Chapter 7

The Origins of Gibbon Ape Leukaemia Virus

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http://dx.doi.org/10.5772/intechopen.71694

Abstract

Gibbon ape leukaemia virus (GALV) was first isolated in the early 1970s after a number of gibbons that were housed at the SEATO medical research in Bangkok, Thailand, were diagnosed with lymphoid tumours including malignant lymphoma. It is a novel gamma retrovirus that has never been isolated from wild gibbons. It appears that GALV occurred as a result of a species jump from another as yet unidentified vertebrate host. The full sequence of GALV suggests that it is related loosely to murine leukaemia viruses and a number of rodent species from Southeast Asia have been suggested as possible hosts of the ancestor to GALV. However, no proviral sequence from any Southeast Asian vertebrate has been so far isolated which could be a candidate virus. More recently, two closely related viruses have been found in koalas and a native Australian rat, the grassland melomys (*Melomys burtoni*). These are koala retrovirus (KoRV) and *Melomys burtoni* retrovirus (MbRV). A number of theories have been published recently which endeavour to explain the origins of GALV and its relationship to other viruses including KoRV. Here, the history of GALV is documented and the strengths and weaknesses of current theories on the origin of this virus are discussed.

Keywords: gibbon ape leukaemia virus, koala retrovirus, *Melomys burtoni* retrovirus

1. Introduction

Retroviruses are a unique group of viruses, which have evolved a novel reproductive strategy. They are single-stranded positive-sense, non-segmented RNA viruses which use a unique enzyme, reverse transcriptase to turn their RNA back into DNA, hence the name "retro" virus [1]. Once this is achieved, they use a second enzyme, integrase to insert the viral cDNA into the infected cells chromosomes [2]. This chromosomal DNA is then transcribed and translated to make new viral RNA and proteins, which are then assembled into new virions [3] (**Figure 1**). The viral DNA is referred to as the provirus. Ordinarily,

this provirus is inserted into chromosomes of somatic cells, often lymphocytes or their precursors. These viruses are infectious, transmitted horizontally from one individual to another and are said to be exogenous [4]. Should the provirus become inserted into chromosomes in a germ line cell (sperm or ova) there is the potential for the provirus to be passed from parent to offspring and be inherited as with other genes. In this specific scenario, the virus is now said to be endogenous and it is transmitted vertically [5, 6]. Almost all endogenous retroviruses are ancient and considered to be "viral fossils" or the relics of ancient infections [7, 8]. The proviral DNA in these circumstances has often incurred fatal mutations over time and is now no longer capable of producing infectious virions. This proviral DNA is part of the non-coding portion of the host's chromosomes, sometimes referred to as "junk" DNA [9, 10].

Currently, there are seven genera of retroviruses based on their genetic organisation. Alpharetroviruses, betaretroviruses and gammaretroviruses are simple retroviruses for which the genome encodes three genes, *gag*, *pol*/*pro* and *env*. Deltaretroviruses, epsilonretroviruses, lentiviruses and spumaviruses are more complex retroviruses, with a genome

