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# The potential of the stem cells composite hydrogel wound dressings for promoting wound healing and skin regeneration: *In vitro* and *in vivo* evaluation

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**Abstract:** In this study, the wound healing properties of the gelatin-based hydrogel (GBH) wound dressing combined with adipose-derived stem cells (ADSCs) were investigated using the mouse and porcine models. The analytical results showed that the ADSCs harvested from the porcine significantly increased cell growth and promoted cell differentiation (adipogenesis and osteogenesis) in comparison to the ADSCs harvested from the mouse *in vitro*. Moreover, the *in vivo* results also indicated that the GBH wound dressing combined with ADSCs and its culture medium could potentially accelerate wound healing in the mouse and porcine models.

The ADSCs presented a possibility of recovery from wounds and injuries through skin regeneration. Therefore, both *in vitro* and *in vivo* results demonstrated that the ADSCs can potentially be an effective clinical treatment through the GBH wound dressing, which is a promising evidence-based complementary and alternative medicine for skin regeneration. © 2018 Wiley Periodicals, Inc. *J Biomed Mater Res Part B: Appl Biomater* 00B: 000–000, 2018.

**Key Words:** adipose-derived stem cells, hydrogel, wound healing, skin regeneration

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## INTRODUCTION

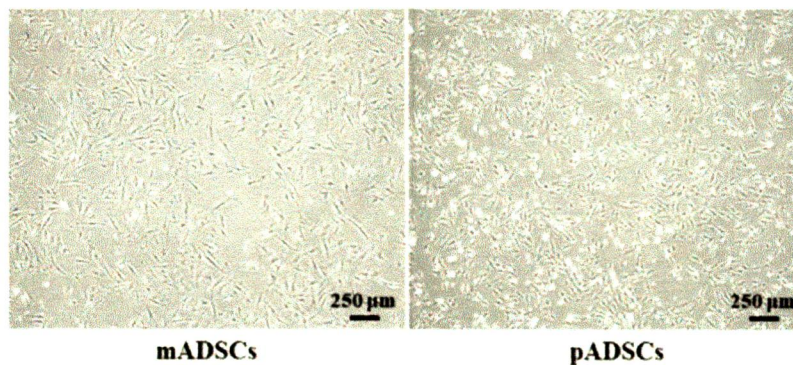
In recent years, numerous studies have indicated that adipose-derived stem cells (ADSCs) can be used as an alternative therapeutic approach to heal wounds and recover damaged skin.<sup>1–3</sup> The ADSCs secretion of various skin regenerating factors including collagen, fibronectin, transforming growth factor beta (TGF-beta), platelet-derived growth factor (PDGF), fibroblast growth factors (FGF), and vascular endothelial growth factor (VEGF) play an important role in skin regeneration.<sup>4–6</sup>

Although bone marrow derived stem cells (BMSCs) also release the same secretory factors for clinical application.<sup>7,8</sup> However, the BMSCs are not easily collected due to the need of potentially painful spinal anesthesia and the yield of mesenchymal stem cells may still be low.<sup>9</sup> Thus, the ADSCs for cell-based therapy in skin regeneration might be potential treatment option in future clinical applications.

It is well known that cell-based therapy requires sufficient number of cells for skin regeneration and could easily

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**FIGURE 1.** Cell morphology of the mADSCs and pADSCs cultured at passage 3. Both ADSCs were spindle-shaped fibroblast and had the same morphology at passage 3.

be expanded *in vitro*.<sup>10</sup> Previously studies found that ADSCs and the use of soluble factors from their culture media are favorable candidates for preventing skin damage.<sup>2,3,11</sup> Additionally, researchers have also developed a more ideal wound dressing that enhances the wound healing process and presents a superior biocompatibility in inflammatory response prevention<sup>12,13</sup> instead of the traditional wound dressing (such as cotton wool and gauze) only possesses functions of protecting and preventing bacterial infection on the wound healing.<sup>14</sup>

