The tale of xenotropic murine leukemia virus-related virus

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In 2006, a new retrovirus was isolated from prostate cancer patient tissue. Named xenotropic murine leukemia virus-related virus (XMRV), this was potentially the third class of retrovirus to be pathogenic in humans. XMRV made a more dramatic impact on the wider scientific community, and indeed the media, in 2009 when it was reported to be present in a remarkably high proportion of patients with chronic fatigue syndrome as well as a significant, albeit smaller, proportion of healthy controls. The apparent strong link to disease and the fear of a previously unknown retrovirus circulating in the general population lead to a surge in XMRV research. Subsequent studies failed to find an association of XMRV with disease and, in most cases, failed to find the virus in human samples. In 2011, the case against XMRV and human disease strengthened, ending with several decisive publications revealing the origin of the virus and demonstrating contamination of samples. In this review, we outline the passage of research on XMRV and its potential association with disease from its isolation to the present day, where we find ourselves at the end of a turbulent story.

A new gammaretrovirus

Xenotropic murine leukemia virus-related virus (XMRV) was first described in 2006 in a study seeking infectious agents in prostate cancer (PC) (Urisman et al., 2006). Familial PC has been linked to mutation in the RNASEL gene, which encodes RNase L, an endoribonuclease functioning as part of the innate immune response to virus infection (Hassel et al., 1993; Zhou et al., 1993). Urisman et al. (2006) isolated RNA from the prostate tissue of individuals with familial PC and used this to probe a ViroChip bearing conserved virus sequences. Samples, mostly from patients carrying a missense mutation in RNASEL, hybridized to virus sequences, specifically those related to murine leukemia virus (MLV). Full-length viral genomes were constructed and were found to have homology to genomes of endogenous MLVs, with the env sequence being related most closely to that of endogenous xenotropic MLV envelopes, hence the naming of this new virus as XMRV. The sequences were so similar that XMRV could be considered a strain of xenotropic MLV. This was potentially the first pathogenic gammaretroviral infection of humans.

MLVs were first described in the 1950s and have since been of enormous value in the understanding of cellular processes and pathologies (particularly carcinogenesis), retroviral vector development and virology itself. The genome consists of a dimer of positive-stranded RNA molecules carrying the gag, pol and env genes, which encode the structural, enzymic and envelope proteins, respectively. Retroviruses are now divided into seven genera: Alpha-, Beta-, Gamma-, Delta- and Epsilonretrovirus, and Lenti- and Spumavirus (Linial et al., 2005). Classification is based on sequence similarity, but also includes features such as the presence or absence of additional genes to the canonical gag, pol and env, separating retroviridae broadly into simple and complex viruses. This latter criterion distinguishes the simple gammaretrovirus MLV, and therefore XMRV, from those viruses that are known to cause disease in humans. These are the lentiviruses human immunodeficiency virus (HIV) type 1 and 2, which cause severe immunodeficiency, and the deltaretroviruses human T-lymphotropic viruses (HTLVs), which can lead to either adult T-cell leukaemia/lymphoma or the nervous-system disorder tropical spastic paraparesis/HTLV-1-associated myelopathy. These are both complex retroviruses.

Retroviruses normally infect somatic cells and the virus integrates into the host-cell DNA (Fig. 1). The provirus will be maintained in this position in one daughter cell and will remain until the last cell of this clone dies. The integrated provirus may remain dormant, but more normally is actively transcribed, resulting in virus production. Particles produced during the lifetime of this cell can infect other cells of the host, and exogenous transmission can occur to other hosts. Occasionally, a retrovirus will infect a cell of the germline. If this cell survives, and goes on to produce offspring, then every nucleated cell in the organism produced from that germ cell will contain a copy of the retrovirus. Retroviruses that become part of a host genome in this way are referred to as endogenous retroviruses. These are then passed onto further generations via classical Mendelian inheritance.
As a result of this process, approximately 37% of the mouse genome is made up of retroelements, including 40–60 endogenous MLVs (Frankel et al., 1990; Stocking & Kozak, 2008; Waterston et al., 2002). The latter are subcategorized into four groups based on their host range (Stoye & Coffin, 1987). Ecotropic viruses (from the Greek oikos, meaning home) are limited to rodent species; xenotropic viruses (from the Greek xenos, meaning foreign) can infect a broad range of species with the exception of most commonly used laboratory mice, which express a resistant variant of the receptor; polytropic viruses (from the Greek poly-, meaning many) can infect both murine and some other cells; the fourth group consists of the modified polytropic viruses. Of these groups, only xenotropic and ecotropic viruses include infectious members, although infectious polytropic viruses can be generated by recombination. Some mice also carry infectious amphotropic viruses (from the Greek amphos, meaning both), which use a different receptor for entry from xenotropic/polytropic viruses, but endogenous amphotropic viruses have not been observed. For a more detailed consideration of MLV tropisms, see reviews by Kozak (2010) and Levy (1999). Xenotropic MLVs were originally identified in the 1970s (Levy & Pincus, 1970) and use xenotropic and polytropic retrovirus receptor 1 (Xpr1) for entry into the target cell (Battini et al., 1999; Tailor et al., 1999; Yang et al., 1999).

