Title: Is gibbon ape leukaemia virus still a threat?

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Abstract

1. In the late 1960's and early 1970's, an outbreak of lymphoma and leukaemia in gibbons (Hylobatidae), attributed to the retrovirus gibbon ape leukaemia virus (GALV), was widely reported in the literature. The virus was described as infecting 11% of captive gibbons in the USA and as a worldwide threat, with cases in both south east Asia, which is the native habitat of gibbons, and in gibbon colonies across north America
2. Since this time, GALV has been discussed as a danger to captive gibbons, a risk to humans handling primates and a potential confounding factor in primate based research
3. The virus is a widespread cell culture contaminant and in particular research into HIV can be impeded by expression of GALV particles by HIV permissive cell lines .
4. In this review, we bring together published work, laboratory records from early GALV research, correspondence about the transportation of gibbons during the 1960s and 1970s, phylogenetic analyses, laboratory screening and zoological records for the first time to discover more about the origin and transmission of GALV.
5. Based on this evidence, we propose that GALV was the result of a cross-species transmission event, most likely during a laboratory experiment, and was never widespread. Instead, all infected gibbons were most likely either transported from the site of the original outbreak, were housed with gibbons from this site or were infected with material derived from gibbons from this site.
6. We also propose that GALV is not an ongoing pathogen of contemporary wild or captive gibbons.

Lymphoma and Leukaemia in Gibbons

Lymphoma and leukaemia were not described in gibbons until the 1960's, when several case reports of haematopoietic neoplasia in *Hylobates* gibbons in, or imported from, south east Asia were published (De Paoli and Garner, 1968; DiGiacomo, 1967; Lingeman et al., 1969; Newberne and Robinson, 1960) . In 1969, four further cases of malignant lymphoma were reported within a single colony of white-handed gibbons (*Hylobates lar*) and were attributed to an infectious agent, however the agent could not be identified (Johnsen et al., 1969) (Table 1). This agent was identified as an exogenous gammaretrovirus in 1971, when five further gibbons in this colony were diagnosed with granulocytic leukaemia (De Paoli et al., 1971; Eiden and Taliaferro, 2011; Theilen et al., 1971) (Table 1). The colony was located at the South East Asian Treaty Organisation (SEATO) laboratory, a US military research facility in Bangkok, Thailand. Soon afterwards, in 1971, a type C (gammaretrovirus-like) retrovirus was identified in a woolly monkey (*Lagothrix lagotricha*) which was diagnosed with fibrosarcoma (Eiden and Taliaferro, 2011; Theilen et al., 1971) (Table 1). This monkey was kept as a pet in an apartment in San Francisco, alongside a lar gibbon (*Hylobates lar*) (Eiden and Taliaferro, 2011). Less than a year later, this gibbon was diagnosed with lymphosarcoma and another strain of the same retrovirus was identified as the cause (Kawakami et al., 1972) (Table 1).

GALV (as this virus became known) was soon reported in several other locations. Kawakami et al. (1973) looked for antibodies to GALV in the sera of gibbons in various locations and found them to be widespread (Table 1). The virus was then identified in frozen brain samples stored at the Gulf South Primate Center (GSPC) in New Iberia, Louisiana (Todaro et al., 1975) and in a gibbon colony on Hall's island in Bermuda (Gallo et al., 1978) (Table 1). It was during this period that GALV was described as infecting 11% of captive gibbons (Kawakami et al., 1973; Kawakami et al., 1975). GALV has also appeared as a cell line contaminant on several occasions. Gallagher and Gallo (1975), Okabe et al. (1976) and Chan et al. (1976) reported GALV in cells cultured from a single patient with acute

myelogenous leukaemia (Table 1). Later, in the 1990's, this strain was identified in Belgium in HUT78 cells infected with HIV-1 strain ARV-2 (Burtonboy et al., 1993; Parent et al., 1998) (Table 1). Expression of GALV by HIV permissive cell lines has also been observed more recently (Takeuchi et al., 2008).

There are five known strains of GALV: GALV San Francisco (GALV-SF), identified in the pet gibbon in San Francisco described above and later in gibbon colonies in San Francisco and at the University of California at Davis (UC Davis) Comparative Oncology Laboratory (COL); GALV-SEATO, found only in gibbons originating from the SEATO gibbon colony; GALV-X, found in cell culture in Louvain, Belgium and at the National Cancer Institute (NCI) in Maryland, USA; GALV-H, only identified in gibbons at the Hall's Island colony in Bermuda and GALV-Brain, identified in frozen brain samples at the GSPC in Louisiana (Figure 1).

