AWARD NUMBER: W81XWH-20-1-0327

TITLE: Evaluation of Adipose-Derived Stem Cells and Metformin Combination Therapy for Radiation Fibrosis

PRINCIPAL INVESTIGATOR: Dr. Asim Ejaz, PhD

CONTRACTING ORGANIZATION: The University of Pittsburgh

REPORT DATE: SEPTEMBER 2023

TYPE OF REPORT: Final

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
SEPTEMBER 2023	Final	1JUN2020 - 31MAY2023

4. TITLE AND SUBTITLE

Evaluation of Adipose-Derived Stem Cells and Metformin Combination Therapy for Radiation Fibrosis

5a. CONTRACT NUMBER
W81XWH-20-1-0327

5b. GRANT NUMBER
PR192308

5c. PROGRAM ELEMENT NUMBER

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

6. AUTHOR(S)

Dr. Asim Ejaz, PhD

E-Mail: ejaza@upmc.edu

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

The University of Pittsburgh
3520 Fifth Ave, Pittsburgh
Pennsylvania 15213-3320

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

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

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Radiation fibrosis (RF) is a long-term side effect of either therapeutic or accidental exposure to radiations. There is currently no therapy for treatment of RF. Through execution of our proposed work, we are trying to develop a therapy approach using a combination of adipose derived stem cells (ASCs) and metformin. We are testing the dose and time of the therapy and in addition testing the use of allogeneic ASCs as a mitigator for mass exposure scenarios. Data from our ongoing studies indicated that 3 million dose of ASCs showed better mitigation compared to 1 million cells. Allogeneic ASCs showed promising mitigation of RF and can be further evaluated for adaptation to countermeasure reserves. Combination of ASCs and metformin showed better mitigation compared to alone use of these agents for acute RF but is not in the significant range. Ongoing experiments will help to reach a more concrete conclusion. Mechanistic studies reveal no side effects of metformin treatment on ASCs rather metformin improves the health of ASCs by reducing oxidative stress and pro-oncogenic signaling.

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:	17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
			USAMRDC

a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
U	U	U	UU	19	

TABLE OF CONTENTS

1- Introduction:

Radiation fibrosis (RF) following cancer therapy or accidental radiation exposure or radiation terrorist fission bomb event causes severe functional sequelae depending on the exposed anatomical site including loss of tissue function, chronic pain and discomfort from scarring, restricted range of motion, and dysphagia. This delayed complication of radiation exposure to humans commonly damages the skin and subcutaneous muscles, as well as other internal tissues, organs, and organ systems. There are currently very limited treatment options for these symptoms, and they have low efficacy. The *long-term goal* is to develop a potent therapy for radiation fibrosis. The *overall objectives* of this proposal are to (i) evaluate the use of adipose derived stem cells (ASCs) and metformin as a combination therapy to treat radiation fibrosis and (ii) determine the molecular mechanism by which ASCs and metformin combination therapy inhibit fibrosis. The research scope comprises of two *specific aims*: 1) Determine the efficacy of ASCs and metformin combination therapy in resolution of RF. 2) Elucidate the molecular pathways by which ASCs and metformin combination therapy inhibit fibrosis: In *vitro* mechanistic studies and in *vivo* bone marrow cells migration analyses.

2- Keywords:

Radiations, cancer, fibrosis, adipose stem cells, cell therapy, metformin, adult stem cells

3- Accomplishments:

3.1: Summary of Year 1 activities:

- During the first year we accomplished successful approval of IACUC protocol from the University of Pittsburgh which was presented to ACURO and was approved. In addition, we also obtained the Institutional IRB approval for use of human tissue-derived cells and got the approval from HRPO.

- We determined the dose and timings of the syngeneic adipose-derived stem cells (ASCs) and metformin combination therapy for mitigation of radiation fibrosis. Based on our experimental results, we selected a dose of 3×10^6 ASCs to be administered.

- We determined the dose and timings of allogeneic ASCs and metformin combination therapy for mitigation of radiation fibrosis. Based on our experimental results, we selected a dose of 3×10^6 ASCs to be administered.

- As part of the mechanistic studies, we studied the effects of metformin on ASCs biology. The results were published in Journal Biomedicines.[1]

3.2: Summary of Year 2 activities:

- We tested the mitigation efficacy of autologous ASCs alone, metformin alone and a combination of ASCs and metformin for radiation induced skin fibrosis. The treatment was started at day 1 post 40Gy irradiation. Measuring the degree of limb excursion as a functional assay of fibrosis development, we observed that 40 Gy irradiation exposure resulted in a significant decrease in the limb excursion ability in control mice by days 35 and 42 post-irradiation. A single injection of 3×10^6 autologous ASCs on day 1 post-irradiation or metformin injection 3 times weekly starting at day 1 post-irradiation resulted in a significant recovery of the irradiated limb movement by day 42 post-irradiation. Combination therapy of autologous ASCs injected on day 1 post-irradiation and metformin 3 times weekly starting day 1 post-irradiation showed improved recovery in limb excursion as compared to the single treatment regime but the extent of the improvement was not significant. Evaluation of the skin section for inflammation score, fibrosis score, vascular score, and cellular alteration score was performed following the published scoring criteria.[2] Results revealed that both single therapy regimes or a combination resulted in a significant improvement in the scores.

- We tested the mitigation efficacy of ASCs alone, metformin alone and a combination of ASCs and metformin for radiation induced skin fibrosis starting at day 14 post irradiation exposure. Measuring the

degree of limb excursion as a functional assay of fibrosis development, we observed that 40 Gy irradiation exposure resulted in a significant decrease in the limb excursion ability in control mice by days 35 and 42 post-irradiation. A single injection of autologous ASCs on day 14 post-irradiation resulted in a significant recovery of the irradiated limb movement by day 42 post-irradiation. Interestingly, although metformin-only injection resulted in improvement of limb excursion the magnitude of the recovery was not significant. We observed a significant improvement in limb excursion upon treatment with a combination of autologous ASCs and metformin therapy compared to control, ASCs alone, or metformin alone.

- We conclude that both autologous ASCs and metformin showed mitigation of radiation fibrosis. At the very early stage post-exposure when fibrosis has not developed metformin showed a higher mitigation efficiency and the combination therapy of ASCs and metformin showed a non-significant improvement compared to both agents used alone. While at the later time points post-radiation exposure when the fibrosis has progressed metformin showed a relatively weak mitigation effect compared to autologous ASCs. A combination of both showed the best mitigation of fibrosis. Based on these results we hypothesize that mechanistically metformin blocks the development of fibrosis but has relatively lesser regeneration capability to reverse the already established fibrotic wound. On the other hand, autologous ASCs compensate and provide the regeneration property.

