AST T3 Webinar "Improving Rigor and Reproducibility in Animal Models"

Additional Q&A

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Q: Should there be a required pathway that before clinical trial you need at least 1 non rodent model?

A: I wish that there was an easy answer to this since there is no clearly defined path for taking pre-clinical findings to clinical application. The general sense is that testing in a large animal model (usually non-human primate, NHP) is preferred prior to clinical application. However, in some cases – such as in autoimmune diseases – there often is not a validated large animal model. For example, this is true in my own area of interest in autoimmune Type 1 diabetes for which there is no corresponding large animal model of spontaneous disease. In autoimmune diseases and some neurologic disorders, clinical trials have been launched directly from small animal studies with varied success. Where possible, experimental testing of new therapeutics for solid organ transplant (such as costimulation blockade) has almost always included a large animal stage prior to clinical testing. However, this additional step does not always ensure patient safety: The use of anti-CD154 (anti-CD40L) for transplantation was tested in NHP prior to initial clinical trials. Despite this, early anti-CD154 clinical trials resulted in reported unanticipated thromboembolic events (see Nat. Med. 6(20):114, 200). So, there is no guarantee that results in small or large animal models will ensure clinical efficacy and safety. My own opinion is that a large animal model definitely should be used when issues such new surgical techniques, scale-up (such as islet and bone marrow transplantation), or therapeutic dosing are key elements of new interventions.

Q: If not already or recently done, it could be useful to review and summarize preclinical transplant models that did, or did not, translate well to the clinic, and then analyze and present the characteristics and clues that differed between those that did, and those that did not, translate to the clinic. This review should include both studies that predicted positive efficacy as well as those that predicted lack of efficacy but were followed by clinical trials nonetheless.

A: I couldn't agree more with this suggestion. As you say, I believe that this would be tremendously important and helpful to get a better sense of what aspects of pre-clinical models do or do not translate well to clinical application. However, an important caveat to this idea is the assumption that a single published pre-clinical study in fact is even reproducible/validated in the pre-clinical setting. This issue of replication and publication bias was an important message from my webinar and probably needs to be taken seriously. That is, it is not clear how many 'false positive' published results there are using therapeutics in pre-clinical studies. Thus, when results do not translate well to the clinic, is it because the animal model is not useful for studying a given clinical indication or can it be that some pre-clinical findings are simply not reproducible? Another related issue is that the protocol specifics (e.g., reagent/treatment dosing, timing, etc.) may obscure the translation between pre-clinical and clinical application. For example, rapamycin + IL-2 therapy was shown in pre-clinical models of Type 1 diabetes (NOD mouse) to arrest the progression of new-onset disease. However, an initial clinical trial of new-onset diabetes found just the opposite; rapamycin + IL-2 resulted in accelerated islet beta cell loss and host NK cell activation. Interestingly, a later NOD mouse study using higher dose IL-2 + rapamycin also saw NK activation and disease acceleration as found in clinical trials. I would think that more extensive validation and dosing studies in pre-clinical studies might help mitigate this type of problem (such as detected unanticipated high/low dose effects) to help guide clinical studies. While important, there is the obvious problem of current limitations of research funding to support these types of careful pre-clinical validation studies.