Abstract

The Predictive Safety Testing Consortium (PSTC) is a public-private partnership that brings together pharmaceutical companies to share and validate each other’s safety testing methods with input from the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). PSTC is one of seven consortia of the Critical Path Institute (C-Path), a nonprofit organization that is dedicated to accelerating drug development by delivering on the mission outlined by FDA’s critical path initiative. The current 19 corporate members of the consortium share internal experience with nonclinical and clinical safety biomarkers in six working groups: cardiac hypertrophy, nephrotoxicity, hepatotoxicity, skeletal myopathy, testicular toxicity, and vascular injury.

Mission

The mission of PSTC is to identify new and improved translational safety testing methods for use in nonclinical and clinical studies. Many of these approaches are subsequently submitted for formal regulatory qualification. The ultimate goal of the consortium is to improve the current approach to drug
safety testing and to offer assurance to the drug developers that these approaches will be accepted by the regulatory authorities in their drug development programs.

Through PSTC, members are able to share their expertise, resources, data, and internally developed approaches in a neutral, precompetitive, confidential environment. There are more than 250 participating scientists and C-Path serves as the “trusted third party,” leading the collaborative process by collecting and summarizing the data, and leading the interactions with global health authorities.

Projects:

1. **Nonclinical Kidney Biomarkers: Phase I**

Following review of the first ever biomarker qualification data submission by PSTC, FDA (2008), EMA (2007), and PMDA (2010) issued a formal regulatory opinion that urinary beta-2-microblobulin, urinary total protein, urinary albumin, urinary KIM-1, urinary clusterin, urinary cystatin c, and urinary trefoil factor 3 (TFF-3) can be utilized on a voluntary basis, in addition to serum creatinine and blood urea nitrogen, in GLP rat toxicology studies to monitor drug-induced kidney injury. The translatability of these biomarkers in canine and non-human primate is currently being evaluated.

2. **Nonclinical Kidney Biomarkers: Phase II**

In Phase II of PSTC’s nonclinical qualification, the seven previously qualified biomarkers, plus serum cystatin c, urinary retinol-binding protein 4 (RBP-4), GST-alpha, GST-pi/mu, NAG, NGAL, osteoactivin, and osteopontin, are being further investigated for their mechanistic specificity, potential to detect very early kidney injury (i.e., before microscopic evidence of injury to the tissue), utility in monitoring injury reversibility, and specificity to drug-induced renal injury.

3. **Clinical Kidney Biomarkers**

Several putative drug-induced kidney biomarkers, including those currently under investigation in the rat model, are being evaluated for their utility in monitoring patient renal safety in a series of studies that will characterize inter- and intra-subject variability, as well as the impact of gender, age, and diurnal variation in healthy volunteers. In collaboration with the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium, PSTC will also determine thresholds for drug-induced renal
tubular injury. In addition to the serum biomarker cystatin C, the urinary biomarkers to be evaluated include: albumin, creatinine, alpha-1-microglobulin, beta-2-microglobulin, calbindinD28, clusterin, cystatin c, kidney injury molecule-1 (KIM-1), IL-18, total protein, trefoil factor 3 (TFF-3), NAG, GST-alpha, GST-pi, RBP4, NGAL, osteopontin, Tamm-Horsfall Protein (uromodulin), VEGF, and connective tissue growth factor (CTGF). Newly qualified biomarkers will enable safer drugs to be developed in order to reduce drug-induced injury in patients.

4. Nonclinical Skeletal Muscle Injury Biomarkers

Muscle pain is an unfortunate common side effect of treatment in popular classes of drugs, including cholesterol-lowering statins. Aspartate aminotransferase (AST) and creatinine kinase activity (CK), traditional measures of drug-induced skeletal muscle injury, lack both specificity and sensitivity. Skeletal troponin I (Tnni1, Tnni2), skeletal troponin T (Tnnt1, Tnnt3), creatinine kinase protein M (Ckm), parvalbumin (Pvalb), myosin light chain 3 (Myl3), fatty acid binding protein 3 (Fabp3), aldolase A (Aldoa), and myoglobin—all measured in serum or plasma—are proposed as more sensitive and specific biomarkers of drug-induced skeletal muscle injury, that additionally may distinguish between injury to fast and slow twitch muscle fiber types in rats. Adoption of these newer biomarkers should allow therapeutics with fewer muscle side effects to be developed.

