AWARD NUMBER: W81XWH-17-2-0059

TITLE: Optimizing Skin-Implant Interface of Osseointegrated Device

PRINCIPAL INVESTIGATOR: Jonathan Forsberg, MD, PhD

RECIPIENT: Henry M Jackson Foundation, Bethesda, MD

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PREPARED FOR: U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012

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15. SUBJECT TERMS None listed					
16. SECURITY CLASSIF	FICATION OF:		17. LIMITATION OF	18. NUMBER	19a. NAME OF RESPONSIBLE PERSON USAMRDC
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1. INTRODUCTION:

The study addresses two focus areas of research with pressing clinical need: 1. Optimization of the skin-implant interface for osseointegrated (OI) implants, and 2. Prevention of infection at the skin-implant interface. The goal is to address both these issues while maintaining residual limb skin integrity and durability. We address the issue of skin-to-implant healing and attachment for osseointegrated (OI) prostheses by focusing on integration and durability of their microbially, mechanically and biologically challenging skin-to-implant interface. This study focuses on an OI prosthetic implant anchored in the long bone of a residual limb and exiting through the skin. Implant and soft tissue infections (29-38%) and implant loosening (13-29%) are common complications for both upper and lower extremity boneanchored implants, resulting in revision surgeries and increased morbidity. These complications develop due to lack of a tight, impervious seal at the skin-percutaneous implant interface, resulting in exposure of soft tissue and vasculature, thereby increasing chances of infection as well as implant loosening. For both focus areas, we explore the possibility of creating a tight, durable skin-implant interface for OI implants using mesenchymal stem cells (MSCs) derived from naturally occurring porcine integumentary and connective tissues or human induced pluripotent stem (iPS) cells, which have the intrinsic potential to form an impervious seal at hard and soft tissue junctions. We hypothesize that comparative analysis of the differentiation and adhesion properties of naturally occurring cells of the integumentary system, present at hard and soft tissue junctions at the dermis, nails or hoof, periodontal ligament, adipose tissues, as well as iPS cells could enable us to engineer durable and impervious cell-based scaffolds for placement at the skin-implant interface.

2. **KEYWORDS**:

Osseointegration, implants, titanium, scaffold, MSCs, iPS cells, differentiation, adhesion, tissues, bone, cartilage, adipose, muscle, ligament, tendon, dermis

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Research-Specific Aims and Tasks	Mos.	Percent complete	Su b-
 Administrative Aims and Tasks: Establish subaward agreement between HJF and MMRF Develop and sign USU-MMRF CRADA Recruit and hire support personnel a. Stem Cell Biologist (USU) b. Research Associate (USU) c. Stem Cell Biologist (MMRF-UMN) 	1-4	100% 100% 100% a. 100% b: 100% c: 100%	
Specific Aim 1 Specific Aim 1 : in ex vivo culture (a) steer differentiation for human and swine MSC, iPS cells and mature site-specific (gingival and hoof/nail bed) cells to adhesive/epithelial phenotypes, (b) Characterize and rate the ingrowth of these cells into scaffold and their adhesive potential to metal substrate.	1-24	100%	X
Major Task 1: Develop cell culture	1-16	100%	
Subtask 1.1: In vitro isolation and characterization of <i>porcine</i> cells.	1-16	100%	
Subtask 1.2: In vitro development and characterization of <u>human</u> cells.	1-16	100%	Х
Major Task 2: <u>In vitro</u> : evaluate cell adhesion to metal substrate	7-16	100%	Х
Subtask 2.1a: Test porcine cells for adhesion	7-16	100%	Х
Subtask 2.1b: Test human cells for adhesion	7-16	100%	х
Major Task 3 : Scaffold development for cell growth and anchorage to underlying tissue.	5-24	100%	Х
Subtask 3.1: Complete scaffold design (constructs) for "sleeve" & "transition designs	5-16	100%	Х
Subtask 3.2 : Seed and grow porcine cells on flat collagen sheets, assemble scaffolds	17-24	100%	
Subtask 3.3: Seed and grow human cells on flat collagen sheets, assemble scaffolds	17-24	100%	Х
Major Task 4: Complete full statistical analysis, complete/submit 2-4 manuscripts.	18-24	80%	Х
<u>Milestone(s) Achieved</u> : Characterization of 3-4 cell choices for optimal adhesivity - in vitro; submission of 2-4 manuscripts.	1-24	90%	X
Specific Aim 2 Specific Aim 2 : <u>In vivo large animal (swine) testing of</u> transdermal implants with and without subdermal cellular augmentation (SA2a), +/- septal /strain limiting scaffold (SA2b), and topical bacterial challenge (SA2c).	25-60	15%	Х
Major task 5 : (SA2a) Implant 8 implants/animal with "best of" cells from Specific Aims 1 and 2 x 10 animals at University of Minnesota	25-35	5%	Х
Subtask 5.1: Implant initial 5 animals with 3-4 types of cell augmentation per animal	25-27	0%	Х
Subtask 5.2 : Initial evaluation of skin integration - assessment of initial results; experiment modification as necessary.	28-29	0%	Х

What was accomplished under these goals?

<u>Specific Aim 1</u>: *Ex vivo* culture (a) steer differentiation for human and swine MSC <u>Subtask 1.1</u>: In vitro isolation and characterization of *porcine* cells

Isolation of Hoof and Tendon MSC cells

Objective: Development of biobank of isolated, expanded and characterized swine multipotent mesenchymal stem cells in order to complete the large animal study.

Methods: Porcine MSCs were isolated from female Gottingen, Yucatan or Yorkshire minipigs under USUHS Surgery and Veterinary Medicine tissue sharing protocol (LAM-17-540 entitled "Education and Training Protocol for Techniques in Animal Care and Use"). All tissues were collected in sterile collection media (1:1 DMEM-F12, containing 2% FBS and 2X antibiotics; namely penicillin, streptomycin and fungizone), as described in previous reports.

Results: In this past year, we increased the size of our swine cell biobank by isolating and freezing mainly the two most pertinent Swine MSCs cell types (Hoof- and Tendon-derived pMSCs). We updated our inventory shown **in Table 1.**

Conclusion: We successfully isolated enough Hoof- and Tendon-derived MSCs to accomplish the entire large animal study.

Tendon MSC	Number of vials	Total of frozen cells
Passage 0	5	2,300,000
Passage 1	31	25,000,000
Passage 2	10	5,940,000
Passage 3	35	189,000,000
Passage 4	1	450,000
Passage 5	4	3,100,000

Hoof MSC	Number of vials	Total of frozen cells
Passage 0	3	1,200,000
Passage 1	15	20,000,000
Passage 2	12	11,000,000
Passage 3	22	11,000,000
Passage 5	6	6,800,000

Table 1: Inventory of Hoof- and Tendon-derived MSC cells localized at USU

Large scale ex vivo expansion tendon-derived swine MSCs for in vivo application

Objective: We tested the efficiency of Human Platelet Lysates and heparin (HPL+H) on cellular proliferation rate of multipotent MSCs derived Achilles tendon in order determine the maximum cell density that could be obtained after 10 and 15 days of culture.

Methods: The Tendon-derived MSCs (passage 1) were thaw and seeded at 350,000 cells in a 10 cm culture dish in standard MSC growth media (GM) (1:1 DMEM-F12, supplemented with 2% FBS and antibiotics (2x) consisting of penicillin, streptomycin and fungizone) After 24h the GM was exchanged with fresh GM supplemented with 2% of HPL (StemCell) plus 2 IU/ml of sodium heparin (StemCell) every 72h for 10 days at which point adherent confluency was ~ 90%. Cells were trypsinized, collected washed and counted. Cells were expanded for another 5 days by passaging at 1:3 ratio (**Figure 1**).

Results: The addition of Human Platelet Lysates and heparin promoted robust Tendon-derived MSC growth. The number of MSC cells increased 28-fold (1x107 total cells) and 200 fold (7x107) after 10 and 15 days of ex vivo culture, respectively (**Figure 2**). Culturing swine MSCs rendered significant large number of undifferentiated adherent fibroblastic cell-type in only 15 days of culture, giving us enough material to pursue the in vivo experiment.



Figure 1: Cell expansion diagram showing the experiment flow, the confluency and cell density to expect after 1, 4, 7, 10 and 15 days of culture.



Figure 2: Tendon-derived MSC expansion characterization in sterile growth media supplemented with 2% of Human Platelets lysate and 2 IU/ml Sodium Heparin. Average of cell numbers at Day 1, Day 10 and Day 15 of Tendon-derived MSCs cultivated in cMSC-GM+HPL+Heparin.

Evaluation of platelet lysate and heparin as media additives on porcine MSCs marker transcription level.

Objective: We tested the effect of Human Platelet Lysate and Heparin (HPL+H) on both Hoof and Tendon-derived MSC marker transcription using real time quantitative Polymerase Chain Reaction (RT q-PCR).

<u>Methods:</u> Hoof-associated superficial flexor tendon and Achilles tendon-derived MSCs were cultivated in parallel with commonly used growth media DMEM-F12+10% FBS and antibiotics (cMSC-GM) and in cMSC-GM supplemented with 2% Human Platelet Lysate and Heparin (2 IU/ml as final concentration) (cMSC-GM+HPL+H). We assessed comparative gene expression profiles for 2 housekeeping genes (B-actin and B2M) and 2 MSCs marker (CD90 and CD29) using quantitative Polymerase Chain Reaction (qPCR).

<u>Results:</u> Remarkably, in addition of HPL+H promoted robust swine MSC growth (**Figure 2**), we wanted to validate that HPL+H does not affect gene expression of porcine MSCs markers. We compared the transcript expression of two housekeeping genes (B-actin, B2M) and two putative MSCs markers (CD90 and CD29) after 11 days in culture either in cMSC-GM or in cMSC-GM+HPL+H (**Figure 3**). All transcripts were highly expressed independent of the culture conditions, and no marked changes in gene transcript expression were observed.



Figure 3: Hoof and Tendon-derived MSC gene expression study. A. Forward (FW) and reverse (RV) primer sequences used for the qPCR study. B. Average of CT values obtained from quantitative Polymerase Chain Reaction (qPCR) using of B-actin, B2M, CD90 and CD29 primers and comparing Hoof and Tendon-derived MSCs cultured 12 days in cMSC-GM or cMSC-GM+HPL+H. Data presented as mean +/- SD.

Evaluation of platelet lysate and heparin as media additives on Tendon-derived MSCs cytoskeleton structure and morphology

Objective: The objective of this study was to evaluate the effect of platelet lysate and heparin as media additive on cytoskeleton of tendon-derived MSCs selected for in vivo implantation. To do so, we optimized a cytoskeleton-staining protocol to stain filamentous actin (F-actin) on MSCs cultured in standard (DMEM) and platelet lysate and heparin supplemented (DMEM+HPL+H) MSC growth medium. The cytoskeleton of cells plays important roles in cell morphology, adhesion, growth, and signaling. The actin network has been shown to play a major role in the mechanical properties of cells.

<u>Methods</u>: The Tendon-derived MSCs were seeded on a 0.2% gelatin-coated glass coverslip in either a standard MSC growth media (1:1 DMEM-F12, containing 2% FBS and 2X antibiotics) or MSC growth media supplemented of HPL+Heparin for 48h. Cells were fixed using cold 4% paraformaldehyde (Thermofisher) and permeabilized using 0.25% Triton-X100 (Thermofisher)-Phosphate Buffered Saline (PBS, Gibco). Cells were stained with ActinGreen 488 Readyprobes reagent (Thermofisher) which has a high-affinity for filamentous actin, main components of the cytoskeleton. The coverslip was mounted in a microscope slide using EverBrite[™] Hardset Mounting Medium (Biotium) containing Dapi dye. The microcopy slide was imaged on an epifluorescence microscope (Zeiss) using an oil-immersion 40X objectives.

Conclusion: The ActinGreen staining highlights the structure and morphology of well-spread Tendon-derived MSC cytoskeleton by binding directly to actin filaments (grey) (**Figure 4**). Since implants will be coated with cells cultured in the presence of HPL, we assessed if this method of culture results in any cytoskeletal structural changes in MSCs that may be impact cell adhesion and differentiation. No significant difference was observed on cell cytoskeleton structure and

morphology using standard (DMEM) or platelet lysate and heparin supplemented (DMEM+HPL+H) MSC growth medium. In both cases, the actin filaments appear long, thin and well organized (**Figure 4**).



Figure 4: Tendon-derived MSCs cytoskeleton image using ActinGreen 488nm (grey) and Dapi (blue) staining. Scale bars equal 100 µm.

One of the microscopy image obtained was submitted to "USU Research Day 2022- Art of Science Competition" and was awarded first place (see Appendix 1).

<u>Conclusion on using platelet lysate and heparin as media additives:</u> The use of HPL+H has a highly stimulatory effect on swine MSC proliferation while maintains cytoskeleton morphology, and the expression of B-actin, B2M even CD90 and CD29 (MSC markers) and consequently can be used to rapidly accelerate the ex vivo growth of hoof-associated superficial flexor tendon and Achilles tendon-derived MSCs.

Shipment of frozen cells from USU to the University of Minnesota

Eleven vials were successfully shipped from USU to The University of Minnesota on July 26th 2022 (see Table 2). A cell expansion standard operational procedure have been validated at USU and forwarded to the University of Minnesota.

			Tendo	n-derived MSCs	
Passage	Pig #	Freeze date	Cell numbers in the shipped vial	Expected cell numbers after expansion	Purpose
P1	11	06/05/2020	500,000	100,000,000	Cell expansion protocol testing
P1	19	11/25/2019	690,000	138,000,000	Implant coating for Large animal study
P1	19	11/25/2019	690,000	138,000,000	Implant coating for Large animal study
P1	19	11/25/2019	690,000	138,000,000	Implant coating for Large animal study
P1	19	11/25/2019	690,000	138,000,000	Implant coating for Large animal study
P1	20	11/20/2019	700,000	140,000,000	Implant coating for Large animal study
P1	20	11/20/2019	700,000	140,000,000	Implant coating for Large animal study
P1	20	11/20/2019	700,000	140,000,000	Implant coating for Large animal study
P1	20	11/20/2019	700,000	140,000,000	Implant coating for Large animal study
P1	20	11/20/2019	540,000	108,000,000	Implant coating for Large animal study

Table 2: Inventory of Tendon-derived MSC cells which have been shipped to the UMN Image: Comparison of the UMN

Training and education

During the performance period, our team mentored H2M Shruti Kamath, an EMPD2- upcoming medical student, in a variety of molecular and cell culture methodologies and techniques pertinent to studies in this proposal. Dr. Ronzier served as her mentor.

