

# The Feline Sarcoma Viruses

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*The oncogenic RNA containing viruses (oncoviruses) can be divided into one of three classes; the chronic leukemia viruses, the acute leukemia viruses and the sarcoma viruses. Sarcoma viruses have been found in birds, mice, rats, cats and some subhuman primates. The feline sarcoma virus (FeSV) causes multicentric fibrosarcomas in young pet cats in their natural (nonlaboratory) environment. Of the eight FeSV isolates that have been obtained to date, three, the Snyder-Theilen (ST), Gardner-Arnstein (GA) and Susan McDonough (SM) strains, have been well characterized, and a total of seven FeSVs have been shown experimentally to induce sarcomas in kittens. Most tumors that were induced in the kittens were progressor tumors from which FeSV could be readily recovered. However, some kittens were resistant to tumor development altogether, or developed tumors which subsequently regressed. These kittens were found to have high titers of antibody to the FeSV- and FeLV-induced tumor-specific antigen FOCMA. In addition to multicentric fibrosarcomas, one strain of FeSV, the GA-FeSV, has been found to induce feline melanomas of the skin and eye. Sarcoma viruses such as FeSV are recombinant viruses, that is, they are formed by a recombination between the genes of a chronic leukemia virus such as FeLV, and some of the genes of the host cells known as sarc. Sarcoma viruses are also replication defective and cannot replicate without the help of a chronic leukemia virus which supplies some necessary viral proteins. FeSV, therefore, is always found in the presence of excess "helper" FeLV. FeSV has been shown, experimentally, to be able to cause tumors in a large number of vertebrate species and can transform human cells grown in tissue culture. It must be considered, therefore, to be a potentially severe public health hazard and cats with FeSV-induced multicentric fibrosarcomas should not be kept as pets.*

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## Introduction

The first sarcomagenic oncovirus (oncogenic RNA virus) to be discovered was the Rous sarcoma virus which was discovered in 1911 in a spindle cell sarcoma of a chicken.<sup>1</sup> In the same year Fujinami and Inamoto isolated another avian sarcoma virus (ASV).<sup>2</sup> However, it was not until the 1960s that mammalian sarcoma viruses were discovered.

## Types of Oncoviruses

Oncoviruses are now classified into one of three general categories: 1) chronic leukemia viruses, 2) acute leukemia viruses and 3) sarcoma viruses. The chronic leukemia viruses, such as the feline, murine and avian leukemia viruses replicate to high titers in their hosts and cause leukemias or lymphosarcomas only after a long latent period. They are often called "replication competent" or "helper" leukemia viruses and are not, in themselves, thought to be transforming viruses since they do not directly transform fibroblasts in culture. The acute leukemia viruses are formed by recombination between chronic leukemia viruses and host cell sequences and are replication defective viruses which transform fibroblasts in culture and cause lymphoid tumors in animals after short latent periods.<sup>3,4</sup> The Abelson murine

leukemia virus (A-MuLV) is an example of an acute leukemia virus of mice which is always found in association with excess helper MuLV. A-MuLV is a laboratory isolate that arose in a steroid treated BALB/c-Cr mouse injected with Moloney MuLV.<sup>5</sup> Unlike the AKR-MuLV which causes leukemia in six to nine months in AKR mice,<sup>6</sup> the A-MuLV induces non-thymic lymphosarcoma in only three to five weeks after injection and will transform lymphoid cells, hematopoietic cells and fibroblasts in culture.<sup>7-9</sup> The third group of oncoviruses are the sarcoma viruses of birds and mammals. Sarcoma viruses are acute transforming viruses which are also unable to replicate, *ie*- they are replication defective, and can transform fibroblasts *in vitro* and induce sarcomas in animals (for reviews see references 10, 11, 12). They occur as mixtures of defective sarcoma virus and excess helper replication competent leukemia virus. The only replication competent sarcoma viruses are the Rous and B77 avian sarcoma viruses.<sup>10,11,13</sup> Sarcoma viruses appear to be recombinant viruses generated by recombination between portions of the genomes of replication competent leukemia viruses<sup>14-16</sup> and host cell genetic sequences.<sup>17-19</sup> For example, the murine and feline sarcoma viruses are generated from MuLV and FeLV, respectively, by recombination with mouse and cat host cell sequences.<sup>18,19</sup> The host cell sequences analogous to the transforming gene of sarcoma viruses (*src*) are called *sarc*, however, a new nomenclature system for these genes is under review.

### Mammalian Sarcoma Viruses

Mammalian sarcoma viruses were not discovered until the early 1960s and are classified, as are the leukemia viruses, by the host species from which the viruses were originally isolated [Table 1].

#### Rat Sarcoma Viruses

In 1964 Harvey isolated the first mammalian sarcoma virus, the Harvey murine sarcoma virus (Ha-MuSV) during passage of Moloney MuLV in Chester-Beatty rats.<sup>20</sup> Pleomorphic sarcomas were induced in BALB/c mice at the site of injection of filtered plasma from a leukemic rat. Sarcomas were also induced in newborn rats and hamsters and erythroblastosis and splenomegaly occurred in the animals developing sarcomas.<sup>21</sup> The Kirsten murine sarcoma virus, Ki-MuSV, was isolated in 1967 in a similar fashion by passage of Ki-MuLV in Wistar-Furth rats.<sup>22</sup> It should be remembered that these sarcoma viruses were thought to be of mouse origin since they were MuLVs passaged in rats. At

that time the mechanism of generation of sarcoma viruses by recombination between leukemia virus genomes and host cell sequences was not known. It is now known that these rat sarcoma viruses are composed of a MuLV genome with an inserted rat cellular gene.

In contrast to the generation of the Harvey and Kirsten rat sarcoma viruses by MuLV *in vivo*, Rasheed and her associates isolated a completely rat sarcoma virus by *in vitro* co-cultivation of Sprague-Dawley rat embryo cells, which release an endogenous ecotropic rat oncovirus, with chemically transformed rat cells. The newly isolated rat sarcoma virus, RaSV, can transform rat cells in culture, but it is not yet known if it will induce tumors in animals.<sup>23</sup> The virus is composed of a rat leukemia virus genome with an inserted rat cellular gene.

#### Mouse Sarcoma Viruses

In 1966 Moloney isolated the Moloney murine sarcoma virus, Mo-MuSV, by inoculating high doses of mouse-derived Mo-MuLV into mice.<sup>24</sup> Mo-MuSV induces rhabdomyosarcomas in mice in only three to five days after inoculation. Unlike the Ha-MuSV, Ki-MuSV and Mo-MuSV which were generated experimentally by passage of helper leukemia viruses in animals, several MuSVs have been isolated from naturally occurring tumors of mice. The FBJ osteosarcoma virus, FBJ-MuSV, was isolated by Finkel, Biskis and Jinkins in 1966 from a naturally occurring osteosarcoma of a CF-1 mouse and induces osteosarcomas when inoculated into newborn mice.<sup>25</sup> Another sarcoma virus was isolated by Peters and his associates from a hemangiosarcoma of a BALB/c-Cr mouse and produces hemangiosarcomas when inoculated into mice.<sup>26</sup> The MuSVs are recombinant viruses composed of partial MuLV genomes with an insertion of a mouse cellular gene.

