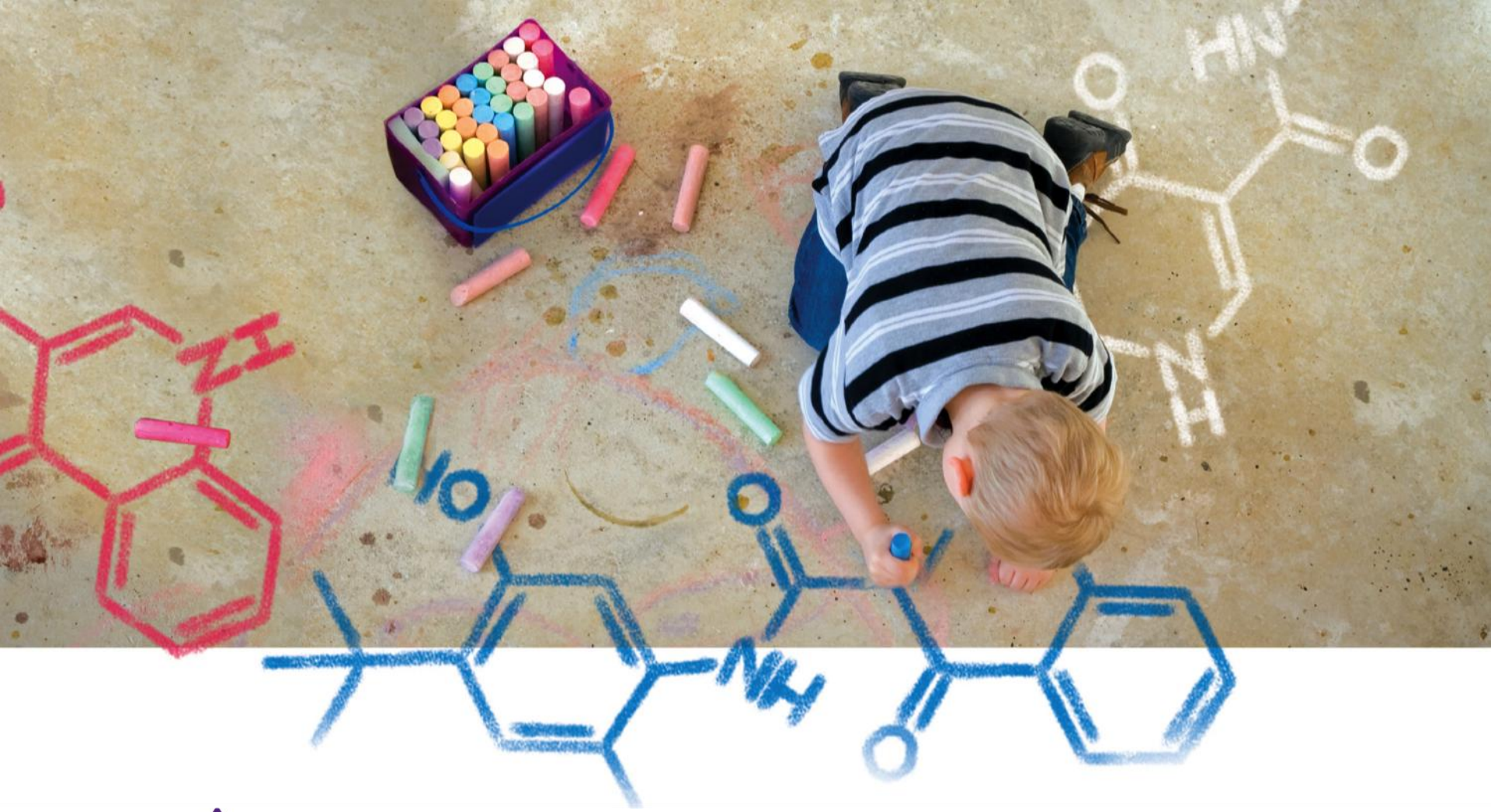

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THE SCIENCE *of* POSSIBILITY

Drug Discovery Toxicology Webinar

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Toxicologist, Discovery and Investigative Fellow

Vertex Pharmaceuticals, San Diego Site

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

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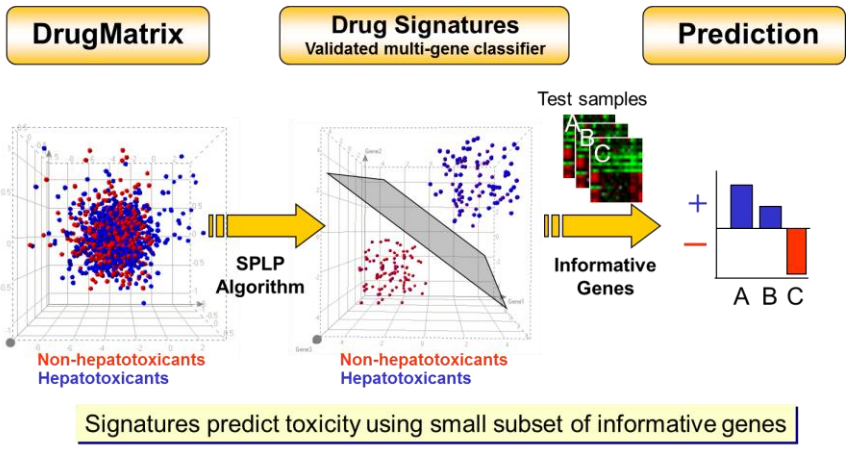
My Career Path - Continued

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

CeeTox

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My Career Path – Continued (again!)

2008-2010

- Prinicipal 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 Prinicipal 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!

