National Heart, Lung, and Blood Institute
State of the Science Workshop

Factor VIII Inhibitors: Generating a National Blueprint for Future Research

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FDA-CERSI Collaborative Workshop
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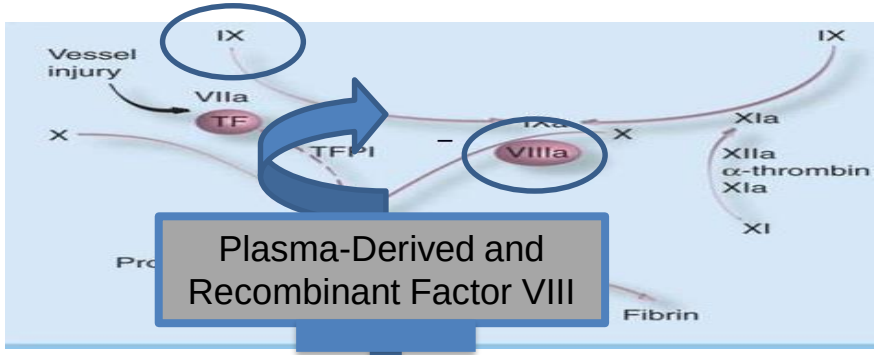
National Heart, Lung, and Blood Institute

Disclosures

- No conflicts of interest to disclose

Inhibitors of Healthy Outcomes in Hemophilia A



Plasma-Derived and Recombinant Factor VIII

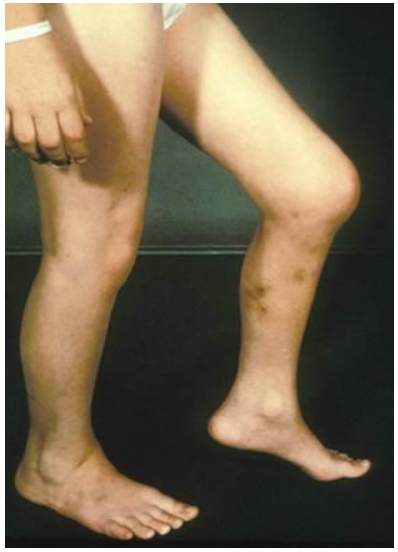
Polyclonal Neutralizing Anti- Factor VIII IgG4 Antibody