Recently, we have focused on developing the gelatin-based hydrogel (GBH) wound dressing to carrying the ADSCs as a promising cell therapy method for facilitating the matrix formation and rapid vascularization in damaged skin repair. Gelatin has a unique combination of chemical and biological properties such as thermal degradable, optimal ingrowth of cells, low immunogenic and superior biocompatibility, and so forth. Hence, it is highly attractive for future cell therapy and clinical applications.<sup>15-17</sup> In our pilot study testing, it was found that the damaged skin showed a significantly stronger repair and promotion of wound healing as using the self-established GBH combined with ADSCs and its culture medium. Therefore, the hydrogel combined with ADSCs and the soluble factors can potentially be effective clinical treatments for facilitating wound healing without sacrificing any useful biological properties. For the biomedical application considerations, this study was aimed to investigate the *in vivo* wound healing properties of the GBH wound dressing combined with ADSCs (harvested from the mouse and porcine) and its culture medium, and thus provide information that would be valuable in wound healing and skin regeneration applications.

## MATERIALS AND METHODS

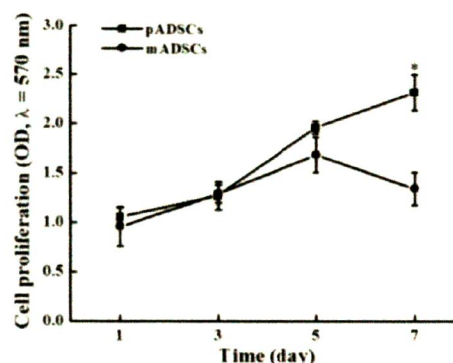
### Animal models

The animal models for wound healing investigation were performed using FVB mice (100-150 g, BioLASCO, Taiwan) and *Sus barbatus sumatranus* (35-40 kg, Taitung Animal Propagation Station, Taiwan) in the present study. The animals were maintained in accordance with the guidelines for

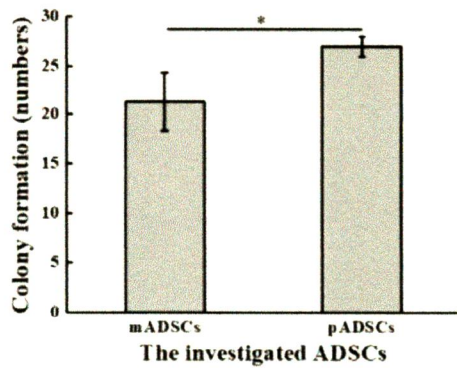
the care and use of laboratory animals. They were fed and housed in an environment controlled for temperature, humidity, and light. Moreover, the animals were marked to permit individual identification and were kept in their cages for 14 days prior to experimentation to allow for acclimatization to the laboratory conditions. The experiment protocol was approved by the Institutional Animal Care and Use Committee of Taipei Medical University under number LAC-2015-0094.

### Isolation of adipose stem cells

The adipose tissues were collected from the mice and pigs before testing. The collected adipose tissues were washed twice in phosphate buffer saline (PBS, Gibco pH 7.4) and then digested in 0.075% collagenase type I for 45 min. The cells were selected by 0.4 µm filter and centrifuged at 1500 rpm for 5 min. Subsequently, the cell sediments were collected and resuspended in αMEM (Gibco) with 10% fetal bovine serum (Gibco). Finally, the ADSCs were seeded into dish followed by culturing and passaging. The ADSCs in the third passage were used for subsequent experiments.



**FIGURE 2.** Comparative profiles of cell proliferation in ADSCs between the mouse and porcine. Cells were analyzed by MTT assay after 1, 3, 5, and 7 days incubation. Representative results of three experiments were demonstrated. \**p* < 0.05.



**FIGURE 3.** The mADSCs and pADSCs were cultured for 21 days and determined the single stem cells have capacity to produce colonies potential. Representative results of three experiments were demonstrated. \* $p < 0.05$ .