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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!

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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…

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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

R...	Molecular Mechanism	P-val	Endpoint Category	Molecules Inside
1	Axon guidance (biological_process) (GO:0007411)	0.0001	Gene ontology biological ...	12: FEZ2, KLF7, ROBO3, UNC5C, FEZF2, SLIT3, CNT...
2	Pattern specification process (biological_process)	0.0001	Gene ontology biological ...	8: ZIC1, HOXB1, SIX1, SMO, BMPR1A, GLI2, TP63, S...
3	Ureteric bud branching (biological_process)	0.0001	Gene ontology biological ...	6: SIX1, PGF, PAX2, AGT, BMP2, SHH
4	Negative regulation of neuron differentiation	0.0001	Gene ontology biological ...	5: IRX3, CNTN4, HES5, ISL2, SOX2
5	Dorsal/ventral pattern formation (biological_process)	0.0001	Gene ontology biological ...	5: AIDA, TBX20, LHX2, SMO, GLI1
6	Embryonic limb morphogenesis (biological_process)	0.0001	Gene ontology biological ...	5: ACD, HOXD10, DLX5, WNT5A, TP63
7	Cerebellar cortex morphogenesis (biological_process)	0.0001	Gene ontology biological ...	4: RFX4, SMO, GLI2, GLI1
8	Anatomical structure formation involved in	0.0001	Gene ontology biological ...	4: HOXB1, DLX5, GATA3, TP63
9	Positive regulation of neuron differentiation	0.0001	Gene ontology biological ...	4: IRX3, GLI2, SOX2, SHH
10	Neuron fate commitment (biological_process)	0.0001	Gene ontology biological ...	4: ISL2, SOX2, NOTCH1, SHH
11	Smoothened signaling pathway involved in regulation of	0.0001	Gene ontology biological ...	4: SMO, GLI2, GLI1, SHH
12	Developmental growth (biological_process)	0.0001	Gene ontology biological ...	4: DMBX1, SMO, GLI2, SHH
13	Spinal cord dorsal/ventral patterning	0.0001	Gene ontology biological ...	GLI2, SHH
14	Midbrain development (biological_process)	0.0001	Gene ontology biological ...	RFX4, SHH
15	Hindbrain development (biological_process)	0.0001	Gene ontology biological ...	GLI2, SHH
16	Dorsal/ventral neural tube patterning	0.0001	Gene ontology biological ...	GLI2, SHH
17	Regulation of smoothened signaling pathway	0.0001	Gene ontology biological ...	ZIC1, GLI1
18	Cell development (biological_process) (GO:0048468)	0.0001	Gene ontology biological ...	CYB5R4, SMO
19	Telencephalon development (biological_process)	0.0001	Gene ontology biological ...	LHX2, SIX3
20	Heart morphogenesis (biological_process)	0.0001	Gene ontology biological ...	SMO
21	Multicellular organismal development	0.0005	Gene ontology biological ...	84: CHURC1, UNC45B, DBX1, AIDA, SPATA18, BZW2...
22	Transcription factor activity (molecular_function)	0.0005	Gene ontology molecular f...	70: LZTR1, ZNF207, DBX1, HMBOX1, ZFHX4, TEAD3,...
23	Sequence-specific DNA binding (molecular_function)	0.0005	Gene ontology molecular f...	50: DBX1, HMBOX1, ZFHX4, SIX4, HOXC5, DMBX1, ...
24	Cell differentiation (biological_process) (GO:0030154)	0.0005	Gene ontology biological ...	40: UNC45B, SPATA18, BZW2, HES4, MSGN1, NGEF,...
25	Nervous system development (biological_process)	0.0005	Gene ontology biological ...	28: BZW2, HES4, DOK4, FEZ2, METRN, NGEF, SEMA...
26	Positive regulation of transcription from RNA	0.0005	Gene ontology biological ...	22: NOBOX, RFX4, MEOX1, BMP3, AGRN, HOXD10, ...
27	Transcription regulator activity (molecular_function)	0.0005	Gene ontology molecular f...	13: OLIG3, SSBP3, HES4, SSBP4, MSGN1, NPAS3, EBF...
28	Transcription activator activity (molecular_function)	0.0005	Gene ontology molecular f...	13: CHURC1, BRF1, TBX20, HOXB9, TCF1, PAX8, GLI...
29	Regulation of transcription from RNA polymerase II	0.0005	Gene ontology biological ...	13: TEAD3, HOXC5, SAP18, SUB1, KLF7, TARBP2, CH...

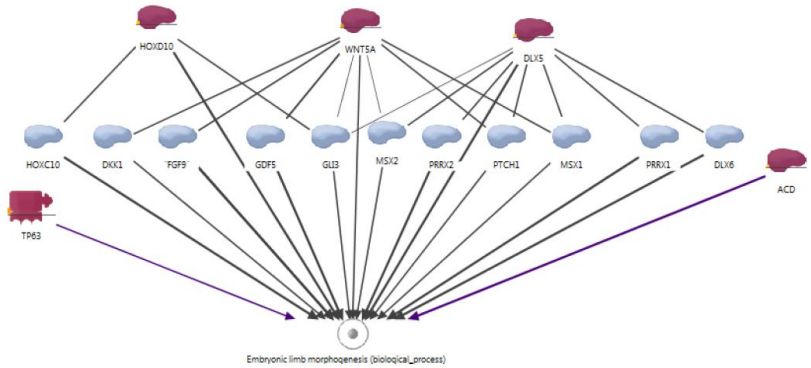

Figure 4. Induction of embryonic forelimb morphogenesis ontology genes by thalidomide only at 6 hours.

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

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