Newsletter:
Summer 2015

Drug Discovery Toxicology Specialty Section (DDTSS)

President's Message

DDTSS President Dan Kemp

I feel very fortunate to be able to take on the role of President for the Drug Discovery Specialty Section. This past year we developed many opportunities for our members to help give back to this section as well as recruited outside scientists to develop an interactive program that hopefully, provided opportunities for our membership to learn year round. The first opportunity came in the form of our Fall 2014 newsletter where Dolo Diaz contributed an article on "*Weight of evidence criteria to differentiate on-target from off-target toxicity for small molecules*."

This article was well received and if you haven't had a chance to read it I would recommend stopping by our website and pulling up the newsletter (http://www.toxicology.org/groups/ss/DDTSS/index.asp). The second opportunity came from a webinar which was titled, "*You are what your Microbiome eats, the impact of the Microbiome on Drug Discovery.*" This webinar was hosted by Charles River and provided us the opportunity to hear from Drs. Peter Turnbaugh, Matt Redinbo, and Martin Kriegel about the exciting things that are beginning to occur in the Microbiome. Finally, at the annual meeting we held our graduate student and post-doc poster competition (supported by the Emil A. Pfitzer endowment), a grad student/post-doc networking lunch and at the reception an expert panel of pharma and CRO scientists to debate the drug discovery landscape. Moving forward this specialty section remains on solid ground with a steadily growing membership, increasing funds in the Emil A. Pfitzer endowment, and the engagement we are receiving from graduate students and post-docs.

We are hoping to increase our engagement in years to come. The DDTSS officers are working on new ideas for webinars and possibly providing a rolling webinar series throughout the year, we are also debating the merits of having short (1-2 day) focused meetings in local hubs for drug discovery, as well as using the blog function from ToXchange. Our overall strategy for the future is to provide members with as many opportunities as they would like to contribute to building a truly great specialty section. In addition, we would like to continue the engagement and the opportunity for our members to network at the 55th Annual Society of Toxicology Meeting in New Orleans. We hope to see many of you there!

Officers

President
Dan Kemp
(dkemp@thehamner.org)

Vice President
Ray Kemper
(raymond_kemper@vrtx.com)

Vice President-Elect
Pete Newham
(peter.newham@astrazeneca.com)

Secretary/Treasurer
Dinah Lee Misner
(misner.dinah@gene.com)

Past President
Andrew Olaharski
(andrew.olaharski@agios.com)

Councilors
Leanne Bedard
(lbedard@admetoxsolutions.com)

Jonathan Phillips
jonathan.phillips@boehringer-ingelheim.com

Student Representative
Melanie Abongwa
(mabongwa@iastate.edu)

Postdoctoral Representative
Vacant

Table of Contents

Special Guest Contribution

Are traditional animal models sufficient in predicting human drug safety?

Rachel Strittmatter, DVM, MS, DACLAM; Senior Principal Clinical Veterinarian; Animal Resources, Boehringer-Ingelheim Pharmaceuticals

In this article we intend to debate the question of whether common toxicology species are adequate for anticipating human adverse responses. We also aim to look at emerging approaches to augment animal use, improving on the caveats they present and what can be reasonably achieved to fill translational gaps.

In order to most accurately predict human toxicities, there is a clear need to use relevant animal models during the drug development process. Traditional approval of therapeutic agents requires safety testing in a both a rodent and non-rodent species, although in some cases testing in a single nonhuman species can be justified. Typically, healthy animals with low or no background incidence of natural disease and assumed homogeneity are chosen for nonclinical safety studies. Dependency on animal models to deliver confidence for safe human studies has been met with increasing impatience due to poor translation of nonclinical outcomes. Clinical failure estimates vary widely, but equally wide is the consensus around the current pace of attrition dragging traditional drug development into unsustainability.

The drawbacks of using animals to approximate human response have been thoroughly described. One of the most heroic failures of animal models to provide safety warnings was realized in the Phase 1 trial for TGN1412, a monoclonal antibody superagonist of CD28. The clinically safe starting dose for TGN1412 was calculated at 0.1 mg/kg, which was 500 times less than the 50 mg/kg top dose used in nonhuman primate toxicology studies. Mechanistic investigations suggest a lack of CD28 expression on cynomolgus CD4+ effector memory T-cells is likely responsible for underestimating the cytokine storm response eventually seen in all six Phase 1 subjects *(1)*.