25-30% Severe Hemophilia A

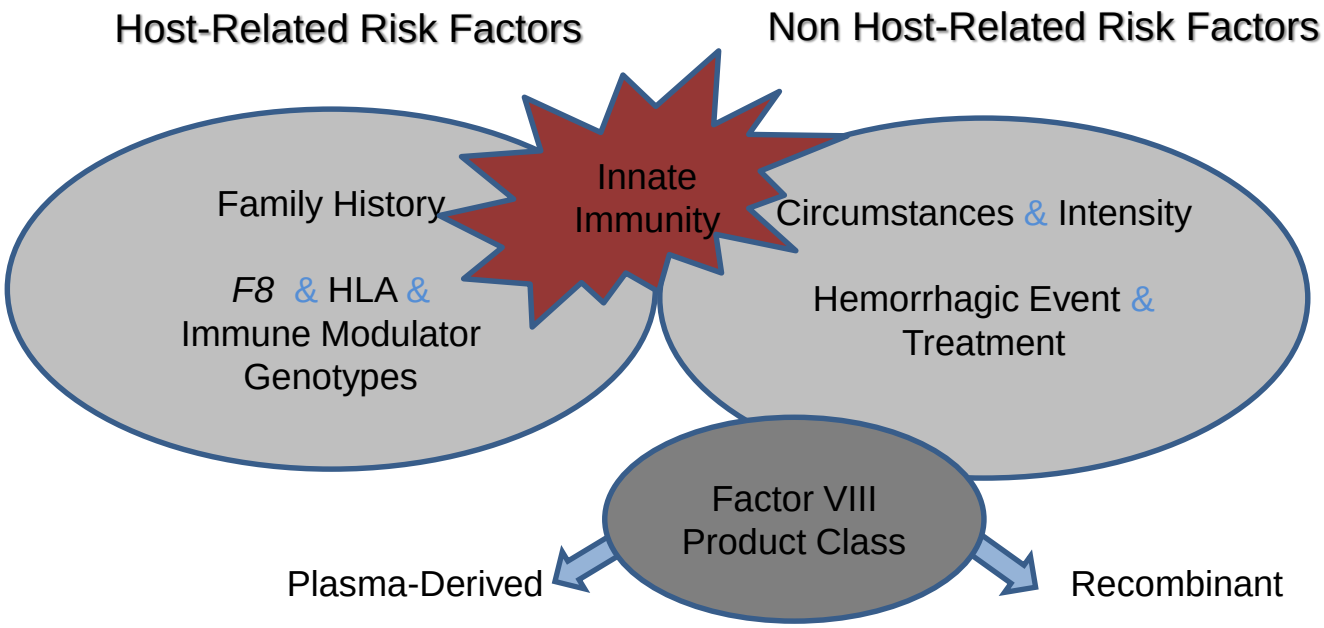
Median FVIII Exposures: **14.5**

Median Age : **15.5 mo**

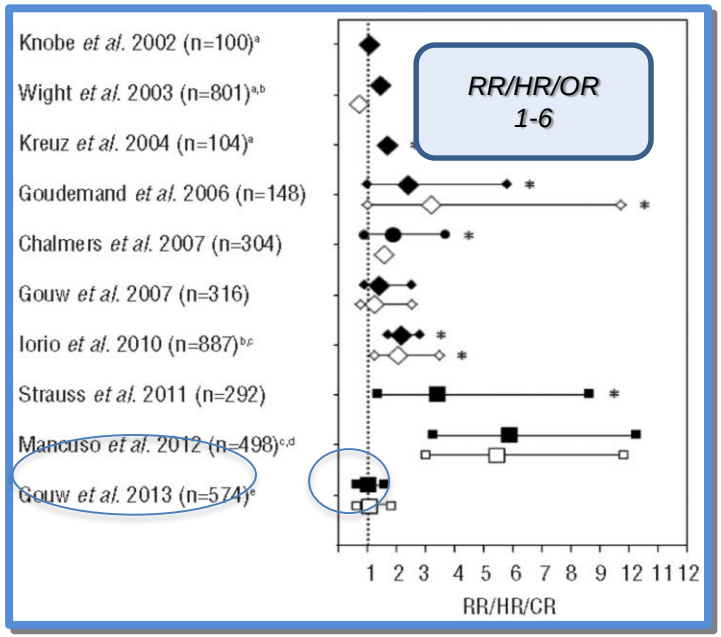
Impacts Treatment and Health Outcomes



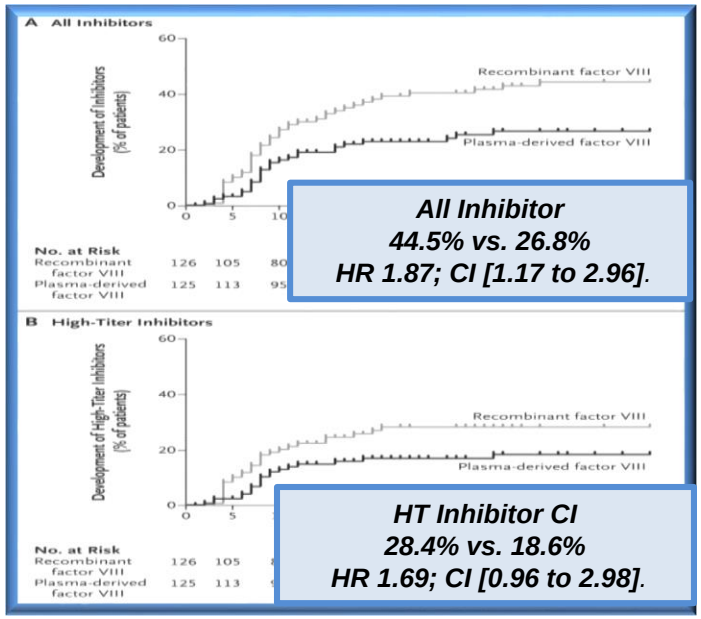
Complexity of Factor VIII Immunogenicity