Specific Aim 2: In vivo large animal (swine) testing of transdermal implants

- A Material Transfer Agreement (MTA) was executed on March 17th 2020 between Zimmer, Inc., and the Henry M. Jackson Foundation to provide 150 OsseoTi Transdermal Collars to support projected in vivo studies.
- Transdermal implants were fabricated by Zimmer Biomet and received by the University of Minnesota.
- The ex-vivo study to assess skin attachment onto titanium rods in the presence of cell-laden hydrogel was completed and the samples have been provided to the University of Minnesota imaging center for tissue clearance and imaging to analyze cellular responses. The center is optimizing the staining protocols to minimize strong background fluorescence which should be completed soon after which the samples will be imaged.
- Two swine cadaver pilot studies were performed to optimize surgical techniques and to refine the IACUC protocol and address potential IACUC questions and concerns. These studies determined the optimal spacing of the implants, incision placement, sizing of the transdermal hole and the optimal procedure for applying scaffold treatments during surgery (**Figure 5**). The scaffold treatment was stained to allow visual inspection of the placement and ensure even distribution on the implant.

- The large animal protocol for the in vivo study was approved by IACUC on May 06th 2022 (see Appendix 2) and approved by ACURO on July 05th 2022 (see Appendix 3). The approved protocol is presented in Appendix 4.
- An ex-vivo cell culture study to assess skin attachment onto titanium rods in the presence of cell-laden hydrogel was completed and the samples have been provided to University Imaging Center at UMN for tissue clearance and imaging to analyze cellular responses.

Conclusion: Significant progress has been made in regards to developing the experimental design and surgical procedures in order to conduct the in vivo-large animal study. All materials have been procured. Protocol optimization and mock surgical implantation procedures have been developed and optimized using pig cadavers at UM. Personal, facilities and supplies are in place to commence with the proposed in vivo studies once IACUC/ACURO approval is obtained and the custom-made titanium implants from Zimmer Biomet are received.



Figure 5: A. Picture shows the placements of implants on the cadaver along with the incisions made for inserting the implant, post-insertion ~17mm of the implant post protrudes out of the skin whereas. B. A picture of the base of the implant with scaffold residue (black arrows) after the scaffold was injected through the space between the post and the skin and cross-linked using visible light ($\lambda = 405$ nm). C-D shows spatial distribution of colored scaffold (carmine was incorporated within scaffold for better visualization) demonstrating that there is a layer of cross-linked scaffold around the central hole (where the metal post was) and underneath the skin between the tissue and the base plate of the implant (as marked by black arrow).

Major Task 4: Complete full statistical analysis, complete/submit 2-4 manuscripts

A peer-reviewed manuscript entitled "Culture and characterization of various porcine integumentary-connective tissue-derived mesenchymal stromal cells to facilitate tissue adhesion to percutaneous metal implants" was accepted for publication in an International peer-reviewed journal "Stem Cell Research and Therapy' on November 19th 2021 and is available on-line as of December 19, 2021 (see Appendix 5).

What opportunities for training and professional development has the project provided?

During the past year, Dr. Ronzier from the USU team mentored H2M Shruti Kamath, an EMPD2- upcoming medical student, in a variety of molecular and cell culture methodologies and techniques pertinent to studies in this proposal.

How were the results disseminated to communities of interest?

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?

- Finalize the second manuscript entitled "Use of iMSCs-laden scaffolds for epithelial attachment onto metal abutment for improved performance of osseointegrated devices for amputees: in vitro and ex vivo analysis".
- Complete ~ 25% of the large animal study and submit 6-week tissue integrated implants for histological evaluation (uncoated implants, scaffold coated implants and scaffold-coated/plus cell-coated implants).

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

5. CHANGES/PROBLEMS:

Nothing to Report

Changes that had a significant impact on expenditures

Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Not applicable

Significant changes in use or care of vertebrate animals

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

6. PRODUCTS:

• Publications, conference papers, and presentations

Journal publications.

Publication:

Dey D, Fischer NG, Dragon AH, Ronzier E, Mutreja I, Danielson DT, Homer CJ, Forsberg JA, Bechtold JE, Aparicio C, Davis TA. Culture and characterization of various porcine integumentary-connective tissue-derived mesenchymal stromal cells to facilitate tissue adhesion to percutaneous metal implants. Stem Cell Res Ther. 2021 Dec 18;12(1):604. doi: 10.1186/s13287-021-02666-2. PMID: 34922628; PMCID: PMC8684200.

Poster presentation:

Mutrejal I. et al. Human iMSC-laden photocurable hydrogel for improved durability of the skin/implant interface – An in vitro and ex vivo analysis. MHSRS 2022 poster presentation.

Books or other non-periodical, one-time publications.

Nothing to Report

Other publications, conference papers and presentations.

Nothing to Report

• Website(s) or other Internet site(s)

Nothing to Report

• Technologies or techniques

Nothing to Report

- Inventions, patent applications, and/or licenses
- Other Products

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Funding Support:

The Ford Foundation (Complete only if the funding support is provided from other than this award.)

Name:Jonathan A Forsberg, MD, PhD.Project Role:Principal InvestigatorNearest person month worked:1Contribution to Project:CAPT Forsberg responsible for overall project coordination.

Name:Joan Bechtold, PhDProject Role:Site PI (MMRF)Researcher Identifier (e.g. ORCID ID): 0000-0002-7090-4270Nearest person month worked:3Contribution to Project:Responsible for overall project coordination at sub award site(s).

Name:Thomas A. Davis, PhDProject Role:Associate Investigator (USUHS)Nearest person month worked:3Contribution to Project: Oversight of project conducted at USUHS.

Name: Conrado Aparicio, PhD. Project Role: Associate Investigator (UMN) Researcher Identifier (e.g. ORCID ID): 0000-0003-2969-6067 Nearest person month worked: 3

Contribution to Project: Oversight of iPSC in vitro studies and cell adhesion studies conducted at UMN.

Name:Isha Mutreja, PhDProject Role:Postdoctoral Associate (UMN)Researcher Identifier (e.g. ORCID ID): 0000-0002-8998-7563Nearest person month worked:6Contribution to Project: Oversight of in vitro iPS cells studies conducted at UMN.

Name:Nicholas Fischer, B.S.Project Role:Graduate Student (UMN)Researcher Identifier (e.g. ORCID ID): 0000-0003-2230-5158Nearest person month worked:6Contribution to Project: Performance of porcine cell adhesion experiments conducted at UMN.

Name:Elsa Ronzier, PhDProject Role:Associate Investigator (USUHS))Researcher Identifier (e.g. ORCID ID): 0000-0003-1008-4271Nearest person month worked:12Contribution to Project: Extraction of porcine tissues, cell isolation and characterizationconducted at USUHS.

Name:Andrea Dragon, B.S.Project Role:Research Associate (USUHS)Researcher Identifier (e.g. ORCID ID): 0000-0002-3257-1567Nearest person month worked:3Contribution to Project: Extraction of porcine tissues, cell isolation and characterizationconducted at USUHS.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations were involved as partners?

<u>Organization Name: Stem Cell Institute – Professor Jakub Tolar's lab</u> <u>Location of Organization: University of Minnesota, Minneapolis, MN</u> <u>Partner's contribution to the project</u>: Facilities, collaboration, personnel exchange (Isha Mutreja-Aparicio's lab, Kirk Twaroski-Tolar's lab).

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES:

Appendix 1: USU Research Day 17th-19th May 2022 – Art of Science Competition Winner announcement

Art of Science Competition Winners



1st Place Award HM2 Shruti Kamath US Navy, Enlisted to Medical Degree Preparatory Program



Herman Morris PhD MRI physicist in the USU Department of Radiology and Radiological Science Structural Brain Connectivity visualized using the USU MAGNUS MRI scanner at



3rd Place Award

WRNMMC Brain

Pig Cell Actin' Nuclear!

2nd Place Award

Rohini Manickham PhD candidate Molecular and Cell Biology PhD Program, GEO, School of Medicine-USU Department of Biochemistry and Molecular Biology



Stress Fibers in Color

Appendix 2: IACUC protocol approved letter

From:	1acuc@umn.edu
Sent Date:	Friday, May 06, 2022 16:39:20 PM
To:	sugorr@umn.edu, bechtold@umn.edu, carne115@umn.edu, pluha006@umn.edu
Cc:	
Bcc:	
Subject:	IACUC Protocol Approved: 2112-39687A, Gorr, Sven-Ulrik
Message:	
Dear Dr. Go	rr. Sven-Ulrik.

The Institutional Animal Care and Use Committee (IACUC) reviewed your recent IACUC submission. We are happy to inform you that the information provided satisfies the requirements set by the IACUC and as such, you have received approval for the following project.

Please note that while the IACUC has approved your proposal, initiation of the project cannot begin without adherence to any additional restrictions that have been implemented by federal and local government and/or the University of Minnesota in response to the COVID-19 pandemic. IACUC approval does not supersede mandates made by these agencies and their requirements must be followed before initiating any research at this time.

Ongoing guidance about University of Minnesota research activities during the COVID-19 pandemic can be found at the OVPR page, COVID-19 Guidance for the Research Community: https://research.umn.edu/covid-19

IACUC approved protocol:

Protocol ID: 2112-39687A Principal Investigator: Gorr, Sven-Ulrik Department: Protocol Title: The development and characterization of a soft-tissue attachment to a transdermal skin-implant interface in a swine model of osseointegration Approval Date: May 06, 2022

For your records and for grant certification purposes, the approval date for the referenced project is May 06, 2022. The date of our last AAALAC accreditation was October 2021. The University's NIH Animal Welfare Assurance number is D16-00288 (A3456-01). The code number and the title of your study should be used in all communication with the IACUC office.

Approval for this protocol will expire three years from this date and a new application will be required in order to work past that time. If annual Continuing Review is required by your funding source, please contact the IACUC to arrange for a Continuing Review of your protocol. You are required to participate in the post-approval monitoring process and IACUC inspections during the life of your protocol, if applicable.

As Principal Investigator of this project, you are required by federal regulations to inform the IACUC of any proposed changes in your research involving the use of animals. Changes should not be initiated until written IACUC approval is received. It is also the responsibility of the Investigator to notify the appropriate funding agency of any changes to your proposed animal care and use that have occurred as a result of IACUC review and approval. Finally, the Investigator is responsible for maintaining copies of this application within the laboratory for reference by individuals conducting the work described in this protocol.

If you would like certification of approval sent to your funding agency or a paper copy of this approval letter, please email your request and the relevant information to iacuc@umn.edu.

Appendix 3: ACURO protocol approved letter



DEPARTMENT OF THE ARMY HEADQUARTERS, U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND 810 SCHREIDER STREET FORT DETRICK, MD 21702-5000 July 05, 2022

Director, Office of Research Protections Animal Care and Use Review Office (ACURO)

Subject: Approval of Proposal Number BA150755, Award Number W81XWH-17-2-0059 entitled, "Optimizing Skin-Implant Interface of Osseointegrated Device"

Dr. Jonathan Forsberg, MD, PhD Naval Medical Research Center Silver Spring, MD, US

Dear Dr. Jonathan Forsberg, MD, PhD:

Reference:

(a) DOD Instruction 3216.01, "Use of Animals in DOD Conducted and Supported Research and Training"
(b) US Army Regulation 40-33, "The Care and Use of Laboratory Animals in DOD Programs"

In accordance with the above references, ACURO protocol BA150755.e001 entitled, "The development and characterization of a soft-tissue attachment to a transdermal skin-implant interface in a swine model of osseointegration," IACUC protocol number 2112-39687A, Protocol Principal Investigator Dr. Sven-Ulrik Gor, is approved by ACURO as of 06/30/2022 for the use of pigs and will remain so until modification, expiration or cancellation. This protocol was approved by the University of Minnesota Twin Cities IACUC on 05/06/2022; IACUC approval expires 05/06/2025.

Required Actions:

A. Submit to ACURO for review and approval prior to implementing:

- · IACUC-approved de novo reviews of the protocol
- · IACUC-approved significant changes to this protocol (see guidance document)

B. Notify ACURO within 5 business days of any of the following:

- · Any noncompliance, suspensions or adverse events (see guidance document)
- · Receipt of notification that the institution is under investigation by USDA
- · AAALAC, International accreditation status change

For further assistance, please contact ACURO at (301) 619-6694, FAX (301) 619-4165, or via e-mail: usarmy.detrick.medcom-usamrmc.other.acuro@mail.mil.

NOTE: Do not construe this correspondence as approval for any contract funding. Only the Contracting Officer or Grant Officer can authorize expenditure of funds. It is recommended that you contact the appropriate Contract Specialist or Contracting Officer regarding the expenditure of funds for your project.

