

The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease

Bharat B. Aggarwal
Yung-Joon Surh
Shishir Shishodia

Editors

The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease

With xxx Illustrations

 Springer

Editors

Bharat B. Aggarwal, Ph.D.
Ransom Horne, Jr., Professor of Cancer Research
Professor of Cancer Medicine (Biochemistry)
and Chief, Cytokine Research Section
Department of Experimental Therapeutics
The University of Texas M. D. Anderson Cancer Center
1515 Holcombe Boulevard, BOX 143; Houston, TX 77030
Email, personal: aggarwal@mdanderson.org

Yung-Joon Surh, Ph.D.
Chief and Professor
National Research Laboratory of Molecular Carcinogenesis
and Chemoprevention College of Pharmacy
Seoul National University
Shillim-dong, Kwanak-gu; Seoul 151-742, South Korea
Email, personal: surh@plaza.snu.ac.kr

Shishir Shishodia, Ph.D.
Assistant Professor
Department of Biology
Texas Southern University
3100 Cleburne Street; Houston, Texas 77004
Email, personal: shishodia@gmail.com

Library of Congress Control Number: xxxxxxxxx

ISBN-10 0-387-46400-x
ISBN-13 978-0-387-46400-8

Printed on acid-free paper.

© 2007 Springer Science+Business Media, LLC

All rights reserved. This work may not be translated or copied in whole or in part without the written permission of the publisher (Springer Science+Business Media, LLC, 233 Spring Street, New York, NY 10013, USA), except for brief excerpts in connection with reviews or scholarly analysis. Use in connection with any form of information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed is forbidden.

The use in this publication of trade names, trademarks, service marks, and similar terms, even if they are not identified as such, is not to be taken as an expression of opinion as to whether or not they are subject to proprietary rights.

9 8 7 6 5 4 3 2 1

springer.com

Dedicated to our gurus and parents whose guidance continues to inspire us!

Sarve bhavantu sukhinah sarve santu niramayah
Sarve bhadrani pasyantu ma kascid duhkhabhag bhavet

“May all be happy; may all be healthy;
may all enjoy prosperity; may none suffer.”

CONTENTS

FOREWORD.....	ix
PREFACE.....	xiii
EDITORS.....	xv
CONTRIBUTORS	xvii
 CURCUMIN: THE INDIAN SOLID GOLD	 1
Bharat B. Aggarwal, Chitra Sundaram, Nikita Malani, and Haruyo Ichikawa	
 HIGHLY ACTIVE ANTICANCER CURCUMIN ANALOGUES.....	 77
Cara A. Mosley, Dennis C. Liotta, and James P. Snyder	
 ANTIOXIDANT AND ANTI-INFLAMMATORY PROPERTIES OF CURCUMIN.....	 105
Venugopal P. Menon and Ram Sudheer. A	
 MODULATION OF TRANSCRIPTION FACTORS BY CURCUMIN.....	 127
Shishir Shishodia Tulika Singh, and Madan M. Chaturvedi	
 CANCER CHEMOPREVENTIVE EFFECTS OF CURCUMIN.....	 149
Young-Joon Surh and Kyung-Soo Chun	
 ANTITUMOR, ANTI-INVASION, AND ANTIMETASTATIC EFFECTS OF CURCUMIN.....	 173
Girija Kuttan, Hari Kumar. K. B, Guruvayoorappan C, and Ramadasan Kuttan	
 CURCUMIN AS AN INHIBITOR OF ANGIOGENESIS.....	 185
Sulochana S. Bhandarkar and Jack L. Arbiser	
 NEUROPROTECTIVE EFFECTS OF CURCUMIN.....	 197
Greg M. Cole, Bruce Teter, and Sally A. Frautschy	
 REGULATION OF COX AND LOX BY CURCUMIN.....	 213
Chinthalapally V. Rao	