#### Primate Sarcoma Virus

In 1971 Theilen and his associates isolated the woolly monkey sarcoma virus, WoSV, also known as the simian sarcoma virus type 1 (SSV-1).<sup>27</sup> The virus was isolated from a naturally occurring fibrosarcoma of a pet woolly monkey in California, but also induces fibromas and fibrosarcomas in marmoset monkeys.<sup>28</sup> It is interesting, and somewhat frightening, to learn that a Gibbon ape, which was kept as a pet in the same house as the woolly monkey that developed fibrosarcoma, died of an undetermined disease and may have been infected with the Gib-

Table 1

## Origin of Mammalian Sarcoma Viruses\*

Sarcoma Virus	Helper Viral Sequences	Host Cell Sequences	Isolation History
<b>Rat Sarcoma Viruses</b>			
Kirsten-MuSV	Ki-MuLV	Wistar-Furth rat	Passage of Ki-MuLV in rat
Harvey-MuSV	Mo-MuLV	Chester-Beatty rat	Passage of Mo-MuLV in rat
Rasheed-RaSV	RaLV (Sprague-Dawley)	Fischer rat?	Co-cultivation of SD-1 rat cell with chemically transformed rat cells
<b>Mouse Sarcoma Viruses</b>			
Moloney-MuSV	Mo-MuLV	BALB/c mouse	Passage of Mo-MuLV in mice
FBJ osteosarcoma virus	FBJ MuLV? (AKR MuLV?)	?	From a naturally occurring osteosarcoma of CF-1 mouse
BALB/c-MuSV	BALB/c-MuLV	?	From a hemangiosarcoma of a BALB/c-Cr mouse
<b>Feline Sarcoma Viruses</b>			
Snyder-Theilen FeSV	FeLV	Cat	A naturally occurring fibrosarcoma
Gardner-Arnstein FeSV	FeLV	Cat	A naturally occurring fibrosarcoma
Susan McDonough FeSV	FeLV	Cat	A naturally occurring fibrosarcoma
Parodi-Irgens FeSV	FeLV	Cat	A naturally occurring fibrosarcoma
Hardy-Zuckerman FeSV	FeLV	Cat	A naturally occurring fibrosarcoma
<b>Primate Sarcoma Virus</b>			
Woolly monkey sarcoma virus SSV	SSAV	Woolly monkey	From a naturally occurring fibrosarcoma of a woolly monkey

\*Adapted from Shih, T.Y. and Scolnick, E.M. Ref. 12.

bon ape leukemia virus (GeLV).<sup>29</sup> The SSV and GaLV are closely related antigenically.

### Feline Sarcoma Viruses

#### Naturally Occurring FeSV Isolates

After the discovery of the association of oncoviruses with avian and murine leukemias and sarcomas it was only logical, after the discovery of FeLV, to search for a corresponding feline sarcoma virus in cats with sarcomas. Fibrosarcomas account for between 6% to 12% of all cat tumors and usually occur in old cats as solitary, relatively slow growing, tumors.<sup>30-35</sup> They comprise about 37% of all feline skin tumors and 10% of all tumors of the oral cavity. In the late 1960s I began testing cats with fibrosarcomas for the feline leukemia virus. All of the clinical cases that I tested occurred as solitary fibrosarcomas in old cats and none of the cats tested had

FeLV antigens. Thus, since the mammalian sarcoma viruses share structural antigens with their leukemia virus progenitors it was concluded that no feline sarcoma virus (FeSV) was present.<sup>36-38</sup> Then, in 1969 Snyder and Theilen found a young (two year old) female domestic short-hair cat with multiple subcutaneous fibrosarcomas and multiple metastases.<sup>39</sup> The tumors were removed and frozen at -70 C for six months. The tumor tissue was examined by electron microscopy and C-type virus was found. The tumor was then homogenized and cell-free materials were used to induce fibrosarcomas in newborn kittens. This was the first isolate of a feline sarcoma virus and was designated, as were the murine sarcoma viruses, by the names of the investigators who discovered the virus. Since then two other FeSVs have been isolated and characterized and numerous naturally occurring fibrosarcomas of pet cats have been studied [Table 2].

**Table 2**  
FeSV Isolates From Pet Cats with Fibrosarcomas

FeSV Isolate	Age	Sex	Breed	Number of Tumors	Site(s) of Tumor	Electron Microscopy for C-type Virus	FeLV Antigens	Transmission Experiments
Snyder-Theilen <sup>39</sup> (ST-FeSV) 1969	2 yrs	F	DSH	Multiple	Subcutaneous with multiple metastases	Many seen	Not done	Transmitted to kittens & puppies
Gardner-Arnstein <sup>40</sup> (GA-FeSV) 1970	5½ yrs	M	Siamese	Multiple, recurrent after surgery and 1000 rad irradiation 5 mos earlier	Subcutaneous in left flank, no metastases mentioned	Many seen	Positive by complement fixation	Transmitted to 37 of 46 kittens, 2 of 2 adult cats and to fetal, newborn and adult dogs.
Susan McDonough <sup>41</sup> (SM-FeSV) 1971	1½ yrs	F/ohe	DSH	Multiple	Recurrent subcutaneous and cutaneous in right thigh, right flank, left shoulder, no metastases	Many seen	Positive by immunodiffusion	Transmitted to kittens & puppies
Snyder-1971 <sup>42</sup> (S-2 FeSV)	14 mos	F	Not given	Multiple	Subcutaneous with multiple metastases	Many seen	Not done	Transmitted to 5 of 5 kittens
(S-3 FeSV)	7 yrs	M	Not given	Solitary though recurrent after X-irradiation	Subcutaneous in left thorax: recurred in the lung & pleural metastases	Some C-type virus seen	Not done	Transmitted to 5 of 5 kittens
(S-4 FeSV)	7 yrs	M/c	Not given	Solitary	Deep fascia of neck	None Seen	Not done	Regressing tumors in 2 of 5 kittens
Parodi-Irgens <sup>43</sup> (PI-FeSV) 1973	1½ yrs	F	DSH	Multiple	Subcutaneous with metastases in lungs and peritoneum	Particle seen	Positive by immunodiffusion	Transmitted to 39 of 41 kittens
Hardy-Zuckerman (HZ-FeSV) (SKI 3465) 1980	4 yrs	M/c	DSH	Multiple	Subcutaneous in right & left hock & right foreleg	Not done	Positive by immunofluorescence	Tissue culture foci induced in cat & mink cells. Transmitted to 1 of 3 kittens.

Shortly after the isolation of the ST-FeSV, two other isolates were reported, one by Gardner and Arnstein and their associates, the GA-FeSV, and the other by Susan McDonough and her associates, the SM-FeSV. The GA-FeSV was isolated in 1970 from a five and one-half year old male Siamese cat with recurrent multiple subcutaneous fibrosarcomas in the left flank.<sup>40</sup> The first tumor was removed surgically and the cat was given 1,000 rads when the tumor recurred at the surgical site only two months later. The recurrent tumor consisted of eight to 10 firm 1 cm nodules in the subcutaneous tissue at

the original tumor site but no metastases were reported. Cell-free extracts of the tumor induced sarcomas in newborn kittens, adult cats and in newborn and adult dogs. The SM-FeSV was isolated in 1971 from a one and one-half year old female ovariohysterectomized domestic short-hair cat with recurrent multiple subcutaneous and cutaneous fibrosarcomas in the right thigh, right flank and left shoulder.<sup>41</sup> No distant metastases were seen. Cell free extracts of the tumor induced sarcomas in newborn kittens and we found that the original tumor had FeLV antigens by immunodiffusion.