Sincerely,

Krinon Moccia, DVM, MPH, DACLAM LTC, VC, USA Director, Animal Care and Use Review Office

Copies Furnished: University of Minnesota Twin Cities IACUC Patrick Struzky Dr. Sven-Ulrik Gor Dr. Lynn Impelluso Mr. D. Jason Ghannadian Lisa Straker

Appendix 4: IACUC protocol approved



Protocol # 2112-39687A May 11, 2022 The development and characterization of a soft-tissue attachment to a transdermal skin-implant interface in a swine model of ossecintegration IACUC-R1S1 05/06/2022-05/05/2025 This Print View may no of the online protocol. reflect all comments and contingencies for approval. Please check the com Department Name Experimental Surgical Services Pager Dept ID 11884 Fax Mailing Address Job Title Experimental Surgical Services MMC 195 Mayo 81958 Researcher 5 Job Code Group 8195B 420 Delaware St SE Minneapolis MN 55455 Civil Service Job Code 8351 City / State / Zip Minneapolis / MN / 55455 Works with Animals* Yes is this person experienced with all the species that he/she will use and all procedures Y he/she will be performing on this protoco?* Indicate with which procedures or species this person is not experienced and how they will be trained.* Click here for additional information about training. Click to check Medgate Status No training data is available. If you have completed training that is not indicated above, please describe training you received (include name of course provider, course number and brief description of coursework): This individual will be copied on emails from IACUC. Page 2 of 45 Protocol # 2112-39687A May 11, 2022 The development and characterization of a soft-lissue attachment to a transdermal skin-implant interface in a swine model of osseointegration 05062022-0505/2025
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Page 4 of 45



