranostic applications, viz. targeted drug delivery, MR imaging, and hyperthermia. This drug delivery system can act as an efficient nanocarrier in the cancer micromilieu for synaphic targeting, diagnosing, and killing of the cancer cells, thus rescuing the life of patients.

Mexico City, Mexico

Ravichandran Manisekaran

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3. Park, K., Lee, S., Kang, E., Kim, K., Choi, K., Kwon, I. C. New generation of multifunctional nanoparticles for cancer imaging and therapy. *Adv. Funct. Mater.* **19**, 1553–1566 (2009).

# Compilation Thesis

This thesis is a compilation of one book chapter and three research articles. The contribution of the candidate and coauthors includes Chaps. 1 and 2, 4, 5, and 6 are hereby set forth.

**Chapters 1 and 2:** based on published book chapter. (Reprinted from Application of Nanobiomaterials, Copyright (2016), with permission from Elsevier.)

*Goldie Oza, M. Ravichandran, Pravin Jagadale, S. Velumani, Engineering of Nanobiomaterials, Chapter 14: Inorganic nanoflotillas as engineered particles for drug and gene delivery, 1<sup>st</sup> Edition, Volume 2, Applications of Nanobiomaterials, Edited by A. Grumezescu, pages 429–483; 01/2016, Elsevier, ISBN: 9780323415323. Doi: <https://doi.org/10.1016/B978-0-323-41532-3.00014-2>*

**Chapter 4:** based on published research article. (Reprinted from International Journal of Pharmaceutics, Copyright (2017), with permission from Elsevier.)

*M. Ravichandran<sup>#</sup>, Goldie Oza<sup>#</sup>, S. Velumani, Jose Tapia Ramirez, A. Vera, & L. Leija, Design and evaluation of surface functionalized superparamagneto-plasmonic nanoparticles for cancer therapeutics, International Journal of Pharmaceutics, 524, 16–29; Doi: <https://doi.org/10.1016/j.ijpharm.2017.03.071> (2017)*

**Chapter 5:** based of published research article. (Reprinted from Scientific Reports, Copyright (2016), with permission from Springer Nature. Open access journal)

*Ravichandran, M, Goldie Oza, S. Velumani, Jose Tapia Ramirez, Francisco Garcia-Sierra, Norma Barragan Andrade, A. Vera, L. Leija and Marco A. Garza-Navarro, Plasmonic/Magnetic Multifunctional nanoplatfom for Cancer Theranostics, Sci. Rep. 6, 34874; Doi: <https://doi.org/10.1038/srep34874> (2016)*

**Chapter 6:** based on research article under communication.

*Nano-Flotillas MnFe<sub>2</sub>O<sub>4</sub>@Au core-shell nanoparticles: An efficient MRI contrast agent, magneto-hyperthermal and drug-delivery armada for cancer*

# Acknowledgements

*“The more I study science, the more I believe in God”*

—**Albert Einstein**

Performing a doctorate research has been a phenomenal experience. This journey made me to expand my skills and learning process of different aspects which will be very helpful for my life and also for the future research. The two most important skills I developed for life long was patience and emotions ranging from thrilling excitement to disappointment happened during the last 4 years.

*“If a country is to be corruption free and become a nation of beautiful minds, I strongly feel there are three key societal members who can make a difference. They are the father, the mother and the teacher”*

—**Abdul Kalam**

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*“A good teacher can inspire hope, ignite the imagination, and instill a love of learning”*

—**Brad Henry**

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*“Collaborate with people you can learn from”*

—Pharrell Williams

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*“We rise by lifting others”*

—Robert Ingersoll

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*“We are a studying nation. Scholarship from science is important to the whole world and those people need to be able to be safe and secure in what they do”*

—Malcolm Wallop

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*“A friend is one that knows you as you are, understands where you have been, accepts what you have become, and still, gently allows you to grow”*

—William Shakespeare

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*“Colleagues should take care of each other, have fun, celebrate success, learn by failure, look for reasons to praise not to criticize, communicate freely and respect each other”*

—Richard Branson

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*“Rejoice with your family in the beautiful land of life!”*

—**Albert Einstein**

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*“I can no other answer make but thanks, and thanks, and ever thanks...”*

—**William Shakespeare**

**Thank you all!**

*Best wishes & Regards,*  
**Ravichandran Manisekaran**

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# Abbreviations

AA	L-Ascorbic acid
AC	Alternating current
Ag	Silver
AgNO <sub>3</sub>	Silver nitrate
Al	Aluminum
AMF	Alternating magnetic field
APCs	Antigen-presenting cells
Au	Gold
Ba	Barium
C	Carbon
CAR	Coxsackie and adenovirus receptor
CARS	Coherent anti-Stokes Raman scattering
CD	Cluster of differentiation
CLSM	Confocal laser scanning microscopy
Co	Cobalt
CO <sub>2</sub>	Carbon dioxide
CSNPs	Core-shell nanoparticles
CTAB	Hexadecyltrimethylammonium bromide
CT	Computed tomography
Cu	Copper
3D	Three dimensional
Da	Daltons
D-Ala/L-Ala	D-Alanine/L-Alanine
DC	Dendritic cells
D-Glu	D-Glutamic acid
D-Lac	D-lactate
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DI	Deionized water
DM	Dextran magnetite
DMEM	Dulbecco's Modified Eagle Medium
DMSO	Dimethyl sulfoxide

