Feline mesenchymal stem cells (MSCs; sometimes referred to as mesenchymal stromal cells) were first mentioned in the literature in 2002.¹ Significant interest has been placed on the potential of MSC and related animal cell and tissue-based products (ACTPs) to address the unmet therapeutic need in veterinary and human medicine. Despite this pressing need and interest, there are still no approved veterinary stem cell products available for use in cats in the US. To evaluate the current state of mesenchymal stem or stromal cell (MSC) research in cats, a scoping review of published literature was performed, which identified 108 publications related to feline MSCs. Twenty-six of the articles described administration of MSC products to a total of 215 cats. Twelve of the studies included a control group. These experimental and clinical trials used 7 cell sources, 9 administration routes, 12 delivery vehicles, and a 300-fold range in dosages for initial studies in healthy cats and cats with 12 naturally occurring and induced diseases. The majority of studies administered 2 doses of allogeneic, adipose-derived MSC IV and monitored a median of 6.5 treated cats for a median of 90 days. The majority (150/215 [69.8%]) of cats had no reported adverse events associated with treatment. Although an increase in feline MSC publications in the past 10 years indicates progress, the wide variety and small number of studies using MSCs and MSC products in cats demonstrate that current evaluations are mostly still in the discovery phase, and several issues remain related to larger scale trials using MSC products in cats. The current available publications provide information to direct further clinical study development and informed owner consent for study enrollment.

**Keywords:** stem cell, stromal cell, feline, mesenchymal, safety
Methods

An online bibliographic database (PUBMED) was searched in January 2024 for relevant publications of sufficient detail for analysis. The bibliographies of identified studies were further evaluated for relevance. Additional keyword searches were performed in PUBMED and Google Scholar for cross-reference and validation. Study information was summarized for review and descriptive analysis using Microsoft Excel and GraphPad Prism 10.

Results

Available articles

PUBMED search terms included ((feline) AND ((stem cell) OR (stromal cell) OR (stromal vascular fraction))), which resulted in 1,664 articles. A filter was applied to limit dates from 2002 to 2024 based on the date of the first publication describing feline mesenchymal stem cells,1 which resulted in 138 articles. Articles were individually reviewed for relevance, and a total of 108 articles were included for review. The number of articles published annually related to feline MSC notably increased starting in 2014 (Figure 1). The most articles published per year was 17 in 2023.

Study types

Out of the 108 relevant articles, 23 were review articles (21.2%). Forty of the articles (37.0%) were basic science articles primarily describing cell characterization, differentiation, processing, culture, and donor effects, and 14 articles primarily described mechanisms of action (13.0%). Four articles were unclassified and descriptive in nature (3.7%).

Twenty-six articles (26/108 [24.1%]) described primary administration of MSC or MSC products to cats in experimental and clinical studies (Figure 1). Of these 26 publications, 16 were studies in healthy cats (2 publications)9,10 or cats with naturally occurring disease (14 publications),11-24 8 were studies in induced models of disease,25-32 and 2 were single case studies.33-34 One retrospective study35 reported on long-term follow-up on some of the cats included in the previous 26 articles and was not included in the results due to overlap.

Twelve of the 26 publications (46.2%)9,13,14,20,23,25–29,31,32 describing primary administration of MSCs or MSC products to cats included a control group.

Study size

The 26 articles described the use of MSCs or MSC products in a total of 215 cats. Eighty of the cats (80/215 [37.2%]) had induced disease, 23 were healthy cats (23/215 [10.7%]), and 112 had naturally occurring disease (112/215 [52.1%]; Figure 1). The number of cats treated per publication ranged from 1 to 24, with a median of 6.5.

Donor type

Information on donor type was available in 25 of the 26 articles (ie, 191 cats). The majority used allogeneic cells, ie, from another individual of the same species (15/25 studies [60%]), accounting for 61.8% (118/191; Figure 2) of the treated cats. Autologous cells, ie, from the same individual, were used in 11 of the 25 (44.0%) studies and 33.0% (63/191) of the treated cats, and xenogeneic cells, ie, from another species, were used in 1 study (1/25 [4.0%]) and 5.2% (10/191) of the treated cats.