- We tested the mitigation efficacy of allogeneic ASCs alone, metformin alone, and a combination of ASCs and metformin for radiation-induced skin fibrosis. The treatment was started at day 1 post 40Gy irradiation. Measuring the degree of limb excursion as a functional assay of fibrosis development, we observed that 40 Gy irradiation exposure resulted in a significant decrease in the limb excursion ability in control mice by days 35 and 42 post-irradiation. A single injection of allogeneic ASCs on day 1 post-irradiation or metformin injection 3 times weekly starting at day 1 post-irradiation resulted in a significant recovery of the irradiated limb movement by day 42 post-irradiation. No synergism in mitigation improvement was observed by the combination therapy of allogeneic ASCs injected on day 1 post-irradiation and metformin 3 times weekly starting day 1 post-irradiation. Evaluation of the skin section for inflammation score, fibrosis score, vascular score, and cellular alteration score was performed following the published scoring criteria.[2] Results revealed that both single therapy regimes or a combination resulted in a significant improvement in the scores.

- Establishment of a robust and reproducible model of radiation-induced skin/muscle fibrosis. During this research, we optimized the radiation-induced fibrosis model and established assays for the evaluation of the functional outcome of the fibrosis. The manuscript based on this model establishment is published in the Journal JOVE.[3]

3.3: Summary of Final Year Activities

- During the final year, we finished the proposed experiments and finalized the figures for the manuscript submission. Currently, we are in the process of manuscript writing.

<u>Experiment:</u> Analyze the efficacy of ASCs alone, metformin alone, or combination therapy in mitigating late effects of radiation-induced fibrosis.

To study the combined effect of autologous (ASCs isolated from C57BL/6 mice injected in C57BL/6 host) or allogeneic ASCs (ASCs isolated from FVB mice injected in C57BL/6 host) and metformin combination therapy, we tested a dose of $3x10^6$ ASCs alone, metformin alone, or a combination of $3x10^6$ ASCs or metformin starting at day 14 post 40 Gy irradiation. Our experimental groups were:

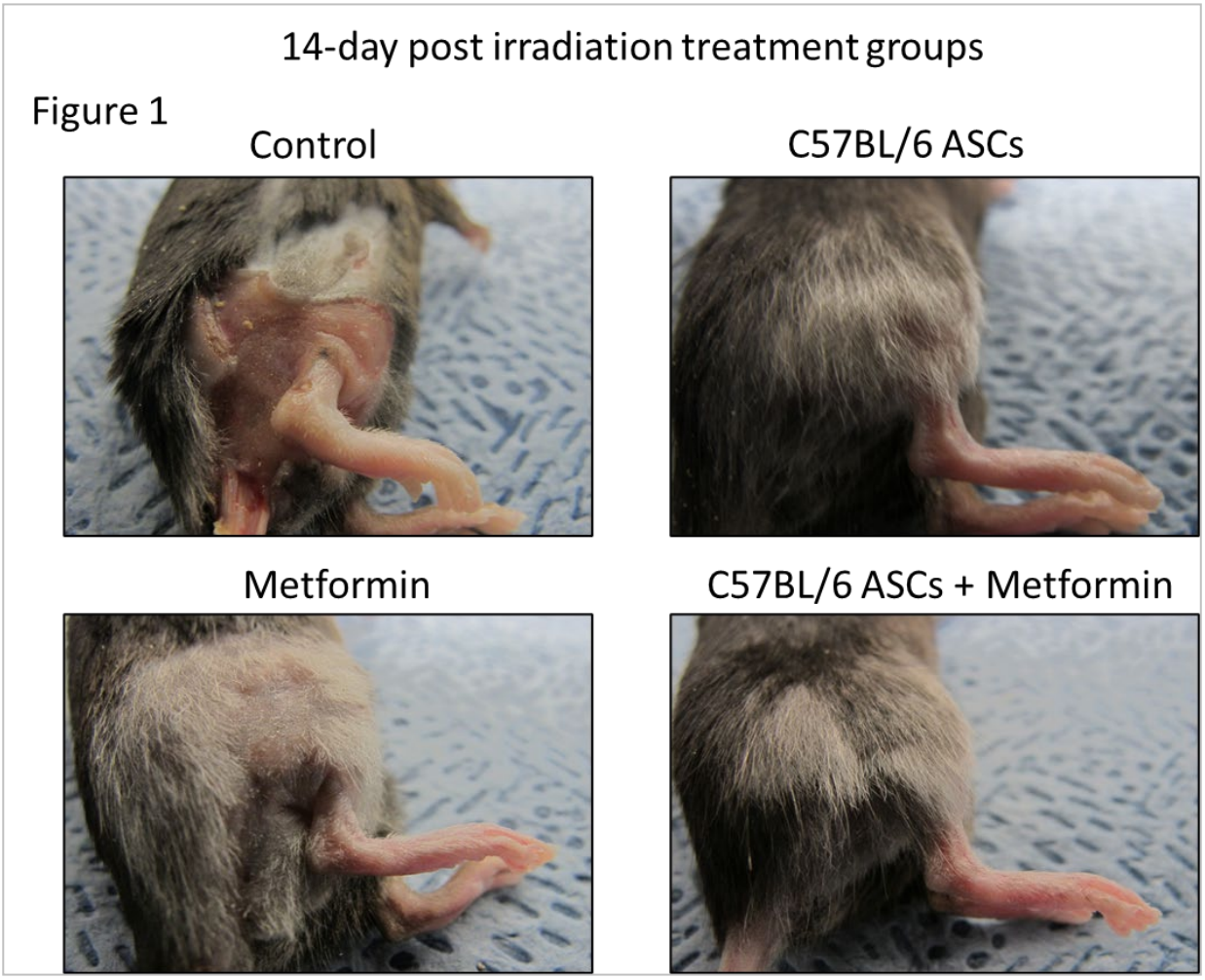
1- Irradiated-control / PBS injection
2- Irradiated / $3x10^6$ autologous ASCs injection
3- Irradiated / $3x10^6$ allogeneic ASCs injection
4- Irradiated / Metformin alone injection
5- Irradiated / $3x10^6$ autologous ASCs + Metformin injection
4- Irradiated / $3x10^6$ allogeneic ASCs + Metformin injection

ASCs were injected subcutaneously at the irradiation site 14 days post-irradiation and metformin was given intraperitoneal 3 times a week until sacrifice at day 42 post-irradiation. Analyses included visual observation