In 1971 Snyder reported on three additional fibrosarcomas of cats which were transmissible by cell free extracts.<sup>42</sup> One of these occurred in a 14 month old cat (breed not given) with multiple subcutaneous fibrosarcomas and distant metastases. Numerous C-type viral particles were seen by electron microscopy. Cell free extracts from this tumor, designated here as S-2 FeSV, were able to induce progressive tumors in three of five kittens inoculated and regressor sarcomas in the remaining two kittens. Another fibrosarcoma occurred in a middle-aged cat, a seven year old male (breed not specified). This tumor was a solitary fibrosarcoma of the left thorax that recurred after radiation therapy and there were metastases in the lung and pleural cavity. This cat was similar to the GA-FeSV cat since both cats had received radiation as part of the treatment for their primary tumors. It is possible that radiation may have activated latent FeSV in these tumors.<sup>42</sup> Only a few C-type particles were seen by electron microscopy in the original tumor. Cell free extracts from this tumor, designated here as S-3 FeSV, were able to induce progressive sarcomas in three of five kittens inoculated and regressor tumors in the remaining two kittens. The third transmissible fibrosarcoma reported by Snyder, designated here as S-4, occurred in a middle-aged cat, a seven year old castrated male (breed not specified) who had a solitary fibrosarcoma in the deep fascia of the neck. No metastases were present and no C-type viral particles were seen by electron microscopy in 200 sections of the tumor examined. However, cell free tumor extracts from this cat did not induce regressor sarcomas in the five kittens inoculated, but did induce regressor sarcomas in two of the five kittens. In the same study, Snyder also examined the fibrosarcomas of three cats (9, 10 and 14 year old cats) with solitary tumors but did not find C-type particles by electron microscopy. No cell free transmission experiments were done from these older cats with fibrosarcoma. However, virus particles were seen in all of the experimentally induced kitten sarcomas induced with S-2 and S-3 extracts and even in the two kittens who developed regressor sarcomas from passage of cell-free S-4 extracts, despite the fact that there were no observable viral particles in the original S-4 tumor. There are no reports that the S-2, S-3, or S-4 FeSVs have been characterized or that tissue culture lines from these experimentally induced tumors were established.

Another isolate of FeSV was reported in 1973 from France by Parodi and Irgens and their colleagues.<sup>43</sup> The existence of this FeSV isolate is not

well known among FeLV researchers since the report was in a French journal. The PI-FeSV isolate was obtained from a one and one-half year old female domestic short-hair cat with multiple subcutaneous fibrosarcomas and metastatic lesions in the lung and peritoneum. C-type virus was seen by electron microscopy and FeLV antigen was detected by immunodiffusion in the original tumor. Cell free extracts of this tumor induced sarcomas in 39 out of 41 newborn kittens.

Recently Zuckerman and I have isolated a new FeSV from a four year old castrated male domestic short-hair cat with multicentric fibrosarcomas of the right and left hocks and the right foreleg. The tumor was recurrent at the site of surgical removal. Cell cultures of the original tumor have been established and cat fibroblasts and mink CCL-64 cells have been transformed by tumor homogenates. One of the three kittens inoculated with our HZ3465-FeSV developed a fibrosarcoma

### Occurrence of FeSV Fibrosarcomas in Pet Cats

My laboratory has been studying the occurrence of FeLV and FeSV in pet cats for the past 12 years. During this period 61 pet cats with naturally occurring fibrosarcomas were tested by the immunofluorescent antibody test for FeLV.<sup>44</sup> It was assumed that cats with fibrosarcomas who were FeLV positive had FeSV in their tumors and that such cats would be good candidates from which to isolate new FeSVs. The cats that we studied were not representative of a random population of cats with fibrosarcomas because we requested young cats with multiple sarcomas for our study. Twenty-three of the 61 cats had multiple (multicentric) fibrosarcomas. Nineteen of the 23 cats were five years of age or younger and all 19 cats were positive for FeLV-FeSV by the IFA test. In contrast, three of the four cats who were five years of age or older were FeLV-FeSV negative [Table 3]. Thus, in our study, only one FeSV infected cat with multicentric fibrosarcomas was over five years of age (seven years old).

Of the 38 pet cats with solitary fibrosarcomas, 34 were older than five years of age and all were FeLV-FeSV negative. The mean age of cats with FeLV-FeSV positive multicentric fibrosarcomas was 3.0 years (median age was also 3.0 years). In contrast, the FeLV-FeSV negative cats with solitary fibrosarcomas were significantly older—their mean age was 10.4 years and their median age was 10 years [Table 4, Figures 1, 2].

Table 3

FeSV Status and Age of Pet Cats  
with Solitary and Multicentric Fibrosarcomas

	Age	Number of Cats Tested	Number of FeLV-FeSV Antigen* Positive	Percent FeLV-FeSV Antigen Positive
Multicentric	<5 yrs	19	19	100%
	>5 yrs	4	1	25%
		23	20	
Solitary	<5 yrs	4	0	0%
	>5 yrs	34	0	0%
		38	0	
Total		61	20	32.8%

\*Determined by the immunofluorescent antibody test for FeLV.<sup>44</sup>

Thus, FeSV induced fibrosarcomas occur in young cats, usually less than five years of age, and these tumors are usually multicentric rather than solitary. However, it should be emphasized that FeSV induced multicentric fibrosarcomas occur very rarely in pet cats, occurring only about once for every 40 cats that develop solitary non-FeSV fibrosarcomas [Figures 3, 4, 5].<sup>45,46</sup>

#### Histological Characteristics of Feline Fibrosarcomas

The structural organization of fibrosarcomas consists of whorls and interwoven bundles of immature fibroblasts with variable amounts of intercellular collagen. The cytoplasm of the tumor cells is distinct from the collagen fibers and their nuclei are round or oval, hyperchromatic, and have two to five prominent nucleoli.