Cell source

Seven cell sources for MSCs and MSC products were used in the described 26 articles. The most common source was adipose tissue, which was used in 18 of the studies and a total of 119 cats (Figure 2). The second most common cell source was bone marrow, which was used in 6 of the publications and 43 cats.11,22,26,27,29 The remaining cell sources were only used once: placenta in 8 cats,24 uterine in 18 cats,30 peripheral blood in 10 cats,10 amniotic membrane in 10 cats,10 and cardiac in 7 cats.26 Three studies11,26,29 used more than 1 cell source.

Route of administration

The majority of studies (17/26) used IV administration in a total of 146 cats (Figure 2). Intrarenal (7/215 cats),11,16 intrathecal (8/215),22,32 and implant-associated (2/215)33-34 delivery were used in 2 publications each. The remaining administration

Figure 1—Publications by year on feline mesenchymal stem or stromal cells and derivatives. Total publications (n = 108), in vitro and in vivo (A), publications of in vivo studies (26) in cats (B), and disease categories of cats (215) in the in vivo studies (C) are shown.
routes were only described in 1 publication each: IP (10/215 cats), intra-arterial (5/215), intracoronary (11/215), intravitreal (24/215), and subconjunctival (5/215). Three cats received both IV and intrathecal injections.

**Dosage**

The dose of cells used ranged from \(0.1 \times 10^6\) to \(30 \times 10^6\). Most publications described the total dose used although several studies dosed based on body weight, and the total dose of cells used was then estimated based on the average cat weight (eg, 4.5 kg). Studies using SVF or EVs described total nucleated cell count (TNCC) or the number of cells used to generate the EVs in a specified time frame. The dose was not clearly stated in 1 study or available in the case report using fresh bone marrow.

The dose range for IV administration was \(0.3 \times 10^6\) to \(30 \times 10^6\), with the lowest dose used for the single xenogeneic study, which used equine peripheral blood-derived MSCs. The median IV dose was \(9.5 \times 10^6\), excluding the xenogeneic administration dose. The doses used for the remaining 8 administration routes were as follows: intrarenal (2 studies), \(0.1 \times 10^6\) and \(4 \times 10^6\); intrathecal (2 studies), \(4 \times 10^6\) MSC and \(10 \times 10^6\) TNCC; implant-associated (2 studies, 1 unspecified), \(5 \times 10^6\); IP (1 study), \(1 \times 10^6\); intra-arterial (1 study), \(1.5 \times 10^6\) to \(5.7 \times 10^6\) TNCC; intracoronary (1 study), \(10 \times 10^6\); and subconjunctival (1 study), \(2 \times 10^6\). The dose for the intravitreal administration was not clearly stated in the article.

The majority of studies delivered the treatment dose more than 1 time (15/26 [57.7%]). Twelve publications described a single administration (12/26 [46.2%]). The maximum reported administration times per cat was 6, with a median of 2 administrations. In studies that used more than 1 dose, the time between doses ranged from 12 to 70 days with a median of 14 days.

**Delivery vehicle**

Twelve different delivery vehicles were described in the 22 publications for which the information could be determined. The most common was PBS (6/22 publications) followed by Dulbecco PBS and heparin (5/22). Three studies used \(0.9\%\) NaCl and 2 studies used an implant: a polycaprolactone scaffold for a chronic oronasal defect and a 3-D–printed metal spacer for a large osseous defect in the tarsus. The remaining studies used various different solutions or mixtures: unspecified commercial freezing media containing 5% DMSO (1/22 publications), 6% hydroxyethyl starch and 2% DMSO diluted with 3.3% wt/vol trehalose in 0.9% NaCl (1/22 publications), platelet-rich plasma (1/22), Dulbecco modified Eagle medium alone (1/22) or with 10% DMSO (1/22), and Hank balanced salt solution with heparin (1/22).

**Follow-up**

Patient follow-up ranged from 3 days to approximately 1,460 days (4 years). Taking the shortest follow-up reported for cats in each publication, the median follow-up period was 90 days; median

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**Figure 2**—Donor types (A), cell sources (B), and administration routes (C) used in cats treated (n = 215 total) with mesenchymal stem or stromal cell products.
follow-up for cats with induced disease (47 days, range, 3 to 365) and healthy cats (38.5 days, range, 7 to 56) was less than that reported for cats with naturally occurring disease (182 days, range, 7 to 547).

