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
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