There is a histological difference between the FeSV positive multicentric fibrosarcomas of young cats and the FeLV negative solitary fibrosarcomas of older cats.<sup>39-42</sup> The solitary fibrosarcomas are usually compact, well differentiated, slowly invasive tumors which contain considerable amounts of collagen and reticulum. Mitotic activity is usually modest and thus the tumors are slow growing and can reach considerable size. In contrast, the multicentric FeLV positive fibrosarcomas are less compact (multiple lesions), less well differentiated, more invasive tumors which contain less collagen and reticulum. The fibrosarcoma cells are often in-

Table 4

Age of Pet Cats with Fibrosarcomas

Age	FeLV-FeSV Antigen Positive	FeLV-FeSV Antigen Negative
Average age	3.0 yrs	10.4 yrs
Median age	3.0 yrs	10.0 yrs

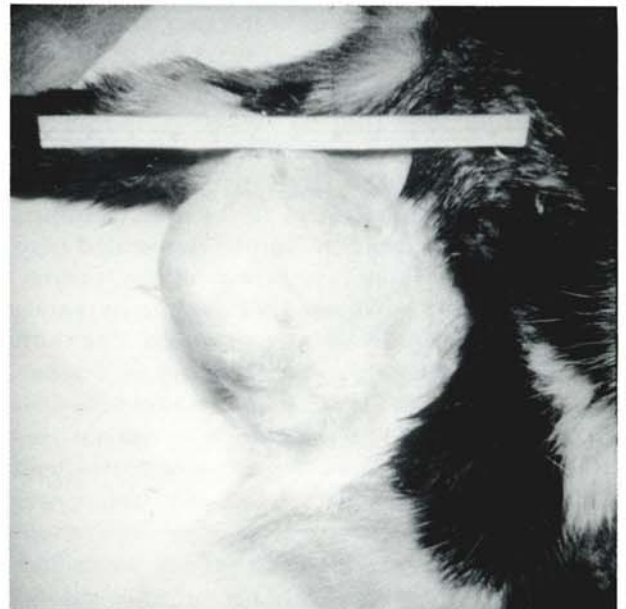


Figure 1— A solitary non-FeSV-induced fibrosarcoma of the hind leg in an old (11 years) pet cat.



Figure 2— A solitary non-FeSV-induced fibrosarcoma of the face in an old (13 years) pet cat.



**Figure 3 (Above)—** Multiple large FeSV-induced fibrosarcomas in the right foreleg and thorax of a young (four year old) pet cat. FeSV was isolated from the tumors of this cat (HZ-3590-FeSV) (this cat was obtained from Dr. Denis Macy, Colorado State University).

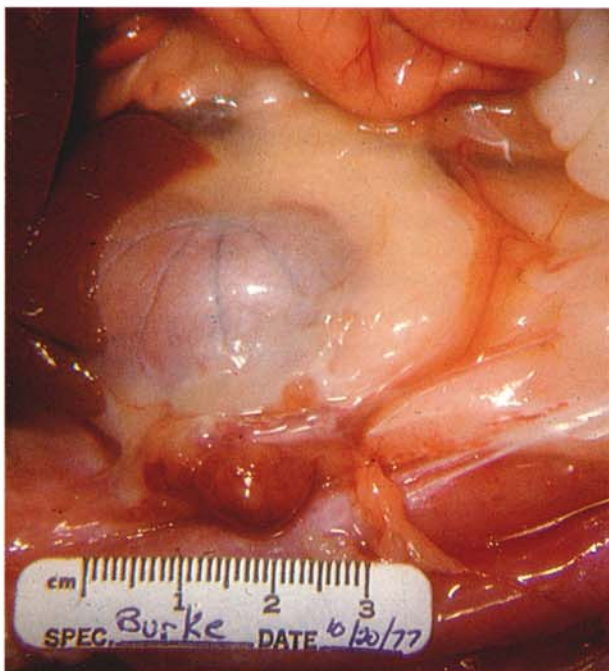


**Figure 4 (Right)—** Multiple small FeSV-induced fibrosarcomas in the skin of a young (three year old) pet cat.

vasive into surrounding tissues and grow rapidly. The tumors are usually pleomorphic, containing fusiform, polygonal and giant fibroblasts with numerous mitotic figures. The tumors are highly vascular and the center of the tumor nodules may be necrotic since the nodules grow so rapidly that they often outgrow their blood supply. Frozen sections of these tumors contain FeLV-FeSV antigens in the tumor cell cytoplasm.

#### Horizontal Transmission of FeSV

Although it is clear that FeLV is spread contagiously among cats there is no evidence, to date, that FeSV is also transmitted contagiously. In our studies of the biology of FeLV and FeSV we have attempted to determine if FeSV is spread contagiously or if it is generated *de novo* in FeLV infected cats. We have obtained detailed epidemiological data for 10 of the 20 cats with multicentric FeSV fibrosarcomas that we have studied. Seven of the 10 cats lived with either FeLV infected or lymphosarcomatous cats. In one household the FeSV fibrosarcoma cat had lived with two cats who had previously died of FeLV positive lymphosarcomas. Another household in our study was unique in that four cats died of lymphosarcoma and three other cats developed fibrosarcomas. This is the only household in our study where there were multiple cases of fibrosarcoma. Of the three cats that developed fibrosarcomas in this household only one cat was tested for FeLV-FeSV and was found to be positive.



**Figure 5—** An FeSV-induced fibrosarcoma metastatic lesion in the perirenal fat of a young pet cat (five year old).

In order for FeSV to be spread contagiously the virus must be able to be shed in the saliva or urine of infected cats. It is not known if FeSV can replicate, with the help of excess FeLV, in salivary glands or tracheal mucosa. However, it has been shown that FeSV can persist in the blood for up to three

months in experimentally inoculated kittens who have rejected their fibrosarcomas.<sup>47</sup> That observation indicates that either microscopic foci of virus-producing tumor cells remained or that virus replication occurred in normal, nonsarcoma, cells. Very recently, Donner and his associates have found that some FeSV infected and transformed mink nonproducer cells can revert to normal nontransformed cells and can retain the FeSV provirus that is integrated into their chromosomes.<sup>48</sup> It is possible that a similar situation may occur in cats with FeSV fibrosarcomas where the FeSV provirus may integrate into normal salivary gland or epithelial cells of the trachea in which FeLV also replicates. In this situation the FeLV could rescue the FeSV genome and FeSV could then be shed into the oral cavity where it could be transmitted contagiously. No studies have been done, to date, to determine if FeSV is present in the saliva of pet cats with naturally occurring FeSV positive fibrosarcomas. If FeSV is spread contagiously it must be a rare event since only one of our 10 cases occurred in a multiple case fibrosarcoma household. It appears then, that FeSV is probably generated *de novo* very rarely in FeLV infected cats by recombination with FeLV and cat cellular genes.

#### FeSV Experimentally Induced Fibrosarcomas in Cats

A total of seven different FeSV isolates have been reported, all of which are able to induce fibrosarcomas in newborn kittens [Table 5].<sup>39-43,49,50</sup> To date a total of 204 kittens have been inoculated with one of the seven FeSV isolates and 149 (73%) devel-

oped tumors, 113 (75.8%) of which were progressor tumors and 36 (24.2%) were regressor sarcomas. Most of the experimentally induced tumors examined by electron microscopy were found to contain numerous C-type virus particles. The induced sarcomas yielded transforming virus which induced sarcomas on subsequent passages into kittens, dogs, pigs, rabbits, goats and monkeys.<sup>49,51-56</sup>

Of the three well characterized FeSV isolates the GA- and SM-FeSVs appeared to be the most oncogenic. However, the Parodi-Irgens FeSV induced fibrosarcomas in 95% of the inoculated kittens.<sup>43</sup> The latent periods for tumor induction for most isolates was between two and three weeks in cats inoculated at a young age.<sup>57,58</sup>