Phylogenetic History

Phylogenetically, GALV falls within a cluster of retroviruses which are otherwise largely found in rodents (Figure 1). No other exogenous or endogenous retroviruses from primates fall within this cluster (Figure 1). Until recently, koala retrovirus (KoRV) was the most similar known retrovirus to GALV. KoRV is an active pathogen in koalas, most likely having entered their population within the last several hundred years (Tarlinton et al., 2006). As gibbons and koalas are distant both evolutionarily and geographically, it is generally considered that the virus originated separately in both groups via another host, most likely an Asian rodent or a bat (Eiden and Taliaferro, 2011; Simmons et al., 2014). Early reports suggested that GALV was closely related to relatives of MLV in south east Asian rodents, most notably *Mus dunni* endogenous virus (MdEV) in the Earth-coloured mouse (now known as *Mus terricolor*) and *Mus caroli* endogenous virus (McEV) in the Ryukuyu mouse (Callahan et al., 1979; Lieber et al., 1975). However, these results were derived from low resolution serological and DNA homology methods, including cross-reacting but poorly defined

epitopes of the capsid subunit. Sequence information from these viruses is now available and phylogenetic analysis shows that they cluster separately to GALV and KoRV (Figure 1) with sequence identity to GALV-SEATO of only 68-69% for pol and 55% for env. As KoRV is found only in Australian marsupials and GALV only in south east Asian primates, Simmons et al. (2014) screened species of bats and rodents which are found in both Australia and southeast Asia for GALV-like ERVs. Pol and env gene fragments were identified clustering closely between GALV and KoRV in the Grassland mosaic-tailed rat (*Melomys burtoni*) (Simmons et al., 2014) (Figure 1). There is no clear ecological overlap between gibbons and *M. burtoni*, as *M. burtoni* is restricted to north eastern Australia and Papua New Guinea and no *Melomys* species occur in any part of mainland south east Asia, while gibbons are limited to mainland south east Asia (Nowak, 1999). No primate retroviruses are known with a close genetic relationship to GALV.

GALV in Contemporary Primates

No scientific publications have reported GALV in a live gibbon for almost 40 years, but it is still considered by many to be an active pathogen. A recent study screened gibbons held in north American zoological institutes for GALV and reported no animals with PCR or culture detectable virus (Siegal-Willott et al., 2015). This study reported serum antibodies cross-reacting with cell culture GALV isolates in a bespoke ELISA in 28% of the 76 animals tested, however without data on the potential cross-reactivity of this serum with other retroviruses (including the fragments of other gammaretroviruses within the gibbon genome) it is difficult to interpret the specificity of this seroreactivity.

We have used a combination of zoological records and PCR screening to search for contemporary cases of GALV. Zoological records of 48 gibbons and 20 woolly monkeys dating from 1964 to 2008 were obtained from records held at a UK zoo. None of these primates was described as infected with GALV and only one had clinical signs consistent

with GALV at post-mortem, listed as “mediastinal and intestinal lymphadenopathy, lymphatic enlargement of spleen, liver and kidney and gastric ulceration”. This gibbon died in 2006, long after the major GALV outbreak was described, and was not tested for GALV. Samples from gibbons sourced from throughout the EU, of diverse origins, were obtained from the Deutsches Primatenzentrum, Goettingen, Germany. DNA was extracted from 23 blood samples from seven species of gibbon. Despite being subjected to multiple PCR screens, none of the contemporary gibbon samples tested positive for GALV or KoRV in any analysis (details of samples and PCR screening are available as Supplementary Methods). A control PCR using β-actin primers confirmed that all samples were all of sufficient quality for PCR amplification. These primers and conditions have previously been used successfully to amplify GALV and KoRV. Therefore, consistent with the findings of Siegal-Willott et al. (2015), it appears that GALV and KoRV are absent in these gibbons.

Endogenous Elements Related to GALV

We also performed a similarity based *in silico* screen for endogenous retrovirus (ERV) elements related to KoRV, GALV and *M. burtoni* ERV in the gibbon genome, plus all available rodent and primate reference genomes (listed in Supplementary Methods), using previously published methodology (Brown et al., 2014). Briefly, using the Exonerate algorithm (Slater and Birney, 2005), regions of reference genomes with high similarity to known retroviruses were identified. For each of these regions, the Smith-Waterman algorithm (Smith and Waterman, 1981) was used, via the EMBOSS water function (Rice et al., 2000) to generate a similarity score with the *pol* gene of the GALV reference sequence (Genbank accession NC_001885.2). The highest scoring sequence from each host was considered to be the closest endogenous relative to GALV in that host.