Inflammatory responses have been notoriously challenging to translate from preclinical models into humans. As the classical animal model for immunology investigations, the mouse has been especially unsatisfactory at mimicking the human response *(2)*. A recent study catalogs the numerous disagreements in gene expression profiles between mice and humans under various inflammatory conditions *(3)*. In addition, neurologic adverse effects are also difficult to predict. A recent review cataloging adverse drug reactions associated with approved drugs in Japan found only a 26% correlation between clinical and nonclinical findings. These subjective clinical signs (somnolence, headache, weakness and dizziness) are typically not perceptible in traditional species used for safety studies *(4)*. While these types of neurologic events may be under-predicted, nonclinical studies using Beagle dogs may over-predict seizurogenic potential of compounds, as this breed is associated with an increased incidence of idiopathic epilepsy *(5)*. These prominent examples clearly indicate the need to properly characterize preclinical test species to minimally understand the pharmacological relevance of the species selected. A few of the criteria to be evaluated when selecting species are listed below:

- Pharmacological relevance:
  - Tissue cross reactivity (biologics)
  - target specificity/potency; animal to human
  - Target engagement and pharmacodynamics
- Metabolite profiling
- Pharmacokinetics
  - Half-life
  - Clearance mechanisms
  - Ability to achieve exposure targets
  - Dose limiting tolerability; e.g., exposure limiting emesis
- Ethically appropriate use of animals

With any animal species selected for toxicology studies, there will be a range of caveats. Even the chimpanzee, which is broadly considered the most similar species, demonstrates frequent disconnect from human. What happens when there are no pharmacologically relevant test species? What if the drug target is not expressed in a healthy animal model, as is the case for most infectious disease targets, or many oncology targets? For small molecules, these questions are often considered less important, but some would argue that on-target pharmacological activity often contributes to the overall toxicity profile.

Altering a model to include disease physiology presents an additional challenge for interpretation of toxicology results. Separating the influence of disease from drug-related effects adds a new level of complexity. Experience with animal models is a key enabling feature for reliable use, especially for safety evaluation. Even with healthy, conventional toxicology species, spontaneous findings are sometimes hard to differentiate from drug effects. The more exotic the model, the less confident investigators are when attributing observations to test articles. Regulatory acceptance of a model tends to follow depth of experience and mechanistic understanding. Vast amounts of validation data are often required for a new test system to be adopted for regulatory decision making. Fresh discussions with health authorities are now focusing on ways to accelerate implementation of new approaches to evaluate safety and efficacy. The FDA's Critical Path Initiative is the most deliberate attempt at identifying catalysts to improve some of the gaps in translational medicine *(6)*.

Can we use logic within the species selection process to include disease physiology? If steps are taken to adequately characterize toxicology species for pharmacological relevance, then certain cases may warrant consideration of disease features. The earliest opportunities to bring disease relevance to preclinical toxicity assessments may lie within therapeutic indications where toxicities tend to translate better. For example, we discussed how inflammatory toxicities tend to be more challenging to translate than cardiovascular risks. Incorporating cardiovascular disease features into nonclinical safety assessments may help improve confidence in on-target vs. off-target toxicities. These types of evaluations may also help bring a more parallel context to therapeutic indexes, where efficacy and safety could be evaluated using the same model. There are examples of clinical disease features making toxicities more or less severe.

Use of a knock-out mouse mimicking a lysosomal processing disorder illustrates one such example. The acid sphingomyelinase knock-out (ASMKO) mouse was developed as a model of Niemann-Pick disease in humans. Single and repeat dose studies evaluating the therapeutic potential of a recombinant human acid sphingomyelinase (rhASM) in the Sprague-Dawley rat, beagle dog, and cynomolgus monkey revealed that all doses were safe and well tolerated. Despite this finding, single doses of rhASM lower than the determined NOAEL led to cardiovascular shock, systemic inflammation and death within 24 hours in the ASMKO mouse. The rapid breakdown of large loads of sphingomyelin (present only in the diseased model) was responsible for this finding. To address this toxicity, modified dosing regimes (debulking with dose escalation) were evaluated in the ASMKO mouse and used to predict safe dosing regimes for patients in clinical trials *(7)*. This case study demonstrates that animal models of disease can provide very practical information for planning clinical studies, they may be essential in elucidating hidden toxicities associated with altered physiology of some conditions. Clear proof that a toxicity is on-target is hard to obtain, but a through consideration of the criteria described above can provide a weight-of-evidence that is adequate to reasonably conclude whether a toxicity is on-target, and therefore enable decision-making.

Initially, use of these types of models would be most beneficial when approached from a mechanistic or investigative angle. Deeper characterization at the beginning of a drug discovery effort would build an experience base that could be later relied upon for more confident hazard identification. As we better understand the translational connections between these, and other non-animal models, it is conceivable that we could quickly move toward fewer animal studies to support safe clinical starts.

References:

(1) Eastwood, D., Findlay, L., Poole, S., Bird, C., Wadhwa, M., Moore, M., Burns, C., Thorpe, R., and Stebbings, R. (2010) Monoclonal antibody TGN1412 trial failure explained by species differences in CD28 expression on CD4+ effector memory T-cells. *Br. J. Pharmacol.* **161**(3), 512-526.