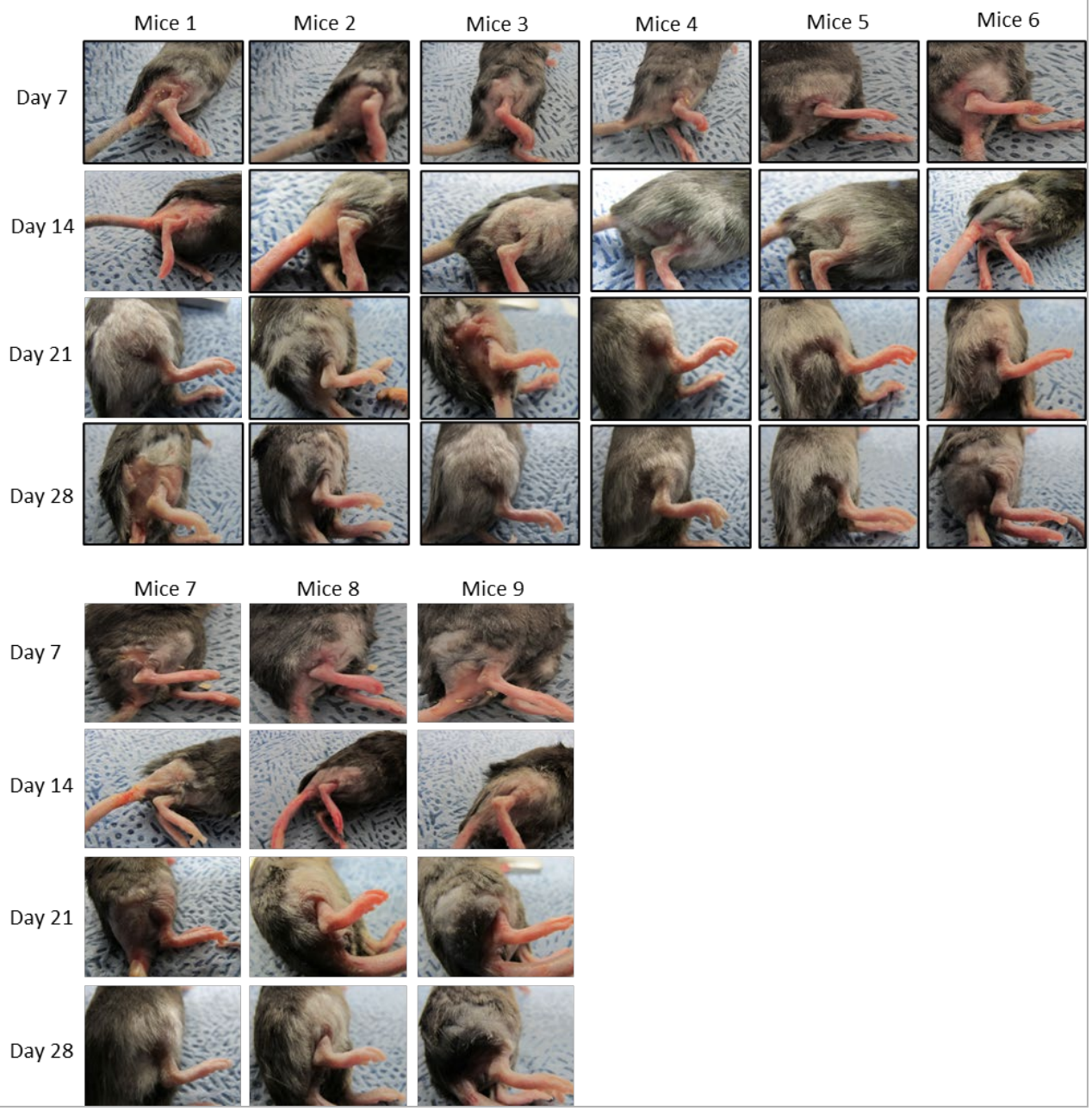
and recording of the wound healing and skin texture improvement, functional analysis by measurement of limb excursion motion, and histological analyses of irradiated skin tissue using H&E and Masson's Trichrome staining. The thickness of the skin epithelium was measured and plotted. The histological sections of the skin were graded for inflammation score, fibrosis score, vascular score, and cellular alterations score following the published guidelines.[2]

Results:

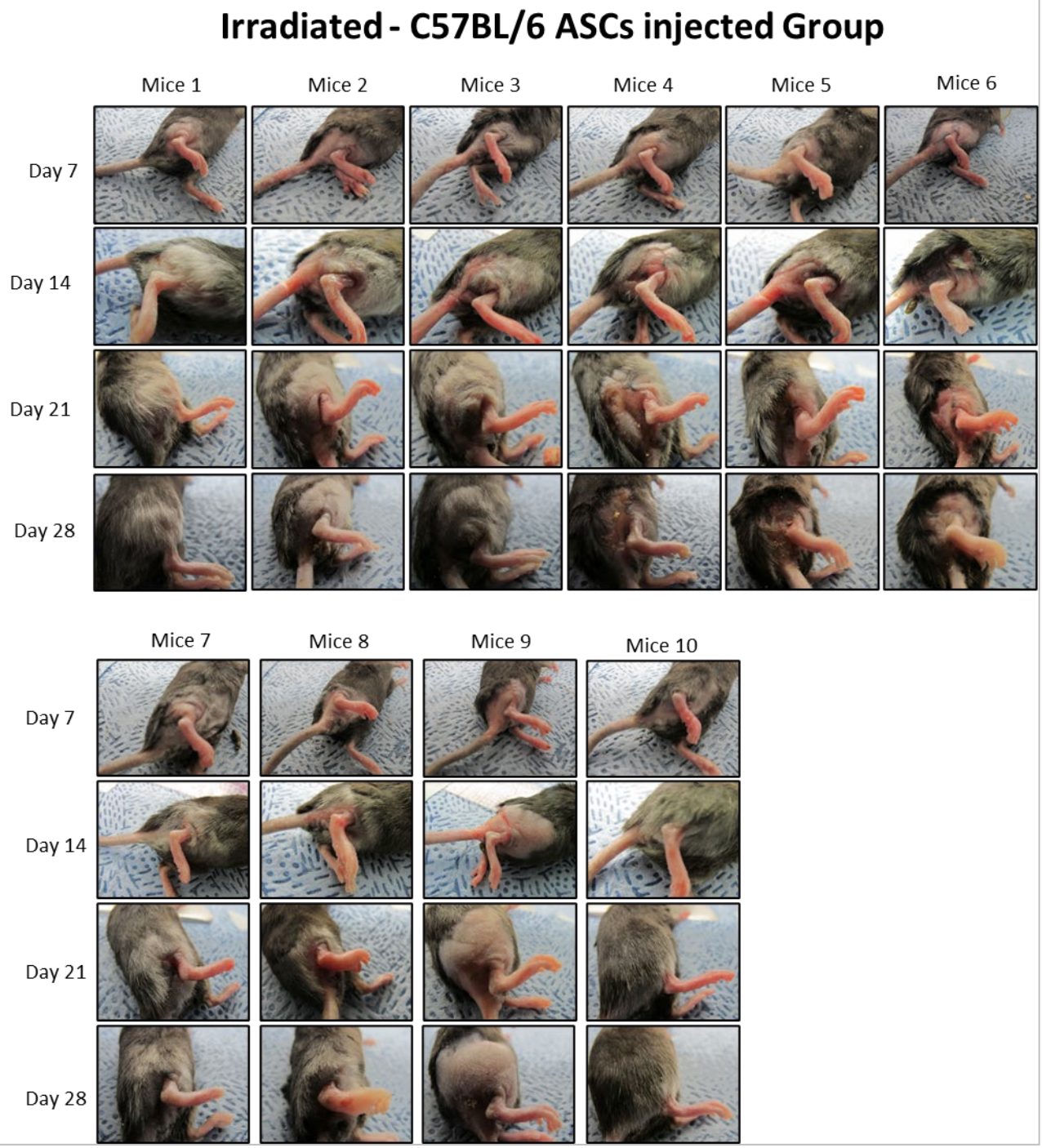
We observed and imaged the progression of irradiation-induced fibrotic wounds starting on day 21 post-irradiation. Most of the mice in the irradiated control group developed fibrotic wounds reflected by skin constriction and hair loss (Fig 1, supplementary 1). Injection of autologous ASCs (Fig 1, supplementary 2), metformin (1, supplementary 3), or a combination of both autologous ASCs and metformin (1, supplementary 4) resulted in improvement in skin architecture and heeling of fibrotic wounds.



