of dietary supplements labeled as ephedra free is an example of important work that protects the public by helping rid the garden of pharmaceutical weeds. If laws such as DSHEA were reversed, less weeding would be necessary.

CONFLICT OF INTEREST
The author declared no conflict of interest.

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Phenotypic vs. Target-Based Drug Discovery for First-in-Class Medicines

DC Swinney[1]

Current drug discovery strategies include both molecular and empirical approaches. The molecular approaches are predominantly hypothesis-driven and are referred to as target-based. The empirical approaches are referred to as phenotypic because they rely on phenotypic measures of response. A recent analysis revealed the phenotypic approaches to be the more successful strategy for small-molecule, first-in-class medicines. The rationalization for this success was the unbiased identification of the molecular mechanism of action (MMOA).

Drug discovery and development in the past quarter century has focused on the promise of molecular medicine to identify medicines to treat unmet medical need by targeting specific gene products. For example, mutations, or defects, at specific molecular locations in human DNA were found to be responsible for some cancers, raising the hope of developing successful therapies tailored to individual patients. The gene-to-medicine approach has had success, as demonstrated by imatinib (Gleevec)[1] and gefitinib (Iressa),[2] and it has raised expectations for the majority of drug discovery to follow the same path.

Before the advent of target-based drug discovery, new medicines were discovered by evaluating different chemicals against phenotypes—an organism's observable characteristics—in authentic biological systems, such as animals or cells. Many factors influenced the shift from a phenotypic approach to a target-based approach, including the idea that a rational, measurable progression from gene to clinic to registration would increase research and development success and productivity. Rational, informed target-based approaches use molecular tools of genetics, chemistry, and informatics to drive drug discovery and also provide criteria and boundaries for choosing patient populations, setting doses, and quantitatively measuring efficacy and toxicity. Unfortunately, this shift in approach has not yet transformed the industry.

To investigate whether some strategies have been more successful than others in the discovery of new drugs, my group analyzed the discovery strategies and the MMOA for new molecular entities and new biologics approved by the US Food and Drug Administration between 1999 and 2008 (**Figure 1**).[3] Of the 259 agents approved, 75 were first-in-class drugs with new MMOAs. Of these, 50 (67%) were small molecules and 25 (33%) were biologics. The results also show that the contribution of phenotypic screening to the discovery of first-in-class small-molecule drugs exceeded that of target-based approaches—with 28 and 17 of these drugs coming from the two approaches, respectively—in an era when the major focus was on target-based approaches.

The first-in-class medicines discovered by phenotypic screening included those discovered using animal models such as ezetimibe (Zetia) for reducing levels of blood cholesterol; those discovered with cellular assays such as vorinostat (Zolinza), the first histone deacetylase inhibitor, which was reported to come from the observation that dimethyl sulfoxide had an

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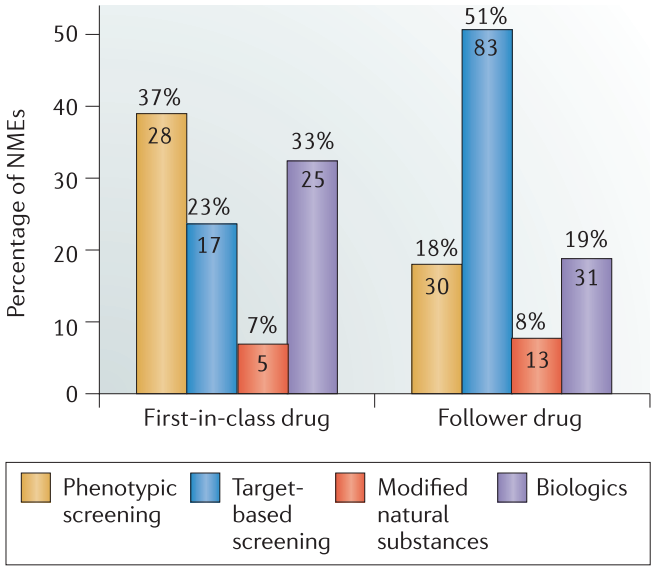

