HESI

ILSI Health and Environmental Sciences Institute

Developmental and Reproductive Toxicology (DART) Technical Committee

Program Strategy and Stewardship Committee Review
January 2009

Chair: Robert Chapin, Ph.D.

Vice Chair: Bruce Beyer, PhD

Past Chair: Dana Shuey, Ph.D.

Staff: James Kim, Ph.D.

DART Members

- Amgen, Inc.
- AstraZeneca
- Bayer HealthCare
- Bristol-Myers Squibb
- The Dow Chemical Company
- E.I. duPont de Nemours & Company
- Endo Pharmaceuticals
- Merck
- Novartis
- Pfizer Inc.
- Procter & Gamble Company
- sanofi-aventis
- Takeda

DART Scientific Advisors

Dr. Bob Brent, A.I. DuPont Hospital for Children

Dr. Sue Fenton, US EPA

Dr. Wafa Harrouk, US FDA

Dr. Mary Hixon, Brown University

Dr. James Lamb, The Weinberg Group

Dr. Anthony Scialli, Georgetown University and Tetra Tech Sciences

DART Public Sector & Other Participants

- Brown University
- Cincinnati Children's Research Foundation
- European Medicines Agency
- Georgetown University
- Johns Hopkins University
- Instituto Nacional da Farmacia e do Medicamento, Portugal
- Medical University of South Carolina
- National Institute for Public Health and the Environment (RIVM, the Netherlands)
- Texas A&M University
- U.S. CDC – NIOSH
- TNO
- PETA
- Wake Forest Univ.
- U.S. Environmental Protection Agency – NHEERL; OPP; National Center for Computational Toxicology
- U.S. Food and Drug Administration – CDER; CFSAN; NCTR
- U.S. NIEHS
- University of Arizona
- University of California – Davis
- Children's Memorial Res. Center, Chicago
- Celgene
- Cellartis, Sweden
- Zygogen
- Davidson College
- InVitrogen
- NICEATM, NIEHS
- Univ. de Louvain, Belgium

DART Committee Mission

The HESI Developmental and Reproductive Toxicology (DART) Technical Committee provides a forum where scientists from industry, government and academia can exchange information and initiate activities to advance science related to reproductive and developmental toxicology, and to develop consensus on the appropriate use of experimental toxicity data for human health risk assessment.

Overview of DART Projects

Legacy Projects

- Interpreting Reproductive Endpoints-Daston
- Organ System Development Series
- Skeletal Variations and Malformations
- Developmental Neurotoxicity I
- Female Reproductive physiology and tox
- In Vitro testing methods I

Overview of DART Projects

Current Projects

- Rodent Repro Endpoints-Marty
- Developmental Tox New Directions
- In Vitro testing methods II
- Maternal Toxicity Workshop
- Behavioral Testing II

Overview of DART Projects

New Proposals

- Placental Transfer of Biologics
- Vaccines
- Developmental Immunotoxicity
- The Value of Juvenile Animal Studies

Current DART Projects

Rodent Repro Endpoints – Marty

(Reevaluation and Interpretation of Reproductive Endpoints for Human Health Risk Assessment)

Steering Committee

- Dow Chemical
- DuPont
- Environ
- HESI
- NIEHS
- Pfizer, Inc.
- Procter & Gamble Company
- US-EPA (NHEERL, OPPTS)
- Research Triangle Institute
- University of Maryland

Current DART Projects

Reevaluation and Interpretation of Reproductive Endpoints for Human Health Risk Assessment

- **Leader: Sue Marty, Dow Chemical**
  - Objectives: To provide a retrospective evaluation of the utility of the expanded endpoints added to the EPA Reproductive Toxicity Testing Guidelines, 1998
  - Asking the questions: how often are the “new” endpoints affected, do they correlate with other findings, and have they determined the NOEL?
  - Data collected by voluntary data submission; 44 studies contributed by 11 companies.

Current DART Projects

Reevaluation and Interpretation of Reproductive Endpoints for Human Health Risk Assessment

- **Status:**
  - There were not enough studies with positive findings to provide a definitive evaluation.
  - Planned workshop was cancelled.
  - Two publications planned for 2008/09:
    - Compilation of control data and discussion of appropriate use of control ranges in interpreting findings. Under HESI review now.
    - General evaluation of the new endpoints.
  - Should end in ’09 with publication of summaries.

Current DART Projects

In Vitro Assays for Evaluating Developmental Toxicity II

- Leaders: Jane Stewart, Astra Zeneca
  Aldert Piersma, RIVM
  Katie Turner, Merck
  Bob Chapin, Pfizer

No Steering Committee for this project because it's following so closely in the path of the preceeding workshop (In Vitro I).

Current DART Projects

In Vitro II

- Objective: To bring the discussion on the use of these alternative assays (whole embryo culture, zebrafish and stem cells) to Europe, to update our current state of knowledge, and to disseminate the latest advances in this active research area.
- In Vitro II will be a 1-day workshop immediately following the European Teratology Society on September 10, 2009 in Arles, France
- Probably a recurring effort (>3 yrs), given the interest in and global movement towards *in vitro* techniques.