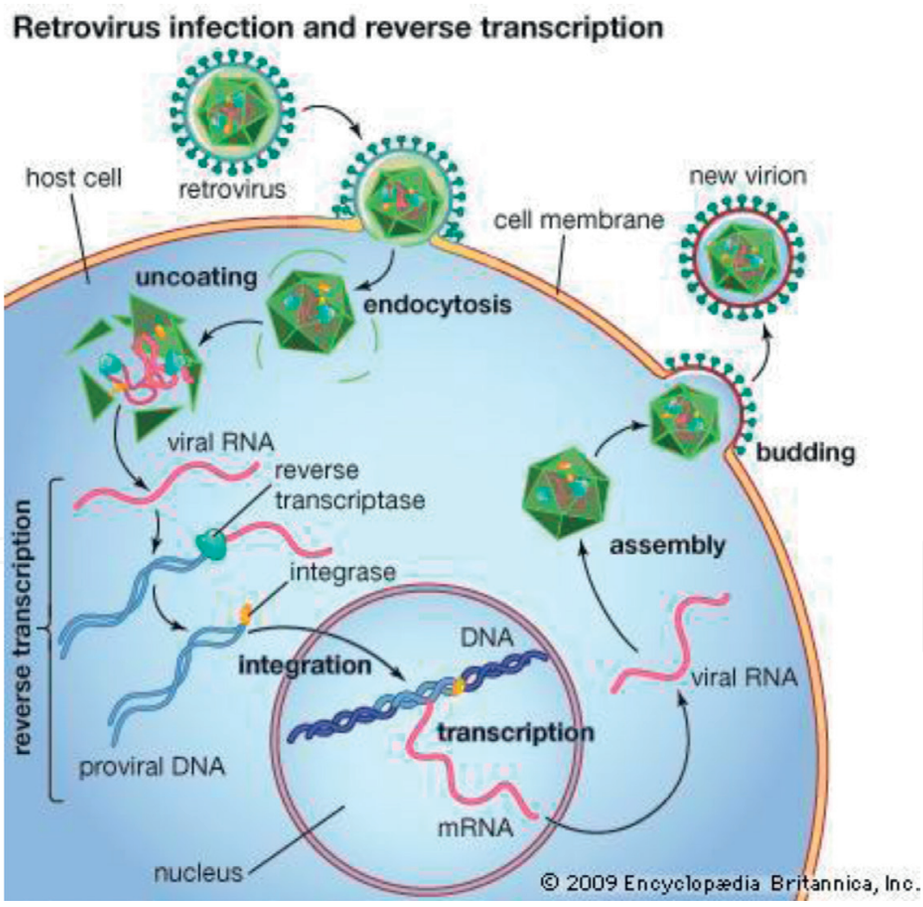

Figure 1. Following retrovirus infection, reverse transcriptase converts viral RNA into proviral DNA, which, by the action of integrase, is then integrated (incorporated) into the DNA of the host cell. This integrated proviral DNA is then transcribed and translated to give new viral RNA and proteins that later give new virions. (From Britannica and King [11], Encyclopaedia Britannica).

encoding additional small regulatory proteins. Gamma retroviruses, formally "type C" retroviruses, have a simple genome approximately 8–10,000 bases long [12].

Retroviruses commonly cause disease by one of two mechanisms. They are often oncogenic and induce cancers by disruption of normal cellular control mechanisms [13, 14]. Many also induce immunodeficiency leading to opportunistic infections in the host [15, 16].

2. History of gibbon ape leukaemia virus

In the mid 1960s, the SEATO medical research facility, now the Armed Forces Institute of Medical Sciences (AFRIMS), was established in Bangkok, Thailand. This organisation conducted medical research on a number of diseases and used a number of different animal species for their research [17, 18]. A number of SEATO annual progress reports, available at (http://www.afrims.org/weblib/apr/aprF.shtml), shed light on some of those early experiments. In 1965, the first white-handed gibbons (*Hylobates lar*) were acquired and the colony grew over the following years [19]. These gibbons were used for research on a range of diseases but a major focus appears to have been malaria and dengue fever virus (DFV). In1969, it was reported that four gibbons over a 20-month period were diagnosed with malignant lymphoma [20, 21]. As this seemed to be an unusually high incidence of an uncommon disease, endeavours were made to look for a viral aetiology. Prior to this episode, there had been very few reports of lymphoid tumours in gibbons or primates other than man [22, 23].

Subsequently, a novel gamma retrovirus was isolated and it was given the name gibbon ape leukaemia virus (GALV) [24]. In the following years, a number of strains of GALV were isolated and the full sequence of their genetic codes has now been published [25]. Gibbon ape leukaemia virus is an infectious exogenous gammaretrovirus. Currently, there are four strains, which have been isolated from gibbons. These are GALV-SEATO for the strain detected at the AFRIMS (SEATO) facility [24], GALV-H from a colony of gibbons kept at Halls Island, Bermuda [26], GALV-SF from a gibbon housed in San Francisco [27] and GALV-Br isolated form gibbon brain material [28].

