Foreword

What is Multi-Targeted Drug Discovery (MTDD)?

This book consists of chapters concerned with a variety of aspects related to 'multi-targeted drug discovery' (MTDD). A good definition of MTDD is given by Metz and Hajduk[1] 'Multi-targeted drugs are promiscuous and exhibit activity against a wide range of molecular targets. In fact, it is now commonly accepted that the polypharmacology of these drugs (i.e. their ability to modulate the activity of multiple protein targets) is at least partly responsible for their efficacy'. MTDD is also described by the term 'designed multiple ligands' as described in multiple publications by Morphy.[2]

The terms 'promiscuous' or 'dirty drug' may have a pejorative aspect in that although multiple biological activities can be useful, leading to enhanced efficacy, they also may not be useful, leading to enhanced undesirable pharmacology (toxicity). Not to be confused with multi-targeting, the term 'promiscuous' has also been used in the realm of high throughput screening (HTS) to denote HTS assay biological activity related to usually undesirable chemical or physicochemical features. This phenomenon may be associated with covalent bond formation between ligand and target,[3] or undesirable *in vitro* biophysical effects such as colloidal particle aggregate formation.[4] In both cases, the observed promiscuity is not associated with useful biological activity. In contrast to the *in vitro* situation, it should be noted that colloidal aggregate formation *in vivo* in the gastrointestinal tract may be beneficial by enhancing oral absorption.[5] There is also a drug discovery viewpoint in favor of ligands with the potential to form covalent bonds between ligand and target.[6] However, in this author's opinion, these are minority viewpoints in dedicated drug discovery.

RSC Drug Discovery Series No. 21
Designing Multi-Target Drugs
Edited by J. Richard Morphy and C. John Harris

Published by the Royal Society of Chemistry, www.rsc.org

Why is there an Upsurge in Interest in MTDD?

The existence of polypharmacology, which provides the foundation for MTTD, has been known to medicinal chemists for decades. For example, the concept of privileged chemistry structures was first described by Evans *et al*. in 1988,[7] reviewed by Patchett in 2000,[8] and discussed in a drug discovery and library design context in 2010.[9] The Merck group's work on the use of the benzodiazepine scaffold originally found in anxiolytics provides a rich example of how relatively small structural changes to a scaffold can lead to a variety of unrelated biological activities. In their words, 'What is clear is that certain ''privileged structures'' are capable of providing useful ligands for more than one receptor and that judicious modification of such structures could be a viable alternative in the search for new receptor agonists and antagonists'. It is clear that in this early work that the concept of polypharmacology was well understood although it was uncertain if compounds with polypharmacology might be rare and difficult to find. We now know that privileged structures (i.e. promiscuous scaffolds) are much more numerous than previously supposed.[10]

This work on MTTD is being published in 2012. The reader may well ask what has changed over the last two decades to bring MTTD to greater attention. In this author's opinion, one major change is the gradual realization, especially in this last decade, that the superbly selective single drug with high affinity for a single biological target coupled with clinical efficacy is, charitably speaking, 'the exception'; more critically, some view this as a 'fundamentally flawed' approach to drug discovery.[11–14] Illustrating the charitable viewpoint, it is estimated that a complete single point pathway knockout results in a phenotypic response in only about 10–15% of cases. This low efficacy of the single-mechanism drug discovery approach is the explanation for the intense interest in target validation. How does one find the magic 10–15% of potential targets where the single-mechanistic approach has a chance of working? The low efficacy of the single-mechanism approach places HTS into context. HTS is only a tool and the HTS approach to drug discovery is critically dependent on target validation. Explaining the 'fundamentally flawed' viewpoint is the genomics-driven 'drug discovery factory' approach[15] of the early 1990s which wasted hundreds of millions of dollars and the efforts of many talented scientists.

A second major change is the realization that polypharmacology is the rule rather than the exception among clinically useful drugs.[16,17] Finally, the wealth of ligand to target database information in the current era allows the exploitation of a more chemo centric as opposed to molecular biology centric view of drug discovery. This change is well described in the following quote from the review by Shoichet:[18] 'What is new in the past few years is the quantitative restatement of classical ideas, allowing formal comparisons among targets and ligands at a scale not previously attempted. This has suggested unexpected relationships among receptors, identified targets active in phenotypic screens, and predicted off-targets and new disease indications for drugs.'

Chemical Space, Polypharmacology and MTDD

The distribution of biologically active compounds in chemistry space is critical to the concepts of polypharmacology and MTDD. If biologically active compounds are widely or uniformly distributed in chemical space then one might expect polypharmacology to be rare and MTDD would likely not work. Conversely, if biologically active compounds are clustered in chemistry space then polypharmacology should be common and MTTD should be tractable.

Chemical space is finite but exceedingly large. As discussed in a review by Reymond *et al.*[19] 'Is chemical space finite? Yes, if boundaries are defined. For small molecule drug discovery the natural limit is the molecular weight, which must be capped at 300–500 Da to ensure reasonable bioavailability. This chemical space of drug-like molecules has been estimated to be in excess of 10^{60} molecules.' The key medicinal chemistry question relevant to MTDD is whether biologically active compounds are evenly distributed in this incredibly large chemical space. In this and other authors' opinion the answer for synthetic compounds is a resounding 'no'. Multiple papers in the literature attest to the very uneven distribution of biologically active synthetic compounds in chemistry space.[20–22] Synthetically made biologically active compounds (as might be made by medicinal chemists) are most definitely not evenly distributed in chemical space. In fact, even without consideration of biological activity, the distribution of chemical structure scaffolds in the chemical literature is highly biased.[23] Screening truly diverse compounds is the worst way to discover a drug because the current evidence suggests that most of chemistry space is not populated by biologically active synthetic compounds.

