Gingivostomatitis (GS) is a common finding in veterinary feline patients. This oral disease is called by various descriptive names, such as recurrent oral ulceration, lymphoplasmacytic stomatitis, lymphocytic plasmacytic gingivitis stomatitis, plasmacytic stomatitis, chronic ulcerative paradental stomatitis, plasma cell gingivitis-stomatitis-pharyngitis, chronic ulcerative stomatitis and feline chronic gingivostomatitis (FCGS). Oral changes in cats are widespread, and in a study group of 109 cats all of them had some form of periodontal inflammation, with 94% of cats also showing signs of FCGS (37). In many cases, feline gingivostomatitis, even if properly treated, develops into its chronic form: feline chronic gingivostomatitis. FCGS is a well-known condition commonly encountered in veterinary practice, with prevalence ranging from 0.7% to 12.0% (37, 41, 93).

The most common clinical signs are dysphagia, halitosis, sialorrhea, weight loss, oral discomfort, oral hemorrhage, unkempt coat associated with different grades of gingivitis and uni- or bilateral lesions across the palatoglossal fold to the lateral tongue base (74) that can be erosive, proliferative or both. These lesions tend to localize in the palatoglossal arches, gums, palate, buccal mucous membrane and tongue (9). Dental radiographs of cats suffering from FCGS showed alveolar bone loss, which was dominated by horizontal bone loss, as well as inflammatory root resorption in 49% of cats and retained roots in 56% of cases (30). This chronic inflammatory disease is
characterized by the presence of lymphocytes and plasma cells in affected oral tissues, with less plentiful neutrophils, Mott cells (plasma cells containing intracellular inclusions of immunoglobulins) and mast cells (74).

**Etiopathogenesis**

Many conditions and infectious agents have been suggested to play a part in the pathogenesis of FCGS, including infectious pathogens, such as feline calicivirus (FCV), feline herpesvirus (FHV-1), feline immunodeficiency virus (FIV), feline leukemia virus (FeLV), *Chlamydomphila felis*, and various bacteria, as well as noninfectious factors, such as old age, dental disease, stress, and immunological disorders (36, 49, 74). Lommer et al. found that 88% of cats with FCGS were shedding both FCV and FHV-1, while only 21% of cats without FCGS were positive for these pathogens (55). Another research group found a similar association between FCGS and FCV, with 80% of cats suffering from FCGS being positive for FCV compared to only 24% of control cats (83). In a multicenter study conducted in Spain, 154 cats with gingivostomatitis (GS) were tested for FHV-1, FCV, *Chlamydophila felis*, and *Mycoplasma felis*. Positive results were noted, respectively, for 5.6%, 58.4%, 9.1%, and 37.7% of the cats. Only FCV was strongly associated with GS (32). A strong correlation between signs of FCGS and the presence of FCV antibodies and/or RNA was confirmed in a study conducted by Dowers et al., who also showed no significant correlation between the occurrence of FCGS and the presence of antibodies against either *Bartonella* species or FHV-1 (28). Correlation between FCV and FCGS was also confirmed by next-generation RNA sequencing, and FCV was detected in 21 of 23 affected cats, but in none of control cats (34). Another known predisposing factor for FCGS is the multicat household. Each additional cat in the household increases the odds of developing FCGS by more than 70% (66). Poorly managed multicat households are a known factor for many cat illnesses because of increased amounts of stress due to improper living conditions. No association between access to outdoors and FCGS has been found so far (23). In cats, most common oral microorganisms are *Bacteroidetes*, *Proteobacteria*, *Firmicutes*, *Spirochetes*, and *Fusobacteria*, regardless of the periodontal status (23, 73, 81). Oral bacterial flora in cats with FCGS is less diverse than it is in normal cats, with a greater abundance of Gram-negative bacteria (25). *Pasteurella multocida* subsp. *multocida* is more abundant in FCGS cats, suggesting its importance in the development of this illness (40). The phylum *Spirochaetes* was proven by some researchers to be more abundant in periodontally diseased cats compared to healthy ones, as seen in humans and dogs (40, 73, 89). It is worth noting that in one study 98% of cats with FCGS had signs of esophagitis, compared to 0% in the FCGS-free group (51).