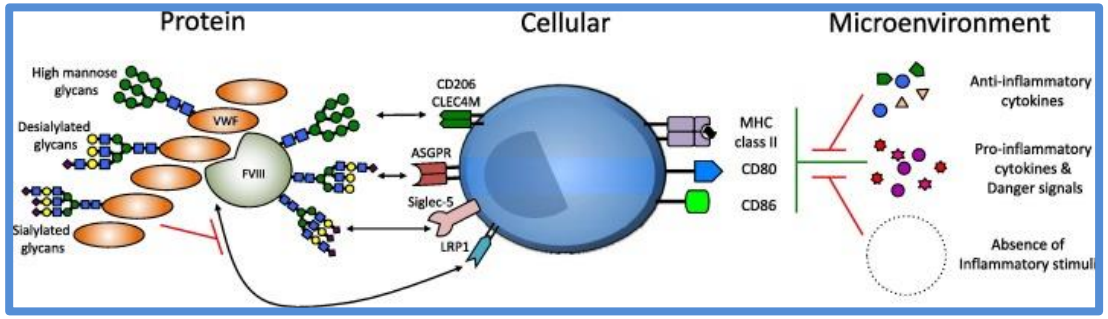
Bedside to Bench: Back to Basic



Oldenburg et al, Haematologica ,2015



Peyvandi *et al*, NEJM, 2016



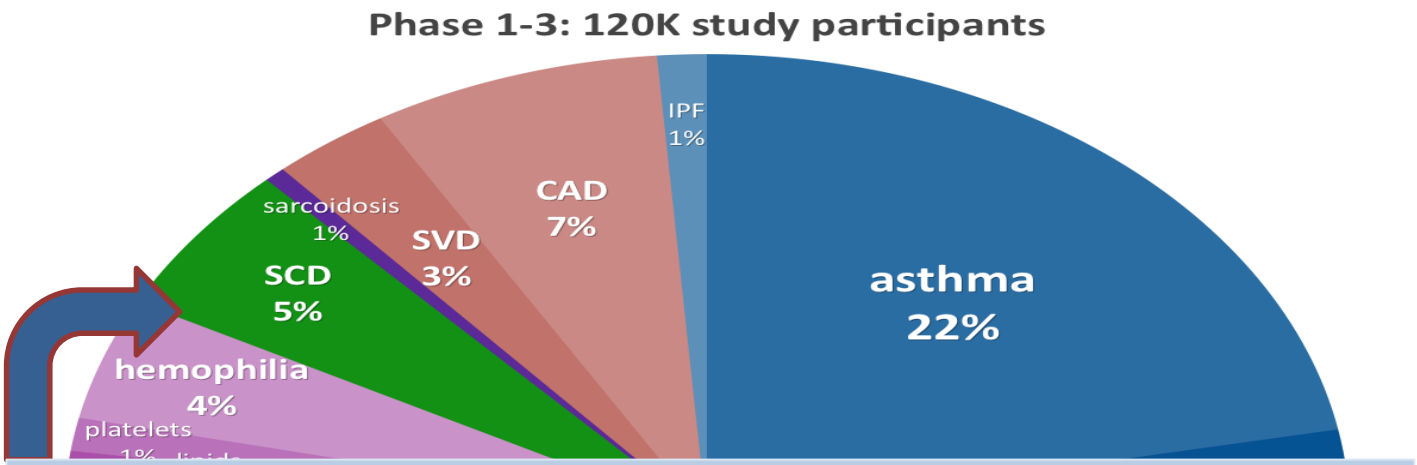
Lai *et al*, Cellular Immunology,2015

NHLBI: Centers for the Investigation of Factor VIII (FVIII) Immune Response in Patients with Hemophilia A (U54)

Published March 30, 2017; Awards July 2018
https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-18-014.html

- *Research Centers of Excellence with the aim of investigating and definitively elucidating the mechanistic and translational mechanisms of FVIII immunogenicity,*
- *Using novel, interdisciplinary, bold new approaches to defining FVIII protein-specific triggers and mechanisms underlying development of anti-FVIII neutralizing antibodies.*
- *In addition to the currently active scientific disciplines in this field, Centers will be required to include emerging sciences and technologies not currently being exploited in this research area in proposed research*
- *Cross-training of the next generation of physicians/scientists with interdisciplinary research skills.*

NHLBI: TOPMed Program
Opportunity to Look Beyond the Lamp Post



Hemophilia Blood Disease Cohort (*Genetic Modulation of Inhibitor Risk in Hemophilia)*

- **Source:**
  - MLOF: biospecimens
  - ATHN: clinical phenotype data
- Cohort sample size: 5142
- PI: Barbara Konkle