MLVs are able to cause their naming pathology, leukaemia, as well as lymphoma, via insertional mutagenesis. Inoculation of mice with particular MLVs can cause a range of pathologies (Kai & Furuta, 1984; Ruscetti, 1999), and mice carrying active endogenous ecotropic MLVs develop lymphomas spontaneously, but reproducibly (Hartley et al., 1977). Hence, although MLVs are usually non-pathogenic in mice, some are capable of causing both oncogenic and neurodegenerative disease. The ability of MLVs to cause pathology in other hosts, including humans, has not been documented.
Initial implication of XMRV in disease

XMRV was initially isolated from PC patients, with the virus specifically present in tissue from individuals with RNASEL missense mutations. The naturally occurring missense mutation R462Q causes a reduction in enzymic activity (Casey et al., 2002) and mice lacking RNase L are highly susceptible to virus infections (Zhou et al., 1997). The gene has been linked to an increased risk of PC (reviewed by Silverman, 2007). However, in 2009, a report was published demonstrating an association with PC in general (Schlaberg et al., 2009). In this study, the incidence of XMRV correlated with the severity of cancer, although there was no link to RNASEL mutations. Then, in late 2009, a study was published by scientists at the Whittemore Peterson Institute (WPI) and collaborators (Lombardi et al., 2009), demonstrating the isolation of XMRV from patients with chronic fatigue syndrome (CFS), otherwise known as myalgic encephalitis (ME). CFS is a debilitating disease with an unknown cause. The authors looked for XMRV in CFS patients as many sufferers display immunological abnormalities, including RNASEL deficiencies (Bansal et al., 2012). Many infectious agents, including the retrovirus HTLV-2 (DeFreitas et al., 1991), have been implicated in CFS in the past, but none has shown a consistent correlation.

The paper by Lombardi et al. (2009) generated great excitement, as the authors were able to detect XMRV in peripheral blood mononuclear cell (PBMC) DNA from 67% of their patient cohort compared with 4% of controls using nested PCR. In addition, a subset of the positive samples was tested by other means, including reactivity to anti-MLV or XMRV antibodies using immunoblotting and intracellular flow cytometry. Viral antigen was detected in T- and B-cells, as well as PBMCs, using immunoblotting. Importantly, the authors were also able to detect replicating virus in PBMCs and plasma by co-culturing these patient samples with an indicator cell line. This caused a huge impact in the patient community. Given that such a high proportion of patients were positive for the virus, this could not only have provided validation for a disease that is not recognized globally by clinicians, but potentially could have provided a diagnostic tool. If a causal role was demonstrated, then there was the possibility of treatment. A number of licensed drugs were found to be active against XMRV (Paprotka et al., 2010; Sakuma et al., 2010; Singh et al., 2010; Smith et al., 2010), and some CFS patients began taking antiretroviral drugs to lessen their symptoms, without waiting for the association to be confirmed.

The XMRV detection rate in healthy blood donors also caused a stir. This, together with the apparent ease of isolating virus from blood, raised questions about the safety of the blood supply. The Blood XMRV Scientific Research Working Group and the AABB International XMRV Task Force were set up to determine the prevalence of XMRV in the donor population, whether it was transmissible by blood transfusion and, if so, whether there were any pathological consequences for the infected recipient. Despite few data and no reliable diagnostic test, several countries imposed a ban on CFS patients donating blood or organs.