There have also been two isolates derived as a contaminant from cell cultures. These are GALV-X, found in a HUT-78 cell culture line, which had been infected with HIV [29, 30] and GALV-Mar, which was detected in a cell culture derived from Marmoset cells (unpublished sequence GenBank: U20589.1). There is also a related virus, initially named Simian Sarcoma Associated Virus (SSAV) and now Woolly monkey Virus (WMV). It was isolated from a pet Woolly monkey from California that developed fibrosarcomas and had apparently been housed with a gibbon. Woolly monkey virus is a defective recombinant virus, which has lost its envelope gene and acquired a cellular oncogene [31].

The discovery of a novel oncogenic retrovirus, which was highly pathogenic and which infected sub human primates promoted a great deal of research following its initial discovery. Some researchers believed it might lead to the discovery of a novel human leukaemia virus.

3. GALV-related viruses

Following the discovery of GALV, one of the lines of query focused on what might be the origin of this virus. It had never been isolated before that initial lymphoma outbreak in Bangkok and there are no reports it has ever been seen in wild gibbons. Initially, the focus for the origin of the virus was Southeast Asian rodents because GALV is loosely related to the murine leukaemia viruses. The lack of evidence for prior gibbon infection and the relationship with murine leukaemia viruses suggested that GALV represented a novel cross species transmission event of an unknown virus from a yet to be identified host, possibly a rodent. In the 1970s, several papers were published positing possible candidates for the host of the ancestor virus. These included the Asian rodents *Vandeleuria oleracea*, *Mus dunni* and *Mus caroli* [32–34]. However, these early papers were based on relatively low specificity technology such as DNA hybridisation, and there is no published retroviral sequence from these rodents that indicate they are the host of a GALV variant.

4. Koala retrovirus

An interesting new chapter on this virus was opened in 2000 when Hanger et al. published the full sequence of a gamma retrovirus isolated from koalas, which was named koala retrovirus (KoRV) [35]. The search for such a virus was prompted by the clinical observation that many wild and captive koalas appeared to be suffering from a high incidence of lymphoid tumours and immunosuppressive like disorders, diseases often associated with retroviral infection [36]. Koala retrovirus is interesting because it appears to be the only known naturally occurring exogenous virus, which is actively undergoing a process of endogenisation in its host [37].

When the full sequence of KoRV was published, it became apparent that it was closely related to GALV, suggesting that the two viruses almost certainly shared a common ancestor [35]. The obvious question from this observation is by what mechanism is a virus able to infect a primate on the Southeast Asian mainland and a marsupial in Australia when the host species are phylogenetically diverse and are separated by thousands of kilometres. It appears there has been some cross species transmission events which are yet to be determined.

5. *Melomys burtoni* retrovirus

Another intriguing aspect was uncovered in 2014 with the publishing of four partial proviral sequences obtained from a native Australian rodent, the grassland melomys, *Melomys burtoni*. This was named *Melomys burtoni* retrovirus (MbRV) and it shares close homology with both GALV and KoRV across the published sequences. A total of 2880 bp were sequenced from the *pol* and *env* genes and they had 94, 93, 92 and 90% nucleotide identity with GALV-SEATO and 84, 82, 74 and 79% identity with KoRV, respectively [38]. *M. burtoni* has a geographic range which in part overlaps that of koalas. It inhabits dry sclerophyll forest similar to that of koala