Origins of FVIII Inhibitor SOS Workshop

- *MASAC Inhibitor Prevention & Eradication WG Working Group.*
  - Approved by MASAC 10/16.
  - Charter established 3/17
  - *Mandate to engage the hemophilia community in the development of a national scientific agenda that would ensure the coordinated future conduct of the most efficient and impactful research on FVIII inhibitor prevention and eradication*

NHLBI/DBDR FVIII Inhibitor State of the Science Workshop

Goal of the Workshop

To solicit input from the wide hemophilia community and experts from outside the field into the development of a coordinated US- based blueprint for future basic, translational, and clinical research focused on FVIII immunogenicity and FVIII inhibitor prevention/eradication

May 15 -16, 2018

Executive Steering Committee Workshop Co-Chairs

Workshop Co-Chairs

Keith Hoots
NHLBI

Craig Hooper
CDC

Mike Soucie
CDC

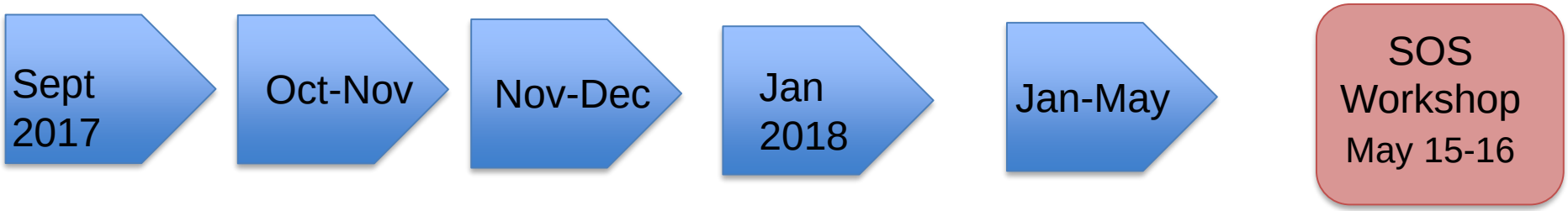
Diane Nugent
CHOC

Denise Sabatino
CHOP, U Penn

Steven Pipe
U Michigan

Assembly of the SOS Inhibitor Workshop

Evolution of the SOS Workshop



Executive Steering Committee (EC) Finalized

EC established scientific focus and leadership for scientific Working Groups (WG)

WG member expertise identified and candidates nominated

WG members appointed and WG formed

WG and subgroup bi-weekly discussions to determine scientific priorities in designated area to be presented

NHLBI FVIII Inhibitor State of the Science Workshop WGs

- ***Working Group # 1***
  - Scientific priorities for clinical trials including GT; as well as novel approaches and strategic partnerships for facilitating clinical trials.
- ***Working Group # 2***
  - Scientific priorities and platforms for optimized 21st century data and bio-specimen collection for observational cohort studies and beyond.
- ***Working Group # 3***
  - Scientific priorities for achieving an actionable understanding of FVIII immunogenicity and the immunology of host immune response and tolerance, for predictive modeling and design of novel interventions.
- ***Working Group # 4***
  - Design of longitudinal pregnancy/ birth cohorts that leverage 'omics', existing phenotypic data, and *in silico* predictive modeling to study FVIII immunogenicity, and precision medicine interventional approaches to inhibitor prevention and eradication

Working Group Chairs

Working Group 1

Lindsey George

Margaret Ragni

Working Group 2

Barbara Konkle

Michael Recht

Working Group 3

Roland Herzog

Shannon Meeks

Working Group 4

Deborah Brown

Jill Johnsen

NIH National Heart, Lung, and Blood Institute

Generating a National Blueprint for Future Research

Welcomed >200 registered participants

- 50% : Academia/ HTC staff
- 20% : Industry (19 companies)
- 18% : Federal Partners (7 agencies)
- 8% : Patient Advocacy (6 non-profit organizations)

Broad geographic representation

- 29/50 states & DC
- 9 countries

videocast home page.

