

Transformative Concepts for Drug Design: Target Wrapping

Ariel Fernández

Transformative Concepts for Drug Design: Target Wrapping

Prof. Dr. Ariel Fernández
Karl F. Hasselmann Chair in Engineering
Rice University
Department of Bioengineering
E200K George R. Brown Hall
Houston TX 77005
USA

ISBN 978-3-642-11791-6 e-ISBN 978-3-642-11792-3
DOI 10.1007/978-3-642-11792-3
Springer Heidelberg Dordrecht London New York

Library of Congress Control Number: 2010922998

© Springer-Verlag Berlin Heidelberg 2010

This work is subject to copyright. All rights are reserved, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilm or in any other way, and storage in data banks. Duplication of this publication or parts thereof is permitted only under the provisions of the German Copyright Law of September 9, 1965, in its current version, and permission for use must always be obtained from Springer. Violations are liable to prosecution under the German Copyright Law.

The use of general descriptive names, registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

Cover design: WMXDesign GmbH, Heidelberg

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

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.

Houston, USA

Ariel Fernández

Contents

1	Protein Cooperativity and Wrapping: Two Themes in the Transformative Platform of Molecular Targeted Therapy	1
1.1	Many-Body Problems for the Drug Designer	1
1.2	Cooperative Protein Interactions: The Need for the Wrapping Concept	3
1.3	Poorly Wrapped Hydrogen Bonds are Promoters of Protein Associations	6
1.4	Wrapping Defects Are Sticky	9
1.5	Cooperative Drug–Target Associations: A Window into Molecular Engineering Possibilities	12
	References	14
2	Wrapping Defects and the Architecture of Soluble Proteins	17
2.1	How Do Soluble Proteins Compensate for Their Wrapping Defects?	17
2.2	Thermodynamic Support for the Dehydron/Disulfide Balance Equation	22
2.3	Evolutionary Support for the Balance Equation	24
2.4	Wrapping Translates into Protein Architecture	24
	References	26
3	Folding Cooperativity and the Wrapping of Intermediate States of Soluble Natural Proteins	27
3.1	Many-Body Picture of Protein Folding: Cooperativity and Wrapping	27
3.2	Hydrogen Bond Wrapping Requires Cooperative Folding . . .	30
3.3	Generating Cooperative Folding Trajectories	32
3.4	Wrapping Patterns Along Folding Trajectories	37
3.5	Nanoscale Solvation Theory of Folding Cooperativity: Dynamic Benchmarks and Constant of Motion	41
3.6	Dehydronic Field Along the Folding Pathway and the Commitment to Fold	45
	References	46

4	Wrapping Deficiencies and De-wetting Patterns in Soluble Proteins: A Blueprint for Drug Design	49
4.1	Hydration Defects in Soluble Proteins	49
4.2	Wrapping as a Marker of Local De-wetting Propensity	50
4.3	Dehydrons Are Loosely Hydrated	52
4.4	Displacing Loose Hydrating Molecules: A Blueprint for the Drug Designer	56
	References	57
5	Under-Wrapped Proteins in the Order-Disorder Twilight: Unraveling the Molecular Etiology of Aberrant Aggregation	59
5.1	Dehydron Clusters and Disordered Regions	59
5.2	Discrete Solvent Effects Around Dehydrons	61
5.3	Dielectric Modulation of Interfacial Water Around Dehydrons	65
5.4	A Study Case: Dielectric Quenching in the p53 DNA-Binding Domain	67
5.5	Proteins with Dehydron Clusters	69
5.6	Misfolding and Aggregation: Consequences of a Massive Violation of Architectural Constraints	72
	References	77
6	Evolution of Protein Wrapping and Implications for the Drug Designer	79
6.1	An Evolutionary Context for the Drug Designer	79
6.2	Wrapping Across Species: Hallmarks of Nonadaptive Traits in the Comparison of Orthologous Proteins	80
6.3	Wrapping and Natural Selection	83
6.4	How Do Humans Cope with Inefficient Selection?	84
6.4.1	Regulatory Patterns for Paralog Proteins	85
6.4.2	Wrapping Deficiency Causes Dosage Imbalance and Regulation Dissimilarity	87
6.5	Human Capacitance to Dosage Imbalances in the Concentrations of Under-Wrapped Proteins	93
6.6	Why Should the Drug Designer Be Mindful of Molecular Evolution?	94
	References	95
7	Wrapping as a Selectivity Filter for Molecular Targeted Therapy: Preliminary Evidence	97
7.1	The Specificity Problem in Drug Design	97
7.2	Ligands as Wrappers of Proteins in PDB Complexes: Bioinformatics Evidence	103
7.3	Poor Dehydron Wrappers Make Poor Drugs	105
7.4	Wrapping as a Selectivity Filter	106
7.5	Wrapping as a Selectivity Filter: An Exercise in Drug Design	107
7.6	Wrapping-Based Selectivity Switch	113
	References	113