The most similar endogenous relatives of GALV were identified in the mouse (*Mus musculus*), rat (*Rattus norvegicus*) and hamster (*Cricetulus griseus*) genomes. These

sequences cluster together phylogenetically and are similar to *Mus caroli* endogenous virus and *Mus dunni* endogenous virus and somewhat distant from GALV (Figure 1). The most similar endogenous element identified in the gibbon genome was considerably more distant from GALV, clustering with the human endogenous retrovirus HERV-T (Figure 1). This shows that there is unlikely to be a longstanding evolutionary relationship between GALV and their gibbon hosts.

Linking Historical Cases of GALV

The absence of confirmed GALV in contemporary gibbons is surprising, given the worldwide distribution, rapid diversification and high prevalence of GALV reported during the initial outbreak. The absence of GALV in gibbons in the UK during the GALV outbreak period suggests that the documented prevalence of 11% in the USA. which is still cited today (e.g. Voevodin and Marx (2009) , originally from Kawakami et al. (1973) and Kawakami et al. (1975), was never the case worldwide. Therefore, besides these early publications, we obtained the 1963 to 1983 SEATO Medical Research Laboratory Annual Progress reports (http://www.afrims.org/weblib/apr/aprF.shtml), archived documentation from the US Department of State concerning gibbon transportation (documents 1974BANGKO17800, 1974STATE260768_b, 1974BANGKO17734_b,1974STATE260770_b, 1974TAIPEI06749_b, 1974STATE244644_b, 1974BANGKO19028_b, 1975BANGKO15111_b, available at www.wikileaks.org) and scanned documents from this period maintained by the International Primate Protection League (IPPL) (available at https://www.ippl.org).

The two studies which provide the statistic of 11% GALV prevalence were based on 133 gibbons from five US colonies, of which 15 had antibodies reactive to a GALV antigen. However, breaking down this statistic, the 15 gibbons with these antibodies were all from one of three research colonies, those at the UC Davis COL, SEATO and the SFMC. None

of the remaining 31 gibbons, from colonies elsewhere in the USA, had these antibodies. Therefore, rather than a worldwide prevalence of 11%, this study, which is the largest known study of GALV, documents 15 potential cases of GALV. These cases were all within colonies located at research facilities known to have worked on GALV prior to this publication (after GALV was first described at SEATO, it was detected at UC Davis COL in a gibbon obtained from the SFMC) (Table 1). This raises the possibility of a link between these cases. SEATO gibbons appear to have been exported to primate laboratories at UC Davis on at least one occasion during the 1960s and 1970s (Table 2). Gibbons from unknown locations in Thailand are also known to have been exported to UC Davis via animal dealers on a number of occasions during this period (Table 2). Therefore, an outbreak of GALV at the UC Davis and SFMC colonies coinciding with the outbreak at SEATO may be the result of shipment of an infected gibbon, either from within SEATO or from a more widespread outbreak in Thailand. The isolated GALV-SF and WMSV cases identified in a gibbon and woolly monkey kept together as pets in a San Francisco apartment building (Eiden and Taliaferro, 2011) can be similarly explained by the numerous legal and illegal shipments of gibbons from south east Asia during this period. The SEATO colony included a group of free-ranging gibbons (Berkson, 1968), so direct capture from this colony is even a possibility, as primate dealing was lucrative and poorly regulated in Thailand at this time.

GALV-H, from gibbons in Bermuda, and GALV-Brain, from frozen tissue at the GPC, are similar to GALV-SEATO, with which they form a slightly distinct phylogenetic group to GALV-SF and GALV-X (Figure 1). This suggests a close relationship between GALV-SEATO, GALV-H and GALV-Br. This would be consistent with a direct link between the gibbons in these locations, which is not initially apparent from the publications describing these strains. However, during the 1970's the IPPL, an organisation campaigning for primate welfare, kept and published records of movement of gibbons around the world, and information published by this organisation provides us with a possible link. In their March 1976 and February 1977 newsletters (before the first publication relating to GALV-H in 1979), the IPPL reported on

