
# Chemotherapeutic Engineering

## Collected Papers of Si-Shen Feng
## A Tribute to Shu Chien on His 82nd Birthday

edited by

Feng Si-Shen
Jenny Rompas
Stanford Chong

A Tribute to Professor Shu Chien
on His 82nd Birthday

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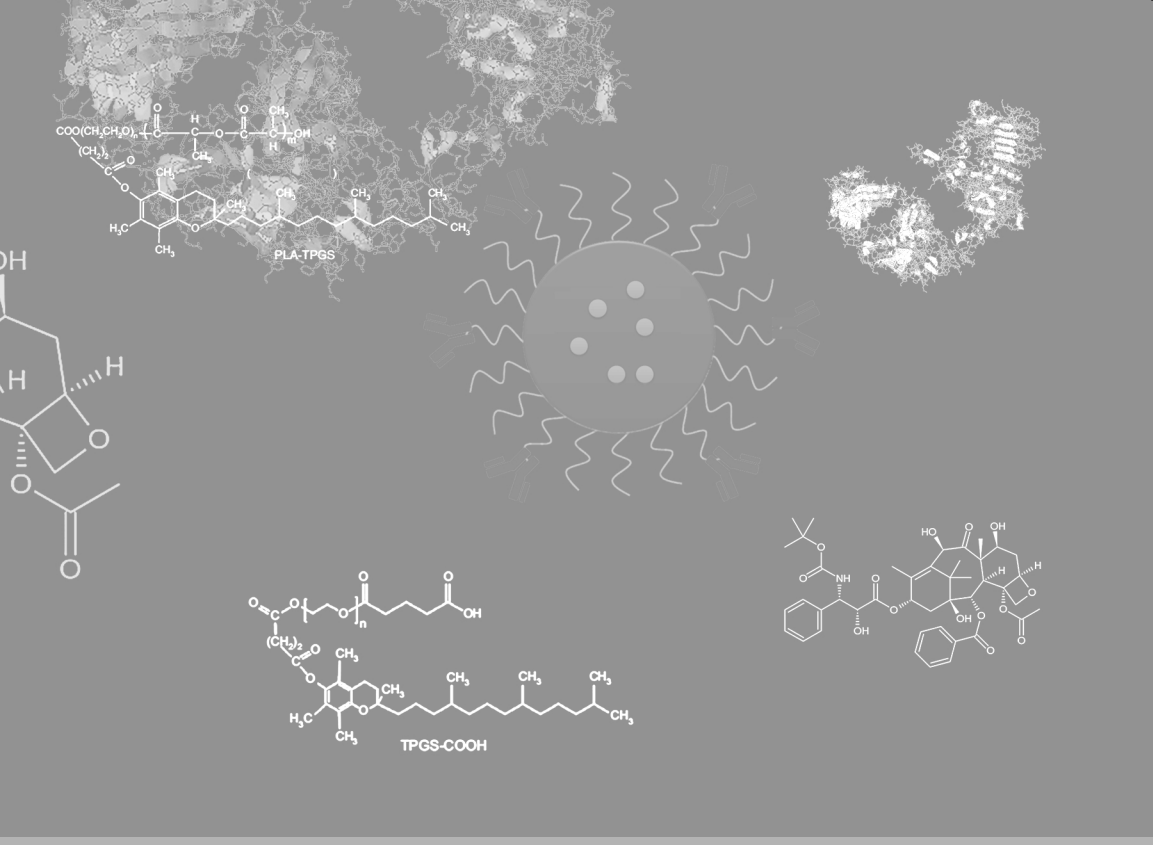


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# Preface

Cancer is a leading cause of death worldwide and has become the number one killer in many countries, including China and Singapore. It was responsible for approximately 23.1%, 23.2%, 23.1%, 23.4%, and 23.3% of disease mortality from 2006 to 2010 in the United States and 27.7%, 29.3%, 29.3%, 28.5%, and 30.0% from 2007 to 2011 in Singapore, respectively. The World Health Organization estimates that global cancer rates could increase by 50% to 15 million patients and cancer rates in Asia could increase by 60% to 7.1 million patients by 2020. In spite of such a serious situation, no substantial progress in fighting cancer could be observed before the end of the past century. The cancer death rate in the United States was 1.939‰ of the total population in 1950 and still remained 1.940‰ in 2001. Beyond these staggeringly dismal numbers, however, recent statistics have found that the cancer survival rate is slightly increasing for the first time in the first decade of the 21st century, which led to a slight decrease in the cancer death rate to 1.901‰ in 2003, 178.4‰ in 2007 and 172.8‰ in 2010 in the United States. This may have largely resulted from the significant achievements in cellular and molecular biology, from which new knowledge of cancer has been acquired and new diagnostic and therapeutic techniques could thus be developed. The US National Cancer Institute, the National Institutes of Health, and the US Department of Health and Human Services jointly published a white paper on cancer nanotechnology in 2004, which predicted that cancer nanotechnology will radically change the way we diagnose, treat, and prevent cancer (http://www.nci.org).

