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References

1 Gorman, C. and Park, A. (2004) Inflammation – the secret killer. *Time Magazine* 163, February
2 Topol, E.J. (2004) Failing the public health – rofecoxib, Merck, and the FDA. *N. Engl. J. Med.* 351, 1707–1709
3 Meadows, M. (2002) Why drugs get pulled off the market. *FDA Consumer* 36, 11–17
4 Lipinski, C.A. *et al.* (2001) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* 46, 3–26
5 Egan, W.J. *et al.* (2002) Guiding molecules towards drug-likeness. *Curr. Opin. Drug Discov. Devel.* 5, 540–549
6 Lee, T.H. (2004) 'Me-too' products – friend or foe? *N. Engl. J. Med.* 350, 211–212
7 Mobley, J.L. (2004) Is rheumatoid arthritis a consequence of natural selection for enhanced tuberculosis resistance? *Med. Hypotheses* 62, 839–843
8 Reichert, J.M. (2003) Trends in development and approval times for new therapeutics in the United States. *Nat. Rev. Drug Discov.* 2, 695–702
9 Arnason, B.G.W. (1999) TNF neutralization in MS: results of a randomized, placebo-controlled multicenter study. *Neurology* 53, 457–465

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High-throughput drug discovery: what can we expect from HTS?

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Fuelled by the successes and optimism of the 1980s, the concepts of HTS and combinatorial chemistry, which heralded a new age of drug discovery, were embraced by the pharmaceutical industry. However, attrition rates in later stages of drug discovery soon led to questions being raised about the viability of the high-throughput paradigm. Here, examples from the experience at Pfizer (Sandwich, UK) are used to illustrate how the quality of the compound file, the target and the screening process act in concert to define the output from HTS. This is discussed within the context of the available literature, taking into account opinions from across the pharmaceutical industry.

HTS fuels the drug discovery pipelines of the majority of pharmaceutical companies and is one of the central paradigms of modern drug discovery. The need for HTS is a consequence of our limited knowledge – it is impossible to make accurate predictions about the interactions of biological macromolecules with small compounds for the assessment of the activity of new chemical entities. Biological screening is the practical answer to this conundrum, and the concept of scale has been introduced by the proposal that screening a greater number of compounds should provide more leads of improved quality. It was expected that this strategy would deliver multiple new starting points for drug discovery projects and would sustain the double-digit growth of major pharmaceutical companies. Despite the continuous introduction of more sophisticated screening technologies and ever increasing compound collections (predominantly driven by combinatorial chemistry), HTS has, in the minds of many scientists and analysts, fallen short of this target [1–3]. Although there is the widespread belief that, in the absence of alternative solutions, HTS will remain an important tool for the foreseeable future, it is now often perceived as a costly necessity rather than a method of choice. More importantly, attrition in later stages of drug development, as a result of poor physicochemical properties, has been attributed to the nature of HTS itself [4].

Here, HTS is dissected to give a better understanding of how the compound file, target and screening process act in concert to define the output from HTS and how changes in our knowledge can have a direct impact on this output. Understanding trends and drivers within biological screening should help to set the expectations about what HTS can and cannot deliver to the business.

Physicochemical properties of compounds and HTS

Poor solubility, permeability and metabolic instability of compounds are a major source of attrition in early development [5,6], and it has been suggested that the introduction of HTS and combinatorial chemistry contributes to this through the selection of compounds with properties outside ADMET space [4,7]. To assess this impact, changes in physical properties indicative of *in vivo* properties, such as absorption and permeability, were monitored over time. This process involved the analysis of the molecular weight, calculated logP (clogP) and predicted solubility of compounds registered at Pfizer in a time-dependent manner (grouped by registration date) from 1960 to 1997, when, after Lipinski

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and colleagues introduced the concept of drug-likeness with the Rule of Five [4], Pfizer entered into the process of actively selecting compounds based on their physicochemical property profile. Additionally, the output from 25 HTS campaigns against a variety of target classes, on the level of confirmed HTS actives (>22,000 compounds), was analysed.

