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Education & Training

03/01/92 − 05/30/93	M.D.	Clinical rotations and clerkships Medical Scientist Training Program Emory University School of Medicine
07/01/88 − 02/30/92	Ph.D.	*Mentor: Kenneth E. Bernstein, M.D.* Pathology and Laboratory Medicine Emory University School of Medicine
07/01/86 − 06/30/88	M.D.	Preclinical coursework Medical Scientist Training Program Emory University School of Medicine
01/03/82 − 06/10/86	B.S.	Biochemistry (Departmental Honors) University of California at Los Angeles

Postgraduate Training

07/01/98 – 06/30/00	NRSA Post-Doctoral Fellowship (NHLBI; T32 funded) *Mentor: Steven T. Warren, Ph.D.* Professor Department of Biochemistry Emory University School of Medicine
07/01/97 – 06/30/98	NRSA Post-Doctoral Fellowship (NHLBI; T32 funded) *Mentor: J.S. (Pete) Lollar, M.D.* Professor Dept. of Medicine, Division of Hematology and Oncology Emory University School of Medicine
01/01/97 – 12/30/97	Clinical Hemostasis Laboratory Fellowship *Mentor: Alexander Duncan, M.D.* Director, Special Hemostasis Laboratory

	Pathology and Laboratory Medicine Emory University School of Medicine
07/01/93 – 12/31/96	Internship & Residency Anatomic and Clinical Pathology Pathology and Laboratory Medicine Emory University School of Medicine

Major Research Interests & Areas of Technical Expertise

PREDICTIVE & PERSONALIZED MEDICINE

Developing an Immunogenomics-based Diagnostic for Hemophilia A with Improved FVIII Immunogenicity Risk Prediction as well as Personalized FVIII Protein & Gene-based Therapeutics with Greater Safety and Efficacy:

Intravenous infusion of either plasma-derived (pd) or recombinant (r) concentrates of wild-type FVIII molecules is the standard therapy for arresting and preventing bleeding in patients with HA. Unfortunately, ~25% of all patients develop neutralizing anti-FVIII alloantibodies ("inhibitors") that leave them refractory to further replacement therapy. Because patients with inhibitors have higher levels of morbidity and mortality, alloimmunization is the most significant complication of treating this disorder. Race is a well-established risk factor for inhibitor development in that the same FVIII therapeutics are immunogenic about twice as often in black compared to white HA patients managed by the same medical teams at the same treatment centers. We discovered four nonsynonymous-single-nucleotide polymorphisms (ns-SNPs) in the FVIII gene (*F8*) whose allelic combinations (haplotypes) encode six distinct wild-type forms of the FVIII protein designated H1-H6. While all but H6 are expressed by blacks, only H1 & H2 --- which represent the two rFVIII products available clinically and the two FVIII proteins expected to predominate in existing pdFVIII concentrates due to the demographics of blood donors --- are expressed by whites. Moreover, ~27% of blacks express H3, H4 or H5, which differ structurally from the H1 & H2 rFVIII products at three ns-SNPs (R484H, D1241E & M2238V), two of which are located in immunodominant inhibitor epitopes and have black-restricted minor alleles. We recently found that allogeneically-mismatched therapy (i) is a novel risk factor for inhibitor development, but only in patients whose HA-causing *F8* mutation types are "pharmacogenetically-relevant" --- we coined this phrase to indicate those *F8* abnormalities that encode all or most of an endogenous (albeit dysfunctional) FVIII protein, whether it is expressed in one polypeptide chain or in two, or whether it is secreted or trapped intracellularly (we observed the latter characteristic of each of these two possibilities for the recurrent intron-22-inversion mutation, which accounts for almost half of all new severe HA patients) --- and (ii) contributes to the greater frequency of alloimmunization in patients of black African-descent. We are developing a pharmacogenomics strategy for predicting and reducing the frequency of FVIII immunogenicity based on a given patient's: (i) *F8* mutation type and its impact on the intracellular synthesis of an endogenous FVIII protein; (ii) Alleles at *F8* ns-SNPs; and (iii) HLA-class-II repertoire for exogenous peptide presentation.

