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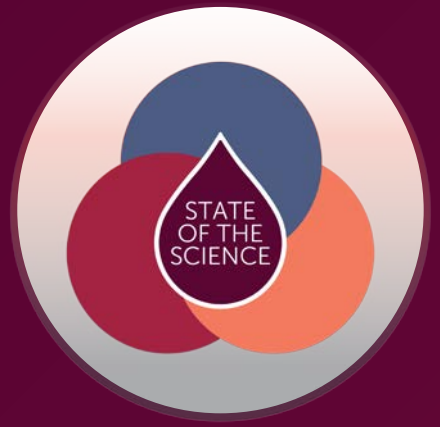

State of the Science Working Group 2

Von Willebrand Disease, Platelets, and Other Mucocutaneous Inherited Bleeding Disorders

Welcome!

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Robert F. Sidonio Jr.

Emory University

Veronica Flood

Medical College of Wisconsin

Working Group 2 Membership

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Name	IBD Community Representation
Paulette Bryant	NHF Board Member
Sarah Hale	Takeda/Industry
Meadow Heiman	Genetic counselor
Shellye Horowitz	Patient
Christi Humphrey	Social Worker
Lora Joyner	Physical Therapist
Barbara Konkle	Bleeding Disorders (Adult); SOS Steering Committee
Nikole Scappe	Patient
Kelly Tickle	Advanced Practice Nurse

Name	Expertise
Jorge Di Paola	Platelet Biology; Genomics; Vascular
Julie Jaffray	Bleeding Disorders (Pediatric)
Raj Kasthuri	HHT; Bleeding Disorders (Adult)
Peter Kouides	Bleeding Disorders (Adult)
Cindy Leissinger	Bleeding Disorders (Adult)
Bob Montgomery	VWD biology; Genomics
Keith Neeves	Microfluidics; systems biology
Anna Randi	Angiogenesis; Endothelial cell biology
Cristina Tarango	Bleeding Disorders (Pediatric)
Pamela Trapane	EDS; Connective Tissue Disorders
Michael Wang	Bleeding Disorders (Pediatric)
Brittany Waters	Dental

Working Group 2 Mandate

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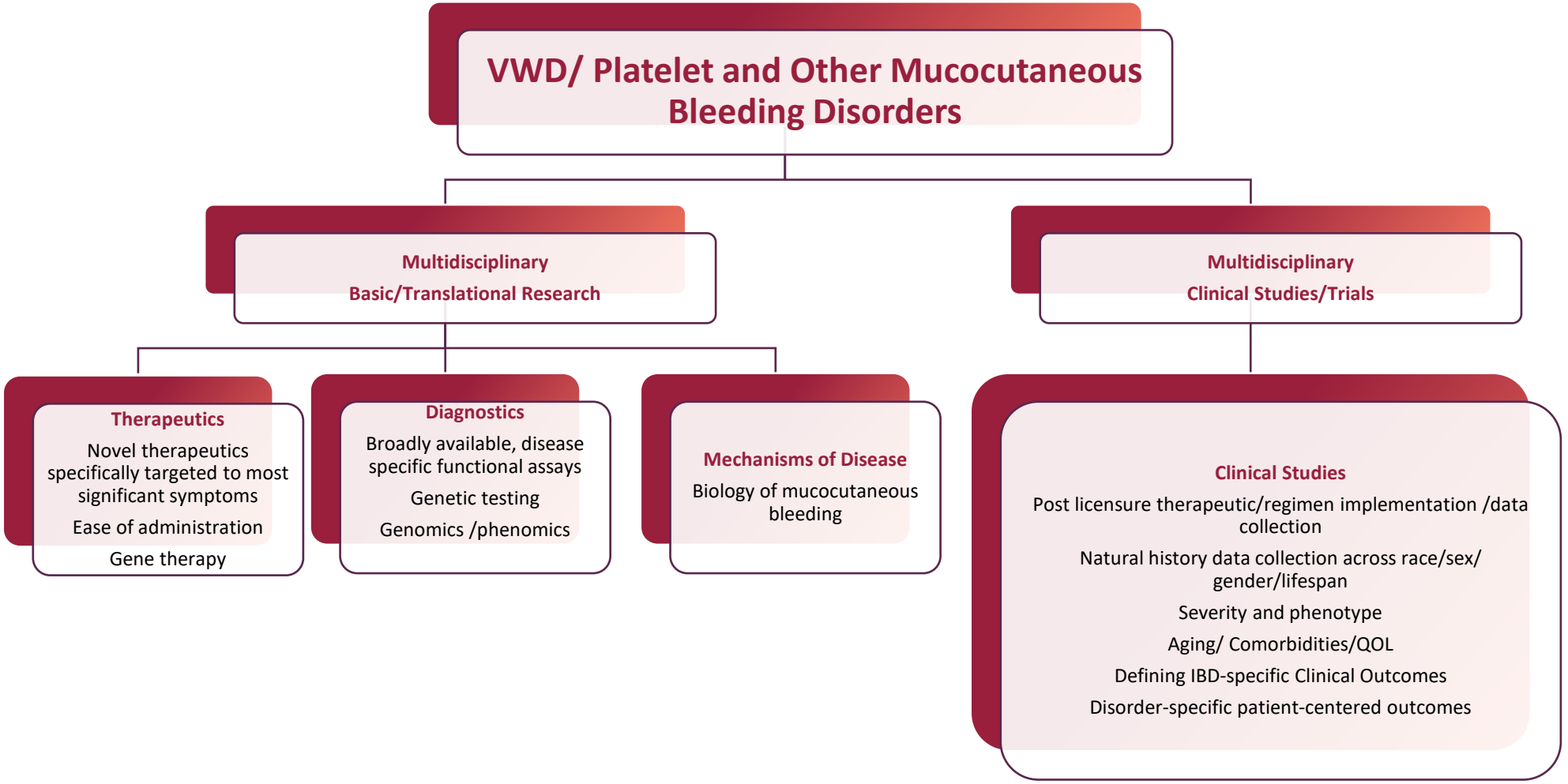