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Name*	Pager	Department Name	Name*	Pager	Department Name
Ulferts, Teri Lynn	612/526-3885	Research Animal Resources Mpls	Tollison, Lewis	-	Experimental Surgical Services
Internet ID/x.500	Fax	Dept ID	Internet ID/x.500	Fax	Dept ID
manzx001		11342	Itolliso		11884
	Mailing Address	Job Title		Mailing Address	lob Title
	Experimental Surgical Services	Researcher 3		Experimental Surgical Services	Researcher 2
Email*	MMC 195 Mayo	Job Code Group	Email*	MMC 195 Mayo	lob Code Group
manzy001@umn.edu	420 Delaware St SE	Civil Service	Itolliso@ump.edu	420 Delaware St SE	Civil Service
manzxoo n@umm.eou	Minneapolis		itoliiso@diili.edd	Minneapolis	
Phone	MN 55455	Job Code	Phone	MN 55455	Job Code
612/624-8100	00400	8352R2		55455	8352R2
Cell Phone	City / State / Zip		Cell Phone	City / State / Zip	
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 Background and significance (1-2 sentences Oeseointegration is a method of attaching a implant (rod) is inserted into the meduliary or 	s); a prosthesis to the residual limb of an amputer canal of the residual limb. Over time the titanic	e. Surgically, a threaded titanium um implant becomes infused with bone	ן	Total by Acquisition	25	0	0	0	25
becoming a solid-stable structure (osseoints and brought through the soft tissue and skin the exposed titanium abutment. Superficial	egration). A titanium metal extension (abutme n at the amputation site (transdermal interface and deep infection remains unsolved. The bo	ent) is surgically attached to the implant b). A prosthesis can then be attached to one/implant/skin interface is critical in		method 2. For animals that	are acquired by fra	insfer from anothe	r IACUC protoco	I, please provid	e IACUC
the maintenance of skin barrier function and (permanent skin seal at the implant-skin inte the presence or absence of ex vivo cultured transdemails in the docaal implant ranks of	d detense against infection erface). Porous titanium discs will be coated w d cells derived from swine and human stem ce f clos	with biodegradable vehicle material in ell populations and then implanted		protocol Number	r(s):				
b. What is the question the research addresses	s (1-2 sentences):			 Rationale for Sp a. Why are the spe 	ecies Selection	cted the most app	ropriate for these	studies?	
Porous titanium discs will be coated with bio cells derived from swine stem cell populatio We will investigate new approaches to deve	odegradable vehicle material (GeIMA) in the p ons and then implanted transdermally in the do elop ex vivo engineered living tissues which cr	presence or absence of ex vivo cultures orsai lumbar region of domestic pigs. an be transplanted and integrate with		There are advan	tages of the swine	model over other a	animal models. S	wine share with) ogical
soft tissue, bone and metal to form a seal at study is optimization of the skin-implant inte tissue during wound-healing processes, pre	It the transformal interface to prevent bacteria rface, including skin-to-implant healing and at svention of infection and control strategies.	al leakage. The ultimate goal of this ttachment, remodeling of connective		and immunohist healing. Pig skin	ological features as and underlying fas	sociated with tissu cia/muscle tissue	e regeneration a has been shown	to be the most	kin similar
c. How will the results of this study be used? (1 We will investigate new approaches to deve	1-2 sentences): alop ex vivo engineered living tissues which ca	an be transplanted and integrate with	_	to human and ha surgical treatme	ave made the pig a nts. The utilization of	standard model of of another species	f wound healing a other than swine	and reconstruct e would require	ve use of
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Protocol Title : The developm swine model Protocol Type : IACUC-R151 Approval Period : 05/06/2022-0	nent and characterization of a soft-tissue attachr of osseointegration 5/05/2025	nent to a transdermal skin-implant interface in a	Protocol Title Protocol Type Approval Period	The development and swine model of osseoi IACUC-R1S1 05/06/2022-05/05/2029	characterization of a soft-tissue attachment to a transdermal skin-implant interface in a negration
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Anesthetic Regimen	* * * Anesthetic Regimen * * *				
Will you be performing this proced	ure with anesthesia?	Y	It is expecte grade comp	d that investigators use p ounds whenever they are	harmaceutical- N available in
If yes, please add at least one Ane Anesthetic Agent(s) and Sed	esthetic/Sedative, Analgesic and/or Paralytic latives(s)	c Agent.	exception to	this guideline ? *	eeu an
Agent Name *	Tiletemine/zolaze	pam	compound.	usary exception to guide	ne, and detail preparation and storage or non-pharmaceutical-grade
Dosage (in mg/kg if possible Route of Administration *)* 1-8 mg/kg Intramuscular(IM)	Analgesic a	gents (Prophylactic and I	ntra-procedural)
			Paralytic Ag	ent(s)	
It is expected that investigate grade compounds whenever non-experimental research. exception to this guideline ?	ors use pharmaceutical- N they are available in Do you need an		Please describe in Sedation drugs ar undue stress to th	ntended use if agents will e included in this proced e animals.	be used in combination. are so that blood samples by venipuncture can be collected minimizing
If yes, then justify exception to compound. *	to guideline, and detail preparation and stor	age of non-pharmaceutical-grade	Tileteminexzolaze	pam and xylazine may b	e mixed in the same syringe and administered in a single IM injection.
Agent Name *	Xylazine		In the case of diffi mixture, Route: IN 2.5 mL xylazine (1	cult sedation recovery, a 1, Preparation: Reconstitution 100 mg/mL). This results	nother option is to use all 3 in a pre-mix (Dose: 0.02-0.04 mls/kg of ute an unused vial of Telazol with 2.5 mL ketamine (100 mg/mL) and in 100 mg/mL dissociative (tiletamine and ketamine), and 50 mg/mL
Dosage (in mg/kg if possible)* 1-3 mg/kg				
Route of Administration *	Intramuscular(IM)	Yohimbine 1-2 mg	nts used during procedu j/kg, IM or IV OR	re:
It is supported that in configura			1 mg atipmaezole	for every 10 mg of xylaz	ine given.
grade compounds whenever non-experimental research. I exception to this guideline ? If yes, then justify exception	they are available in Do you need an to guideline, and detail preparation and stor	age of non-pharmaceutical-grade	Parameters monit Please indicate m analgesics. Includ or heart rate of 10	ored during procedure: ethodology and physiolo e the acceptable ranges 0-150 bpm).	pical parameters used to assess depth of anesthetics, paralytics and for these procedures, (e.g., respiratory rate range of 60-60 per minute,
Agent Name *	Ketamine Hvdroc	hloride	We will used the lo breaths per min) a	owest dose possible to a and heart rate (60-140 be	chieve sedation, generally we only monitor respiratory rate (6-20 ats per min).
-			What specific step Still our goal is lig	s will be taken in case a	ny of the measured values are outside acceptable ranges?
Route of Administration *	Intramuscular(IM)	tubes, a scope an the partial reversa	d an ambu bag to intuba I agent as this time as w	e and ventilate the animal to provide respiratory support. We can use ell.
		Page 21 of 45			Page 22 of 45
PROTOCOL IACUC-R1S1 UMN	Protocol # 2112- May 1	39687A 1, 2022	PROTO IACUC- UM	DCOL R1S1 N	Protocol # 2112-39687A May 11, 2022
Protocol Title : The developm swine model	nent and characterization of a soft-tissue attachm of osseointegration	nent to a transdermal skin-implant interface in a	Protocol Title	The development and c swine model of osseoin	haracterization of a soft-lissue attachment to a transdermal skin-implant interface in a legration
Protocol Type : IACUC-R1S1 Approval Period : 05/06/2022-0	5/05/2025		Protocol Type Approval Period	: IACUC-R1S1 : 05/06/2022-05/05/2025	
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Anesthesia and Intra-operative Sur ESS personnel will record the drug	rgery Records. Please describe your record as administered, along with the dose, time, a	keeping plans and forms: ind route of administration.		••••F	Procedure Description * * *
All animals experiencing anesthes	ia or surgical procedures must have a concu	irrently recorded and readily	Please select one:		S
available record detailing anesthes documentation is expected to be re Sample Anesthesia, Surgery, and	sia data, intra-operative monitoring, and pos ecorded at a minimum of 15 minute intervals Post-Procedural Recordkeeping Forms	t-procedural care. Continuous	Description of Surg	jical Procedure letail, including closure, u	ise of eve lubricant and other support drugs used. Helpful quidelines
cumple / alcourtedut, curgery, and			and tips can be fou General Surgery T	ind at the link below: ips and Requirements	ao or eye nanicant and other adport drugs used. Theipin guidennes
Do you need a recording frequency If yes, then provide details includin	y different than the guidelines? g the scientific justification:	N	Three days prior to of their acclimation surgical site.	the surgical implantation prior to surgery. This wi	of transdermal titanium discs, pigs will be fitted with jackets as part II allow comfort in wearing the jackets post-surgery and protection of
	-		Animals will be and room, the animal w leads, and the dors	esthetized, intubated, and vill be placed in ventral re sal aspect of the animal of	I prepared for aseptic surgery. Once transported into the operating cumbency, connected to mechanical ventilation and vital monitoring repared for aseptic surgery for chronic implant and evaluation.
Procedure Type: * Procedure Title: *	surgery Titanium Disc Insertion and Application of E	Experimental Therapies	Six areas on each	animal's dorsal aspect w	Il be selected for subcutaneous implant of the titanium disc. Small
Species: * Pain/Distress Category: *	Pig (Biomedical) B		be made with a ski communication be	n biopsy punch or blade tween the disc and the ex	to facilitate externalization of the titanium disc plug, so that there is ternal aspect of the dorsum.
Copy procedure location details			Upon completion o suture. Concurrent outlined by the app	f the implant insertions, a ly, the test / control thera proved study group and d	III skin incisions will be closed in a standard manner with absorbable pies will be applied to the externalized disc sections in a manner osing strategy.
Procedure Location: Other:		KE / DVCCRC	Once therapies had and anesthesia, and recovery from anest	ve been applied and incis id recovered to sternal / a sthesia, jackets or wrans	ions closed, the animals will be weaned from mechanical ventilation imbulatory prior to transfer to RAR postoperative housing. During may be placed on animals to facilitate protection of the survical sites
Room Number: Will you be moving Animals from	Primary Housing for this Procedure?	ESS Basement ORs Y	from mechanical d practices as recom	amage associated with a mended by the attending	recovering large animal. Wrapping will be performed in line with best RAR postoperative veterinarian.
Information on Animal Transport From where to where will animals	be transported?	Animals will be moved from RAR housing to ESS	Please describe as http://www.ahc.um	eptic technique (e.g. inst n.edu/rar/surgery.html#P	rument sterilization methods, surgical incision/site preparation, etc.) reparation tex will be charged and cleaned for this proportion. Acoustic preparation
Via what mute will the enimole be	transported?	induction room for prep for surgery Animals will be moved	is necessary with a sites) will then be o	betadine alcohol solutio draped with sterile towels	a applied to the surgical site. The entire animal (except the surgical
		from RAR housing, be transported from PWB to blue tube hallway to passenger elevators to KE	Sterilization: All equipment will t and supplies.	be sterile for this procedu	re. This includes surgical instruments, drapes, supplies, instruments,
Who will transport the animais?		ESS personnel	Will any animal un (This includes sur institution.)	dergo more than one sur geries the animals may h	rival surgical procedure? N ave had on another protocol or at another
What equipment will be used to the	ansport them?	Transport cages and gurneys	Indicate the entire	ted time between each o	urvival surgerv.
At what time(s) of the day will tran	nsport occur?	6 AM to 6 PM	increase are codina		
		Page 23 of 45			Page 24 of 45
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PROTOCOL IACUC-R1S1 UMN	Protocol # 2112-39687A May 11, 2022	PROTO IACUC-F	COL R1S1 N	Protocol # 2112-39687A May 11, 2022
col Title : The development and character	prization of a soft-lissue attachment to a transdermal skin-implant interface in a	Protocol Title	: The development and characterization	on of a soft-tissue attachment to a transdermal skin-implant interface in a
swine model of osseointegratio	n	Protocol Type	swine model of osseointegration : IACUC-R1S1	
val Period : 05/06/2022-05/05/2025 rtant Note : This Print View may not reflect a	all comments and contingencies for approval. Please check the comments section	Approval Period	: 05/06/2022-05/05/2025 : This Print View may not reflect all come	ments and contingencies for approval. Please check the comments section
of the online protocol.	in commente and communication approval rease crieck the commente accion	important Note	of the online protocol.	mente and contrigencies for approval. Prease creck the commente section
, please provide justification for exception rec	quest,	Anesthetic Regimer	* * * Anesthetic	Regimen * * *
ame project. Include in your justification any p such distress will be minimized.	pain, distress, or functional deficit that may result and describe	Will you be perform	ing this procedure with anesthesia?	Y
		If yes, please add a	t least one Anesthetic/Sedative, Ana	algesic and/or Paralytic Agent.
* * * Sur	geon Details * * *	Anesthetic Ag	ent(s) and Sedatives(s)	Propofol
eon Details		Agent Name		
personnel listed below will be approved to pe	erform surgery on this protocol.	Dosage (in m	g/kg if possible) *	1-2 mg/kg
Surgeon Details		Route of Adm	inistration -	Intravenous (IV)
Surgeon Name *	Lahti, Matthew Theodore			
(Month/Year) (Name of the individual perform (Name of the trainer) who has (X-number) view	ming surgery) was trained to perform the (name of surgery) by aars of experience with the technique.".*	It is expected grade compou	that investigators use pharmaceutica unds whenever they are available in	ai- N
Matt has over 25 years of experience perform	ming complex cardiac and vascular surgery in swine.	non-experime exception to t	ntal research. Do you need an his guideline? *	
Surgeon Name *	Carney, John	if yes, then jus	stify exception to guideline, and deta	il preparation and storage of non-pharmaceutical-grade
Please provide relevant training and experie (Month/Year) (Name of the individual perform	nce with this species and surgical procedure. E.G., "In ming surgery) was trained to perform the (name of surgery) by	Agent Name *	•	Isoflurane
John has over 12 years of experience perfor	ming complex cardiac and vascular surgeries in large and			
amaii animai modeis, with an extensive publ	ueuon record in the use of animal models of Numan disease.	Dosage (in me	g/kg it possible) * inistration *	1-4%
Surgeon Name *	Pluhar, Liz	Note of Adm	in iisu duon	Innarauun (IN)
(Month/Year) (Name of the individual perform (Name of the trainer) who has (X-number) who	ince when this species and surgical procedure. E.G., "In ming surgery) was trained to perform the (name of surgery) by ears of excertience with the technique.".*			
Dr. Pluhar is a practicing clinical veterinary s Sciences. Her research interests include imp	surgeon at the UMN Department of Clinical Veterinary proving total joint longevity, development of bone graft	It is expected grade compou	that investigators use pharmaceutica unds whenever they are available in untal meaarch. Do you read on	al- N
substitutes, the study of osteoclasts and bon immunotherapies for brain tumors.	e graft incorporation, and the investigation of novel gene and	exception to t	his guideline ? *	
		If yes, then just compound. *	stify exception to guideline, and deta	il preparation and storage of non-pharmaceutical-grade
		Agent Name	•	Tiletemine/zolazepam
		Desers (in m	afka if seesible) t	1.0
		Route of Adm	inistration *	Intramuscular(IM)
	Page 25 of 45			Page 26 of 45
	Page 25 of 45			Page 26 of 45
PROTOCOL	Page 25 of 45 Protocol # 2112-39687A	PROTO	COL	Page 26 of 45 Protocol # 2112-39687A
PROTODOL IACUCRIST UNN	Page 25 of 45 Protocol # 2112-38687A May 11, 2022	PROTO IACUC-R UMN	COL 2151 1	Page 26 of 45 Protocol # 2112-39687A May 11, 2022
PROTOCCU LACUC-R151 UNN stocol Title : The development and charact	Page 25 of 45 Protocol # 2112.30867A May 11, 2022 infization of a soft-lissue attachment to a transdormal skin-implant interface in a	PROTO IACUC-F UMM Protocol Title	COL 151 1 The development and characterization	Page 26 of 45 Protocol # 2112-39687A May 11, 2022 n of a soft-lissue attachment to a transformal skin-implant interface in a
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totocol Title : The development and characterization swine model of osseointegration totocol Type : IACUC-R1S1 yproval Period : 0506/2022-05/05/2025	of a soft-tissue attachment to a transdermal skin-implant interface in a	Protocol Title : The development and characterization of a soft-tissue attachment to a transdermal skin-imple swine model of ossecintegration Protocol Type : IACUC-R1S1 Aproval Period : 0506/2022-0505/2025	lant interface i
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Agent Name *	Lidocaine	atropine 0.04 mg/kg, IM cettiofkr, 3 mg/kg, IM alternatively Cefazolin may be administered 50mg/kg IV during anesthesia induction normal saline (1-15 ml/kg/hour, IV)	n
Dosage (in mg/kg if possible) * Route of Administration *	1-2mg/kg Intramuscular(IM)	In the case of difficult postoperative recovery, another option is to use all 3 in a pre-mix (Dose: 0.02-0.04 n of mixture, Route: IM, Preparation: Reconstitute an unused vial of Telazol with 2.5 mL ketamine (100 mg/r 2.5 mL vulgarior (100 mg/mL). The results in 200 mg/mL discretizitier diffusion and Retarging and Retarging and	mls/kg mL) and
Duration and Frequency *	may be injected IM at the site of disc insertion at the time of closure	each of xylazine and zolazepam))	g/mc
It is expected that investigators use pharmaceutical grade compounds whenever they are available in non-experimental research. Do you need an exception to this guideline ? *	⊦ N	Parameters monitored during procedure: Please include methodology and physiological parameters used to assess depth of anesthetics, paralytics or heat rate of 100-150 bpm).	s and minute,
If yes, then justify exception to guideline, and detail compound. *	preparation and storage of non-pharmaceutical-grade	We monitor:ECG, heart rate, respiratory rate, temperature, end tidal CO2, & oxygen saturation. HR 60-140 beats per min blood pressure: mean >60 mmHa, systolic > 90 mmHa	
Agent Name *	Bupivicaine	oxygen saturation 90-100% is preferred end tidal CO2 35-40 mmHg is preferred, 30-45 mmHg is acceptable	
Dosage (in mg/kg if possible) *	1.0-2.0 mg/kg	What specific steps will be taken in case any of the measured values are outside acceptable ranges?	nore
Route of Administration *	Intramuscular(IM)	parameters are indications of an esthetic depth. -If the change in the animals intrinsic values are significant (approximately 20% increase or decrease from begeing the following stops will be taken:	n
Juration and Frequency	may be administered at sites of disc insertion prior to closure		
It is expected that investigators use pharmaceutical grade compounds whenever they are available in non-experimental research. Do you need an exception to this guideline ? *	⊢ N	 It parameters are above the expected ranges, the animal may be to lightly anesthetized. Anesthesia will taincreased. IV anesthesia may be given if needed. If the pupils become too dilated, the animal may be too deeply anesthetized. Anesthesia will be increased if the animal may be too deeply anesthetized and an another the structure of the structure of	be V
If yes, then justify exception to guideline, and detail compound.	preparation and storage of non-pharmaceutical-grade	anesthesia maybe given if needed. -If a palpebral reflex is present, this is an indication that anesthesia is too light. Anesthesia will be increas IV anesthesia maybe given if needed.	ed, and
Paralytic Agent(s)		Anesthesia and Intra-operative Surgery Records. Please describe your recordkeeping plans and forms: Records will document personnel, procedures, and drugs used (dose, time, and route of administration). V parameters will be recorded every 15 min.	Vital
asse describe intended use if agents will be used in cor termine/Zolazepam and xylazine will be administered as opofol will be administered to anesthetize the animal fo oparation. Once in the OR, isofurane will be administer tamine will be used only if difficult recoveries are obse- likely that this conclail will be mercessary. In the well po-	mbination. s described in the table above to sedate the animal. relacement of an endotracheal tube and surgical red IN to maintain anesthesia throughout the case. vec), and was requested in previous reviews. It is a result of the second second second second second second the second sec	All animals experiencing anesthesia or surgical procedures must have a concurrently recorded and readily evailable record detailing anesthesia data, hrzn-operative monitoring, and post-procedural care. Continuor documentation is expected to be recorded at a minimum of 15 minus intervals. Sample Anesthesia, Surgery, and Post-Procedural Recordiseping Forms	y us
intery that this cocktain will be necessary, but we will con ending veterinarians.	nsider it, at the instruction of the reviewers and RAR	Do you need a recording frequency different than the guidelines? N	
and support agents about caring procedure.		If yes, then provide details including the scientific justification:	
PROTOCOL LACUC-RTST UMN	Protocol # 2112-39687A May 11, 2022	PROTOCOL Protocol # 2112-39887A IACUC-R1S1 May 11, 2022 UMN	
rotocol Title : The development and characterization swine model of osseointegration rotocol Type : IACUC-R1S1 pproval Period : 05/06/2022-05/05/2025	n of a soft-lissue attachment to a transdermal skin-implant interface in a	Protocol Title : The development and characterization of a soft-tissue attachment to a transdermal skin-imple swine model of cessorintegration Protocol Type : IACUC-R1S1 Approval Period : 05090222-0505/2025	ant interface i
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		*** Post-operative Care *** Post-operative Care	
		1. How long will animals be maintained after surgery?	
		Maximally 12 weeks tollowing surgery. The current anticipated duration of the study is 8 weeks tollowing set but will be guided by procedural and intel outcomes following surgery and initial study groups.	surgery,
		Y A. Post-operative care will be provided by RR or under RAR direct supervision for dogs, cats, non 1 Dimates of the maintails by burear on the Minnasoville carevus	human
		1) Does this study have requirements for specific antipole, antibiotic or other post- reporting another that PAR back on a study and before a study of the study	
		a. List the specific study requirements in the text box below. You must also list these requirem	nents
		on the RAR Intake forms when animals are brought to RAR post-op. We will induce immunosuppression by treating with cyclosporine (15-30 mg/kg SID PO starting the variation of the transmission of the transmis	
		day profito xerotransplanation on the miniplants for animals enrolled in Experiment 2, rece.	ng 1 iving
		Dary pilot to xel load alphaniation of the 1 minutes on animals entitled in the permitter 2, rece humans MSC based therapy. Clavamox- Antibiotic 13-20mg/kg PO BID for 10-14 days; Alternatively Cephalexin 500mg PC persent eventility. doi: 10.12.04.04.04.04.04.04.04.04.04.04.04.04.04.	ng 1 iving O BID
		Clavarmox-Antibiotic 13-20mg/kg PO BID for 10-14 days; Alternative's departed with 500mg PC on post-operative day 1(f clarazon is administered 50mg/kg I on DOS) Carprofen-Analgesic 1-4mg/kg POIM q 12-24 hours, PRN	ng 1 iiving O BID
		Clavamor. Antibioti 13:20mg/kg POIID for 10-14 days: Alternative's intrase encoded in Experiment 2, recentuments of a second se	ng 1 living O BID
		Clavamox-Antibiotic 13-20mg/kg PO BID for 10-14 days; Alternatively Caphalexin 500mg PC on post-operative day 1 (if Celazolin is administered 55mg/kg IV on DOS) Carprofen-Analgesic 1-4mg/kg POIM q 12-24 hours, PRN B. Post-Operative Care will not be provided by RAR. 1) Describe post-operative care: State the physiological parameters assessed (e.g. hydration, t post-procedural care details.	ng 1 tiving D BID body ty other
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Please describe Intended us te vill administer an opioid, n anagement. SR Buprenorphill il be administered as describ- grical procedure as describ- terinarian's guidance. . All animals experiencing su stailing anesthesia data, Intra cords are expected to be rec	se if agents will be used in combination. nay administer local blocks, and nasids in combination to provide multi modal pain ine will be administered prior to surgery as indicated in the table above. Carporfen ed in the table above. Liocacine and bupivacaine may be administered during the d in the table above. In cases of breakthrough pain, we will defer to RAR ingloal procedures must have a concurrently recorded and readily available record operative monitoring, and post-procedural care. Post-operative/procedural provided daily for a minimum of 3 degs.	Pig (Biomedi	cai)	There is always a risk of complications with anesthesia. There could be liness and/or dash due to a non-ficacious infection prevention therapy administered during disc insertion, or infection occurring during the postoparative in-file period that does not respond to antibiotic therapies as suggested by RAR veterinarians. To minimize the possibility of infection, animals will be singly housed with other pips, suggestion lists will be wrapped in lormir jackets with the addition rapid and sustained antimicrobial action of ionic silver with the banefits of Safetac soft silcone adhesive technology. The combined attributes of each component of this dressing allow both the control of pain and infection to be achieved simulaneously.
Do you need a reco If yes, then provide	ording frequency different than the guidelines ? N details including the scientific justification.			Fresh dressings will be applied daily until circumferential healing is observed in relation to the portion of the externalized implant, anticipated to be within the first 7-10 days of postoperative recovery. Once observed, jackets and dressings will be removed and animals will be socially housed (multiple pois in a pen). The investigators will defer to best practices
5. IACUC guidelines indicate	that analgesics must be administered for 72 hours post-operatively.	2. How will pain an monitoring by pa	d/or distress be monitor reconnel on this protocol	suggested by the attending RAR veterinarians in all cases. ed? Provide the specific clinical signs which will be monitored as well as the frequency of and indicate if this monitoring will include weakands and holdings.
Do you need an ex If yes, then provide	ception to this guidelines ? N details including the scientific justification.	Species		Description
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ase provide Species - Specific resp u must add at least one species on	ponese to the questions below the Species tab to answer questions 1, 2, and 3. durations of created phases half h conditions that the entimals might excertance (i.e. nam, distance			
List the anticipated specific stu complications, etc.) or any heal momentary pain or distress do repeated handlingand/or confir	dy-included or related adverse health conditions that the animals might experience (i.e. pair, distress, this problems that will or might result from the genotype or phenotype of the animal. Notes that se not need to be described (e.g. venipuncture or injectione). If applicable, consider and include any enerst stress associated with maintenance on a scientific study.			
Species	Description			
	Page 33 of 45			Page 34 of
	Page 33 of 45			Page 34 of
PROTOCOL IACUC-R1S1	Page 33 of 45 Protocol # 2112-39687A May 11, 2022	PROT	DCOL R1S1	Page 34 of Protocol # 2112-39687A May 11, 2022
PROTOCOL IACUC-R151 UMN	Page 33 of 45 Protocol # 2112-39687A May 11, 2022 Protocol # 2112-39687A May 11, 2022 Protocol # 2012-39687A May 11, 2022 Protocol # 2012-39687A Protocol # 2012	PROTI IACUC UM Protocol Title	COL R1S1 N	Page 34 of Protocol # 2112-39687A May 11, 2022
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Yotocol Title : The development and characterization swine model of osseointegration	Protocol # 2112-39687A May 11, 2022	PROTOCOL IACUC-R1S1 UMN	Protocol # 2112-39687A May 11, 2022
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of the online protocol.		of the online protocol.	
* * * Experimental	Endpoints * * *	behavior in multiple species. All ESS personnel	are trained to document any abnormal observations and contact the veterinarian so
xperimental Endpoints		Euthenasia Criteria for Animals Used in Research	h, Teaching, & Display
The endpoint is when an animal or a group of animals will no lon	ger be used in the protocol. To the extent possible, endpoints should	These criteria apply to all animals on experiment	al protocols, whether manipulated or not. Additional criteria may be specified on the
trials required for statistical significance, or the relative change in endpoint is not time dependent (such as the latter han exemples	a measured parameter (e.g. a 50% decrease in tumor size). If an	the Committee as part of the protocol review pro appropriate measures are taken to minimize pair	cess (i.e. the clinical signs listed below are expected as part of the experiment and or discoming in the animals):
protocol (whether or not the endpoint is achieved) should be indi	ated. Study endpoint(s) should be both humane and scientifically relation of animals and the study of animals and in the protocol. Make	a. Weight loss: loss of 20-25% (depending	on attitude, weight recorded at time of arrival, and age: growing animals may not lose
sure the endpoints match those identified in your experimental d consideration.	sign. You may provide a range of endpoints for committee	b. Inappetance: complete anorexia for 24 h	hours in small rodents, up to 5 days in large animals; partial anorexia (less than 50%
We estimate that it will take 12 weeks (84 days) on this protocol postoperative in-life period of 8 weeks (+/, 7 days) This experin	to complete the work. The pilot study is tentatively schedule to have a	c. Weakness/inability to obtain feed or wat	Il rodents, 7 days in large animals. ar: Inability or extreme rejuctance to stand, which pensists for 24 hours, assuming that
days based on the scientific needs of the sponsor.		the animal has recovered from anesthee d. Mothurd state: In protects, measured by	in.
Animals may be euthanized earlier if there are complications the	it are not responsive to treatment.	response- weak attempt to get up; if ani measured by depression counied with b	mail is on its side, attempts should be asymmetrical in nature); in larger animals, odd temperature below 99F (assuming in either case that the animal has recovered
Ine canical symptoms that would prompt examination are alread	y listed in the relation and Monitoring Section.	from anesthesia).	valem (alther overt, or indicated by increased byty temperature or WBC parameters)
requested method. "Not euthanized" and "Other Euthanasia Met	addinariasia metroda per apectes, re-email die species for each	which fails to respond to antibiotic therap	py within an appropriate time and is accompanied by systemic signs of illness.
Euthenesia Standard Methods and CO2 Instructions		 Signs of severe organ system dystunctor veterinarian; 	on non-responsive to treatment, or with a poor prognosis as determined by an PAPC
		Do the IACUC Criteria for Euthanasia Interfere with Yes. Provide the criteria to be used by	n your experimental objectives? by the PI to determine that euthanasia would be required prior to the
Species*	Pig (Biomedical)	approved endpoint AND provide scie	ntific justification for why earlier IACUC guideline-based euthanasia
Method of Euthanasia Primary *	Other Euthanasia	criteria cannot de used:	
Provide agent name, route of administration and	Beuthanasia, Euthasol, Sleepaway, or similar		
dosage when applicable. You may provide a range options for committee consideration.*	of euthanizing agent	Y NO. All of the personnel on this study euthanasia.	r nave read and will comply with the IACUC Guidelines for early
	87-90 mg/kg, IV	N/A. Client owned animals - the deci	sion to euthanize a client-owned animal is between the owner and
Method to Ensure Euthanasia (optional)		their veterinarian and cannot be requ	ured as an endpoint for clinical studies.
It is expected that investigators use pharmaceutical	· N	4. Will death or moribund condition be used as the Humane Endpoints in Animal Care and Lise Prote	experimental endpoint? locols
non-experimental research. Do you need an		Yes (Select "Death" or "Moribundity"	below and provide justification for exception request.)
exception to this guideline?"	preparation and storage of non-phormacoulical grade	Death	
compound. *	proparation and storage of non-pharmaceutical-grade	Moribundity will be used as the Provide justification for experie	experimental endpoint. These animals are classified as pain class C. mental endpoint exception:
		Y No. IACUC Criteria for Euthanasia g	uidelines will be followed.
Animals that are experiencing unrelieved pain or distress prior to	the defined experimental endpoint must be humanely euthanized,	5. Food Chain Approval	N
unless doing so would interfere with, or compromise the scienting animals who may be experiencing unrelieved pain/distress, the t documented in the percennel training records), and the specific	along of personnel on what to look for (this should also be	Describe the treatment to be administered.	
For three days post operatively, animals will be under RAR post	operative care. For the duration of study, ESS will check on animals	Note that senarate sections are provided for ch	amicals biologics and devices. Chamicals (nart &) include drups and hormones.
Once an animal has been identified as having clinical symptom	s we request an examine by a veterinarian. Together with the	Biologice (part B) include innoculants (i.e. bacte transponders or other electrical or mechanical of	rial or viral suspension, vaccine) and antibodies. Devices (part C) include sevices that might be implanted, retained in the digestive tract, etc. In some instances,
veterinarian, we develop a treatment and monitoring plan based	on the severity of the symptoms.	more than one section may need to be filled out completion of part A (chemicals) or B (biologics	t. For example, use of implantable items, such as the Alzet minipump, would require b) depending upon the item being administered and part C for the device.
We have an Animal Observations SOP that describes what to lo	ok for when observing animals, such as normal versus abnormal		
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PROTOCOL	Protocol # 2112-39687A	PROTOCOL	Protocol # 2112-39687A
IACUC-R1S1 UMN	May 11, 2022	IACUC-R1S1 UMN	May 11, 2022
Protocol Title : The development and characterization swine model of osseointegration	of a soft-tissue attachment to a transdermal skin-implant interface in a	Protocol Title : The development and ch swine model of osseoint	naracterization of a soft-tissue attachment to a transdermal skin-implant interfac egration
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of the online protocol.		of the online protocol.	
Chemicals / Biologics			
		Please note that while the keywords section is ensure that the keywords and general search	s auto-populated with procedural titles, these fields should be expanded upon to are completed to identify potential options for not only replacement but also
Deutose (transpondere numpe etc.)		NOTE: At least one detabase must be used	imais used without sacrificing statistical validity.
Devices (italisponders, pumps, etc.)		(See http://www.ahc.umn.edu/rar/ethics.h	ntml#Alternatives or http://www.nal.usda.gov/awic for resources to assist in the
		Search Data	
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temative Search	or and the second secon	Keywords	
is protocol is using pain class B and/or C		Scheduled Blood Collections	Alternative to "Scheduled Blood Collections (Pig
in Classes (Instructional Text)		(Pig (Biomedical))	(Biomedical))"
		Titanium Disc Insertion and	Alternative to "Titanium Disc Insertion and Application of Experimental Therapies (Pig (Bigmedical))*
ain Class B and/or C	tives or how they are not applicable.	(Pig (Piges))	
ain Class B and/or C iefly describe how you have considered each of the following alternat	models or less sentient animals)	(Fig (Biomedical))	
am Class B and/or C lefty describe how you have considered each of the following alterna splacement of vertebrate animals (e.g. with in vitro models, computer the animal model must be of following the animal model, computer	nero umzeu rur this surgery. Less sentrent animal models have	Name of the database(s)	
Bin Class B and/or C isfly describe how you have considered each of the following alterna splacement of vertebrate animals (e.g. with in vitro models, computer he animal model must be of sufficient size to accommodate the mate ready been utilized in early evaluation of this technology and in the te lowed on to all arcs animal whole hear.	song of various infection prevention therapies. This investigator has been used previously in this type of research.	I I Medline / Dub Med	
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Appendix 5: Dr. Dey's published manuscript.

