Transformative Concepts for Drug Design: Target Wrapping

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Preface

To a man with a hammer everything looks like a nail.
Mark Twain

Notwithstanding the enticing promises of the post-genomic era, the pharmaceutical world appears to be in a state of disarray. Drug discovery seems riskier and more uncertain than ever as projects get routinely terminated in mid-stage clinical trials, as the dearth of new targets becomes apparent, and as successful therapeutic agents are often recalled whenever an idiosyncratic side effect is detected. Exploiting the huge output of genomic data to make more efficacious and safer drugs has proven to be much more difficult than anticipated. More than ever, the lead in the pharmaceutical industry depends on the ability to harness innovative research, and this type of innovation can only come from one source: *fundamental knowledge*. This book has a place in this scenario, as it introduces fundamental discoveries in basic biomolecular research that hold potential to become transformative and broaden the technological base of the pharmaceutical industry.

The book takes a fresh and fundamental look at the problem of how to design an effective drug with controlled specificity. Within the pharmaceutical industry, it is of course superfluous to recall that the principal bottleneck in developing new drugs is the clinical uncertainty stemming from the lack of control of specificity. Chemists know how to increase affinity, but when they do this, the affinity of the drug to structurally similar molecules also increases, target discrimination becomes very difficult, and adverse side-effects due to unwanted binding are usually sufficiently severe to render the drug unusable.

The secret of how nature manages to design molecules with extraordinarily high and specific affinities lies in cooperativity. In medicine, we are nearly always working in aqueous media and therefore cooperativity needs to be looked at in the specific context of aqueous systems.

Recognizing that these concepts are unfamiliar to most practitioners, the first part of this book (Chaps. 1, 2, 3, 4, 5, and 6) explains these matters very carefully starting from a fairly elementary physico-chemical level. The second part of the book (Chaps. 7, 8, 9, 10, 11, 12, 13, and 14) is devoted to practical applications. We are aiming at nothing less than a paradigm shift in drug design.

Thus, cooperativity emerges as a molecular design principle in Chaps. 7, 8, 9, 10, 11, 12, 13, and 14, but this incarnation is only possible after the concept is explored from architectural, biophysical, bioinformatics and evolutionary perspectives in the preparatory Chaps. 1, 2, 3, 4, 5, and 6.

This book is above all addressed to scientists working at the cutting edge of research in the pharmaceutical industry, but the material is at the same time fully accessible to senior undergraduates or graduate students interested in fundamental concepts on drug discovery. It essentially covers my lectures on systems biology and molecular design, an elective undergraduate and graduate level course for bioengineering majors at Rice University.

It has been a pleasure to work with the talented staff at Springer. I am especially grateful to Marion Hertel (executive editor), and to Cornelia Kinsky, Beate Siek and Sam Roobesh for their helpful cooperation and enduring patience.

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