Potential for human infection and transmission

So what was the evidence that XMRV could infect and replicate in humans? The Xpr1 receptor is expressed widely on human cells (Kozak, 2010) and XMRV was demonstrated to infect various human cell lines, including those derived from prostate tissue (Dong et al., 2007; Groom et al., 2010b; Rodriguez & Goff, 2010; Stieler et al., 2010). However, infection appeared to be inhibited in other cell types in vitro (Groom et al., 2010b; Stieler et al., 2010). As well as requiring the correct receptor, the species specificity and tissue tropism of a virus are in part determined by the expression of a range of cellular restriction factors. Some restriction factors found in human PBMCs have previously been shown to inhibit MLV replication (Fig. 1), so it was surprising that XMRV could reportedly be isolated from blood (Lombardi et al., 2009). Intrigued by the possibility that XMRV had mechanisms to overcome restriction factors that other MLVs lacked, we and others investigated the susceptibility of XMRV to these factors (Bogerd et al., 2011; Groom et al., 2010b; Paprotka et al., 2010; Stieler & Fischer, 2010). We showed that members of the human APOBEC3 family, as well as tetherin, were able to restrict XMRV infection, although human TRIM5α was not. APOBEC3G and tetherin are expressed in PBMCs, so it was unlikely that XMRV could maintain an efficient spreading infection in these cells.

These data impacted on the potential for blood-borne transmission. However, data were also published on the isolation of virus from expressed prostatic secretions and, like HIV, XMRV infectivity was stimulated by proteins found in semen (Hong et al., 2009). No APOBEC3G was detected in PC cell lines or primary prostatic stromal fibroblasts (Paprotka et al., 2010; Stieler et al., 2010), perhaps explaining the efficient replication of XMRV in these cells. These data pointed to a potential for sexual transmission, a route common to other human retroviruses, but not suggested by the incidence of CFS cases. Worryingly, one group also detected XMRV in respiratory secretions (Fischer et al., 2010). Clearly the issue of transmission was unresolved. In the meantime, two mammalian species were experimentally infected intravenously and monitored: the rhesus macaque and Gairdner’s shrewmouse, Mus pahari (Onlamoon et al., 2011; Sakuma et al., 2011). Evidence for infection of different tissues was seen to varying extents in both models; however, this was not always accompanied by seroconversion and in neither model was there any evidence of disease.

Meanwhile, further studies had been published detecting XMRV in PC cases (Arnold et al., 2010; Danielson et al., 2010; Hong et al., 2009), although control subjects were not always compared. Others, however, failed to find an association (Martinez-Fierro et al., 2010). So, could XMRV
be associated with disease and, if so, could it have a causative role? The virus grows well in PC cell lines (Dong et al., 2007; Rodriguez & Goff, 2010), has an androgen-responsive promoter (Dong & Silverman, 2010) and is stimulated by proteins present in semen (Hong et al., 2009), suggesting that, even if the virus did not play an aetiological role in PC, it might be an opportunistic infection that could be useful as a marker for disease.

In 2009, the PC cell line 22Rv1 was shown to harbour multiple integrated copies of XMRV; if XMRV was present in the original tumour, then this would go far to support the association hypothesis. This followed the detection of integrated virus in DNA from PC patients (Dong et al., 2007; Kim et al., 2008), the most convincing evidence for human infection. Yet, experiments infecting cells with XMRV suggested that XMRV lacked direct transforming ability (Metzger et al., 2010). Equally, studies of XMRV integration did not highlight any integration hotspots, making insertional mutagenesis an unlikely oncogenic mechanism (Kim et al., 2008). Hence, it was proposed that XMRV infection might alter the cellular environment of the prostate or increase inflammation, thereby increasing the potential for malignancy. Overall, the case for an association with the prostate or increase inflammation, thereby increasing the potential for malignancy. Overall, the case for an association with PC, either as a bystander or as an aetiological agent, seemed reasonable. With regard to an association with CFS, pathological or not, the publication of several negative studies and the lack of replication in blood left the question open to serious doubt.

