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There have been a number of reviews written in the past several years indicating that there has been a decline in thenumber of new chemical entities being approved by the FDA for marketing.8z-84 There have been almost as manysuggestions on how the drug discovery process can be fixed.82 s3 85-89 Drugs for oncology have one of the lowest success ratesfrom first-in-human to registration of any of the therapeutic areas.Many companies launched efforts into thedevelopment of oncology drugs, attempting to respond to the great unmet medical need. Additionally, the severity of thedisease would require shorter clinical trials, and the tolerance for side effects in this disease is greater than for othertherapeutic areas. However, many of these efforts have foundered on lack of sufficient efficacy and unacceptable side effects. A number of concepts are beginning to mature, facilitated by improving technologies that are predicted to increasethe success rate of compounds moving into clinical testing. The concept of biomarkers has become almost universal,and returns to center stage the study of pharmacodynamics. During the drug discovery phase, increased effort andemphasis has been placed on developing assays that will allow the determination of target inhibition in a functionalassay. A simple example is to monitor the phosphorylation of a kinase substrate within the cell environment afterexposure to the respective kinase inhibitor. Elaboration of this assay to in vivo and then the clinical setting would allowmonitoring of target inhibition following dosing. These types of assays will allow the assessment of the magnitude,duration, and consequence of inhibition, leading to a more rapid conclusion of whether inhibition of the target will havetherapeutic benefit. However, often with such assays, translation from discovery to development can be difficult, andalternatives need to be considered. The increasing use of gene chip arrays has prompted some to consider global geneexpression of some readily sampled tissue in response to treatment as an alternative. Moving to this type of assayshould more generally be considered a surrogate of response, rather than a marker of inhibition. Additionally, as diseasesare becoming more molecularly defined, both in etiology and progression, the opportunity for more specific therapies ispresented. A recent example of this would be imatinib, a compound approved for CML.s3 Ninety-five percent of CMLpatients have a particular chromosomal translocation that creates a mutant tyrosine kinase called bcr-abl. Imatinib wasdeveloped to target this particular mutation. Looking to the future, the potential of defining a disease by the molecularpathology and employing specific antagonists to create a 'tailor-made' therapy can be imagined.   The major difficulty with any new technologies introduced into drug discovery is the long time frames before theresults are realized by new drugs on the market.91 There are two facets of drug discovery where improvements in theindividual processes would speed the approval process and decrease the amount of money required to bring drugs tomarket. The first area where improvements need to be made is in the overall attrition rates of compounds from first-in-human to approval. Recent estimates put the overall success rate for new chemical entities at 11%.1"83 90 By reducingattrition rates, the expense for the whole process would decrease due to failures in clinical trials, which are the mostexpensive part of the discovery process.

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