An Issue of Timing: When is MTDD/Polypharmacology Undesirable?

Polypharmacology can be undesirable in a chemical biology context as opposed to a drug discovery context. Broadly speaking, chemical ligands can be tested in biology assays for two purposes: to discover drugs or to discover something about a biological process.[24] From a drug discovery perspective, polypharmacology is extremely useful. However, in a chemical biology context where one may be using a molecule as a tool or probe to learn something about a biological process,[25] perhaps to interrogate a step in a pathway or to discover a mechanism, selectivity is a key attribute and polypharmacology is a detriment. This is especially the case in phenotypic screening where the active chemical ligand becomes the tool or probe that is the starting point for the detective work to discover mechanism. Even when the stated screening goal is a chemical biology tool or probe, selectivity is difficult to achieve. For example, in a crowd sourcing evaluation of the 64 tools and probes resulting from the NIH roadmap HTS screening effort,

about one-quarter were judged to be deficient with respect to selectivity.[26] The use of chemical biology probes with truly high selectivity can play a key role in understanding how to rationally design multi-targeted drugs, which is the key theme of this book.

Christopher Lipinski

References

1. J. T. Metz and P. J. Hajduk, *Curr. Opin. Chem. Biol.*, 2010, **14**, 498–504.
2. R. Morphy and Z. Rankovic, *Curr. Pharm. Des.*, 2009, **15**, 587–600.
3. J. B. Baell, *Future Med. Chem.*, 2010, **2**, 1529–1546.
4. A. Jadhav, R. S. Ferreira, C. Klumpp, B. T. Mott, C. P. Austin, J. Inglese, C. J. Thomas, D. J. Maloney, B. K. Shoichet and A. Simeonov, *J. Med. Chem.*, 2010, **53**, 37–51.
5. A. K. Doak, H. Wille, S. B. Prusiner and B. K. Shoichet, *J. Med. Chem.*, 2010, **53**, 4259–4265.
6. D. S. Johnson, E. Weerapana and B. F. Cravatt, *Future Med. Chem.*, 2010, **2**, 949–964.
7. B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber and P. S. Anderson, *et al.*, *J. Med. Chem.*, 1988, **31**, 2235–2246.
8. A. A. Patchett and R. P. Nargund (Merck Research Laboratories, Rahway, NJ, USA), *Annu. Rep. Med. Chem.*, 2000, **35**, 289–298.
9. M. E. Welsch, S. A. Snyder and B. R. Stockwell, *Curr. Opin. Chem. Biol.*, 2010, **14**, 347–361.
10. Y. Hu and J. Bajorath, *J. Chem. Inf. Model.*, 2010, **50**, 500–510.
11. R. L. Ho and C. A. Lieu, *Drugs in R&D*, 2008, **9**, 203–216.
12. H. Kitano, *Nat. Rev. Drug Discovery*, 2007, **6**, 202–210.
13. D. Brown, *Drug Discovery Today*, 2007, **12**, 1007–1012.
14. F. Sams-Dodd, *Drug Discovery Today*, 2006, **11**, 465–472.
15. U. A. K. Betz, R. Farquhar and K. Ziegelbauer, *Curr. Opin. Chem. Biol.*, 2005, **9**, 387–391.
16. A. L. Hopkins, *Nat. Chem. Biol.*, 2008, **4**, 682–690.
17. Y. Hu and J. Bajorath, *J. Chem. Inf. Model.*, 2010, **50**, 2112–2118.
18. M. J. Keiser, J. J. Irwin and B. K. Shoichet, *Biochemistry*, 2010, **49**, 10267–10276.
19. J.-L. Reymond, R. van Deursen, L. C. Blum and L. Ruddigkeit, *MedChemComm*, 2010, **1**, 30–38.
20. J. Hert, J. J. Irwin, C. Laggner, M. J. Keiser and B. K. Shoichet, *Nat. Chem. Biol.*, 2009, **5**, 479–483.
21. P. Ertl, S. Jelfs, J. Muehlbacher, A. Schuffenhauer and P. Selzer, *J. Med. Chem.*, 2006, **49**, 4568–4573.
22. C. Lipinski and A. Hopkins, *Nature*, 2004, **432**, 855–861.

23. A. H. Lipkus, Q. Yuan, K. A. Lucas, S. A. Funk, W. F. Bartelt, III, R. J. Schenck and A. J. Trippe, *J. Org. Chem.*, 2008, **73**, 4443–4451.
24. T. Kodadek, *Nat. Chem. Biol.*, 2010, **6**, 162–165.
25. S. V. Frye, *Nat. Chem. Biol.*, 2010, **6**, 159–161.
26. T. I. Oprea, C. G. Bologa, S. Boyer, R. F. Curpan, R. C. Glen, A. L. Hopkins, C. A. Lipinski, G. R. Marshall, Y. C. Martin, L. Ostopovici-Halip, G. Rishton, O. Ursu, R. J. Vaz, C. Waller, H. Waldmann and L. A. Sklar, *Nat. Chem. Biol.*, 2009, **5**, 441–447.