DNA	Deoxyribonucleic acid
Dox	Doxorubicin hydrochloride
Dox-FA-CSNPs	Doxorubicin-coated folic acid attached core-shell nanoparticles
EDS	Energy dispersive X-ray spectrometer
EGFR	Epidermal growth factor receptor
EM	Electromagnetic waves
EPR	Enhanced permeability and retention effect
Er	Erbium
$f$	Frequency
FA	Folic acid
FA-CSNPs	Folic acid attached core-shell nanoparticles
FBS	Fetal bovine serum
FDA	Food and Drug Administration
Fe	Iron
Fe <sub>2</sub> O <sub>3</sub>	Maghemite
Fe <sub>3</sub> O <sub>4</sub>	Magnetite
FOV	Field of vision
FR	Folate receptors
FTIR	Fourier transform infrared spectroscopy
FWHM	Full width at half maximum
Gd	Gadolinium
H	Hydrogen
$H$	Applied magnetic field
H <sub>2</sub> O <sub>2</sub>	Hydrogen peroxide
Hb	Hemoglobin
HC	Coercivity
HAADF-STEM	High-angle annular dark-field scanning transmission electron microscopy
HAuCl <sub>4</sub>	Chloroauric acid
He-Ne	Helium-neon
HPG	Hydrostatic pressure gradient
HRTEM	High resolution transmission electron microscopy
HSP70	Heat shock protein 70
Hz	Hertz
IFP	Interstitial fluid pressure
IONPs	Iron oxide nanoparticles
IV	Intravenously
JCPDS	Joint Committee on Powder Diffraction Standards
L-Lys	L-lysine
LNA	Locked nucleic acids
LSCM	Laser scanning confocal microscopy
$M$	Magnetization
Mb	Myoglobin
MCL	Magnetite cationic liposomes
Mf	Manganese ferrite nanoparticles

Mf@A	Gold-coated manganese ferrite nanoparticles
MGCE	Magnetic glassy carbon electrode
MIC	Minimal inhibitory concentration
Mn	Manganese
MnFe <sub>2</sub> O <sub>4</sub>	Manganese ferrite
MNPs@Au	Gold-coated magnetic nanoparticles
Mr	Remanence
MR	Magnetic resonance
MRS	Magnetic resonance spectroscopy
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MS	Magnetic saturation
MTT	3-(4,5-Dimethylthiazol-2-yl) 2,5-diphenyltetrazolium bromide
Mw	Microwave
MwA	Microwave ablation
MW	Molecular weight
N <sub>2</sub>	Nitrogen
NaBH <sub>4</sub>	Sodium borohydride
NaOH	Sodium hydroxide
NaCl	Sodium chloride
NdFeB	Neodymium iron boron
NHS	N-Hydroxysuccinimide
NIR	Near-infrared
Nk@A	Gold-coated cobalt iron oxide nanokernels
NPs	Nanoparticles
O	Oxygen
OD	Optical density
ODNs	Oligodeoxynucleotides
PBS	Phosphate buffered saline
Pd	Palladium
PD	Pharmacodynamics
PDDA	Poly(diallyldimethylammonium chloride)
PECA	Poly(ethyl-2-cyanoacrylate)
PEG	Polyethylene glycol
pH	Potential of hydrogen
PK	Pharmacokinetics
PL	Photoluminescence
PPTT	Plasmonic photothermal therapy
PTT	Photothermal therapy
PZS	Poly(cyclotriphosphazene- <i>co</i> -4,4'-sulfonyldiphenol)
QDs	Quantum dots
R <sup>2</sup>	Regression coefficient
RES	Reticuloendothelial system
RF	Radio frequency
RGB	Red-green-blue
RNA	Ribonucleic acid

ROS	Reactive oxygen species
S	Thiol functional group
SAR	Specific absorption rate
SAED	Surface analysis of electron diffraction
SEM	Scanning electron microscopy
SERS	Surface enhanced Raman spectroscopy
SiO <sub>2</sub>	Silicon dioxide
siRNA	Small interfering RNA
SLP	Specific loss power
SPIONs	Superparamagnetic iron oxide nanoparticles
SPR	Surface plasmon resonance
SQUID	Superconducting quantum interference device
SWR	Standing wave ratio
$T_1$	Spin-lattice relaxation
$T_2$	Spin-spin relaxation
TB	Blocking temperature
TBO	Toluidine blue O
TE	Echo time
TEA	Triethylamine
TEOS	Tetraethyl orthosilicate
TGA	Thermogravimetric analysis
Tm	Thulium
TNF	Tumor necrosis factor
TR	Repetition time
USD	United States dollar
UV–Vis	Ultraviolet-visible
VRE	Vancomycin-resistant Enterococci
WHO	World Health Organization
XPS	X-ray photoelectron spectroscopy
XRD	X-ray diffraction
Yb	Ytterbium
Z	Atomic number

# List of Symbols

$\alpha$	Alpha
C	Celsius
cm	Centimeter
emu	Electromagnetic unit
eV	Electron-Volt
$\gamma$	Gamma
GHz	GigaHertz
g	Gram
h	Hour
J	Joule
K	Kelvin
kcal	kilocalories
kDa	KiloDalton
kOe	KiloOersted
M/mol	Molarity
mg	Milligram
min	Minutes
mL	Milliliter
mm	Millimeter
mM	Millimolar
ms	Millisecond
mW	MilliWatt
mV	MilliVolt
nm	Nanometer
$\chi$	Magnetic susceptibility
%	Percentage
$r_2$	Transverse relaxivity
s	Seconds
U	Units

$\theta$	Theta
$\mu\text{g}$	Microgram
$\mu\text{L}$	Microliter
W	Watt
$\zeta$	Zeta