DRUG DISCOVERY TODAY TARGETS

How many genomics targets can a portfolio afford?

Ulrich A.K. Betz

The pharmaceutical industry can look back at a history of successful innovations. Although genomics technologies have provided drug discovery pipelines with a plethora of new potential drug targets, solid target validation is crucial to avoiding high attrition rates. Biomarkers for patient stratification and approaches for personalized medicine will further help to reduce the risk associated with new targets. To achieve an overall risk balance, portfolios have to be supplemented with precedented targets, me-too approaches and line extensions of existing drugs. However, capitalizing on genomics investments and working on unprecedented targets is essential for a continuous stream of innovative drugs.

The pharmaceutical industry can look back at a long history of successful innovations. The beginning of the modern drug industry can be dated back to the introduction of the first synthetic antipyretics antipyrine, antifebrin and acetophenetidin (phenacetin) in the 1980s [1]. The still widely used Aspirin® was synthesized in a pure and stable form for the first time by Felix Hoffmann at the Bayer laboratories on 10 August 1897. Since these early times, further breakthrough medications have continued to emerge (some examples are shown in Table 1).

The medical, sociological and economic impact of pharmaceuticals has been substantial and is reflected in a list of essential drugs that was published by the World Health Organization (WHO) in 1977, which has since been regularly updated (www.who.int/medicines/organization/par/edl/expcom13/eml13_en.pdf). The drugs included in this list are selected with due regard to disease prevalence and evidence on efficacy, safety and comparative cost-effectiveness. According to the WHO, these drugs should be available within the context of functioning healthcare systems at all times and in adequate amounts. However, despite the existence of all these drugs, new agents are urgently needed, and a tremendous medical need still remains. This is compounded by the fact that many diseases still cannot be treated causally. Western societies are undergoing demographic changes and age-related multimorbidity, and the increasing prevalence of cancer, diabetes, Alzheimer's disease and heart disease is putting tremendous pressure on healthcare systems. Another lingering threat is infectious diseases with multiple resistances spreading among pathogenic bacteria, as well as the emergence of new viral diseases such as HIV, severe acute respiratory disease or avian flu. Likewise, many diseases predominantly abundant in the developing world are still awaiting the emergence of suitable treatment solutions.

The current productivity crisis

Addressing this persisting medical need by bringing new drugs to the market requires considerable R&D efforts and, indeed, with an average of 16% of sales spent on R&D, the pharmaceutical industry is one of the most research-intensive industries, much more so than, for example, the computer and software industry, and is second only to the aerospace

Ulrich A.K. Betz
Bayer HealthCare, Pharma Research & Development, Apratherweg, D-42096 Wuppertal, Germany
e-mail: ulrichbetz@yahoo.de

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TABLE 1

Breakthrough innovations from the pharmaceutical industry

Activity	Comment	Name	Year
COX inhibitor	Beginning of the modern drug industry	Acetophenetidin	1887
COX inhibitor	The beginning of Aspirin®	Acetylsalicylic acid	1899
Cell-wall synthesis inhibitor	First modern antibiotic	Penicillin	1941
Dihydrofolate reductase inhibitor	Anti-cancer drug	Methotrexate	1948
NHR agonist	First synthetic NHR agonist	Cortisone	1949
Monoamine oxidase inhibitor	First neuroleptic agent	Chlorpromazine	1952
Na^+ and Cl^- transporter blocker	Diuretic	Thiazides	1958
GABA-receptor agonist	Tranquilizer	Benzodiazepines	1960
Ca^{2+}-channel blocker	First Ca^{2+}-channel blocker	Verapamil	1963
β-Adrenoceptor antagonist	First β-blocker	Pronethalol	1967
H_2-receptor blocker	First anti-histamine ulcer treatment	Cimetidine	1977
ACE inhibitor	First ACE inhibitor	Captopril	1981
Insulin	First recombinant protein drug	Humulin®	1982
DNA-gyrase inhibitor	Quinolone antibiotic	Ciprofloxacin	1986
HMG-CoA reductase inhibitor	First statin	Lovastatin	1987
Reverse transcriptase inhibitor	First anti-HIV drug	Zidovudine (AZT)	1987
AMPA agonist	First anti-Alzheimer's disease drug	Aniracetam	1993
Anti-CD20	First anti-cancer monoclonal antibody	Rituximab	1997
COX-2 inhibitor	First selective COX-2 inhibitor	Celecoxib	1999
Anti-CD33+ enediyne antibiotic	First antibody-targeted cancer chemotherapy	Gemtuzumab ozogamicin	2000
BCR-Abl kinase inhibitor	First anti-cancer kinase inhibitor	Imatinib	2001
M3 antagonist	First specific COPD drug	Tiotropium	2002
IgE blocker	First anti-asthma antibody therapy	Omalizumab	2003
Anti-EGFR	First anti-EGFR antibody	Cetuximab	2003
Anti-VEGF	First angiogenesis inhibitor	Bevacizumab	2004