**Adverse events**

Reported adverse events, defined as any untoward medical occurrence associated with the use of a drug whether or not considered drug-related, are listed (Table 1). One death was reported and stated to be an anesthetic event. The majority of the 93 adverse events were reported to be transient. Up to 65 cats (65/215 [30.2%]) were reported to have adverse events after MSC product administration, with no adverse events reported in at least 69.8% (150/215) of treated cats. Some cats were reported to have more than 1 adverse event. One study did not state the total number of cats experiencing adverse events, and the adverse events were then counted as occurring individually.

Adverse events were reported in up to 25/80 cats (31.3%) with induced disease, 18/112 cats with naturally occurring disease (16.1%), and 22/23 (95.7%) healthy cats (Figure 3). The 3 most common adverse events came from 2 studies in healthy cats in which all treated cats had significantly increased lymph node size and increased creatine kinase after IP administration or significantly decreased protein and albumin levels after xenogeneic IV administration. The creatine kinase changes were reported to be mildly above the reference range, and the increased lymph node size was present at both 1 and 5 weeks postinjection. The significantly decreased protein and albumin levels noted after xenogeneic IV MSC administration remained within the reference range. Vomiting, increased respiratory rate, diarrhea or loose stool, and fever were the next most common adverse events reported, and these each occurred in less than 5% (6 to 9 out of 215; Table 1) of treated cats during the reported follow-up periods. These adverse events were only noted with IV administration. Cessation of treatment and supportive care were implemented in some cases.

Other noteworthy adverse events were reported in 3 cats. One cat developed skin necrosis at the catheter site that required surgical intervention after IV administration in the forelimb of adipose-derived MSC for refractory feline chronic gingivostomatitis (FCGS). One cat developed a scrotal sarcoma approximately 1 month post treatment with 6 doses of allogeneic, adipose-derived MSC. Additionally, 1 healthy cat developed a hypersegmental cortical lesion suspected to be a renal infarct 1 week after a single IP injection of autologous, adipose-derived MSC, and similar lesions were seen in the other kidney at the 1-year follow-up. The majority of adverse events were reported with IV administration, which occurred in 52.9% of

**Table 1**—Adverse events (n = 93) reported in 26 publications describing studies of cats (n = 215) receiving mesenchymal stem or stromal cells (MSCs) or MSC products.

<table>
<thead>
<tr>
<th>Reported adverse events</th>
<th>No.</th>
<th>Percentage of cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>None*</td>
<td>150</td>
<td>69.8</td>
</tr>
<tr>
<td>Increased lymph node size**</td>
<td>10</td>
<td>4.7</td>
</tr>
<tr>
<td>Increased creatine kinase*</td>
<td>10</td>
<td>4.7</td>
</tr>
<tr>
<td>Decreased protein and albumin***</td>
<td>10</td>
<td>4.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9</td>
<td>4.2</td>
</tr>
<tr>
<td>Increased respiratory rate</td>
<td>8</td>
<td>3.7</td>
</tr>
<tr>
<td>Diarrhea or loose stool</td>
<td>7</td>
<td>3.3</td>
</tr>
<tr>
<td>Fever</td>
<td>6</td>
<td>2.8</td>
</tr>
<tr>
<td>Edema at catheter site</td>
<td>4</td>
<td>1.9</td>
</tr>
<tr>
<td>Mild topical wound</td>
<td>4</td>
<td>1.9</td>
</tr>
<tr>
<td>Otitis</td>
<td>3</td>
<td>1.4</td>
</tr>
<tr>
<td>Hematuria</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Urination</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Apathy</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Lethargy or decreased activity</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Horner syndrome or anisocoria</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Trace frank blood in litter</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Alopecia</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Skin necrosis at injection site</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Bruising/discomfort at harvest site</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Inappetence</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Open-mouthed breathing</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Ptyalism</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Scrotal sarcoma#</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Hyperechoic renal segmental cortical lesion</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Worsening inflammatory signs</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Death##</td>
<td>1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*Number inferred from information provided in publications. **IP only. ***Xenogeneic only, remained within reference range. #Occurred 1 month poststudy. ##Anesthetic event at Day 120.
studies using this route (9/17 studies). IV administration accounted for up to 78.5% (51/65) of cats with adverse events, and up to 34.9% (51/146) of all cats treated by the IV route (Figure 3). Adverse events were also reported in 40.0% (2/5) of cats treated in the single intra-arterial and 100% (10/10) of cats treated in the single IP study. Both of the intrarenal studies reported hematuria with 28.6% (2/7) of cats treated by this route. Adverse events were not reported with any of the other administration routes.

