

Translational Toxicology and the Work of the Predictive Safety Testing Consortium

WB Mattes¹ and EG Walker¹

Toxicology has always been translational—at least with respect to its primary focus on human “health.” The earliest “toxicologists” explored the effects of plant and animal poisons on humans, conducting experiments on (often unsuspecting) human subjects.¹ Not until the sulfanilamide disaster of 1937, the 1938 US Federal Food, Drug and Cosmetic Act, and the Nuremberg Code did animals become central to the experimental assessment of chemical safety.^{2,3} Now, with harmonization of requirements among various international regulatory agencies, the types and design of safety evaluation studies conducted to support first-in-human investigations have been reasonably standardized.⁴ Most drug safety studies are conducted in both a rodent and a nonrodent species, with the aim of identifying adverse reactions relevant to human health, potential target organs of toxicity, a dose for first-in-human studies, a margin of safety between the efficacious and toxic doses, and strategies for monitoring safety during clinical trials.⁵

The incidence of drug failure due to toxicity during clinical development⁶ and the unacceptably high rate of severe adverse events, including death, after drugs reach the market point to the need to develop animal model end points and studies that are more predictive of toxicity in humans.⁷ More sensitive and specific safety biomarkers for injury in both test animals and humans would help ensure more efficient movement of safer drugs into the clinic. New technologies offer the promise of such tools.^{8,9,10} We refer here to the study and development of such safety biomarkers and tools relevant to animal models and humans as “translational toxicology.”

The Predictive Safety Testing Consortium (PSTC) is a collaboration of scientists from the pharmaceutical industry, and advisors from the US Food and Drug Administration, the European Medicines Agency, and academia working to cross-qualify new safety biomarkers for regulated drug development.^{11–13} Formed in 2006,¹⁴ the consortium’s goal is to use the combined resources and expertise of its members to develop “evidentiary datasets”¹⁵ to qualify new safety biomarkers

for regulatory decision making. The consortium is governed by a legal agreement that addresses intellectual property, confidentiality, publication, and material transfer. It is managed by the independent, nonprofit Critical Path Institute.¹⁶ The consortium is organized into working groups focused on biomarkers of drug-induced nephrotoxicity, hepatotoxicity, myotoxicity, and vascular injury, as well as a gene signature for nongenotoxic carcinogenicity in rodents.¹⁷ These working groups have mainly considered protein biomarkers in blood or urine. Although the initial focus was on the qualification of biomarkers for preclinical use, most projects aim to qualify these biomarkers for clinical use as well; thus, their overall strategy is informed by, and in some cases incorporates, clinical research.

TECHNICAL ISSUES WITH TRANSLATING BIOMARKERS

Testing a new drug in two species of animals—typically a rodent and a nonrodent—in multiples of the estimated therapeutic dose prior to clinical trials is the accepted paradigm of safety testing. This paradigm relies implicitly on the ability to extrapolate to humans from the drug’s activity and dose response in the animal model. The preclinical scientist’s first step, then, is to choose the most appropriate species for testing. Although specific pharmacokinetic and pharmacodynamic parameters and a standard battery of toxicological end points are routinely measured, the many factors that affect the comparative disposition of the drug in the animal model vs. the human are rarely fully elucidated. Postsacrifice microscopic histopathology plays a central role in identifying drug-induced lesions in diverse tissues in animal studies; extrapolating these findings to clinical trials requires a noninvasive, monitorable end point.¹⁸ However, studies in healthy, genetically homogeneous animals can hardly be expected to predict low-incidence toxicities that arise clinically as a result of individual human differences in response due to genetic variations in metabolism or drug–target pathways or to coexisting conditions and subsets of disease phenotypes. This cross-species conundrum can lead the clinical development team to assign little relevance to the preclinical work that enabled the Investigational New

¹Department of Toxicology, The Critical Path Institute, Tucson, Arizona, USA. Correspondence: WB Mattes (wmattes@c-path.org)

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Drug application and clinical trials. The PSTC addresses this conundrum by fully exploiting all scientifically sound information regarding the extrapolation from animal to human, following the working principles of translational research. The consortium aims to make any drug development program more predictable and efficient by transforming laboratory discoveries in animal models into useful clinical tools.