Mounting evidence against an association with disease

Given the implications for human health, several groups endeavoured to replicate the findings associating XMRV with PC and CFS. Immediate attempts to confirm the association of XMRV with CFS failed to find a link (Erlwein et al., 2010; Groom et al., 2010a; van Kuppeveld et al., 2010), and these negative data were met with resistance by those in support of an association. At the time, various technical concerns were raised about both the positive and the negative CFS studies. A trio of letters to the journal Science highlighted potential shortcomings in the Lombardi et al. (2009) paper in terms of design, analysis and interpretation. These points were addressed in an accompanying response from the authors and in a subsequent addendum (Lloyd et al., 2010; Mikovits et al., 2010; Mikovits & Ruscetti, 2010; Sudlow et al., 2010; van der Meer et al., 2010). The latter gave details about the relative sensitivities of various methods of XMRV detection and cited technical differences and patient selection as the reasons why other groups had failed to find the virus in CFS patients. Both the addendum and a commentary at the time (Singh, 2010) called for efforts to be made to conduct a thorough replication of the study using their techniques and others. Discussions in the scientific literature were accompanied by the constant attention of the media and increasing patient interest.

This reached a peak with news that a second study had detected the presence of MLV-like sequences in 86% of CFS patient PBMCs compared with only 7% of healthy volunteers (Lo et al., 2010). However, the env sequences were more similar to those of modified polytropic MLVs than those of xenotropic viruses, a result that confounded rather than supported previous observations by Lombardi et al. (2009). Additionally, evidence of replicating virus was lacking. This was accompanied by a report from Switzer et al. (2010), who failed to find XMRV in CFS patients, or other cohorts, using a range of tests. Proponents of an association suggested that the variation in the sequences detected explained why previous studies had failed to detect the virus. But why had Lo et al. (2010) found only polytropic and Lombardi et al. (2009) only xenotropic viruses? It seemed more likely that these could be artefacts.

Both the Urisman et al. (2006) and Lombardi et al. (2009) studies reported very little inter-isolate sequence variation, which was surprising given the hypothesis that the virus was circulating in a relatively high proportion of the human population. The sequences also bore a very high percentage of sequence identity to common endogenous xenotropic sequences in mice; hence, if XMRV was a zoonotic transmission from mice to humans, very few rounds of replication must have occurred to give such limited sequence diversity. This would suggest a recent transmission, potentially individual transmission events, which seemed unlikely.

Despite the ardent support by the WPI and some CFS patients, the evidence against an association with disease was mounting. Further papers failed to find an association of XMRV with CFS or PC (Henrich et al., 2010; Hong et al., 2010), leaving the positive studies in the minority. In addition to these, a range of other disease cohorts were tested for XMRV, with all studies failing to find an association with virus, or even any evidence of XMRV infection at all (Table 1). The arguments were two sides of the same coin. Those believing in an association argued that extremely sensitive detection methods were needed to find the virus, but these detection methods would also increase the likelihood of false positives by detecting contamination. At the end of 2010, things began to unravel further.

The demise of XMRV as a human pathogen

At this time, four papers were published in Retrovirology dealing with the problem of contamination. As mentioned above, XMRV is related to the abundant endogenous retroviruses in mice; hence, with the very sensitive techniques in use, one would detect even a tiny amount of contaminating murine DNA, in addition to plasmid or viral contaminant. Robinson et al. (2010) reported false positives during detection of XMRV in PC tissue slices, despite careful handling and convincing evidence of concordance between positive samples and geographical correlations. This contamination problem was echoed in a
second study, this time with CFS patients (Oakes et al., 2010). Additionally, false positives resulting from commercial reverse-transcription kits were described (Sato et al., 2010).

The most contentious report put forward the hypothesis that published patient isolates were detected as the result of contamination from the chronically XMRV-infected cell line 22Rv1 (Hué et al., 2010). The 22Rv1 cell line is widely used and generates high titres of XMRV in culture. Hence, there was great potential for contamination of other cell lines with virus or for contaminating reagents with viral DNA/RNA. To understand the origins of XMRV, Hué et al. (2010) compared proviral DNA sequences derived from 22Rv1 cells with other documented MLV and XMRV sequences, including those reportedly isolated from patients. Published isolate sequences interspersed with 22Rv1-derived sequences forming a monophyletic cluster, i.e. sequences from both origins were equally similar and could not be distinguished. In addition, some cell line-derived sequences were phylogenetically basal to the patient isolates, implying that the 22Rv1 sequences were ancestral to the patient isolates, meaning that the 22Rv1 cells were probably the source of these isolates. In fact, there was greater sequence diversity within the 22Rv1 proviruses than in patient isolates, something not compatible with an infectious-transmission model.

