



Welcome!

- First CFIDS Association webinar of 2010
- Cindy, Suzanne, Kim are in 3 different places
- 589 registrants for today's program
- Time delay as slides are advanced by speaker
- Time for questions & answers after presentation – send them as you think of them

XMRV

and implications for CFS

Lucinda Bateman MD

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Science. 23 October 2009:

Vol. 326. no. 5952, pp. 585 - 589

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Detection of an Infectious Retrovirus, XMRV, in Blood Cells of Patients with Chronic Fatigue Syndrome

Vincent C. Lombardi, Francis W. Ruscetti, Jaydip Das Gupta, Max A. Pfof, Kathryn S. Hagen, Daniel L. Peterson, Sandra K. Ruscetti, Rachel K. Bagni, Cari Petrow-Sadowski, Bert Gold, Michael Dean, Robert H. Silverman, Judy A. Mikovits (*University of Nevada at Reno, National Cancer Institute, Cleveland Clinic, Whittemore-Peterson Institute in Reno*)



Abstract

- Chronic fatigue syndrome (CFS) is a debilitating disease of unknown etiology that is estimated to affect 17 million people worldwide.
- Studying ...[blood] from CFS patients, we identified DNA from a **human gamma retrovirus, xenotropic murine leukemia virus-related virus (XMRV)**, in **68 of 101 patients (67%)** as compared to **8 of 218 (3.7%) healthy controls**.
- Cell culture experiments revealed that patient-derived XMRV is *infectious* and that ...transmission of the virus [is] possible. Secondary viral infections were established in uninfected primary lymphocytes... after their exposure to ...cells....or plasma...from CFS patients.
- These findings raise the possibility that XMRV may be a contributing factor in the pathogenesis of CFS.



National Media Goes Crazy!

Excitement explodes in CFS and
retroviral science community



Xenotropic murine leukemia virus-related virus

- From Wikipedia, the free encyclopedia (11/09)
- **Xenotropic murine leukemia virus-related virus (XMRV)** is a [gammaretrovirus](#) that was first described in 2006.^[1] XMRV has been isolated from human biological samples, and several reports associate the virus with familial and sporadic [prostate cancer](#).^{[2][3]} A 2009 publication reports a possible association with [chronic fatigue syndrome](#).^[4]



PLOS. 5(1):e8519. doi:10.1371/journal.pone.0008519.
Published January 6, 2010.

Failure to Detect the Novel Retrovirus XMRV in Chronic Fatigue Syndrome.

**Otto Erlwein, Steve Kaye, Myra O. McClure, Jonathan Weber,
Gillian Wills, David Collier, Simon Wessley, Anthony Cleare.**

*(Imperial College London Jefferiss Research Trust Laboratories.
King's College London Institute of Psychiatry.)*



Abstract

- *In October 2009 it was reported 68 of 101 CFS patients in the US were infected with a novel gamma retrovirus, xenotropic murine leukaemia virus-related virus (XMRV). This finding, if confirmed, would have a profound effect on the understanding and treatment of an incapacitating disease affecting millions worldwide.*
- We investigated CFS sufferers in the UK to determine if they are carriers of XMRV. DNA from 186 CFS patients meeting CDC criteria for CFS were screened for XMRV provirus and murine leukaemia virus by nested PCR.
- Neither XMRV nor MLV ...were detected in the CFS patients.
- We found no evidence XMRV is associated with CFS in the UK. May be a result of populations differences between North America and Europe regarding general prevalence of XMRV infection.



xenotropic **murine** leukemia virus–related virus

- **mu·rine**
- **–*adjective.*** belonging or pertaining to the Muridae, the family of rodents that includes **mice**.
- **–*noun.*** a murine rodent.



xenotropic murine leukemia virus–related virus

- **Ecotropic:** Infect only mouse cells.
- **Xenotropic:** Infect only non-mouse cells (e.g. rat, hamster)
- **Amphotropic:** Infect both mouse and non-mouse cells.