Current DART Projects

Maternal Toxicity and its Impact on Study Design and Data Interpretation

- Leader: Bruce Beyer, sanofi-aventis

Steering Committee

- Amgen
- AstraZeneca
- Brown University
- Merck
- U.S. EPA
- RTI International
- sanofi-aventis
- U.S. FDA
- Tetra Tech Sciences
- Univ. Alabama

Current DART Projects

Maternal Toxicity and its Impact on Study Design and Data Interpretation

- Some degree of maternal toxicity is required for regulatory DART studies
- However, there is no clear consensus on:
  - How much toxicity is enough
    - Minimal toxicity vs. MTD
    - Transient effects
  - Endpoints for evaluating maternal toxicity
    - Body weight, food consumption, clinical signs
    - Appropriate use of clinical and anatomic pathology
  - “Exaggerated pharmacology” vs. toxicity
  - Impact of maternal toxicity on developmental outcome

Current DART Projects

Maternal Toxicity and its Impact on Study Design and Data Interpretation

Objectives: To drive consensus on expectations for maternal toxicity in developmental toxicity studies and impact on study outcome.

- Workshop at SOT March 2009
- Workshop at the Teratology Society June 2009
- Workshop at the European Teratology Society Sep 2009
- Manuscript to summarize the discussions/conclusions from the workshops
- Sunset the activity once the MS(s) are published

Current DART Projects

Behavioral Endpoints in Developmental Toxicity Testing II

Steering Committee

- **AstraZeneca LP**
- **DuPont Haskell Laboratory**
- **Endo Pharmaceuticals Inc.**
- **Procter & Gamble Company**
- **NCTR, US-FDA**
- **Cincinnati Children's Research Foundation**
- **Georgetown University and Sciences International**
- **Instituto Nacional de Farmacia e do Medicamento, and University of Lisboa, Portugal**
- **Merck**
- **Pfizer, Inc**
- **Hoffman-LaRoche**
- **CDC/NIOSH**
- **US-EPA**

Leaders:
Dana Shuey – Endo Pharmaceuticals
Tony Scialli – Georgetown Univ., Tetra Tech

Current DART Projects

Behavioral Endpoints in Developmental Toxicity Testing II

Purpose:

- Results of Part 1 can have varied interpretation regarding the value of behavioral testing in regulatory safety studies.
- Part 2 will further define the value of these tests. Focus on defining “value”, possible triggers, and/or possible alternative testing strategies to assess behavioral effects (as opposed to routine screening)

Current DART Projects

Behavioral Endpoints in Developmental Toxicity Testing II

Status:

- There is continued lack of agreement among the steering committee members regarding the objective of this project, how to define “value”, and strategies to move the project forward.
  - The committee will try to craft a position paper that lays out the nature of the difficulties faced by such a task.
- Will sunset once paper is published.

Current DART Projects

Developmental Toxicity New Directions

- Background: Regulatory developmental toxicity testing has remained unchanged for over 30 years while our understanding of developmental biology has advanced tremendously.
- Objective: Develop an opinion piece on the state of developmental toxicity testing to address:
  - **How can/should these knowledge advances be incorporated into developmental tox testing and risk assessment?**
  - **Define research needs to bridge current gaps that prevent full utilization / integration**.

Current DART Projects

Developmental Toxicity New Directions

Leader: Dana Shuey
(Endo Pharmaceuticals)

Steering Committee

- Bristol-Myers Squibb
- Brown University
- Dow Chemical
- NIEHS
- Pfizer
- Tetra Tech Sciences
- U.S. EPA
- U.S. FDA

Current DART Projects

Developmental Toxicity New Directions

- Goals: To provide a comprehensive, critical evaluation of developmental toxicity testing. Specifically:
  - Evaluation of current needs and methods
  - Utility and application of new technologies for developmental toxicity testing and risk assessment
  - Identification of research needs

- Timeline and Deliverables:
  - Workshop April 29-30, 2009 in Washington, DC
  - Review / opinion piece published 2009
  - We anticipate that the defined research needs will lead to follow-on DART project(s) to address these needs

Current DART Projects

Developmental Toxicity New Directions

- Working Group #1: Defining testing needs
  - Leader: Sue Makris, U.S. EPA
- Working Group #2: Critical evaluation of current testing
  - Leader: Ed Carney, Dow Chemical
- Working Group #3: Defining alternative testing strategies
  - Leader: Dana Shuey, Endo Pharmaceuticals
- Working Group #4: New approaches and technologies
  - Leader: Thomas Knudsen, U.S. EPA and Univ. of Louisville

New DART Projects

Placental Passage of Monoclonal Antibodies

Background: The placenta handles antibodies differently than small molecules (receptor-mediated endocytosis, not diffusion). Because significant passage only occurs in the second and third trimesters, organogenesis is not exposed to the therapeutic. This undermines the key component of EFD studies.