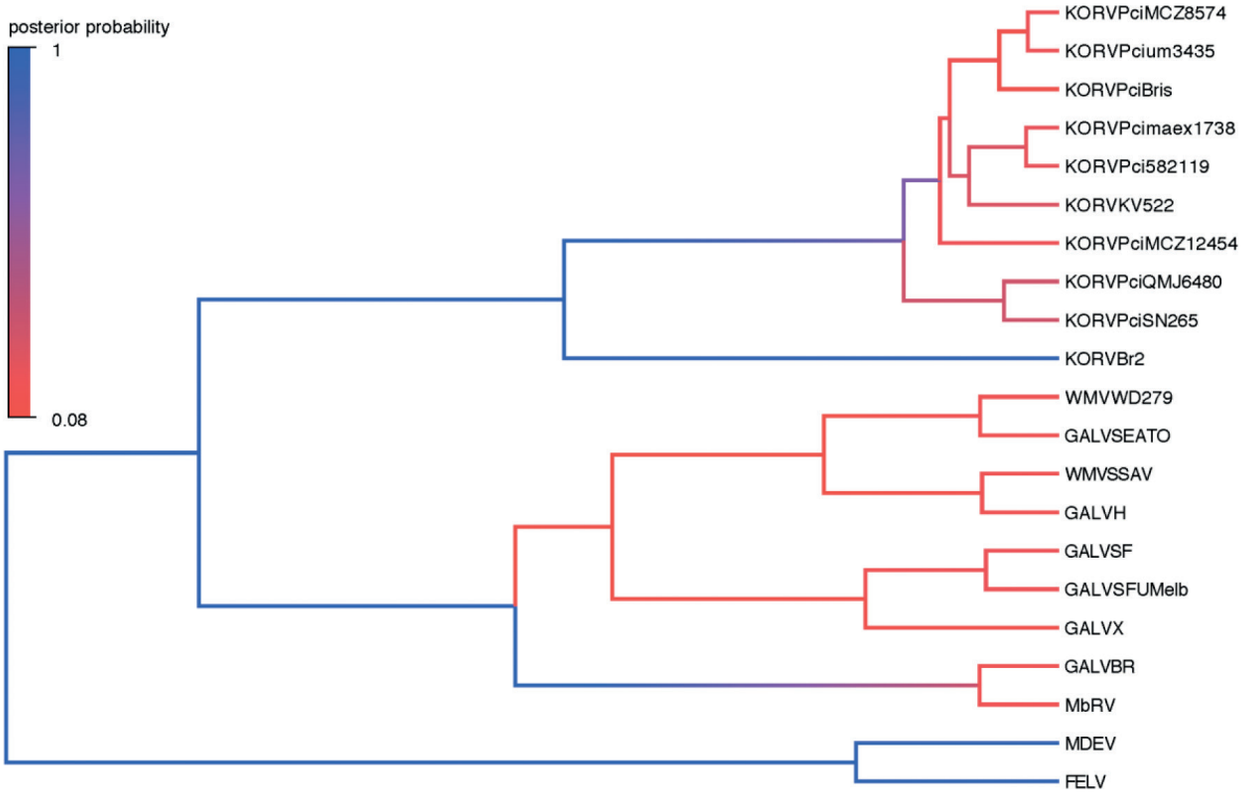

Figure 2. Consensus multi-locus phylogeny showing evolutionary relationships of various gammaretroviruses. Analyses were performed using the *BEAST Bayesian algorithm, which co-estimates multiple gene trees within a shared species phylogenetic matrix. Untrimmed pol (3606 bp) and env (2391 bp) genes were included as separate alignments with unlinked substitution models (HKY + G for pol; GTR + I for env) and evolutionary rates (allowing the sampler to estimate strict clock rates from a uniform (0–1*e100) prior distribution). The two gene partitions were embedded in a species tree matrix using a Yule speciation prior. Two MCMC chains were run for 40,000,000 iterations each, sampling every 2000 iterations (resulting in 30,000 posterior estimates after a 25% burnin). Chains were examined visually to confirm adequate mixing and ensure that estimated parameter sample sizes were above 200. Colours of branches represent posterior probabilities of node placement, with warmer reds showing relatively low support and cooler blues showing high support. GenBank accession numbers for each taxa are as follows: KORVPciMCZ8574 (KF786282); KORVPcium3435 (KF786286); KORVPciBris (AF151794); KORVPcimaex1738 (KF786281); KORVPci582119 (KF786280); KORVKV522 (AB721500); KORVPciMCZ12454 (KF786283); KORVPciQMJ6480 (KF786284); KORVPciSN265 (KF786285); KORVBr2 (KC779547); WMVWD279 (KX059700); GALVSEATO (KT724048); WMVSSAV (KT724051); GALVH (KT724050); GALVSF (KT724047); GALVSFUMelb (X13194); GALVX (U60065); GALVBR (KT724049); MbRV (KF572483–KF572486); MDEV (AF053745) and FELV (NC_001940). (From McKee et al. [40], virus genes).