Topics Evaluated

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- Von Willebrand disease (VWD)
- Inherited platelet defects (IPD)
- Ehlers-Danlos syndrome (EDS)
- Hereditary Hemorrhagic Telangiectasias (HHT)
- Bleeding of Undetermined Cause (BUC)
- Novel Therapeutics
- Aging
- Biology of Mucocutaneous Bleeding

Major Themes

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Better understanding of basic biology

How do blood cells and proteins interact with their environment?

How does this interaction differ in various tissues?

What happens to this interaction with VWD/EDS/HHT?

Natural history of mucocutaneous bleeding disorders

What happens as patients age?

Better diagnostic testing (and definitions) for these disorders

Creative use of novel therapies

Biology of Mucocutaneous Bleeding

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Question	Score
Can we define the differences in the biology in the various parts of the mucocutaneous locations (environment differences between GI tract, nasal tissue and uterus; different mucins, rheology etc).	19
In patients with VWD is there an inherent defect in wound healing, and if so in which tissues?	19
What is the role of hormones (including gender), menstruation, pregnancy, and periomenopausal time period on the vessel environment related to mucocutaneous bleeding?	18
Can we characterize the pathways mediating the interaction of platelets and plasma proteins with the different, tissue-specific vascular beds and extravascular space?	18
What is the role of vascular mural cells (e.g. pericytes) in the control of haemostasis and mucocutaneous bleeding?	17
Are there functions of VWF in regulating vascular integrity and other functions that are not currently measurable which could contribute to mucocutaneous bleeding?	17

Biology of Mucocutaneous Bleeding

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Question	Score
What is the contribution of blood vessel associated pathways and the extracellular matrix and the microenvironment to mucocutaneous bleeding?	16
How do we develop better animal and in vitro (organ and blood vessel on a chip, ECFC cells/personalized) models that better capture the contribution of the microenvironment to mucocutaneous bleeding?	14
What is the role of the interaction between VWF and various proteins (ECM, growth factor interactions) in the regulation of hemostasis and vascular integrity?	14
What is the biologic difference in in the microenvironments (uterus, nose, GI tract) of EDS and HHT compared to VWD?	13

Von Willebrand Disease

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Question	Score
Can we longitudinally characterize the joint health in patients with VWD? (to include bone and joint changes, physical therapy assessment, pain symptoms and clinical function for all VWD subtypes)	21
Can we improve diagnostic VWD testing that does not rely on specialized coagulation labs?	19
Can emicizumab be used effectively as subcutaneous therapy (prophylaxis) for patients with severe VWD?	18
What can be done to better understand the male journey with VWD?	13
How can we use anti-angiogenesis agents for management of certain bleeding symptoms in patients with severe VWD?	12

Inherited Platelet Defects

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Question	Score
What is the natural history in patients with mild qualitative platelet function defects? (to include quality of life as well as bleeding symptoms evolution as patients age)	19
How can we optimize management of mild qualitative platelet function defects?	15
What is the relationship of medications with some mild qualitative platelet function defects?	13
How can we improve and standardize platelet function testing beyond platelet aggregation and establish standardization for the diagnostic testing for IPDs?	13

EDS, HHT, and BUC

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Question	Score
Can we define a cohort of patients with bleeding of unknown cause and characterize them longitudinally? (would require definition of BUC, and standardize the workup to exclude other causes)	24
Can we develop a collaborative effort in longitudinal evaluation and surveillance of EDS, HHT and BUC within the HTC network?	24
How does iron deficiency affect the bleeding and thrombotic risk in HHT?	23
What is the risk of thrombosis in HHT and why? Can we determine the prevalence of thrombosis?	21
What is the mechanism of the coagulation defect in HHT?	20

EDS, HHT, and BUC

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Question	Score
What is the appropriate hemostatic evaluation for patients with BUC, particularly rare fibrinolytic defects and TFPI disorders?	17
Can we develop a national biorepository for samples from patients without a diagnosis including those with BUC?	13
Is there a molecular diagnosis that can confirm of diagnosis of hypermobile EDS?	10

Novel Therapeutics

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Question	Score
Is it possible to develop aptamer-based treatments for hemostatic management of mild MC bleeding disorders?	16
Can VWF be modified to be given subcutaneously to treat patients with VWD?	12
Are there other drugs with crosssover potential to treat BUC and mild qualitative platelet function defects?	12
Do genetic differences in endothelial cells affect desmopressin response?	11
Can DDAVP be optimized for management of bleeding in VWD?	9

Aging

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Question	Score
Do persons with mild MC bleeding disorders develop joint damage and does this change with age (includes how this affects ADLs and venous access)?	20
Does QOL change with age in patients with mild MC bleeding disorders?	20
Is there an effect on bone and joint health in mild MC bleeding disorders (including VWD and platelet defects) and is it accelerated over time?	19
How can we optimize antiplatelet therapy in older patients with CVD and mild MC bleeding disorders including VWD?	19
Does the surgical bleeding risk change with age in patients with mild MC bleeding disorders?	18
What happens with VWF levels over the lifespan? (to include normal values for age and what value is needed to prevent bleeding by age, which gets at the question of whether one can outgrow VWD?)	16

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Discussion