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Editorial

A Systems Approach to Drug Development and to Drug Therapy

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The meeting report, "*What IS training in the pharmacological sciences?*" published in the December 2002 issue of this journal (1) raises some very important and critical issues. Dr. Preusch reports that at that meeting there was strong consensus on a *compelling need for people trained in systems and integrative (in vivo) pharmacology*. This understanding, that drug development and action should to be viewed using a *systems* approach, has been overlooked for too long. There is a need to understand the molecular events that will determine that a drug is able to exert an effect at a given target site. There is a need to understand the physiologic determinants that will allow that drug to be transported to and be taken up at that target site. And there is a need to understand how the genotype and the phenotype of a given subject will affect the ability of that drug to be effective in that specific individual. Because 5-fluorouracil (5-FU) is a drug that has been studied very extensively, it may be used to illustrate what is meant by a systems approach in drug development and therapy.

The currently prevailing view is that the primary intracellular target of 5-FU is its irreversible binding to thymidylate synthase (TS, EC 2.1.1.45), although incorporation into RNA in lieu of uracil and into DNA in lieu of thymine also play roles that have not yet been fully clarified (2,3). Competing with these anabolic processes is the catabolism of 5-FU, which starts with its hydrogenation to 5,6-dihydro-5-fluorouracil (DHFU) by the action of dihydropyrimidine dehydrogenase (DPD, EC 1.3.1.2) (4). Hence, an understanding of the genotype of the target site(s)—the ability to express these enzymes and how one may manipulate their expression—is one key element in defining the system.

For 5-FU to act at its target site, it must be transported to and taken up by the target cells. As a xenobiotic, there is always a strong competition between drug targeting to the desired site and elimination from the individual, a competition that will depend primarily on the pathophysiologic (phenotypic) characteristics of the individual. The presence of the fluorine atom makes 5-FU uniquely suitable for noninvasive studies of drug biodistribution using either nuclear imaging with ^{18}F or nuclear magnetic resonance spectroscopy of the ^{19}F atom (5). There is indeed a strong association ($p < 0.00001$) between the tumoral pharmacokinetics of 5-FU and the response of a given patient (5). Moreover, to understand the functional characteristics of the human (or animal) subject, a good understanding of the physiologic characteristics may be as important as an understanding of the genetic characteristics of the target (6).

A greater focus on the role of kinetic processes is necessary. Living systems are characterized both by their composition and by their dynamic behavior. There is a need to gain a much better understanding of rate processes at all levels—of molecular events, of physiologic processes, and of whole-organ processes. We can measure with exquisite details the kinetics of chemical reactions and of enzymatic processes, and we must make it a priority to integrate all these kinetic processes in a physiologically meaningful manner in living systems. Again, studies of the kinetics of transport of 5-FU from the point of administration to its target sites and/or sites of elimination, its uptake by the tumor cell, and its metabolism inside the tumor cell provide a good model of how a systems approach to kinetics may be developed (7).

The above systems analysis of 5-FU can be generalized to all drugs: there will be molecular determinants of drug action, there will be physiologic determinants, and there will be kinetic determinants. Thus, the following statement in the meeting report is extremely important: *There is a compelling need for people trained in systems and integrative (in vivo) pharmacology. However, an even greater value is placed on people with training in both molecular/cellular approaches AND training in* in vivo *approaches, who are able to integrate results from the molecular level to the human clinical situation.* A systems approach that integrates the molecular, the physiologic, and the kinetic components of drug development and action is absolutely critical. The parable of the three blind men and the elephant is appropriate. We cannot afford to continue focusing only on the parts. We need to understand the system as a whole.

What should be done? The recommendations of the report should be considered seriously by the academic, industrial, and government communities. We need to develop a novel systems approach at the Ph.D. level, incorporating a much better understanding of translational studies. We need to develop innovative programs at the postdoctoral level, so that professionals and scientists who are very highly specialized in one aspect of drug-related studies can understand how the various parts of the system relate to one another and thereby both allow for an effective interdisciplinary drug development and move toward the individualized optimization of drug treatment. Would a scientist steeped in molecular/cellular aspects of drug action be apt to reconstruct the molecular/cellular events in the context of the whole body?

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Would a scientist well versed in studies in the living organism be likely to think molecularly and cellularly? I believe that the results will be in favor of the latter. Hence, postdoctoral experience in the clinical/translational research setting appears to be inevitable for the nurturing of a competitive scientist wishing to be at the forefront of drug development and drug utilization studies.

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