Enabling Research in Rare Hematologic Disorders

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Taking stock of clinical research priorities, 2009

- **NHLBI State of Science (SoS) Symposium in Transfusion Medicine and Hemostasis/Thrombosis (9/2009)**
  - Aims to identify Phase II and III clinical trials that could have significant impact in advancing transfusion therapies or treatment for hemostatic or thrombotic disorders, and
  - To provide a forum for investigators to discuss clinical research needs

- **NHLBI Working Group (11/2009)**
  - Aim to identify clinical priorities and the resources needed to advance research for hemophilia and rare hemostasis and thrombosis disorders
Clinical research priorities, 2009 (con’t)

- SoS identified 19 clinical trial concepts in hemostasis and thrombosis area
  - treatment of DVT in children, prophylaxis for adults with severe hemophilia, treatment of ITP, and prevention or therapy for venous thromboembolism in specific patient populations

- Expert panel concluded
  - no shortage of investigators with an excellent grasp of next problems to be solved
  - numerous phase II-III clinical trials that if conducted successfully could have impact on the standard of healthcare
  - subject matter experts most aware of the clinical needs may not have the resources necessary to successfully develop, conduct and complete these challenging trials
Recommendations

- 2-stage process for investigator initiated clinical trials
  - The first stage provides opportunity for early interaction with the core investigators and support for finalizing the protocol, identification of participating centers, approval of the clinical trial by IRBs, submission of an IND/IDE to FDA if required, refining recruitment strategies etc.
  
  - The second stage would be full-scale implementation.
Recommendations

- Need for a mechanism for pairing investigators with a clinical trials core organization that can support the investigators for functions typically carried out by a contract research organization
  - clinical trial design and recruitment strategies in rare diseases
  - biostatistical support
  - regulatory support for IND/IDE submission
  - preparing clinical protocol, manual of procedures, training materials, consent forms and data safety monitoring plan
  - data capture and data management systems
NHLBI’s response to SoS recommendations

- Promote investigator-initiated clinical research by providing mechanisms and resources to aid in development and successful completion of studies

  - NHLBI Clinical Trials Planning Studies for Rare Thrombotic and Hemostatic Disorders (U34)
    - Ragni: Feasibility of the Hemophilia INHIBIT Trial
    - Bussel: Determining Optimum Medical Therapy for ITP
    - Manco-Johnson: Clinical Trial Planning Grant in Catheter-Directed Thrombolysis of Occlusive DVT
    - 3 more U34 awards in 2014
NHLBI’s response to SoS recommendations

- NHLBI Clinical Trials Development Resource for Hematologic Disorders (U24) initiative
  - serves as a resource to U34 planning grant recipients and R34 pilot grant recipients
  - expert scientific and statistical advice, review of protocols and study materials, and training in areas relevant to the design or implementation of clinical trials in hematology
Other current NIH/NHLBI activities that enable clinical research in rare hematologic disorders

- Although U34 planning grant program is over – NHLBI supports investigator-initiated research
  - R01
  - R34 (Clinical Trial Pilot Studies)
  - Collaborative R01 (Multicenter Clinical Trials)

- Encourage investigators to talk to NHLBI project staff to find out which mechanism is best for your concept
Other current NIH/NHLBI activities that enable clinical research in rare hematologic disorders

- Recent FOA for Rare Disease Clinical Research Network (RDCRN)
  - re-issued every 5 years

- RDCRN established in 2003 by the NIH Office of Rare Diseases (overseen by NCATS)
  - Network is composed of about 2,600 researchers including NIH scientific program staff, and investigators and members of 98 patient advocacy groups; 29,000 patients enrolled in 91 clinical studies.
Other current NIH/NHLBI activities that enable clinical research in rare hematologic disorders

- Examples rare blood diseases
  - Acquired aplastic anemia, Antiphospholipid syndrome, Creutzfeldt-jakob disease (CJD), Cooley’s Anemia, Fanconi Anemia, Hemophagocytic lymphohistiocytosis, Hemophilia, Hereditary Hemorrhagic Telangiectasia (HHT), Heparin-induced Thrombocytopenia (HIT), Lymphedema, Myelodysplastic Syndrome (MDS), Myeloproliferative Disorders (MPD), Paroxysmal Nocturnal Hemoglobinuria (PNH), Rare Bleeding Disorders, Rare Nutritional Anemias, Rare Thrombotic Disorders, Rare Hemolytic Anemias, Sickle cell disease, Thalassemia, Thrombocytopenias of Different Etiologies, Thrombotic Thrombocytopenic Purpura (TTP).
Other NIH training and career development for clinical research in hematology

- Mentored Research Scientist Development Award (K01)
- Mentored Clinical Scientist Development Award (K08)
- Career Transition Award (K22)
- Mentored Patient-Oriented Research Career Development Award (K23)
- Pathway to Independence (PI) Award (K99/R00)
Other mechanisms for developing and implementing clinical research

- HTRS – Hemostasis and Thrombosis Research Society
  - Mentored Research Awards
- THSNA- Thrombosis and Hemostasis Societies of North America
  - Mentored Research Award
- NASTH- North American Society of Thrombosis and Hemostasis
- ASH – American Society for Hematology
  - Research Training Award for Fellows (RTAF)
  - Scholar Awards (basic or clinical; 1-3 years; fellow or junior faculty)
  - ASH/Harold Amos Medical Faculty Development Program
Successes and Missed Opportunities

- Clinical trial planning grants (U34) and pilot study grants (R34) allow researchers protected time “off the clock” to plan and beta-test complex clinical trials provided valuable funding and time to develop concept.
Existing infrastructure

- Hemophilia Treatment Centers & field clinics (HRSA, CDC)
- Transfusion Medicine Hemostasis Network (NHLBI)
- US Thrombosis and Hemostasis Centers (CDC network)
- Oncology groups: COG etc., (for thrombosis and cancer)
- American Thrombosis and Hemostasis Network (ATHN)
  - database development, emergency preparedness, support for data managers at HTC’s

- Registries
  - HTRS: also does research, training of professionals
  - Rare Diseases Clinical Research Network
  - National/International registries (e.g. through ISTH)
### Planning the Path to Research Independence

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Young faculty has idea but needs prelim data

Applies to ATHN to interrogate national database

Uses preliminary data to obtain apply for HTRS MRA; gets statistical support thro Rho, inc

Applies for K23 using HTRS co-investigators

Attends ASH CRTI, HTRS Clinical Methodology/Grant Writing Course
Existing resources

- Federal funding for HTCs:
  - CDC (surveillance)
  - HRSA for HDS

- State support for hemophilia factor

- Industry resources: grants and clinical trials

- Professional organizations
  - ASH, ASPHO, ACOG, HTRS, ISTH, AABB, American Blood centers, American Society of Gene therapy, Venous disease coalition, PPTA, IPSS, NASCOLA

- CBO/Foundations/Advocacy organizations
  - National Hemophilia Foundation
  - Hemophilia Federation of America
  - NATT
  - HHT foundation
  - NORD