The PSTC process incorporates several principles for prioritizing safety biomarkers for qualification: urgency of need (related to the sensitivity and specificity of existing biomarkers for a particular mechanism or target organ toxicity), weight and breadth of preclinical and clinical evidence, technical feasibility, and mechanism of toxicity. For biomarkers to be useful for predicting and monitoring drug safety in a clinical population, key attributes, such as temporal response, must be compared clinically and preclinically. The PSTC’s prospective preclinical qualification studies incorporate serial sampling to correlate a biomarker’s response with injury progression and reversibility (as documented for existing well-characterized biomarkers and histopathology) and multiple dose groups to characterize the response of the biomarker to different levels of injury. Thorough preclinical qualification ideally includes studies of acute and chronic dosing, a range of toxicants with varying mechanisms of injury in the target organ, negative control compounds, and several toxicants known to affect other organs to assess the specificity of the biomarker.

Obvious limitations exist to how we can study a biomarker’s behavior in a clinical population. Histological examination of tissue, the “gold standard” comparator, is not possible in most circumstances; scheduled sampling is more complex in an outpatient population; and ethical issues prevent the deliberate administration of toxicants to humans. However, strategies for qualifying biomarkers in humans can take advantage of marketed therapeutics with known toxicities. For example, the PSTC’s first clinical study for qualifying nephrotoxicity biomarkers considered several clinical populations with known kidney injury—including patients with shock trauma, aminoglycoside-treated cystic fibrosis patients, and cisplatin-treated patients—before deciding to monitor cardiac catheterized patients with an unfortunately high event rate of contrast dye–induced nephropathy.¹⁹ This study required (i) a consensus definition of kidney injury that was independent of serum creatinine levels (which are known to be a highly insensitive marker), (ii) resolution of intellectual property issues and commercialization status as well as technical validation of assays for each of the biomarkers, and (iii) an understanding of the comparative biomarker kinetics in rats (measured with continuous urine capture) and humans (measured with the first morning void every 24 h after discharge).

SOCIOLOGICAL BARRIERS TO TRANSLATIONAL BIOMARKERS

The goal of toxicology testing (i.e., safety assessment) in pharmaceutical development is to identify and predict safety issues to inform the risk–benefit decision about using a drug for a particular indication. In practice, this safety assessment is not

always fully predictive, and limitations exist to extrapolating from animal studies to clinical studies, for example, as mentioned above, the availability of histopathology as an end point in animal, but not clinical, studies.

The development of improved safety assessment tools and paradigms will depend on intentional communication between many disciplines, and especially between nonclinical and clinical scientists, notwithstanding their localization in specialized departments.²⁰ In academic institutions, nonclinical and clinical disciplines are for the most part separate departments with separate training programs and minimal interaction.²¹ However, new tools for improving drug safety would be expected to entail technologies that can be deployed in both nonclinical and clinical settings, compliant with both Good Laboratory Practice and Clinical Laboratory Improvement Amendments standards. They should also be cost-effective in both settings. No single discipline or training program could be expected to address all aspects of developing such translational safety assessment tools; translational research as a goal in pharmaceutical drug development²² must be a team effort. Cross-disciplinary dialogue can inform decisions about both the types of biomarkers needed and the studies required to evaluate them. An example is provided by the increases in serum transaminases that are often seen in clinical trials and in statin therapy.²³ In many cases, these increases resolve to normal levels with continued treatment, and the question of whether they serve as portents of serious liver injury remains.²⁴ Prediction and evaluation of such transient