Arterial & Venous Thrombosis:

My lab identifies and characterizes genetic & environmental determinants of thrombosis risk, the greatest cause of morbidity and mortality across human populations. We are focused currently on coagulation FVIII, FIX and VWF, as the plasma levels of these functionally interrelated hemostasis proteins is deficient in patients with HA, HB, and VWD, respectively, but

(often) elevated in thrombosis patients. Congenital and acquired deficiencies of ADAMTS13, which is also known as the VWF-cleaving protease, cause thrombotic-thrombocytopenic purpura (TTP), a severe thrombotic microangiopathy. Because “normal” variation in ADAMTS13 activity across its reference range contributes to thrombosis risk in larger caliber vessels, we also study this (patho)physiologically related protein. Finally, we study the genetic contribution to variability in platelet parameters (e.g. platelet count, mean platelet volume, and platelet distribution width) and other CBC traits as novel quantitative determinants of thrombosis risk. We anticipate translating our findings into the development of (i) improved diagnostic algorithms that allow earlier and more accurate identification of “at risk” individuals, (ii) prophylactic regimens for asymptomatic risk reduction, and (iii) new therapeutic agents that are more efficacious and/or safe.

Publications

Published, accepted or submitted research in peer reviewed journals

Howard, T.E., Shai, S., Langford, K., Martin, B., and Bernstein, K. Transcription of testicular angiotensin-converting enzyme (ACE) is initiated within the 12th intron of the somatic ACE gene. Mol Cell Biol. 10(8):4294-4302, 1990.

Langford, K., Shai, S., **Howard, T.E.**, Kovac, M., Overbeek, P., and Bernstein, K. Transgenic mice demonstrate a testis specific promoter for angiotensin converting enzyme (ACE). J Biol Chem. 266(24):15559-15562, 1991.

Howard, T.E., Balogh, R., Overbeek, P., and Bernstein, K. Sperm-specific expression of angiotensin-converting enzyme (ACE) is mediated by a 91-base pair promoter encoding a CRE-like element. Mol Cell Biol. 13(1):18-27, 1992.

Esther, C., **Howard, T.E.**, Marino, E., Goddard, J., Capecchi, M., and Bernstein, K. Angiotensin converting enzyme (ACE) deficient mice have low blood pressure, renal pathology, and reduced male fertility. Lab Invest. 74(5):953-965, 1996.

Hardman, W., Benian, G., **Howard, T.**, McGowan, J., Metchock, B., and Murtagh, J. Rapid detection of mycobacteria in inflammatory necrotizing granulomas from paraffin embedded tissue by PCR in clinically high risk patients with acid fast stain and culture negative biopsies. Amer J Clin Path. 106(3): 384-389, 1997.

Esther, C., Marino, E., **Howard, T.E.**, Machaud, A., Corvol, P., Capecchi, M., and Bernstein, K. The critical role of tissue angiotensin-converting enzyme (ACE) as revealed by gene targeting in mice. J Clin Invest. 99(10):2375-2385, 1997.

Howard, T.E., Marusa, M., Channell, C., and Duncan, A. A patient homozygous for a mutation in the prothrombin gene 3’-untranslated region associated with massive thrombosis. Blood Coagul Fibrinolysis. 8(5):316-319, 1997.

Howard, T.E., Marusa, M., Boysza, J., Young, A., Sequeira, J., Channell, C., Guy, C., Benson, E., and Duncan, A. The prothrombin gene 3’-untranslated region mutation is frequently associated with factor V Leiden in thrombophilic patients and shows ethnic-specific variation in allele frequency. Blood. 91(3):1092, 1998.

Meng, X., Cui, D., Murphy, T., and **Howard, T.E.** Terminal intron splicing of the prothrombin pre-mRNA is associated with 3'-cleavage site recognition and polyadenylation. ISTH Abstract. J Thromb Haemost. 1(1):P0367, 2003.

Howard, T.E., Channell, C., Waddy, S., Benson, E., and Duncan, A. Phospholipid-dependent impairment of the inhibitory properties of hirudin: the cause of false-positive assays for lupus anticoagulants (LAs). ISTH Abstract. J Thromb Haemost. 1(1):P2059, 2003.

Viel, K., Almasy, L., Soria, J., Khachidze, M., Machiah, D., Souto, J., Fontcuberta, J., Blangero, J., and **Howard, T.E.** Functional resequencing of the factor (F)VIII gene: identifying quantitative trait nucleotides (QTNs) underlying the variation in plasma FVIII activity levels in the GAIT project. ISTH Abstract. J Thromb Haemost. 1(1):OC313, 2003.