It is apparent that the trend to synthesize compounds with higher molecular weight and clogP or reduced solubility is not a recent phenomenon, but has been continuous since the 1960s (Figure 1). With regards to the registered compounds represented in Figure 1, there is no shift in pace at the time of introduction of HTS or combinatorial chemistry. Although there is a marked increase in the percentage of compounds with predicted low solubility (≤5 μg ml^{-1}) from 1985 to 1997, this pattern does not coincide with the introduction of combinatorial chemistry (the first citations for combinatorial chemistry appear in the early 1990s). From the analysis of confirmed HTS hits at Pfizer (Sandwich, UK) (Figure 1), it would appear that, with respect to the physical properties monitored here, the overall output from HTS mirrors the composition of the compound file, although a general trend towards slightly higher molecular weight and clogP is evident.

The most probable explanation for the relationships observed within the collection of registered compounds is the continuous drive to expand the compound file to map a greater proportion of chemical space, which in the absence of restrictions leads to the synthesis of more complex molecules with the accompanying increase in molecular weight, and often clogP. The compounds confirmed as being active by the screening process follow this pattern and, as a consequence, compounds with higher molecular weight and lipophilicity have been selected as candidates for further development, a trend that has been well-documented for Pfizer candidates [8] but has also been observed elsewhere [9]. Meanwhile, no such change is observed when analysing the set of marketed oral drugs [10], illustrating that there is a selection pressure against this increase in the later stages of drug development. The analysis illustrates that the quality of the file is paramount in screening