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RESEARCH

Open Access

Culture and characterization of various porcine integumentary-connective tissue-derived mesenchymal stromal cells to facilitate tissue adhesion to percutaneous metal implants

Devaveena Dey^{1,2†}, Nicholas G. Fischer^{3†}, Andrea H. Dragon^{1,2}, Elsa Ronzier^{1,2}, Isha Mutreja³, David T. Danielson¹, Cole J. Homer^{3,5}, Jonathan A. Forsberg¹, Joan E. Bechtold^{4,5,6}, Conrado Aparicio³ and Thomas A. Davis^{1*}

Abstract

Background: Transdermal osseointegrated prosthesis have relatively high infection rates leading to implant revision or failure. A principle cause for this complication is the absence of a durable impervious biomechanical seal at the interface of the hard structure (implant) and adjacent soft tissues. This study explores the possibility of recapitulating an analogous cellular musculoskeletal-connective tissue interface, which is present at naturally occurring integumentary tissues where a hard structure exits the skin, such as the nail bed, hoof, and tooth.

Methods: Porcine mesenchymal stromal cells (pMSCs) were derived from nine different porcine integumentary and connective tissues: hoof-associated superficial flexor tendon, molar-associated periodontal ligament, Achilles tendon, adipose tissue and skin dermis from the hind limb and abdominal regions, bone marrow and muscle. For all nine pMSCs, the phenotype, multi-lineage differentiation potential and their adhesiveness to clinical grade titanium was characterized. Transcriptomic analysis of 11 common genes encoding cytoskeletal proteins *VIM (Vimentin)*, cell–cell and cell–matrix adhesion genes (*Vinculin, Integrin* β *1, Integrin* β *2, CD9, CD151*), and for ECM genes (*Collagen-1a1, Collagen-4a1, Fibronectin, Laminin-a5, Contactin-3*) in early passaged cells was performed using qRT-PCR.

Results: All tissue-derived pMSCs were characterized as mesenchymal origin by adherence to plastic, expression of cell surface markers including *CD29*, *CD44*, *CD90*, and CD105, and lack of hematopoietic (*CD11b*) and endothelial (*CD31*) markers. All pMSCs differentiated into osteoblasts, adipocytes and chondrocytes, albeit at varying degrees, under specific culture conditions. Among the eleven adhesion genes evaluated, the cytoskeletal intermediate filament vimentin was found highly expressed in pMSC isolated from all tissues, followed by genes for the extracellular matrix proteins *Fibronectin* and *Collagen-1a1*. Expression of *Vimentin* was the highest in Achilles tendon, while

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Fibronectin and Collagen-1a1 were highest in molar and hoof-associated superficial flexor tendon bone marrow, respectively. Achilles tendon ranked the highest in both multilineage differentiation and adhesion assessments to titanium metal.

Conclusions: These findings support further preclinical research of these tissue specific-derived MSCs in vivo in a transdermal osseointegration implant model.

Keywords: Transdermal osseointegrated implant, Mesenchymal stromal cells, Integumentary tissues, Cell adhesion, Titanium surfaces

Introduction

Osseointegration is the direct apposition of bone onto a metallic implant, ideally, without fibrous tissue interposition [1]. Transdermal systems have been recently popularized for the use in patients with limb amputations. In amputees, bone anchored devices traverse the skin-boneimplant interface in order to form a direct mechanical connection between the bone and the external prosthesis [2]. Indeed, transdermal systems have revolutionized the quality of life for patients living with major limb amputations, particularly for military service members and veterans. In a national survey of wounded service members and veterans with unilateral upper limb amputations, using traditional (non-osseointegrated) socket prosthesis, it was found that nearly a third completely abandoned their prosthetic device due to skin irritation, discomfort, prosthesis weight and associated morbidities [3]. Unlike socket-based prosthesis, osseointegration results in direct load transfer to the skeleton, elimination of the need for prosthetic revisions due to residual limb shape changes, optimum control of the prosthetic movement, and minimal risk of nerve compression or skin irritation. Anchoring the prosthetic directly to bone also affords the same restitution of sensory and tactile function, osseoperception, as well as a sense of proprioception, a sensory function thought to be impossible to achieve with conventional socket prostheses [4]. All these advantages culminate in overall improved quality of life, increased functional independence, and prompt return to an active lifestyle [5, 6].

While the transdermal nature of osseointegrated implants enables the attachment of a variety of prosthetic devices, the skin-implant interface, known as the aperture, is a unique and ill-defined microenvironment that is integral to prolonged implant stability and homeostasis. The possibility of deep and superficial infection complications remains a major clinical concern for both patients and surgeons, posing a substantial barrier to widespread use. Further, excessive soft tissue motion at the aperture result in progressive exposure of adjacent soft tissues thereby increasing chances of infection, osteomyelitis, implant loosening, surgical revisions and implant failure [7]. Techniques to augment adhesion and durability of the skin and underlying connective tissue to metal at the aperture may improve the durability and long-term viability of the skin-implant 'seal', resulting in reduction of infection and implant loosening. Natural transdermal structures such as nail bed, hoof and tooth, generate an effective mechanical barrier to prevent infections and create a strong, durable hard-soft tissue interface. Recapitulating an analogous cellular transdermal musculoskeletal-connective tissue interface for osseointegrated implants may be a potentially powerful strategy to reduce infection and enhance long-term clinical outcomes [8].

Mesenchymal stromal cell (MSC) therapies have become a widely explored method for treating diseases and potentiating regeneration [9]. Integration with tissue engineering approaches have successfully incorporated MSCs into biomaterial carriers to reduce immediate clearance of transplanted MSC, prolong survival and localization of these cells, thereby enhancing the longterm paracrine effector function of MSCs [10]. However, predicting clinically meaningful outcomes has been difficult for many reasons, such as MSC heterogeneity based on tissue and isolation methods, thus necessitating robust characterization prior to delivery [11-13]. Given the multi-lineage differentiation potential of MSCs into bone, cartilage and fat tissues, our approach for recapitulating cellular transdermal barriers is to deliver MSCs in a biomaterial construct to form a flexible and durable impervious seal.

Here, as a necessary first step toward translation, we characterized the phenotype, multi-lineage differentiation potential and adhesiveness of various tissue-derived porcine MSCs (pMSCs) to clinical grade titanium. The tissues selected for this study can be categorized into two broad groups: 1) those present at the junction of a hard and soft tissue (such as periodontal ligament), present at the interface of the tooth cementum and the supporting bone, and the superficial flexor tendon (anchoring the hoof bone to the soft tissue) and 2) connective tissues such from dermis, adipose tissue and Achilles tendon tissue. We hypothesized that multi-lineage differentiation and metal adhesion properties of porcine integumentary and associated connective tissues would be different than muscle and bone marrow-derived MSCs commonly used for MSC therapy. Porcine musculoskeletal tissues are similar to humans with respect to clinical, histological and immunohistological features associated with tissue regeneration and cutaneous skin healing [14, 15]. Findings from this study will subsequently be tested in vivo using a porcine transdermal implant model developed by our team for studying wound healing and infections at percutaneous titanium (Ti) implant sites. Overall, our detailed characterization and comparative analysis of a broad panel of integumentary and connective tissuederived MSCs will enable selection of best cell candidates and contribute to developing therapies to enhance transdermal system outcomes.