Khachidze, M., Soria, J., Almasy, L., Souto, J., Viel, K., Blangero, J., Fontcuberta, J., and **Howard, T.E.** Functional resequencing of the factor (F)IX gene: identifying quantitative trait nucleotides (QTNs) underlying the variation in plasma FIX activity levels in the GAIT project. ISTH Abstract. J Thromb Haemost. 1(1):P0365, 2003.

Howard, T.E., Meng, X., Cui, D., Khachidze, M., Porter, S., Wilusz, J., Warren, S., and Murphy, T. The G20210A mutation is a common thrombosis risk factor that modulates prothrombin mRNA stability independent of cleavage and polyadenylation. ASH Abstract. Blood. 102(11): 118(#179), 2003.

Howard, T.E., Machiah, D., Tran, T., Viel, K., Channell, C., Soria, J., Ameri, A., Iyer, R., Brown, C., Doering, C., Almasy, L., Watts, R., Davis, J., and Abshire, T. African-Americans express multiple haplotypic forms of the wildtype factor (F)VIII protein: a possible role for pharmacogenetics in FVIII inhibitor development? ASH Abstract. Blood. 104(11):384, 2004.

Ameri, A., Machiah, D., Livingston, D., Tran, T., Channell, C., Toren, K., Crenshaw, V., and **Howard, T.E.** A novel 5-bp deletion mutation in the factor (F)X gene, designated FX-Augusta, causes severe FX deficiency possibly by a unique mechanism involving mRNAs that lack in-frame stop codons. ASH Abstract. Blood. 104(11):1045, 2004.

Sabater, M., Soria, J., Khachidze, M., Meng, X., Almasy, L., Souto, J., Fontcuberta, J., Blangero, J., and **Howard, T.E.** Confirmation of a new statistical method for comprehensively dissecting QTLs using in vitro transcription, the model factor VII gene and a novel modification of the G-free cassette. ASH Abstract. Blood. 104(11):4002, 2004.

Viel, K., Khachidze, M., Buil, A., Soria, J., Souto, J., Fontcuberta, J., Blanco-Vaca, F., Ordoñez, J., Almasy, L., and **Howard, T.E.** A quantitative trait locus for cholesterol and low-density-lipoprotein within the promoter of the factor IX gene. ASH Abstract. Blood. 104(11):4000, 2004.

Howard, T.E., Machiah, D., Viel, K., Channell, C., Ameri, A., Iyer, R., Watts, R., Lutcher, C., Davis, J., Abshire, T., and Almasy, L. The Pharmacogenetics and Inhibitor Risk (PIR) study: establishing the spectrum of factor VIII gene mutations in African-American hemophilia-A patients. ASH Abstract. Blood. 106(11):3207, 2005.

Viel, K., Warren, D., Buil, A., Dyer, T., **Howard, T.E.**, and Almasy, L. A comparison of discrete versus continuous environment in a variance components based linkage analysis of COGA data. BMC Genetics. 6(Suppl 1):S57, 2005.

Khachidze, M., Buil, A., Warren, D., Viel, K., Shen, M., Porter, S., Channell, C., Ameri, A., Soria, J., Souto, J., Lathrop, M., Blangero, J., Fontcuberta, J., Warren, S., Almasy, L., and **Howard, T.E.** Genetic determinants of normal variation in coagulation factor IX levels: genome-wide scan and examination of the F9 structural gene. J Thromb Haemost. 4(7):1537-1545, 2006.

Howard, T.E., Viel, K.R., Fernstrom, K.M., Deshpande, S., Ameri, A., Ali, M.S., Channell, C., Iyer, R.V., Watts, R.G., Lutcher, C., Nakaya, S., Kasper, C.K., Thompson, A.R., Abshire, T.C., and Almasy, L. Allelically mismatched replacement therapy due to common African-restricted haplotypes of the factor (F)VIII protein may underlie the increased incidence of FVIII inhibitors observed in hemophilia-A patients of African-descent. ASH Abstract. Blood. 108(11):765, 2006.