#### Cell proliferation and colony formation

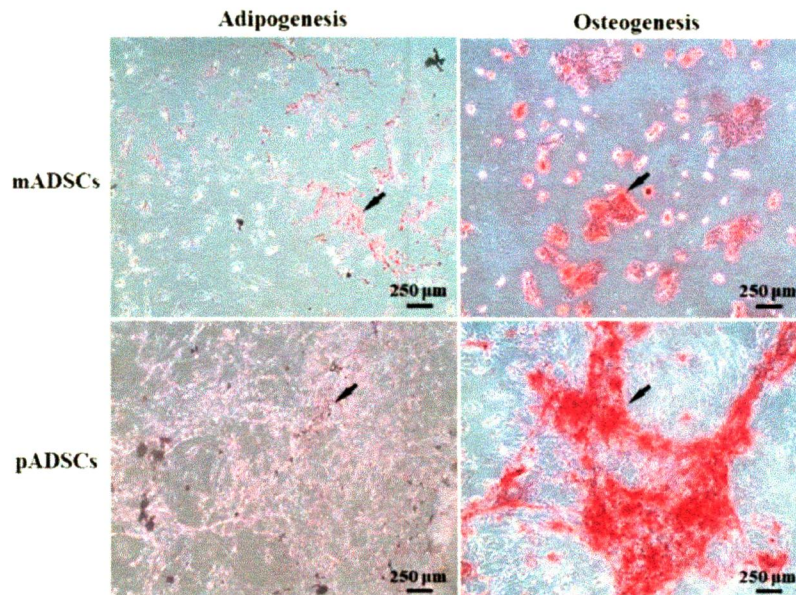
Cell proliferation rates of the ADSCs isolated from the mice and pigs were monitored at different time points (day 1, 3, 5, and 7) using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The optical density (OD) value was determined at 570 nm using an enzyme-linked immunosorbent assay reader (BioTek-Epoch). For the colony formation assay, the  $1 \times 10^4$  ADSCs per mL were seeded in the diameter of 10 cm dish and incubated at 37°C in 5% CO<sub>2</sub> atmosphere. The medium was changed every two days. After 21 days of culture, the cells were fixed with 4% paraformaldehyde and stained with 1% crystal violet solution. Hereafter, the number of colonies was counted carefully.

#### Adipogenic and osteogenic differentiation

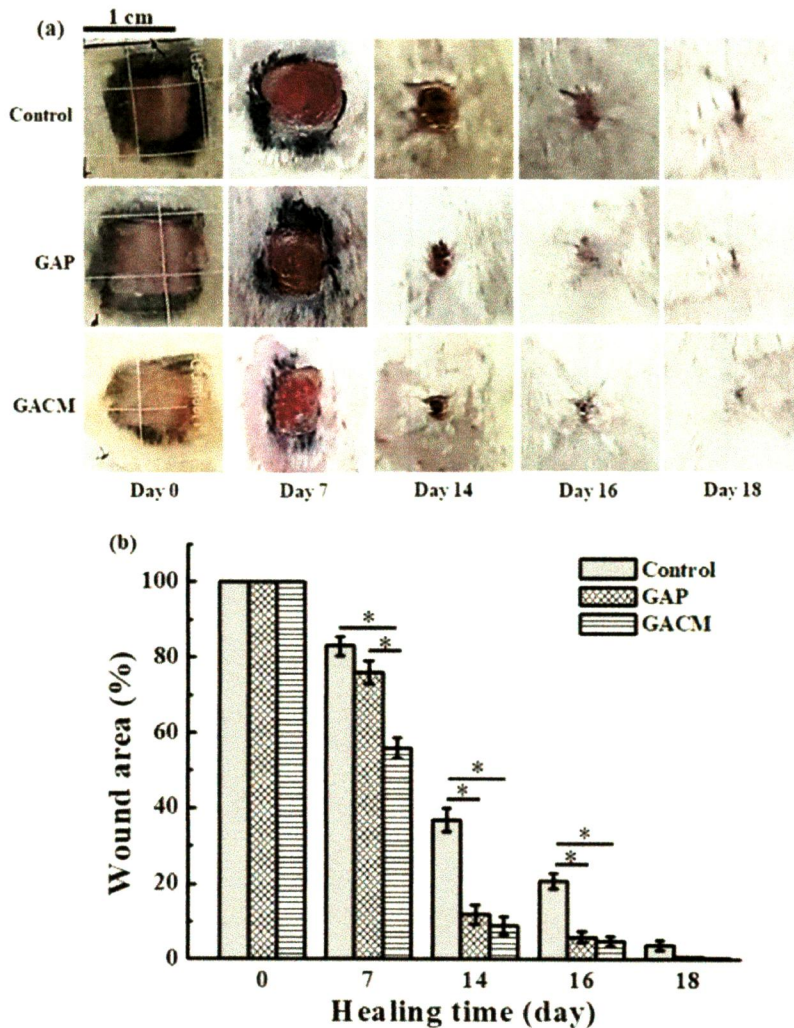
The ADSCs were mechanically dissociated by 0.25% trypsin-EDTA treatment for 5 min at 37°C to induce adipogenic and osteogenic differentiation. Then, the cells were washed once with basal medium and suspended in differentiation medium. The medium contained  $\alpha$ MEM with 10% FBS in dexamethasone, IBMX, insulin, and indomethacin was adopted to induce adipogenic differentiation. While, the medium contained  $\alpha$ MEM with 10% FBS in TGF- $\beta$ 1 was utilized to induce osteogenic differentiation. The  $1 \times 10^5$  cells per mL were seeded in the diameter of 3 cm dish and replaced by a fresh differentiation medium three times every two days. After 21 days incubation, the adipogenic and osteogenic differentiation of the cells were observed using Oil Red O staining and Alizarin Red S staining, respectively.<sup>18</sup>