habitat [39]. Thus, it appears possible that there may have been a direct viral transmission between koalas and *M. burtoni* in the past. This would explain the origin of KoRV in koalas. However, what is intriguing is that while MbRV and KoRV are clearly closely related, MbRV and GALV are closer still. If MbRV had been isolated from a gibbon, it would be listed as another strain of GALV (**Figure 2**).

6. Current theories on the origin of GALV

Recently, there have been three papers published putting forward different scenarios which might explain the origin of GALV.

Brown and Tarlinton suggested that GALV arose iatrogenically by the inoculation of biological material derived from Southeast Asian rodents housed at the SEATO facility [41]. They cite a number of SEATO Medical Research Laboratory Annual Progress Reports from the 1960s and 1970s, which give details of those early experiments. These reports shed some light on possible mechanisms of iatrogenic transmission to gibbons. For example, a colony of the Asian house mouse, *Mus musculus castaneus*, was maintained at the SEATO facility and presumably this colony provided the mice used in experiments there [42]. A colony of laboratory rats presumed to be Wistar rats, which were imported from Malaysia in February 1964, was also maintained [43].

Gibbons were used in many experiments where they were inoculated with biological material including blood and viruses obtained from a range of sources. One SEATO report indicates that gibbons were inoculated with material taken directly from rodents. Mice were used to passage viruses and on one occasion two gibbons were inoculated with "…. a low passage suckling mouse brain (SMB) suspension …" [44]. While the origin of these mice is not stated, it is reasonable to assume that they came from the *M. musculus castaneus* colony. In addition, one of the prototype DFV strains (type 2 New Guinea C strain) injected into gibbons was repeatedly passaged through suckling mice, at least in the early years [45].

Some research gibbons were kept free ranging on Ko Klet Kaeo, an island just off the coast in the Gulf of Thailand. Rodents known to live on the island were *Rattus rattus* and *Bandicoota indicus* [46]. Since these gibbons were free ranging, it may have been possible for a close interaction allowing a cross-species transmission event. Thus, there were occasions where gibbons were in close proximity with rodents or were injected with biological material acquired from rodents, and this may have allowed the transfer of a GALV progenitor to gibbons. However, there are currently no retroviral sequences from any of the rodent species mentioned above, which indicate they are the host of the ancestral virus.

Bats are known to harbour a large number of endogenous retroviruses and it has been suggested that retroviruses may have first evolved in bats [47, 48]. Denner published an alternative hypothesis suggesting that bats may be the host species for the origins of both GALV and KoRV [49]. Bats, especially fruit bats, unlike most birds and other mammals, freely cross Wallace's line and thus may have carried a virus between Southeast Asia and Australia. Wallace's line is an imaginary line, which passes between the Indonesian islands of Bali and Lombok. It divides the fauna of the region into typically Southeast Asian fauna to the northwest and typically Australasian fauna to the southeast (**Figure 3**). It is named after the nineteenth century zoologist and explorer Alfred Russel Wallace [50]. While there have been some published sequences from bats which are loosely related to GALV, as is the case with rodents from Thailand, there is currently no published sequence which can be considered a GALV ancestor. In addition, there is no single species of bat, which is known to have its geographic distribution extend from Australia to Thailand. Thus, if bats were hosts for a KoRV/GALV ancestor, it would require yet more cross transmission events as more than one species of bat would be needed to account for the spread of a virus between Australia and Thailand.

