



United States Department of  
**Health & Human Services**

*Leading America to Better Health, Safety and Well-Being*

**HHS Coordinating  
Xenotropic Murine Leukemia  
Virus-Related Virus (XMRV)  
Scientific Activities  
Blood, Organ and Tissue Safety**

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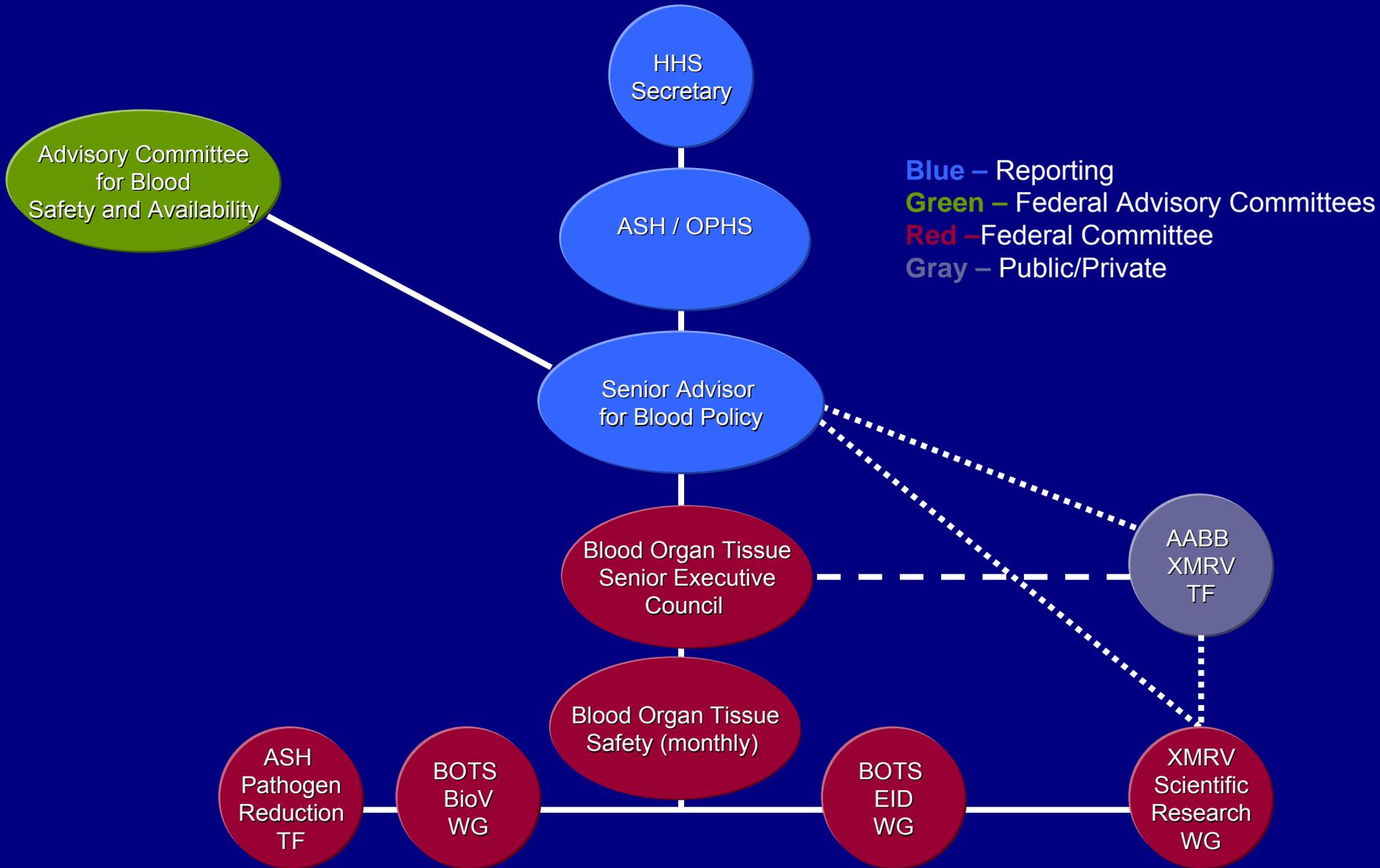
# *“Mobilizing Leadership in Science and Prevention for a Healthier Nation”*

**Goal:** To coordinate the Department’s response in the understanding XMRV detection, prevalence, epidemiology and if disease causing in humans, the prevention of disease transmission through blood and blood products.