MOLECULAR TARGETS OF CURCUMIN.....	227
Jen-Kun Lin	
CELL GROWTH REGULATION.....	245
Devarajan Karunagaran, Jeena Joseph, and T. R. Santhosh Kumar	
CURCUMIN AS CHEMOSENSITIZER.....	269
Pornngarm Limtrakul	
RADIOPROTECTION AND RADIOSENSITIZATION BY CURCUMIN.....	301
Ganesh C. Jagetia	
IMMUNOMODULATION BY CURCUMIN.....	321
Subhash C. Gautam, Xiaohua Gao, and Scott Dulchavsky	
BENEFICIAL ROLE OF CURCUMIN IN SKIN DISEASES.....	343
Rajesh L. Thangapazham, Anuj Sharma, and Radha K. Maheshwari	
CARDIOPROTECTIVE EFFECTS OF CURCUMIN.....	359
Sumitra Miriyala, Manikandan Panchatcharam, and Puvanakrishnan Rengarajulu	
PROTECTION FROM ACUTE AND CHRONIC LUNG DISEASES BY CURCUMIN.....	379
Narayanan Venkatesan, Durairaj Punithavathi, and Mary Babu	
NEPHROPROTECTIVE AND HEPATOPROTECTIVE EFFECTS OF CURCUMINOIDS.....	407
Toshihiko Osawa	
CURCUMIN AND AUTOIMMUNE DISEASE.....	425
John J. Bright	
PHARMACOKINETICS AND PHARMACODYNAMICS OF CURCUMIN.....	453
Ricky A. Sharma, William P. Steward, and Andreas J. Gescher	
CLINICAL STUDIES WITH CURCUMIN.....	471
Chih-Hung Hsu and Ann-Lii Cheng	
INDEX.....	481

FOREWORD

It is indeed a matter of pride and privilege to write the Foreword to this scholarly contribution on curcumin—the major constituent of turmeric. The volume has been successful in seamlessly connecting the traditional knowledge available on turmeric to the findings of systematic modern research on turmeric and, based on this effort, building the possibilities of developing novel drugs to treat diverse diseases. Turmeric (*Curcuma longa*)—a widely cultivated tropical plant—has been used since ancient times as a spice, as a beauty care agent, and as a traditional medicine.

The rhizome of turmeric is highly aromatic and antiseptic. The medicinal properties of turmeric have been expounded in Ayurvedic and Traditional Chinese Medicine (TCM) texts. Turmeric is traditionally known as a stomachic, blood purifier and is useful for the common cold, leprosy, intermittent fevers, afflictions of the liver, indolent ulcer, pyogenic (forming pus) afflictions, wound-healing, and inflammation.

In recent years, the medicinal properties of turmeric have increasingly been recognized. It is being researched systematically even in the Western world. I remember fighting the “turmeric battle” on the wrong patent on the wound-healing properties of turmeric that was given by the US Patent Office almost a decade ago.

As per the US National Library of Medicine, 256 research papers were published last year on curcumin. The researchers have found in curcumin a near-perfect starting material for drug discovery. Thus, a variety of curcumin analogues have been prepared and evaluated biologically. Curcumin exhibits a wide range of activities [e.g., antibacterial, anti-inflammatory, hypolipidemic, hepatoprotective, lipoxigenase (LOX), cyclooxygenase (COX), protease inhibitory effects, in addition to being effective as an active oxygen scavenger and lipid peroxidase (a class of oxidoreductase enzymes) inhibitor]. Curcumin and the curcuminoids also lower cholesterol, reduce platelet aggregation, inhibit the proliferation of cancer cells, and improve digestion by increasing the flow of bile from the gallbladder. The desirable preventive or putative therapeutic properties of curcumin have been considered to be associated with its antioxidant and anti-inflammatory properties.

Curcumin has been found to modulate the activity of several key transcription factors and, in turn, the cellular expression profiles. The effect of curcumin has been examined on most of the targets discovered within the last three decades. Curcumin modulates several different transcription factors, cytokines, growth factors, kinases, and other volume book and explanations provided would add to the knowledge pool.

The National Institutes of Health has four clinical trials in progress on curcumin treatment, namely for pancreatic cancer, multiple myeloma, Alzheimer’s disease, and colorectal cancer. Curcumin has been found to possess potential

chemopreventive activities. It shows phytotoxic potential against tumor cells both *in vitro* and *in vivo*. Thus, curcumin fits well in the effort of chemoprevention by edible phytochemicals, which is now considered to be an inexpensive, readily applicable, and accessible approach to cancer management. The optimization of intervention trials of diet-derived putative chemopreventive agents is currently under development in normal populations as well as in high-risk groups. Curcumin is also a good immunomodulator. These biological activities warrant further studies of curcumin in the treatment and prevention of human neoplasm.