McKee et al. suggested an alternative theory which provides a possible if unlikely route by which an ancestor virus might have been iatrogenically transmitted to gibbons [40]. Their

http://dx.doi.org/10.5772/intechopen.71694

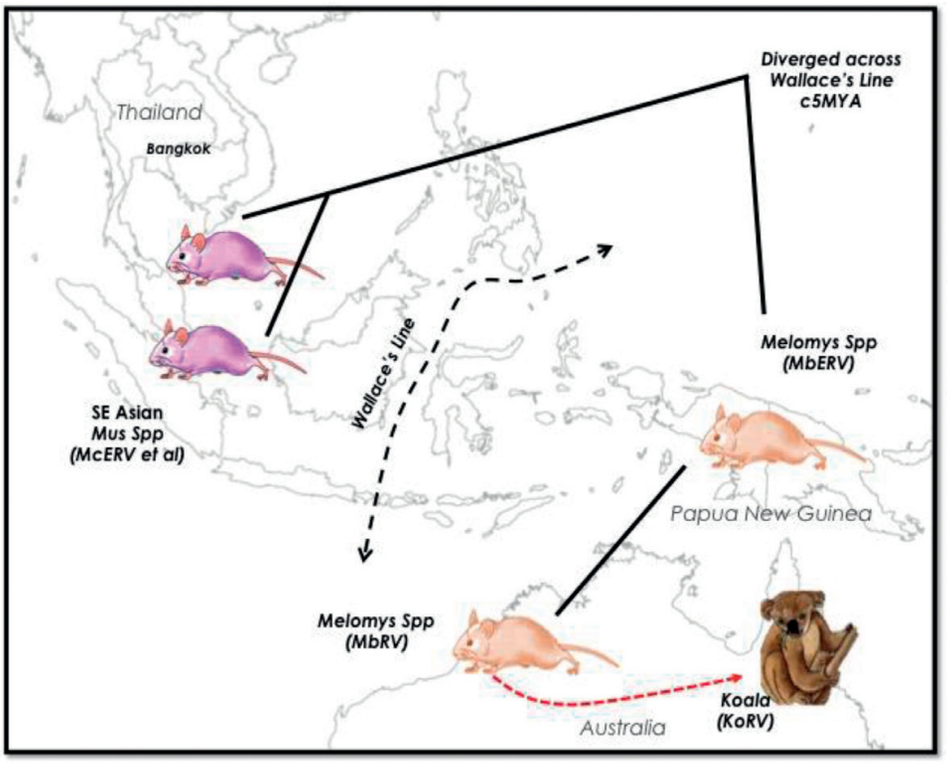

Figure 3. Divergence of Southeast Asian and Australasian rodents: Southeast Asian rodents diverged from the Australasian old endemic rodents around 5 million years ago presumably after being isolated by sea level rise. Wallace's line marks the geographic discontinuity that separates Asian from Australasian fauna. We propose that this also marked the co-divergence in murine ERV hosted by each group with Melomys eventually giving host to MbRV. Some Melomys are semiarboreal raising the possibility of niche overlap and eventual cross-species transmission of MbRV to koalas (*Phascolarctos* spp.). This scenario implies that MbRV is a progenitor murine-like ERV, which stabilised in the Melomys genome but retained infectivity over a few million years. Of note is that MbRV appears to be a complete RV with intact ORFs but it remains to be seen whether it is in fact infective. (From McKee et al. [40], virus genes).

theory is that an infectious MbRV/GALV-related virus is present in melomys species in Papua New Guinea, and further that this virus has been able to infect people or at least was a contaminant when samples were collected from human patients and biologic material derived from these samples later injected into gibbons. They suggest that this happened on at least two separate occasions. In the first, gibbons were inoculated with a New Guinea strain of DFV [51]. Details on how this virus was obtained are not available, but if a dengue fever patient in PNG from whom the New Guinea strain was obtained was concurrently infected with MbRV; this would theoretically have allowed transmission to gibbons. Sometime after this inoculation, the first strain of GALV appeared. No gibbons had been diagnosed with GALV infection prior to these experiments.