Table 1 Organizations participating on the PSTC translational team

Abbott Laboratories
Amgen
AstraZeneca Pharmaceuticals
Boehringer-Ingelheim Pharmaceuticals
ClinXus
Critical Path Institute
European Medicines Agency
Eli Lilly
GlaxoSmithKline
Harvard University
Johnson & Johnson Pharmaceutical Research & Development
Merck
Novartis Pharmaceutical
Pfizer
Roche Palo Alto, LLC
sanofi-aventis US
Schering Plough Research Institute
University of Alabama at Birmingham
University of California, San Diego
University of North Carolina
US Food and Drug Administration
Wyeth Pharmaceuticals

increases during preclinical safety studies are complicated by standard study designs⁴ that do not *a priori* incorporate interim serum sampling, whereby transient increases could be detected in animals that subsequently displayed normal serum enzyme clinical pathology and no histopathological evidence of liver injury. Similarly, noninvasive tools, such as imaging, that are part of the standard armamentarium of clinical studies are now finding their way into preclinical safety assessments,²⁵ and dialogue between clinical and nonclinical scientists will be critical to their qualification.

Just as communication within institutions is vital to the success of such improvements in safety assessment, communication among institutions such as private-sector pharmaceutical companies, academic laboratories, and regulatory agencies must be strengthened. Communication must overcome real and perceived barriers, including concerns about intellectual property and technology transfer²⁶ and reluctance to share information before publication,²¹ to expedite translation between animal and clinical studies.

Although not necessarily generally applicable, certain steps taken by the PSTC have served to facilitate such cross-institutional and cross-disciplinary communication. As noted above, the consortium agreement contains provisions that protect preexisting intellectual property and provide for the disposition of new intellectual property by decision of an advisory committee on which each member organization has one vote. Publications arising from consortium efforts, or from information an organization learns by being part of the consortium, must also be approved by the advisory committee. This process discourages “scooping” of one member’s preliminary work by another and thus sharing of preliminary results is encouraged. Other approaches to encouraging open collaboration can include listing contributing authors in alphabetical order, as is conventional in physics articles, to avoid creating conflict by ascribing highest value to the first author. Granting agencies and academic institutions can emphasize approaches that identify, recognize, and reward teams, not individuals. If team leadership is required, it can be determined by election or rotation. Ultimately, collaboration, rather than competition, can be rewarded and protected through formal and thoughtful structures.

TRANSLATIONAL TOXICOLOGY IN THE PSTC

The PSTC was formed by preclinical scientists, but a consensus rapidly emerged that truly translational biomarkers can greatly improve the safety assessment process. That is, they must show comparable value in identifying or predicting adverse reactions in both preclinical and clinical studies. Accordingly, the consortium expanded to include clinical scientists with experience and expertise in particular types of organ injury and in issues specific to clinical drug development.

The PSTC’s current translational team (Table 1) of clinical and preclinical, industry, academic, and regulatory scientists is uniquely qualified to guide the development of translational biomarkers for drug testing. This team advises on clinical and preclinical studies that, together, can provide data to support the

use of biomarkers for monitoring drug-induced injury both in animals and in humans—data that will be persuasive to regulatory health authorities. The clinical experts identify critical knowledge gaps relating to safety monitoring in clinical drug development (as well as standard of care). They also share their experience of working with specific biomarkers under consideration by the preclinical scientists. The clinicians from health authority agencies advise on what data can inform regulatory decisions, while the academic clinicians provide information that facilitates connections among studies of biomarker behavior in various disease states. The team has produced a document (“Points to Consider for Guiding Applications of New Kidney Safety Biomarkers in Early Clinical Drug Trials”), provided guidance on a protocol for a novel clinical study of kidney safety biomarkers, and considered many avenues for sharing clinical data and samples. Overall, it represents a true breakdown of “silos” and promises to deliver on the vision of enhancing drug safety and reducing drug development failures due to adverse events.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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