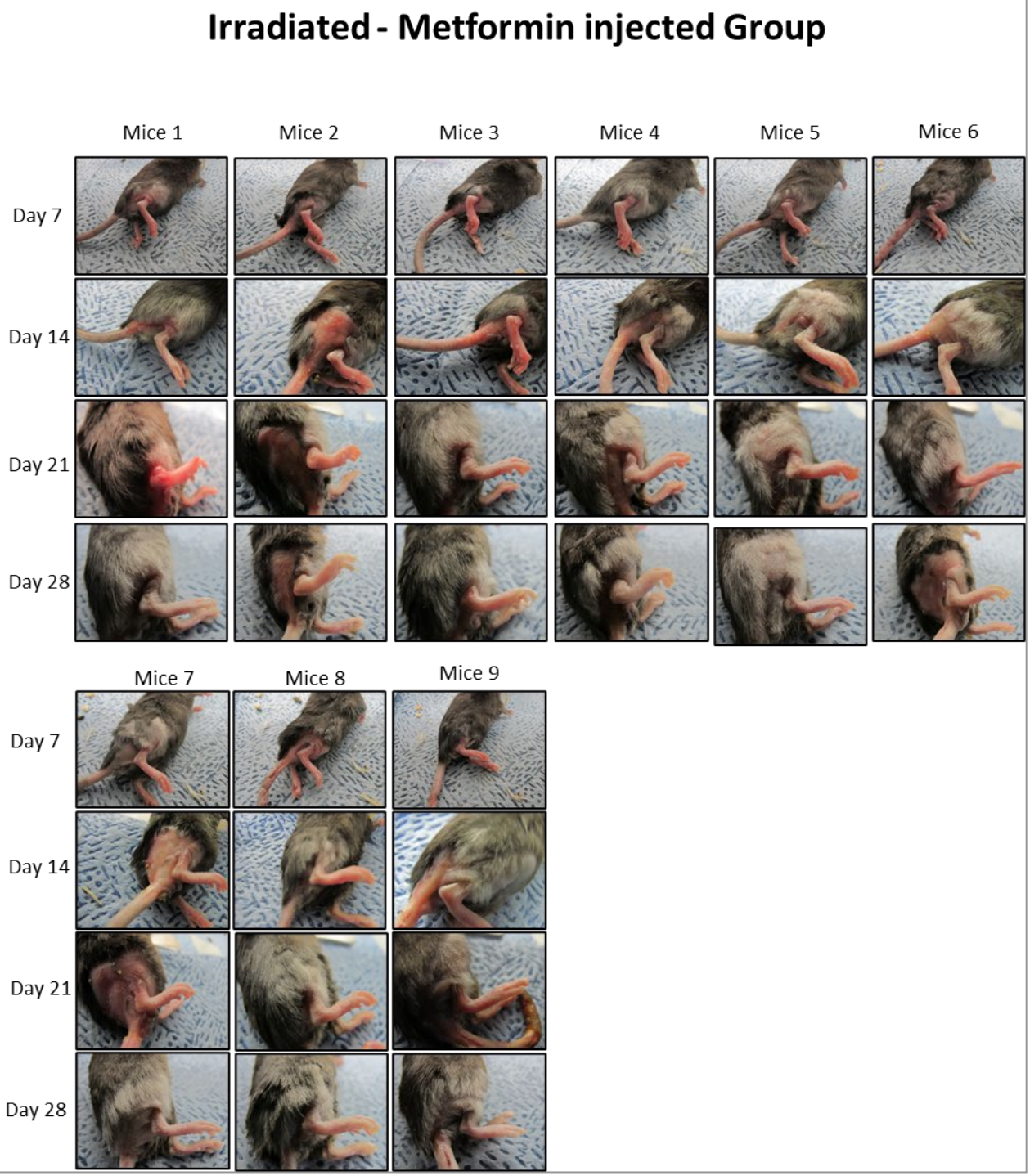
Supplementary figure 1



Supplementary figure 2

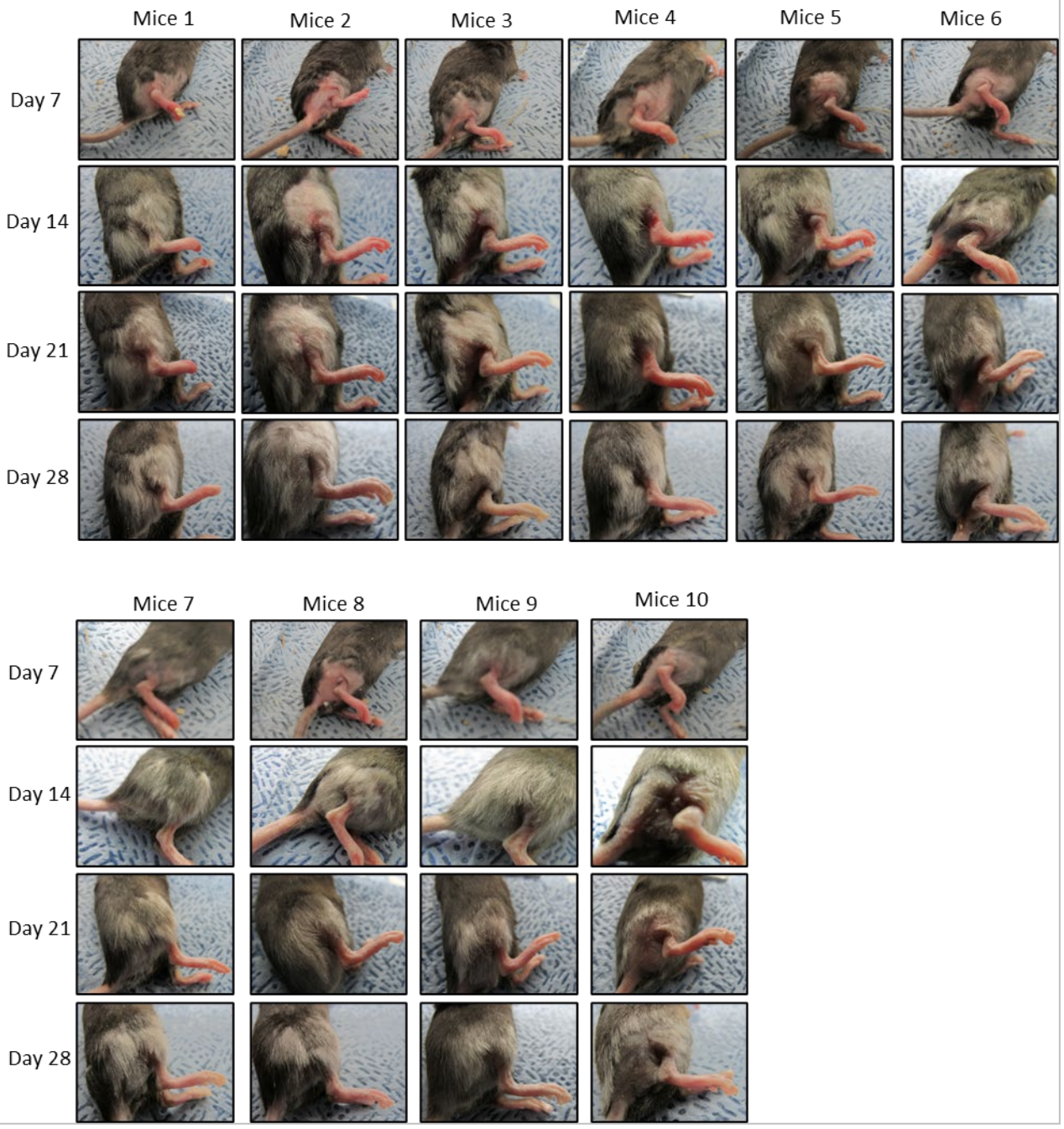


Supplementary figure 3



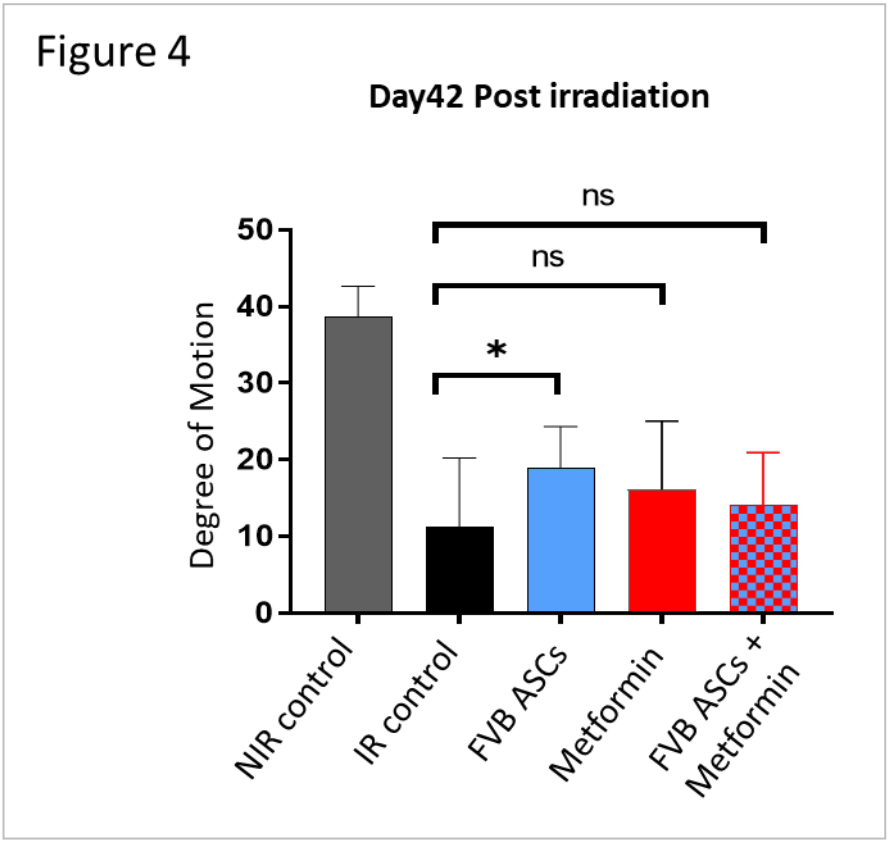
Supplementary figure 4

Irradiated - C57BL/6 ASCs + Metformin injected Group



Measuring the degree of limb excursion as a functional assay of fibrosis development, we observed that 40 Gy

irradiation exposure resulted in a significant decrease in the limb excursion ability in control mice by day 42 post-irradiation (Figure 4). A single injection of allogeneic ASCs on day 14 post-irradiation resulted in a significant recovery of the irradiated limb movement by day 42 post-irradiation. Metformin treatment 3 times a week starting at day 14 post-irradiation was unable to exert significant improvement in limb excursion. No synergism in mitigation improvement was observed by the combination therapy of allogeneic ASCs injected and metformin 3 times weekly starting day 14 post-irradiation (Figure 4).