xenotropic murine **leukemia virus**–related virus

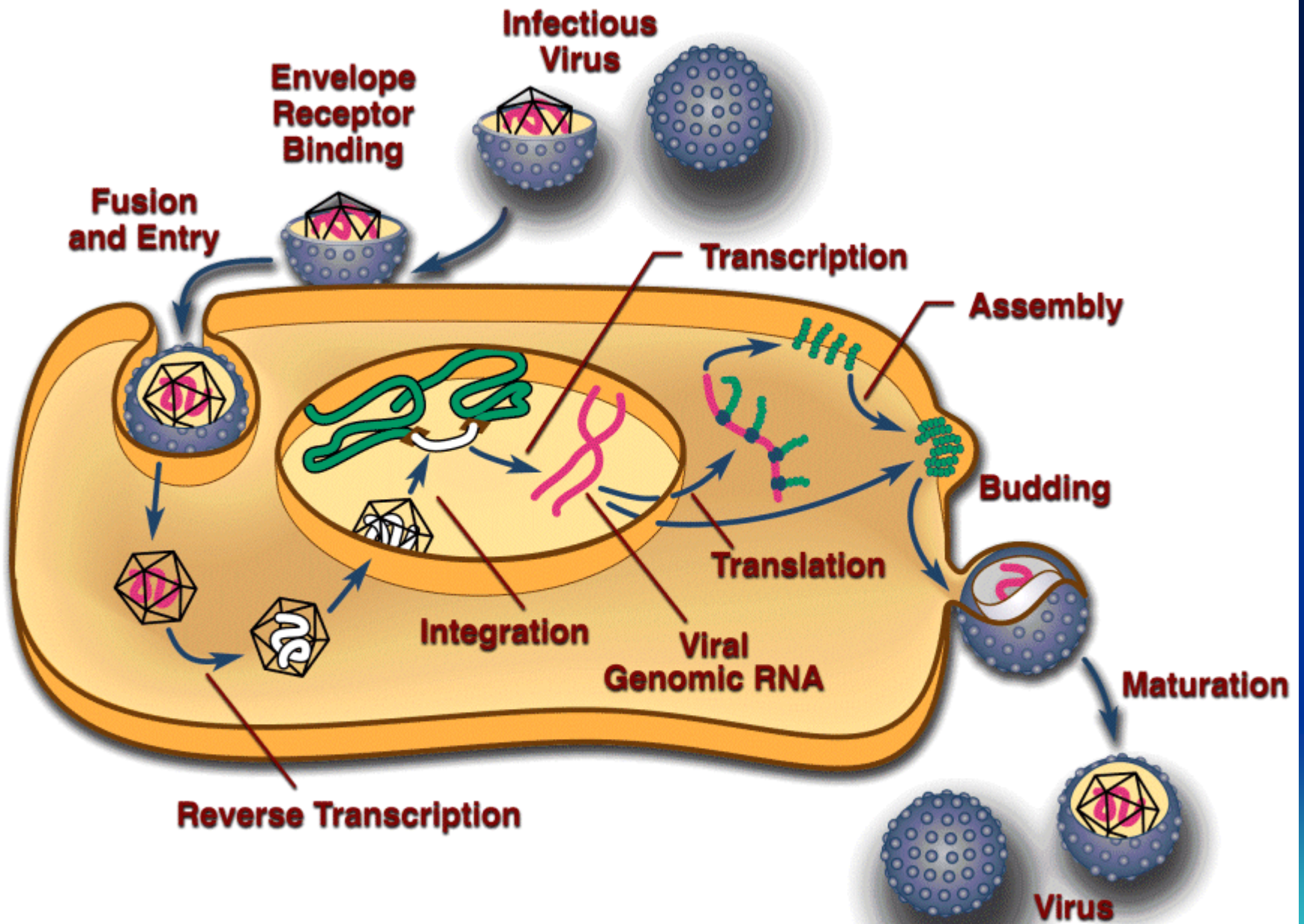
A virus that contributes to the development of leukemia. In this case, in mice.



retrovirus

- A **retrovirus** is an RNA virus that is replicated in a host cell via the enzyme reverse transcriptase to produce DNA from its RNA genome.
- The DNA is then incorporated into the host's genome. The virus thereafter replicates as part of the host cell's DNA.





Retrovirus family

FAMILY	GENUS	SPECIES	HOSTS
Retroviridae	Alpharetrovirus	Avian leukosis virus	Vertebrates
	Betaretrovirus	Mouse mammary tumor virus	Vertebrates
	Gammaretrovirus	Murine leukemia virus	Vertebrates Including humans
	Deltaretrovirus	Bovine leukemia virus	Vertebrates
	Epsilonretrovirus	Walley dermal sarcoma virus	Vertebrates
	Lentivirus	Human immunodeficiency virus 1 (HIV)	Vertebrates Including humans
	Spumavirus	Chimpanzee foamy virus	Vertebrates

Known retroviral infections in humans

- **1981:** Human T-cell leukemia virus discovered, the first pathogenic human retrovirus. (HTLV-1)
- **1983:** Human immunodeficiency virus discovered. (HIV, formally called HTLV-III)
- **2006:** **Xenotropic Murine Leukemia-virus related virus** (XMRV) discovered in prostate cancer cells. (Silverman)
- **10/09:** **XMRV** associated with CFS.



