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Editorial

Introduction and foreword to the Special Issue from the ACS COMP symposium on QSAR in vivo

Introduction

It is my pleasure to welcome Dr. Robert D. Clark as Guest Editor of this special issue. The papers in the issue derive from talks presented at the American Chemical Society (ACS) National Meeting in Washington, DC, held in August 2000. Dr. Clark's symposium on "QSAR in vivo" was part of the ACS Computers in Chemistry Division (COMP) program; hence this journal is an ideal forum for the publication of these papers.

Dr. Clark obtained his B.S., summa cum laude, in chemistry from the Honors Tutorial College of Ohio University in 1976. He remained in Athens, OH, and earned his M.S. degree in chemistry a year later. His Ph.D. in biochemistry is from Cornell University, where his doctoral research was on energy transduction in *Halobacterium halobium*. His interest in computing was enhanced by minors in statistics and biometry at Cornell. From 1982 to 1984, he served as research associate in the Biology Department of Brookhaven National Laboratory. Returning to the Midwest, he became a senior research chemist in the Agricultural Group at Monsanto Company (St. Louis, MO) from 1984 to 1994. In June 1994, he joined Tripos, Inc. (St. Louis, MO). At both Monsanto and Tripos, he advanced rapidly through the ranks. Presently he is director of software research at Tripos. Dr. Clark is a member of the American Chemical Society, International Chemometrics Society, QSAR and Modelling Society, and American Association for the Advancement of Science. Dr. Clark has published more than 30 papers including two articles in this journal and 10 book chapters. He is co-inventor on five patents from his Monsanto research; in addition, he has two patents pending on algorithmic developments at Tripos.

Dr. Clark pursued his editor's job with great diligence and not only collected the papers for this special issue but also carried out the process of selecting referees and handling correspondence with the referees and authors. The contributions that Dr. Clark has made to the ACS Computers in Chemistry Division (COMP) and to this journal are greatly appreciated.

Foreword

In drug development and in computational chemistry, as in most areas of life, there are ebbs and flows of interest in one or another particular aspect of the field. It is tempting to dismiss such shifts in focus as "fads", particularly when the latest area of interest seems to be an old one in a new guise. It would, however, be misleading to see such recurrent themes as some kind of futile recycling. More often, the shifts in research emphasis are simply evidence that science is more prone to advance in spirals than in straight lines.

The study of quantitative structure–activity relationships (QSAR) originated with the classical studies of Corwin Hansch and Toshio Fujita [1]. The use of the QSAR approach spread widely. Nevertheless, by 1990, when I was working on modeling herbicide efficacy and selectivity at Monsanto, in vivo QSAR studies were still generally regarded as hopelessly messy and "primitive" in some sense. Indeed, some such studies probably went unpublished because of a misguided conviction that only titration data obtained from pure enzymes could support scientifically substantive QSAR analyses.

Here at start of the 21st century, the use of intact cells in high-throughput screening (HTS) programs is growing steadily, in part because of increasing interest in G-protein coupled receptors (GPCRs) as therapeutic targets. In addition, screening for potential pharmacokinetic problems (collectively referred to as absorption, distribution, metabolism, excretion, and toxicology — ADME/Tox), experimentally or through modeling, has become the focus of intense research activity. Although most of this work involves surrogate in vitro or ex vivo (i.e. cell culture) systems, the ultimate goal is to predict behavior of particular chemical structures in complex biological systems, i.e. in vivo.

Even in ex vivo and in vitro contexts, such studies often exhibit many of the characteristic complications encountered in historical whole animal and greenhouse studies. Analytical responses exhibit relatively high levels of noise in the response variable. The data may suffer from hard-to-predict biases due to variation in the assay over time or across

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populations. The observable effects often entail a series of penetration and distribution barriers and can involve multiple, potentially overlapping sites and modes-of-action. In fact, similar complications constitute the most daunting challenges faced in attempting to analyze HTS results in general, even when the assays in question do not involve intact cells.

With the advance of science and computational efforts, it seemed timely to bring together people with experience in modeling complex biological systems to share their successes and "tricks of the trade" for overcoming the difficulties inherent in assaying responses of living things to xenobiotics, as well as their (many) frustrations. Late in 1999, these considerations prompted me to start organizing the day-long symposium titled "QSAR in vivo", which was sponsored by Tripos, Inc., and held as part of the 220th National ACS Meeting on 20 August 2000. The 12 talks presented [2] were well attended and seemed uniformly well received.

It is in the nature of the topic that much of the work presented had already been published in whole or in part, but there was enough novel material to justify organizing proceedings for the symposium. It has been my honor and privilege to put together these papers for the *Journal of Molecular Graphics and Modelling* as a way to share the content of some of those talks with the broader community in a permanent form. I would like to thank Don Boyd for suggesting that I do so. Four full papers are included here, along with an overview of selected presentations at symposia related to computational ADME/Tox. In addition, a paper presented at a companion ACS symposium has already appeared in this journal [3].

I would like to take this opportunity to thank all the scientists who participated in the symposium, as well as COMP Program Chair Ralph Wheeler, plus Jamie Heritage and Heather Hunter at Tripos; each was indispensable in the mechanics of getting the symposium organized. I would also like to thank the contributing authors, the reviewers, and Don Boyd for their insights, patience, and good humor throughout the process of compiling these proceedings. Thanks, too, go to Tripos, Inc., for sponsoring the symposium; to Dr. Matthew D. Wessel (Pfizer Global Research and Development) for soliciting my help in co-organizing a symposium on "Computational ADME"; and to Dr. Robert W. Snyder (MDL Information Systems) who organized a Division of Chemical Information (CINF) symposium on "Use of Toxicological Information in Drug Design". These three symposia at the Washington, DC, ACS meeting complemented each other and provided substantial synergism.

References

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