Drug Discovery Toxicology Webinar

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05 APR 2017
Outline

1. Career Path

2. Job Description (day in the life of discovery toxicologist)

3. Career Development
My Career Path

1999-2003: Ph.D. in Cancer Biology/Toxicology

• University of Arizona Cancer Center and Center for Toxicology

  • Interdisciplinary program in Cancer Biology/Toxicology with emphasis on xenobiotic-mediated mechanisms of carcinogenesis via interactions between AhR, ER, p53, and BRCA-1 in breast cancer cells

  • Ready to head out into the ‘real’ world!

2004-2006: Postdoctoral Fellowship in Investigative Toxicology

• Pfizer Global Research and Development – Worldwide Safety Sciences, La Jolla CA

  • “Early days” of drug discovery toxicology

  • Postdoc project = development and validation of reporter gene-based assay for prediction of genotoxicity

  • First opportunity to learn about pharma industry toxicology and drug discovery
My Career Path - Continued

2006-2007

- **Scientist, Molecular and Investigative Toxicology, Iconix Biosciences** (my first ‘real’ job!)
  
  - Leading toxicogenomics company in era of ‘promise of toxicogenomics’
  
  - Expanded my knowledge of toxicogenomics, computational toxicology, and *in vivo* toxicology data (clinical pathology and histopathology endpoints)
  
  - Company was acquired by Entelos in 2006 (my first introduction to corporate acquisition)

2007-2008

- **Head of *in vitro* toxicology R&D, CeeTox**
  
  - Leading *in vitro* toxicology CRO – spin-off company from Pharmacia/Pfizer/Upjohn in Kalamazoo, MI
  
  - Led development of novel *in vitro* toxicology models and endpoints for clients in pharmaceutical, cosmetic, and personal care industry
  
  - I missed working in pharmaceutical toxicology
My Career Path – Continued (again!)

2008-2010
• Principal Scientist, Molecular Toxicology at AstraZeneca (my first ‘real’ discovery toxicology job!) Safety Assessment US, Wilmington, DE
  • Toxicology project team representative
  • Investigative toxicology project leader
  • Wilmington site closure announced 3/2010 – first personal experience with site shut down…and really getting tired of moving/changing jobs

2010-2016
• Senior Principal Scientist, Exploratory Toxicology at Celgene, San Diego, CA
  • Toxicology project team representative
  • Investigative toxicology project leader
  • In vitro toxicology lab manager
  • Obtained DABT certification in 2011
  • Finally – able to stay in a job for 6 years without company being acquired or site shut down! But…left for great career development opportunity
A Day in the Life of a Pharmaceutical Drug Discovery Toxicologist

Core Team/Project Team Functional Representation

- **Core Team** = small focused team (5-10 people) to lead drug discovery project; objective of project is to funnel thousands of molecules down to one candidate drug to advance into development phase.
  - Core team has one representative (leader) from each discovery function

- **Project team** = all scientists from all functions who are working on a particular drug target program (can be ~50 people – includes core team members and lab scientists)

- Both teams have many meetings! Core team meetings focus more on project strategy and decision-making related to project direction, project team meetings are more for data sharing

- Discovery toxicologist is on core and project teams for multiple projects = busy!
A Day in the Life of a Pharmaceutical Drug Discovery Toxicologist – Responsibilities

Core Team/Project Team Functional Representation – Responsibilities

Discovery Toxicologist responsibilities include:

• Assessment of target safety risks at beginning of project – target safety assessment document

• Deploy *in vitro* toxicology assays to assist medicinal chemists in identifying and mitigating structure-based safety liabilities. Assays include genetox (Ames and *in vitro* micronucleus), cardiac safety (hERG), secondary pharmacology, cytotoxicity, specialized assays (organoids, cardiomyocytes, neuronal cultures, iPSCs, etc)

• *In vivo* toxicology studies: Design and oversee short-term (7-14 day) rodent and non-rodent *in vivo* toxicology studies. Purpose of these studies is to differentiate molecules on basis of safety to select ‘best’ one to advance into development

• Success (to me) is catching major safety issues prior to taking molecule into development – do not want any unexpected toxicology surprises!
A Typical Day in the Life of a Pharmaceutical Drug Discovery Toxicologist – Daily Activities

Typical Daily Activities:

• Attend meetings and present study designs and/or data from ongoing studies (*in vitro* or *in vivo*), provide interpretation and recommend next steps

• Attend meetings to **understand** what other functions are working on optimizing, and to review data for current top and emerging molecules (med chem, pharmacology, DMPK data)

• Design/review *in vitro* and *in vivo* toxicology study protocols

• Analyze and interpret toxicology study data

• Prepare data presentations/interpretation for various meetings

• Educate, educate, educate!

• Answer hundreds of emails from study directors, core team members, project team members, management, external collaborators, vendors, CROs…
Pharmaceutical Drug Discovery Toxicologist – Investigative Toxicology Projects

Investigative Toxicology: Sounds like CSI? Yes – it actually is!

- Investigative toxicology projects: Toxicology issue is identified either in discovery, development, or clinical trials and stakeholders need to understand mechanisms and implications of issue

- Use established and novel technologies to elucidate mechanism of toxicity: Toxicogenomics, proteomics, 3d tissue models, organoids, specialized animal models (humanized mice, knockout animals)

- Potential to make a large impact – can save a molecule or program (i.e. demonstrate that tox is species-specific, find that toxicity is off-target

- Example: Celgene 2015 ACT poster on developmental pathways impacted by thalidomide which lead to pectoral fin malformation in zebrafish embryos

![Figure 4. Induction of embryonic forelimb morphogenesis ontology genes by thalidomide only at 6 hours.](image-url)
Pharmaceutical Drug Discovery Toxicologist – Concluding Thoughts

My experience has been that Drug Discovery Toxicology is:

• Always learning – need to understand data from all functions in drug discovery

• Always teaching – other functions often have limited knowledge of toxicology

• Fun, interesting, and exciting!

• Opportunity to make major impact on direction of drug discovery and development programs

• Stressful – deadlines, corporate issues (site closures, corporate mergers…things that you have no control over) – note that I have lived in SoCal, NorCal, MI, DE during course of my career

• Rapidly developing field with opportunities to use cutting-edge technologies to answer interesting scientific questions

• Always changing and busy…never a moment of boredom or complacency. Similar to Oklahoma weather – if you don’t like it, wait 10 minutes and some new issue will come your way