Building the Future of Developmental and Reproductive Toxicology Testing (DART): Our Legacy – Our Responsibility

Josef Warkany Lecture

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Conflict of Interest

- No conflict of interest

Reflections

Beginnings

- University of Minnesota - Morris Smithburg/Joan Spyker
- University of Cincinnati
- IRDC – Ed Goldenthal ("Goldenthal Letter,"1966, surge of outsourced DART studies), Susan Poppe
- Teratology Society – St. Jovite, Quebec 1973 (member, 1974)
- Invited participant - FDA Inspection of Searle Pharmaceutical, Skokie IL/Hazleton, Vienna, VA – October 6 – December 19, 1975
  - Based on findings of inspections resulted in final GLP regulations published, 12/22/78 and into law, 6/20/1979

Development

- Upjohn – Stuckhardt
- NCTR – FDA Inspection
- SAI – Built a CRO focusing on DART/DNT (closed)
- Ashville, NC – Dr. Wilson

Maturation

- Stephen B. Harris Group established - 1982
- SDSU (GSPH) – Adjunct/Part-time faculty
- Opinion you are about to hear is based on my experience over the past 50+ years evaluating DART data, teaching and training DART Study Directors, DART technicians, and toxicologists within the CRO, chemical, cosmetic, food, beverage, and pharmaceutical industries globally

DART STUDIES & PRECLINICAL CROs

Rapid Growth of DART

- Need for preclinical DART testing continues to accelerate
- Since original FDA Reproductive Testing Guidelines ("Goldenthal Letter," 1966) – numerous revisions of regulatory requirements have changed and become more complex
- Multinational corporations have closed or reduced in-house DART work – resulting in the increase in outsourced DART studies
- Increasingly, DART studies are basis for classification in the EU making them a focal point in safety assessment

Complexity and Size of DART Studies

- Much greater than any other safety tests
  - EFD typically - 1200+ animals (including offspring)
  - Multigeneration study can run for >6 months - ~3880 animals
  - Extended one-generation reproductive toxicity studies
    - Multiple cohorts
    - Triggers for potential neurodevelopment, immunotox, embryo-fetal arms
    - ~1400 animals

Need for DART Testing Is Increasing

- As more vivarium space becomes available for DART studies, where will CROs find skilled people to fill DART job opportunities?
- There is a need for talent…
  - Does not matter where you went to school
  - Does not necessarily matter what you studied for your, A.A., B.S., M.S., or PhD
  - If you have ability to learn, ability to get results and collaborate with others, you will fit in
- But the current question remains: How will "industry" train individuals to become DART Study Directors (SDs) to manage in-house DART testing programs, Study Monitors (SMs) to manage DART outsourced programs and technicians to conduct DART studies?

PERSONNEL

DART Teams

- Best technicians and scientists at CROs frequently have 10+ years of experience
  - Most of the knowledge and training were received on-the-job
- Newer personnel
  - Have excellent backgrounds in computational biology, molecular biology, *in vitro* techniques
  - Often no experience
    - Handling animals
    - Performing dosing techniques
    - Surgical/necropsy skills
    - Understanding how maternal health & postnatal maternal care can impact study results
  - Oral and written communication skills are weak
  - Management skills (for projects and personnel) are typically lacking

The Looming Crisis

- Declining numbers of proficient, senior DART scientists
- Diminishing availability of training for entry-level DART professional/technical staff
- Who is going to perform these increasingly important, and complex studies?
- Where do we find competent replacements?

The Looming Crisis (con't)

- Individuals entering DART testing workforce as new SDs, SMs, or technicians have minimal or no prior relevant experience
- New DART Study Director (SD)
  - Must be able to analyze/interpret data scientifically
  - Has overall responsibility for technical conduct of study
- New DART Study Monitor (SM)
  - Represents sponsor
  - Responsible for overseeing proper conduct of DART studies outsourced to CROs
- Presently - graduates are NOT qualified to accept positions like these when offered

The Looming Crisis (con't)

- "The tipping point is coming: Unprecedented exodus of young life scientists is shaking up academia" Jonathan Wosen, STAT, November 10, 2022 Exodus of young life scientists is shaking up academia - STAT (statnews.com)

- "Academia's postdoc system is teetering, imperiling efforts to diversify life sciences" Jonathan Wosen, STAT, June 6, 2023 Teetering postdoc system imperils life sciences diversity - STAT (statnews.com)