#### In vivo wound healing evaluation

Before *in vivo* wound healing testing, the GBH wound dressing was prepared using the high purity gelatin powder (CAS 9000-70-8, Merck, Taiwan) and deionized water at a concentration of 20% w/v by magnetic stirring at room temperature overnight. Subsequently, the GBH wound dressing was used to combine with ADSCs, PBS and its culture medium, respectively. In this study, it divided into three groups including the GBH wound dressing (control,  $N = 6$ ), the GBH wound dressing combined with ADSCs and PBS (GAP,  $1 \times 10^6$  cells/mL,  $N = 6$ ) and the GBH wound dressing combined with ADSCs and its culture medium (GACM,  $1 \times 10^6$  cells/mL,  $N = 6$ ). The period of experiment on porcine was 35 days. After acclimatization in the animal facility for 14 days, the pigs were anesthetized with



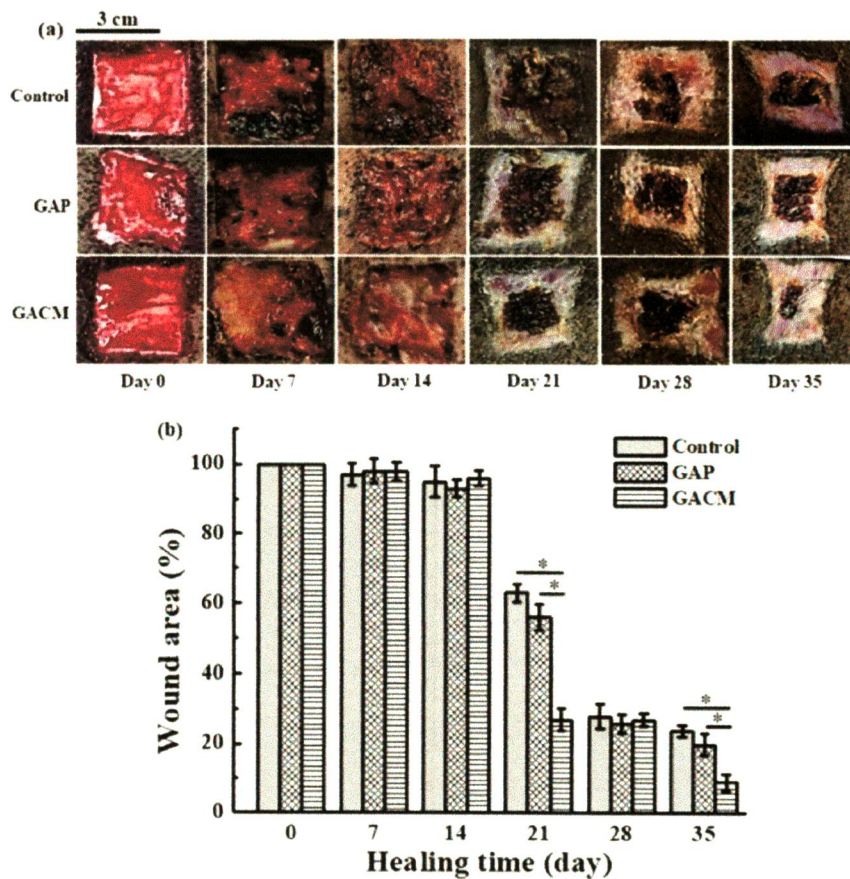
**FIGURE 4.** Multi-differentiation potential analysis of the mADSCs and pADSCs. The adipogenic and osteogenic differentiation were examined by Oil Red O staining (left panel) and Alizarin Red S staining (right panel), respectively.