Figure 1 Distribution of new drugs discovered between 1999 and 2008, according to the discovery strategy. The graph illustrates the number of new molecular entities (NMEs) in each category. Phenotypic screening was the most successful approach for first-in-class drugs, whereas target-based screening was the most successful for follower drugs during the period of this analysis. The total number of medicines discovered via phenotypic assays was similar for first-in-class and follower drugs—28 and 30, respectively. The total number of medicines discovered via target-based screening was nearly five times higher for follower drugs than for first-in-class drugs (83 vs. 17, respectively). Reprinted from ref. 3 with permission.

unexpected effect on cancer cells; and those identified in bacterial assays such as linezolid (Zyvox), an oxazolidinone antibiotic. Target-based successes included tyrosine kinase inhibitors for cancer, including gefitinib (Iressa) (target, EGFR), imatinib (Gleevec) (target, BCR-ABL), sorafenib (Nexavar) (target, Raf), and sunitinib (Sutent) (targets, VEGFR/PDGFR), and antivirals, including maraviroc (Selzentry) (target, CCR5), raltegravir (Isentress) (target, HIV integrase), and zanamivir (Relenza) (target, influenza neuraminidase).

Our previous paper[3] proposed that lower productivity partly reflects target-based discovery's lack of consideration of the molecular complexities of the drugs' action. Knowing the parts of an efficient machine—a watch, an automobile, or a computer—is not sufficient to describe how it works. The parts must collaborate in precise ways to provide accurate time, reliable transportation, or processed information.

Biology is infinitely more complex. The phrase "molecular mechanism of action" describes the way that biological parts collaborate to provide an effective and safe medicine. Addressing the MMOA would contribute to reversing the low productivity of target-based discoveries because merely knowing the identity of a part involved in a defect may not be sufficient to repair a malfunctioning machine. We postulate that a target-centric approach for first-in-class drugs, without consideration of an optimal MMOA, may contribute to the current high attrition rates and low productivity in pharmaceutical research and development.

These observations led to the proposal that the progression of drug discovery from unmet medical need to best-in-class medicines is facilitated by the use of phenotypic assays to identify first-in-class medicines and their respective MMOAs. Progression correlates with an iterative increase in knowledge to specifically address a phenotype related to the unmet medical need. Early in the progression, the knowledge is achieved by empirical analysis. Ideally, as more knowledge is gained to link a specific molecular mechanism of action (MMOA) to the desired phenotype, drug discovery can focus efforts toward addressing specific hypotheses (**Figure 2**).

Each of these two approaches has its strengths and weaknesses, and advocates and detractors. Although phenotypic approaches use semiempirical methods that do not require understanding of the mechanism, they do require an understanding of biology to the extent that biomarkers that translate to human disease must have been identified. Additionally, it is difficult to accept the risk of moving a compound into development without some understanding of mechanism to help evaluate dose–response relationships. Fortunately, there are many classic technologies that can aid in the identification of a new mechanism, including biochemical fractional isolation of activity and affinity purification. This problem-solving approach can also enable researchers to utilize new molecular technologies of chemical biology, proteomics, and network biology. An example of a medicine whose predecessor was discovered in a phenotypic assay is ezetimibe (Zetia), whose target was subsequently identified using a genetic approach as the sterol transporter Niemann-Pick C1-Like 1 (NPC1L1).[4] More recently, Chung and co-workers from GlaxoSmithKline demonstrated the use of chemoproteomics to identify BET bromodomains as the target for inhibitors identified in phenotypic assays.[5]

An interesting question is whether more time and resources are required to follow up empirical findings from phenotypic assays than to test multiple-target hypotheses. In the phenotype approach, the early risk is decreased as a result of the activity in a translational phenotypic assay. Obviously, the predictive value of translational assays for human biology must be tested and validated for both approaches. The lack of understanding of mechanism may slow progression of the drug candidate because subsequent studies will need to be empirical. Perhaps more resources and time will be required earlier in order to understand the mechanism. With