REQUIREMENTS TO ADDRESS THE CRISIS

Education & Training Needs

Technical (not inclusive)

- Animal Handling
- Animal Dosing
- Estrous Cyclicity
- Necropsy
- Postnatal Evaluations
- Semen Evaluations
- Surgery
- GLPs
- Fetal Evaluations - External/Visceral/Skeletal

Education & Training Needs (con't)

Scientific Knowledge Base (not inclusive)

- Anatomy
- Embryology
- Reproductive Physiology
- Teratology Principles
- Toxicology
- Endocrinology
- Pharmacology

Education & Training Needs (con't)

Regulatory

- Local/Country/International Regulations
- Guidelines for DART, Juvenile Toxicology, EOGRT Studies

Education & Training Needs (con't)

Basic Management Skills (People Skills)

- Leadership
  - Managing Personnel - most college graduates DO NOT get training in management skills
  - Personnel (interviews/hiring/setting goals/dismissal)
  - Interpersonal Relationships
  - How to give/receive feedback
- Work Schedules
- Budgets

Education & Training Needs (con't)

Communications

- Oral & Written - most college graduates DO NOT get training in communication skills
- Hiring and effectively communicating with upper management and managing a staff (technical and professional) is essential for DART scientists' careers
- Mediation

DART trainees MUST RECOGNIZE these non-scientific skills are as important as their scientific ones

Action Plan

Proposal

NEED:

- Critical gap in DART training - no graduate programs currently fulfill this training
  - DART training programs could supply some needs

SOLUTIONS

- Suggestions for content of curricula will be discussed later
- Universities, community colleges, and veterinary technician programs - MUST expand curricula to provide SOME training in whole animal testing
  - Academic training programs demand a great deal of money and time
  - If carried out correctly will produce immediate benefits to students and potential employers
- To meet requirements for DART employment opportunities in an industrial or regulatory setting - universities SHOULD offer students not only chance to conduct original research but also time to participate in internships

Proposal (con't)

- We must not lose sight of importance of technical staff
  - Animal husbandry technicians
  - Live animal phase technicians
  - Technicians performing laparohysterectomies/fetal exams
  - Technicians who collate data

Proposal (con't)

- Strengthen educational programs in DART
  - Formalized "hands-on" laboratory animal courses should be required
  - Could be modeled after or incorporated into laboratory technician certification courses offered by American Association for Laboratory Animal Science (AALAS)
  - Certification could be modeled after International Registry of Fetal Morphologist (IRFM) – Royal Society of Biology

Proposal (con't)

- DART space has a limited audience
- No illusion academia SHOULD or COULD take on sole responsibility of training individuals in specific techniques required in DART testing and data evaluation
- Encourage establishment of new partnerships to establish creative solutions
- Solution might be to establish TRAINING CENTERS formed by multiple universities in conjunction with stakeholders (CROs, Government, Industry)

Proposal (con't)

- Instruction could be acquired by…
  - Combination of instructive coursework with academia
  - Specialized hands-on training provided at cooperative CRO locations where DART testing is ongoing
- Provide stipends for students technical, undergraduate, and advanced degree education
  - CROs
  - Cooperative industrial financing through industry consortia and/or trade associations or individual companies
  - Government

Proposal (con't)

- Convince federal granting agencies to commit a portion of existing funding for undergraduate and graduate programs to train students in whole animal testing and computational biology
- Universities can help address needs - by gathering information from government and industry about design specifications for incoming talent

Proposal (con't)

- Much interest in alternative models
- Most hands-on training is related to *in vitro* work, biochemical assays, and computational biology is at expense of learning basics of animal handling, dosing procedures, and necropsy
- Foreseeable future - data from traditional whole animal testing will continue to define potential for human reproductive toxicity

Concluding Remarks

Apologies & Admonitions

- No intention to diminish…
  - Current undergraduate and graduate programs
  - Work conducted in academic laboratories
  - Efforts to develop high throughput and non-animal models
- Academic programs demand a great deal of money and time
- Much will remain responsibility of specific contract, industrial, or governmental organizations

Vision for an Improved Future

- Universities will be better informed and positioned to develop undergraduate, and graduate training programs that produce suitably qualified DART trainees
- DART trainees will be more prepared to contribute if they become aware of challenges and various functions throughout a company or government organization during training
- My vision - aimed at populating the DART world with well-trained and productive DART scientists who will lead us over the next decades to come

Thank You for Your Attention and Consideration