**FIGURE 5.** Effects of the control, GAP, and GACM wound dressing samples on wound healing in mice after treatment at day 0, 7, 14, 16, and 18: (a) macroscopic observation of wound healing and (b) wound area analysis. \* $p < 0.05$ .

zoletil by intramuscular injection for wound preparation. Six square target areas (each area of the target was set as 3 cm by 3 cm) were marked with a surgical pen on the back of pigs. Subsequently, the target area was cut carefully using operation knife and the investigated samples were added randomly in the wounds. Then, each wound was covered with the transparent hydrocolloid thin dressing (Comfeel® Plus Transparent, UK) which allows for wound inspection without removing the dressing and provides the protection for wounds. Wound healing was observed at each time point (0, 7, 14, 21, 28, and 35 days) and then euthanasia at day 35. Furthermore, the period of experiment on mice was 18 days. After acclimatization in the animal facility for 14 days, the mice were anesthetized with zoletil by intraperitoneal injection for wound

preparation. One square target area (the target area was set as 1 cm by 1 cm) was marked with a surgical pen on the back of mice. Afterward, the target area was cut carefully using operation knife and the investigated samples were added in the wounds. Then, each wound was also covered with the transparent hydrocolloid thin dressing for wound protection and inspection. Wound healing was observed at each time point (0, 7, 14, 16, and 18 days) and then euthanasia at day 18. The area of wound healing was analyzed by Image J software. Sample preparations for histological analysis were followed by fixing, decalcifying, paraffin wax embedding, ultramicrotome sectioning, and Masson's trichrome staining. The stained slides were observed using a high-quality digital image capture pathology scanner (Aperio CS, Germany) under different magnifications.



**FIGURE 6.** Effects of the control, GAP, and GACM wound dressing samples on wound healing in pigs after treatment at day 0, 7, 14, 21, 28, and 35: (a) macroscopic observation of wound healing and (b) wound area analysis. \* $p < 0.05$ .

#### Statistical analysis

All results were represented as mean  $\pm$  standard deviation. Significant differences between two groups were determined by student's *t* test (Microsoft Excel 2016 version). *P* values  $\leq 0.05$  were considered statistically significant.

#### RESULTS

##### Cell growth and morphology of the ADSCs

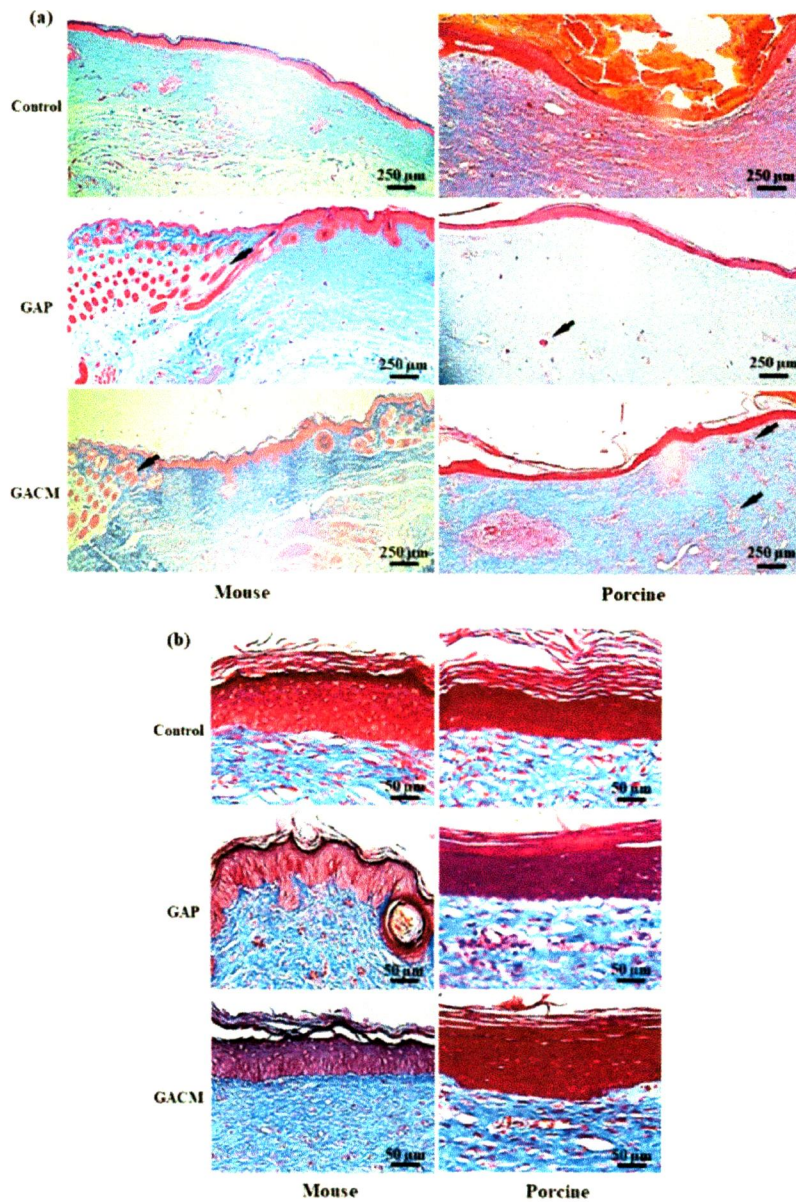
In order to investigate the cell potential of the ADSCs isolated from the mouse (mADSCs) and porcine (pADSCs), the cell growth and morphology of both ADSCs cultured at passage 3 were observed as shown in Figure 1. Clearly, the result showed that the morphology of both ADSCs was spindle-shaped fibroblast and had the same morphology at passage 3. Moreover, the MTT and colony formation results also indicated that the pADSCs induced a higher growth rate (Figure 2) and significantly increased colony units formation as compared to the mADSCs (Figure 3). These findings demonstrated that the pADSCs have a higher cell growth potential as an alternative stem cells source.