Abbreviations: ACE, angiotensin-converting enzyme; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AZT, 3′-azido-2′,3′-dideoxythymidine; BCR, breakpoint cluster region; c-Abl, cellular homolog of the transforming sequence of Abelson murine leukemia virus; CD, cluster of differentiation; COPD, chronic obstructive pulmonary disease; COX, cyclooxygenase; EGFR, epidermal growth factor receptor; GABA, gamma-aminobutyric acid; M, muscarinic receptor; VEGF, vascular endothelial growth factor.

industry (www.nsf.gov/sbe/srs/seind04/pdfstart.htm). Moreover, the proportion of pharmaceutical R&D within the total industry R&D is substantial and, for example, in Europe, as much as 14% of all business enterprise expenditure on R&D is allocated within the pharmaceutical industry (http://europa.eu.int/comm/research/press/2003/pdf/indicators2003/reist_2003.pdf). Phase III of clinical development is the single most expensive stage in the R&D of a new drug [2], and the percentage of total R&D spending allocated to the preclinical stage has decreased from >60% in 1976 to ~30% in 2002 [3]. Bringing a new molecular entity (NME) to the market is associated with considerable expense, and the Tufts Center for the Study of Drug Development has estimated that pharmaceutical companies face expenditures of approximately US$800 million for discovery, evaluation and clinical trials for each NME that enters the market (http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=6). A more recent study by Gilbert and co-workers [4] has even calculated total costs of US$1.7 billion to bring a single drug to the market for 2000–2002, an increase of 54% compared with the period 1995–2000. The financial power of the industry to continue to finance these rising R&D costs is questionable. Only three out of every ten marketed prescription drugs produces revenues that match or exceed average R&D costs [5]. In addition, competition from generics has increased, and the volume share of generic prescription drugs has increased from 19% in 1984 to 47% in 1999 (www.phrma.org/publications/publications//2003-11-20.870.pdf). Rising sales in the past have been largely achieved by increased commercialization efforts with a focus on areas with high business opportunities and by implementing portfolio management activities to eliminate low-profit endeavors at an early stage. To support the sales growth, marketing spending has increased overproportionately. Total promotional costs were 61% of total R&D costs in 1999, but rose to 76% in 2003. Interestingly, the total retail value of samples alone was 32% of total R&D costs in 1999, but rose to 50% in 2003 (www.phrma.org/publications/policy//2004-11-10.1095.pdf; www.imshealth.com/ims/portal/front/articleC/0,2777,6025_44304752_44889690,00.html).

Although the amount spent by the pharmaceutical industry on R&D has almost risen exponentially in the

past, the output, as measured by NMEs entering the market, has not grown commensurately with the increase in R&D spending [3]. The FDA approved 35 NMEs in the USA in 1999; this number was reduced to 27 in 2000, 24 in 2001, 17 in 2002 and 21 in 2003 (www.fda.gov/cder/rdmt/pstable.htm). By contrast, 2004 saw a sudden strong upward swing, with 31 newly FDA-approved NMEs. However, the NME status for some of these drugs has been challenged, and it is noteworthy that eight of these 31 drugs were approved during the last two weeks of 2004. In addition, it is generally expected that the number of FDA-approved NMEs will again decrease in 2005. A continuing negative trend for new drug approvals is visible when looking at launches worldwide, where an upward swing did not occur in 2004 (Figure 1), despite a 360% increase in R&D spending in Pharmaceutical Research and Manufacturers of America companies from US$8.4 billion in 1990 to US$38.8 billion in 2004 (www.phrma.org/publications/publications//2005-03-17.1143.pdf). This can be called a productivity crisis and, if not resolved, could challenge the long-term future of the industry [4,6]. To address the innovation deficit, the FDA recently released an intriguing report, entitled *Innovation or Stagnation? – Challenge and Opportunity on the Critical Path to New Medical Products* (www.fda.gov/oc/initiatives/criticalpath/whitepaper.html). In addition, expanding the universe of drug targets currently in use is crucial to maintaining a continuous stream of innovative drugs.