XMRV and prostate cancer

- Prostate cancer affects 200,000 men in US. Second most common cancer in men (except skin cancer).
- XMRV present in 27% of prostate cancer biopsies, and associated with the more aggressive tumors. *Ila Singh, MD PhD, senior author, Sept 7 2009, online edition, Proceedings of the National Academy of Sciences. 2009 Sep 22;106(38):16351-6. Schlager et al.*
- *Robert Silverman, Cleveland Clinic, cancer biologist, discovered XMRV in 2006 (with researchers from Cleveland Clinic and UCSF) and studies the 2-5A/RNase L antiviral/immune pathways.*



What can retroviruses do?

Retroviral pathogenesis research has concentrated on oncogenesis (cancer causation) and more recently, AIDS.

Retroviruses cause a variety of haematopoietic (blood) and neurological disease, including subtle nonspecific changes like:

- Weakness
- Wasting
- Ataxia (imbalanced gait or walk)
- Arthritis
- Dementia
- Neuropathy (damage to nerves)

Any condition characterized by immune dysfunction, immune modulation or immune suppression (including medication use) may change our innate immune “control” over infectious agents that we live with normally, thereby allowing these otherwise benign organisms to cause disease.



Who has XMRV?

- 68 of 101 CFS patients (Peterson, Cheney). Debilitating illness. Many related to cluster outbreak. Severely ill, cognitive dysfunction, immune dysfunction (low NK cell function, abnormal RNase L pathway, elevated cytokines)
- It is unclear how this relates to all patients who meet the CFS Case Definition and/or ME or FM Criteria. **MORE RESEARCH NEEDED!!!**
- 3-4% of the healthy population.
- A portion of prostate cancer patients.



XMRV association with CFS in the WPI study

- XMRV has not been proven to be the cause of CFS, even in the Reno cohort.
- XMRV may be present for other reasons, including because of underlying illness that has caused immune dysregulation.
- There have been hints of retrovirus in previous CFS studies (DeFritas, 1991, HTLV II. Holmes 1997, lentivirus by EM. Presence of reverse transcriptase...)



Tests to identify XMRV are new, imperfect and not standardized, even within the research community. They are not yet generally available commercially.

- PCR (polymerase chain reaction) identifies the viral DNA. (amplifies DNA/RNA, very sensitive and subject to contamination)
- Antibodies that are produced by the host to fight the virus can be measured. Can be nonspecific or confounded. Proves only prior infection, not specific for active or recurrent infection.
- The virus can be collected, put in a new medium, and cultured. Culturing viruses is time consuming and technically difficult, but the “gold standard” for virology.
- The virus can be seen by electron microscopy

Treatment of XMRV

- At this point, there are **no drugs that have been tested in patients** as a treatment for XMRV infection.
- While XMRV is related to HIV as a retrovirus, XMRV is different in ways that may mean HIV drugs are not effective for XMRV. (John Coffin MD PhD, Tufts Univ, Boston)
- HIV drugs are toxic and should not be used to treat XMRV without scientific studies to prove safety and efficacy.




Who is studying XMRV now?

- Retrovirologists across the US (and world).
 - NIH San Francisco meeting (the summer before publication of the CFS XMRV paper)
 - Cleveland Clinic meeting. Nov 11, 2009. 75 top scientists from 14 institutions.
- Scientists who study the national blood supply.
- Centers for Disease Control and Prevention.
- CFS centers—several across the US...
 - Utah: Ila Singh MD PhD, Huntsman Cancer Center. XMRV and prostate cancer expert. Yale PhD. Stanford post-doc. Columbia clinical pathology residency and faculty.



Misc Questions...