Materials and methods Animals and tissue collection

Tissues were aseptically collected under institutional tissue sharing protocols from 6-month-old female Gottingen, Yucatan or Yorkshire minipigs, Sus scrofa domesticus, immediately after humane euthanization, per approved IACUC guidelines. Bone marrow cells were harvested and isolated from ribs or iliac crest by marrow aspiration using a heparin pre-coated syringe fitted with a Jamshidi bone marrow biopsy aspiration needle. For all other tissues the collection sites were aseptically cleansed prior to incision with ethanol and iodine wipes, then irrigated with phosphate-buffered saline (PBS; Gibco, Gaithersburg MD) supplemented with 200 U/ml penicillin, 200 µg/ml streptomycin and 250 µg/ml amphotericin B (Gibco, Gaithersburg MD). Details regarding tissue description and the sites of tissue collection are listed in Additional file 1: Table S1.

Cell culture

Heparinized bone marrow was washed twice, treated with ACK lysing buffer to deplete RBCs, and resuspended in complete MSC stromal growth medium (cMSC-GM; DMEM-F12 (1:1); Sigma Aldrich, St. Louis, MO), supplemented with 2% FBS and antibiotics (200 units/ml penicillin, 200 µg/ml streptomycin and 250 µg/ ml amphotericin B; Gibco, Gaithersburg MD). Periodontal ligament tissue was scraped off the outer surface of the molars. Harvested tissues were placed in a 10 cm tissue culture dish (Fisher Scientific, Waltham MA) containing 5-7 ml of cMSC-GM, then finely minced into a slurry of small pieces (<1mm³) using fine sterile scissors. Refer to Additional file 1: Table S1 for enzyme concentrations and tissue digestion conditions. Digested tissue cell suspensions were washed, resuspended in 15 ml of cMSC-GM and filtered through 100, 70 and 40 μm cell strainers sequentially (Fisher Scientific) to obtain a single-cell suspension. Cells were placed into a 10-cm sterile tissue culture dish. Cultures were maintained at 37 °C in a humidified atmosphere containing 5% $\rm CO_2$ until 70–80% confluent.

Dermal tissue was processed differently to preserve viability [16]. Briefly, the epidermal skin layer was gently scraped using a scalpel blade to remove hair prior to overnight enzymatic digestion. Digested skin was vigorously vortexed to mechanically remove the epidermal layer. Dermal tissue explants ($\sim 4 \text{ cm} \times 2 \text{ cm}$) were cut into small pieces, and evenly placed on a 10-cm tissue culture dish (Fisher Scientific). A minimum volume of cMSC-GM was added and replenished every 3–5 days near the explants dropwise, ensuring no tissue movement.

Osteogenic differentiation

For induction of osteogenic differentiation, Passage-2 pMSCs resuspended in cMSC-GM were seeded in either in a 96-well plate (100 cells/well) for assessing early osteogenic differentiation via a pNPP based alkaline phosphatase assay, in a 6-well plate $(1 \times 10^5 \text{ cells/well})$ for osteogenic gene expression studies or at 2.5×10^5 cells / well in a 6-well plate for assessing long term osteogenic differentiation potential, as previously described [17-19]. Media was changed from growth media to StemPro® Osteogenic Differentiation media ('OM'; Life Technologies, Carlsbad CA) for half of the wells 24 h post seeding, with the other half (control wells) maintained in growth media (GM). Both OM and GM were replaced every 3 days. For pNPP-based assay, media was aspirated after 7 days, washed with PBS, followed by cell lysis in 1% TritonX-100 and addition of the pNPP substrate (Sigma Aldrich). Absorbance was measured immediately at 405 nm on a kinetic mode for 20 cycles on a Tecan Infinite 200 PRO fluorometer (Tecan; Morrisville NC). Cultured pMSCs were harvested in QIAzol Lysis Reagent (Qiagen, Germantown, MD) for gene expression studies. For long term osteogenic differentiation studies, adherent cell cultures after 14-28 days of culture were fixed in 0.5% glutaraldehyde for 20 min, followed by multiple PBS washes, and mineralization (presence of calcium-rich hydroxyapatite of the extracellular matrix) was assessed by staining with 2% alizarin red solution (prepared in distilled water; pH=4.2) for 3-5 h at room temperature. Post staining, adherent cells were washed multiple times with tap water, followed by deionized water, and imaged microscopically (Axio Observer Z1, Zeiss). For quantification, alizarin red stained calcium crystals were solubilized using 10% formic acid, incubated for 45-60 min with shaking at room temperature, and absorbance measured at 414 nm (Tecan Infinite 200 PRO fluorometer; Tecan, Morrisville NC). Osteogenic differentiation experiments were carried out for all nine tissues in triplicates; i.e., isolated from 3 different animals.

Chondrogenic differentiation

Chondrogenic differentiation of Passage-3 pMSCs was performed using pellet cultures. Briefly, cells were expanded in GM until attaining 80% confluency, after which cells were dissociated with trypsin and re-suspended in chondrogenic differentiation medium in V-well polypropylene plates at a density of 5.0×10^5 cells /well. Cells were centrifuged at 200 g for 4 min and maintained in the media for 21 days with media changes every three days. The standard chondrogenic differentiation media consisted of DMEM (high glucose) media supplemented with 1% ITS+(Sigma, USA; St. Louis, MO), 100 nM dexamethasone (Sigma, USA; St. Louis, MO), 1.25 mg/ml bovine serum albumin (Sigma, USA; St. Louis, MO), 10 ng/ml TGF-B1 (R&D systems, USA), and 0.1 mM ascorbic acid 2 phosphate (Sigma, USA; St. Louis, MO). Pellets (in triplicates) were collected either at 7 days for gene expression analysis (in QIAzol Lysis Reagent), or after 21 days for histological and quantitative assessments of differentiation. Synthesis of glycosaminoglycans (GAG) was measured to quantify chondrogenic differentiation. For GAG analysis, collected pellets (in triplicates) were digested at 56 °C in 300 µL of 1 mg/mL proteinase-K solution to digest the matrix, followed by addition of dimethyl-methylene blue (DMMB) dye. Total GAG content was determined by measuring the absorption of the molecular complex at 492 nm (Synergy TM 2, Biotek multi-mode microplate reader). Chondroitin sulphate B was used to prepare a standard curve. GAG content was normalized against the total DNA content, measured using the cell lysate following the manufacturer's protocol (CyQuant cell proliferation assay). Briefly, diluted cell lysate was mixed with 2X GR-dye and incubated for 1 h at room temperature following which the fluorescence was measured at λ_{ex} of 480 nm and λ_{em} of 520 nm (Synergy TM 2, Biotek multi-mode microplate reader). Chondrogenic differentiation was quantified as the ratio of GAG to the DNA content (GAG/DNA). For histological analysis, collected pellets (in triplicates) were fixed in 4% paraformaldehyde for 30 min at room temperature, cryo-sectioned (30 µm thick sections) and stained with Alcian blue to assess levels of sulphated glycosaminoglycans and counterstained with Nuclear Fast Red. The set of pellets collected at day 7 post chondrogenic differentiation was used to assess the expression of three chondrogenic genes: SOX9, Collagen-2a1 and Aggrecan.

Adipogenic differentiation Adipogenic differentiation of Passage-2 pMSCs resuspended in cMSC-GM seeded in either in a 6-well plate $(1 \times 10^5$ cells/well) for adipogenic gene expression studies, or at 2.5×10^4 cells/well in a 6-well plate for assessing long term adipogenic differentiation potential. Media was changed from GM to AdipoQual adipogenic media ('AM'; Obatala Sciences; New Orleans, LA) for half of the wells when cells reached 40-60% confluency, with the other half (control wells) continued in GM. Both AM and GM were replaced every 3 days. For gene expression studies, cells were harvested after 7 days in differentiation or growth media, via cell scraping, and stored at - 80 °C in 1 ml of QIAzol Lysis Reagent until further processing. For long term adipogenic differentiation studies, cultured pMSCs were harvested between 14-28 days; fixed in 0.5% glutaraldehyde for 20 min, followed by multiple PBS washes, and stained with Oil Red O Staining Solution (Obatala Sciences; New Orleans LA) for 30 min to an hour. Post staining, wells were washed multiple times with DI water and imaged microscopically (Axio Observer Z1, Zeiss). For quantification, Oil Red O-stained lipid droplets were solubilized using 100% isopropanol, incubated for 10 min with shaking at room temperature, and fluorescence measured at λ_{ex} of 500 and λ_{em} of 595 nm (Tecan Infinite 200 PRO fluorometer; Tecan, Morrisville NC). All adipogenic differentiation experiments were carried out for nine tissues in triplicates; i.e. each of the nine tissues isolated from 3 different animals.

Gene transcripts associated with cell adhesion

Adhesion gene profiling was conducted using Passage-5 pMSCs (1×10⁵ cells/well) grown in cMSC-GM, OM, CM and AM for 7-days. Adherent cell cultures were washed twice with PBS, scraped from the plate, and pelleted by centrifugation, stored at - 80 °C in 1 ml of QIAzol Lysis Reagent (Qiagen, Germantown MD). Total RNA was isolated using the miRNAeasy Mini Kits (Qiagen). Quantitative and qualitative evaluation measurements of RNA samples were conducted using NanoDrop and Agilent 2100 Bioanalyzer instruments (Thermo Scientific, Waltham, MA). cDNA was synthesized using a high-capacity cDNA synthesis kit (Applied Biosystems, Foster City, CA) and qPCR was carried out using a Syber Green based detection (BioRad, Hercules, CA) on the Quantstudio (QuantStudio 7 Flex Real-Time System; Applied Biosystems, Waltham, MA). The list of primers and sequences used for this study have been listed in Additional file 1: Table S2 with β-actin as a housekeeping gene.

Immunophenotype

Passages 3-5 pMSCs were harvested for flow cytometric analysis, pMSCs were washed once with room temperature PBS, incubated with 15 mM EDTA in PBS solution for 12 min at 37 °C and detached off the plate. Detached cells were washed in DMEM media supplemented with 10% FBS, centrifuged and counted. Aliquots of 2×10^5 cells were suspended in 2 ml of Flow Cytometry Staining buffer (eBioscience[™], Invitrogen, Waltham, MA), washed (centrifugation for 5 min at 1400 rpm). Cell pellets were resuspended in 100 µl of FACS buffer then incubated on ice for 30 min with FITC-conjugated anti-CD44 (#MA1-10228; Invitrogen, Waltham, MA), anti-CD90 (#A15761; Invitrogen), and anti-CD29 (#MA1-19566; Invitrogen, Waltham, MA), and anti-CD105 (#NB11081749; Novus Biologicals, Centennial, CO). FITC-conjugated isotype matched IgG1 (#50-204-9474; Cell Signaling Technology, Danvers, MA) and IgG2 (#PA5-33239, Invitrogen) were used as controls. After 30 min of incubation in the dark, cells were washed twice with 2 ml of Flow Cytometry Staining buffer and then resuspended 300 µl of cold FACS buffer. To detect dead cells, 1ul of SYTOX[™] Blue Dead Cell Stain (Invitrogen, #S34857) was added to the cells 5 min prior to being analyzed using a BD LSRII Flow Cytometry System (BD BioSciences, Rockville, MD). Viable cells were gated in a dot plot of forward versus side scatter signals wherein 10,000 gated events were acquired over a log fluorescence scale. Flow cytometric data were analyzed, and histograms generated using FlowJo software version 10 (TreeStar Inc, Ashland, OR).

Cell adhesion experiments on titanium alloy Intracellular focal adhesion quantification

Passages 2–3 cells were seeded on Ti-6Al-4 V (Ti) polished to a 20–60 nm colloidal silica finish (President Titanium, Hanson, MA) and glass disks (Harvard Apparatus, Holliston, MA) at 1×10^3 cells/disk for 4 h, 1 day, and 3 days. NIH-3T3 (CRL-1658, ATCC, Manassas, VA) embryonic murine fibroblasts (hereafter, NIH-3T3 fibroblasts) which adhere, proliferate and migrate on metal and glass surfaces served as controls Overmann [20]. Cell spreading and focal adhesion characteristics were determined with immunofluorescence. Seeded disks (n=10) were washed in PBS (Gibco), fixed in 4% paraformaldehyde for 10 min, permeabilized with 0.1% Triton X-100 Page 5 of 20

in PBS, blocked in 5% bovine serum albumin (BSA), followed by overnight anti-vinculin primary antibody staining (MAB3574; MilliPore Sigma, Burlington, MA), incubation with secondary antibody (ab97037; Abcam, Cambridge, UK) in PBS for 1 h at room temperature, followed by incubation with 4,6-diamidino-2-phenylindole (DAPI; 300 nM in PBS; D9542; Fisher Scientific, Waltham, MA) for 10 min. After each step, the cells were rinsed in PBS. Disks were mounted with ProLong (Fisher) and imaged (Olympus FV1000, Tokyo Japan or Leica DM 6B, Wetzlar Germany). Cytoskeletal architecture was assessed by rhodamine-phalloidin (R415, ThermoFisher Scientific, Waltham, MA) based actin staining on the remaining disks (n=5). These slides were processed using the same protocol as described above, counterstained with DAPI and mounted. ImageJ (NIH) was used for image analysis of all fluorescent images, with 5 fields of views (FOVs) per sample. Proliferation (number of DAPI-positive nuclei), cell surface area per FOV, individual cell area, vinculin (focal adhesion) intensity per FOV, average vinculin (focal adhesion) intensity per cell, and average vinculin (focal adhesion) intensity per cell area were calculated and normalized to NIH-3T3 fibroblasts on Ti at 4 h for each measure to account for differences in microscope usage. All experiments were repeated on pMSCs derived from at least 3 animals.

Cell proliferation and viability

A colorimetric assay (CCK-8) was used to compare the proliferation and viability of pMSCs on both Ti and control glass. At 4 h, 1 day and 3 days, seeded disks (n=7; both Ti and glass) were washed thrice in PBS to remove weakly adherent cells, transferred to a virgin 48 well-plate, and incubated for 2.5 h in a 1:10 dilution of CCK-8 solution (Dojindo Laboratories, Japan) in culture media. Afterward, 100 µL of the CCK-8/media solution was transferred to a 96-well plate for absorbance reading (Synergy, BioTek—450 nm) expressed as optical density (O.D.). A blank, comprising of CCK-8/media solution, without cells was used to subtract background absorbance. All experiments were repeated on pMSCs derived from at least 3 animals.