Current drug targets

The molecular target of a given drug is an important parameter affecting its efficacy and safety. One way of seeking innovative medicines is to address unmet medical needs by attacking so far unused molecular targets revealed in the human genome. It is currently estimated that all known drugs address only ~500 different molecular targets [7,8]. Hopkins and Groom [9] identified 399 nonredundant drug targets that have been shown to bind rule-of-five-compliant compounds [10] with a binding affinity below 10 μM. However, of these, only 120 proteins are the targets of actually marketed drugs [9]. Finally, fewer than 100 drug targets are responsible for all prescription drugs currently marketed, and the top 100 selling prescription drugs aim at only 43 distinct drug targets [11]. Current sales are primarily generated from drugs attacking classical druggable target classes such as enzymes, G-protein-coupled receptors (GPCRs), carriers and nuclear hormone receptors (NHRs) and ion channels (Figure 2a). 'Druggable' means that the activity of a target can be modulated by a small molecular inhibitor, ideally with oral bioavailability. These target classes are used to a varying extent in the different therapeutic areas (Figure 2b). In the field of anti-infectives, for example, current drugs primarily address enzymes. The same is true for cancer, for which, in addition, a substantial number of drugs addressing NHRs are involved. By contrast, in the field of central nervous system diseases, drugs usually attack GPCRs and ion channels or carriers. Finally, in cardiovascular disease, drugs are directed against GPCRs, enzymes, proteases and ion channels or carriers. There are also differences regarding the chemical nature of the drugs themselves. Synthetic drugs usually address GPCRs, enzymes, ion channels and carriers. By contrast, natural products predominantly target NHRs, whereas biologicals (antibodies or recombinant factors) mainly target other nondruggable membrane receptors.

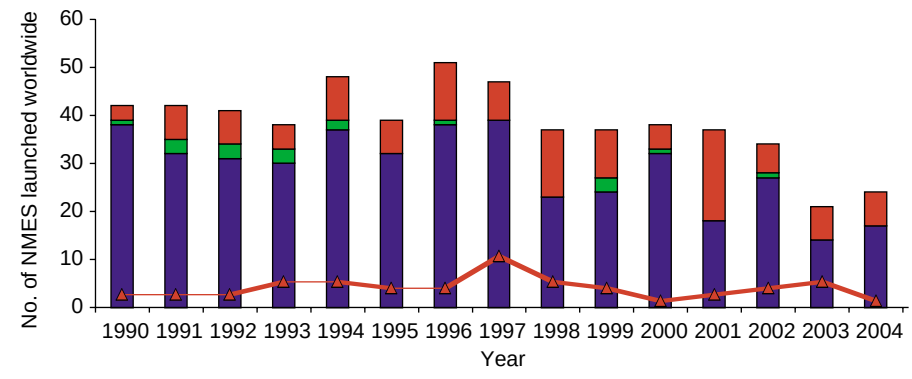

FIGURE 1

Global new molecular entity drug launches. Bars show the number of NME drugs launched worldwide per year, according to their origin (synthetic, natural product, biological). The line shows the number of new drug targets addressed by synthetic drugs launched in a given year. The number of launches has been decreasing over the past decade. Only ~three new drug targets are addressed per year with synthetic drugs (Sources: Pharmaprojects, FDA, IMS R&D Focus, ADIS R&D Insights, Market Letter and SCRIP).