- How did humans acquire XMRV?
 - Unknown, but possibly from mice. Mice have probably had Xenotropic proviruses in their genome for 1 million years.
 - How is XMRV spread?
 - Unknown. Research in progress. So far it is found in blood cells and plasma of humans, suggesting blood transmission is possible. Known epidemiology of CFS not suggestive of sexual transmission.
 - Does XMRV cause cancer?
 - It plays a role in animals. We do not know the answer in humans yet, but the question is now of intense interest.
 - Are there treatments for XMRV?
 - Not yet.
- 

On a positive note: worst case scenario

- Even if we eventually determine that XMRV only infects a small subset of CFS patients, and/or that it is not the primary, but rather a secondary infection, at very least...
- This important breakthrough has succeeded in bringing international attention to CFS in the research, medical and pharma communities, and to policy makers.
- **Our job is to help sustain this interest!**



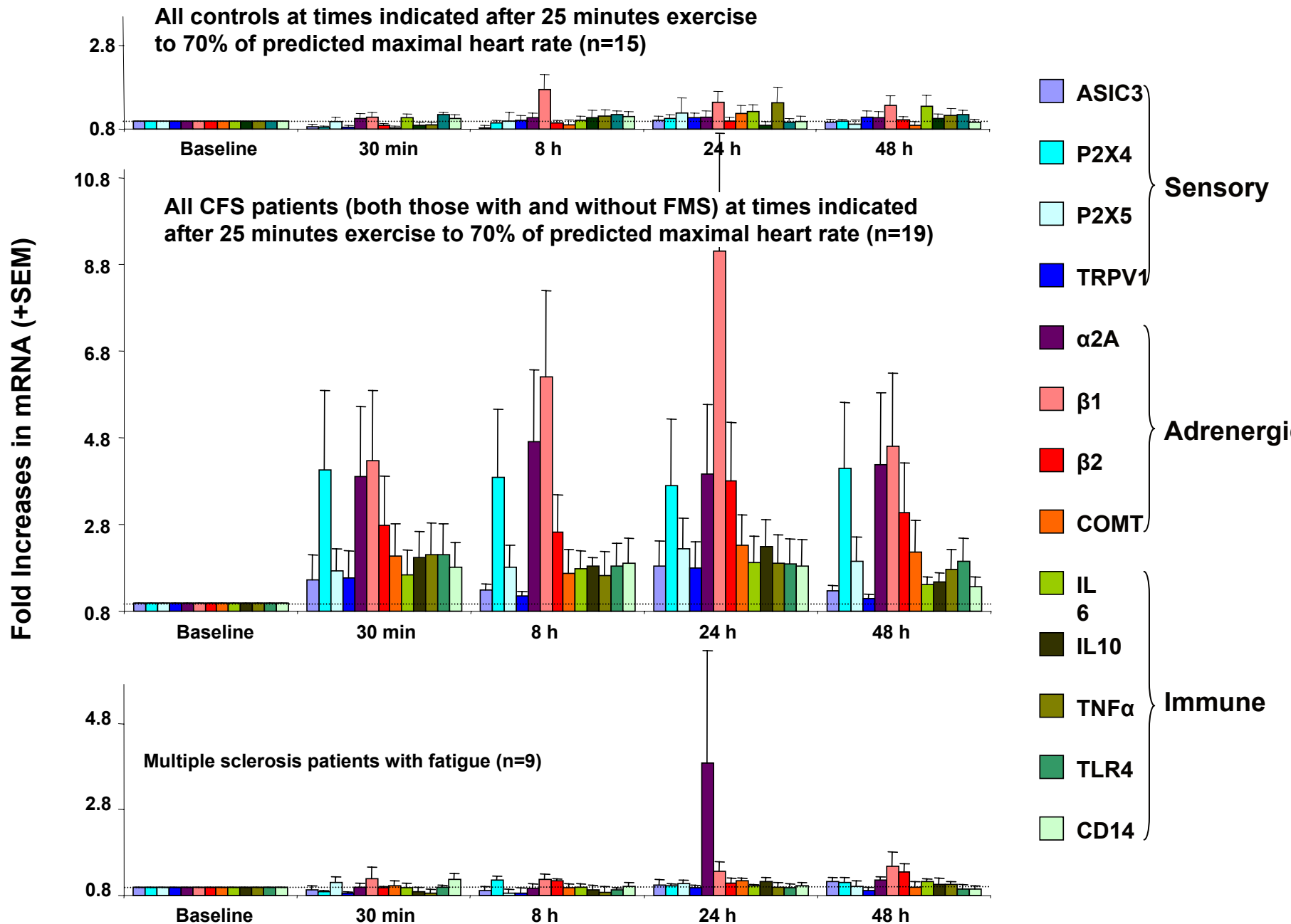
VIP dx (Viral Immune Pathology)