The majority of adverse events were seen with adipose-derived MSC products, accounting for at least 44.6% (29/65) of the cats experiencing adverse events and 24.3% (29/119) of the cats receiving adipose-derived MSC products (Figure 3). Up to 17 of 18 (94.4%) cats receiving uterine-derived MSC had adverse events, accounting for up to 26.2% (17/65) of the cats experiencing adverse events. Ten cats receiving peripheral blood-derived products had noted adverse events, accounting for at least 15.4% (10/65) of cats experiencing adverse events and 100% (10/10) of cats receiving peripheral blood-derived products. Five of the cats receiving bone marrow-derived products accounted for at least 7.7% (5/65) of all cats with noted adverse events and 11.6% (5/43) of cats receiving bone marrow-derived products. Two out of 8 cats receiving placenta-derived (25.0%) and 2 out of 10 cats receiving amniotic membrane-derived (20.0%) MSC product also had reported adverse events.

Adverse events were seen across the range of doses, in healthy cats, and in cats with both induced and naturally occurring diseases.

Discussion

Despite continued research in the 14 years since feline MSCs were first mentioned in the literature, there are currently no FDA-approved veterinary stem cell products for use in cats. To date, 108 publications describe feline MSCs and MSC products including 26 experimental and clinical trials administering them to 215 cats. These trials use 7 cell sources, 9 administration routes, 12 delivery vehicles, and a 300-fold range in dosages for initial studies in healthy cats and cats with 12 naturally occurring and induced diseases (Figure 4). Although an increase in feline MSC publications in the past 10 years indicates progress, the wide variety and small number of studies using MSCs and MSC products in cats, over half lacking a control group, demonstrates that current evaluations are mostly still in the discovery phase.

To date, the majority of studies have administered 2 doses of allogeneic, adipose-derived MSC IV and monitored a small number (median 6.5) of treated cats for a median of 3 months. The majority of cats have had no reported adverse events associated with treatment.

Are MSCs and MSC products safe in cats?

For a product to be considered safe based on FDA guidelines, valid scientific evidence must provide reasonable assurance that when used for its intended uses under the explicit conditions of use, the benefits to health outweigh any probable risks. Based on the 26 available studies including 215 cats, approximately 69.8% (150/215; Table 1) of cats that have been treated with MSCs or MSC products did not have a reported adverse event. There was 1 reported anesthetic-related death. The accuracy of this information is dependent on the patient numbers, monitoring, and follow-up performed and information reported in the available publications.

Several adverse events were noted in the studies. Transient, transfusion-like reactions with variable combinations of respiratory, gastrointestinal, and urinary symptoms, fever, and lethargy were reported in approximately 11% (23/215) of treated cats. Other adverse events appear to be related to the procedure, such as hematuria with intrarenal injection or bruising at the tissue harvest site. Some adverse events, such as the scrotal sarcoma, otitis, and renal infarcts, may or may not be related to the MSC treatment. Specific study variables may have a higher rate of side effects than others, such as IP administration or administration of allogeneic uterine-derived MSC or xenogeneic peripheral blood-derived cells; however, the numbers are based on very few animals and studies, the overall observed adverse events were relatively minor and/or potentially unrelated to treatment, and they may alternately represent more
thorough monitoring and reporting. The highest rate of adverse events was seen in healthy cats treated with MSCs, which may be due to the experimental nature of these studies; the impact of these treatment protocols on cats with naturally occurring diseases is less known.