The pool of druggable targets

How many new drug targets can we hope to discover in the target universe of the human genome? Although the first analysis of the draft sequence resulted in an estimate of ~31,000 protein-coding genes in the human genome [12], the current estimate has dropped to 22,287 genes [13], consisting of 19,438 known and 2188 predicted genes. It is generally estimated that 3000 of these are druggable [9,14], based on a survey of the predicted human proteome for molecules containing druggable (InterPro) domains [15]. To be a suitable point of attack for a drug, the modulation of a given target has to ameliorate or cure a disease or its signs and symptoms. In this definition, modulation of a target can mean upregulating its activity via an agonist or downregulating its activity via an antagonist or inhibitory molecule. The number of targets with disease relevance

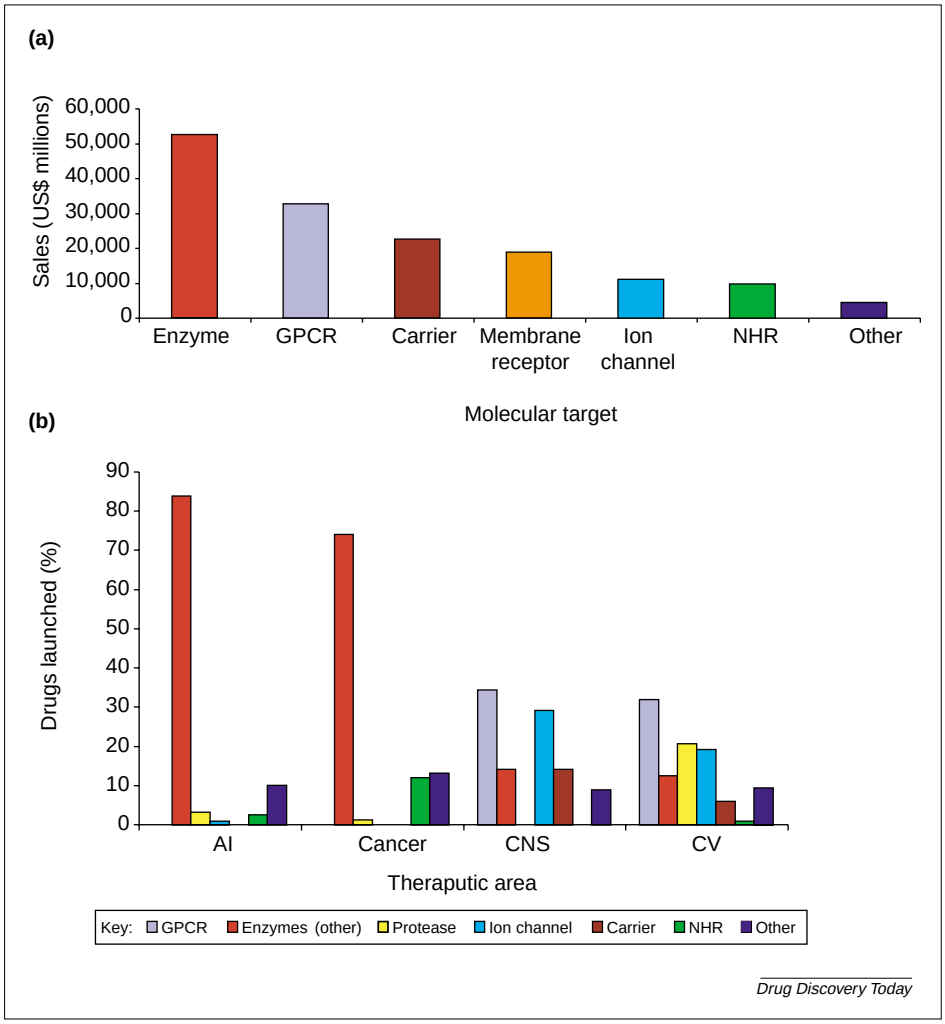

FIGURE 2

Drugs and drug targets. (a) 100 best-selling drugs, arranged according to their molecular targets. The graph shows the global sales of the 100 best-selling drugs in 2002, according to the target class to which they belong (Source: Pharmaprojects, National Center for Biotechnology Information Entrez Gene and Target Information System Bayer HealthCare AG). The three highest-selling enzyme inhibitors at the bottom of the respective bar are the HMG-CoA reductase inhibitors atorvastatin, simvastatin and the cyclooxygenase-2 inhibitor celecoxib. The highest-selling GPCR drug is the dopamine receptor antagonist olanzapine. **(b)** Target classes of launched drugs according to their therapeutic area. Bars show the percentage of launched drugs for a given therapeutic area that address a target falling into the classes of GPCRs, channels or carriers, proteases, other enzymes, NHRs or others (Sources: Pharmaprojects, National Center for Biotechnology Information Entrez Gene and Target Information System Bayer HealthCare AG). Abbreviations: AI, anti-infectives; CV, cardiovascular.