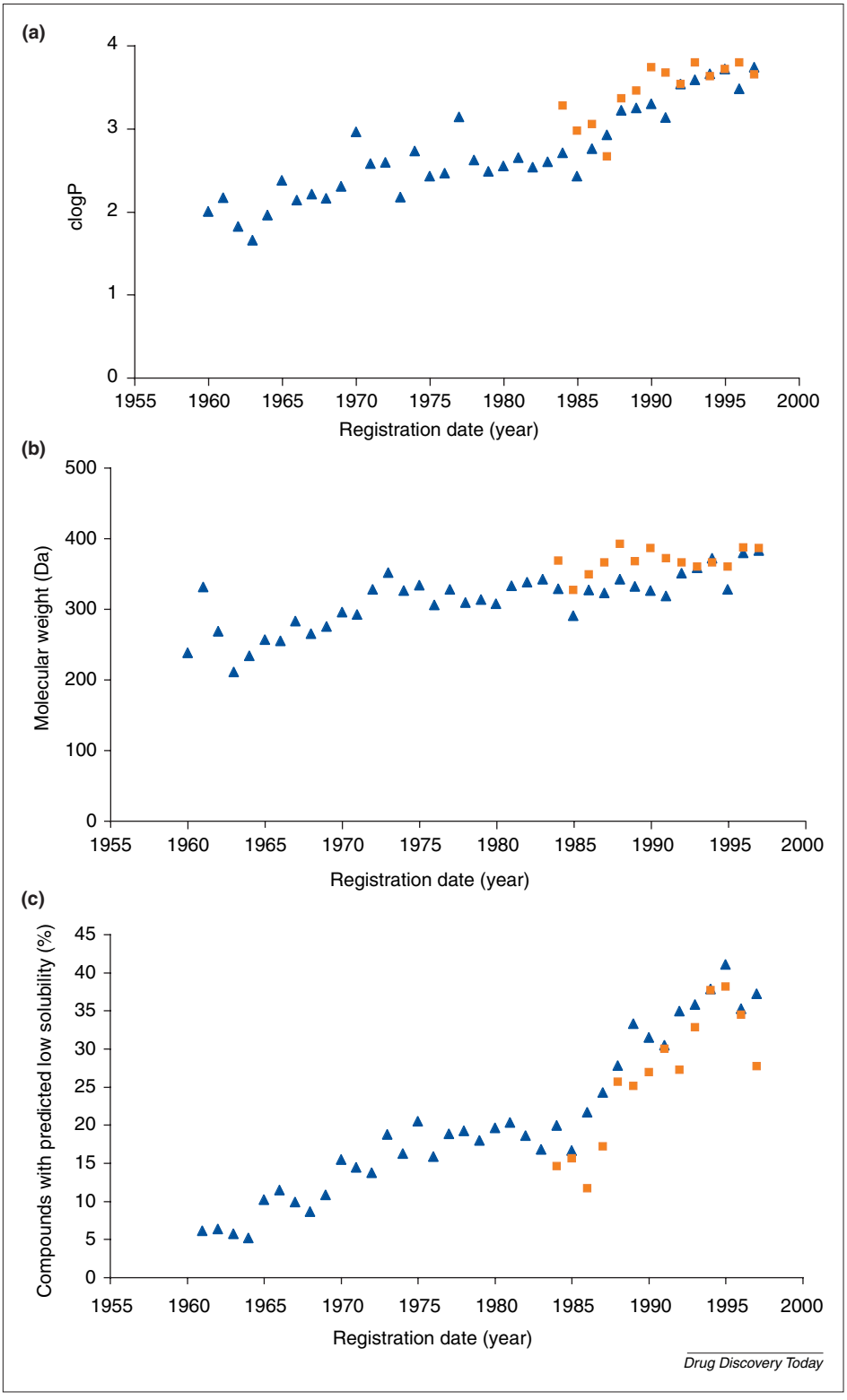

FIGURE 1

Historical analysis of the Pfizer compound file and confirmed HTS actives. Median values for **(a)** clogP; **(b)** molecular weight; and **(c)** the fraction of compounds with predicted low solubility (≤5 μg ml^{-1}) are shown for compounds registered 1960–1997 (blue triangles), not including any additions from merger activities during this time. The confirmed actives from 25 HTS campaigns (approximately 22,000) at Pfizer (Sandwich, UK) have been analysed according to the same criteria (orange squares). Results are only presented for compounds registered 1984–1997 because of limited available data.

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and this realization has had a direct impact on the direction of the further growth of the compound file (which is known as 'file enrichment' at Pfizer), as well as the hit-to-lead strategies in medicinal chemistry.

Knowledge-based development of corporate compound files

Once the importance of the careful selection of compounds for screening became apparent, a drive to filter the screening file and remove undesirable material began. This process focussed initially on the purity of the compounds [11]. In the next stage, the emphasis shifted to the removal of reactive species [12,13] and then advanced further to concentrate on physicochemical properties that predict the *in vivo* behaviour of compounds [13,14]. At Pfizer, the first major selection of compounds in the screening file (driven by the presence of 'desirable' and 'undesirable' features) started as long ago as 1997.

The retrospective analysis of the properties of known drugs by Lipinski [4] and subsequent work by several groups [15–19] have changed the focus of medicinal chemistry at Pfizer and across the whole industry, and have also highlighted the importance of *in vitro* and *in silico* predictors for *in vivo* pharmacokinetic properties to a wider audience. Although the term 'drug-likeness' is only loosely defined, there is now widespread agreement that a focus on molecular properties that affect *in vivo* properties is equally important as *in vitro* compound potency and selectivity when choosing candidates for further development. This knowledge can be applied at the lead selection stage or, within a more productive paradigm, should be incorporated into the design and synthesis of compounds and libraries to focus HTS on compounds with a higher probability of success, namely those compounds with:

- Confirmed structure and high purity.
- Favourable physicochemical properties.
- Absence of known toxicophores or reactive groups.
- Tractability to high speed, parallel chemistry for rapid follow-up and optimization.

Although restricting the range of physicochemical properties of compounds in a screening set is a widely accepted concept, the exact limits for this are a matter of debate and discussion. An analysis of drugs and their parent leads by Oprea and colleagues [18,19] suggests that there is a clear distinction between lead compounds and drugs, with drugs having, for example, higher molecular weights and clogP values. This underlines that the development from hit-to-lead to drug is often accompanied by the addition of more lipophilic moieties and increases in molecular weight, a proposition supported by several authors [4,9,13]. As a consequence, it has been suggested that screening compound collections should be lead-like (i.e. MW <350 and clogP <3 [15]) instead of drug-like (i.e. MW <500, clogP <5, H-bond donors <5 and H-bond acceptors <10 [4]).

An area of additional intense effort is the enrichment of compound collections based on target information, predominantly crystal structures and model-building [20–23]. Although a powerful approach within individual projects, this cannot be solely relied on for extending corporate files because current knowledge is clearly limited and rapidly changing.

The size of compound files: is bigger better?