- ❖ Method of detection
  - Test methodology
  - Standardization
  - Validation
- ❖ Risk assessment (prevalence studies, epidemiology studies, etc.)
- ❖ Risk management

# Blood, Organ, and Tissue Collaboration

(Reporting Structure with Internal and Federal Advisory Committees)



# Blood XMRV Scientific Research Working Group

## □ Quantitation Phase (December-January)

- ❖ Blood Systems Research Institute, central lab for Retrovirus Epidemiology Donor Study-II (REDS-II)
- ❖ Cells and supernatant sent for quantitation

## □ Analytical Panels (Distributed in March 2010)

- ❖ Developed 15 panels (50 coded plasma, 50 coded whole blood)
- ❖ Human prostate cell line, 22Rv1
- ❖ Six participating labs (CDC, FDA(2) NCI, WPI, and BSRI)
- ❖ Expected results June 2010

## □ Pilot Study ( June/July 2010)

- ❖ Processing time from collection to processing
- ❖ Whole blood preps or peripheral blood mononuclear cell (PBMC)
- ❖ IRB approval needed for samples (5 CFS patient samples)

# Blood XMRV Scientific Research Working Group

## □ Clinical Panel

- ❖ IRB approval needed for samples (25 CFS patient samples)
- ❖ Plasma and whole blood panels matched
  - 250 plasma or whole blood specimens from blood donors in Reno area
  - 25 WPI XMRV+ CFS blood samples
  - 25 control plasma/whole blood samples (positive and negative controls)

## □ Serological assays

- ❖ Research serological under development
- ❖ Will need to be validated and tested with clinical panels

# Publications

- Oct 8, 2009 Lombardi VC et al. Detection of an infectious retrovirus, XMRV, in blood cells of patients with CFS. *Science*. 2009; 326:585-589.
- Jan 5, 2010 Erlwein O et al. Failure to detect the novel retrovirus XMRV in CFS. *PLoS ONE*. 5(1):e8519. doi:10.1371/journal.pone.0008519.
- Feb 15, 2010 Groom HCT et al. Absence of XMRV in UK patients with chronic fatigue syndrome. *Retrovirology*. 2010;7:10 doi:10.1186/1742-4690-7-10.
- Feb 25, 2010 van Kuppeveld FJM et al. Prevalence of XMRV in patients with CFS in the Netherlands: retrospective analysis of samples from an established cohort. *BMJ* 2010;340:c1018 doi:10.1136/bmj.c1018.

# Epidemiological

## □ What we know today...

- ❖ Confounding association between XMRV and CFS
- ❖ No epidemiological association has been demonstrated
- ❖ Confounding association between XMRV and familial cases of prostate cancer
- ❖ Prevalence of XMRV in blood donors is not known at the present time
- ❖ XMRV assays (serological and NAT) need further development and evaluation

## □ Potential sources of data and biospecimens

# Prostate Cancer

1. Inoue et al. *History of blood transfusion before 1990 is associated with increased risk for cancer mortality independently of liver disease: a prospective long-term follow-up study.* *Environ Health Prev Med* (2010) 15:180–187.
2. Shogo Kikuchi. *Personal Past History and Mortality in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC).* *Asian Pacific Journal of Cancer Prevention, Vol 8, 2007: JACC Supplement pp 9-20.*
3. Blomberg et al- *Cancer Morbidity in Blood Recipients-Results of a Cohort Study.* *Eur J Cancer, Vol. 29A, No. 15, pp. 2101-2105, 1993.*
4. Hjalgrim Henrik et al. *Cancer Incidence in Blood Transfusion Recipients.* *J Natl Cancer Inst* 2007;99: 1864 – 1874.

# CFS and Transfusion History

- *Bell et al. Risk Factors Associated with Chronic Fatigue Syndrome in a Cluster of Pediatric Cases. Reviews of Infectious Diseases, Vol. 13, Supplement 1. Considerations in the Design of Studies of Chronic Fatigue Syndrome (Jan. - Feb., 1991), pp. S32-S38 Published by: The University of Chicago Press Stable. At <http://www.jstor.org/stable/4455800> Accessed: 29/03/2010.* Bell et al. conducted a case control study involving a cluster of 21 students 10-16 years old with symptoms of CFS in a farming community in upstate new York (Lyndonville) in 1985 (cases). Two controls were matched for age and sex to each case. No cases received a blood transfusion while 2 of the controls did. The associations between CFS and raw milk ingestion, or a history of allergies or asthma were significant.

# Current Blood Donor Screening

## ❑ AABB Standard 5.4.1A

“The prospective donor shall appear to be in good health and shall be free of major organ disease (e.g., heart, liver, lungs), cancer, or abnormal bleeding tendency, unless determined eligible by the medical director.”