Chair: Meredith Rocca, Amgen

Steering Committee:

- Astra Zeneca
- BMS
- Pfizer
- Lilly

New DART Projects

Placental Passage of Monoclonal Antibodies

Objective: Bridge the gap between the issue of non-passage of Ab's across the placenta and the desire to expose the conceptus during organogenesis.

Methods: Literature reviews, draft proposed position paper, solicit regulatory input and comments early on, hold workshop to air the suggestions, publish paper, continue regulatory engagement to change guidances if appropriate.

***Draft* Timeline:** workshop probably 4Q09/1Q10, paper to be submitted shortly thereafter, discussions to continue until resolution reached. Sunset group with resolution.

New DART Projects

Developmental and Reproductive Safety of Vaccines

Background: The US-FDA (CBER) recently published Guidance for Industry: Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications (Feb 2006).

New vaccines is among the fastest growing area of new drug development.

Proteins have different ADME and internal exposure profiles than small molecules, which has implications for assessing developmental safety.

Immunization during last few weeks of pregnancy is used medically to confer some protection for the newborn.

Sponsored a well-attended symposium at Teratology Society Meeting, June 2008

New DART Projects

Developmental and Reproductive Safety of Vaccines

Objectives:

To gain consensus on appropriate nonclinical developmental toxicity testing strategies for new vaccines, including:

- **Appropriate species**
- **Timing and frequency of dosing**
- **Endpoints of exposure (maternal and fetal)**

Status: There is interest in this project among the Technical Committee members, but committee representatives generally feel they do not have the expertise to lead this effort. Trying to identify scientists within member companies that might participate. Potential for collaboration with BioSafe.

New DART Projects

Developmental Immunotoxicity

Background: We don't know

- which are the best measures to monitor the health of the immune system in juvenile animals,
- which is the best animal model to use, or
- the cross-species extrapolation at different ages.

This becomes more critical as more companies get into immune-modulating therapies and biotherapeutics.

New DART Projects

Developmental Immunotoxicity

Chairs: Mark Collinge (Pfizer)
Tom Kawabata (Pfizer)

Steering Committee:
- **BMS**
- **HESI**
- **Lilly**
- **Schering Plough**
- **Virginia Commonwealth Univ.**

NB: HESI's Immunotox Committee has been driving this. DART involvement is recent but committed.

New DART Projects

Developmental Immunotoxicity

Objectives:

- **Crystalize the triggers for Dev Immunotox studies,**
- **identify probable protocols,**
- **define specifics for biologicals vs. LMW compounds,**
- **identify unknowns in the science and propose remedies,**
- **based on these gaps, make recommendations for experiments and optimizations of regulatory guidance**

Write paper, have a workshop, impact guidance and industry behavior. Workshop ideally 3Q09

New DART Projects

The Value of Juvenile Studies

Background: HESI DART TC completed a project that published a series of papers (2004) on the timing of development for many body systems, and held a workshop to build consensus on optimal design and species for juvenile studies.

In the 10 years since the first regulations appeared, there seems to be increasing separation between the EU and US on when to ask for these studies and what is considered adequate information for decision-making.

New DART Projects

The Value of Juvenile Studies

Chairs: Mark Hurtt (Pfizer)

Steering Committee: being formed from stakeholders in the DART TC, European and US regulatory communities, and academia.

New DART Projects

The Value of Juvenile Studies

Objective: Optimize the use of these studies: determine the conditions under which they are most useful, and work to build consensus about when they are worth the animal use.

Methods: Data call-in to determine how many of these studies have been done, how they were constructed (species, purposes, endpoints, outcomes) and importantly, what their impact was.

Call in from industry and regulatory agencies

Workshop with key stakeholders to discuss key lessons: when have these been of value, and when do they only contribute vague comfort?

Workshop probably 4Q09 / 1Q10

DART Projects – Impact

Legacy projects have had huge impact:

- Several publications or series are daily resources for both regulators and the regulated:
  - **•The "Evaluation and Interpretation of Reproductive Endpoints" book**
  - **•Target Organ Development series: used by study directors and DART staff when developing the most appropriate study designs, and by regulators when interpreting these studies.**
  - **•Female Reproductive Physiology and Toxicology series**
- The output has influenced regulatory positions (e.g., EPA Reproductive Tox Guidelines, FDA/EMEA juvenile toxicity guidelines)
- The workshops have been attended by standing-room-only crowds, and widely applauded for presenting the state of the science:
  - **•Neurobehavioral testing I**
  - **•In Vitro Methods I (Best Paper nomination in BDR-B)**
  - **•Juvenile Animal Studies: Testing Strategies and Design**
- There is a long track record of working with all relevant stakeholders to identify gaps, develop solutions and improved methods, and align the interpretation with the best science.

DART Projects – Summary

The current and proposed projects are at the edge of the science happening in the member companies, and if they are like the preceeding projects, they will

improve our confidence in our methods,

help shape the science and

optimize our data interpretation.

Not half bad for sweat equity !