Given the number of potential low molecular weight compounds (estimates range from 10^{40} to 10^{100} [8,24]), it is apparent that – even if it was desirable – no organization will be able to cover this chemical space (there are obvious financial limits, but 10^{100} also exceeds the estimates for the number of atoms in the universe). Based on current knowledge, it is also not a desirable goal because pharmacological and drug-like compounds occupy only a restricted subregion of chemical space [18,25]. If we agree with this concept, the question is reduced to how densely do we need to cover this subspace. The answer is dependent on the strategy of the organization and on some fundamentals in HTS, namely that HTS is suited to identifying series but not single compounds, therefore the screening file must incorporate a degree of redundancy from the onset [26]. This observation is a consequence of the nature of single-point biological screening, which inevitably produces some 'false negatives' as a result of data variability. In this context, closely related compounds will act as 'replicates'.

If it is anticipated that several compounds representing different chemical series will be identified as starting points for the lead development process, a 'real' screening file of 2–3 million should be sufficient to deliver multiple starting points that can be expanded on by follow-up procedures [27], but the 'real' file will be increasingly augmented by huge virtual libraries selected via knowledge-based approaches [28]. However, if it is expected that hits with nM potency will be identified for every target screened, the targets shift and a significantly larger file size is examined. Wintner and Moallemi [29] present a calculation that requires a screening file of at least 24,000,000 distinct compounds to deliver nM potency hits for all targets; this calculation does not allow for the need for multiple chemical series. However, a strategy that is based solely on potency could be fundamentally flawed and the concept of initially screening for starting points rather than nM hits is also the more cost-effective approach. Overall, we do envisage continued growth in the size of corporate compound files. However, at the same time, the screening file (i.e. the percentage of the corporate file that will be screened against a given target) will not see the same expansion and will be tailored to the target by our growing knowledge, for example, through the application of focused subset screening [30,31] or an iterative screening concept [28,32].

Can screening processes be designed to find more attractive hits?

It has been suggested that the use of binding assays and the solubilization of compounds in dimethyl sulfoxide (DMSO) are the drivers for the undesirable increase in molecular weight and clogP in compounds nominated for further development [4,7]. Although the impact of chemistry on screening processes has been the focus of the article thus far, HTS can intrinsically drive the selection of higher molecular weight compounds in a context where scientists concentrate on potency and in the boundaries generated by the property range defined by the screening file. This

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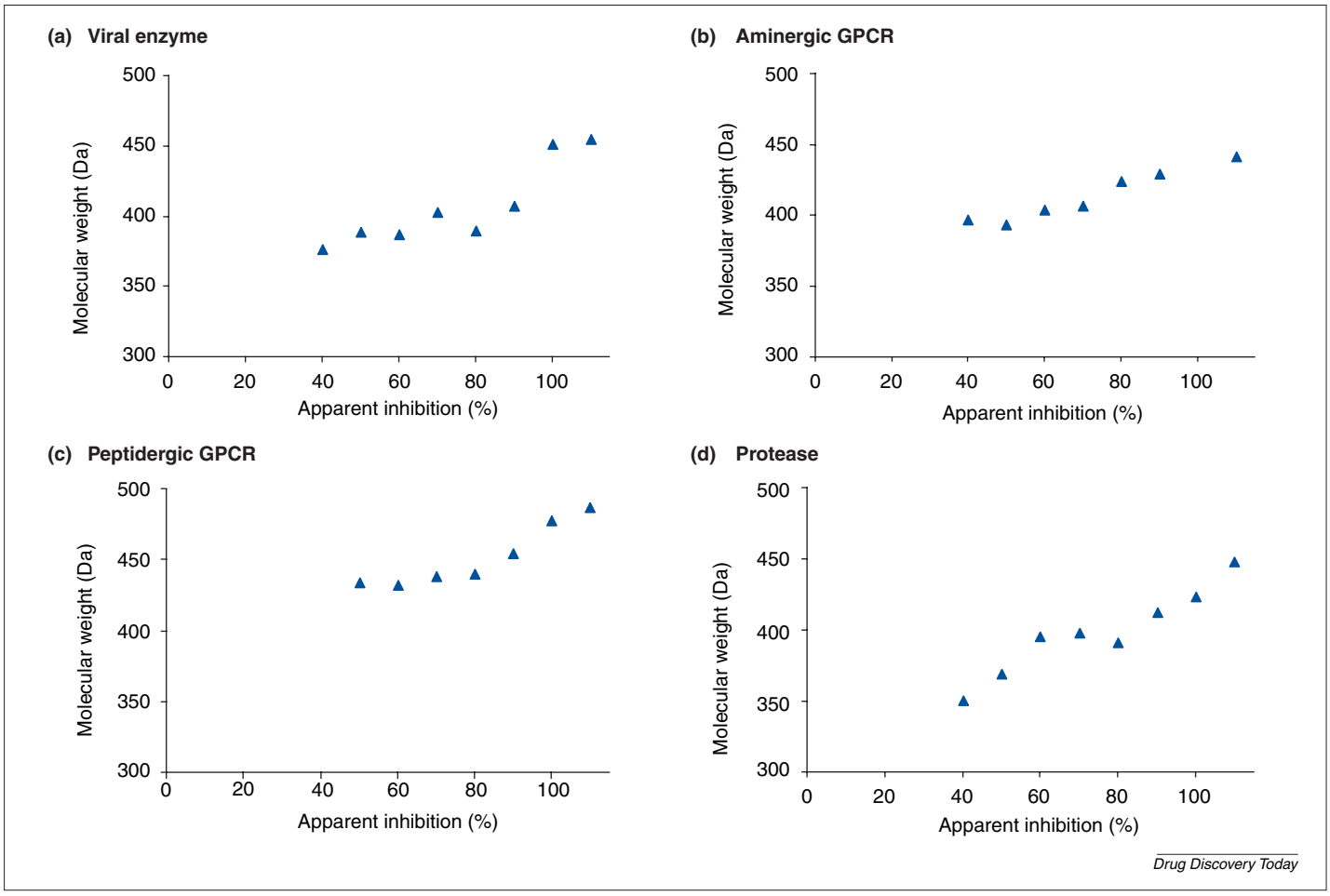