Essex's group and my group have detected FOCMA on the cell membranes of all naturally-occurring and all experimentally FeSV-induced fibrosarcomas that we have tested.<sup>59-61</sup> In addition, all FOCMA positive feline fibrosarcomas were found to be positive for FeLV antigens by the IFA test.<sup>45,59,60</sup>

#### FeSV Experimentally Induced Melanomas in Cats

McCullough and his coworkers induced malignant melanomas by inoculating kittens subcutaneously with the GA strain of FeSV.<sup>62</sup> Palpable tumors developed at the site of injection in all six kittens within 21 to 45 days but the melanin pigmentation was observed in only one tumor when it was first palpable and developed in the other five tumors six weeks after their initial appearance. The melanocytes were primarily found in the upper

Table 5  
FeSV Experimentally Induced Fibrosarcomas in Cats

FeSV Isolate and Reference	Number of Cats Inoculated	Number of Tumors Induced	% of Cats Developing Tumors	Behavior of Tumors:	
				Progressors	Regressors
ST-FeSV <sup>39,49</sup>	65	39	60%	33	6
GA-FeSV <sup>40,50</sup>	73	55	75%	50	5
SM-FeSV <sup>41</sup>	10	8	80%	8	0
PI-FeSV <sup>43</sup>	41	39	95%	20	19
Snyder <sup>42</sup>					
<sup>s</sup> 2-FeSV	5	3	60%	1	2
<sup>s</sup> 3-FeSV	5	3	60%	1	2
<sup>s</sup> 4-FeSV	5	2	40%	0	2
	204	149		113	36



Table 6

## FOCMA Antibody Response in Cats Inoculated with FeSV

Cats with FeSV Induced Sarcomas: Regressor vs. Progressor Tumors	Number of Cats with Detectable FOCMA Antibody/ Number Inoculated	FOCMA Antibody Titers:			Geometric Mean Titer
		>1:4	>1:8	>1:16	
Regressor tumors or no tumor development	41/41 (100%)	41/41 (100%)	33/41 (80%)	28/41 (68%)	20.30
Progressor tumors	29/57 (51%)	13/57 (23%)	1/57 (2%)	1/57 (2%)	0.87

Adapted from Essex, et al, reference 67.

dermis but were also scattered throughout the fibroblastic areas. Virus particles were observed by electron microscopy in these melanomas.

Recently, Niederkorn and Shadduck have induced ocular melanomas by inoculating kittens intraocularly with GA-FeSV.<sup>63,64</sup> FeSV can induce solid tumors of mesodermal origin, can transform fibroblasts in culture, and in addition, the GA-FeSV can induce solid tumors of ectodermal origin; melanomas of the skin and eye. It appears therefore that the sarcomagenicity of FeSV is a *de novo* property of these viruses acquired by them concomitant with their acquisition of cat genetic information (Chen and Essex, manuscript in preparation).

#### Immune Response to FeSV Induced Tumors

The outcome of FeSV inoculation in experimental kittens depends on the: 1) age at inoculation, 2) dose of FeSV and 3) response to FeSV/FeLV and to FOCMA. FOCMA is an FeLV and FeSV-induced tumor-specific antigen found on the membranes of cells transformed by FeLV or FeSV, regardless of whether or not these viruses replicate in the transformed cells.<sup>45,59,60</sup> Antibody to FOCMA was first detected by Essex and his coworkers in cats that had been inoculated with FeSV.<sup>65-67</sup> More than two-thirds of the cats that developed tumors that regressed, or that did not develop tumors at all, had titers of FOCMA antibody greater than 16 [Table 6]. The geometric mean FOCMA antibody titer of these cats was more than 20-fold higher than in cats which developed progressing tumors. Conversely, only one of 57 cats that developed progressive sarcomas had a FOCMA antibody titer above 16. In addition, Essex noted that neonatal kittens who had maternally derived FOCMA antibody were resistant to progressive FeSV induced tumors.<sup>65</sup>

Although we have found that most FeLV uninfected cats that have protective titers of FOCMA antibody also have protective titers of FeLV neutralizing antibody,<sup>68</sup> Schaller and his coworkers did not find significant titers of neutralizing antibody in those FeSV-FeLV infected cats that had high FOCMA antibody titers and who had regressed their tumors.<sup>69</sup> In addition, FeSV inoculated (and persistently viremic) cats had significant levels of infectious FeSV remaining in their blood after regression of FeSV-induced sarcomas, indicating that FOCMA antibody and not neutralizing antibody was responsible for their tumor regressions.<sup>47</sup>

Histological examination of regressing FeSV-induced sarcomas showed evidence of an inflammatory cell infiltration indicating that the cellular immune system was also active in the regression process.

#### Host Range of FeSV

FeSVs are pseudotype viruses, that is, the FeSV RMA genome is enclosed in an FeLV envelope. The wide host range of the FeSV strains is dependent on the FeLV envelope component of the pseudotype viruses. Sarma and his associates have shown that the ST-, GA- and SM-FeSV strains are pseudotyped in FeLV-B envelopes.<sup>70-72</sup> However, since all three strains occur in nature with excess FeLV-A and -B it is probable that some FeSV particles were also pseudotyped with FeLV-A envelopes. FeSV with FeLV-A envelopes would have a restricted host range, being able to infect only cat and dog cells. Much of the research with FeSV has employed heterospecies cells and only FeSV with FeLV-B envelope is able to infect a broad range of heterospecies cells. However, Sarma demonstrated that neutralizing antiserum to FeLV-B and not to FeLV-A was able to inhibit all FeSV focus formation on

cat cells for ST-, GA- and SM-FeSV isolates thus suggesting that there was no FeSV with FeLV-A envelope present.<sup>70-72</sup>

Sarma was also able to construct a new pseudotype of the ST-FeSV with FeLV subgroup C as helper virus by superinfecting feline embryo fibroblasts, which were actively producing FeLV-C, with the ST-FeSV stock which consisted of FeSV (FeLV-A) and FeSV (FeLV-B).<sup>73,74</sup> Phenotypic mixing resulted in the production of ST-FeSV (FeLV-A), ST-FeSV (FeLV-B) and ST-FeSV (FeLV-C) pseudotypes, and the ST-FeSV (FeLV-C) of the mixture was isolated on guinea pig embryo cells in which only FeLV-C and not FeLV-A or-B can replicate. This new pseudotype was then able to induce sarcomas in guinea pigs because the FeLV-C envelope of the new ST-FeSV enabled infection of guinea pig cells.<sup>74</sup> Others have constructed FeSV pseudotypes using the amphotropic MuLV as helper virus.<sup>75,76</sup> Amphotropic MuLV is able to replicate in mouse and numerous other species' cells. Thus, by rescuing the FeSV genome in a MuLV envelope from nonproducer cells transformed by FeSV, mouse cells can be infected by the FeSV (Amph-MuLV) pseudotype and the FeSV genome can then transform the murine cells. There have been no reports concerning the ability of FeSV (Amph-MuLV) to induce sarcomas in mice or kittens.