## ❑ 21 CFR 640.3 for Whole Blood and a corresponding provision for Source Plasma in 640.63

(a) *Method of determining.* The suitability of a donor as a source of Whole Blood shall be determined by a qualified physician or by persons under his supervision and trained in determining suitability.

(b) *Qualifications of donor; general.* Except as provided in paragraph (f) of this section and for autologous donations, a person may not serve as a source of Whole Blood more than once in 8 weeks. In addition, donors shall be in good health, as indicated in part by: ...

## ❑ October 2006 Guidance for Industry, Implementation of Acceptable Full-Length Donor History Questionnaire and Accompanying Materials for Use in Screening Donors of Blood and Blood Components

“1. Feeling healthy and well today?”

# Other Country Actions

- ❑ **Canadian Blood Service (not Hema-Quebec)** – indefinite deferral for history of CFS, although no question
- ❑ **Australia Red Cross** – implemented a two year moratorium on accepting blood donors with history of CFS (no question); previous policy deferred donors only for active CFS
- ❑ **New Zealand**- changed policy from indefinite deferral for active CFS to indefinite deferral for history of CFS; no specific screening question

# Communications

## □ Chronic Fatigue Syndrome Advisory Committee (CFSAC)

### ❖ XMRV Questions and Answers posted on CDC website

- [http://www.cdc.gov/ncidod/dhqp/bp\\_xmrv\\_ga.html](http://www.cdc.gov/ncidod/dhqp/bp_xmrv_ga.html)
- Should an individual with diagnosed chronic fatigue syndrome donate blood?
  - At the present time, there are no specific recommendations to defer donors who have chronic fatigue syndrome. However, FDA regulations require that a donor should be in good health. Medical Directors at blood collection centers should exercise judgment in determining whether individuals with a history of CFS are in good health at the time of donation.

## □ National Institutes of Health, National Cancer Institute

### ❖ [http://www.cancer.gov/newscenter/pressreleases/XMRV\\_QandA](http://www.cancer.gov/newscenter/pressreleases/XMRV_QandA)

# Communication

## □ AABB Fact Sheets

❖ TRANSFUSION August 2009 Supplement Appendices

❖ XMRV Fact Sheet, April 2010 (first page to right)

### Xenotropic Murine Leukemia Virus-Related Virus (XMRV)

#### Disease Agent

- Xenotropic murine leukemia virus-related virus (XMRV)

#### Disease Agent Characteristics

- Family: *Retroviridae*; Subfamily: *Orthoretrovirinae*; Genus: *Gammaretrovirus*; Species: Xenotropic murine leukemia virus-related virus (XMRV)
- Virion morphology and size: Virions have a complex construction and consist of an envelope, a nucleocapsid, and a nucleoid. Virions are spherical to pleomorphic measuring 80-100 nm in diameter. Virions have a buoyant density in sucrose of 1.15-1.17 g cm<sup>-3</sup>.
- Nucleic acid: The genome is a dimer of linear, positive-sense, single-stranded RNA, 8300 nucleotides long.
- Physicochemical properties: As enveloped retroviruses, the virions should be susceptible to heat, detergents and many disinfectants such as 1% sodium hypochlorite, 2% glutaraldehyde, formaldehyde and ethanol.

#### Disease Names

- No confirmed disease associations

#### Priority Level

- Scientific/Epidemiologic evidence regarding blood safety: Theoretical; transmission from transfusion has not been documented in humans, although pathogenic retroviruses (i.e., HIV and HTLV) are clearly transfusion transmitted.
- Public perception and/or regulatory concern regarding blood safety: Moderate based on the characteristics of other retroviruses and investigations that have linked some disease states to human infection with this agent. Concern has been publicly expressed regarding transfusion transmission of XMRV following publication of data associating it with chronic fatigue syndrome (CFS).
- Public concern regarding disease agent: Low based at least partly on lack of familiarity with a virus that is potentially linked to human disease; however, may be higher in groups with diseases associated with XMRV.

#### Background:

- A diverse range of mammalian species are susceptible to infection by gammaretroviruses. These retroviruses have genomes that contain only *gag*, *pro*, *pol*, and *env* genes. They include murine leukemia virus, feline leukemia virus, koala retrovirus, and gibbon ape leukemia virus that cause leukemia and other syndromes in their host species.
- Evidence of human infection with gammaretroviruses was lacking until 2006 when genomes of a previously undescribed gammaretrovirus, XMRV, were detected in a cohort of US men with localized prostate cancer undergoing radical prostatectomy. The hypothesis was that these men harbored a homozygous mutation of the *RNASEL* gene (R462Q) that

impaired the function of the ribonuclease L antiviral enzyme rendering patients unusually susceptible to the oncogenic potential of the virus. However, a subsequent study found XMRV DNA or proteins in 6% and 23%, respectively, of malignant prostate cancers irrespective of the RNase polymorphism. Studies in 833 Irish and German subjects with prostate cancer, including 139 with the RNase L mutations, found XMRV in only one patient. Correspondingly, no antibodies were detected among 146 patients from these cohorts.