the origin of the gibbons at the newly established Hall's Island colony (Table 1, Table 2). The gibbons were reported to have originated in Thailand and 10 of the gibbons as from the "US army gibbon laboratory", likely to be the SEATO colony, in Bangkok (Table 1, Table 2). This would be consistent with our phylogenetic and other analyses. The GALV-Br strain in Louisiana is harder to trace, but reviewing the literature leads to two potential routes. The Delta Primate Center (now the Tulane National Primate Research Center) in Covington, Louisiana, is reported by the IPPL in their April 1978 newsletter to have received 20 gibbons from SEATO in 1963 (Table 2). The Gulf South Primate Center, in New Iberia, Louisiana, is situated approximately 130 miles away and it is feasible that gibbons were moved between these locations during the 1960's. The gibbon brain samples in which GALV was identified were from gibbons exported from southeast Asia in 1968. They may therefore have been in contact with SEATO or other gibbons in south east Asia prior to this shipment or interacted with gibbons from SEATO while in the US. These gibbons were inoculated with kuru affected human brain tissue from Papua New Guinea (Todaro et al., 1975), so laboratory exposure is also possible. Alternatively, as the brains from which GALV-Br was isolated were from seemingly healthy gibbons, the cell lines with which the gibbon brain tissue was co-cultured may have been contaminated with GALV-Br.

Cell lines contaminated with GALV-X can also be traced back to laboratories where significant amounts of work on GALV have been carried out (Table 1). For example, Gallagher and Gallo (1975) identified GALV-X at the NIH National Cancer Institute in Maryland, USA, where Lieber et al. (1975) and Todaro et al. (1975) cultured strains of GALV (Table 1). Burtonboy et al. (1993) and Parent et al. (1998) worked at the University of Louvain, Belgium but the HIV-1 infected cell line from which they isolated GALV was established at the University of California, and some reagents used in this process were obtained from GALV researchers at the NIH National Cancer Institute (Levy et al., 1984). The GALV-X strain is highly similar to GALV-SF (Figure 1) and may represent GALV-SF simply preserved in a cell line and shipped to another laboratory.

Archived documents from the SEATO medical research laboratory provide further information about the SEATO gibbons. The colony was established in 1966 with 71 gibbons (most likely *Hylobates lar*) purchased in Thailand (Morris et al., 1966). SEATO gibbons were used as models for human disease pathogenesis and transmission (primarily of malaria and dengue fever) and were inoculated frequently with blood and tissue from humans, rodents and other gibbons [e.g. (Bancroft et al., 1975; Cadigan et al., 1967; Smith et al., 1968)]. The earliest identification of GALV was in four gibbons in this colony which had all been part of the malaria or dengue virus studies at the centre. Both of these studies were long-term, involved many gibbons and used transfusion of blood between gibbons and from humans to gibbons, viruses grown in live rodents and rodent tissues and transmission experiments using mosquitoes fed on infected blood from rodents and gibbons (Diggs and Pavanand, 1969; Halstead, 1964; Johnsen et al., 1969; Muangman, 1971). A large collection of Asian rodents was held at this facility and also used in these disease studies (Marshall, 1974, 1975). This colony provides an attractive candidate for the location of the overspill event from rodents to gibbons, either through laboratory inoculation with material from humans or other species or via direct contact between animals. At least two of the gibbons with confirmed GALV at this colony (identified as gibbons S-76 and S-77) were involved in the same malaria study (Cadigan et al., 1967; De Paoli et al., 1971). The identification numbers of gibbons involved in studies were only sporadically reported, so the exact transmission path of the disease cannot be tracked.

As several previous studies have proposed [e.g. (Eiden and Taliaferro, 2011; Hayward et al., 2013; Lieber et al., 1975; Tarlinton et al., 2008)] , we hypothesise that GALV in gibbons originated as a cross-species transmission from rodents. The presence of a GALV/KoRV like ERV in an Australian rodent (Simmons et al., 2014) adds strength to this hypothesis. GALV strains are extremely similar to each other genetically and the divergence of the *env* gene between strains of GALV, which ranges from 85% to 99%, is no greater than the divergence of *env* genes in the viral population within a single HIV-1 infected individual, so they may

represent different isolates from a single outbreak (Andréoletti et al., 2007). Laboratory analysis suggests that GALV is absent in contemporary European and North American Gibbons (Siegal-Willott et al., 2015) and analysis of veterinary records suggests it was absent in the UK when the virus was circulating elsewhere. We propose that the spillover event from rodents to gibbons occurred either at the SEATO research colony or elsewhere in southeast Asia during the mid to late 1960's. Gibbons from this region were exported to COL, SFMC and Hall's Island, where GALV was again detected. GALV became a common cell culture contaminant in the laboratories where this work was carried out, so was later detected in cell lines linked to these laboratories. The lack of documented cases of GALV worldwide since 1978, along with these results, suggest that this virus is no longer an active pathogen of gibbons and that it was never widespread amongst the gibbon population.

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Table 1: Key publications concerning the initial outbreak of GALV and the virus host, the geographical origin of the primates or cells in which the virus was identified, the location at which the virus was identified, the location of the laboratory work performed and the strain of GALV described.