Curcumin has enormous potential as an antiangiogenic drug. It has been elaborately explained in the chapter discussing this. The property has been attributed to curcumin's ability to downregulate certain transcription factors and proangiogenic factors. Curcumin also has the necessary characteristics of a neuroprotective drug. The activity has been proven in a variety of disease models. Thus, it has great potential for the prevention of multiple neurological conditions for which current therapeutics are less than optimal. The chapter entitled "Neuroprotective Effects of Curcumin" embodies the research carried out on the subject and the existing necessity for further efforts. The curcumin-mediated regulation of COX and LOX enzymes for obtaining their beneficial effects in preventing diverse inflammatory diseases has been dwelt upon in another chapter. Interestingly, curcumin has an edge over conventional nonsteroidal anti-inflammatory drugs and selective COX-2 inhibitors. This might pave the way for path-breaking research in the domain.

This volume in fact covers the length and breadth of research undertaken on curcumin and research results thus far obtained. The diversity ranges from molecular targets, cell growth regulation, antioxidant and anti-inflammatory properties, chemosensitivity, radio protection, and radio sensitivity to immunomodulation, anticancer effects, cardioprotective effects, nephroprotective to hepatoprotective effects, protection from acute and chronic lung diseases to pharmacokinetics and pharmacodynamics and clinical studies undertaken with curcumin. The canvas thus covered is indeed brilliant.

As research advances, it poses newer challenges as well. Several questions in the light of the new drug development effort thus remain to be answered in order to put curcumin in a higher orbit. These pertain to the solubility and stability of curcumin, its optimum dose, pharmacokinetics, mechanism of action of curcumin for a given disease, bioavailability profile, and intricacies of prevention and cure of an identified disease. Further research is thus necessary on these aspects. There is also a need to find out whether other components of turmeric than curcumin have beneficial effects, either alone or in combination with curcumin.

I am happy to see that the contributions in this book have proven beyond doubt that curcumin—an ingredient of the traditional Indian spice turmeric—has enormous potential against a variety of malignant and nonmalignant diseases. I am confident that the state-of-the-art on curcumin research so nicely compiled and analysed throughout this volume would provide an insight and learning not only to professionals in the field but also to budding researchers. I hope that they would be inspired to answer the unanswered questions on curcumin based on new research

FOREWORD

xi

endeavors. I congratulate the editors of the volume and the contributors of the various chapters for creating this unique and scholarly marvel.

R.A. Mashelkar, FRS
Director General
Council of Scientific & Industrial Research, New Delhi, India
October 19, 2006

PREFACE

The subject of this monograph, curcumin, which gives the yellow color to turmeric, best known as *Haridra* in Sanskrit (means dear to Hari or Lord Krishna). Turmeric is known by several synonyms related to its appearance or use, including *Pita* (yellow, leading to the name *Peethamber dhari* for Lord Krishna based on wearing only yellow clothes), *Gauri* (brilliant), *Kanchani* (looks like gold), *Nisha* (beautiful as a full moon night), *Krimighni* (antibacterial and antihelmenthic), *Mahaghni* (antidiabetic), and *Yoshit priya* (gynecological disorders). In Hindi, turmeric is known as *Haldi*, in Japanese as *Ukon*, and in Korean as *Ulgeum* or *Gangwhang*.

Turmeric is mentioned in the writings of the Italian explorer Marco Polo, who was introduced to it during his voyage to China and India around 1290 AD. Although he gets credit for bringing Far East spices to Europe, turmeric was actually introduced in Europe in the 13th century AD by Arab traders. The Portuguese explorer Vasco de Gama visited the Indian subcontinent during the 15th century and brought turmeric and other spices of the Orient to the West. It was only during the rule of the British in India that turmeric was combined with various other spices and renamed “curry powder,” as it is called in the West.

Turmeric became of special importance to man with the discovery that when added to various food preparations, its dried and powdered rhizome preserved their freshness and nutritive value and improved the palatability and presentation of food. The brilliant yellow color of turmeric, which persists even at very high dilutions, found its way to commercial use as a coloring agent for various items, including cotton, silk, paper, wood, foodstuffs, and cosmetics. In Ayurveda (science of long life), turmeric has been used internally as a stomachic, tonic, and blood purifier and topically in the prevention and treatment of skin diseases. Turmeric concoctions have been traditionally used for the treatment of flatulence, dyspepsia, liver disorders, jaundice, urinary tract diseases, colds, chronic otorrhea, parasitic skin infections, bruises, sprains, wounds, infected wounds, and inflammations.