Viel, K., Machiah, D., Warren, D., Buil, A., Souto, J., Perlito, J., Blangero, J., Smith, T., Porter, S., Fontcuberta, J., Soria, J., Flanders, D., Almasy, L., and **Howard, T.E.** A sequence variation scan of the coagulation factor (F)VIII structural gene and associations with FVIII activity levels. Blood. 109(9):3713-3724, 2007.

Sabater-Lleal, M., Chillón, M., **Howard, T.E.**, Gil, E., Almasy, L., Blangero, J., Fontcuberta, J., and Soria, J.M. Functional analysis of the genetic variability in the F7 gene promoter. Atherosclerosis. 195(2):262-8, 2007.

Ameri, A., Machiah, D.K., Tran, T.T., Channell, C., Crenshaw, V., Fernstrom, K., Khachidze, M., Duncan, A., Fuchs, S., and **Howard, T.E.** A nonstop mutation in the factor (F)X gene of a severely haemorrhagic patient with complete absence of coagulation FX. Thromb Haemost. 98(6):1165-9, 2007.

Viel, K.R., Ameri, A., Abshire, T.C., Iyer, R., Watts, R., Lutcher, C., Channell, C., Cole, S.A., Fernstrom, K.M., Nakaya, S., Kasper, C.K., Thompson, A.R., Almasy, L., and **Howard, T.E.** Inhibitors of Factor VIII in black hemophilia patients. N Engl J Med. 360(16):1618-27, 2009.

Freed, K.A., Blangero, J., Abboud, H.E., **Howard, T.E.**, Johnson, M.P., Curran, J.E., Garcia, Y.R., Lan, H-C., and Moses, E.K. The 57-kb deletion in cystinosis patients extends into TRPV1 causing dysregulation of transcription in peripheral blood mononuclear cells. J Med Genet. 48(8):563-6, 2011.

Jankowski W, Park Y, McGill J, Maraskovsky E, Hofmann M, Diego VP, Luu BW, **Howard T.E.**, Kellerman R, Key NS, Sauna ZE. Peptides identified on monocyte-derived dendritic cells: a marker for clinical immunogenicity to FVIII products. Blood Adv. 2019 May 14;3(9):1429-1440. doi: 10.1182/bloodadvances.2018030452. PubMed PMID: 31053570; PubMed Central PMCID: PMC6517663.

Howard T.E., Diego VP, Luu BW, Curran J, Blangero J, Williams-Blangero S. Health disparities in inhibitor development in Hemophilia A: Hypotheses on the differential prevalence by race/ethnicity. University of Texas Rio Grande Valley School of Medicine 2nd Annual Research Symposium. 2018 September.

Howard T.E., Diego VP, Hofmann M, Almeida M, Luu BW, Dinh LV, Rajalingam R, Escobar M, Curran J, Williams-Blangero S, Powell J, Blangero J, Maraskovsky E, Key NS, Sauna ZE. Analysis of HLACII peptidomes presented by dendritic cells (DCs) from healthy donors and Hemophilia A (HA) patients with or without Factor VIII (FVIII) inhibitors after ex vivo administration of different therapeutic FVIII proteins (tFVIIIs). Human

Immunology. 2018; 79(Supplement):103-104.

Sauna ZE, V D, Almeida M, Luu B, Hofmann M, Hernandez J, Rajalingam R, Blangero J, **Howard T.E.** Analysis of HLA-class-II (HLAcII) peptidomes in response to several therapeutic factor (F)VIII proteins (tFVIIIs) in healthy donors and Hemophilia A (HA) patients with and without FVIII Inhibitors (FEIs). Research and Practice in Thrombosis and Haemostasis. 2018; 2(S1):94.

Sauna ZE, Lozier JN, Kasper CK, Yanover C, Nichols T, **Howard T.E.** The intron-22-inverted F8 locus permits factor VIII synthesis: explanation for low inhibitor risk and a role for pharmacogenomics. Blood. 2015 Jan 8;125(2):223-8. doi: 10.1182/blood-2013-12-530113. Epub 2014 Nov 18. Review. PubMed PMID: 25406352; PubMed Central PMCID: PMC4287634.

