Toxicology

Understanding the toxicology profile of investigational drugs is a key part of drug development; our two interviewees highlight the collaborative nature of the discipline.

William B. Mattes, Ph.D.

Director of Toxicology, The Critical Path Institute, Tucson, Arizona and Rockville, Maryland, USA.

The Critical Path (C-Path) Institute leads the Predictive Safety Testing Consortium (PSTC), which brings together 15 pharmaceutical companies to share and validate their safety testing methods, with advice from the US FDA and the European Medicines Agency (EMEA).

As Director of the PSTC, William Mattes works alongside 2 others to coordinate the activities of over 200 scientists, spread among 17 organizations and pursuing 5 research projects. "Our goal is to 'qualify' new safety biomarkers, and to do so we attempt to amass a body of evidence that a new biomarker is suitable for use," says Mattes. In June 2008, seven new biomarkers of drug-induced kidney injury identified by the PSTC were approved by the FDA and the EMEA.

Following his Ph.D. in biological chemistry at the University of Michigan, USA, Mattes continued his postdoctoral training by examining the interaction of the UvrABC endonuclease with carcinogen-modified DNA at the Johns Hopkins University in Baltimore, Maryland, USA. Through his postdoctoral advisor he found his first position at the National Institutes of Health's National Cancer Institute (NCI), investigating the variations of nitrogen mustard reaction with DNA at the DNA sequence level. "From that point on I was steered to positions through my colleagues — that is, by word of mouth," he says.

In this way, Mattes progressed from the NCI, applying his molecular toxicology expertise to different divisions in various organizations in the United States: the Plant Protection Division, Farmington, Connecticut; Ciba–Geigy's Pharmaceutical Division, Summit, New Jersey; Pharmacia & Upjohn, Kalamazoo, Michigan; Gene Logic, Gaithersburg, Maryland and currently the C-Path Institute, Rockville, Maryland. "Through scientific societies and through the dynamics of the multi-site and multinational organizations I've worked for, I've been drawn to the power of the scientific community," he says. "In its best form it is a functional and synergistic family." He sees his position at C-Path as a natural step, "…to formally take on a role helping that family achieve its goals." He was particularly attracted by the opportunity to truly integrate emerging science into standard, regulated pharmaceutical safety assessment.

At C-Path, Mattes' major role is to liaise with the consortium members' project leaders, and advise them on strategy and coordination. An important experience that prepared Mattes for this was his involvement in collaborations such as the International Life Sciences Institute genomics effort. "Bringing scientists together, with their diverse personalities, backgrounds, perspectives and motivations, is clearly the greatest challenge of collaborative leadership," he says.

However, this challenge also brings Mattes the greatest reward: achieving a consensus with regard to the purpose of a project and connecting that purpose with the larger goal of improving regulatory safety assessment. "Of course," he concludes, "having the data come together on a project from several sources, having members share their results and know-how, and having the resulting dataset move new safety tests into common practice is the true fruit of that consensus."

Jeffrey A. Kramer, Ph.D.

Director of Toxicology, Drug Metabolism and Pharmacokinetics, Lexicon Pharmaceuticals, The Woodlands, Texas, USA.

Identifying and characterizing the dose-limiting toxicity of companies' lead compounds before they are tested in clinical trials is an essential part of drug development. At Lexicon Pharmaceuticals, Texas, USA, Jeffrey Kramer is responsible for discovery and investigative toxicology. "I work closely with synthetic and analytical chemists, pharmacologists, biologists, geneticists, pathologists, process chemists, pharmaceutical scientists and individuals from clinical research, informatics, business development, commercial, legal and project management," he says.

The ability to gain knowledge and experience in the breadth of fields that support the drug discovery and development process is an essential learning skill that Kramer attributes to his B.S. in chemistry at Messiah College, Grantham, Pennsylvania, USA, and his Ph.D. in chemistry at the University of Toledo, Ohio, USA. "Although I am a long way from a synthetic organic chemistry laboratory, I have always felt that my firm grounding in chemistry has prepared me very well," says Kramer.

After a postdoctoral fellowship at Wayne State University, Michigan, USA, Kramer responded to a job advert in a scientific journal for a position at the Human Nutrition Sector at Monsanto/Searle. A reduction in work-force drove him into drug safety. "I worked for a scientist who had worked in Bruce Ames's laboratory during the time when the 'Ames assay' was being developed. When Pharmacia and Monsanto merged, and the Human Nutrition Sector was discontinued, I was able to take advantage of my boss's network in the field of toxicology to get a job in molecular toxicology and toxicogenomics (using technologies similar to those I was applying to discover new targets for nutraceuticals)," explains Kramer.

For someone with no formal graduate training in toxicology, this twist of fate has provided a satisfying career path. "I am passionate about discovery and investigative toxicology, which I believe has great potential to reduce safety-related attrition in all stages of drug development. Additionally, it allows me to work with cross functional teams, while providing an opportunity for continuous learning, particularly in new areas of pharmacology," he says.

Prior to joining Lexicon Pharmaceuticals, Kramer was head of the molecular toxicology laboratory in the Worldwide Safety Sciences organization at Pfizer in St Louis, Missouri, USA. The opportunity to build a new discovery toxicology team at a promising young biotechnology company intrigued him, and led him to leave Pfizer in 2005. "Since that time we have delivered five new molecular entities into development [at Lexicon], with several more on the way," says Kramer.

The most important lesson that Kramer feels he has learnt is knowing when to admit if he does not know the answer to a question. "Drug discovery and development requires input from experts in so many scientific fields that no single individual can know everything needed to bring forward a promising lead. The ability to rely upon and learn from experts in one's own and other fields is key to working effectively in the sorts of cross-functional teams needed in drug research."