State of the Science Workshop Agenda at a Glance

Day 1

Working Group Co-Chairs presented research priorities; implementation plans f/b general discussion

WG discussion introduced by key note address on the topic by speakers from outside field

Day 2

Working Group breakouts with Workshop participants

Revised presentations by Working Group Co-Chairs based on Workshop input f/b final large group discussion

Key Note Speakers

Charles Bailey, M.D., Ph.D.
CHOP, U Penn

Elizabeth Mellins, M.D.
Stanford University

Jennifer Gladys Mulle, MHS, Ph.D.
Emory University

Nicholas J. Schork, Ph.D.
City of Hope/TGen
J. Craig Venter Institute
UCSD

Clinical Working Group # 1

Scientific priorities for clinical trials; novel approaches and strategic partnerships for facilitating clinical trials

- ***Scientific priorities included:***
  - The design of investigator- initiated CTs to determine optimal integration of non-IV, non-factor novel therapeutics, including gene therapy, into care plans for FVIII inhibitor pts.
  - The design of follow-on gene therapy trials in children and adults with inhibitors

- ***Clinical trial implementation discussion encompassed:***
  - Challenges associated with conducting small clinical trials in rare diseases; resources and partnerships required to facilitate them
  - Leveraging the existing infrastructure
  - Optimizing private-public partnerships to fund clinical trials
  - Engaging the patient community in clinical trials
  - Embedding training opportunities for workforce development

State of the Science Working Group Expertise Working Group# 1 Team

Clinical Trialists (Phase 1-3)

- International expert included

Clinical Design

Biostatistics

Industry

HA Patients/ Parents

Clinical Working Group # 2

Scientific priorities and infrastructure for 21st century data and bio-specimen collection.

- *Scientific priorities discussion included:*
  - The design of prospective cohorts to ascertain comparative short and medium-term outcomes resulting from the incorporation or not, of non-IV, non-factor novel therapeutics, including GT, into care plans for FVIII inhibitor patients
  - The design of prospective cohorts to ascertain short and medium-term outcomes following ITI/ IM in children and adults with FVIII inhibitors

- *Clinical Cohort Study implementation discussion encompassed:*
  - Leveraging current data platforms
  - Incorporation of standard measures and PROs for prioritized outcomes
  - Models for direct data transfer from EMRs
  - Streamlined data sharing policies for individual patient level data
  - Challenges associated with developing and maintaining data repositories and biobanks in rare diseases; required resources and partnerships
  - Training opportunities

State of the Science Working Group Expertise Working Group# 2 Team

Epidemiology
Data Science
Cohort Development
Laboratory/ Specimen Processing
Biobanking/Repository
Human Subjects/Ethics/Data Sharing
Industry
Hemophilia Community

Basic Science Working Group # 3

Scientific priorities for generating predictive models for inhibitor development, and for acquiring an actionable understanding of FVIII immunogenicity and the immunology of both the host immune response and tolerance

- ***Scientific priorities discussion included:***
  - Application of novel ideas, technologies, cross-disciplinary science
  - Role of host cell expression of FVIII/VWF in immunogenicity
  - Gene therapy as a model for FVIII tolerance
  - Potential for rational drug design as a goal for this research

- ***Technological and logistical challenges discussion encompassed:***
  - Appropriate animal /ex vivo models (e.g., IPSCs) for immunogen expression and peptide generation
  - Characterization of biospecimens required to study mechanisms
  - Challenges, as well as resources and partners required to facilitate successful models for cross-disciplinary science

State of the Science Working Group Participants
Working Group # 3 Team

Molecular Genetics / Omics
Factor VIII Biochemistry
Immunology/ Ag-Generated Peptides
Drug Development
Gene Therapy
Animal & Ex Vivo Models
Microbiome
In Silico Protein Modeling
Industry
Patient Community/Advocacy

Working Group #3: Integrating mechanistic studies into cohort studies and clinical trials

- Adapt flow cytometry panels and T cell activation assays from clinical allergy/autoimmunity studies to the hemophilia field
- Collect samples for detailed transcriptomics and proteomics studies, as well as biomarker identification to address mechanism of inhibitor formation and of tolerance
- Study shifts in immunoglobulin subclasses/titers, B and T cell epitopes in subjects receiving conjugated FVIII or GT
- Incorporate mechanistic studies into clinical development of GT for ITI
- Microbiome studies in pregnant mothers, neonates, infants
- PUP studies on innate immune responses early in treatment