We are currently living in an era when 80% of the world’s population cannot afford modern medicine. Even for those 20% who can, much of modern medicine is ineffective and has numerous side effects. It is a good time to revive the medicinal use of the ancient medicine curcumin. In this volume we bring together the contribution of modern science to one of the most ancient spices known to mankind. Curcumin’s beneficial role in health and disease and its molecular targets are the focus of this monograph. This volume is directed at clinicians and scientists working in the areas of experimental and molecular therapeutics, molecular medicine, translational cancer research, Ayurveda, herbal medicine, naturopathy, and biomedical sciences in general and, most importantly, to the end users of curcumin. We hope that this book will “add spice to everybody’s life.”

We would like to thank all of the contributors for their valuable contributions to this work. We would also like to thank those who have contributed significantly to curcumin research but could not, because of limitations on space, be invited to contribute.

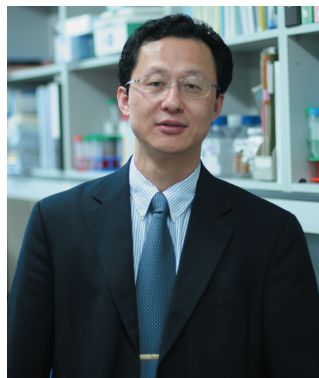
Bharat B. Aggarwal, Ph.D.
Yung-Joon Surh, Ph.D.
Shishir Shishodia, Ph.D.

EDITORS

Dr. Bharat B. Aggarwal received his Ph.D. in biochemistry from the University of California, Berkeley, did his postdoctoral fellowship in endocrinology at the University of California Medical Center San Francisco, and then worked for a biotechnology company (Genentech Inc.) where he discovered two different TNFs, both essential components of the immune system. In 1989, Dr. Aggarwal accepted a position as a Professor and Chief of the Cytokine Research Section at the University of Texas M. D. Anderson Cancer in Houston. He currently holds the Ransom Horne Jr. Professorship in Cancer Research. He has published over 400 original peer-reviewed articles and reviews, edited 9 books, and been granted almost 35 patents. Since 2001, Dr. Aggarwal has been listed as one of the world's most highly cited scientists by the Institute of Scientific Information. Dr. Aggarwal received an Outstanding Scientists Award from Ranbaxy in 2005 and from the American Association of Indians in Cancer Research in 2006.



Dr. Young-Joon Surh is a professor of biochemistry and molecular Toxicology, College of Pharmacy, Seoul National University, South Korea as well as and Chief of National Research Laboratory of Molecular Carcinogenesis and Chemoprevention. Professor Surh earned a Ph.D. degree at the McArdle Laboratory for Cancer Research, University of Wisconsin–Madison and completed postdoctoral training at the Massachusetts Institute of Technology. In 1992, he was appointed as a tenure-track assistant professor at Yale University School of Medicine. Since relocating to Seoul National University in 1996, he has been leading the Chemoprevention Working Group, investigating the molecular mechanisms of cancer prevention by edible phytochemicals, with emphasis on intracellular signaling molecules as prime targets.



He is currently a member of the editorial boards of more than 10 international journals, including *Carcinogenesis*, *Molecular Carcinogenesis*, *Cancer Letters*, *Mutation Research*, *Food and Chemical Toxicology*, and *Biofactors*. He is also

co-editor of the book *Oxidative Stress, Inflammation and Health* published by CRC Press in 2005. Dr. Surh has published more than 120 papers in peer-reviewed international journals and about 50 invited editorials, reviews, and book chapters. Dr. Surh has recently published a seminal article, entitled “Chemoprevention with Dietary Phytochemicals,” in *Nature Reviews Cancer*.

