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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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

Host-Related Risk Factors
- Family History
- $F8$ & HLA & Immune Modulator Genotypes

Non Host-Related Risk Factors
- Circumstances & Intensity
- Hemorrhagic Event & Treatment

Innate Immunity
- Factor VIII Product Class
  - Plasma-Derived
  - Recombinant

Factor VIII Product Class
- Circumstances & Intensity
- Hemorrhagic Event & Treatment

Innate Immunity
- Family History
- $F8$ & HLA & Immune Modulator Genotypes
Bedside to Bench: Back to Basic

Knobe et al. 2002 (n=100)*
Wight et al. 2003 (n=801)*
Kreuze et al. 2004 (n=104)*
Goudemand et al. 2006 (n=148)
Chalmers et al. 2007 (n=304)
Gouw et al. 2007 (n=316)
Iorio et al. 2010 (n=887)*
Strauss et al. 2011 (n=292)
Manzari et al. 2012 (n=498)*
Gouw et al. 2013 (n=574)*

RR/HR/OR 1-6

Oldenburg et al, Haematologica, 2015

Peyvandi et al, NEJM, 2016

All Inhibitor
44.5% vs. 26.8%
HR 1.87; CI [1.17 to 2.96].

HT Inhibitor CI
28.4% vs. 18.6%
HR 1.69; CI [0.96 to 2.98].

Lai et al, Cellular Immunology, 2015

RR/HR/OR

NIH
National Heart, Lung, and Blood Institute
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.
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
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
Assembly of the SOS Inhibitor Workshop

**Evolution of the SOS Workshop**

- **Sept 2017**: Executive Steering Committee (EC) Finalized
- **Oct-Nov**: EC established scientific focus and leadership for scientific Working Groups (WG)
- **Nov-Dec**: WG member expertise identified and candidates nominated
- **Jan 2018**: WG members appointed and WG formed
- **Jan-May**: WG and subgroup bi-weekly discussions to determine scientific priorities in designated area to be presented

**SOS Workshop May 15-16**
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 biospecimen 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

Working Group 2
- Margaret Ragni
- Michael Recht

Working Group 3
- Barbara Konkle
- Roland Herzog
- Shannon Meeks

Working Group 4
- Deborah Brown
- Jill Johnsen
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

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<th>Day 1</th>
<th>Day 2</th>
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<td>Working Group Co-Chairs presented research priorities; implementation plans f/b general discussion</td>
<td>Working Group breakouts with Workshop participants</td>
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<td>WG discussion introduced by key note address on the topic by speakers from outside field</td>
<td>Revised presentations by Working Group Co-Chairs based on Workshop input f/b final large group discussion</td>
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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
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
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
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
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
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.
December, 2018

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