has been estimated to be between 3000 and 10,000 [16–18], corresponding to a frequency of ~10–30% of human genes in the genome. In mouse knockout programs, ~10% of gene knockouts result in medically and pharmaceutically relevant phenotypes [19]. Based on these data, an estimate of only 100–150 new druggable drug targets was calculated. However, this estimate might be too low because it should be borne in mind that the targets of many of the best drugs currently available produce, or can be expected to produce, lethal knockout phenotypes, such as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase, thrombin, the cardiac Ca^{2+} channel, erythropoietin and the glucocorticoid receptor, among others. [11]. Therefore, additional drug targets are hidden among the 16% of gene knockouts that result in a lethal phenotype [19], which could potentially be identified by analysis using conditional gene-targeting technology [20]. In addition, although it has been shown that the targets of the top 100 pharmaceutical drugs are key biochemical switches that, when modulated, produce a desirable change in the physiological state of the organism [11], it is probable that further disease-modifying targets will be discovered when the phenotypes of knockout mice are analyzed on various disease backgrounds. On this basis, this author estimates that ~20% of genes have the potential to modify disease, and calculates that there are ~480 new drug targets yet to be mined from the human genome for small molecular drug therapy (calculated by multiplication of 3000 druggable targets with 0.2, followed by subtraction of 120 drug targets that are already addressed by marketed compounds). This number is in line with proposals from Hopkins and Groom [9], which estimated that there are 600–1500 druggable drug targets, based on an extrapolation from antifungal targets. Of course, several of these new drug targets are likely to be components of already known key physiological pathways.

Expanding the target universe

The number of suitable binding sites for drugs is higher than the number of druggable drug targets. This is because a given gene can give rise to several different transcripts via alternative splicing, resulting in different proteins that lack or have particular domains. Attacking different domains of a given target can result in different phenotypes, and even a single domain can contain various binding sites for small molecular drugs, resulting in different effects according to the specific binding site used. Therefore, the biological potential of a given drug target can be further exploited, even though the target is already addressed by small molecules currently on the market. Nitric oxide (NO)-releasing drugs, for example, have been helping patients suffering from angina pectoris for more than a century. In the 1970s, NO-sensitive soluble guanylate cyclase (sGC) was identified as the target of NO. Recently, Bayer has identified novel NO-based sGC activators [21,22]. These compounds have revealed two previously unrecognized regulatory sites on sGC that might be important physiologically and, consequently, in the development of new therapeutic strategies.

