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accelerating drug development. exactly.

The Drivers and Principles for DIT Studies:
Treating Mothers with Immunomodulatory Drugs and Assessing Impact on Children

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Background

- **DIT movement started in environmental toxicology**
  - Drug toxicologists are moving a committee at a time
- **With the evolution of selective intentional immunomodulators (IM)**
  - DIT has found its footing in drug toxicology
- **These drugs are intended to**
  - "Modify the structure and function of the body"
    - *i.e. the immune system*
  - The immune system is the most sensitive target organ

We use IM Drugs for Moderate to Severe Autoimmune Disease (AID)…

- **…Transplantation, cancer**
  - Dose IM drugs to achieve NOAEL / LOAEL cusp effect
- **So for accurate dose setting**
  - Immune assessment may require a two-prong approach
  - Assess structure to avoid frank pathology
  - Assess function to identify PAD / MABEL
    - Similar to classic, safety pharmacology risk assessment

Thesis

- **Immunomodulatory drugs raise strong concerns for DIT**
  - Policy consideration will help harmonize DIT assessment across
  - General, developmental, immunotox, and juvenile tox
- **Steps will involve**
  - Resolving policy artifact arising from different committees
  - Returning to basic risk assessment principles
  - Re-evaluating DIT “drivers”
    - Not current guidelines, rather
    - Mother, Child, Ethics, and Drug MOA
  - Collating known clinical developmental immunity insights
  - Revising existing guidance to accommodate IMs

Cover

- **Risk Assessment Principles**
  - Tox Study Aims / Challenges / Purposes
  - Relevant Animal Models
  - Target Organ Assessment
- **Immune System Complexity and Immunomodulators**
  - Orthogonal Assessments are Needed
    - Titrate MABEL Vs Adverse Doses
- **DIT drivers**

Risk Assessment Principles:
Aims and Challenges

- **Apply equally to all Tox**
  - Including developmental tox (DT) or developmental immunotox (DIT)
- **Same aim**
  - Animal studies identify human hazards and inform patients
- **Same translational challenges**
  - Differences in animals' immune development require
    - Knowledge of physiologic differences among species
    - Creative designs to
      - Exploit similarities
      - Work around differences

Risk Assessment Principles:

Purpose of Tox Programs - Advise on Clinical Use

- **Show order of target organ sensitivity**
- **MTD, overdose, pathology / lethality**
- **Dose / response, NOAEL, LOAEL**
- **Chronicity - onset and reversibility**
- **Monitorable / premonitory effects at LOAEL**
  - Show sensitive indicators of immune impact
  - Provide insight into clinical active dose and monitoring

Risk Assessment Principles:
"Relevant" Animals -- Model / Approximate Humans

- **Relevance criteria**
  - Physiologic parity
  - Simulate human pharmacologic impact
    - Potency, dose, exposure, pharm response, chronicity
  - Emulate human ADME
    - Metabolites, distribution to fetus
- **Relevant models enable translation**
  - Tox, DT or DIT --- either biologics or SMDs
    - Biologics sometimes require "extremes"

Risk Assessment Principles:
The Immune System is a "Target Organ"

- **Newer immunomodulatory SMDs and biologics?**
  - No dose-limiting toxicity to kidney / liver / bone marrow
    - Permits dose escalation
    - Extremifies immunotoxic potential
    - *The immune system is the most sensitive target organ*
- **Immune system can**
  - Bend = pharmacologic desired (activity) or
  - Break = undesired nature or duration of immune impact

Immunity / Immunomodulatory Drug Complexity

Okay! The Immune System is Not an "Organ"

- **Complex "system"**
  - Organs, tissues and blood components
- **Difference?**
  - No simple, direct assessment
  - Requires 360° review of
    - Clinical Observations
    - Veterinary health/infectious disease
    - Hematology, clinical pathology, pathology…

…But for Immunomodulators, Pathology Assessments Are Not Enough

- **Immunity consists of complex functions**
  - Important for survival
  - Redundant controls and fail safes
    - Help ensure it's not easy to "kill"
- **Immunomodulators are designed to act as a rheostat**
  - (Hopefully) not extreme
  - Knocking out one player among many
  - Competing down immune receptor- or ligand-driven signals

…Since Adverse Impacts Are Not Always Detected by Morphologic Pathology…

- ***We need orthogonal functional assessments built into toxicology studies to***
  - Characterize immunopharmacologic dynamics
  - Contrast activity and toxicity
  - Enable safety margins calculation
    - Based on expected Vs. undesired changes
- **Similar to logic / role of safety pharmacology…**

Immunotox as Pharmacodynamics / Safety Pharmacology?

- ***Drug toxicologists usually employ functional assessments without thinking twice!***
- **Part of most drug toxicology programs (pre-IND)**
  - BUN and Creatinine – kidney clearance
  - HR and ECG (QT prolongation) – heart conduction
  - Behavioral testing – CNS assessment
  - APTT– coagulation function
- **Can build most endpoints into toxicology studies**
  - Not increasing animal use

Can we Apply the Same Safety Pharmacologic Principles to Immunotoxicology?