Pandey GS, Yanover C, Miller-Jenkins LM, Garfield S, Cole SA, Curran JE, Moses EK, Rydz N, Simhadri V, Kimchi-Sarfaty C, Lillicrap D, Viel KR, Przytycka TM, Pierce GF, **Howard T.E.**, Sauna ZE. Endogenous factor VIII synthesis from the intron 22-inverted F8 locus may modulate the immunogenicity of replacement therapy for hemophilia A. Nat Med. 2013 Oct;19(10):1318-24. doi: 10.1038/nm.3270. Epub 2013 Sep 15. PubMed PMID: 24037092; PubMed Central PMCID: PMC4123441. (NOTE: T.E. Howard is co-corresponding author).

Pandey GS, Yanover C, **Howard T.E.**, Sauna ZE. Polymorphisms in the F8 gene and MHC-II variants as risk factors for the development of inhibitory anti-factor VIII antibodies during the treatment of hemophilia a: a computational assessment. PLoS Comput Biol. 2013;9(5):e1003066. doi: 10.1371/journal.pcbi.1003066. Epub 2013 May 16. PubMed PMID: 23696725; PubMed Central PMCID: PMC3656107.

Lewis KB, Hughes RJ, Epstein MS, Josephson NC, Kempton CL, Kessler CM, Key NS, **Howard T.E.**, Kruse-Jarres R, Lusher JM, Walsh CE, Watts RG, Ettinger RA, Pratt KP. Phenotypes of allo- and autoimmune antibody responses to FVIII characterized by surface plasmon resonance. PLoS One. 2013;8(5):e61120. doi: 10.1371/journal.pone.0061120. Print 2013. PubMed PMID: 23667433; PubMed Central PMCID: PMC3648518.

Pandey GS, Tseng SC, **Howard T.E.**, Sauna ZE. Detection of intracellular Factor VIII protein in peripheral blood mononuclear cells by flow cytometry. Biomed Res Int. 2013;2013:793502. doi: 10.1155/2013/793502. Epub 2013 Feb 28. PubMed PMID: 23555096; PubMed Central PMCID: PMC3600256.

Sauna ZE, Ameri A, Kim B, Yanover C, Viel KR, Rajalingam R, Cole SA, **Howard T.E.** Observations regarding the immunogenicity of BDD-rFVIII derived from a mechanistic personalized medicine perspective. J Thromb Haemost. 2012 Sep;10(9):1961-5. doi: 10.1111/j.1538-7836.2012.04830.x. PubMed PMID: 22734827.

Kim B, Sauna ZE, Carless MA, Curran JE, Viel KR, Cole SS, Raja R, Blangero J, **Howard T.E.** F8 and HLA-II Haplotypes in the Hispanic Population: Implications for Inhibitor Risk Development in Hispanic Hemophilia A Patients. Blood. 2012; 120:3365.

Yanover C, Jain N, Pierce G, **Howard T.E.**, Sauna ZE. Pharmacogenetics and the immunogenicity of protein therapeutics. Nat Biotechnol. 2011 Oct 13;29(10):870-3. doi: 10.1038/nbt.2002. PubMed PMID: 21997623.

Howard T.E., Yanover C, Mahlangu J, Krause A, Viel KR, Kasper CK, Pratt KP. Haemophilia management: time to get personal? Haemophilia. 2011 Sep;17(5):721-8. doi: 10.1111/j.1365-2516.2011.02517.x. Epub 2011 Jun 8. Review. PubMed PMID: 21649795; PubMed Central PMCID: PMC5319386.

Viel KR, Ameri A, Abshire TC, Iyer RV, Watts RG, Lutcher C, Channell C, Cole SA, Fernstrom KM, Nakaya S, Kasper CK, Thompson AR, Almasy L, **Howard T.E.** Inhibitors of factor VIII in black patients with hemophilia. N Engl J Med. 2009 Apr 16;360(16):1618-27. doi: 10.1056/NEJMoa075760. PubMed PMID: 19369668; PubMed Central PMCID: PMC2761028.

Ameri A, Machiah DK, Tran TT, Channell C, Crenshaw V, Fernstrom K, Khachidze M, Duncan A, Fuchs S, **Howard T.E.** A nonstop mutation in the factor (F)X gene of a severely haemorrhagic patient with complete absence of coagulation FX. Thromb Haemost. 2007 Dec;98(6):1165-9. doi: 10.1160/th07-02-0125. PubMed PMID: 18064309.