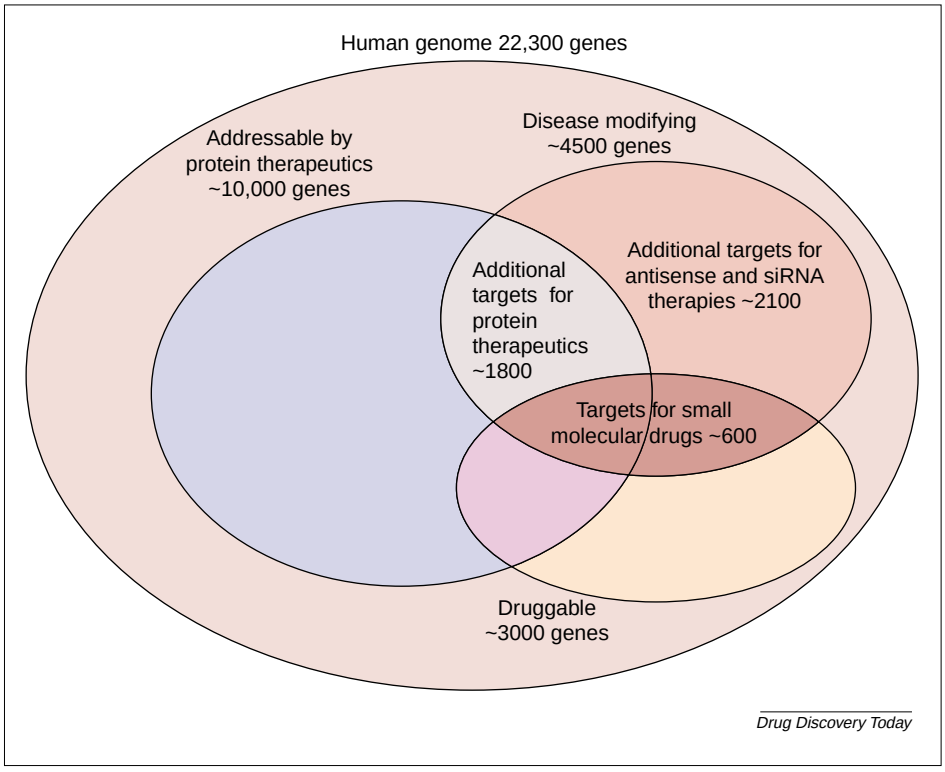

FIGURE 3

The target universe. Within the human genome, potential targets can be separated as being addressable by small molecules for the druggable target classes comprising enzymes, GPCRs, carriers or channels and NHRs, or by protein therapeutics for the target classes comprising membrane proteins and soluble factors. Only a proportion of these potential targets are functionally relevant for ameliorating or curing a disease. The given numbers show current estimates for the size of these various target populations.

It can be expected that the number of targets considered as druggable will increase further with new advances in medicinal chemistry. Reports on attacking protein–protein interactions with small molecules, for example, can increasingly be found in the literature [23]. Of course, the universe of potential drug targets is even larger when taking into account nondruggable target classes, which can be addressed via protein therapeutics. Assuming that 8% of gene products are extracellular and that 39% are transmembrane proteins [24], this would mean ~2000 [$(0.08 + 0.39) \times 22287 \times 0.2 = 2095$] drug targets addressable by protein therapeutics (estimating again that ~20% of all genes have disease relevance). If, in addition, gene-therapy or short interfering RNA (siRNA) therapeutics are considered, the target universe can be expanded to all genes with disease relevance, although, of course, the technical difficulties involved in realizing such therapies are enormous. Overall, the expected drug target pool can be represented by ~600 drug targets for small molecules, ~1800 more drug targets for protein therapeutics and an additional ~2100 drug targets for gene therapy and siRNA therapeutics (Figure 3).

The industry so far has been slow to exploit the available target pool fully, and only around three new druggable targets are addressed with new drug launches each year [9] (Figure 1). Based on the estimate of 480 yet to be exploited targets, and assuming that only three of these are launched each year, it can be estimated that this would enable the industry to launch new first-in-class drugs for >150 years. Interestingly, some of the most successful older drugs are able to address more than one target (e.g. Aspirin® and Clozapine®), and there is currently much discussion on whether it is now time to abandon the 'one drug, one target' paradigm that molecular biology and HTS have encouraged.

Drug discovery portfolios

The opportunity to address unmet medical needs with drugs attacking new targets comes at a cost. The age of applied human genomics was heralded by the announcement in 2000 that Celera had almost completed a first draft of the human genome. However, although several therapeutics labeled as 'genomics derived', such as the 5-lipoxygenase-activating protein (FLAP) inhibitor DG031 [25] and lipoprotein-associated phospholipase A2 inhibitor 480848 (www.albuferon.com/news/press/03-12-05_GSK.html), have already reached clinical development, the initial enthusiasm for genomics has gradually reversed to a phobia as a result of high attrition rates encountered with genomics targets throughout the industry. The situation was intriguingly described as 'Genomics threatens to increase not only the associated R&D costs, but also the average cost per new chemical entity or drug' [26]. However, it should be taken into account that increased risk is not restricted to genomics targets – that is, targets identified with genomics technologies – but is generally associated with unprecedented targets – that is, targets that have not yet achieved proof-of-concept via compounds on the market or in successful clinical trials. The probability for a compound with a novel mode of action to make the transition from first patient dose to the market is only 8%, versus 16% for a drug with an established mode of action [27]. Sound target validation is mandatory for reducing these high attrition rates for unprecedented targets to benchmark levels but the degree of target validation observed can range widely – for example, from evidence based solely on the expression profile of the target in a diseased versus healthy state, to evidence from the phenotype observed in knockout mice, to evidence via demonstration of a sound pharmacological effect with a corresponding small molecule in an established disease animal model, or even first evidence in humans.