Publication	Host	Origin of primates or cells	Location of material when tested	Location of laboratory work	Strain
Johnsen et al., 1969	4 gibbons	Purchased in Thailand (Morris et al., 1966) then SEATO Medical Research Colony	SEATO Medical Research Colony.	Unknown	GALV-SEATO
De Paoli et al., 1971	5 gibbons	Purchased in Thailand (Morris et al., 1966) then SEATO Medical Research Colony	SEATO Medical Research Colony.	UC Davis Comparative Oncology Laboratory	GALV-SEATO
Theilen et al., 1971	1 woolly monkey	Unknown, kept as a pet in an apartment in San Francisco	UC Davis Veterinary Center.	UC Davis Dept of Veterinary Medicine	WMSV
Kawakami et al., 1972	1 gibbon	Unknown, kept as a pet in an apartment in San Francisco with the woolly monkey described by Theilen et al. (1971)	San Francisco Medical Center, University of California.	UC Davis Comparative Oncology Laboratory	GALV-SF
Kawakami et al., 1973	15 gibbons	Various	UC Davis Comparative Oncology Laboratory (sera only)	UC Davis Comparative Oncology Laboratory	GALV-SEATO GALV-SF
Todaro et al., 1975	5 gibbons	Imported from south East Asia to the Gulf South Primate Center, Louisiana in 1968, inoculated with brain tissue from humans from Papua New Guinea with kuru.	Gulf South Primate Center, Louisiana.	National Cancer Institute, Maryland.	GALV-Br
Gallagher and Gallo, 1975 **Okabe et al., 1976** **Chan et al., 1976**	Cultured cells from a human with acute myeloid leukaemia.	Patient from Houston, Texas.	Laboratory of Tumor Cell Biology, National Cancer Insititute, Maryland	National Cancer Institute, Maryland	GALV-X
Gallo et al., 1978	1 gibbon	"US army gibbon laboratory" and elsewhere in Thailand then Hall's Island, Bermuda	Rockland Research Institute, New York.	National Cancer Insititute, Maryland	GALV-H
Burtonboy et al., 1993	HUT78 cells infected with HIV-1	Cancer Research Institute, San Francisco, then Vrije Universiteit, Brussels	University of Louvain, Brussels.	University of Louvain, Brussels.	GALV-X

Table 2: Details of documented international shipments of gibbons during the 1960s and 1970s.

Shipment	Date	Evidence	
SEATO, Bangkok to Delta Primate Center, Louisiana	May 1963	IPPL newsletter, April 1978 based on information supplied by the M.D. Director of SEATO.	http://www.ippl.org/newsletter/1970s/014_v05_n1_1978-04.pdf
"US Army Gibbon Laboratory", Bangkok, Dusit Zoo Bangkok and unknown other locations in Thailand to Hall's Island, Bermuda	1970-1972	IPPL newsletter, Feb 1977 and IPPL newsletter, Mar 1976	https://www.ippl.org/newsletter/1970s/011_v04_n1_1977-02.pdf https://www.ippl.org/newsletter/1970s/008_v03_n1_1976-03.pdf
Unknown locations in Thailand to UC Davis Comparative Oncology Laboratory, California	1972-1974	US Fish and Wildlife Service	https://www.wikileaks.org/plusd/cables/1974STATE260768_b.html
SEATO, Bangkok to UC Davis Comparative Oncology Laboratory, California	Aug 1973	IPPL newsletter, April 1978 based on information supplied by the M.D. Director of SEATO.	http://www.ippl.org/newsletter/1970s/014_v05_n1_1978-04.pdf

Figure Legends

Figure 1

The phylogenetic relationship of the *pol* gene of strains of gibbon ape leukaemia virus, koala retrovirus, *Melomys burtoni* retrovirus and related retroviruses. Orange dots mark rodent sequences, blue crosses primate sequences and green lines marsupial sequences. GALV and WMSV are labelled and shown in blue. Newly identified sequences identified in our *in* silico screen are shown in capital letters and in pink. Sequence identifiers are shown in grey, these are Genbank accession numbers where available, otherwise Repbase identifier or chromosome with start and end positions are provided. Chromosome positions are for the following genome builds: mouse GRCm38.p1, rat Rnor_5.0, gibbon Nleu_3.0. Sequences were aligned using the MAFFT L-INS-I algorithm (Katoh et al., 2002) with 1000 iterations and the tree was generated using PhyML NNI (Guindon et al., 2010) with optimised tree topology, no invariable sites, optimised across site rate variation and a BioNJ starting tree. Branch support is aLRT-like.

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