Chemotherapy is often related to cancer treatment. Nevertheless, a more general definition of chemotherapy could mean “curing disease by drugs” or as given by Dr. Paul Ehrlich, the father of modern chemotherapy, “curing by chemicals.” With recent achievements in cellular and molecular biology, drugs can now also include biologically active macromolecules such as proteins and peptides. Chemotherapy is, thus, involved in the entire internal medicine. Chemotherapy is a complicated procedure in which many factors are involved in determining its success or failure. It carries a high risk due to drug toxicity, and the more effective drugs tend to be more toxic; its unfavorable pharmacokinetics and biodistribution are also a concern. Even successful chemotherapy is associated with problems. The patients have to tolerate severe side effects and

sacrifice their quality of life. Chemotherapy should become more important and more effective if its problems in pharmacokinetics and pharmacodynamics could be solved, which include the toxicity of the drugs; drug targeting; drug adsorption, distribution, metabolism, and excretion (ADME); drug resistance at various physiological levels from organs such as the first pass by the liver and the kidneys to cellular and molecular levels such as the various physiological drug barriers, including the gastrointestinal (GI) barrier and the blood–brain barrier (BBB). The problems could be solved by adopting two kinds of approaches: medical solution and engineering solution. The former is to use other drug or drugs to overcome the complications caused by the prescribed one. A typical example is the co-administration of cyclosporine A, a P-gp/P450 inhibitor, to make paclitaxel orally bioavailable, i.e., deliverable into the blood system through the oral route. However, cyclosporine A suppresses the body immune system and thus may cause severe side effects. Moreover, cyclosporine A has its own difficulty in formulation. It is clear that such medical approach is not a preferable solution. The engineering solution is to modify the molecular structure of the drug or to formulate the drug in various nanoscale carriers such as prodrugs, micelles, liposomes, dendrimers, nanohydrogels, and biodegradable nanoparticles, i.e., "to engineering the drugs" for delivery, which, in this case, can bring the drug across the GI barrier. Drugs formulated in the various nanoscale carriers for sustained, controlled, and targeted delivery are also called nanomedicine. Si-Shen Feng at the National University of Singapore, under the advice of Prof. Shu Chien at the University of California, San Diego, recognized the challenge by applying engineering, especially chemical engineering principles, to solve the problems in chemotherapy and defined the strategy as chemotherapeutic engineering in 2003. He believes that together with tissue engineering, which will revolutionize the concept of surgery from "cut and throw the diseased tissue or organ" to "repair and replace them by biologically engineered tissue or organ," chemotherapeutic engineering will contribute towards the 21st-century medicine.

This book is the collection of the peer-reviewed scientific and technological articles published from 2003 to 2012 by Prof. Si-Shen Feng, which are closely relevant to chemotherapeutic engineering. The collection comprises contributions ranging from founding articles to proof-of-concept experimental reports and covers the synthesis of novel molecular biomaterials design and preparation of drug carriers at the nanoscale, ligand conjugation for targeting, the characterization of the drug-loaded nanocarriers, in vitro cellular uptake of nanocarriers and in vitro assessment of the cytotoxicity of the formulated drug, in vivo investigation on pharmacokinetics and biodistribution and the xenograft tumor model. Paclitaxel and docetaxel are used as model drugs owing to their role as the number one seller in the global market of anticancer drugs and great difficulties in their formulation for clinical application. The methodology is also

applicable for the formulation of imaging agents such as supraparamagneric iron oxides for magnetic resonance imaging. Chemotherapeutic engineering is thus relevant to pharmaceutical nanotechnology in the pharmaceutical industry. Formulation and combined diagnostic and therapeutic agents are now called nanodiagnostics

This book provides necessary knowledge for scientists, engineers, and master's and PhD students who want to be well prepared to work in the fields of chemotherapeutic engineering, cancer nanotechnology, and nanomedicine, or more generally in biomedical engineering. It also provides the basic knowledge and models for people who work in cancer clinics as well as in the pharmaceutical industry. It can also be used as a textbook or a reference book in teaching of courses such as drug delivery, chemotherapeutic engineering, and overview of nanomedicine. In fact, most of the contributions in this book have been used in the undergraduate course Engineering Principles of Drug Delivery, which is given by Prof. Si-Shen Feng in the National University of Singapore since 2002.

The editors thank the Agency for Science, Technology and Research (A*STAR) and the National University of Singapore (NUS) for financial support for the research conducted in the Chemotherapeutic Engineering Laboratory in the past decade. Prof. Feng sincerely acknowledges his postdoctoral fellows and PhD students. Among them, Drs. Li Mu, Lin Mei, M. S. Muthu, S. A. Kulkarni, Zhiping Zhang, K. Y. Win, Lingyun Zhao, Gang Ruan, Yuancai Dong, Jie Pan, P. Chandrasekharan, Bingfeng Sun, Yutao Liu, Yu Mi, and Jing Zhao made significant contributions in the various key steps. Finally, we would like to thank Mr. Arvind Kanswal of Pan Stanford Publishing for his commitment and assistance.

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