Working on new targets can be rewarding, as indicated by the considerable number of examples of breakthrough innovations that have been generated from new targets

(Table 1), and as many as seven out of the 20 best-selling drugs worldwide were originally launched as first-in-class drugs. However, to secure their investments, it is of utmost importance for companies to protect their intellectual property relating to new targets properly and to combine this with a broad protection of the associated suitable chemical space for the design of drugs utilizing this target. This is particularly important because competition on new mechanisms has dramatically increased and the time of market exclusivity for a new mechanism of action to the appearance of the first competing fast follower is shrinking [28]. Whereas periods of market exclusivity were five years and longer in the 1970s and 1980s [e.g. the histamine H_2-receptor antagonist Tagamet® (cimetidine) was launched in 1977, with the first 'fast follower' Zantac® (ranitidine) appearing in 1983], the time of exclusivity is now less than a year [e.g. the cyclooxygenase-2 inhibitors Celebrex® (celecoxib) and Vioxx® (rofecoxib) were both launched in 1999]. Quite often, the sophisticated fast followers ('best-in-class drugs') are also commercially more successful than the innovators ('first-in-class drugs'). The first bacterial DNA-gyrase inhibitor, the quinolone antibiotic Noroxin® (norfloxacin), for example, was launched in 1983 but was effective only in urinary infections and never reached peak sales above US$200 million. However, Ciprobay® (ciprofloxacin) and Levaquin® (levofloxacin), which entered the market four and ten years later, respectively, achieved blockbuster status, with >US$1 billion sales, as a consequence of their improved efficacy and side-effects profile. This level of success for sophisticated fast follower over first-in-class drugs is not restricted to antibiotics but is encountered quite frequently [29]. Companies should therefore also aim to exploit their new targets with a series of back-up and follow-up approaches, at least as soon as proof-of-principle has been obtained in the clinic for the forerunner compound.

Because the ambition for true innovation comes with the promise of breakthrough success, but also with considerable associated risk and cost, companies need to supplement their portfolios with less risky endeavors, for example, by identifying new improved chemical matter for precedented drug targets, thereby providing a therapeutic benefit to the patient. A good portfolio also needs the inclusion of low-risk 'bread-and-butter' projects, such as life-cycle management for existing drugs – for example, new combination therapies, improved formulations or the identification of appropriate new indications. Indeed, new formulations accounted for 56% of new drug applications at the FDA in 2004: there were 113 new drug applications in total, comprising 31 NMEs and 63 new formulations (www.fda.gov/cder/rdmt/pstable.htm).

Outlook

Genomics, without doubt, has already had a tremendous impact on drug discovery pipelines. More than 70% of all companies now have at least some genomics-derived targets among their targets used in HTS [30]. Nevertheless, it seems that after the initial genomics euphoria, the need to reduce risk has recently led to a reduction in the proportion of unprecedented targets in the R&D portfolios of major pharmaceutical companies. An overall balanced drug-discovery portfolio should consist of highly innovative unprecedented genomics targets, new improved chemical matter for precedented targets, me-too approaches and line extensions. The precise composition of such a portfolio is not a science but an art, and is also highly dependent on the overall business model applied by the respective company. Large companies might be able to place new products successfully in already-crowded markets by sheer marketing power, whereas a smaller company will have to depend more on a unique selling point to gain their market space, potentially provided by a new mechanism of action. With developing expertise in biomarkers that are able to predict efficacy and side-effects for patient stratification in clinical trials, the attrition rates of new approaches can be expected to decrease in the future. In this sense, identification and utilization of genomics targets and biomarker research with 'theranostics' applications are synergistic endeavors. In addition, with the dawning age of personalized medicine, it is predicted that the marketing environment will change dramatically and that diagnostics, rather than the impact of advertising, will have a greater role in determining the treatment that a patient receives [31]. If new drugs entering the market are supported with diagnostic tests to identify the patients that will benefit most from these products (theranostics), it will be possible for smaller companies with limited marketing power to gain market share, even in competitive situations. Fragmented markets will put the economies of scale and the competitive advantage of large versus midsize pharmaceutical companies in general to the test. With the advent of more and more validated drug targets, and the resulting individual treatment options, medical standards will further improve, and the pharmaceutical industry will continue to produce new breakthrough innovations.