Sabater-Lleal M, Chillón M, **Howard T.E.**, Gil E, Almasy L, Blangero J, Fontcuberta J, Soria JM. Functional analysis of the genetic variability in the F7 gene promoter. Atherosclerosis. 2007 Dec;195(2):262-8. doi: 10.1016/j.atherosclerosis.2006.12.031. Epub 2007 Feb 9. PubMed PMID: 17292373.

Viel KR, Machiah DK, Warren DM, Khachidze M, Buil A, Fernstrom K, Souto JC, Peralta JM, Smith T, Blangero J, Porter S, Warren ST, Fontcuberta J, Soria JM, Flanders WD, Almasy L, **Howard T.E.** A sequence variation scan of the coagulation factor VIII (FVIII) structural gene and associations with plasma FVIII activity levels. Blood. 2007 May 1;109(9):3713-24. doi: 10.1182/blood-2006-06-026104. Epub 2007 Jan 5. PubMed PMID: 17209060; PubMed Central PMCID: PMC1874571.

Khachidze M, Buil A, Viel KR, Porter S, Warren D, Machiah DK, Soria JM, Souto JC, Ameri A, Lathrop M, Blangero J, Fontcuberta J, Warren ST, Almasy L, **Howard T.E.** Genetic determinants of normal variation in coagulation factor (F) IX levels: genome-wide scan and examination of the FIX structural gene. J Thromb Haemost. 2006 Jul;4(7):1537-45. doi: 10.1111/j.1538-7836.2006.02024.x. PubMed PMID: 16839351.

Viel KR, Warren DM, Buil A, Dyer TD, **Howard T.E.**, Almasy L. A comparison of discrete versus continuous environment in a variance components-based linkage analysis of the COGA data. BMC Genet. 2005 Dec 30;6 Suppl 1:S57. doi: 10.1186/1471-2156-6-S1-S57. PubMed PMID: 16451669; PubMed Central PMCID: PMC1866726.

Howard T.E., Marusa M, Boisza J, Young A, Sequeira J, Channell C, Guy C, Benson E, Duncan A. The prothrombin gene 3'-untranslated region mutation is frequently associated with factor V Leiden in thrombophilic patients and shows ethnic-specific variation in allele frequency. Blood. 1998 Feb 1;91(3):1092. PubMed PMID: 9446674.

Howard T.E., Marusa M, Channell C, Duncan A. A patient homozygous for a mutation in the prothrombin gene 3'-untranslated region associated with massive thrombosis. Blood Coagul Fibrinolysis. 1997 Jul;8(5):316-9. doi: 10.1097/00001721-199707000-00010. PubMed PMID: 9282798.

Esther CR, Marino EM, **Howard T.E.**, Machaud A, Corvol P, Capecchi MR, Bernstein KE. The critical role of tissue angiotensin-converting enzyme as revealed by gene targeting in mice. J Clin Invest. 1997 May 15;99(10):2375-85. doi: 10.1172/JCI119419. PubMed PMID: 9153279;

PubMed Central PMCID: PMC508076.

Esther CR Jr, **Howard T.E.**, Zhou Y, Capecchi MR, Marrero MB, Bernstein KE. Lessons from angiotensin-converting enzyme-deficient mice. Curr Opin Nephrol Hypertens. 1996 Nov;5(6):463-7. doi: 10.1097/00041552-199611000-00001. Review. PubMed PMID: 8978990.

Esther CR Jr, **Howard T.E.**, Marino EM, Goddard JM, Capecchi MR, Bernstein KE. Mice lacking angiotensin-converting enzyme have low blood pressure, renal pathology, and reduced male fertility. Lab Invest. 1996 May;74(5):953-65. PubMed PMID: 8642790.

Bernstein KE, **Howard T.E.**, Shai SY, Langford KG, Balogh R. Tissue specific expression of angiotensin converting enzyme. Agents Actions Suppl. 1992;38 (Pt 1):376-83. doi: 10.1007/978-3-0348-7321-5_47. PubMed PMID: 1334622.

Langford KG, Shai SY, **Howard T.E.**, Kovac MJ, Overbeek PA, Bernstein KE. Transgenic mice demonstrate a testis-specific promoter for angiotensin-converting enzyme. J Biol Chem. 1991 Aug 25;266(24):15559-62. PubMed PMID: 1651914.