FIGURE 2

Potency driven properties: the impact of potency on molecular weight. Actives from the corresponding HTS were binned according to their apparent potency in the primary assay and the median molecular weight was calculated for each potency bin.

observation (Figure 2) is a consequence of the notion that the free energy of binding increases with the number of non-hydrogen atoms [33] and therefore, although the overall chance to hit is lower for a larger, more complex molecule, if it binds well, the potency can be higher [34]. This theoretical concept is translated into practice when using assays that monitor binding events either in cell-based or biochemical formats (e.g. receptor antagonists and enzyme inhibitors). Because the focus on potency tends to select for higher molecular weight compounds, Pfizer has introduced the concept of ligand efficiency, where the binding energy per atom of a ligand is calculated to aid prioritization for follow-up and lead series selection by 'normalizing' potency [35].

Beyond this biophysical restraint, the target itself strongly influences the properties of the resulting HTS hits. A retrospective analysis of ~22,000 confirmed HTS actives at Pfizer (Sandwich) showed clear differences in molecular weight or polar surface area when actives were classified by target type. For example, unsurprisingly, the median molecular weight of ligands of aminergic G-protein-coupled receptors (GPCRs), as derived directly from HTS, is approximately 50 Da less than the corresponding value for ligands of peptidergic GPCRs. These differences in properties are apparent on comparison of several target classes. Altering the screening procedure by, for example, introducing a step involving re-solubilization of dried down compounds within the assay (instead of using diluted DMSO solutions), can enrich hit populations towards more favourable properties, particularly lower clogP values (Figure 3). Generally, the output from HTS is dependent on multiple factors and, although *in vitro* assays can and do contribute to the observed shift towards less favourable ADME properties, it is too simplistic a view to attribute this solely to the current *in vitro* screening approach.

What can be expected from HTS?

The prospects for a successful exploitation of corporate compound collections are now better than ever. The considerable expenditure, with respect to time and money, has improved HTS methods and the quality of results during the past decade, and miniaturized and, perhaps more importantly, biologically relevant plate-based assays are now available for virtually all target classes. From the experience of past years, it is evident that truly random, empirical screening of large unselected compound files

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cannot succeed without additional information relating not only to the target but also to the compounds, which for the most part must be transformed into orally bioavailable drugs to achieve success. Changes in the strategic balance of many companies, to encompass a greater proportion of knowledge-based approaches, are evident from several publications [23,24,28,36] and work is ongoing to incorporate more of this information at the onset of projects. Biological screening alone cannot guarantee more and improved leads, but with the additional knowledge acquired, the quality of leads will be significantly enhanced and attrition rates reduced.

