**Results:** First we examined the capacity of PTH(1-34) to re-distributed BP in the non-fractured femora. By confocal microscopy, AlexaPam647 was seen as a bright (red) BP line in the saline treated samples (Fig. 1A). PTH(1-34) treatment considerably reduced this signal indicating remobilization of the BPs (Fig. 1 B). Quantification of the fluorescent signal indicated a significant reduction in bound BP in the PTH(1-34) treated groups in comparison to the saline control group (P<0.01) (Fig. 1C).

Next we investigated both bone healing and re-distribution of BP in the femoral fracture model. In controls receiving only BPs, the ZA/AlexaPam647 were found to preferentially distribute to the fracture side (right leg) in comparison to the unfractured contralateral leg (left leg) (#P=0.023) (Fig. 2). These data support the concept that bisphosphonates accumulate in regions of high blood flow and bone activity (turnover) [2]. This could lead to stress fractures receiving a disproportionately high dose of BPs, resulting in delayed healing and potentiation of atypical fractures. Parathyroid hormone (PTH) is known to increase both bone formation and resorption [3]. We hypothesized that treatment with Teriparatide (PTH (1-34)) could increase bone and BP turnover, leading to decreased BP load. In the context of fractures, this could improve repair. This study aimed to 1) fluorescently label and track BPs in non-fractured femurs in response to PTH(1-34) treatment, 2) identify preferential distribution of BPs to sites of fracture in order to examine the impact on fracture repair and 3) to identify whether PTH(1-34) can redistribute the BP away from the fracture site and restore remodeling.

**Discussion:** Our results demonstrate that PTH(1-34) treatment can remobilize and re-distribute bound BPs in vivo away from sites of initial binding. It is likely that this further leads to BPs being eliminated and an overall decreased BP load, but this will...
need to be evaluated in subsequent studies using metabolic cages. In the closed femoral fracture model, BP treatment led to increased callus size associated with decreased remodeling. This is consistent with prior fracture healing experiments using this model. While PTH(1-34) has been reported to augment repair in a closed fracture model, PTH acts mechanistically differently from BPs to increase anabolism rather than suppress catabolism. Notably, in this study PTH(1-34) remobilization of BP did not translate to improved callus remodeling or fracture healing compared to BP-treated alone. It is hypothesized that a longer PTH(1-34) dosing regimen may more show a more rapid initiation of callus remodeling, as negligible remodeling was seen in both BP and BP/PTH at the 6 week time point. Thus we propose extending the study design to 12 weeks.

**Significance:** Due to concerns regarding chronic bisphosphonate dosing and adverse events including atypical femoral fractures, a number of solutions have been proposed. The most common is BP holidays, although there is no evidence for what period of interruption is sufficient to allow for BP washout. Our data support the concept of developing PTH(1-34) to decrease the BP burden in this patient population using a therapy that is itself anabolic for bone. This has the potential to have a profound impact on clinical practice.

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**References:**
Figure 1: AlexaPam647 (red) was given 6 weeks before harvest. A) a daily dose of saline was administered starting 4 weeks before harvest. B) a daily dose of PTH (1-34) was administered starting 4 weeks before harvest. Calcein labeling (green) represents bone formed in the last 4 weeks. C) Quantification of fluorescent BP (* P<0.001 in relation to Saline)

Figure 2: (A) Fluorescent images of AlexaPam647 (red) in fractured femurs. (B) Quantification of fluorescent BP in fractured (right) and contralateral unfractured (left) femurs. *P<0.0143, #P<0.0233