molecular pharmaceutics

editorial

A Dogma in Need of a Reformation

A few months ago, I ran across a headline in the business section of the *New York Times*, "Despite Billions for Discoveries Pipeline of Drugs Is Far From Full." The article describes the relatively small number of new drugs approved over the past decade, while research and development spending has increased exponentially. One industry expert was quoted as saying, "It makes you wonder what we are doing. Are they spinning their wheels or is it just a matter of time?" There are several reasons for this failure, such as idiosyncratic side effects, unanticipated toxicities, and a lack of sufficient clinical efficacy. The industry has maintained that the only way out of this is to design more specific drugs, specificity being defined as target molecule selective. However, to my knowledge, a drug devoid of associated toxicities and side effects does not exist. This dogma is one of the reasons for the "irrational" confidence placed in combinatorial chemistry in the early 1990s and recently in genomics. Even exquisitely target selective drugs such as Gleevec and anti-HIV protease inhibitors have unforeseen clinical toxicities. In other words, dogmatic adherence to a reliance on target selectivity alone is not going to be enough. This was really brought home to me recently when I attended a meeting at the National Institutes of Health in which a researcher from a well-known and respected combinatorial chemistry company stated that, "It was highly unlikely that any one will ever develop a totally specific kinase inhibitor!" One possible solution to this problem is to instill in a drug an increased level of specificity that takes into account other levels of biological differentiation. Efforts to create a more specific cellular addressing system could pay great dividends. We would then be able to ask, "Which community of cells and which cells in the community are the ones to target?" Future efforts employing chemical genetics and genomics/proteomics will better define the characteristics of tissue specific receptors and bioactivating enzymes, thus greatly enhancing the future design of "smarter" drugs. By more closely considering the prerequisites for successful drug delivery and the drug target, one can envision a new era that finally captures the potential of recent technological advances, and demonstrates that we do, after all, "know what we are doing!"

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