Dr. Shishir Shishodia earned his Ph.D. in biotechnology from Banaras Hindu University, Varanasi, India and did his postdoctoral fellowship at the University of Texas M. D. Anderson Cancer Center. Before joining M. D. Anderson Cancer Center, he served as an assistant professor at Patna University, Patna, India. He is currently an assistant professor at the Texas Southern University, Houston. Dr. Shishodia's research interests include cytokine signaling, the role of transcription factors in tumorigenesis, and regulation of transcription by natural products. He has identified several natural compounds that exhibit anticancer properties. He has published over 50 peer-reviewed papers and co-edited the book *Resveratrol in Health and Disease*. Dr. Shishodia is a recipient of the BHU Gold Medal and the Theodore N. Law Odyssey Award for outstanding scientific achievements.



Au: Many
contribu-
tors were
missing.
Please
provide
affiliations
for the
added con-
tributors

CONTRIBUTORS

Bharat B. Aggarwal, Ph.D.

Ransom Horne, Jr., Professor of
Cancer Research
Professor of Cancer Medicine
(Biochemistry) and
Chief, Cytokine Research Section
Department of Experimental
Therapeutics
The University of Texas M.D.
Anderson Cancer Center
1515 Holcombe Boulevard
BOX 143
Houston, TX 77030.
Tel: 713-794-1817
Fax: 713-794-1613
Email: aggarwal@mdanderson.org

Jack L. Arbiser, M.D., Ph.D.

Associate Professor
Department of Dermatology, Emory
University School of Medicine
Winship Cancer Institute
1639 Pierce Drive WMB 5309
Atlanta, GA 30322.
Tel: 404-727-5063
Fax: 404-727-0923
Lab: 404-727-1662
Email: jarbise@emory.edu

Mary Babu

Sulochana S. Bhandarkar

John J. Bright, Ph.D.

Senior Investigator
Methodist Research Institute
Clarian Health, 1800 N Capital Avenue
Noyes Building, Suite E504
Indianapolis, IN 46202.

Phone: 317-962-8722

Fax: 317-962-9369

Email: jbright1@clarian.org

Madan M. Chaturvedi

Ann-Lii Cheng, M.D.

National Taiwan University
College of Medicine No.1 Jen Ai Road
Section 1
Taipei, 100, Taiwan.
Email: andrew@ha.mc.ntu.edu.tw
(<http://www.mc.ntu.edu.tw>)

Kyung-Soo Chun

Gregory M. Cole, Ph.D.

Greater Los Angeles Veterans Affairs
Healthcare System
Geriatric Research, Education, and
Clinic Center 11E
16111 Plummer Street
Sepulveda, CA 91343.
Tel: 818-891-7711, ext 9949
Email: gmcole@ucla.edu

Scott Dulchavsky

Sally A. Frautschy

Xiaohua Gao

Subhash C. Gautam, Ph.D.

Division of Hematology/Oncology
Department of Medicine, K-13
Henry Ford Health System
2799 West Grand Boulevard
Detroit, MI 48202.
Email: SGAUTAM1@hfhs.org

Au: Name as
provided in
chapter.

Andreas J. Gescher

Guruvayoorappan C.

Chih-Hung Hsu

Haruya Ichikawa

Ganesh C. Jagetia, Ph.D.

Professor & Head
Department of Radiobiology
Kasturba Medical College
Manipal—576 104, India
Tel: 091-820-2922122
Fax: 091-820-2571919
Email: gc.jagetia@gmail.com

Jeena Joseph

Devarajan Karunakaran, Ph.D.

Scientist E-II
Rajiv Gandhi Centre for Biotechnology
Thiruvananthapuram
Kerala 695014, India.
Tel: 2342315 (W); 2346310 (H)
Fax: 91-0471 2348096
Email: dkarunakaran@hotmail.com
Website: www.rgcb.res.in

Au: Name as
provided in
chapter.

Hari Kumar. K. B

T. R. Santhosh Kumar

Girija Kuttan

Ramadasan Kuttan, Ph.D.

Research Director
Amala Cancer Research Centre
Amala Nagar, Thrissur
Kerala, India.
Tel: 91 487 2307868 (W);
91 487 2307197 (H);
9447123071 (Mobile)
Email: amalaresearch@rediffmail.com

Pornngarm Limtrakul, Ph.D.

Chairperson, Department of
Biochemistry
Faculty of Medicine
Chiang Mai University
Chiang Mai, Thailand 50200.
Tel: 66-53-945323
Fax: 66-53-217144
Moblie: 01-8852902
Email: plimtrak@mail.med.cmu.ac.th

Jen-Kun Lin, Ph.D.