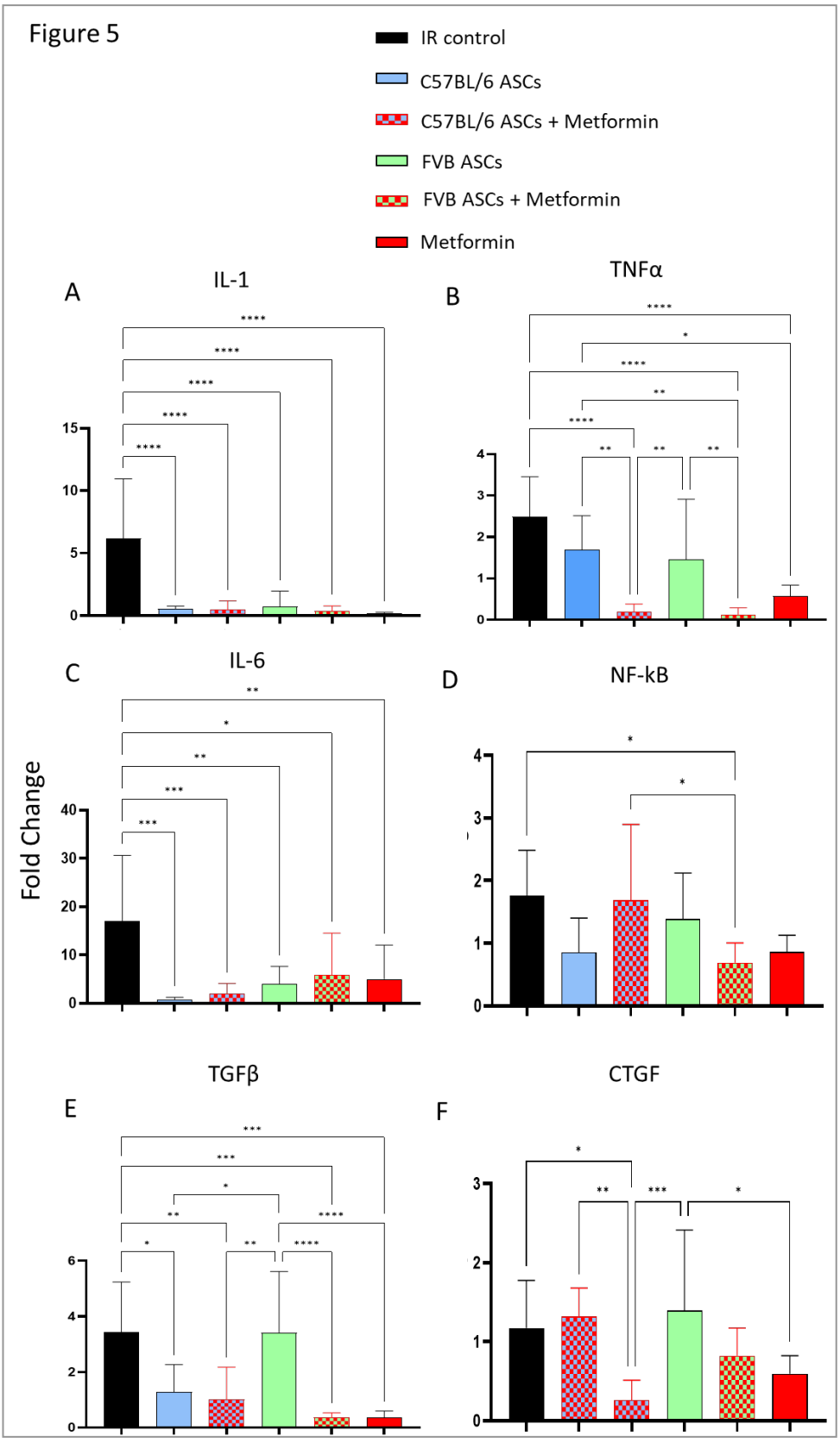
Experiment: Analyze the effect of ASCs and metformin treatment on irradiated tissue at the molecular level

To analyze the effect of autologous ASCs alone, allogeneic ASCs alone, metformin alone, a combination of autologous ASCs and metformin, and a combination of allogeneic ASCs and metformin to mitigate irradiated skin at the molecular level, we analyzed the expression of radiation fibrosis-related genes IL-1, TNF-α, IL-6, NF-κβ, TGFβ, and CTGF in irradiated skin post-treatment using real-time quantitative PCR. A single dose of ASCs was given on day 1 post irradiation and metformin was started on day 1 post irradiation followed by 3 weekly injections. Irradiated skin biopsies were taken on day 42 post-irradiation after sacrificing the mice and snap frozen. RNA was isolated and converted into cDNA by reverse transcription. Genes expression was estimated using real-time quantitative PCR.

Results:

Our quantitative PCR results revealed that both autologous and allogeneic ASCs resulted in significant downregulation of inflammation-associated genes IL-1 and IL-6 (Fig 5 A and C) while the effect of ASCs treatment on TNFα expression was relatively weaker (Fig 5B). Metformin treatment showed remarkable effects on down-modulation of radiation-related inflammation and a significant decrease in expression of IL-1, TNFα, and IL-6 was observed (Fig. 5 A-C). Similarly, we observed that ASCs and metformin combination therapy resulted in a decrease in inflammation (Fig. 5 A-C). The effect on the expression of NF-kB was relatively weaker from the therapies tested in the study that explains the master regulatory nature of the NF-kB (Fig. 5D). Analyzing the effect on TGFβ expression, the key gene involved in fibrosis development, autologous ASCs, metformin, and combination therapies showed a significant down-modulation in expression compared to irradiated control skin (Fig 5 E). Allogeneic ASCs showed no change in the expression compared to the control. A possible explanation could be the effect of the allogeneic nature of the cells. CTGF another important player in fibrosis was downregulated by metformin and the combination approach (Fig. 5F).

Figure 5


IR control
C57BL/6 ASCs
C57BL/6 ASCs + Metformin
FVB ASCs
FVB ASCs + Metformin
Metformin
A
IL-1
B
TNFα
C
IL-6
D
NF-kB
E
TGFβ
F
CTGF
Fold Change

<u>Experiment:</u> Analyze the mechanism of ASCs and metformin mitigation of irradiation-induced fibrosis using mouse fibroblasts and ASCs

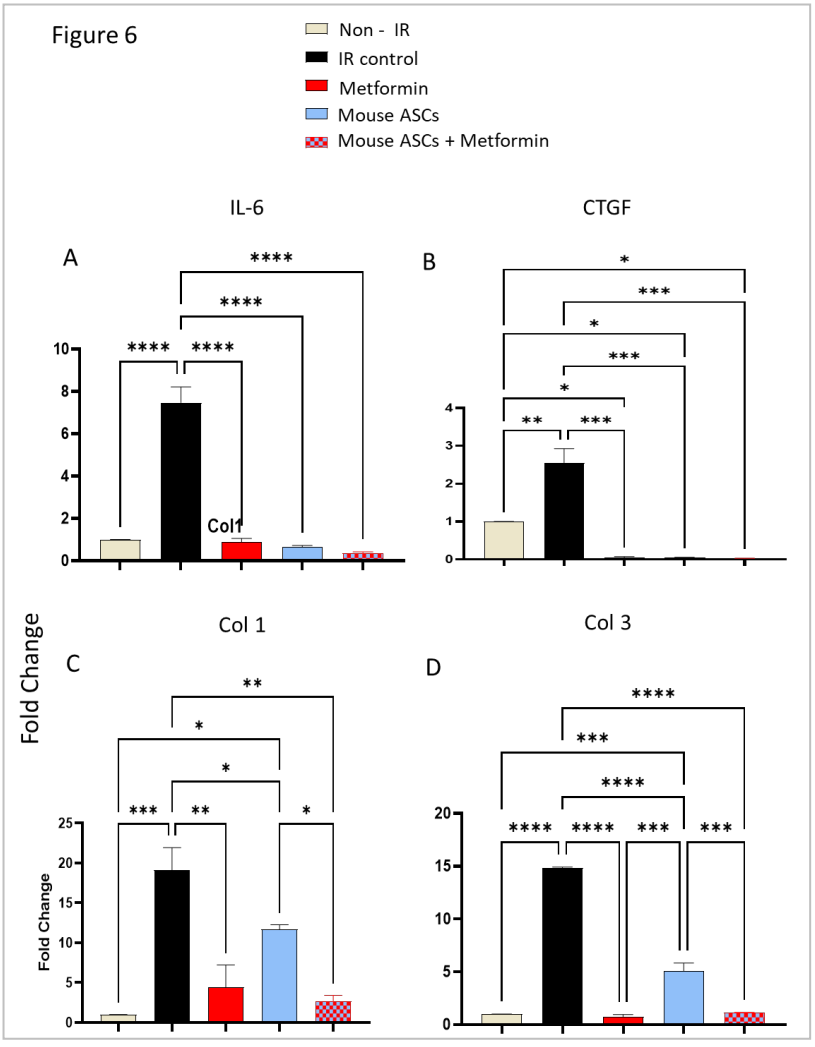
To analyze the direct impact of ASCs, metformin, or combination therapy on irradiated mouse-origin fibroblasts, we performed transwell co-culture experiments where fibroblasts were cultured in the lower chamber and mouse-origin primary ASCs were cultured in an upper chamber separated from fibroblasts through a permeable membrane that allows the two cell types to interact with each other through a paracrine interaction. Our experimental groups were:

