Of mice and men... and alligators! Tales of heterotopic ossification

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Background
Heterotopic ossification is a disease in which the normal healing process goes awry and bone begins to develop outside of the skeleton. Surgical resection of the ectopic bone is the only means to treat heterotopic ossification; however, surgery can also complicate and accelerate the bone formation. A better understanding of the bone formation process in this disease state can help identify novel targets to treat heterotopic ossification. Interestingly, the research animals that best represent heterotopic ossification are an injury-induced model in mice and the American alligator. Alligators undergo a natural ossification of the dermal tissue to form bony scales on their back. This process is very similar to heterotopic ossification seen in humans. To further understand the molecular and genetic changes that underlie heterotopic ossification, we studied a genetically engineered mouse model of synovial sarcoma. This is a muscle cancer that can spontaneously develop heterotopic ossification. We investigated our model of synovial sarcoma in mice by histological, radiographic, and transcriptomic means. We wanted to test the following hypothesis:

Hypothesis
Synovial sarcomas with ossification will have a distinct molecular phenotype from other non-ossifying synovial sarcomas and that mechanisms of ossification in synovial sarcoma will overlap with human and alligator heterotopic ossification.

Results
Three different species exhibit similarities in their heterotopic ossification (Fig. 1). There are critical cellular steps in developing the ossification phenotype, namely a fibrosis stage followed by cellular invasion that triggers cell fate decisions to become bone and start producing matrix (Fig. 2). Synovial sarcoma is a muscle cancer that exhibits ossification. We saw 7.2% ossification, which is similar to human synovial sarcoma. Ossification was higher in mice that lived longer (Fig. 3). Even in the absence of visible ossification, there is underlying gene expression supportive of ossification. Comparison between mice and human synovial sarcomas pinpointed PTHLH as a commonly overexpressed gene. Further TyrRho and Tgfβ1, bone associated genes from macrophages and neutrophils, are overexpressed and present within the tumor microenvironment (Fig. 4). Tgfβ1 is a great candidate as it has been shown to play a significant role in the injury-induced model of heterotopic ossification in mice. The correlation between ossification and survival was opposite of what we predicted in that mice with ossification survived longer than mice without visible and detectable ossification (Fig. 5).

Conclusions
Heterotopic ossification in synovial sarcoma paralleled the phenotypes and molecular profiles seen in other models and in humans. PTHLH and Tgfβ1 are both candidate proteins and pathways that we could target to reverse heterotopic ossification.

References