Primary screening is not the only procedure that is central to the success of HTS, a swift execution of the hit-to-lead process is also crucial and it is this that is the focus of many pharmaceutical companies [37,38]. Consequently, the 'new', widely cited, deliverable (from the high-throughput concept) of high-speed parallel chemistry and screening methods is to shorten the time interval from hit-to-lead to candidate. In this working model, in addition to potency and selectivity, multiple compound characteristics (e.g. ADME properties) drive lead development [37–40]. Multidimensional compound optimization is the new paradigm [38–40], but its rapid realization for multiple parallel projects relies on a compound file where the majority of compounds are amenable to parallel, library-based chemistry and the availability of high-throughput ADME assays or reliable *in silico* models [41]. Although this is a realistic expectation, there is still a lack of publicly available analysis to demonstrate the benefits, and the concept of parallel optimization has yet to be firmly established with all chemists and biologists. Traditional HTS, but with a focus on compound quality rather than quantity, will remain an important tool for a variety of targets. However, this will be only one weapon in our armoury. In our opinion, the key to success is a highly flexible approach selecting the 'right' strategy for the target, be it large-scale screening or knowledge-based methods relying on structures, biology or competitor information. For HTS, this has to be paired with data-mining through computational chemistry to maximize the return from expensive screening campaigns [28,42].

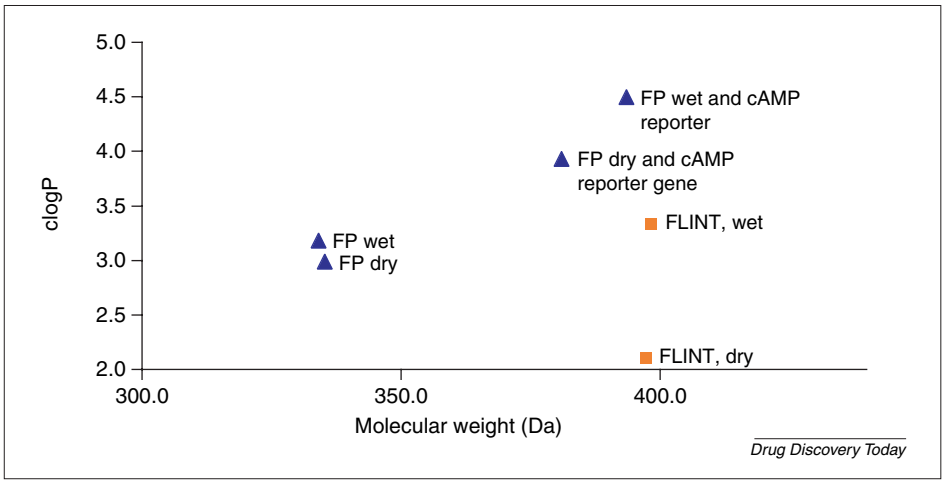

FIGURE 3

Compound delivery and physicochemical properties. Median clogP and molecular weight values are shown for confirmed actives from a peptidergic GPCR and a soluble enzyme assay. For the wet screening (wet), compounds were introduced in diluted DMSO solution, whereas for the dry screening (dry), compounds were dried down and resolubilized through the addition of the aqueous assay components. The same compound sets were used for the dry and wet screening in the respective assays. Three screening methods were applied (FP wet, FP dry and cAMP reporter gene wet). The subset that was functionally active (FP dry and cAMP reporter gene; and FP wet and cAMP reporter gene) was analysed further. Abbreviations: cAMP reporter gene, cAMP responsive element driven β-lactamase reporter gene; FP, fluorescence polarization; FLINT, fluorescence intensity-based assay.