**Conventional treatment methods**

There are two widely used approaches to treating FCGS: medical and surgical ones. In most cases, however, traditional medical treatment does not produce favorable long-term outcomes, and surgical treatment (partial or whole dental extraction) is the only reasonable option in cases of advanced FCGS (93).

**Medical management.** Conservative treatment of cats with FCGS consists of anti-inflammatory, analgesic, and antimicrobial medications. Pain management plays an important role in the treatment of FCGS, since cats with severe oral inflammation often show signs of anorexia. Analgesic medications for cats suffering from FCGS are buprenorphine hydrochloride, tramadol hydrochloride, and butorphanol tartrate. Antimicrobial treatment consists mostly of clindamycin, amoxicillin-clavulanic acid, and cephalosporins, such as cefovecin. Finally, commonly used anti-inflammatory medications are prednisone, methylprednisolone acetate, prednisolone, meloxicam, and cyclosporin (46). Nonsteroid anti-inflammatory agents tend to have a limited efficacy in chronic feline oral inflammation, and long usage of corticosteroids in cats is a known risk factor for the development of diabetes mellitus (31).

**Surgical management.** Partial or whole dental extraction can vastly improve the quality of life of cats suffering from FCGS by decreasing inflammation in the oral cavity. Hennet reported that the removal of teeth with severe periodontitis, feline odontoclastic resorptive lesions, or surrounded by severe buccostomatitis, led to a 60% clinical remission rate, and another 20% of cats improved significantly and needed no further therapy, whereas 13.3% of cats improved slightly, and no improvement was seen in only 6.7% cats (42). In another study, extraction of premolars and molars resulted in 57.1% of the cats recovering completely from the illness, 23.8% of cats showing improvement, and 19.1% suffering from relapses (9). To date, no significant differences have been found between full-mouth and partial-mouth (molar and premolar) extractions. Compared to previous studies, only 28.4% of cats after extractions showed signs of complete resolution of FCGS, 39% of cats improved significantly, 26.3% showed slight improvement, and no change was observed in 6.3% of cats. After surgical treatment, 66.8% of patients required additional medical treatment to keep the illness in check (46).

**New treatment methods**

Both symptomatic and surgical management have limitations, as they produce short-lasting effects or pose a risk of recurrence of the disease. Hence, there is an ongoing extensive research effort to develop new treatments for FCGS.
**Cyclosporin.** Vercelli et al. noted that administration of cyclosporin was the only therapy that resulted in remission of 4 out of the 8 patients. The remaining 4 cats showed a fair to significant improvement (86). The outcome indicates the therapeutic potential of cyclosporin, but an undeniable weakness of that experiment was the small study group, and it seems that further studies in this field are needed. Lommer evaluated the therapeutic efficacy of cyclosporin in cats that had previously undergone tooth extraction. It has been reported that cyclosporin yielded positive results in cats that had undergone partial or complete tooth extraction compared to the placebo group. Seven out of nine cats in the treatment group, and one out of seven cats in the control group showed an improvement of > 40% measured by the Stomatitis Disease Activity Index. It was also observed that peripheral blood cyclosporin levels above 300 ng/ml were associated with reduced oral inflammation in cats (54).

**Dietary supplements.** Increasing the omega-3 to omega-6 ratio in the feline diet was proven to decrease inflammatory response in skin (63), but a diet supplemented with an omega-6 to omega-3 ratio of 10:1 did not result in decreased oral inflammation compared to a standard 40:1 ratio (19). In one of the studies, patients treated with lactoferrin powder applied directly to oral lesions and thalidomide capsules given orally improved only after their diet was changed to additive-free cat food supplemented with vitamins A, D₃, and E (2). These results may suggest that proper diet may be an important factor in cats suffering from FCGS.

**Bovine lactoferrin.** Bovine lactoferrin (bLf) in oral sprays combined with piroxicam, a traditional non-steroidal anti-inflammatory drug, improved the condition of the oral cavity in cats suffering from FCGS. More specifically, Hung et al. observed that after 12 weeks of initial therapy, 50% (4/8) of cats were able to maintain a good quality of life, 25% (2/8) responded to bLf spray alone, 12.5% (1/8) required both piroxicam and bLf oral spray for amelioration, and one patient showed no improvement and was switched to steroid therapy (44).

