Preface

In the common definition of the proteome it is considered to be the set of expressed proteins in a given type of cells or an organism at a given time under defined conditions. It is larger than the genome, due to special mechanisms in the biogenesis of proteins, which render them more numerous than the genes at the end. What, however is very special to the proteome is its enriched complexity which arises both from the protein's 3D structure and the functional interaction of the proteins.

Proteins talk to each other. They do it very frequently and in different ways and obviously in large communication networks of sophisticated structure. For yeast, recent research has suggested kind of social life in protein communication:

> *This distinction suggests a model of organized modularity for the yeast proteome, with modules connected through regulators, mediators or adaptors, the date hubs. Party hubs represent integral elements within distinct modules and, although important for the functions mediated by these modules (and therefore likely to be essential proteins), tend to function at a lower level of the organization of the proteome. We propose that date hubs participate in a wide range of integrated connections required for a global organization of biological modules in the whole proteome network (although some date hubs could simply be 'shared' between, and mediate local functions inside, overlapping modules). (. . .) Finally, it is possible that discriminating between date and party hubs might also help to define new therapeutic drug targets.*[1]

Well, there we are in defining ambitious goals for drug development. Interfering with the party gossip and intruding the clandestine dates of proteins for sake of therapeutic benefits is still the freestyle of drug design. The complexity is huge. Large interfaces that resemble flat landscapes, lacking cosy caves or deep pockets, where small molecules might dock made protein-protein interactions clearly undruggable for a long time. With the advent and success of monoclonal therapeutic antibodies (mAbs) however, this view changed. The benefits of mAbs in the cancer

[1] Jing-Dong J. Han, Nicolas Bertin, Tong Hao, Debra S. Goldberg, Gabriel F. Berriz, Lan V. Zhang, Denis Dupuy, Albertha J. M. Walhout*, Michael E. Cusick, Frederick P. Roth & Marc Vidal. *Evidence for dynamically organized modularity in the yeast protein–protein interaction network.* Nature, 430, 2004, pp. 88-93

and immune-disease areas showed that interfering with protein-protein interactions (PPIs) is indeed a practicable approach. Unfortunately the proteins parties and dates are taken place inside the cell, with no admittance for mAbs. Hence, the challenge or the "reaching for high-hanging fruit"[2] is to interfere therapeutically by use of small molecules.

In the present volume Alexander Dömling and his co-authors depict a scenario that reveals more than a silver lining on the horizon. There is a variety of new (and old) targets and a plethora of new approaches and insights into molecular mechanisms which raise the hope that in the near future small molecule interference of protein-protein interactions will emerge as a new functional class of therapeutics. Twelve chapters illuminate opportunities, strategies, success stories and pitfalls in the discovery of small molecules targeting protein-protein-interactions.

While this volume grants an encompassing view on the state-of-the-art in the PPI field, it is at the same time structuring the future, since it paves the way for a hopefully greater commitment in drug discovery focusing PPIs.

Not least because of this, the series editors are indebted to the authors and the editor who made this comprehensive issue possible. We are convinced that the book represents an important contribution to the body of knowledge in drug discovery and that it matches the interests of many researches who have adjourned to a promising but rocky field.

In addition, we are very much indebted to Frank Weinreich and Heike Nöthe, both at Wiley-VCH. Their support and ongoing engagement, not only for this book but for the whole series "Methods and Principles in Medicinal Chemistry" adds to the success of this excellent collection of monographs on various topics, all related to drug research.

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[2] James A. Wells and Christopher L. McClendon. *Reaching for high-hanging fruit in drug discovery at protein–protein interfaces.* Nature 450, 2007, 1001-1009