Professor
Institute of Biochemistry and
Molecular Biology
Colletge of Medicine
National Taiwan University
No. 1, Section 1, Jen-ai Road
Taipei, Taiwan.
Tel: (886)-2-2356-2213
Fax: (886)-2-2391-8944
Email: jklin@ha.mc.ntu.edu.tw

Dennis C. Liotta

Radha K. Maheshwari, M.D., Ph.D.

Department of Pathology
Uniformed Services University of the
Health Sciences
Bethesda, MD 20814
Email: rmaheshwari@usuhs.mil

Nikita Malani

Venugopal P. Menon, Ph.D.

Professor and Chairman
Department of Biochemistry &
Center for Micronutrient Research
Annamalai University
Annamalai Nagar-608 002
Chidambaram, Tamilnadu, India.
Tel: +91 4144 238343
Fax: +91 4144 238343
Email: biocmr@sify.com

CONTRIBUTORS

xix

Sumitra Miriyala

Cara A. Mosley

Venkatesan Narayanan, Ph.D.

Au:
Narayanan
Venkatesan
in chapter.
Please check.

Associate Professor
Faculte de Medecine
UMR-7561 CNRS UHP; B.P. 184
54505 Vandoeuvre les Nancy
France.
Tel: 33.3.83.68.39.72 (Work)
Tel: 33.3.83.67.42.05 (Home)
Fax: 33.3.83.68.39.59
Email: vnar12@yahoo.com

Toshihiko Osawa, Ph.D.

Professor
Laboratory of Food and Biodynamics
Nagoya University Graduate School of
Bioagricultural Sciences
Chikusa, 46408601, Japan.
Tel: 81-52-789-4125
Fax: 81-52-789-5296
Email: osawat@agr.nagoya-u.ac.jp
<http://www.agr.nagoya-u.ac.jp/~food/index-j.html>

Manikandan Panchatcharam

Duraitaj Punithvathi

Rengarajulu Puvanakrishnan, Ph.D.

Au: Puvanakrishnan
Rengarajulu in
chapter. Please
check.

Deputy Director and Head
Department of Biotechnology
CLRI, Chennai-600 020
India.
Tel: 91-44-24430273
Fax: 91-44-24911589
Email: puvanakrishnan@yahoo.com

RamSudheer. A

Au: Name as
provided in
chapter.

Chintallapalli V. Rao, Ph.D.
Professor of Medicine

Kerley-Cade Endowed Chair in Cancer
Research

Hematology-Oncology Section
Director, Chemoprevention Program
University of Oklahoma Cancer
Institute
OUHSC, P.O. Box 26901
975 NE 10th Street, BRC 1203
Oklahoma City, OK 73104.
Tel: (405) 271-3224
Fax: (405) 271-3225
Email: cv-rao@ouhsc.edu

Anuj Sharma

Ricky A. Sharma, M.D., Ph.D.

Radiotherapy Department
Royal Marsden Hospital
Surrey SM2 5PT
UK.
Tel: 44 208 642 6011 ext. 1201
Fax: 44 208 661 3127
("FAO Dr Sharma")
Email: ras20@le.ac.uk

Shishir Shishodia, Ph.D.

Assistant Professor
Department of Biology
Texas Southern University
3100 Cleburne Street
Houston, TX 77004
Tel: 713 313 7912
Fax: 713 313 7932
Email: shishodia@gmail.com;
shishodias@tsu.edu

Tulika Singh

James P. Snyder, Ph.D.

Director of Biostructural Research
Department of Chemistry
Emory University
1515 Dickey Drive
Atlanta, GA 30322.
Tel: 404-727-2415

xx

CONTRIBUTORS

Fax: 404-712-8679 or 404-727-6586
Email: jsnyder@emory.edu

William P. Steward

Chitra Sundaram

Young-Joon Surh, Ph.D.

Chief and Professor
National Research Laboratory of
Molecular Carcinogenesis and
Chemoprevention

College of Pharmacy
Seoul National University
Shillim-dong, Kwanak-gu
Seoul 151-742, South Korea.
Tel: +82 2 880-7845 (O)
Fax: +82 2 874-9775
Email: surh@plaza.snu.ac.kr

Bruce Teter

Rajesh L. Thangapazham