**Recombinant feline interferon omega.** In one randomised, multi-centre, controlled, double-blind study in 39 cats, Hennet et al. compared the usage of recombinant feline interferon-omega (IFN-omega) and prednisolone (90 and 21 days of treatment respectively), and during the observation period it was found that 55% (IFN group) vs. 54% (prednisolone group) of treated cats were clinically cured or their condition was improved. It was noted that 45% of the animals treated with IFN-omega showed clinical remission or significant improvement, compared to only 23% of the cats undergoing prednisolone therapy (43). Recombinant feline interferon-omega was proven to be safe in the therapy of FCGS patients with concurrent diabetes mellitus due to chronic corticosteroids therapy (52). Interferon treatment also resulted in the improvement of feline stomatitis and the inhibition of feline calicivirus proliferation (59).

**Mesenchymal stem cells.** Arzi et al. reported a successful management of feline gingivostomatitis with a combination of full-mouth tooth extraction and intravenous application of autologous or allogeneic mesenchymal stem cells (MSCs) (8), which confirmed their other studies (4, 6, 7). The benefit of MSCs was limited to co-treatment alongside partial or full-mouth tooth extractions, as monotherapy with MSCs was shown to cause no improvement in feline chronic gingivostomatitis (8). In their study, fresh, autologous adipose-derived mesenchymal stem cells (ADSCs) were given intravenously to 7 cats non-responsive to full-mouth tooth extractions and immunosuppressive therapy as a means of treatment of FCGS. Three cats responded with complete clinical remission, two cats showed clinical improvement, and another two were nonresponders (6). The same research group tested FCGS therapy with allogenic ADSCs, and found that in a group of seven cats, two responded with complete clinical remission, another two with substantial clinical improvement, and three showed no improvement (4). These two studies were broadened later on. Another 18 cats that had failed to respond to full-mouth extractions were treated with autologous or allogeneic ADSCs: 77% (10/13) of cats treated with autologous ADSCs and 60% (3/5) of cats treated with allogeneic ADSCs showed substantial improvement or total remission. In total, 5/18 cats responded to treatment with complete remission, and 8/18 cats showed significant improvement. More than 70% of cats in that study profited from the ADSCs treatment, while 27% did not respond or showed only minimal improvement (7). The novel therapeutic technology of autologous transplantation repair with MSCs is a very promising approach and has already been used in veterinary medicine with success in the treatment of various injuries and diseases affecting the oral cavity, tendons, ligaments, joints, digestive tract, liver, kidneys, heart, respiratory system, skin, eyes, and reproductive system (87). Undoubtedly, the potential therapeutic properties of stem cells arise from their unique biological characteristics, which are described in detail in the next paragraph.

**Mesenchymal stem cells biology**

After the fertilization of the egg, totipotent stem cells arise. In the zygote, cells show totipotent capacity up to 2-3 cell divisions, and then cells become pluripotent (they are unable to create placenta cells) (21). Successive divisions cause the pluripotent stem cells to differentiate to multipotent (with ability to differentiate into different types of cells within a given germ layer), unipotent (with ability to differentiate into only one type of cells, i.e. keratinocytes) and fully...
Differentiated cells. Some of the cells are stalled in the differentiation process and are located in a specific niche in the developing fetus. After birth, stem cells are found in small amounts in various tissues and organs in the whole body and remain dormant for the rest of the organism’s life. In exceptional cases, some of them can be activated, leave the niche and travel to the place of injury.

MSCs are a special population of stem cells isolated from mature tissues. These pluripotent cells can differentiate into osteoblasts, chondrocytes, myoblasts, adipocytes, neurons, and endothelial cells (57, 60, 69). They are distributed throughout post-natal tissues and are reservoirs that can contribute to the maintenance and regeneration of the body. Mesenchymal stem cells may divide asymmetrically (classical model: renewal of the stem cell reservoir and production of a cell for differentiation) and symmetrically (non-classical model: renewal of two stem cells or two cells for differentiation) (12, 76). In the classical model, following the division, the daughter cell starts to differentiate by changing the specific metabolic pathways and phenotype, which causes the transformation of MSCs into a tissue-specific cell type. This process depends mainly on the extracellular matrix (ECM), which plays a crucial role in the activation and differentiation of MSCs and keeping inactive MSCs in the niche (68). It is still unknown which molecules are directly responsible for the release and migration of MSCs from their niche. It has been shown that the main role in this process is played by cytokines from inflammation or tissue injury (65). Regulation in these processes is carried out by multiple chemical factors: stromal-derived factor-1, osteopontin (OPN), or growth factors (GF): basic fibroblast (bFGF), vascular endothelial (VEGF), hepatocyte (HGF), insulin-like (IGF), platelet-derived growth factor (PDGF), and transforming growth factor (TGF-β), as well as mechanical factors: mechanical stretch, shear stress, matrix stiffness, or microgravity (35). Other authors also demonstrated that these processes could be enhanced by arachidonic acid (61).