- In 2009, a statistical association of XMRV infection in CFS patients was reported from a single US center. Peripheral blood mononuclear cells (PBMC) from 67% of CFS patients contained the proviral DNA of XMRV compared to 3.7% of healthy controls. These patients did not have the RNase L polymorphism. Secondary infections in tissue culture could be established from PBMC, B and T cells and plasma of patients. The study concluded, "(T)hese findings raise the possibility that XMRV may be a contributing factor in the pathogenesis of CFS."
- 186 CFS patients from a UK cohort who had been described as being "unwell for a median of 4 years" were screened for XMRV provirus and the closely related murine leukemia virus (MLV) from whole blood preparations. Neither XMRV nor MLV sequences were detected from any of the CFS cases.
- Another UK study tested 170 CFS patients from two cohorts (one with long-term established CFS and the other with samples collected 1.5-4 years after a CFS diagnosis) and 395 controls including 157 blood donors. DNA was extracted from PBMC and tested by RT-PCR targeting two envelope regions (sensitivity of 16 copies). No XMRV sequences were identified from 142 CFS cases and 157 controls tested. However, 26 of 565 (4.6%) samples had XMRV neutralizing antibody activity but only one of the 26 was from a CFS patient. Four samples were XMRV specific but most of the remaining antibody reactivity was due to cross-reactivity with other viruses. The authors note that "XMRV infection may occur in the general population, although with currently uncertain outcomes."
- In a Dutch cohort, PBMC cryopreserved in 1991-1992 from 32 CFS patients and 43 healthy controls tested by RT-PCR targeting the *integrase* gene and/or a nested PCR assay targeting the *gag* gene and having a sensitivity of 10 XMRV sequence copies per 10<sup>6</sup> PBMC failed to detect XMRV sequences in any sample.
- Reasons for the discordant findings are not clear but may include differences in the cohorts studied or selection of patients from cohorts for testing, variable assay procedures, differences in prevalence in different geographic areas, varying properties of XMRV or other factors.

#### Common Human Exposure Routes:

- Unknown

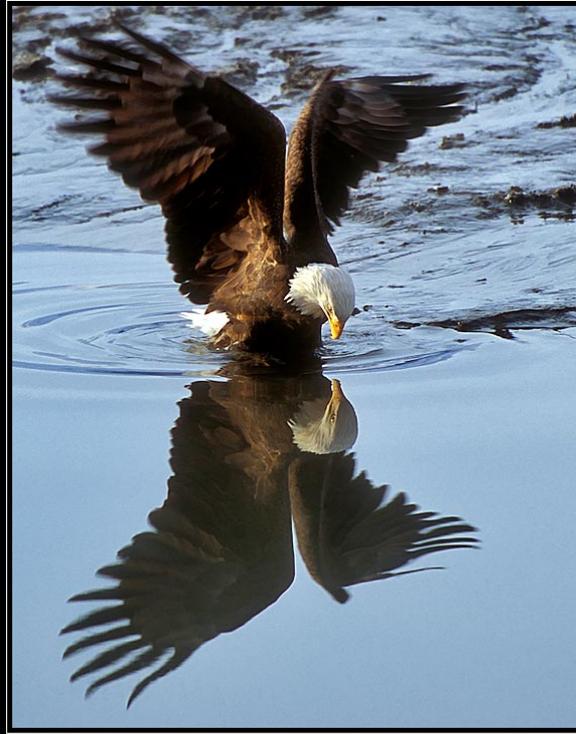
#### Likelihood of Secondary Transmission:

- Unknown

# 1<sup>st</sup> International Workshop on XMRV: Pathogenesis, Clinical and Public Health Implications

- ❑ Lister Hill Center Auditorium, National Institutes of Health, September 7-9, 2010
- ❑ The objective of this scientific conference is to assemble an international group of scientists, physicians and epidemiologists to present and discuss, in a public forum, the latest XMRV studies on a range of topics including virus-host interactions, cell type tropism, mode of transmission, animal models and the efficacy of current antiretroviral drugs.
- ❑ Organizing Secretariat  
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# Questions



Additional slides follow for clarification of talking points