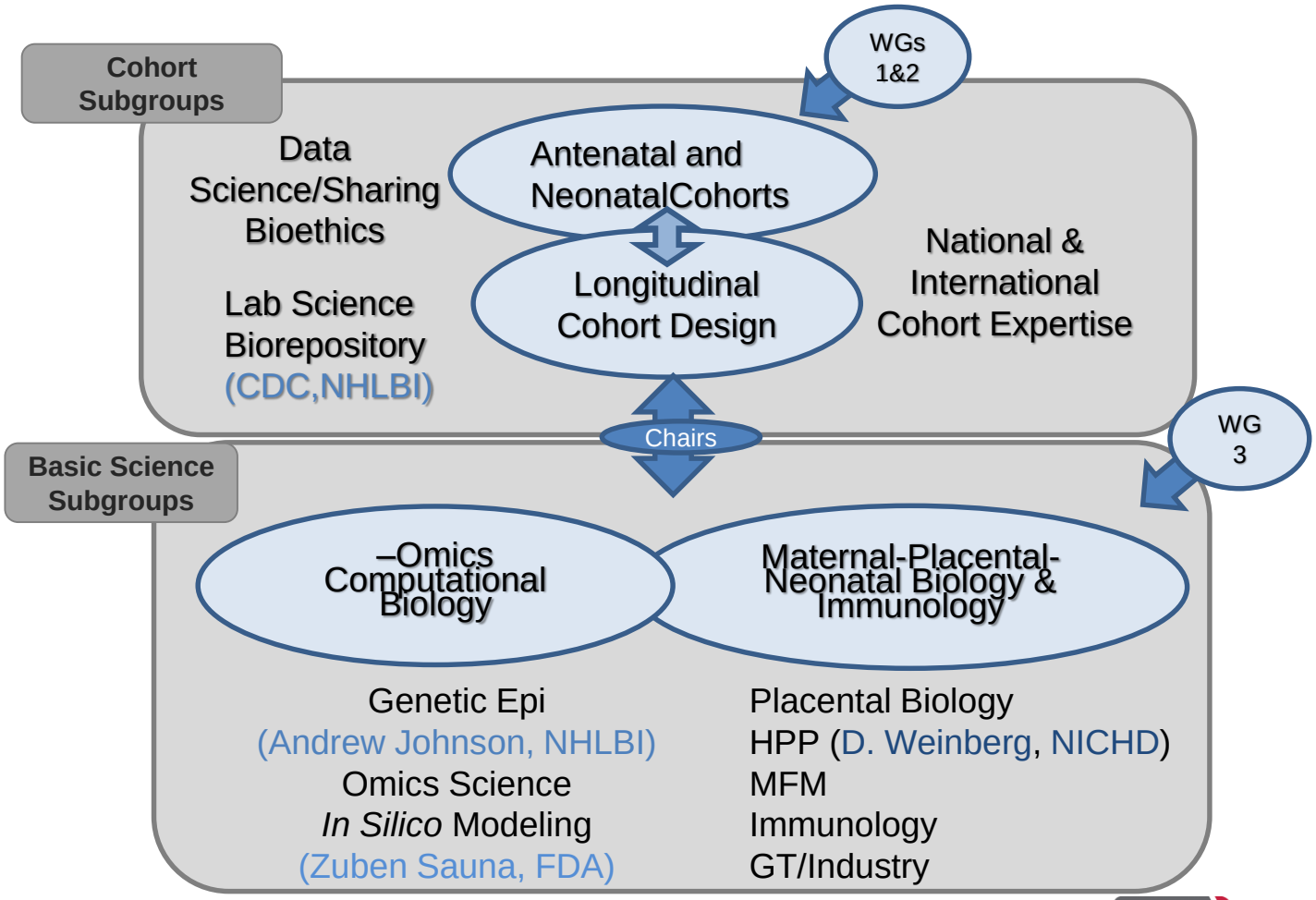
Translational Working Group # 4

Design of pregnancy/ birth longitudinal cohorts that leverage 'omics', existing phenotypic data, & *in silico* modeling to study FVIII immunogenicity & inhibitor development/ eradication

- ***Scientific priorities focused on:***
  - Design a platform for the integration of the data capture and mechanistic required to build precision (personalized) medicine-based clinical decision -making algorithms that can be applied across the lifespan to either avoid or provoke clinical phenotype for the purpose of diagnosis and/or appropriate time-sensitive antenatal and neonatal interventions based on novel target identification

- ***Implementation discussion encompassed:***
  - Challenges associated with, and successful models for building lifespan /intergenerational cohorts, as well as resources and partners required for success, including unique challenges in sample procurement and banking

State of the Science Working Group Participants
Working Group # 4



State of the Science White Paper

December , 2018

Target date for the publication of research blueprint priorities and strategies for implementation for dissemination to the national and international hemophilia community

NIH National Heart, Lung, and Blood Institute