DISPELLING DISCOVERY MYTHS

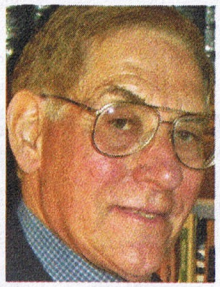
BY MANFRED E. WOLFF

MOST PEOPLE IN THE DRUG discovery community have become familiar with what has been called "the obligatory graph"—a comparison showing a continual increase in R&D investment by the pharmaceutical industry coupled with a disappointingly low production of approved new molecular entities (NMEs). In fact, in 2005, only 18 NMEs were approved by the FDA, the second-lowest count in the past decade. Concomitant with this shortfall is a rising tide of patent expirations of existing blockbuster drugs. Likewise, there has been a steadily increasing proportion of prescriptions dispensed for generics relative to drugs with market exclusivity.

A flourishing industrial R&D establishment is wholly dependent on financial support from senior management, and such funding will continue unabated only if management is convinced that its investment will bring about new products. Management, which typically has a much shorter time horizon than that of the R&D community, has the option to divert funds to other areas to enhance corporate income, such as promotional spending and marketing partnerships.

We are already seeing year-to-year increases in promotional spending as high as 22 percent, particularly in direct-to-consumer advertising on television and in the print media, and in the provision of samples. These marketing strategies have made possible an unprecedented increase in blockbuster drug sales and a continuing rise in global sales, even in the face of a troubling NME output. To put it plainly, a position to hire an entry-level biotechnologist can be left unfilled to pay for a 15-second advertisement.

Although some have claimed that declining productivity is a "myth", arguing that "there has been a steady increase in the number of new chemical entities launched, both in absolute numbers of FDA-approved medicines and in the proportion of priority reviews", the 18 NME approvals last year belie this view. More prevalent is the opinion that "the record of industry productivity over the past decade as measured by drug approvals has, if anything, declined", referring to 1990-2000. Ironically, this productivity gap has continued in an era when substantial increases in drug discovery were predicted as a result of the genomic revolution, with predictions of 5,000-10,000 viable drug targets. And technologies like combichem and HTS were expected to result in accelerated discovery of many new drugs directed to the new targets.



Dr. Manfred E. Wolff, CEO Intellepharm Inc.

What has gone wrong? As a military strategist remarked long ago, "just as some plants bear fruit only if they don't shoot up too high, so in the practical arts, the leaves and flowers of theory must be pruned and the plant kept close to its proper soil: experience." One such "flower" is the "gene→protein→target→hit" paradigm—the belief that promising ligands for newly identified targets from genomics can be quickly selected by membrane-binding HTS of combichem libraries.

A second "flower" is Paul Ehrlich's "magic bullet" concept: "We must strike the parasite, and the parasites only, if possible, and to do this, we must learn to aim with chemical substances!" Especially during the last quarter of the 20th century, this rationale, developed to explain the selective toxicity of desirable antimicrobial agents, was erroneously widely applied to drug discovery for human disease therapeutics. The result was a search for agents with highly targeted pharmacological properties.

Yet, most diseases are multifactorial processes that involve multiple disease-related gene products. Thus, compounds with multiple targets are not necessarily the dreaded "dirty drugs" that are to be avoided, but medicines that can possess uniquely beneficial effects. Bryan Roth has suggested that the term "magic shotgun" more accurately reflects these features.

What important lessons are available from the drug discovery experience of the last decade?

First, estimates suggest a more modest 600-1,500 disease-modifying genes express proteins able to bind drug-like molecules. Second, cell-based HTS assays can provide important additional information for lead identification in comparison to membrane-binding assays, which can be confounded by "promiscuous" binders and are incapable of distinguishing agonists from antagonists or identifying allosteric ligands.

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Third, as recently stated by George Milne: "It is clear that we also need to move away from the seduction of the in vitro assay with highly purified proteins, which produces very clean SAR, to phenotypic assays reminiscent of screening in the spontaneously hypertensive rat of 50 years ago—high in content, but lower in intrinsic precision exactly because they integrate multiple steps." And fourth, the old idea of modulating multiple targets of drug action simultaneously, once derided as "polypharmacy", has been appreciated anew, either in terms of designed multiple ligands or in the context of multicomponent therapeutics.

Drug discovery scientists have learned much from these and other important lessons, such as the significance of poor pharmacokinetics and toxicity as major causes of late-stage failures in NME development. As a result, an end to the doldrums in NME output may more confidently be expected in the coming decade. ◆

Dr. Manfred E. Wolff is president and CEO of Intellepharm Inc.