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References

1 Mackowiak, P.A. (2000) Brief history of antipyretic therapy. *Clin. Infect. Dis.* 31 (Suppl. 5), 154–156
2 DiMasi, J.A. *et al.* (2004) R&D costs and returns by therapeutic category. *Drug Inf. J.* 38, 211–223
3 Cohen, F.J. (2005) Macro trends in pharmaceutical innovation. *Nat. Rev. Drug Discov.* 4, 78–84
4 Gilbert, J. *et al.* (2003) Rebuilding big pharma's business model, *in vivo*, 21, 73–82
5 Grabowski, H. *et al.* (2002) Returns on research and development for 1990s new drug introductions. *Pharmacoeconomics* 20 (Suppl. 3),

11–29
6 Almog, D.M. (2005) Drug industry in 'depression'. *Med. Sci. Monit.* 11, SR1–SR4
7 Hardman, J.G. *et al.*, eds (1996) *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (9th edn), McGraw-Hill Ryerson Ltd.
8 Drews, J. (1996) Genomic sciences and the medicine of tomorrow. *Nat. Biotechnol.* 14, 1516–1518
9 Hopkins, A. and Groom, C. (2002) The druggable genome. *Nat. Rev. Drug Discov.* 1, 727–730
10 Lipinski, C.A. (2000) Drug-like properties and the causes of poor solubility and poor permeability. *J. Pharmacol. Toxicol. Methods* 44, 235–249
11 Zambrowicz, B.P. and Sands, A.T. (2003) Knockouts model the 100 best-selling drugs – will they model the next 100? *Nat. Rev. Drug Discov.* 2, 38–51
12 *International Human Genome Sequencing Consortium* (2001) Initial sequencing and analysis of the human genome. *Nature* 409, 860–921
13 *International Human Genome Sequencing Consortium* (2004) Finishing the euchromatic sequence of the human genome. *Nature* 431, 931–945
14 Orth, A.P. et al. (2004) The promise of genomics to identify novel therapeutic targets. *Expert Opin. Ther. Targets* 8, 587–596
15 Mulder, N.J. *et al.* (2005) InterPro, progress and status in 2005. *Nucleic Acids Res.* 33, D201–D205
16 Wright, S. (1984) *Evolution and the Genetics of Populations: Genetic and Biometric Foundations*, University of Chicago Press
17 Claverie, J-M. (2001) What if there are only 30,000 human genes? Science 291, 1255–1257
18 Drews, J. (2000) Drug discovery: a historical perspective. *Science* 287, 1960–1964
19 Walke, D.W. *et al.* (2001) *In vivo* drug target discovery: identifying the best targets from the genome. *Curr. Opin. Biotechnol.* 12, 626–631
20 Rajewsky, K. *et al.* (1996) Conditional gene targeting. *J. Clin. Invest.* 98, 600–603
21 Stasch, J-P. *et al.* (2001) NO-independent regulatory site on soluble guanylate cyclase. *Nature* 410, 212–215
22 Stasch, J-P. *et al.* (2002) NO- and haem-independent activation of soluble guanylyl cyclase: molecular basis and cardiovascular implications of a new pharmacological principle. *Br. J. Pharmacol.* 136, 773–783
23 Dev, K.K. (2004) Making protein interactions druggable: Targeting PDZ domains. *Nat. Rev. Drug Discov.* 3, 1047–1056
24 Anderson, N.L. et al. (2004) The human plasma proteome. *Mol. Cell. Proteomics* 3, 311–326
25 Hokanarson, H. *et al.* (2005) Effects of a 5-lipoxygenase-activating protein inhibitor on biomarkers associated with risk of myocardial infarction: a randomized trial. *J. Am. Med. Assoc.* 293, 2245–2256
26 Anon. (2001) *The Fruits of Genomics*, Lehman Brothers and McKinsey & Co.
27 van den Haak, M.A. *et al.* (2004) Industry success rates 2004. *CMR International* CMR04-234R
28 DiMasi, J.A. and Paquette, C. (2004) The economics of follow-on drug research and development. *Pharmacoeconomics* 22 (Suppl. 2), 1–14
29 Booth, B. and Zemmel, R. (2003) Quest for the best. *Nat. Rev. Drug Discov.* 2, 838–841
30 Anon. (2002) *High Throughput Screening 2002: New Strategies and Technologies*, HighTech Business Decisions
31 Barton, C.L. (2004) *The Future of Personalized Medicine: The Impact of Proteomics on Drug Discovery and Clinical Trial Design,* Business Insights Ltd.