Howard T.E., Shai SY, Langford KG, Martin BM, Bernstein KE. Transcription of testicular angiotensin-converting enzyme (ACE) is initiated within the 12th intron of the somatic ACE gene. Mol Cell Biol. 1990 Aug;10(8):4294-302. doi: 10.1128/mcb.10.8.4294-4302.1990. PubMed PMID: 2164636; PubMed Central PMCID: PMC360974.

Yanover, C., Jain, N., Pierce, G., **Howard, T.E.**, and Sauna, Z.E. Pharmacogenetics and the immunogenicity of protein therapeutics. Nat Biotechnology. 29(10):870-873, 2011.

Manuscripts in preparation

Almeida MA, Diego VP, Viel KR, Luu BW, Haack K, Rajalingam R, Ameri A, Chitlur M, Ramsey C, Rydz N, Lillicrap D, Barrett JC, Dinh LV, Kim B, Powell JS, Peralta JM, Meade H, Escobar MA, Kumar S, Williams-Blangero S, Kasper CK, Almasy L, Cole SA, Blangero J, the PATH (Personalized Alternative Therapies for Hemophilia) Study Investigators, **Howard T.E.** New Association-Based Statistical Methods Identify the Highly-Polymorphic HLA-class-II Locus DQB1 and Other Pleiotropic Immune-Mediated Disease Genes as Novel Determinants of Factor VIII Inhibitor Risk in Hemophilia A and Confirm Race as an Independent Predictor. Thrombosis and Haemostasis; in submission.

Howard, T.E., Meng, X., Khachidze, M., Jenkins, M., Duncan, A., Dilley, A., Wenger, N., Warren, S., Evatt, B., Hooper, C., and Austin, H. Risk of venous and arterial thrombosis in relation to the Malmo polymorphism of coagulation factor IX. Blood Coagul Fibrinolysis. In preparation.

Published or accepted review articles, correspondence, and commentaries

Bernstein, K., **Howard, T.E.**, Shai, S., Langford, K., and Balogh, R. Tissue specific expression of angiotensin-converting enzyme. Agents Actions Suppl. 38(Pt 1):376-383, 1992.

Bernstein, K., Shai, S., **Howard, T.**, Balogh, R., Frenzel, K., and Langford, K. Structure and regulated expression of angiotensin converting enzyme and the receptor for angiotensin II. Amer J Kidney Dis. 21(4 Suppl 1):53-57, 1993.

Esther, C.R., **Howard, T.E.**, Zhou, Y., Capecchi, M.R., Marrero, M., and Bernstein, K. Lessons from angiotensin-converting enzyme-deficient mice. Curr Opin Nephrol Hypertens. 5(6):463-467, 1996.

Viel, K.R., Kasper, C.K., and **Howard, T.E.** Inhibitors of Factor VIII in hemophilia. N Engl J Med. 361(3):310, 2009.

Howard, T.E., Yanover, C., Mahlangu, J., Krause, A., Viel, K.R., Kasper, C.K., Sauna, Z.E., and Pratt, K.P. Haemophilia Management: Time to Get Personal? Haemophilia. 17:721-728, 2011.

Viel, K.R., Cole, S., Almasy, L., Lozier, J., Yanover, C., Nichols, T., Watts, R., Iyer, R., Kasper, C., Ameri, A., Pierce, G., Sauna, Z.E., and **Howard, T.E.** Factor VIII Inhibitors and the Intron 22 Inversion: A Hypothesis with Implications for the Pharmacogenetics of Immunogenicity Risk Assessment. Haemophilia. In revision.

Published or accepted books and book chapters

Howard, T., and Naeim, F. Disorders of megakaryocytes and platelets. In Naeim, F., Rao, P.N., and Grody, W.W., (Eds.), Hematopathology: Morphology, Immunophenotype, Cytogenetics, and Molecular Approaches. Academic Press, Elsevier, 2008.

Abstracts

V.P. Diego, M.A.A. Almeida, J.M. Peralta, J.E. Curran, B.W. Luu, J.S. Powell, H. Meade, R. Rajalingam, M.A. Escobar, S. Williams-Blangero, L. Almasy, J. Blangero, and **T.E. Howard**. Might Prothrombin-543R>L, A Major Determinant of Mexican American Coagulation Potential, Contribute to the Disparately Elevated FVIII-Inhibitor-Risk in Hispanic Hemophilia-A Patients? The 11th BIC International Conference (Advances in Haemostasis and Bleeding Disorders); September 17-19, 2021; Venice, Italy. This oral poster was presented by T.E. Howard.

