WHAT MAKES AN IDEAL DRUG CANDIDATE? ROLE OF DRUG METABOLISM AND PHARMACOKINETICS IN SUCCESSFUL DRUG DEVELOPMENT

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In today's highly competitive pharmaceutical environment, a successful new drug needs to fulfill one or more of three fundamental requirements, namely (i) the compound satisfies an unmet medical need, (ii) the compound exhibits superiority (in efficacy and/or safety) over existing treatments (e.g. through significantly improved potency, selectivity or *via* a new mechanism of action), or (iii) the compound provides specific advantages in terms of pharmacokinetics and/or metabolism (e.g. more convenient dosing regimen, improved drug interaction profile, etc).

With respect to drug discovery, the proteomics and genomics revolution of recent years has provided the industry with unprecedented opportunities for the identification of new drug targets and for the assessment of drug effect. These developments, coupled with advances over the past two decades in molecular biology, high throughput screening techniques and synthetic organic chemistry, suggest that there may never have been a brighter time for innovation in pharmaceutical research. Yet the discovery and development of novel therapeutic agents has become a more challenging, riskier and expensive proposition than ever before, due to factors such as heightened competition

for market share, the high cost of modern technology, the more stringent regulatory requirements for drug registration, and little change in the relatively high rate of failure ("attrition") in drug development.

As a result of the latter consideration, pharmaceutical companies are focussing increasingly on approaches to raise the "probability of success" of lead candidates in an effort to decrease the rate of attrition in the development process (currently, while many thousands of molecules will be synthesized to generate a single drug candidate, an average of only one in ten candidates entering clinical development actually emerges as a successful drug product). In this regard, information on the pharmacokinetics and metabolism of lead compounds becomes critically important in guiding the selection of a drug candidate for development, and is obtained routinely at an early stage of preclinical evaluation. Cautious predictions of the pharmacokinetic behavior of compounds in humans, based upon animal data and on studies with human tissue preparations *in vitro,* now represent an integral component of the decision-making process whereby new chemical entities are selected for development.

A major contributor to the high attrition rate in drug development continues to be unanticipated toxicity, usually encountered in preclinical (animal) safety evaluation. As a result, toxicology has become an important focus area in the pharmaceutical industry where significant gains could accrue from an improved understanding of basic mechanisms of toxicity, together with the development of predictive models. While many approaches to this objective currently are being pursued, one promising avenue deals with minimizing the formation of chemically reactive drug metabolites which, in

certain cases, are believed to mediate the toxic effects of their respective parent compounds through covalent modification of key structural or functional proteins.

With recent advances in the sensitivity and versatility of analytical techniques (notably those based upon mass spectrometry), and the wider use of radiolabeled compounds early in the drug discovery process, it has become easier to detect, identify and quantify the covalent adducts to peptides and (in favorable cases) proteins, to which reactive intermediates give rise. However, not all reactive metabolites are toxic, and the identities of target proteins for toxicity remain elusive. In light of these and other uncertainties associated with exposure to biological reactive metabolites, it seems prudent in the drug discovery process to select candidates that have a low propensity to undergo metabolic activation to reactive electrophiles. This objective, in turn, requires some appreciation of the mechanisms by which certain functional groups in a new chemical entity may be metabolized to reactive species, so that appropriate chemical modifications can be made to the lead structures.

As an example of a drug discovery program at Merck Research Laboratories in which metabolism data were critical in minimizing the potential for reactive intermediate-mediated toxicity, a family of thrombin inhibitors containing a novel pyrazinone ring system were examined early in the course of preclinical evaluation. Lead compounds in the series, while potent and selective against their pharmacological target, were found to suffer from rapid clearance in animal models, raising the prospect of inadequate pharmacokinetics in humans. This high clearance proved to be a consequence of rapid metabolism at a benzylic center, which led to hydroxylated products that were

essentially inactive as inhibitors of thrombin. Chemical modification at metabolically labile sites to block this oxidation resulted in a second generation of compounds that exhibited significantly decreased clearance in animals, with corresponding increases in elimination half-life. However, these gains in pharmacokinetics were offset by "switching" of metabolism from the benzylic position to the pyrazinone ring system, which generated chemically-reactive, electrophilic species that bound covalently to cellular proteins. Detailed structural analysis of the products obtained by "trapping" these reactive species *in vitro* with the tripeptide glutathione (GSH) afforded indirect information on the nature of the reactive electrophiles from which they were derived, and suggested further chemical modifications to the core structure to minimize this undesirable property. Through a series of iterative processes involving close interaction between Preclinical Drug Metabolism and Medicinal Chemistry, it was possible to minimize the degree of reactive metabolite formation while simultaneously preserving the attributes of the novel structural series, and the resulting drug candidate was advanced into clinical development.

In addition to emphasizing the importance of minimizing reactive metabolite formation in drug discovery, this presentation will highlight a number of other metabolic and pharmacokinetic characteristics that would be viewed as desirable properties in terms of an "ideal" drug, underscoring the key role of early drug metabolism studies in contemporary pharmaceutical research.

Reference: R. Singh *et al., Chem. Res. Toxicol.,* **16**, 198 (2003).