In 1968, brain material taken from human kuru patients from the Eastern Highlands of Papua New Guinea was injected into four gibbons at the Gulf South Primate Center, New Iberia, Louisiana, USA. These animals subsequently died of pneumonia and their brains were frozen for later experiments. When this brain material was added to cell cultures, the GALV-Br strain was isolated. It is worth noting that the authors stated "…contact of these gibbons with animals bearing known,

experimentally induced infections with primate type C viruses was not possible" [28]. Thus, two strains of GALV were detected in gibbons after injection with biological material obtained from people from Papua New Guinea. An alternative explanation for the appearance of GALV-Br is that it may have arisen as cell culture contaminant in the same way the GALV-X appeared [41].

All three of the above theories are interesting and have positive and negative aspects. A deficiency in the theories that Southeast Asian rodents or bats are the ancestral host is that currently there is no retroviral sequence from any of these species with a sufficient high degree of homology to be considered the ancestor virus. The partial MbRV sequence does have such similarity.

Proponents of the bat and Asian rodent theories for the appearance of GALV appear to be suggesting that a GALV variant exists independently in these species. However, it is difficult to understand how there could be another virus circulating in a host in mainland Southeast Asia while a very similar virus is present in Melomys. *Melomys burtoni* occurs in parts of Australia and Papua New Guinea, and the genus Melomys is restricted to the Australasian side of Wallace's line. It does not occur in Thailand [52]. Melomys are termed "old world endemics." They came down through the land bridge that was present as part of Sahul when Australia and Papua New Guinea were connected approximately 5 million years ago during an adaptive radiation in the Pliocene Epoch [53]. Thus, melomys and mainland Southeast Asian rodents have been isolated for at least 5 million years, and over such a time period, it would be expected that their respective genomes would have diverged significantly given the high mutation rate that exogenous retroviruses undergo [54, 55].

It is possible that bats may have been able to have close interactions with some research gibbons, in particular those present on Ko Klet Kaeo, and as noted above, bats do cross Wallace's line. However, it would seem that these interactions could occur equally with wild gibbons and GALV has only been detected in captive animals.

An issue with the Papua New Guinea origin [40] is that there is currently no evidence that MbRV is infectious. A related virus, designated as Melomys/Woolly monkey virus (MelWMV), detected in a novel *Melomys burtoni* subspecies from Wallacea and clearly related to MbRV is endogenous and has suffered fatal mutations. Thus, it is unlikely to be the origin of GALV. Only partial sequences of MbRV have been published and it may also be a defective endogenous virus incapable of infection. In addition, there is currently no evidence for human infection with an MbRV variant in Papua New Guinea, although it is possible that such an infection may be present as a sub clinical entity.

7. Conclusions

The origins of GALV remain a mystery a half century after it was first detected and it remains a fascinating saga in the field of retrovirology. A number of theories have been proposed which might explain the origins and clearly more research is needed to definitively answer this question. Areas of investigation could include screening of possible vertebrate hosts, such as the Asian rodents that may have had close contact with gibbons at

the SEATO facility. These include the *Mus musculus castaneus* and Wistar rat colonies at the facility, and *Rattus rattus* and *Bandicoota indicus* from Ko Klet Kaeo Island. Bats, whose geographic distribution extends to the region around Bangkok, and melomys species from Papua New Guinea could also be examined. In addition, it would be interesting to screen people from Papua New Guinea who live in regions where they may have contact with melomys. Close contact between *Melomys burtoni* and humans is also possible in the coastal regions of northern and eastern Australia where this species occurs, and this again raises the possibility of human infection with this virus. While there is no evidence that any individual working with GALV at the SEATO facility was ever infected, human infection cannot be completely ruled out and screening of people living in close proximity with *Melomys burtoni* would be of interest. In particular, patients suffering from lymphoid tumours could be tested. Lack of appropriate diagnostic facilities in some regions of Papua New Guinea may make this difficult. It should be noted that the ancestor virus may never be found. An infectious exogenous virus circulating in any vertebrate host does not necessarily have a high prevalence of infection. Thus, it is possible that many specimens from the host species could be screened and yield negative results.

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