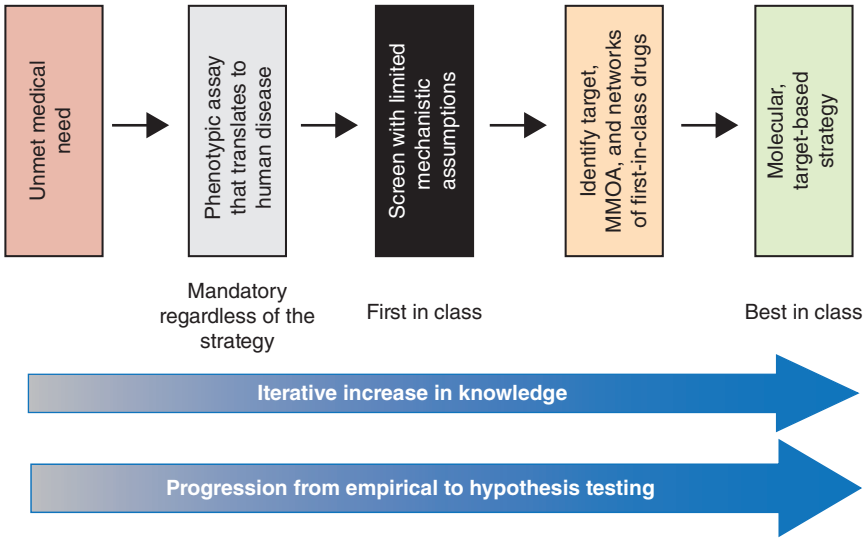

Figure 2 Progression of drug discovery from unmet medical need to best-in-class medicines. This simplified schematic highlights the contribution of empirical approaches to first-in-class medicines, hypothesis-driven approaches for best-in-class medicines, and the role of mechanistic understanding. Progression correlates with an iterative increase in knowledge to specifically address a phenotype related to the unmet medical need. Early in the progression, the knowledge is achieved by empirical analysis. Ideally, as more knowledge is gained to link a specific mechanism of modulation to the desired phenotype, drug discovery can focus efforts to address specific hypotheses. The relative timing of employing empirical vs. hypothesis-driven approaches is influenced by the validation of mechanistic understanding. MMOA, molecular mechanism of action.

target-based approaches, the mechanistic hypothesis should enable rapid, measured progress to clinical proof-of-concept studies, although it may be necessary to evaluate more than one candidate target and MMOA to find a winner. It is therefore possible that a target-based approach will add to the cost of development because of the need to evaluate multiple hypotheses. Interestingly, in current drug discovery discussions the central feature of any approach is the level of mechanistic understanding required to move a compound forward. However, an understanding of mechanism is not required for regulatory approval; the regulatory agencies are less concerned with the MMOA of a compound than with whether it is effective.

Both Paul Janssen and Sir James Black emphasized the importance of using assays that translate to the human disease.[6,7] The decline in productivity in relation to research investment in the pharmaceutical industry has also been matched by a similar decline in translational research in academia. A very important aspect of the debate is the fact that the vast majority of academic biology is also hypothesis-driven. At issue is the value of hypothesis-driven medical research for new discoveries. Is the hypothesis overvalued at the expense of traditional empirical evaluation? It can be argued that in seeking the best path to new medicines, academic science should be focusing not on gene-based, hypothesis-driven research but on translating disease knowledge into disease-relevant phenotypic assays for screening and chemical biology approaches to screening and target identification as well as on systematic approaches to understanding the MMOA. Even with the many new technologies that are now available for phenotypic assays—e.g., high-content screening with stem cells, primary human cells, zebrafish, and *Caenorhabditis elegans*—in many therapeutic areas it is not routine to establish and validate phenotypic assays that translate effectively to human disease. This is particularly evident with animal models whose predictability for human diseases is not always reliable. Greater focus on translational research should lead to greater access to more reliable phenotypic assays.

Our analysis found high success of phenotypic approaches to small-molecule first-in-class drug discovery in an era when the majority of efforts were focused on molecular target–based approaches. This finding is surprising because modern medical research is based on the assumption that a clearer understanding of the molecular mechanism of disease, enabled by genetic and molecular advances, would lead to an increase in new medicines. In drug discovery the preferred scenario has been that molecular mechanisms associated with disease are represented by targets and that quantitation of target modulation facilitates a more rational development. However, the mechanistic details to enable this approach are not always available, validated, or sufficient for the specific medical need. It is unrealistic to assume that we can know the exact molecular and mechanistic details of complex human diseases. Empirical analyses, including phenotypic assay, have been successful in the past and require fewer mechanistic assumptions. The challenge is to use an appropriate combination of empirical and mechanistic research and development to enable good ideas to successfully move forward.

CONFLICT OF INTEREST

The author declared no conflict of interest.

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