In addition to the construction of new pseudotypes of FeSV in order to circumvent the host restrictions imparted by the helper FeLV-B envelope of the ST-, GA- and SM-FeSV pseudotypes, host restrictions for FeSV transformation can be overcome by using FeSV proviral DNA in transfection experiments. In recent years DNA mediated transfer experiments or DNA transfections have become important tools for the study of transforming viruses and their genes.<sup>77,78</sup> The genomic DNA of retroviruses can transform recipient fibroblasts in culture, thus circumventing host restrictions of the transforming virus envelope.<sup>77</sup> Several groups have been able to transform feline, mouse and mink cells by transfection with FeSV proviral DNA<sup>79,80</sup> (Besmer, 1980 personal communication). Thus, by using FeSV DNA, mouse cells in culture can be directly transformed by the FeSV genome even though FeSV cannot infect mouse cells.

It is clear from these experiments that the FeSV genome is able to transform all cells into which it is able to integrate. This finding is extremely important and indicates the wide transforming ability of the FeSV *src* gene which is derived from the cat cellular *sarc* gene.

## FeSV Oncogenicity in Species Other Than the Cat

### Susceptibility of Various Species Cells to FeSV

The avian, murine and now the feline sarcoma viruses have been shown to have a wide host range and are able to induce sarcomas experimentally in several species in addition to their host species. For example, early oncogenicity studies showed that the Rous sarcoma virus appeared to be restricted to birds, but it later became evident that tumors could be induced by this virus in several mammalian species, including primates, and that it could even transform human cells in culture.<sup>80-83</sup> The Kirsten-MuSV is also capable of transforming mouse, rabbit, pig, dog, cat, bovine and human cells *in vitro*.<sup>84</sup> Similarly, the three isolates of FeSV have been shown to induce sarcomas in dogs,<sup>39-41</sup> (Hardy, unpublished observation), rabbits,<sup>49</sup> sheep fetuses,<sup>51</sup> pigs<sup>52</sup> and nonhuman primates,<sup>49,53-56</sup> and they can transform cell cultures from a variety of mammalian tissues, including human cells [Table 7].<sup>19,48,75,79,85-94</sup>

**Table 7**  
Species Cells Susceptible to Transformation by FeSV

Species Cells Transformable by FeSV	Tumors Induced in Animals	Progressor or Regressor Tumors	<i>In Vitro</i> Transformation
Mouse	ND	NA	+*
Rat	ND	NA	+*
Mink	ND	NA	+
Guinea Pig	+	Progressor	+
Rabbit	+	Regressor	+
Cat	+	Progressor or Regressor	+
Dog	+	Regressor	+
Pig	+	Regressor	ND
Goat	+	Regressor	ND
Sheep	+**	Regressor	ND
Bovine	ND	NA	+
Tree Shrew	ND	NA	+
Monkey			
Macaca—old world	+	Regressor	ND
Marmoset—new world	+	Progressor	ND
Squirrel—new world	+	Regressor	ND
Human	ND	NA	+

ND = not done, NA = not applicable

\* by DNA transfection or with FeSV (Amph-MuLV) pseudotype virus.

\*\* Fetal sheep

### FeSV-Induced Tumors in Nonfeline Species

In general, most sarcomas induced by FeSV in nonfeline species are regressor rather than progressor tumors and, unlike the sarcomas induced

**Table 8**  
FeSV-Induced Fibrosarcomas in Dogs

FeSV Isolate & Reference	Tumors Developed/ Dogs Inoculated	Age of Dog Inoculated	Tumor Growth: Progressor or Regressor	C-type Virus or FeLV Antigen/Number Examined
GA-FeSV <sup>40,50</sup>				
Cat to dog transmission	6/6 4/5	Fetus 2 days old	Progressor Progressor	2/4
Dog to dog transmission	42/42 12/17 13/77	Fetus Newborn Older, Postnatal	Progressor Progressor Regressor	15/15 3/5 0/7
ST-FeSV <sup>49</sup>				
Cat to dog transmission	7/8	2 days old	Regressor	0/8
SM-FeSV <sup>108</sup>				
Cat to dog transmission	2/3	1 day old	Regressor	0/3
	86/158 (54%)			

by FeSV in kittens, few if any FeSV particles are present in heterospecies FeSV induced sarcomas.

#### Dogs

In general, fetal and newborn puppies are highly susceptible to FeSV induced fibrosarcomas [Figure 6, Table 8]. Seventy-three of the 81 (90%) fetal or newborn dogs inoculated with FeSV developed fibrosarcomas while, in contrast, only 13 of the 77 (17%) other postnatal dogs developed tumors. Gardner and his associates induced fibrosarcomas in numerous fetal, neonatal and young dogs with GA-FeSV.<sup>40,50</sup> They were able to induce fibrosarcomas in 10 of 11 puppies inoculated with either FeSV induced kitten tumor homogenates or with cell free kitten tumor concentrates. Subsequently, several dog to dog tumor transmissions in canine fetuses with homogenates or cell-free concentrates were 100% successful in the 42 surviving fetuses. In addition, inoculation of tumor homogenates from the canine fetal induced sarcomas into 17 newborn puppies was successful in inducing tumors in 12 puppies. However, young puppies and older dogs were often refractory to induction of fibrosarcomas with dog fibrosarcoma concentrates and only 13 of 77 inoculated young puppies developed fibrosarcomas [Table 8].

The tumors that developed in the GA-FeSV inoculated fetal dogs were invasive, rapidly growing, well differentiated fibrosarcomas. They grew to a large size, metastasized frequently and had little or no inflammatory reaction. Large numbers of C-type



**Figure 6—** A large McDonough-FeSV-induced fibrosarcoma in the right dorsal pelvic region in a young beagle puppy that was inoculated, at the site of tumor development, on the first day of life. Although this tumor was induced by FeSV no FeSV was found in the tumor.

virus was observed by electron microscopy in most of the fibrosarcomas induced in fetal dogs. The fibrosarcomas that developed in dogs inoculated at three days of age were smaller tumors and had a marked inflammatory reaction. Virus particles were observed infrequently in three of seven of the tumors. Fibrosarcomas developed in only 13 of 57 older postnatally inoculated dogs, regressed rapidly and no virus was observed in these tumors.

Theilen and his coworkers were able to induce fibrosarcomas in seven of eight puppies inoculated with the ST-FeSV at two days of age.<sup>49</sup> Tumors developed after a latent period of eight to 28 days but all

regressed within 90 days. Virus was not found in any of these dog tumors by electron microscopy. Essex and his coworkers found that most dogs with regressor fibrosarcomas had high titers of FOCMA antibody which was an early indication that FOCMA antibody was important in immunosurveillance against these FeSV induced tumors.<sup>95</sup>

In general, fetal or newborn dogs appear to be very susceptible to FeSV induced fibrosarcomas and this may reflect the ability of both helper FeLV-A and FeLV-B to replicate in dog cells. It should be noted that most FeSV induced canine fibrosarcomas, except those induced in fetal dogs, do not have detectable FeSV when examined by electron microscopy.