##### Multi-differentiation potential of the mADSCs and pADSCs

To compare multi-differentiation of the mADSCs and pADSCs, both cells were cultured for 21 days inducing adipogenic and osteogenic differentiation. The mADSCs and pADSCs were analyzed by Oil Red O staining and Alizarin Red S staining, respectively. The result showed that a high level of lipid droplet accumulation (as indicated by arrows) was detected in pADSCs in comparison to that of mADSCs (Figure 4, left panel). Moreover, the pADSCs were increased mineralized matrix deposition and mineralization (as indicated by arrows) by Alizarin Red S staining in comparison to those of mADSCs (Figure 4, right panel).

##### *In vivo* wound healing potential of the investigated samples

Based on the above results, it was found that the pADSCs exhibited a significant increase in both cell proliferation and cell differentiation potential. ADSCs can be considered as a superior stem cells source for cell therapy. Therefore, this



**FIGURE 7.** Histological analysis of the healed wound skin. Photomicrographs showing Masson's trichrome stained sections ((a) 40 $\times$  and (b) 200 $\times$ ) from the healed wound skin of the investigated samples in treated mice (18 days) and pigs (35 days).

study further examined the wound healing potential for the GBH wound dressing combined with ADSCs. The wounds of mice and pigs were treated with the control, GAP, and GACM wound dressing samples. The outcomes indicated that the GACM wound dressing sample significantly promoted wound healing and had a smaller wound area of healing morphology in comparison to the control and GAP wound dressing samples

which had bigger wound areas in mice at day 7 [Figure 5(a,b)]. This phenomenon could also be observed at day 14, 16, and 18. However, there was no significant differences between the GAP and GACM wound dressing samples at day 14, 16, and 18. Furthermore, the results also exhibited similar signs that the wounds treated with the GACM wound dressing sample healed faster than those treated with the control and GAP wound

dressing samples in pigs after day 21 [Figure 6(a,b)]. The significantly facilitated wound healing can also be observed in the GACM wound dressing sample at day 35.

#### Histology observation of wound healing

The healing effects of wounded skin of mice (18 days) and pigs (35 days) were further investigated by histological analysis. The outcomes showed that the GAP and GACM wound dressing samples presented significantly lower inflammation response than that of the control sample and had hair follicle formation (as indicated by arrows) [Figure 7(a)]. It was also found that the GAP and GACM wound dressing samples significantly improved wound healing as compared to the control sample as shown by the healing area morphology. Therefore, the wound of the animals treated with GAP and GACM wound dressing samples revealed increased firmness and smoothness in their skin surface as compared to the control sample by Masson's trichrome analysis [Figure 7(b)]. These findings demonstrated that the GACM wound dressing sample possessed an exceptionally high cell potential to efficiently promote wound healing for skin repair.