(See figure on next page.)

Fig. 1 Isolation and phenotypic characterization of nine porcine tissue-derived mesenchymal stromal cells (pMSCs). a Representative phase contrast images (50 × magnification) of Passage-0 cells, 10 days after isolation from the different porcine integumentary and connective tissues as specified. For all figures, Ab Abdominal, HL Hind Iimb, Hoof Hoof-associated superficial flexor tendon, Molar Molar-associated periodontal ligament, Muscle Gastrocnemius muscle b Phenotypic characterization of the pMSCs by gene transcripts of MSC (CD90, CD44, CD29, CD105), hematopoietic (CD11b) and endothelial (CD31) markers in Passage-2 cells cultured in growth media. β-Actin was used for normalization of gene expression. Data presented as mean ± SEM (n=3, *p < 0.05)





Centrifugal assessment of cell adhesion

A centrifuge-based assay was used to apply shear to pMSCs to quantify their physical adhesion to titanium [21]. pMSCs (5×10^3) were seeded onto polished titanium disk surfaces in 48-well plates for 48 h then gently washed thrice with PBS to remove non-adherent cells. Oral keratinocytes (OKF6/TERT-2; BWH Cell Culture and Microscopy Core, Boston, MA) were used as a positive control given their strong adhesion to titanium [22]. One set of disks (n=3)were immediately removed and fixed in 4% paraformaldehyde (hereafter, control-pre). The second set (n=3) were inserted into a three-dimensionally (3D) printed (Dental Resin SG, Formlabs, Somerville, MA) disk-holder (Additional file 1: Fig. S1). This holder fits inside a 48-well such that disks (one disk per holder per well) are oriented perpendicular to the ground when centrifuged. Wells were filled with culture media and then centrifuged (3 min) at 350 g or 500 g (n=3 per sample). Control disks (n=3sample; hereafter, control-post) were treated identically, but placed next to the centrifuge (5810R; Eppendorf, Hamburg Germany) while the other two groups were centrifuged. Disks were then subsequently stained with DAPI for 15 min at room temperature and imaged (Lecia DM6 B). ImageJ (NIH) was used for quantification of nuclei in three random field of views per disk.

Statistical analysis

GraphPad Prism (v8; GraphPad Software, San Diego, CA) was used for statistical analyses and graphic drawings. Experimental data were evaluated by one-way ANOVA, followed by the Tukey HSD multiple comparison test. A *t*-test with False Discovery Rate (FDR) correction (Q=1%) was used to compare titanium vs. glass for each measure. An ANOVA with Dunnett's multiple comparison was used to compare the various pMSCs cell types to NIH-3T3 fibroblasts (control group) for each measure. Inter-cell population differences between control-post, 350 g, and 500 g were detected with a two-way analysis of variance with a Dunnett correction where the control mean (null) was set as keratinocytes. A value of p<0.05 was considered as significant difference.

Results

Isolation and culture of porcine mesenchymal stromal cells (pMSCs) derived from integumentary and connective tissues

As shown in Fig. 1a, a population of "fibroblast-like" cells were successfully isolated from nine distinct porcine tissues, comprising either integumentary (periodontal ligament, hoof-associated flexor tendon) or connective (Achilles tendon, dermis, adipose) tissues, in addition to bone marrow and muscle, using enzymatic and mechanical dissociation as detailed in Methods and Additional file 1: Table S1. Except for dermal tissue, single cell suspensions obtained from post-tissue digestion were seeded on tissueculture treated polystyrene (TCPS). Dermis-resident cells were derived from epithelial layer-depleted skin explants, seeded on TCPS. By day five, distinct foci (clusters of 5-10 cells) of plastic adherent cells were evident in all single-cell suspension derived cultures and retained high viability and proliferation potential after extended in vitro expansion. Outgrowth of pMSCs was greatest in adipose tissue and least from dermal tissue; however, by Passage-2 growth across all cell type were comparable through Passage-5. In contrast, pMSCs derived from periodontal ligament exhibited a mixed population of fibroblast like and spherical cells, while pMSCs derived from hind limb dermis often contained a mixture of fibroblast and cobblestone shaped cells. pMSCs isolated and expanded from all three pig strains (Gottingen, Yucatan and Yorkshire) revealed similar characteristics.

Gene expression of pMSC-surface markers

We used RT-PCR to profile the mRNA expression patterns of MSC-specific cell surface markers in Passage-2 cells (Fig. 1b). All the nine tissue-derived cells expressed high levels of mRNA transcripts for porcine cell surface markers whose expression can be used to functionally characterize isolated pMSCs, such as *CD29*, *CD44* and *CD90*, while negative for hematopoietic (*CD11b*) and endothelial (*CD31*) gene transcripts [23]. The expression of the *CD105* transcript was not strongly detected in any of the nine pMSCs comparing to others MSC markers studied but still significantly higher than the expression of hematopoietic and endothelial markers (Fig. 1b). The expression of *CD105* as a pMSC marker in pigs is still controversial [24, 25]. The pattern of gene transcript

(See figure on next page.)

Fig. 2 Cell surface marker immunophenotype of porcine tissue-derived mesenchymal stromal cell (pMSCs) using flow cytometric analysis. Flow cytometric analysis of cell surface protein expression on pMSCs using FITC-conjugated anti (D29, CD44, CD90, and CD105 antibodies. Cell surface log fluorescent measurements were obtained on 10,000 viable cells using forward versus side scatter (FSC vs SSC) gating. Representative fluorescent histograms of cells stained with isotype matched (control) and MSC surface marker antibodies are shown



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expression for the pMSC-specific markers varied across the nine tissues; molar-derived periodontal ligament (Molar), bone marrow and hind limb (HL) dermisderived cells expressed significantly higher levels of the *CD90* transcript, compared to the other cell types; while abdominal (Ab) dermis, hind limb adipose and tendonderived cells expressed significantly high levels of the *CD44* transcript. Most of the cell types expressed comparable levels of *CD29* gene transcript expression, although the expression levels in molar and muscle-derived cells were significantly higher than in all other cell types.

Cell surface immunophenotype of pMSCs

In order to confirm the gene expression data, cell surface protein expression was assessed using flow cytometric analysis. In comparison to median fluorescent signals on isotype control stained pMSCs, we observed that all of the pMSC-derived cell types strongly expressed CD29 (3–6 fold increase), CD44 (5–14 fold increase) and CD90 (4–26 fold increase), albeit the expression of CD105 (1.5–4 fold increase) was significantly less (Fig. 2). These data and the mRNA transcript results demonstrate that pMSCs isolated from different pig tissues share a similar mesenchymal cell surface marker phenotype (CD29^{low}, CD44^{high}, CD90^{high} and CD105^{dim}) immunophenotype.

pMSCs exhibit trilineage differentiation potency

Further functional characterization of the pMSCs was carried out by assessing the multilineage potential of these cells during expansion. On induction of differentiation conditions, all pMSCs lines differentiated into osteoblasts, adipocytes and chondrocytes, albeit at varying degrees, under specific culture conditions.

Osteogenic differentiation

pMSCs derived from the adipose tissue of the hind limb (HL) adipose, bone marrow and molar-associated periodontal ligament demonstrated the highest potential of early osteogenic lineage commitment, as assessed by the alkaline phosphatase activity assay (Fig. 3a). In long term culture under extended osteogenic differentiation conditions, calcium deposition as a late indicator of osteogenic differentiation, was markedly increased in HL adipose and bone marrow-derived pMSCs (Fig. 3b–c). Analysis

of osteoblast-specific genes in these cells after one week in osteogenic differentiation media demonstrated relatively high expression level of BGLAP (Osteocalcin) and COL1A1 (Collagen-1a1) genes in HL adipose-derived pMSCs (Fig. 3d, e), when compared to cells cultured in growth media. The expression level of these genes in HL adipose-derived pMSCs was comparable to expression in pMSCs derived from other tissues, such as Achilles tendon, muscle, hoof-associated tendon, abdominal adipose and dermal tissues; indicating potent osteoblastic differentiation potential of all these cell types. In addition, the same osteogenic induction signals resulted in induction of other pro-osteogenic genes in the different tissuederived pMSCs. For example, there was pre-dominance of expression of BGLAP (Fig. 3d) and RUNX2 (Runtrelated transcription factor 2) (Additional file 1: Fig. S2a) in abdominal dermis and abdominal adipose; COL1A1 (Fig. 3e) and BSP (Bone sialoprotein) (Additional file 1: Fig. S2b) in muscle, tendon and hoof-associated superficial flexor tendon pMSCs, and OPN (Osteopontin) in bone marrow and molar-derived pMSCs (Additional file 1: Fig. S2c).

Chondrogenic differentiation

As shown in Fig. 4, Achilles tendon-derived pMSCs had the greatest chondrogenic differentiation capacity, as assessed by Alcian blue staining (Fig. 4a) and measurement of normalized glycosaminoglycans (GAG) (Fig. 4b). This was confirmed by gene expression analysis of chondrocyte-specific genes, such as ACAN (Aggrecan), COL2a1 (Collagen-2a1) and SOX9 (SRY-box transcription factor 9) in pMSCs harvested after 7 days in pellet cultures (Fig. 4c–e). Achilles tendon-derived pMSCs demonstrated the highest expression of these pro-chondrogenic genes compared to the corresponding cells cultured in growth media.

Adipogenic differentiation

All the tissue-derived pMSCs populations demonstrated varied low-to-modest levels of intracellular lipid droplets accumulation (Fig. 5a). Isopropanol-based solubilization of the lipid droplets, followed by spectrophotometric quantification, indicated that hoof-associated superficial flexor tendon-derived pMSCs had the highest level of adipogenic differentiation, followed by HL adipose

Fig. 3 Assessment of in vitro osteogenic differentiation of pMSCs. a Quantification of early osteogenic differentiation potential of pMSCs cultured in osteogenic induction media for 7 days, assessed by pNPP-based alkaline phosphatase activity assay. b Quantification of alizarin red stain-based assessment of late osteogenic differentiation of cells cultured in osteogenic induction media for 14–28 days. c Representative phase contrast images (50 x magnification) of cells stained with alizarin Red. d–e Fold change in gene expression of osteogenic transcription factors, *Osteocalcin (BGLAP)* (d) and *Collagen-1a1* (e) in cells cultured in osteogenic media (OM) normalized to their expression under growth media (GM) for 7 days. B-Actin was used for normalization of gene expression. Data presented as mean \pm SEM (n=3; *p < 0.05)

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tissue-derived pMSCs (Fig. 5b). This was corroborated by the highest upregulation of the adipogenic transporter, *AP2 (Adipocyte protein 2)*, in hoof-associated superficial flexor tendon pMSCs observed after a week in adipogenic induction medium (Fig. 5c). While hoof-associated superficial flexor tendon pMSCs also had high expression of another well-known adipogenic transcription factor, *PPARy (Peroxisome proliferator activated receptor gamma)* (Fig. 5d), muscle and tendon-derived pMSCs also demonstrated significantly high upregulation of *PPARy* in early stages of adipogenic induction.

Profiling of cell adhesion-related genes in pMSCs

Others have shown that surface modifications (porosity, surface roughness, scaffold coatings) of the titanium (Ti) metal can improve cell adhesion and osseointegration [20]. One of the critical parameters for selection of a promising cell type to reinforce the aperture is its adhesion strength to metal, scaffold and surrounding tissue. Such adhesion may also result in MSC tissue retention. Thus, non-stimulated pMSCs were profiled for inherent differences in expression of structural and adhesionrelated genes. Using qRT-PCR based expression, an assessment of the expression of 11 common genes encoding cytoskeletal proteins VIM (Vimentin), cell-cell and cell-matrix adhesion genes (Vinculin, Integrin \$1, Integrin β2, CD9, CD151), and for ECM genes (Collagen-1a1, Collagen-4a1, Fibronectin, Laminin- α 5, Contactin-3) in early (Passage 2) and late (Passage 5) cells was performed. At Passage 5, all pMSCs showed high levels of expression of Vimentin, followed by Collagen-1a1, Fibronectin, Vinculin, Integrin β1, Collagen-4a1 (Fig. 6) and CD9, CD15, Laminin- α 5, Contactin-3 and Integrin β 2 (Additional file 1: Fig. S3). Achilles tendon-derived pMSCs had the highest expression level of vimentin. Among all the cell types, hoof-associated superficial flexor tendon pMSCs expressed high levels of the majority of adhesion-related genes tested (6/11; Collagen-1a1, Integrin β1, CD9, CD151, Laminin-a5, Contactin-3), followed by musclederived pMSCs (5/11).

pMSCs adhesion to titanium alloy surface

To further characterize the potential of pMSCs strengthening the skin-implant (*i.e.*, Ti) interface, a CCK-8 Page 11 of 20

based metabolic activity assay, measuring cell adhesion, proliferation and viability on titanium or glass control surfaces, was carried out. Here, we compared pMSCs to control NIH-3T3, whose proliferation on Ti is well described [26], and typical bone marrow pMSCs. These results for the top two performing pMSCs demonstrated significantly higher proliferation and viability of hind limb dermis-derived pMSCs on titanium as early as 4 h (Additional file 1: Fig. 7a), followed by hind limb adipose and bone marrow-derived cells, with significantly higher values on titanium at 72 h and 24 h with respect to glass, respectively. Molar-derived pMSCs also had high cell proliferation and viability on titanium versus glass surface at 72 h (Additional file 1: Fig. S4). As shown in Fig. 7b, abdominal dermis-derived pMSCs cultured on titanium demonstrated significantly high levels of intracellular focal adhesion marker vinculin levels when compared to glass at 72 h. Focal adhesions are known to mediate cell-Ti adhesion and proliferation [27]. This was followed by hoof-associated superficial flexor tendon pMSCs cultured on titanium, with significantly higher vinculin levels compared to cells cultured on glass at 24 h (Fig. 7b). All the other cell types generally demonstrated higher vinculin intensity on glass surface (Additional file 1: Fig. S5). Finally, a stringent functional test of the pMSCs' adhesion to titanium was carried out by subjecting the nine pMSCs seeded on titanium disks to centrifugal forces of 350 g and 500 g, followed by assessing the percentage of cells that remained adhered to titanium post centrifugation. The positive control, keratinocytes with their well described adhesion to Ti [22], had no significant change in percentage of adhered cells on titanium pre- and post-centrifugation (Fig. 7c). However, post centrifugation titanium surfaces showed significantly fewer attached cells for all tissue-derived pMSCs (Fig. 7c and Additional file 1: Fig. S6). Bone marrow-derived pMSCs had the lowest decrease in percentage of cells adhered to titanium post centrifugation at 350 g. HL dermis and Achilles tendon-derived pMSCs had the highest remaining percent amongst the other pMSCs at 500 g (Fig. 7c).

