Δ Targeting Inflammatory Dysregulation with Senolytic Therapy to Address Delayed Fracture Healing in Accelerated Aging Murine Model

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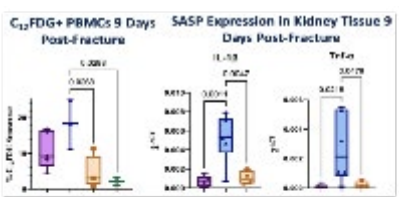
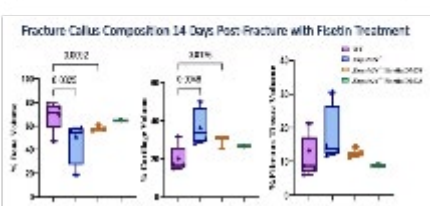
Purpose: It is well established that fracture healing in the elderly population is significantly delayed when compared to younger individuals. Currently there are no pharmocologics established to accelerate fracture repair or prevent impaired healing. The Zmpste24-/- (Z24-/-) mouse model recapitulates premature aged phenotypes of Hutchinson-Gilford progeria syndrome with genomic instability, epigenetic alterations, cellular senescence, stem cell exhaustion, and musculoskeletal deficiencies such as bone density loss, atypical skeletal geometry, sarcopenia, weight loss, osteoporosis, osteoarthritis, and delayed fracture healing. We used this model to investigate whether the therapeutic use of the senolytic fisetin (a phytonutrient) can reduce the senescent cell burden in these mice to improve fracture healing. We hypothesize that the reduction of senescent cells through the administration of fisetin will accelerate fracture repair in the Z24-/- model.

Methods: Age-matched Z24-/- and WT controls (3-4 months) underwent right tibia fracture surgery with intramedullary fixation. Fisetin (50 mg/kg) was given to a cohort of these mice by oral gavage during either the acute inflammatory phase (post-fracture days 2-3) or the endochondral phase (post-fracture days 7-8) of repair. Mice were then sacrificed 9, 14, and 21 days post-fracture for blood and tissue collection to evaluate inflammation, senescence, and fracture healing.

Results: Treatment with fisetin significantly reduced systemic senescence compared to untreated mice. Untreated Z24-/- mice also had significantly higher levels of pro-inflammatory markers interleukin (IL)-1β and tumor necrosis factor (TNF)-α in their organs compared to wild-type (WT) controls, and this was significantly reduced (toward WT levels) in mice treated with fisetin on day 7-8. Early histomorphometry analysis suggested that, while fisetin treatment 7-8 days after fracture had no/limited effect on the rate of fracture repair in Z24-/- mice, fisetin given days 2-3 after fracture resulted in increased bone volume and decreased fibrous tissue volume within the callus 14 days after fracture.

Conclusion: We are currently expanding our sample number to validate these exciting preliminary results, but importantly these data correlate with ongoing clinical studies at our institute suggesting that fisetin can decrease senescent cell burden in healthy individuals and reduce their expression of the bone inhibitory protein sclerostin. Given the link between senescence and age-related bone decline, this model could be leveraged to investigate senescence in the context of fracture repair and to screen senolytic therapies to develop novel treatments for age-related orthopaedic conditions.





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See the meeting website for complete listing of authors' disclosure information. Schedule and presenters subject to change.