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FROM THE ANALYST'S COUCH

Value of novelty?

Philip Ma and Rodney Zemmel

The selection of the right targets for drug discovery is one of the key decisions in pharmaceutical and biotechnology research and development (R&D). A fundamental choice that companies have to make is the balance between going after 'tried-and-true' drug targets, or going after novel targets. Interestingly, the number of tried-and-true drug targets is actually quite small, at around 500[1]. G-protein-coupled receptors (GPCRs) form one important class of drug targets that represents 20% of the top 50 best-selling drugs (FIG. 1), including such well-known brands as Claritin, Zyprexa, Zantac and Cozaar. The success of GPCRs as drug targets over the past 20 years has spawned significant imitation in certain categories, such as beta-blockers against hypertension. Hence, by some estimates, GPCRs account for 50% of all drugs on the market. The review by Chalmers and Behan on constitutively active GPCRs in this issue provides valuable input to discussions on target selection within the GPCR class, which contains many novel as well as known targets. How aggressively should pharmaceutical companies be going after novel targets? This issue represents one of the greatest challenges in portfolio management today, and getting the balance right could create significant value in the future.

Focusing on novel targets

Over the past decade, there has been an increasing focus among many pharmaceutical companies to discover 'first-in-class' novel drugs. Drivers for this strategy include the past success of drugs such as Prozac (for depression), high expectations from financial markets for new blockbuster drugs and an increasing concern that managed care would limit opportunities for 'me-too' molecules. As demand for new drugs has continued, tremendous advances in technology, especially 'high-throughput' technologies, such as genomics, have led many scientists and top pharmaceutical executives to believe that there will soon be a revolutionary improvement in the industry's ability to identify and pursue novel targets. As a result, pharmaceutical companies have migrated much of their R&D investment towards novel targets, beginning in the early 1990s. According to recent research, most pharmaceutical companies devote ~60–70% of their drug discovery portfolios towards novel targets[2]. Today, given that pharmaceutical companies have been working on many novel targets for nearly a decade, the time is right to ask: how much value do novel drugs really create?

No higher returns for novelty

In a recent set of analyses on product launches from 1991–2000 for the top 15 pharmaceutical companies, drugs were divided into two categories: unprecedented/novel and precedented. Analyses showed that novel approaches had higher risk, as seen by the lower survival rate of 5% compared with 8% for precedented approaches. Moreover, the higher risk that is associated with novel approaches did not generate higher returns, as seen by the lower average present value of sales of US $2.8 billion compared with US $3.6 billion for precedented approaches. If the precedented drugs are sorted into 'fast followers', 'differentiators' and 'late comers' on the basis of whether they hit the market from 2–15 years after the launch of the first-in-class drug, fast followers generated the most value, but differentiators and even late comers could be strong value creators. In fact, of the 31 blockbusters (drugs with annual sales greater than US $1 billion) that were launched by the industry throughout the 1990s, 74% (23) have come from precedented approaches.

Implications for drug discovery

The first key message is that there is value to be created from precedented targets. This has been the case in the past, and it will probably continue in the foreseeable future. Prices of new pharmaceuticals will come under increasing pressure in all markets, such that all new drugs will have to show marked improvements to existing drugs in terms of efficacy, reductions in side effects and convenience/effectiveness of dosing. However, clinically meaningful improvements in drug performance can come from new molecules against known targets, and these do not necessarily equate to low value, me-too drugs. Consequently, the second message is that pharmaceutical R&D organizations should reconsider the overall distribution of targets in their R&D portfolios. Individual companies will need to make their own decisions on how much they emphasize novel compared with precedented targets, but they must be quite rigorous in assessing the true risks of undertaking a portfolio that is heavily weighted towards new targets. There is no single correct answer in balancing a portfolio. Overall, however, discovery organizations should consider carefully how much scope for improvement there might be in new compounds that go after established targets before they consider new compounds against new targets.

The third message is that pharmaceutical companies will need to make significant improvements in the process by which they go after novel targets. Analyses indicate that if current 'high-throughput, high-novelty' approaches do not fundamentally improve, there will be significantly higher costs to generate a new chemical entity (NCE). In particular, significant improvements will be needed in R&D stages of biological validation and early clinical development leading up to Phase II 'proof-of-concept' studies. Improvements can come from changes in processes, including decision processes on whether compounds should or should not advance, as well as from investments in the right technologies — for example, predictive toxicology tools, structural proteomics and clinical genomics/pharmacogenomics tools. However, investments in new technologies will require parallel investments in top-rate bench science from biologists, chemists and pharmacologists to truly deliver meaningful improvements. ▶

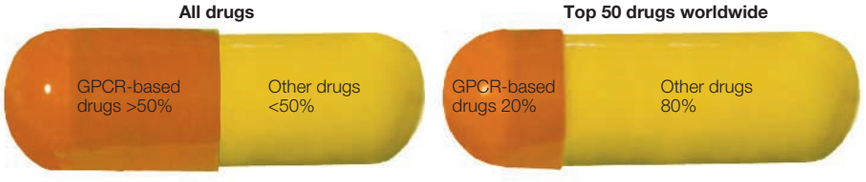

Figure 1 | **Share of GPCR-based targets for drugs on the market.** GPCR, G-protein-coupled receptor.