The argument for false positives was strengthened by a series of additional studies pointing to contamination of cell lines and commercially available reagents (Erlewein et al., 2011; Sfanos et al., 2011; Tuke et al., 2011; Wolff & Gerritzen, 2011; Yang et al., 2011). These were supported by phylogenetic analysis of contaminants and patient isolates, refuting the idea that sequence variation seen in longitudinal samples from patients in the Lo et al. (2010) study was the result of virus evolution (Tuke et al., 2011). Tuke and colleagues isolated contaminating MLV sequences from commercial RT-PCR kits that closely resembled the sequences reported by Lo et al. (2010). They also showed that the claims of Lo et al. (2010) that later isolates from patients had evolved from earlier isolates was incorrect by performing a maximum-likelihood analysis of sequences. A further study showed that two of 14 of the previously sequenced integration sites from PC patients were identical to those reported from deliberately infected cells that were used in the same laboratory (Garson et al., 2011). This removed the best piece of evidence that XMRV had infected humans. Together, the support for contamination and mounting negative data meant that the case for XMRV in human disease was shaky.

### Origins and conclusions

In the latter half of 2011, a series of well-publicized reports put the nails into the XMRV coffin one by one (Fig. 2). The chronically infected PC cell line 22Rv1 was derived by serial passage of a prostate tumour in nude mice. The Coffin and Pathak groups collaborated to analyse DNA and RNA from early and late passages of the tumour, as well as the resulting cell lines 22Rv1 and CWR-R1 (Paprotka et al., 2011). In doing so, they identified two endogenous MLVs with complementary stretches identical to XMRV. Sequence analysis suggested that six crossover events between these viruses would have resulted in XMRV forming from these two ancestor viruses, possibly in a single replication cycle due to template switching during reverse transcription. The likelihood of these exact events happening independently is exceedingly low and thus they concluded that all XMRV sequences were derived from this event in a laboratory in the mid-1990s.

For the majority of researchers this, together with the evidence described above, severely damaged the argument that XMRV was associated with disease. Nevertheless, some researchers and patients awaited the results of attempts to replicate the Lombardi et al. (2009) study precisely,

### Table 1. Analysis of XMRV in non-PC/CFS cohorts

<table>
<thead>
<tr>
<th>Disease cohort</th>
<th>No. of reports</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>8</td>
<td>Barnes et al. (2010); Cornellissen et al. (2010); Gray et al. (2011); Henrich et al. (2010); Kunstman et al. (2010); Luczkowiak et al. (2012); Maggi et al. (2012); Tang et al. (2011b)</td>
</tr>
<tr>
<td>Idiopathic disease</td>
<td>1</td>
<td>Jezierski et al. (2010)</td>
</tr>
<tr>
<td>Autism</td>
<td>2</td>
<td>Lintas et al. (2011); Satterfield et al. (2010)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>2</td>
<td>Maric et al. (2010)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1</td>
<td>Barnes et al. (2010)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1</td>
<td>Henrich et al. (2010)</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>2</td>
<td>Luczkowiak et al. (2011)</td>
</tr>
<tr>
<td>Lymphoma/leukaemia</td>
<td>1</td>
<td>Waugh et al. (2011)</td>
</tr>
<tr>
<td>Neuroendocrine tumours</td>
<td>1</td>
<td>Schmitt et al. (2011)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>1</td>
<td>Balada et al. (2011)</td>
</tr>
<tr>
<td>Blood donors</td>
<td>3*</td>
<td>Dodd et al. (2012); Mi et al. (2012); Tang et al. (2011a)</td>
</tr>
</tbody>
</table>

*Studies devoted solely to examination of blood donors.
something we ourselves had initiated. However, there seemed
to be an unwillingness to participate in such studies
amongst patients who considered themselves XMRV-positive.
Nevertheless, in July 2011, Knox et al. (2011) published a
study evaluating blood samples from 61 patients with CFS, 43
of whom had previously been identified as XMRV-positive by
the WPI and their testing laboratory. None of these patients
was found to be positive for XMRV by any method.
Furthermore, a study from the Singh laboratory analysed
100 CFS patients and 200 controls, in addition to 14 subjects
from the cohort of Lombardi et al. (2009), in a blinded
manner (Shin et al., 2011). Again, they found none of the
samples to be positive for XMRV.