These results align with those reported in the recent retrospective study35 of 38 cats with refractory FCGS treated with MSC IV, which reported adverse effects occurring during or immediately after treatment in 34% of cases, the majority being transient, self-resolving transfusion-like reactions. No long-term adverse events definitively related to the MSC treatments were reported in any of the 26 reviewed studies; however, the median follow-up time was only 90 days. Two reports36,37 totaling 42 treated cats did have longer-term follow-up for cats with inflammatory bowel disease and refractory FCGS going out several years without known complications. The retrospective study35 of 38 cats with refractory FCGS treated with MSC IV followed cats for up to 9 years post-treatment and noted that anemia, hyperthyroidism, renal disease, cardiac disease, gastrointestinal disease, and neoplasia developed in a few cats during this time period; however, the prevalence was similar to or lower than the general population except for anemia and cardiac disease.

It is important to note that all cell-based therapies inherently have the potential for increased risk compared to other non-cell–based therapeutics due to donor-associated issues (ie, infectious disease, compatibility) as well as issues with product generation (contamination, cell viability, product variability, etc) that require careful consideration. These issues make generalizations about safety challenging across manufacturers, products, and delivery details. Additionally, although donor and compatibility issues may not cause treatment-limiting adverse events, similar to blood product administration, they may alter MSC efficacy and thereby patient outcomes. Interestingly, Soltero-Rivera et al35 recently reported that transfusion-like reactions were twice as frequent with autologous MSC administration when compared to allogeneic; a similar relationship with adverse events was not definitively found in this larger review (Figure 3). Research has shown changes in cell therapies related to donor characteristics, such as disease status and age,11,36–38 and further research into donor optimization is warranted.

What barriers exist to moving toward larger clinical trials and clinically available MSCs and MSC products?

The ability to determine the safety and efficacy of feline MSCs or MSC product is limited by available knowledge, the ability to manufacture large amounts of cells or cell-based product consistently, and the logistics of delivering the product to clinics in a timely manner for use. The impact of cryopreservation, or cell storage, and shipping on cell viability, function, and sterility is a major consideration in the regenerative medicine field in general.39–43 At least 6 of the current clinical studies described using cryopreserved cells.10,12,19,24,28,30 with 1 study12 reporting increased adverse events with cryopreserved cells versus fresh cells. Several studies used cryopreserved tissue or cells that were recultured just before use. Only 5 studies19,20,24,25,28 noted that they shipped cells for use, with 1 study20 noting increased growth of bacteria after 48 hours.

Several additional barriers exist related to expansion of feline MSC clinical studies.44 Methods to verify cell function related to desired mechanism of action are needed to help evaluate donors and ensure consistent products. Availability of donor tissues is another limitation; the use of easily accessible, nonessential, or discarded tissues such as peripheral blood, placenta, uterus, and dental pulp are under investigation.10,16,24,30,45–53 Time and cost to generate MSC products are other barriers, and investigations using uncultured bone marrow, SVF, and EVs may help address these issues.19,31,33,54

Next steps

These studies set the stage for further experimentation and development in the field, but much work still needs to be done before feline MSCs and MSC products are ready for use outside of clinical trials. In particular, few of the studies involved shipment of cell products or were multicentered. Issues associated with large-scale manufacturing and shipping of cell products are multifactorial and an additional barrier to clinical application. In 2015 the FDA Center for Veterinary Medicine determined that ACTPs are to be regulated as drugs,4 which means that feline MSC products will need to go through FDA approval before clinical application outside of clinical trials. Additionally, clinical trials using ACTPs in client-owned animals must be included in investigational files opened with the FDA before study initiation.3,4

The basis of drug approval by the FDA is demonstration of safety and efficacy, as well as detailed manufacturing and shipping protocols. The current publications provide some initial information to address the issues of feasibility and potential safety to direct further clinical study development and, importantly, informed owner consent for study enrollment, but no feline MSC product has thus far met FDA safety and efficacy requirements for approval. A summary of current scope and efficacy information provided by these studies is presented in a follow-up review paper.8

In conclusion, 215 cats have been treated with MSC products to date as described in 26 publications using a wide variety of products and protocols. The majority of studies did not have a control group and only evaluated short-term follow-up. The majority of treated cats had no reported adverse events. Further work is needed to determine optimal study design, manufacturing, and delivery logistics to scale clinical studies using MSC products in cats.

Acknowledgments

None reported.
Disclosures

The authors have nothing to disclose. No AI-assisted technologies were used in the generation of this manuscript.

Funding

The authors thank Frankie’s Fund for funding open access to this article.

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