Conclusion

The analysis presented here does not indicate that HTS is selecting for 'undesirable' compounds, but that HTS results merely reflect the properties of corporate compound files. HTS is just a tool to explore the chemical resource presented by corporate compound collections. The thorough validation of targets and the careful selection of compounds for the screening file are a prerequisite for successful HTS. The input for further growth and enrichment of screening files is coming from medicinal chemistry and computational chemistry, and is based on the knowledge acquired, and models built, from 'wet' experiments. Evidence presented in many publications indicates that the introduction of property filters in compound collections is essential [4,13,17–19]. However, it should be clear that current knowledge is imperfect and is based on the limited exploration of chemical and drug-like space. There is reliance on theoretical calculations about the drugability of targets, as well as chemical and drug-like space, and current doctrines on the direction of file extension and restriction of properties should be approached with caution. Room must be left for unprecedented scientific discovery in an overall 'rational' approach, because some discoveries do not happen in incremental steps but present themselves as a 'leap' into new territory [43]. At the same time, it is obvious that information-based approaches will increasingly augment, and eventually replace, large-scale 'random' screening of historical compound collections.

Despite several success stories [44,45], drug discovery that is based on the random screening of large corporate compound collections has not yet fulfilled the original, and with hindsight unrealistic, expectations of delivering large numbers of new chemical entities to the market. To reap the benefits of the large-scale investment into high-throughput technologies in biology and chemistry, companies have to develop a portfolio of highly flexible solutions to drug discovery, seamlessly integrating different strategies from large-scale HTS to focused, information driven methods paired with optimized 'hit-to-lead' processes.