At this time, Science issued an editorial expression of
concern about the Lombardi et al. study (Alberts, 2011a).
This was followed by the eagerly anticipated results of the
Blood XMRV Working Group multi-laboratory study
(Simmons et al., 2011). Samples that previously tested
positive for XMRV by the WPI, or for MLV by the Lo
group, along with pedigreed negatives, were blinded and
sent out to nine laboratories, including both the WPI and
Lo laboratories. Each laboratory chose their own tests,
including 11 nucleic acid, five serological and three co-
culture tests. Only the WPI and their co-workers, the
Ruscetti laboratory at the National Cancer Institute,
reported positives, despite their tests being the least

**Fig. 2.** Timeline of significant publications in XMRV research from 2006 to the present. References for each publication are
given in the text. AZT, Azidothymidine; EPS, expressed prostatic secretions; SEVI, semen-derived enhancer of virus infection.
sensitive, as determined using spiked controls. Crucially, there was no statistical difference between the detection of XMRV in previously positive samples compared with negative controls. After the publication of these replication studies, a partial retraction was issued by Science (Silverman et al., 2011). Two authors had found contamination in their original nucleic acid analyses and so withdrew the figures involved.

Several reports failing to find XMRV in large cohorts of blood donors have since been published, again suggesting that XMRV has not entered the human population (Dodd et al., 2012; Mi et al., 2012; Tang et al., 2011a). The results of another large XMRV/CFS study, costing US $2.3m, should be published later in 2012, but the majority of researchers now consider this to be case closed. However, the main scientific proponents of the disease association still believe that XMRV plays a role in CFS, as quoted in a recent commentary (Cohen & Enserink, 2011). In a sad conclusion to the story, Science is investigating allegations of image manipulation with regard to the publication by Lombardi et al. (2009) and the WPI are currently involved in legal proceedings with Dr Mikovits, the senior author of the study. In the final twist, just before Christmas 2011, Science made an editorial retraction of the Lombardi manuscript (Alberts, 2011b), which was shortly followed by the retraction of the Lo study (Lo et al., 2012). Thus, it seems that the associations of XMRV with disease were based on contamination of samples, which could have occurred by one of four possible routes: contamination with mouse DNA, plasmid DNA, infected cell-line DNA or even virus particles produced from infected lines. Although nobody wants to believe that such contamination happens, this is not the first time that such things have transpired (Voisinet et al., 2008; Weiss, 2010).

In a world where powerful technologies exist for pathogen detection, extreme caution should be exercised in the interpretation of results. The Bradford–Hill criteria (Hill, 1965) originally sought to extend the Koch–Henle postulates to chronic diseases and provided a helpful framework for those investigating causality in epidemiological studies. These include assessments of an association by temporal relationship, strength, dose–response, consistency, plausibility, consideration of alternative explanations, experiment, specificity and coherence. Further adaptations of the Koch–Henle postulates in the molecular diagnostic era have been suggested, with pertinent considerations of the problems associated with extremely sensitive detection techniques (Fredericks & Relman, 1996; Inglis, 2007). Although no set of criteria can provide absolute proof of causation, guidelines such as these are useful to remember when analysing the evidence. Unfortunately, the speed of science and its dissemination can risk bypassing such considerations. In the case of XMRV, the interpretation of data had important public-health implications. It also raised the hopes of CFS sufferers desperate to know the cause of their disease, and to be provided with therapeutic interventions. Patients are the real victims of this cautionary tale. The evolving XMRV story also illustrates the unknowns that endogenous retroviruses present, and the risk of generating recombinant viruses capable of infecting humans. In this case, it would appear that XMRV, and related gammaretroviruses, have not infected humans. Perhaps the remaining question is who will play the relevant characters in the film?

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