#### Guinea Pigs

As mentioned previously, Sarma and Log and their associates constructed a new pseudotype of ST-FeSV with an FeLV-C envelope.<sup>73,74</sup> This pseudotype ST-FeSV (FeLV-C) is now able to infect and transform cells which are susceptible to FeLV-C infection. Guinea pig cells are only susceptible to FeLV-C and not to FeLV-A or -B subgroups. Sarma and Log were thus able to induce fibrosarcomas in one of four newborn Strain-2 guinea pigs with tissue culture grown ST-FeSV-C.<sup>73</sup> The initial tumor was transplantable in four of four Strain-2 guinea pigs. FeSV was detectable and FeLV antigen was present in cultured guinea pig tumor cells for only the first 20 days in culture and not thereafter.

#### Rabbits

ST-FeSV induced fibrosarcomas in three of three two-day-old New Zealand white rabbits 12 to 20 days after inoculation.<sup>49</sup> All tumors regressed and no virus was observed by electron microscopy. Although no serological studies of these animals were reported it should be noted that they may have produced high titered antibody to FeLV antigens and to FOCMA. In general, rabbits produce excellent precipitating antibody to FeLV and they are also able to produce FOCMA antibody in response to FeSV transformation of their own cells (Essex, personal communication).

#### Pig

Pearson and his colleagues were able to induce fibrosarcomas in three of four two-day-old pigs inoculated with ST-FeSV.<sup>52</sup> All three tumors regressed by 24 days after inoculation and no virus was observed by electron microscopy in these tumors. FOCMA antibody was found in the pigs after tumor regression.

#### Sheep

Theilen induced multiple undifferentiated sarcomas in a lamb fetus 40 days after *in utero* inoculation of ST-FeSV.<sup>51</sup> However, he failed to induce sarcomas in three lambs and six other fetuses, although that may have been because of the small dose of virus that was inoculated. No virus particles were observed in the tumors by electron microscopy.

#### Primates

Several groups have studied the induction of sarcomas in subhuman primates using either ST- or GA-FeSV. Both old and new world monkeys are susceptible to tumor induction by FeSV. Three species of old world monkeys were inoculated: *Macaca radiata*, *M. mulatta* and *M. fascicularis*. The new world monkeys that have been studied are the white-lipped (*Saguinus fuscicollis* and *S. nigricollis*) and cotton-topped (*S. oedipus*) marmosets and squirrel monkeys (*Saimiri sciureus*).<sup>41,53-56</sup>

#### Marmoset Monkeys

Deinhardt and his group first showed that the ST-FeSV strain was able to induce progressive sarcomas in newborn marmosets.<sup>53</sup> The marmosets developed multiple fibrosarcomas at the sites of inoculation together with intraabdominal metastases and died 46 days after inoculation. Electron microscopic examination of 100 tumor cells revealed no C-type particles in the original tumor, although, virus was seen in cultured tumor cells derived from these marmosets. In addition, inoculation of marmosets with tumor "minces" from the original marmoset induced tumors resulted in sarcoma development in the recipient marmosets indicating that FeSV was present in the original tumors despite the inability to observe virus by electron microscopy. Theilen and his group were also able to induce progressive multiple fibrosarcomas in two of four marmosets inoculated with ST-FeSV, although it is not clear whether these four animals were also four of the eight marmosets originally described by Deinhardt.<sup>49,53</sup>

Wolfe in Deinhardt's group has also reported on extensive studies of ST- and GA-FeSV induced fibrosarcomas in marmoset monkeys.<sup>56</sup> They were able to induce fibrosarcomas in 53 of the 74 inoculated marmosets using either FeSV derived from experimentally induced kitten fibrosarcomas or experimentally induced marmoset fibrosarcomas. Only marmosets between the ages of four months and eight years were resistant to tumor induction (no tumors developed in the 10 inoculated animals) whereas marmosets younger than four months of

age, and even one nine year old monkey, developed fibrosarcomas when inoculated with FeSV derived from kitten tumors. Of importance was the finding that marmoset fibrosarcoma "minces" and filtered extracts were able to induce fibrosarcomas in other marmosets. Similarly, GA-FeSV derived from kitten sarcomas induced fibrosarcomas in one of two inoculated marmosets and "minces" from this fibrosarcoma induced fibrosarcomas in 16 of 16 newborn marmosets. However, cell-free materials from the marmoset fibrosarcomas induced by GA-FeSV failed to induce fibrosarcomas in two inoculated marmosets. Kittens inoculated with cell free preparations from the ST- and GA-FeSV-induced marmoset fibrosarcomas also did not develop fibrosarcomas suggesting that there may have been a very low amount or no FeSV in the marmoset tumors. However, FeLV gs antigen and C-type virus were detectable in passaged marmoset tumors, in tumor cells grown in culture, and virus derived from marmoset tumor cell cultures was oncogenic. Thus, it appears that virus is repressed or only expressed in low amounts in the animals with tumors, but is expressed and can replicate once the tumor cells are removed from the host and grown in tissue culture.

#### Macaca Monkeys

Theilen and Wolfe and their groups were also able to induce fibrosarcomas in *Macaca* monkeys with the ST-FeSV.<sup>49</sup> Five of six five-to-ten-day old monkeys developed fibrosarcomas 15 to 17 days after inoculation but, unlike the FeSV induced sarcomas of marmosets, the tumors regressed in all five of the *Macaca* monkeys and no C-type virus was seen by electron microscopy in these tumors.

#### Squirrel Monkeys

Rabin and his associates were able to induce fibrosarcomas in all six squirrel monkeys that they inoculated with ST-FeSV.<sup>55</sup> However, only two of the fibrosarcomas, those induced in newborns, were progressive. These two tumors were examined and were found to be composed of pleomorphic cells that grew both in suspension and as monolayers in culture. No virus was seen in the tumors or in early passage cultured cells derived from the tumors. FeLV antigen was detectable in the cultured cells of one of the two tumors. Aviable tumor cell inoculum of one of these tumors induced sarcomas in kittens which were of kitten and not monkey origin. No FeLV-FeSV antigens nor transforming virus were found in the other tumor studied and it appears that FeSV induces either FeSV-producer tumors with low amounts of virus or nonproducer tumors in these monkeys.

## Virology of the Feline Sarcoma Viruses

### Molecular Biology of Feline Sarcoma Viruses

The FeSVs are recombinant viruses generated by recombination between portions of the viral RNAs of FeLVs and genetic information from the cat cell. Thus, FeSV has several FeLV genes together with genetic information, obtained from cat cells called *sarc*. When *sarc* is inserted (transduced) into FeSV it is known as the FeSV *src* gene. The *src* gene is responsible for the transforming function of FeSV which enables FeSV to transform fibroblasts in culture and to induce fibrosarcomas and melanomas in kittens under experimental conditions. In order to understand the generation of FeSV we must first understand the genome of FeLV.