5. Clinical Skeletal Muscle Injury Biomarkers

Drug-induced skeletal muscle injury is an undesirable side effect of some valuable medications, including cholesterol-lowering statins and fibrates. Serum alanine aminotransferase (ALT) and creatinine kinase, as well as clinical outcomes reported by patients and physicians such as muscle pain and weakness, are imprecise and nonspecific. New biomarkers including skeletal troponin I (Tnni1, Tnni2), skeletal troponin T (Tnnt1, Tnnt3), creatinine kinase protein M (Ckm), parvalbumin (Pvalb), myosin light chain 3 (Myl3), fatty acid binding protein 3 (Fabp3), aldolase A (Aldoa), and myoglobin are under investigation for their potential to more specifically and accurately detect and monitor drug-induced skeletal muscle injury.

6. Nonclinical Liver Injury Biomarkers

The most common traditional biomarkers of drug-induced liver injury, ALT and AST, have several limitations. In the course of testing a therapeutic for potential to cause liver injury, transaminase increases are commonly observed in the absence of evidence of injury to tissue, and, conversely, sometimes do not increase even when tissue injury is observed. PSTC is pursuing qualification of
several biomarkers that improve upon this lack of concordance, as well as biomarkers that may truly predict whether a drug-induced injury will progress to a serious outcome (i.e., liver failure) or whether adaptation may occur.

7. Clinical Liver Injury Biomarkers

Drug-induced liver injury (DILI) is one of the most frequent adverse events and can sometimes result in liver failure. Rare (e.g., < 1/10,000) liver safety events have resulted in the withdrawal of drugs from the market that were efficacious for the overwhelming majority of patients. Identifying which patients might be susceptible or succumb to DILI is an active and complex area of research. PSTC is focused specifically on biomarkers that would predict, early in the course of therapeutic treatment, whether a patient might progress to serious liver injury or adapt, and thus safely continue with therapeutic treatment. These biomarkers would be enormously useful in deciding whether to continue or alter the course of treatment, while simultaneously improving patient safety and enabling continued therapy for patients in need.

8. Nonclinical Biomarkers of Cardiac Hypertrophy

Some therapies can cause cardiac hypertrophy leading to left ventricular systolic dysfunction and possibly heart failure. These drug-induced changes are most commonly monitored in patients utilizing echocardiography (imaging), and more recently, natriuretic peptides (NPs)—cardiac hormones synthesized and secreted in response to myofiber stretch. The noninvasive, rapid, and inexpensive nature of NP measurements makes them attractive candidates for both nonclinical species and patients. PSTC is investigating whether NT-proANP, the active cleaved form of atrial NP, is an appropriate biomarker for measurement of drug-induced changes in heart weight and decreased ejection fraction. When ANP is elevated in nonclinical safety studies, it could trigger utilization of clinical BNP (B-type Natriuretic Peptide) measurements to monitor drug-induced hemodynamic stress leading to decreased ejection fraction and/or cardiac hypertrophy. This work will protect patients from potentially serious cardiac side effects from therapeutic treatment.

9. Nonclinical Biomarkers of Vascular Injury

Drug-induced vascular injury (DIVI) is common in nonclinical species such as the rat, dog, or monkey and is classically associated with a class of drugs called PDE inhibitors, including many given safely and effectively to humans for a variety of conditions and diseases. However, observations of histopathology are dissimilar among these species and even more different than histopathology
observed in humans. Moreover, compounds known to cause DIVI in nonclinical species do not appear
to cause vascular injury in humans. PSTC is pursuing biomarkers in rats that are both sensitive and
specific to drug-induced injury to the epithelial or smooth muscle cells of the vasculature, and can be
demonstrated of mechanistic relevance for humans.

10. Clinical Biomarkers of Vascular Injury

PSTC is working to qualify noninvasive biomarkers for DIVI that can be used to monitor safety in
nonclinical and clinical drug development. A major confounding factor is that DIVI seen in nonclinical
species is dissimilar to histopathological observations in man. Additionally, sensitivity/susceptibility to
DIVI from the same therapeutic varies widely from animals to humans. Thus, observations of DIVI in
nonclinical safety studies usually lead to termination of the drug development program, because no
mechanism for monitoring this injury currently exists for use in human clinical trials. This, likely, leads
to the loss of many promising therapies that may have posed no risk for DIVI to humans. PSTC’s new
biomarkers should enable the initiation of clinical trials where patient safety can be confidently
monitored.