(2) Leist, M., and Hartung, T. (2013) Inflammatory findings on species extrapolations: humans are definitely no 70-kg mice. *Arch. Toxicol.* **87**(4), 563-567.

(3) Seok, J., Warren, H. S., Cuenca, A. G., Mindrinos, M. N., Baker, H. V., Xu, W., Richards, D. R., McDonald-Smith, G. P., Gao, H., Hennessy, L., Finnerty, C. C., Lopez, C. M., Honari, S., Moore, E. E., Minei, J. P., Cuschieri, J., Bankey, P. E., Johnson, J. L., Sperry, J., Nathens, A. B., Billiar, T. R., West, M. A., Jeschke, M. G., Klein, M. B., Gamelli, R. L., Gibran, N. S., Brownstein, B. H., Miller-Graziano, C., Calvano, S. E., Mason, P. H., Cobb, J. P., Rahme, L. G., Lowry, S. F., Maier, R. V., Moldawer, L. L., Herndon, D. N., Davis, R. W., Xiao, W., and Tompkins, R. G. (2013) Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc. Natl. Acad. Sci. U. S. A* **110**(9), 3507-3512.

(4) Tamaki, C., Nagayama, T., Hashiba, M., Fujiyoshi, M., Hizue, M., Kodaira, H., Nishida, M., Suzuki, K., Takashima, Y., Ogino, Y., Yasugi, D., Yoneta, Y., Hisada, S., Ohkura, T., and Nakamura, K. (2013) Potentials and limitations of nonclinical safety assessment for predicting clinical adverse drug reactions: correlation analysis of 142 approved drugs in Japan. *J. Toxicol. Sci.* **38**(4), 581-598.

(5) Hoskins, J. D. (2000) Congenital defects of the dog. *Textbook of veterinary internal medicine*, 1983-1996.

(6) Woodcock, J., and Woosley, R. (2008) The FDA critical path initiative and its influence on new drug development. *Annu. Rev. Med.* **59**, 1-12.

(7) Murray, J. M., Thompson, A. M., Vitsky, A., Hawes, M., Chuang, W. L., Pacheco, J., Wilson, S., McPherson, J. M., Thurberg, B. L., Karey, K. P., and Andrews, L. (2015) Nonclinical safety assessment of recombinant human acid sphingomyelinase (rhASM) for the treatment of acid sphingomyelinase deficiency:the utility of animal models of disease in the toxicological evaluation of potential therapeutics. *Mol. Genet. Metab* **114**(2), 217-225.

DDTSS at SOT 2015

DDTSS sponsored a number of special events at the SOT 2015 Annual Meeting in San Diego. On Monday, March 23rd, DDTSS hosted *Lunch with an Expert*, providing an opportunity for students and post-doctoral researchers to discuss the field of Drug Discovery Toxicology with active practitioners from pharmaceutical companies of all sizes. The luncheon was well attended, with ~ 15 participants. On Tuesday, March 24th, DDTSS held our annual reception, which featured an expert panel discussion entitled: *A 10-year retrospective on drug discovery toxicology: Where have we been and where are we going?* The panel was composed of distinguished scientists who have spent much of their careers in the drug discovery arena, and included Ivan Rich (CEO & founder Hemogenix), Kyle Kolaja (VP of business development, Cellular Dynamics), Drew Badger (Director Regulatory Affairs, Amgen), Jos Mertens (Senior Scientific Director, WIL Research), John Davis (Director Investigative Toxicology, Pfizer), Emily Hickey (Vice President, Charles River). This was a lively discussion in which panelists shared their experiences working in drug discovery toxicology over the past decade and fielded questions from the audience of ~ 60 DDTSS members.

In addition to the panel discussion, the 2015 reception also included presentation of the awards for outstanding posters submitted by graduate students and post-docs.

The 2015 student poster competition winners were:
1st Place: Chelsea Snyder - University of California, Davis ($1,000)
2nd Place: Monica Langley - Iowa State University ($400)
3rd Place: Melanie Abongwa - Iowa State University ($150)

The 2015 Post-Doc poster competition winners were:
1st Place: Tamara Tal – US EPA ($1,000)
2nd Place: Amrenda Ajay – Brigham and Women's Hospital ($400)

DDTSS 2015 Reception

Expert panel discussion moderated by DDTSS president, Andrew Olaharski, at the annual reception.

Andrew Olaharski with First Place Graduate Student Poster Competition Winner Chelsea Snyder.

Andrew Olaharski with First Place Postdoc Poster Competition Winner Tamara Tal.

Andrew Olaharski with departing DDTSS Past President Yvonne Will.

Thank you Yvonne for your contributions to DDTSS!

List of Past Presidents

Drew Badger: 2004-2007
Kyle Kolaja: 2008
John Davis: 2009
Cindy Ashfari: 2010
Craig Thomas: 2011
John Wisler: 2012
Yvonne Will: 2013
Andrew Olaharski: 2014

See you in New Orleans in 2016!