8	Re-engineering an Anticancer Drug to Make It Safer:	
	Modifying Imatinib to Curb Its Side Effects	117
8.1	Rational Control of Specificity: Toward a Safer <i>Imatinib</i>	117
8.2	Unique De-wetting Hot Spots in the Target Protein Provide a Blueprint for Drug Design	119
8.3	In Silico Assays of the Water-Displacing Efficacy of a Wrapping Drug	125
8.4	High-Throughput Screening: Test-Tube Validation of the Engineered Specificity	125
8.5	In Vitro Assays: Selectively Modulating Imatinib Impact	127
8.6	In Vitro Assay of the Selective Anticancer Activity of the Wrapping Design	131
8.7	Enhanced Safety of the Wrapping Redesign in Animal Models of Gastrointestinal Stromal Tumor	134
8.8	Controlled Specificity Engineered Through Rational Design: Concluding Remarks	139
	References	139
9	Wrapping Patterns as Universal Markers for Specificity in the Therapeutic Interference with Signaling Pathways	141
9.1	The Need for a Universal Selectivity Filter for Rationally Designed Kinase Inhibitors	141
9.2	Computational Tool Box for Comparative Analysis of Molecular Attributes Across the Human Kinome	143
9.2.1	Wrapping Inferences on Proteins with Unreported Structure	143
9.2.2	Alignment of Targetable Molecular Features Across the Human Kinome	144
9.3	Is Wrapping Pharmacologically Relevant? A Bioinformatics Analysis	144
9.4	A Target Library for the Human Kinome: Broadening the Technological Basis of Drug Discovery	152
9.5	Useful Annotations of a Library of Specificity-Promoting Target Features	153
9.6	The Dehydron Library as a Technological Resource	159
	References	160
10	Fulfilling a Therapeutic Imperative in Cancer Treatment:	
	Control of Multi-target Drug Impact	163
10.1	Is There Really a Case for Promiscuous Drugs in Anticancer Therapy?	163
10.2	Cleaning Dirty Drugs with Selectivity Filters: Basic Insights	165
10.3	Cleaning Dirty Drugs by Exploiting the Wrapping Filter: Proof of Concept	166

10.4	Cleaning Staurosporine Through a Wrapping Modification: A Stringent Test	173
10.5	Systems Biology Insights into Wrapping-Directed Design of Multi-target Kinase Inhibitors	177
10.6	Controlling the Cross-Reactivity of Sunitinib to Enhance Therapeutic Efficacy and Reduce Side Effects	179
10.7	Is a Paradigm Shift in Drug Discovery Imminent?	183
	References	184
11	Inducing Folding By Crating the Target	187
11.1	Induced Folding: The Bête Noire of Drug Design	187
11.2	Wrapping the Target: A Tractable Case of Induced Folding	188
11.3	Kinase Inhibitors Designed to Crate Floppy Regions	190
11.4	Steering Induced Folding with High Specificity: The Emergence of the Crating Design Concept	195
	References	195
12	Wrapper Drugs as Therapeutic Editors of Side Effects	197
12.1	The Editor Concept	197
12.2	Editing Drugs to Curb Side Effects	198
12.3	Designing a Therapeutic Editor Using the Wrapping Selectivity Filter	203
12.4	Therapeutic Editing: Toward a Proof of Principle	205
12.5	Future Perspectives for the Editing Therapy	208
	References	209
13	Wrapper Drugs for Personalized Medicine	211
13.1	Wrapping as a Biomarker in Personalized Drug Therapy	211
13.2	Targeting Oncogenic Mutations with Wrapper Drugs	214
13.3	Closing Remarks	215
	References	215
14	Last Frontier and Back to the Drawing Board: Protein–Water Interfacial Tension in Drug Design	217
14.1	Interfacial Tension Between Protein and Water: A Missing Chapter in Drug Design	217
14.2	Disrupting Protein–Protein Interfaces with Small Molecules	222
	References	223
	Epilogue	225
	Index	227