### FeLV Genome

The molecular structure and sizes of genomic RNAs of leukemogenic oncoviruses (helper-independent type-C viruses) are remarkably similar. The FeLV RNA is contained in the viral nucleoid and is single stranded. After disruption of FeLV and centrifugation of the viral RNA in a sucrose density gradient the RNA has a sedimentation velocity of 60 to 75S.<sup>96-99</sup> The length of the Snyder-Theilen FeLV helper RNA in the ST-FeSV stock is 7.5 kilobases.<sup>79</sup> By heating the FeLV 75S RNA, two subunits of about 26 to 37S are obtained.<sup>98,100</sup> Thus, the FeLV 75S viral RNA consists of two 37S RNA subunits arranged as an inverted dimer structure linked near the 5' ends of the subunit.<sup>101</sup> The two RNA subunits have identical nucleotide sequences which means that the genome is diploid.<sup>102</sup> The viral RNA contains various forms of cellular RNA. The most important of these is a transfer RNA required as a primer for RNA-dependent DNA synthesis [PB in Figure 1].<sup>12,103</sup>

Three genetic functions have been identified in the FeLV genome:<sup>10-12,45,104</sup> 1) the *gag* gene codes for internal FeLV structural proteins; 2) the *pol* gene codes for the viral reverse transcriptase and 3) the *env* gene codes for the envelope glycoproteins. The gene order of the FeLV genome from the 5' end is *gag-pol-env* -3'.<sup>88,91,105,106</sup> The intragenic order of the *gag* gene proteins is N-p15-p12-p30-p10 [Figure 1].<sup>91,105,106</sup>

### FeSV Genome

As mentioned previously, the genomes of the ST-, GA- and SM-FeSV strains are composed of two distinct subsets of nucleic acid sequences.<sup>19</sup> These include those sequences shared in common with the FeLV helper virus and designated *com* sequences and those sequences unique to the sarcoma virus, designated *src*, which confer the trans-

forming properties to FeSV.<sup>19</sup> The *src* sequences are derived from cellular sequences called *sarc* [Figure 7] and although these sequences are closely related they are not identical. In analyses of the ST- GA- and SM-FeSVs, it has been found that the *src* sequences of the ST- and GA-FeSVs are identical and are derived from the same cat cellular sequences (gene), while the *src* sequences of the SM strain are not related to either the ST or GA *src* sequences.<sup>19</sup> This indicates that the *src* sequences of the ST- and GA-FeSVs were derived from the same cat cellular gene whereas the SM-FeSV *src* sequences were derived from a different cat gene. Interestingly, the Fujinami ASV *src* sequence is closely related to the ST- and GA-FeSV *src* but not to the SM-FeSV *src*.<sup>107</sup> Thus, a cellular gene that has been conserved in many species has been transduced to produce sarcoma viruses in two diverse species.

The three FeSVs are defective for replication because they lack the *pol* gene and cannot synthesize the viral enzyme reverse transcriptase which is essential for oncovirus replication. In addition, they lack most of the *env* gene and thus are unable to synthesize the gp70 and p15E which are required for production of the viral envelope.<sup>79</sup> In nature, FeSV exists as pseudotype virus with excess FeLV helper.<sup>70-72</sup> The FeSV particle contains the 4.3 kilobase "defective" RNA which is packaged, at the cell membrane, into an FeLV gp70 and p15E envelope of helper FeLV origin. Cat cells infected with FeSV are also infected with FeLV which replicates from the same cells. Thus, two types of viruses are produced by such cells, replication competent FeLV, where the FeLV RNA is enveloped at the cell membrane by FeLV gp70 and p15E, and FeSV where the FeSV defective RNA genome is also enveloped at the cell membrane by FeLV gp70 and p15E. Thus, the budding FeSV can infect other cells since it has an envelope and can attach to the cell receptor. The reverse transcriptase of excess helper FeLV in FeSV stocks enables the FeSV genome, in the infected cell, to be copied by the process of reverse transcription. (See FeLV paper in this issue.) The resulting FeSV proviral DNA can then become integrated into the infected cell's genome. Since the FeSV provirus contains the transforming *src* gene, the cell can be transformed as a result of provirus transcription.

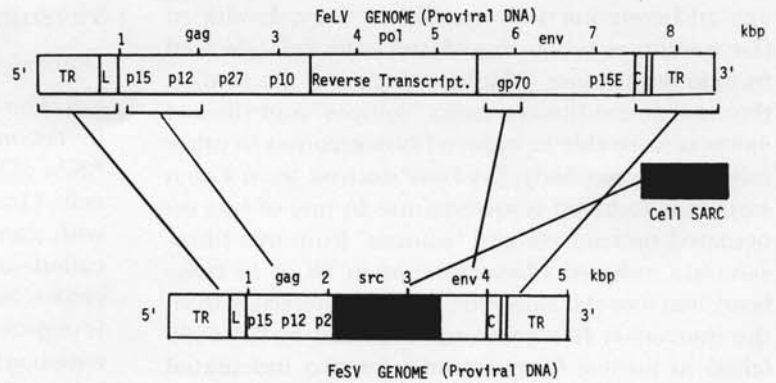


Figure 7— Generation of feline sarcoma viruses by the recombination of the FeLV genome with a cat cellular gene(s) called *sarc*. FeSVs are unable to replicate because some of the FeLV genes that are required for replication are deleted when the FeSVs are generated.

#### Origin of FeSV *src* Transforming Sequences

In elegant molecular biological experiments, Frankel and his coworkers showed that FeSV is replication defective and that the FeSV *src* is present as a single copy gene per haploid cell in domestic, small Mediterranean and large cat DNA, but is only present as less than one-half a copy in other carnivores and little if any copies exist in the DNA from primates, rodents and ungulates.<sup>19</sup> Recently, however, the Fujinami ASV *src* sequence has been shown to be closely related to the ST- and GA-FeSV *src* but not to the SM-FeSV *src*.<sup>107</sup> Frankel also showed that the ST- and GA-FeSV *src* sequences are closely related to each other but that the SM-FeSV *src* is unrelated.<sup>19</sup> In addition, he showed that the FeLV sequences of all three FeSVs are similar. These results indicate that FeLV and at least two different cat cellular genes can generate FeSV. This finding differs from the finding that the *src* sequences of MuSV, RaSV and most ASV are identical for all different isolates within the same species.<sup>41,11,12</sup> It will be interesting to determine if new additional FeSV isolates have *src* sequences related to the ST-GA-FeSV or to the SM-FeSV, or if yet other cat cellular genes are involved in the generation of different FeSVs.

Frankel and his coworkers also studied feline lymphosarcoma (LSA) cells for the expression of FeLV mRNA and *src* specific mRNA.<sup>19</sup> They found FeLV mRNA in FeLV positive LSA cells but not in FeLV negative LSA cells. However, no *src* mRNA was found in either FeLV positive or negative LSA cells. Thus, since FOCMA is induced by FeSV on cells

transformed by this virus and since all LSA cells, regardless of their FeLV status express FOCMA, the absence of *src* mRNA suggests that *src* may not code for FOCMA.<sup>59,60</sup>

## Conclusion

FeSV is the most common naturally occurring sarcoma virus known. It can be generated in any FeLV infected cat by genetic recombination between FeLV and certain genes of the cat. FeLV infection could therefore have an unexpected result,

namely, the production of a highly virulent sarcomagenic virus. FeSV has been shown, experimentally, to be able to cause tumors in a large number of vertebrate species and can transform human cells grown in tissue culture. It must be considered, therefore, to be a potentially severe public health hazard and cats with FeSV-induced multicentric fibrosarcoma should not be kept as pets. From a research viewpoint, however, FeSV is valuable in that it may enable us to obtain a greater understanding of the molecular mechanisms by which oncoviruses cause cancer.

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