#### DISCUSSION

Current studies have shown that the ADSCs are important cells for skin regeneration.<sup>1-3</sup> The results indicated that the mADSCs exhibited increased cell growth (cell proliferation and colony formation) and induced a high-level expression of adipogenic and osteogenic differentiation as compared to those of the pADSCs. These findings demonstrated that the pADSCs could be easily applied to clinical usage. Although ADSCs therapy is considered as a practical and effective approach for tissue regeneration,<sup>19,20</sup> it presents certain limits such as the shortage of autologous ADSCs from older donors who have lower cell numbers and higher rate of cellular senescence when compared to cells from young donors.<sup>21-23</sup> Additionally, cell-based therapy requires sufficient cell number for clinical application that can be easily isolated and harvested for mesenchymal stem cell-based therapies.<sup>24</sup> Moreover, stem cells obtained from older donors with limitations (such as loss of cell potential with aging) are not sufficient for repeated or even second usage.<sup>25</sup> Recent studies suggested that ADSCs harvested from pigs or dogs can be applied in a xenogeneic transplantation for effectively treating canine osteoarthritis,<sup>26,27</sup> and it did not cause any inflammatory or allergic reactions. These studies indicated that the pADSCs is a good source of multipotent stem cells for xenogeneic stem cell therapy and may provide enough healthy cells to regenerate damaged tissues in a xenogeneic transplantation.

Cutaneous wound healing requires a closely orchestrated cascade to restore and repair damage sites, involving cell migration and proliferation, angiogenesis, extracellular matrix deposition and remodeling. The application of stem cells found could reduce cell infiltration, promote faster wound healing, decrease pain and improve neoangiogenesis in burned wound healing,<sup>28,29</sup> because stem cells can contribute to the reconstitution of dermal fibroblasts by

releasing cytokines such as FGF, VEGF, and TGF-beta that promote wound healing.<sup>30</sup> Although cell therapy is a promising approach for wound treatment,<sup>31-33</sup> there are still several difficulties related to clinical use. For example, stem cells need to be cultured in sufficient numbers to treat wounds but would lose cell potential with aging, and thus further decrease cytokine factor production. In this study, the GBH wound dressing combined with ADSCs was applied to promote wound healing and repair damaged skin. It was found that the GBH wound dressing could not only generate gel structure as cell-seeded carrier, but also mimics microenvironment as the ADSCs release cytokines and tissue growth factors when healing skin wound. Furthermore, there is a surprising discovery that wounds received culture medium of ADSCs had an even greater enhanced wound healing when repairing damaged skin in both mice and porcine. Thus, this study demonstrated that the GBH wound dressing combined with ADSCs and its culture medium is a promising cell therapy method that could be applied in wound healing and skin regeneration. Finally, more tests and studies must be carried out to evaluate the collagen density at the site of wound healing, the tensile strength measurement of the healed wound and inflammatory response of the present cell therapy method for promoting wound healing in the future.

#### CONCLUSION

The study has already applied the potential stem cells composite hydrogel wound dressing technique with favorable outcomes on repairing damaged skin tissues. It was found that the pADSCs induced a higher growth rate and significantly increased colony units formation. The pADSCs have a strong potential on cell differentiation as compared to mADSCs. Additionally, the GBH wound dressing combined with ADSCs and its culture medium also proved to be superior in promoting wound healing. All results indicated that no signs of tumorigenesis was detected in any of the animals over the course of this study. Therefore, these findings demonstrated that ADSCs are a safe growth factor and effectively contribute to the study and clinical use of cell therapy.

#### CONFLICT OF INTEREST

The authors report no conflict of interest in this work.

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★ Hao-Jan Lin, Yushan-Sophie Chang, Li-Hsiang Lin, Chiung-Fang Haung, Chia-Yu Wu, Keng-Liang Ou. " An Immunomodulatory Protein (Ling Zhi-8) from a Induced Acceleration of Wound Healing in Rat Liver Tissues after Monopolar Electrosurgery ", Evidence-Based Complementary and Alternative Medicine, 2014

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