MSCs can be stimulated to differentiate into specific cell types in vitro and in vivo (13, 50) and tend to acquire tissue-specific characteristics when co-cultured with specialized cell types or exposed to tissue extracts in vitro (11, 15).

Characteristic features that distinguish mesenchymal stem cells from the other cells of the body are their ability to adhere to plastic as fibroblast colony-like forms; high proliferative capacity in vitro; the expression of specific surface antigens; and capacity to differentiate into a minimum of three cell types (26).

Morphologically, MSCs are long and spindly fibroblast-like cells. These cells exhibit plastic-adherent properties when maintained under standard culture conditions. Most of the authors phenotypically classify MSC cells in humans and rodents as cells positive for CD29, CD73, CD90, CD105 antigens (more than 95% of cells) and negative for CD45, CD34, CD14 or CD11b, CD79alpha or CD19, and HLA-DR surface molecules (less than 2% of cells) (53, 95). However, this evaluation is not complete, because it is necessary to distinguish MSC cells from fibroblasts (some express CD29, CD73, CD90, and CD105). Certain authors postulated that a differentiating factor is the expression of CD146, CD166 (overexpressed in MSCs) or CD9 and CD106 (underexpressed in MSCs) (39). Moreover, markers distinguishing mesenchymal stem cells from fibroblasts might be changed during prolonged in vitro culture (95). There is also an opinion that an MSC and a fibroblast cannot be phenotypically distinguished (22).

### Table 1. Cell surface phenotype of adipose tissue-derived mesenchymal cells in different species

<table>
<thead>
<tr>
<th>Species</th>
<th>Positive markers</th>
<th>Negative markers</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>CD44, CD90, CD105</td>
<td>CD45, MHC-II</td>
<td>(17)</td>
</tr>
<tr>
<td></td>
<td>CD73, CD90, CD105</td>
<td>CD11b, CD14, CD19, CD34, CD45, CD79a, MHC-II</td>
<td>(26)</td>
</tr>
<tr>
<td>Feline</td>
<td>CD44, CD90, CD105</td>
<td>CD4, MHC-II</td>
<td>(90)</td>
</tr>
<tr>
<td></td>
<td>CD44, CD90, CD105</td>
<td>CD18, CD45, MHC-II</td>
<td>(17)</td>
</tr>
<tr>
<td></td>
<td>CD29, CD44, CD90, CD105, CD166, MHC-I</td>
<td>CD14, CD34, CD45, CD73</td>
<td>(48)</td>
</tr>
<tr>
<td></td>
<td>CD44, CD90, CD105</td>
<td>CD45, CD4, MHC class II, CD14, CD34, CD45, CD13</td>
<td>(62)</td>
</tr>
<tr>
<td>Canine</td>
<td>CD44, CD90</td>
<td>CD34</td>
<td>(88)</td>
</tr>
<tr>
<td></td>
<td>CD44, CD54 and CD90</td>
<td>CD34, MHC-II, CD45</td>
<td>(18)</td>
</tr>
<tr>
<td></td>
<td>CD73, CD90, CD105, CD13, CD44, CD49a, CD54, CD140a, CD140b, MHC I</td>
<td>CD11a, CD11b, CD14, CD19, CD33, CD34, CD45, CD86, CD 146, CD 271, MHC</td>
<td>(97)</td>
</tr>
<tr>
<td>Equine</td>
<td>CD90, CD44</td>
<td>CD13</td>
<td>(20)</td>
</tr>
<tr>
<td></td>
<td>CD90, CD44, CD29</td>
<td>MHC II, CD66, F6B</td>
<td>(18)</td>
</tr>
<tr>
<td></td>
<td>CD44, CD90, CD73</td>
<td>CD45, CD34</td>
<td>(3)</td>
</tr>
</tbody>
</table>
fat tissue (adipose-derived cells – ADSCs, which can be collected at any time in life; there are relatively many cells in the tissue, and the collection procedure is fairly simple) (45). Nowadays, ADSCs are considered the best source of MSCs for biological treatment of various diseases. In addition, MSCs have been found in the placenta, milk pulp, dental pulp, synovial fluid, periodontal ligament, tonsils, parathyroid gland, skeletal muscles, dura mater, cartilage, skin, hair bulb, fetal membranes, and recently, even in menstrual blood (10). MSCs isolated from various parts of the body did not differ significantly in their morphology, phenotype, and capacity for multilineage differentiation (84). However, some of the authors suggest that MSCs isolated from different locations may exhibit differences in the speed and intensity of differentiation: BMSCs differentiate easily in osteogenic cells, and ADSCs in adipocytes (94). These differences may be associated with the isolation niche, in which epigenetic changes may play a crucial role.