FROM THE ANALYST'S COUCH

Market indicators

Many of the top-selling drugs today are GPCR-based drugs (TABLE 1). Many pharmaceutical companies have shifted their R&D portfolios towards novel targets in the hope of developing more first-in-class drugs. Drugs that are based on novel targets have created less value on average than drugs that are based on precedented targets, and have had a higher risk of failure (FIG. 1). Many pharmaceutical companies have focused on novel targets over the past decade, but what is the productivity impact of high-throughput, high-novelty approaches (BOX 1)?

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2. *Fruits of Genomics* (Lehman Brothers, New York, 2001).

Online links

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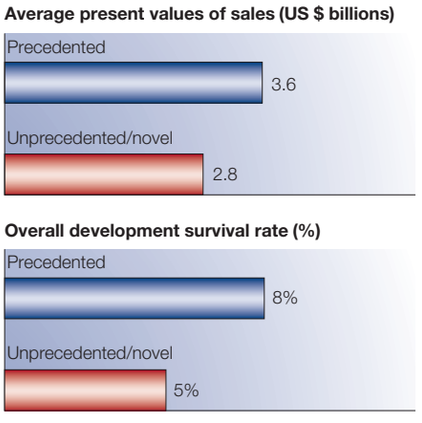
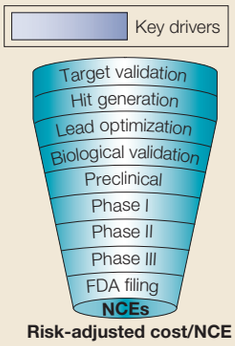


Figure 2 | **Value and survival rate of precedented compared with novel approaches.** Drugs that target precedented approaches create more value on average. Precedented approaches also have higher rates of development success. This data refers to drugs that were launched between 1991–2000. Source: McKinsey Analysis.

Box 1 | **Attrition rates and cost for different R&D models**

In the early 1990s, pharmaceutical companies began to invest substantially in developing a new high-throughput, high-novelty approach to drug discovery. Research indicates that even with recent improvements in the ability of pharmaceutical companies to generate and work with novel targets, there are still significant challenges with the high-throughput, high-novelty approach. A comparison of a low-throughput, low-novelty approach, which was used in the industry pre-1990s, with a high-throughput, high-novelty approach, is shown in the figure below. The numbers shown are for the success rate at each stage of development, and the risk-adjusted cost per New Chemical Entity (NCE). Biological validation and Phase II testing will probably be the key drivers for the relative success of the high-throughput, high-novelty approach. Without substantial improvements, the total risk-adjusted costs of research and development (R&D) for the high-throughput, high-novelty approach could be ~40% higher than the low-throughput, low-novelty approach per NCE generated. The high-throughput, high-novelty approach should not be abandoned, but these data reflect the fact that the industry is in transition, and substantial improvements in processes and technology are required to generate higher returns on R&D investments. B, billion.



Low throughput, low novelty	
Input	50 targets; 30% novel
Success rate	~30
	~90
	~90
	~75
	~50
	~70
	~50
	~70
	~90
Drug output	2
Risk-adjusted cost/NCE	**~US $0.7 B**

High throughput, high novelty	
Input	200 targets; 70% novel
Success rate	~35
	~90
	~90
	~50
	~50
	~70
	~30
	~70
	~90
Drug output	3.6
	~US $1.0 B

Table 1 | **Examples of GPCR-based drugs in the top 200 best-selling prescriptions**

GPCR target	Drug	Disease	Company	2000 sales (US $m)
Histamine receptors	Zantac	Ulcers	GlaxoSmithKline	870
	Pepcid	Ulcers	Merck	850
	Claritin	Allergies	Schering-Plough	2,200
	Allegra	Allergies	Aventis	1,100
5-HT receptors	Risperdal	Psychosis	Johnson & Johnson	1,600
	Imitrex	Migrane	Glaxo SmithKline	1,100
	BuSpar	Anxiety	Bristol-Myers Squibb	714
	Zyprexa	Schizophrenia	Eli Lilly	2,400
Angiotensin receptors	Cozaar	Hypertension	Merck	1,700
Adrenoceptors	Toprol-XL	Hypertension	AstraZeneca	580
	Coreg	Congestive heart failure	GlaxoSmithKline	250
	Serevent	Asthma	GlaxoSmithKline	940
Muscarinic acetylcholine receptors	Atrovent	COPD	Boehringer Ingelheim	600
Gonadotrophin-releasing-hormone receptors	Zoladex	Cancer	AstraZeneca	740
Dopamine receptors	Requip	Parkinson's disease	GlaxoSmithKline	90
Prostaglandin (PGE1) receptors	Cytotec	Ulcers	Pharmacia	100
ADP receptors	Plavix	Stroke	Bristol-Myers Squibb	900
Leukotriene receptors	Singulair	Asthma	Merck	860

Source: McKinsey Analysis. COPD, chronic obstructive pulmonary disease; GPCR, G-protein-coupled receptor; 5-HT, 5-hydroxytryptamine (serotonin).