(See figure on next page.)

Fig. 4 Assessment of in vitro chondrogenic differentiation of pMSCs. a Histological staining (Alcian blue/Nuclear Fast Red) of pellets derived from pMSCs of different tissue sources cultured in chondrogenic media after 21 days in culture (50 x magnification). b Quantification of chondrogenic differentiation by calculating the levels of glycosaminoglycans (GAG) secreted by cells under chondrogenic differentiation conditions, normalized to the cell density in the pellets (DNA) after 21 days in culture. Data presented as mean \pm SD (n = 3 biological replicate with three pellets per replicate). *p < 0.05 and **p < 0.01 c—e Fold change in gene expression profiling of chondrogenic genes, *SOX9* (c) *Aggrecan* (d) and *collagen* II (E) in pMSCs cultured in chondrogenic media (CM) vs growth media (GM) for 7 days. β-Actin was used for normalization of gene expression. Data presented as mean \pm SEM (n = 3; *p < 0.05)

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Summary of key functions tested

A summary table (Table 1) was created to rank the top 3 tissues for each assessment (tri-lineage differentiation, adhesion gene expression, focal adhesion to Ti, proliferation on Ti, and adherence to Ti after centrifugation). The number of times a pMSCs appeared in the list was summed to create an overall ranking, where hoof-associated superficial flexor tendon pMSCs appeared the most.

Discussion

This is the first comprehensive study, in our knowledge, which reports detailed characterization and comparative analysis of a broad panel of porcine integumentary and connective tissue-derived mesenchymal stromal cells. Indeed, the bulk of literature on pMSCs and their preclinical uses in the porcine model are restricted to bone marrow and adipose-derived cells [28-32], with very few reports on the isolation of multipotent pMSCs from porcine skeletal muscle [33-35], dermis [36, 37], and periodontal ligament [38]. While several reports used decellularized porcine tendon as a biological scaffold to seed human tissue-derived stromal cells [39, 40], there exist limited reports on the isolation and characterization of pMSCs derived from porcine tendon tissues. These findings indicate that these tissue-derived regenerative cells can have potential applications in bioengineering a durable skin-implant interface.

Successful isolation, ex vivo expansion, and in vitro multi-lineage differentiation of plastic adherent cells with self-renewal capacity from all nine porcine tissues demonstrated the presence functionally competent MSCs within these tissues. High expression of vimentin in all these cell types corroborated the mesenchymal origin of these cells [41]. Our results indicated that these cells can be steered to any of the three lineages studied here (osteogenic, chondrogenic and adipogenic), based on the combination of in vitro induction signals the cells are exposed to. However, the varying level of expression of the different cell surface marker transcripts across the pMSCs indicated tissue-selectivity of these surface proteins or their compensatory roles in regulating pMSC function. Tissue-specificity and selectivity of the nine pMSCs was also reflected in the differentiation studies, with distinct transcription factors upregulated in the different pMSCs during the early stages of differentiation. It is important to consider species-specific differences between porcine and human MSCs that came up in this study, exemplified by the dim expression of CD105 on pMSCs, which on the other hand, is a well-recognized marker for human MSCs [23, 25]. Others have reported CD105 is [42] and is not [25] expressed by pMSCs, further supporting tissue-specificity. Here, we were able to detect low levels of mRNA gene transcript and cell surface protein expression of CD105.

Cell survival and proliferation assays demonstrated the ability of the different pMSCs to withstand forces on clinical grade titanium alloy, further supporting preclinical research of these cells in vivo. Centrifugation-based functional adhesion test of the pMSCs on titanium indicated that some cell types are more sensitive to handling than the others. For example, muscle-derived pMSCs seeded on titanium disks detached more than others at 500 g centrifugation test indicating that once seeded on titanium, these cells may not be amenable to additional manipulations and handling; thereby making them unfit for clinical purposes. Practical considerations associated with the ease of manipulation of cells are highly relevant as future steps are taken towards translation of this approach into a clinical therapy.

We ranked the nine sources of pMSC-derived with regard to osteogenic, chondrogenic and adipogenic differentiation capacity, expression of genes involved in cell adhesion, and their ability to adhere to and proliferate on titanium metal (Table 1). The results showed that hoof-associated superficial flexor tendon and Achilles tendon ranked the highest in both differentiation and adhesion assessments. Anatomical study of the porcine hoof region provides insights into the different tissue types, whose synchronous function is critical in imparting the strength, flexibility and mechanical stability of this region. Located right below the keratinized hoof is the modified dermis, corium, which generates cells that gradually keratinize to form the outer 'horn' of the hoof [43]. Superficial and deep flexor tendons attach the pedal bone inside the hoof to the muscles at the back of the leg, allowing for movement and flexing of the limb [44], providing a graded tensile strength along the tendon-hoof bone insertion junction, ranging from 200 MPa tensile modulus at the tendon end to 20 GPa tensile modulus

⁽See figure on next page.)

Fig. 7 Adhesion potential of pMSCs to titanium. **a** CCK8-based assessment of pMSCs proliferation and viability demonstrating significantly higher values on titanium versus glass surface at 4, 24 and 72 h. NIH-3T3 has been used as a positive control. (Ti: Titanium; n=3; *p < 0.05 between Ti and Glass) **b** Measurement of intracellular levels of the focal adhesion protein vinculin in pMSCs on titanium versus glass surface at 4, 24 and 72 h. NIH-3T3 has been used as a positive control. (Ti: Titanium; n=3; *p < 0.05 between Ti and Glass) **b** Measurement of intracellular levels of the focal adhesion protein vinculin in pMSCs on titanium versus glass surface at 4, 24 and 72 h. NIH-3T3 has been used as a positive control. (Ti: Titanium; n=3; *p < 0.05 between Ti and Glass) **c** Centrifugation based functional test of pMSCs adhesion to titanium, where control-post is the sham group; 350 g and 500 g are the two centrifugal forces tested. Keratinocytes have been used as a positive control. (n=3; *p < 0.05)



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Fig. 7 (See legend on previous page.)

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Table 1	Summar	y and ranking of	pMSCs potent	ial for application	to transderma	l device thera	pies
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Function tested				Top 3 tissues for each assessment						
Osteogenic differentiation				Hoof* Bone Marrow			HL Adip	HL Adipose		
Chondrogenic differentiation			Ab D	ermis	Molar		Achilles	Achilles Tendon		
Adipo	genic diffe	rentiation		Muso	cle	Achilles	Tendon*	Hoof	Hoof	
Adhes	ion gene e	expression		Ab A	dipose	HL Derm	nis	Hoof	Hoof	
Focal adhesion density on titanium				Bone Marrow Hoof		Ab Dermis				
Proliferation and viability on titanium			on	HL A	dipose	HL Dermis Ab A		Ab Adip	ose	
Adherence to titanium post centrifugation			:	Bone	Marrow	HL Dermis Achilles Tendo			Tendon	
Hoof	Achilles Tendon	Bone Marrow	De	HL ermis	Ab Adipose	HL Adipose	Ab Dermis	Muscle	Molar	
4	3	3		3	2	2	2	1	1	

(Top) Each row represents the cellular characteristic/function studied, and the columns indicate the top 3 pMSCs (in no particular order) with highest values for each function tested. * Based on gene expression results. (Bottom) Summarized table indicating the number of times a given pMSCs appears in the top 3 list

at the bone end [45]. Right below the keratinized portion of the hoof, the fatty, digital cushion, composed of adipose tissue provides a shock absorbing and sensory function to the hoof [46]. pMSCs from Achilles tendon showed robust chondrogenic differentiation potential and relatively high resistance to high shear forces when cultured on titanium, while the cells from the hoofassociated flexor tendon demonstrated high adipogenic and osteogenic differentiation, expression of multiple adhesion-related genes, and high expression levels of the focal adhesion protein, vinculin, when cultured on titanium. These observations corroborated with the intrinsic function of tendons as the tissue connecting a hard tissue (bone) to a soft tissue (muscle), and thus the capability to withstand mechanical loads [47] such as those present at the aperture created by transdermal devices.

Despite the underlying similarities in hoof and Achilles tendon tissues, there is a possibility of the distinct anatomical locations (microenvironment) of the two tendons dictating their structure and function, which reflects in the function of the progenitor cells derived from these tissues. There is limited literature comparing the cellular and acellular features of these two tendon tissues, and what distinguishes them. Interestingly, there were substantial differences in the adhesion gene expression profiles between pMSCs derived from these two tendons, with cells from the hoof-associated superficial flexor tendon expressing significantly more cell–cell and cell– matrix adhesion genes than Achilles tendon derived progenitor cells.

Going forward, the validity of these in vitro findings needs to be tested in vivo before any decision can be taken on the ideal cell type or combination to stabilize the unique aperture created by transdermal bone anchored devices. Cell survival, proliferation and lineage-specific differentiation of transplanted donor MSCs in vivo is highly dependent on the microenvironment and timing of injection/persistence within the receipient tissue [48, 49]. While there are reports of MSCs mediating direct tissue repair in vivo [50-52], multiple studies have reported trophic factors such as growth factors, morphogens, chemokines, cytokines, extracellular vesicles and extracellular matrix proteins triggering activation and homing of recipient's stem cells to the injury site, followed by tissue repair [49, 53-57]. Initial survival and adhesion of donor MSCs to the transplantation site is a critical parameter; however, the fate and contribution of the adhered MSCs to tissue repair and homeostasis would largely depend on their response to the local inflammatory milieu that exists at the site of injury, which in this context is the site of osseointegration [58]. A recent study indicated that ex vivo 'priming' of MSCs in an inflammatory microenvironment, before their transplantation to such an environment, significantly

enhanced MSC survival and tissue reparative functions when transplanted in vivo y [59]. For our current study, it would be interesting to observe the fate of these tissue-specific pMSCs after priming them in 'conditioned media' of cultured tissue explants from the OI abutment site. More broadly, trophic factor expression and pMSCs delivery methods must be defined in our future work.

Conclusions

We characterized nine pMSCs derived from different porcine integumentary and connective tissues, adipose and dermal tissues from the hind limb and abdominal regions, bone marrow and muscle. Hoof-associated superficial flexor tendon and Achilles tendon ranked the highest in both differentiation and adhesion assessments. Tissue-specific differences between MSCs may be exploited toward bioengineering a durable skin-implant interface to reduce failure of transdermal osseointegrated implants.

Abbreviations

Ab: Abdominal; ACAN: Aggrecan; ACK: Ammonium-chloride-potassium; ALP: Alkaline phosphatase; AM: Adipogenic medium; AP2: Adipocyte protein 2; BGLAP: Bone gamma-carboxyglutamate protein; BM: Bone marrow; BSA: Bovine serum albumin; BSP: Bone sialoprotein; CCK8: Cell counting kit 8; CM: Chondrogenic media: cMSC-GM: Complete MSC stromal growth medium COL1A1: Collagen Type I Alpha 1 Chain; COL2A1: Collagen Type 2 Alpha 1 Chain; DAPI: 4',6-Diamidino-2-phenylindole; DMEM: Dulbecco's modified eagle's medium: DMMB: Dimethyl-methylene blue: DNA: Deoxyribonucleic acid; ECM: Extracellular matrix; EDTA: Ethylenediaminetetraacetic acid; FACS: Fluorescence-activated single cell sorting; FBS: Fetal bovine serum; FITC: Fluorescein isothiocvanate: FOV: Fields of views: GAG: Glycosaminoglycans: GPa: Gigapascal; GM: Growth medium; HL: Hind limb; HSD: Honestly significant difference; mRNA: Messenger RNA; NIH: National Institutes of Health; OI: Osteointegration implant; OM: Osteogenic media; OPN: Osteopontin; PBS: Phosphate-buffered saline: pMSCs: Porcine mesenchymal stromal cells: pNPP: P-Nitrophenyl phosphate; RBC: Red blood cell; RNA: Ribonucleic acid; RT-PCR: Reverse transcription- polymerase chain reaction; SEM: Standard error of the mean; SOX9: SRY-box transcription factor 9; Ti: Titanium; TCPS: Tissue-culture treated polystyrene: VIM: Vimentin.

Supplementary Information

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Additional file 1: Supplementary Tables and Figures.

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Author' contributions

DD: conception, design, performed experiments, assembly, analysis, interpretation of the data and wrote the manuscript, final approval of manuscript; NGF: cell adhesion, differentiation studies, and data collection, analysis, assembly and interpretation, and manuscript writing, final approval of manuscript; AHD: samples collection, cell culture, cell differentiation and gene expression studies, and data analysis and assembly, final approval of manuscript; ER: cell culture, flow cytometry experiment and data collection, final approval of manuscript, IM: cell adhesion, differentiation studies, and data collection, analysis, assembly and interpretation, final approval of manuscript; DTD: design, collection and/or assembly of data, data analysis and interpretation, final approval of manuscript; CJH: cell adhesion studies and data collection, final approval of manuscript; JAF, JEB: conception, data interpretation, and final approval of the manuscript; CA: design, analysis and interpretation of data, financial support; TAD: conception, design, collection and/or assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this article and its supplementary information file.

Declarations

Ethics approval and consent to participate

Tissues used in this study were collected under an approved IACUC institutional tissue sharing protocol at Uniformed Services University of the Health Sciences.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Appendix 6: Dr. Mutreja's MHSRS 2022 poster



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