Numerous studies have confirmed that MSCs exhibit multilineage capacity for differentiation in vitro. At minimum, mesenchymal stem cells should be able to differentiate into adipocytes, chondrocytes, and osteogenic cell. Most authors use modified isolation methods derived from human medicine (5, 14, 16, 72, 84). Adipose tissue is obtained by punch biopsy or fine needle aspiration of the abdomen, from intra-abdominal adipose tissue during laparoscopic procedures, or by liposuction aspiration. The sample is collected into a bottle containing phosphate buffer saline (PBS), either with or without 1% penicillin and streptomycin mix. The adipose tissue is washed 3-5 times in PBS to remove blood, small vessels, and connective tissue. The samples are digested with 0.07%-1% collagenase type I or II and with or without 1% fetal bovine serum (FBS) for 30-60 minutes at 37°C in a shaker or a magnetic stirrer. After incubation, the collagenase is neutralized with Dulbecco’s modified Eagle’s culture medium supplemented with 10%-20% FBS and 1% penicillin and streptomycin mix. The adipose tissue is washed 3-5 times in PBS to remove 5 

### Methods for obtaining and culturing feline stem cells

**Isolation of mesenchymal stem cells from adipose tissue.** Most authors use modified isolation methods derived from human medicine (5, 14, 16, 72, 84). Adipose tissue is obtained by punch biopsy or fine needle aspiration of the abdomen, from intra-abdominal adipose tissue during laparoscopic procedures, or by liposuction aspiration. The sample is collected into a bottle containing phosphate buffer saline (PBS), either with or without 1% penicillin and streptomycin mix. The adipose tissue is washed 3-5 times in PBS to remove blood, small vessels, and connective tissue. The samples are digested with 0.07%-1% collagenase type I or II and with or without 1% fetal bovine serum (FBS) for 30-60 minutes at 37°C in a shaker or a magnetic stirrer. After incubation, the collagenase is neutralized with Dulbecco’s modified Eagle’s culture medium supplemented with 10%-20% FBS and 1% penicillin and streptomycin mix. The samples are centrifuged at 135-1200 × g for 3-5 minutes. The supernatant is removed, and the pellet containing cells is resuspended in DMEM, passed through a 70 μm strainer, and then centrifuged again at 135-1200 × g for 3-5 minutes. The stromal vesicular fraction containing cells is collected. The cells are washed with PBS and seeded (5 × 10^4 or 1 × 10^5) in 25 cm² culture flasks filled with Dulbecco’s modified Eagle’s medium (DMEM) supplemented with 10%-20% FBS. The cells are incubated in 5% carbon dioxide at 37°C. After two days of incubation, nonadherent cells are removed by washing with PBS solution. The growth medium is changed every two days until a 70-80% confluency is reached. A schematic
representation of MSC isolation from adipose tissue is shown in Figure 1.

**Isolation of bone marrow-derived mesenchymal stem cells.**

Feline bone marrow is harvested similarly as bone the marrow of other species. The skin is prepared in an aseptic manner, and bone marrow is aspirated with a 13-18 gauge × 25 mm bone marrow aspiration biopsy needle from the greater trochanter of the femur, the greater tubercle of the humerus, or the lateral part of the wing of the ilium (1, 29). Possible puncture sites for bone marrow harvesting in the cat are indicated in Figure 2.