1- Non-irradiated mouse fibroblasts (L929 cells)
2- 10 Gy irradiated fibroblasts
3- 10 Gy irradiated fibroblasts + metformin
4- 10 Gy irradiated fibroblasts + mouse ASCs
5- 10 Gy irradiated fibroblasts + mouse ASCs + metformin

Fibroblasts were grown to confluence and irradiated per the experimental design and ASCs or metformin or both were added 24 hours post-irradiation and co-cultured for 4 days. Cells were lyzed, RNA was isolated, reverse transcribed, and real-time PCR was performed to estimate the expression of IL-6, CTGF, Col1, and Col 3.

Results:

Results revealed that a 10 Gy irradiation dose resulted in the upregulation of IL-6 (inflammation) (Fig 6A), CTGF (Fibrosis) (Fig 6B), Col1(Fibrosis)(Fig 6C), and Col3 (Fibrosis)(6D) in irradiated fibroblasts. Coculture with ASCs alone, metformin alone, or a combination of both resulted in a significant decrease in the expression of the inflammation and fibrosis-related genes in irradiated fibroblasts.



<u>Experiment:</u> Analyze the mechanism of ASCs and metformin mitigation of irradiation-induced fibrosis using mouse fibroblasts and ASCs

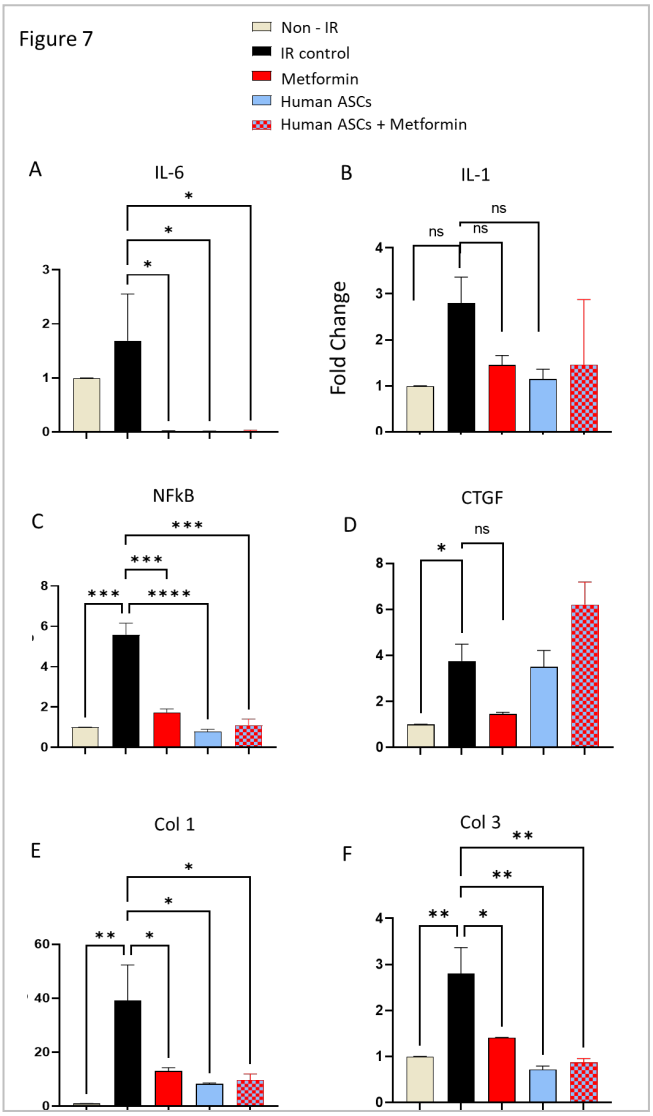
To analyze the direct impact of ASCs, metformin, or combination therapy on irradiated human-origin fibroblasts (human foreskin fibroblast), we performed transwell co-culture experiments where fibroblasts were cultured in the lower chamber, and human primary ASCs were cultured in an upper chamber separated from fibroblasts through a permeable membrane that allows the two cell types to interact with each other through a paracrine interaction. Our experimental groups were:

6- Non-irradiated fibroblasts
7- 10 Gy irradiated fibroblasts
8- 10 Gy irradiated fibroblasts + metformin
9- 10 Gy irradiated fibroblasts + human ASCs
10- 10 Gy irradiated fibroblasts + human ASCs + metformin

Fibroblasts were grown to confluence and irradiated per the experimental design and ASCs or metformin or both were added 24 hours post-irradiation and co-cultured for 4 days. Cells were lyzed, RNA was isolated, reverse transcribed, and real-time PCR was performed to estimate the expression of IL-6, IL-1, NFκβ, CTGF, Col1, and Col 3.

Results:

Results revealed that a 10 Gy irradiation dose resulted in the upregulation of IL-6, IL-1, NFκβ (inflammation) (Fig 7A-C), CTGF (Fibrosis) (Fig 7D), Col1(Fibrosis)(Fig 7E), and Col3 (Fibrosis)(7F) in irradiated fibroblasts. Coculture with ASCs alone, metformin alone, or a combination of both resulted in a significant decrease in the expression of the inflammation and fibrosis-related genes in irradiated human fibroblasts.



Conclusion: Based on the results obtained from the experiments performed during the funding period, we concluded that metformin and ASCs both have mitigation capabilities when used as prophylactic therapy or at the early stage of fibrosis. Metformin seems to be a good prophylactic therapy option but has a weaker effect on late-stage mitigation. For late-stage mitigation, a combination of both ASCs and metformin should be explored further.

Future Direction: Based on these results we are planning to start a clinical evaluation of metformin prophylactic therapy post-radiation to minimize the chance of fibrosis development.