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References

1 Peakman, T. *et al.* (2003) Delivering the power of discovery in large pharmaceutical organizations. *Drug Discov. Today* 8, 203–211
2 Gershell, L.J. and Atkins, J.H. (2003) A brief history of novel drug discovery technologies. *Nat. Rev. Drug Discov.* 2, 321–327
3 Hefti, E. and Bolten, B.M. (2003) Advances in high-throughput screening – do they lead to new drugs? *Decision Resources* (http://www.dresources.com/stellent/groups/public/documents/abstract/dr_005477.hcsp)
4 Lipinski, C. *et al.* (1997) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* 23, 3–25
5 Darvas, F. *et al.* (2002) *In silico* and *ex silico* ADME approaches for drug discovery. *Curr. Top. Med. Chem.* 2, 1287–1304
6 Di, L. and Kerns, E.H. (2003) Profiling dug-like properties in discovery research. *Curr. Opin. Chem. Biol.* 7, 402–408
7 Curatolo, W. (1998) Physical chemical properties of oral drug candidates in the discovery and exploratory development setting. *Pharm. Sci. Technol. Today* 1, 387–393
8 Lipinski, C.A. (2000) Drug-like properties and the causes of poor solubility and poor permeability. *J. Pharmacol. Toxicol. Methods* 44, 235–249
9 Wenlock, M.C. *et al.* (2003) A comparison of physicochemical property profiles of development and marketed oral drugs. *J. Med. Chem.* 46, 1250–1256
10 Vieth, M. *et al.* (2004) Characteristic physical properties and structural fragments of marketed oral drugs. *J. Med. Chem.* 47, 224–232
11 Everett, J. *et al.* (2001) The application of non-combinatorial chemistry to lead discovery. *Drug Discov. Today* 6, 779–786
12 Rishton, G.M. (1997) Reactive compounds and *in vitro* false positives in HTS. *Drug Discov. Today* 2, 382–384
13 Rishton, G.M. (2003) Nonleadlikeness and leadlikeness in biochemical screening. *Drug Discov. Today* 8, 86–96
14 Walters, W.P. and Namchuk, M. (2003) Designing screens: how to make your hits a hit. *Nat. Rev. Drug Discov.* 2, 259–266
15 Teague, S.J. *et al.* (1999) The design of leadlike combinatorial libraries. *Angew. Chem. Int. Ed. Engl.* 38, 3743–3747
16 Oprea, T.I. (2000) Property distribution of drug-related chemical databases. *J. Comput. Aided Mol. Des.* 14, 251–264
17 Muegge, I. (2003) Selection criteria for drug-like compounds. *Med. Res. Rev.* 23, 302–321
18 Oprea, T.I. *et al.* (2001) Is there a difference between leads and drugs? A historical perspective. *J. Chem. Inf. Comput. Sci.* 41, 1308–1315
19 Opera, T.I. (2002) Current trends in lead discovery: are we looking for the appropriate properties? *J. Comput. Aided Mol. Des.* 16, 325–334
20 Kuhn, P. *et al.* (2002) The genesis of high-throughput structure-based drug discovery using protein crystallography. *Curr. Opin. Chem. Biol.* 6, 704–710
21 Stahura, F.L. *et al.* (2002) Methods for compound selection focused on hits and application in drug discovery. *J. Mol. Graph. Model.* 20, 439–446
22 Laird, E.R. and Blake, J.F. (2004) Structure-based generation of viable leads from small combinatorial libraries. *Curr. Opin. Drug Discov. Devel.* 7, 354–359
23 Jimonet, P. and Jaeger, R. (2004) Strategies for designing GPCR-focused libraries and screening sets. *Curr. Opin. Drug Discov. Devel.* 7, 325–333
24 Valler, M.J. and Green, D. (2000) Diversity screening versus focussed screening in drug discovery. *Drug Discov. Today* 5, 286–293
25 Lipinski, C.A. (2001) Avoiding investments in doomed drugs. *Curr. Drug Disc.* 4, 17–19
26 Spencer, R.W. (1998) High-throughput screening of historic collections: observations on file size, biological targets, and file diversity. *Biotechnol. Bioeng.* 61, 61–67
27 Harper, G. *et al.* (2004) Design of a compound screening selection for use in high-throughput screening. *Comb. Chem. High Throughput Screen.* 7, 63–71
28 Bajorath, J. (2002) Integration of virtual and high-throughput screening. *Nat. Rev. Drug Discov.* 1, 882–894
29 Wintner, E.A. and Moallemi, C.C. (2000) Quantized surface complementarity diversity (QSCD): a model based small molecule-target complementarity. *J. Med. Chem.* 43, 1993–2006
30 Stahura, F.L. *et al.* (1999) Molecular scaffold based design and comparison of combinatorial libraries focused on the ATP-binding site of protein kinases. *J. Mol. Graph. Model.* 17, 1–9
31 Balakin, K.V. (2002) Property based design of GPCR-targeted libraries. *J. Chem. Inf. Comput. Sci.* 42, 1332–1342
32 Young, S.S. *et al.* (2002) Initial compound selection for sequential screening. *Curr. Opin. Drug Discov. Devel.* 5, 422–427
33 Kuntz, I.D. *et al.* (1999) The maximal affinity of ligands. *Proc. Natl. Acad. Sci. U. S. A.* 96, 9997–10002
34 Hann, M.M. *et al.* (2001) Molecular complexity and its impact on the probability of finding leads for drug discovery. *J. Chem. Inf. Comput. Sci.* 41, 856–864
35 Hopkins, A.L. *et al.* (2004) Ligand efficiency: a useful metric for lead selection. *Drug Discov. Today* 9, 430–431
36 Viswanadhan, V.N.V. *et al.* (2002) Knowledge-based approaches in the design and selection of compound libraries for drug discovery. *Curr. Opin. Drug Discov. Devel.* 5, 400–406
37 Alanine, A. *et al.* (2003) Lead generation – enhancing the success of drug discovery by investing in the hit to lead process. *Comb. Chem. High Throughput Screen.* 6, 51–66
38 Bleicher, K.H. *et al.* (2003) Hit and lead generation: beyond high-throughput screening. *Nat. Rev. Drug Discov.* 2, 369–378
39 Kerns, E.H. and Di, L. (2003) Pharmaceutical profiling in drug discovery. *Drug Discov. Today* 8, 316–323
40 Caldwell, G.W. *et al.* (2001) The new pre-preclinical paradigm: compound optimization in early and late phase drug discovery. *Curr. Top Med. Chem.* 1, 353–366
41 Smith, D.A. (2002) Hello Drug Discovery, I am from *Insilico*, take me to your President. *Drug Discov. Today* 7, 1080–1081
42 Garyantes, T. (2002) 1536-well assay plates: when do they make sense? *Drug Discov. Today* 7, 489–490
43 Schmid, E.F. and Smith, D.A. (2002) Should scientific innovation be managed? *Drug Discov. Today* 7, 941–944
44 Golebiowski, A. *et al.* (2001) Lead compounds discovered from libraries. *Curr. Opin. Chem. Biol.* 5, 273–284
45 Golebiowski, A. *et al.* (2003) Lead compounds discovered from libraries: Part 2. *Curr. Opin. Chem. Biol.* 7, 308–325

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