The Aryl Hydrocarbon Receptor (AhR) antagonist BAY2416964 prevents age-related skeletal and muscle bone loss in female C57BL/6 mice

Kanglun Yu1, Dima W. Alhamad1, Husam Bensreti1, Anik Tuludhar1, Caihong Dui1, Joseph C. Shaver1, Kehong Ding1, Rafal Pacholczyk1, Marion Cooley2, Roger Zhong2, Sadananad Pulzele1, Carlos M. Isales1, William D. Hill2, Mark W. Hamrick1, Meghan E. McGee-Lawrence1

1Medical College of Georgia and 2Dental College of Georgia, Augusta University, Augusta, GA 3 Medical University of South Carolina, Charleston, SC

kyu@augusta.edu

Disclosures: MEML: ORS Board of Directors [9]

INTRODUCTION: The aryl hydrocarbon receptor (AhR) is a cytosolic nuclear hormone receptor proposed to mediate the effects of the tryptophan metabolite kynurenine (KYN) and a variety of other ligands in [1]. KYN increases with age in mice and humans, is associated with musculoskeletal frailty in humans, and has been identified as a likely causative factor for musculoskeletal decline, as administration of exogenous KYN in young adult mice promoted muscle atrophy, BMSC senescence, osteoblast and osteoclast dysfunction, and bone loss that together mimic a musculoskeletal aging phenotype [2-6]. This raises the possibility that therapeutically targeting the AhR could be beneficial for musculoskeletal health. A novel AhR inhibitor called BAY 2416964 (BAY) is currently in clinical trials as an anti-cancer agent. We recently reported results from preliminary studies demonstrating that BAY improved muscle endurance and grip strength in young (4 month old mice), with positive effects more pronounced in female as compared to male mice [7], but its effects on the aging musculoskeletal system have not yet been reported. The goal of the current study was to test whether BAY treatment could abrogate musculoskeletal decline in aging female mice.

METHODS: All experiments followed NIH guidelines and were approved by the Institutional Animal Care and Use Committee at Augusta University. Female C57BL/6 mice (18 months old; n=40) were obtained from the NIA rodent colony. Two mice died prior to completion of studies due to unknown causes, and two additional mice were excluded for non-study-related aging pathologies. Mice were treated with vehicle (VEH; Ethanol 10/Solutol 40/Water 50) or BAY2416964 (BAY; 30 mg/kg, Targetmol T10270) via daily oral gavage 5 d/wk for 8 wks of treatment (Figure 1B). Moreover, BMSC isolated from the BAY treated mice showed higher cortical bone mass, serum remodeling and grip strength as compared to VEH treated mice [7]. These data suggest that inhibiting AhR via BAY2416964 may prevent age-related declines in bone and muscle function. While grip strength was preserved in BAY-treated mice, no changes were seen in hindlimb muscle fiber size. Further investigations into muscle quality, such as exploring NMJ (neuromuscular junction) morphology and mitochondrial functionality, are ongoing to define the mechanism of the muscle preservation in the BAY-treated mice. The administration of BAY demonstrated a positive impact on cortical bone, although no such effect was observed on trabecular bone; this discrepancy could be attributed to the relatively low abundance of trabecular bone present in the distal femoral metaphysis in 18-month-old female mice at the onset of treatment. Analyses of trabecular bone architecture in a more robust site, such as the lumbar vertebrae, as well as experiments testing the efficacy of initiating treatment at a younger age, are warranted in future studies.


ACKNOWLEDGEMENTS: This work was supported by the National Institute of Aging P01AG036675 (Project 4) and R01AG067510.