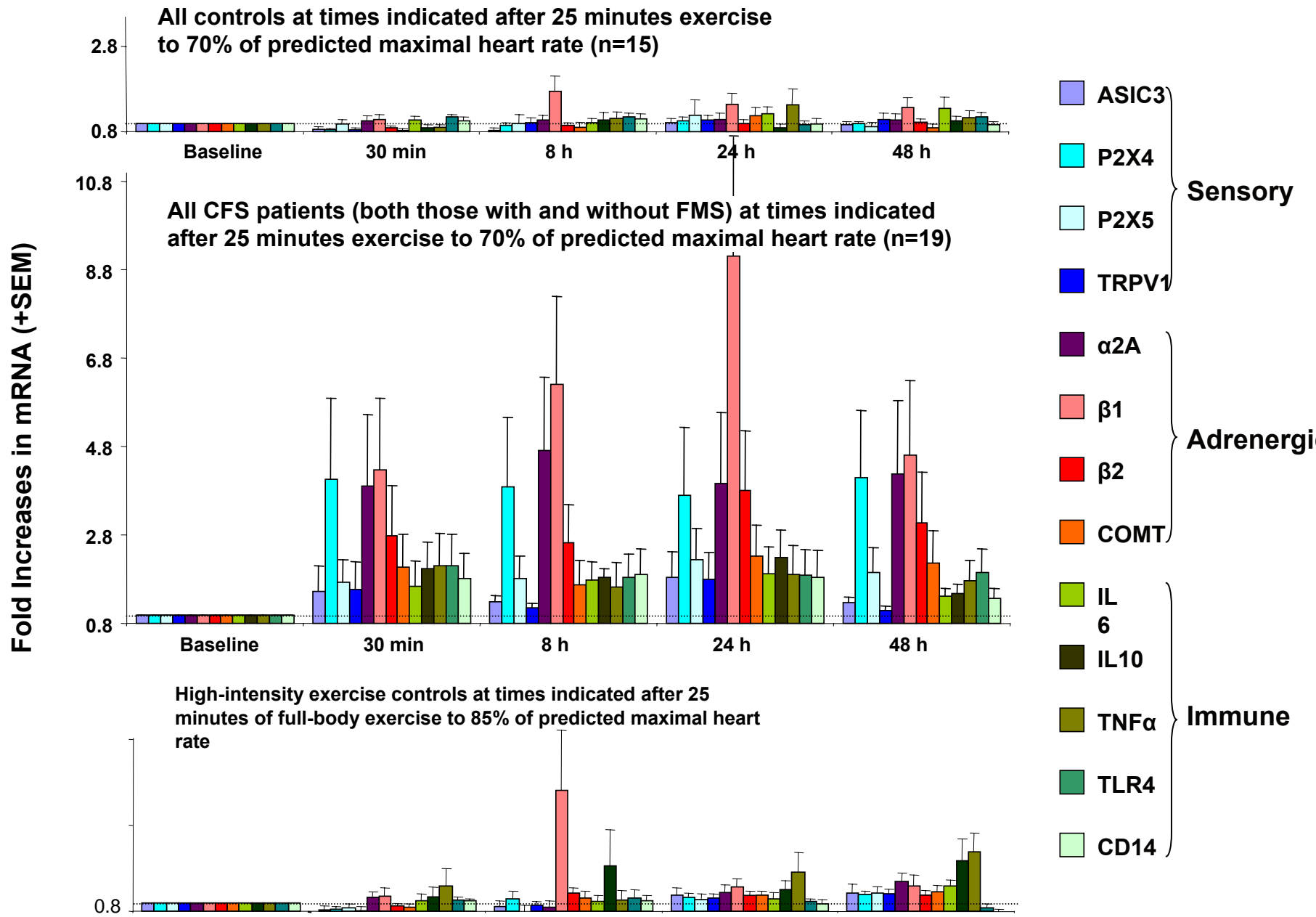
XAND testing in Reno
(XMRV associated neurological disease)

- XAND virus culture \$450

(revised per Whittemore Peterson Institute press release
issued on 1/14/10)









For more information:

- CFIDS Association website: www.cfids.org
- XMRV resources page:
<http://www.cfids.org/XMRV/default.asp#info>
- CFIDS*Link* – monthly e-newsletter:
<http://www.cfids.org/development/checkemail.aspx>
- Facebook: www.facebook.com/cfidsassn



The CFIDS Association of America

Our Mission:

For CFS to be widely understood, diagnosable, curable and preventable.

Our Strategy:

To stimulate research aimed at the early detection, objective diagnosis and effective treatment of CFS through expanded public, private and commercial investment.

Our Core Values:

To lead with integrity, innovation and purpose.