About 1 ml of a sample is collected into a heparin-covered syringe. Some protocols suggest a simple suspension of samples in bottles filled with low-glucose DMEM supplemented with penicillin, streptomycin, L-glutamine, 1% essential amino acids without L-glutamine, 1% non-essential amino acids, 1% bicarbonate solution, and 15% FBS (90). Other protocols are more complicated, and bone marrow samples are collected into 1-5 volumes of Iscove’s modified Dulbecco’s medium (IMDM) containing 200 units/ml of heparin and then centrifuged at 900 × g to pellet cells. Pellets are rinsed twice with PBS, and cells are counted. Next, 10^6 cells are loaded into 12.5 ml Percoll and centrifuged at 1100 × g for 30 minutes. Then, mononuclear cells are collected, rinsed in PBS twice, and seeded at 2 × 10^5/cm² in DMEM supplemented only with 10% FBS (29). In most protocols, nonadherent cells are removed, and media are changed 1-3 days after initial seeding. The remaining cells are incubated until 70-80% confluent, and media are changed every 3-4 days. A schematic of how MSCs can be isolated from bone marrow is presented in Figure 3. The main differences between the protocols of adipose- and bone marrow-derived stem cell isolation are given in Table 2.

![Fig. 1. Schematic showing an illustrative example of the isolation of MSCs from adipose tissue](image)

![Fig. 2. Sites for bone marrow biopsy in cat](image)

**Tab. 2. Differences between adipose- and bone marrow-derived stem cells isolation protocols**

<table>
<thead>
<tr>
<th>Adipose tissue-derived stem cells</th>
<th>Bone marrow-derived stem cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less invasive harvesting procedure; It also can be obtained during routine OVF surgery</td>
<td>Potentially more invasive harvesting procedure</td>
</tr>
<tr>
<td>Obtained by FNA or punch biopsy</td>
<td>Sample aspirated with bone marrow aspiration needle and heparin-covered syringe</td>
</tr>
<tr>
<td>Richer source of MSCs</td>
<td>A relatively low percentage of MSCs</td>
</tr>
<tr>
<td>Isolation requires digestion with the usage of collagenase</td>
<td>Isolation does not require digestion</td>
</tr>
</tbody>
</table>
Until now, no methods of isolating MSCs from feline dental pulp have been described, even though there is an efficient method for humans. Therefore, we present a protocol describing MSC isolation from human teeth in the hope that it may help in the development of a method to isolate MSCs from feline dental pulp.

**Isolation of mesenchymal stem cells from dental pulp (human studies).** Healthy human molars are surgically extracted, placed in phosphate buffered saline (PBS), and cooled for transport to the laboratory, where they are cleaned and disinfected with iodine or sodium hypochlorite solution. A horizontal cut is made around the cemento-enamel junction, using a diamond fissure bur and a high-speed handpiece with water supply under sterile conditions, to expose and extract dental pulp. Tissues are minced into fragments of approximately 1.5 × 2 × 1 mm. The fragments are digested in a 1 mg/ml collagenase/dispase solution for 30 min at 37°C and centrifuged at 500 × g for 5 min. Cells are seeded into culture dishes with a coverslip, containing Minimum Essential Medium alpha modification (α-MEM) supplemented with 20% fetal bovine serum (FBS), 100 U/ml penicillin-G, 100 µg/ml streptomycin, and 1 µg/ml amphotrypsin B. Incubation takes place in 5% CO₂ at 37°C. The medium is changed every 3 days. Cells are passaged 1 : 5 with 0.25% trypsin/1 mM EDTA every 5 days (70).

To date, tooth extraction has been considered the most effective therapeutic treatment for cats suffering from FCGS. However, this radical method produces the expected remission of the disease in less than 30% of cases. More than 1/3 of cats treated this way may still show signs of the disease and require further therapeutic management. Significant improvement in these cats can be achieved with the administration of mesenchymal stem cells. Both the safety and efficacy of allogeneic and autologous mesenchymal stem cell therapy in cats subjected to tooth extraction have been confirmed. Unfortunately, the administration of stem cells alone is not associated with a significant therapeutic effect. When combined with tooth extraction, however, it offers a much better chance of recovery. Therefore, according to the available literature, the combination of tooth extraction and stem cell administration appears to be the most rational and effective therapeutic approach for the treatment of this disease.

**Fig. 3. Schematic showing an illustrative example of the isolation of MSCs from bone marrow**

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Surgical therapy


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