Diego VP, Garcia-Hernández A, Almeida M, Peralta J, Porto A, **Howard TE.**, Blangero J. Gene-environment interaction influencing lipid traits and methylation data for genes influencing lipid metabolism. Abstracts for the 20th Genetics Analysis Workshop, March 4-8, 2017, San Diego, California.

Diego V, Luu B, Almeida M, Hofmann M, Hernandez J, Morelli A, Ameri A, Rajalingam R, Powell J, Blangero J, Marakovsky E, **Howard TE**. Quantizing HLA-class-II (HLAcII) Peptidomic Parameters as Immunologically-Relevant Endophenotypes to Improve Immunogenicity Risk Prediction for Protein Therapeutics ("Biologics") using Factor (F)VIII Inhibitor Development in Hemophilia A (HA) as a Model. Abstracts of the 43rd Meeting of the American Society for Histocompatibility and Immunogenetics, September 11-15, 2017, San Francisco, California.

Garcia-Hernández A, Diego VP, Almeida M, Peralta J, Porto A, **Howard TE.**, Blangero J. Comparing the Subspaces of Gene Methylation Networks Affecting Human Biological Pathways Perturbed by Drug Intervention. Abstracts for the 20th Genetics Analysis Workshop, March 4-8, 2017, San Diego, California.

Luu B, Hofmann M, Diego V, Almeida M, Hernandez J, Morelli A, Ameri A, Rajalingam R, Powell J, Blangero J, Marakovsky E, **Howard TE**. Improved Immunogenicity Prediction using

Composite Variables that Incorporate the Known Patient, Product and Therapy Related Risk Factors for Inhibitor Development with Immunologic Parameters from the HLAclassII (HLAcII)Factor (F)VIII Peptidome. Abstracts of the 63rd Annual Scientific and Standardization Committee Meeting of the International Society on Thrombosis and Hemostasis, July 8 – 13, 2017, Berlin, Germany.

Diego VP, Almeida MA, Luu BW, Haack K, Chitlur MB, Ameri A, Dinh LV, Rajalingam R, Powell JS, Blangero J, Almasy L, Cole S, **Howard TE**. Genetics of Factor VIII inhibitor development in Hemophilia patients: Novel statistical approaches in the PATH Study. Blood 2018;132:1199.
Diego VP, **Howard TE**, Peralta JM, Almeida M, Manusov E, Johnson M, Curran J, Williams-Blangero S. Genotype-by-socioeconomic status interaction modulates gene expression in the hypothalamic-pituitary-adrenal axis. University of Texas Rio Grande Valley School of Medicine 2nd Annual Research Symposium, Sep. 15, 2018, McAllen, TX.

Howard TE, Diego VP, Hofmann M, Almeida M, Luu BW, Dinh LV, Rajalingam R, Escobar M, Curran J, Williams-Blangero S, Powell J, Blangero J, Maraskovsky E, Key NS, Sauna ZE. Analysis of HLACII peptidomes presented by dendritic cells (DCs) from healthy donors and Hemophilia A (HA) patients with or without Factor VIII (FVIII) inhibitors after ex vivo administration of different therapeutic FVIII proteins (tFVIIIs). Hum Immunol. 2018;79:58-187.

Howard TE, Diego VP, Luu BW, Curran J, Blangero J, Williams-Blangero S. Health disparities in inhibitor development in Hemophilia A: Hypotheses on the differential prevalence by race/ethnicity. University of Texas Rio Grande Valley School of Medicine 2nd Annual Research Symposium, Sep. 15, 2018, McAllen, TX.

Sauna Z, Diego V, Almeida M, Luu B, Hofmann M, Hernandez J, Rajalingam R, Williams-Blangero S, Curran J, Powell J, Escobar M, Blangero J, Maraskovsky E, Key N, **Howard TE**. Analysis of HLA-class-II (HLAcII) peptidomes in response to several therapeutic factor (F)VIII proteins (tFVIIIs) in healthy donors and Hemophilia A (HA) patients with and without FVIII Inhibitors (FEIs). Res Practice Thromb Haemost. 2018;2(S1):94.