- **Yes, using in vivo functional assessment**
  - IM impact may show first on vaccine response
    - Suppressed KLH response
    - Enhanced anti-cancer response
- **These functional responses may occur without**
  - H&E path change, increased globulin, or obviously increased cellularity of spleen
    - Detected by ELISA, ELISpot, or bugs
- **Conversely, some IS drugs can inhibit TDAR**
  - No obvious splenic / LN hypocellularity or malformation

Non-Adverse AND Adverse Ranges for Functional Assessments

- **Non-Adverse - set by normal population variation per**
  - On-study controls
  - Pretreatment individual responses
  - Historical experience with animal age and species
- **Adverse - set by linkage to clinical adverse events, i.e.**
  - Increased APTT / INR and bleeding risk
    - 1-2X (okay) but >3X risks bleeding (harm)
  - QT prolongation and TdP
  - Low Ig response and infection susceptibility

For Immunomodulators, Immune Risk Assessment Requires Similar Diligence in All Types of Tox Studies

- ***Orthogonal approaches include structure and function assessments***
  - *Needed for 360° insight*
  - *Why should immune impact be an exception?*
  - If a drug is a cardiovascular drug
    - We enhance CV functional and structural assessments
  - If a drug is related to known liver toxins
    - We enhance assessments of the liver
- **So, for pre-IND tox, PPND tox, and juvenile tox on immunomodulators**
  - These studies should include immune morphology AND function
  - Timed- respectively- to support
    - Adult trials, extensive use in WOCBP, and trials in children

Why Are We Here to Discuss DIT?

- **It falls to us to protect the public health, and particular ensure identification of risks, informing doctors and patients**
  - Mother who is unaware that she is pregnant
    - May be unintentionally exposed, exposing her infant
    - Benefit may be < risk
  - Mother who requires drug treatment for serious disease
    - Despite her pregnancy
    - Benefit is judged > risk
- **In either case, child lacks disease so experiences no drug benefit**
  - Doesn't deserve risks
- **Perform PPND - treat dams and assess F1**
  - All endpoints Including immune structure / function

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Long Term View: Policies Should Dovetail

- **For impacts directly on juveniles treated with IMs**
  - Need to harmonize guidelines
  - Same ethical need for patient protection – juvenile and adult
  - Different charge from PPND DIT
    - The child stands to benefit from disease treatment
    - Risk/Benefit assessment should differ
  - Perform juvenile tox
    - Assess for all endpoints including immune structure / function

DIT for IM Drugs Given to WOCBP:

- **Address treating mother**
- **Assessing impact of in utero exposure on infant**
  - Calls for PPND studies
  - Including immune endpoints

Drivers: Drug

- **Known SAR or target relationship to immunomodulators/immunotoxin**
  - Human, animal, or clinical disease data
- **Potent intentional modulator of immune targets**
- **Other MOA issues**
  - Target known to affect development or immune development
  - Cytotoxic action on dividing cells
- **Distribution to fetus in utero**
  - > concern with SMDs early in development but immunity develops in humans up to 12 years or longer so still a factor with biologics
  - Uncertainties exist for biologics distribution 1st half of pregnancy due to expense and restrictions on NHP use.
- **Long t1/2 and chronic treatment (esp. biologics)**

Drivers: Drug – Enhanced Concern MOA

- **May have extra concerns for novel and highly directed drug MOA**
- **Extremely potent action at immune target**
  - Trace of placental delivery may express full pharmacologic action at fetal target
- **Projected to affect thymic maturation/selection**
- **Intended depletor of immune cells**
- **Disables neoantigen recognition**
- **Affect class switching or antibody maturation**

Drivers: Patient (Mother)

- **Indications in WOCBP**
  - May be pregnancy unaware
    - Drug dosing may result in unexpected exposure to fetus
  - May have serious disease
    - Treatment may be needed to support maternal health
    - Drug may be continued throughout pregnancy (severe AID)
      - Case: anti-TNFs for RA
      - CsA for renal transplant
- **Indications: Complications of pregnancy**
  - May be the intended indication for the drug / vaccine
  - No holds barred - every system needs to be studied
- **Immune dysregulation of mother (lupus anti-self Abs?)**

Drivers: Infant

- **Bystander in maternal treatment**
  - No benefit so low/no risk is warranted
- **Gaps in knowledge of human and NHP immunity**
- **Risk to sensitive windows in developing immunity**
- **Impact of drugs may differ from adults**
  - Qualitative or quantitative differences
- **Lost knowledge of impact short and long term**
  - Need pregnancy registries
  - Even SCID infants dying of infection are often COD labeled “infection” and go undiagnosed
  - Immunity develops over many years
    - Cancer and AID impacts may takes years to show

More Research is Needed on Human Immune Development

- **We can assemble known facts and fill gaps**
  - Fetuses can reject BMT post first trimester
  - Preemies can respond to anti-RSV vaccines
  - In utero exposure can produce DIT in infants
    - Delayed B cells and Ig in infants
  - Human neonates are immune competence at birth
    - Can mount anti-HLA antibodies in first months of life in response to homograft
  - Infants treated with myeloablative and IS drugs can develop lymphoma within a year
  - Post BMT or other states of immunocompromise, child patients often can mount anti-vaccine immune response, but require more boosts and may not achieve lasting memory
  - There are a number of AID that arise in children
  - Asthma and food allergy incidence appear to be rising

Summary

- **We Need Better Risk Assessment and Protection for Immunity in Children**
- **Current guidelines are not the drivers for DIT**
  - Have evolved at different times and locales
  - Under different risk assessment paradigms
  - Require harmonization
- **First principles of toxicology are the drivers, along with human medical ethics**
  - Study of immunomodulatory drugs in humans will give us greater insight on translation
  - Vaccine response has already proven very useful in humans to track immune function in BMT and AIDS patients as well as animal studies of IMs

Conclusion

More consistent drug / biologic risk assessment practices and careful application of current technology will help gather data on immunity in humans and animals

- **This will promote**
  - Organic growth of the field of DIT
  - Harmonized approaches to testing paradigms,
  - Improved drug risk guidance, internationally