11. Nonclinical Testicular Biomarkers

Currently, there are no predictive biomarkers that indicate seminiferous epithelial damage. A reliable,
translatable biomarker of early damage to the seminiferous epithelium would allow clinical testing of
therapeutically useful compounds while monitoring testicular safety. The PSTC Testicular Toxicity
Working Group (TWG) is currently evaluating the potential of microRNAs (miRNAs) to fill this gap in
drug development safety. miRNAs are secreted into the blood stream, and are unique to each cell
type. Thus, it is possible that miRNA that are secreted might be able to be used to detect damage
to seminiferous epithelium. A translational biomarker of seminiferous tubule damage could be used in
nonclinical animal studies to define in vivo safety margins, and further applied in clinical trials for
monitoring testicular safety. Furthermore, for the first time this approach could enable direct
assessment of risk of human testis injury posed by candidate drugs that exhibit testis damage in
nonclinical studies.

Consortium History

2005: FDA and pharmaceutical industry scientists attending the Society of Toxicology Annual Meeting
call for a consortium focused on the qualification of safety biomarkers for drug development and regulatory review.

2006: PSTC is launched by C-Path as a collaboration with FDA.
2007: A qualification package is submitted to FDA and EMA to evaluate seven biomarkers of nephrotoxicity.
2008: The first set of biomarkers is submitted to FDA and EMA, qualified for use in testing for renal safety in rodents to detect drug-induced kidney injury.
2010: PMDA accepts seven biomarkers for nephrotoxicity in nonclinical rat models.

Structure & Governance

C-Path is the umbrella organization that oversees seven different consortia focused on accelerating the drug discovery and development process, including PSTC. C-Path utilizes a Leadership Team to provide oversight on all consortia. Each consortium has a dedicated C-Path staff member who serves as the executive director and has subject-matter expertise in the topic area of the consortium. In many cases, the C-Path executive director works closely with a co-director, who is appointed by the sponsoring companies. Because of the regulatory focus of the consortium’s work, PSTC utilizes a director of regulatory strategy and submissions, who serves as a liaison between the different regulatory agencies and the consortium. C-Path also employs a project manager who manages the projects and resources provided by the sponsoring organizations. C-Path consortia also employ project coordinators for each consortium and in some cases, an associate director.

For PSTC, an Advisory Committee provides oversight on all PSTC activities and is composed of representatives from the sponsoring companies, as well as academic consultants and regulatory officials who participate as observers. Supporting the Advisory Committee are six topical working groups that include industry and regulatory representatives who share data and expertise in the development of a program to qualify promising biomarker assays in the areas of cardiac hypertrophy, nephrotoxicity, hepatotoxicity, skeletal myopathy, testicular toxicity, and vascular injury. These working groups are supported by data management, statistical, regulatory, and translational strategy teams.

Financing

As the umbrella organization for PSTC, C-Path revenue is generated mostly from membership dues
and grants. C-Path receives financial support through a grant sponsored by the FDA.

Member companies provide financial contributions via annual dues to help with the operations of the consortium, as well as in-kind contributions. The latter includes scientific expertise and laboratory resources to conduct the research projects.

**Intellectual Property**

Each PSTC member signs a common legal agreement prior to participation in the consortium. Typically, the output of the collaboration is within the precompetitive space and intellectual property (IP) created is owned by the consortium as a whole. According to the membership agreement, the content and information from the consortium is deemed confidential to PSTC members and all external disclosures are approved by members.

**Patent Engagement**

Although patients with specific diseases are not directly targeted for involvement in PSTC’s projects, some programs involve individuals exposed to drugs with known side effects such as nephrotoxicity to evaluate the utility of biomarkers in clinical trials. Furthermore, existing clinical data from industry sponsored trials are used in some programs.

The goal of PSTC is to identify, evaluate, and qualify biomarker assays indicative of drug safety at the nonclinical and clinical drug development stages. Of the 11 projects identified by the working group, one of them has already resulted in the qualification of a nonclinical kidney safety biomarker that has been approved by FDA, EMA, and PMDA.

**Data Sharing**

C-Path established a PSTC database that utilizes a common histopathology lexicon and study design elements. Tissue, sample handling, and data reporting are also standardized to facilitate combining data from studies performed at multiple sites.
Impact/Accomplishment

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Updated: 04/28/2016