Human Adipose ECM Alleviates Radiation-Induced Skin Fibrosis via Endothelial Cell-Mediated M2 Macrophage Polarization

Summary

Radiation therapy can lead to late radiation-induced skin fibrosis (RISF), causing movement restriction, pain, and organ dysfunction. This study evaluated adipose-derived extracellular matrix (Ad-ECM) as a mitigator of RISF. Female C57BL/6J mice that were irradiated developed fibrosis, which was mitigated by a single local Ad-ECM injection, improving limb movement and reducing epithelium thickness and collagen deposition. Ad-ECM treatment resulted in decreased expression of pro-inflammatory and fibrotic genes, and up-regulation of anti-inflammatory cytokines, promoting M2 macrophage polarization. Co-culture of irradiated human fibroblasts with Ad-ECM down-modulated fibrotic gene expression and enhanced bone marrow cell migration. Ad-ECM treatment also increased IL-4, IL-5, and IL-15 expression in endothelial cells, stimulating M2 macrophage polarization and alleviating RISF. Prophylactic use of Ad-ECM showed effectiveness in mitigation. This study suggests Ad-ECM's potential in treating chronic-stage fibrosis.

The results from this study are published in the journal iScience.[4]

3.4 Opportunities for training and professional development:

This grant opportunity has provided the PI (Asim Ejaz Ph.D.) the opportunity to develop as an independent researcher. The award of this grant was followed by an award from the National Institute of Health to develop a human skin culture model to study the effects of radiation injuries in vitro. This award has also helped the PI to achieve an independent tenure track position at the Department of Plastic Surgery, University of Pittsburgh. During the funding period, the PI has been able to publish a study using allogeneic stem cells for treating acute radiation syndrome as a corresponding author in a very well-reputed journal Stem Cells Translational Medicine. In addition, the mechanistic studies proposed in the grant were recently published under the title “Metformin improves stemness of human adipose-derived stem cells by downmodulation of the mechanistic target of rapamycin (mTOR) and extracellular signal-regulated kinase (ERK) signaling”. In addition, the mouse irradiation model was established and used to fulfill the tasks proposed for this grant. This method is published in the Journal JOVE.

Dr. Somaiah Chinnapaka Ph.D. worked on this grant. He was a post-doc in PI’s lab. This award has significantly helped his training and provided him the opportunity to learn new techniques and establish himself as an independent researcher in the field of cellular therapeutics. Yusuf Surucu MD worked as a

post-doc and got the training in PI's lab. He has contributed significantly to the establishment of the mouse model.

3.2.6. Results dissemination to communities of interest:

Results have been disseminated through publications[1,3-5] and we will continue to disseminate the results in form of publications and conference presentations.

4. Impact

Our published work[5] for the first time has shown the use of allogeneic ASCs as a mitigator of radiation-induced acute syndrome. We consider that this work has set the platform for further investigation of the approach in higher animal models and developing strategies to add allogeneic ASCs to the National Stock Pile for radiation countermeasures.

We showed[1] the beneficial effects of the commonly used drug metformin in improving the health of adipose-derived stem cells. These results showed the effect of combining these two therapeutic agents which is the central idea of the proposal that a combination of these two agents can have synergistic effects.

Our results from the experiments investigating the use of metformin and ASCs have revealed that metformin can be used as an efficacious prophylactic option. Metformin is widely used for different indications and has a very safe profile therefore we will be moving forward to clinically test the prophylactic use of metformin to prevent the development of radiation-induced fibrosis post-radiotherapy for cancer treatment.

Impact on other disciplines

We believe that our work using the metformin or ASCs as a mitigator for radiation fibrosis will result in rapid adaptation of this strategy in radiation oncology clinics.

Impact on technology transfer

Nothing to report

Impact on society beyond science and technology

Nothing to report

5. Changes/problems

Nothing to report

6. Products

Journal publications.

1. Chinnapaka, S., Yang, K.S., Flowers, Q., Faisal, M., Nerone, W.V., Rubin, J.P., and Ejaz, A. (2021). Metformin Improves Stemness of Human Adipose-Derived Stem Cells by Downmodulation of Mechanistic Target of Rapamycin (mTOR) and Extracellular Signal-Regulated Kinase (ERK) Signaling. Biomedicines *9*, 1782.
2. Surucu, Y., Bengur, F.B., Yang, K.S., Schilling, B.K., Baker, J.S., Shabbir, S., Fisher, R., Epperly, M.W., Greenberger, J.S., and Rubin, J.P. (2022). Establishment of a Robust and Reproducible Model of Radiation-Induced Skin and Muscle Fibrosis. JoVE (Journal of Visualized Experiments), e64251.
3. Chinnapaka, S., Yang, K.S., Surucu, Y., Bengur, F.B., Arellano, J.A., Tirmizi, Z., Malekzadeh, H., Epperly, M.W., Hou, W., and Greenberger, J.S. (2023). Human Adipose ECM Alleviates Radiation Induced Skin Fibrosis via Endothelial Cell-Mediated M2 Macrophage Polarization. iScience, 107660.
4. Chinnapaka, S., Yang, K.S., Samadi, Y., Epperly, M.W., Hou, W., Greenberger, J.S., Ejaz, A., and Rubin, J.P. (2021). Allogeneic adipose-derived stem cells mitigate acute radiation syndrome by the rescue of damaged bone marrow cells from apoptosis. Stem cells translational medicine.

7. Participants & Other Collaborating Organizations

Not applicable.

8. Special Reporting Requirements

Not applicable.

1. Chinnapaka, S., Yang, K.S., Flowers, Q., Faisal, M., Nerone, W.V., Rubin, J.P., and Ejaz, A. (2021). Metformin Improves Stemness of Human Adipose-Derived Stem Cells by Downmodulation of Mechanistic Target of Rapamycin (mTOR) and Extracellular Signal-Regulated Kinase (ERK) Signaling. Biomedicines *9*, 1782.
2. Gallet, P., Phulpin, B., Merlin, J.-L., Leroux, A., Bravetti, P., Mecellem, H., Tran, N., and Dolivet, G. (2011). Long-term alterations of cytokines and growth factors expression in irradiated tissues and relation with histological severity scoring. PloS one *6*, e29399.
3. Surucu, Y., Bengur, F.B., Yang, K.S., Schilling, B.K., Baker, J.S., Shabbir, S., Fisher, R., Epperly, M.W., Greenberger, J.S., and Rubin, J.P. (2022). Establishment of a Robust and Reproducible Model of Radiation-Induced Skin and Muscle Fibrosis. JoVE (Journal of Visualized Experiments), e64251.
4. Chinnapaka, S., Yang, K.S., Surucu, Y., Bengur, F.B., Arellano, J.A., Tirmizi, Z., Malekzadeh, H., Epperly, M.W., Hou, W., and Greenberger, J.S. (2023). Human Adipose ECM Alleviates Radiation Induced Skin Fibrosis via Endothelial Cell-Mediated M2 Macrophage Polarization. iScience, 107660.
5. Chinnapaka, S., Yang, K.S., Samadi, Y., Epperly, M.W., Hou, W., Greenberger, J.S., Ejaz, A., and Rubin, J.P. (2021). Allogeneic adipose-derived stem cells mitigate acute radiation syndrome by the rescue of damaged bone marrow cells from apoptosis. Stem cells translational medicine.