



# KMN-159 Induces Osteogenesis In Novel 3D Model Of Osseointegration

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# Implant Failure and Osseointegration

- Failure rate of dental implants is as high as 10%
- Approved biological therapies (BMP2, PDGF) require special formulations, are not shelf-stable, and are costly
- **There is a critical need for novel osteogenic therapeutics**

## Discovery of KMN-159: An EP<sub>4</sub> agonist

We discovered a potent and highly selective EP<sub>4</sub> small-molecule agonist<sup>1,2</sup>:



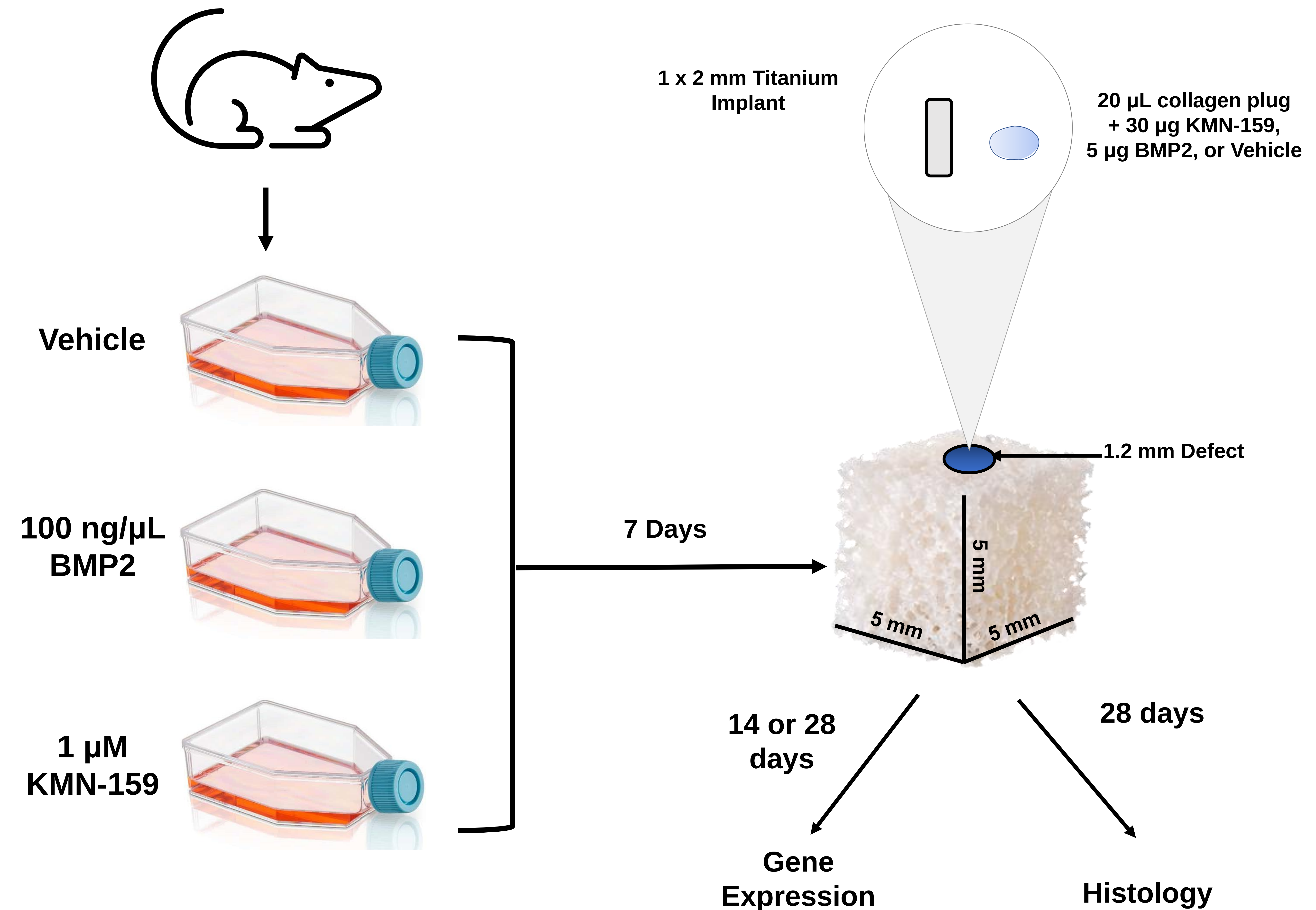
[Owens et al. 2020](#)

- Osteogenic at low doses and short exposures
- Local administration induces bone formation
  - Absence of off-target effects
  - Little to no systemic exposure
- Shelf-stable
- Healing rates similar to BMP2



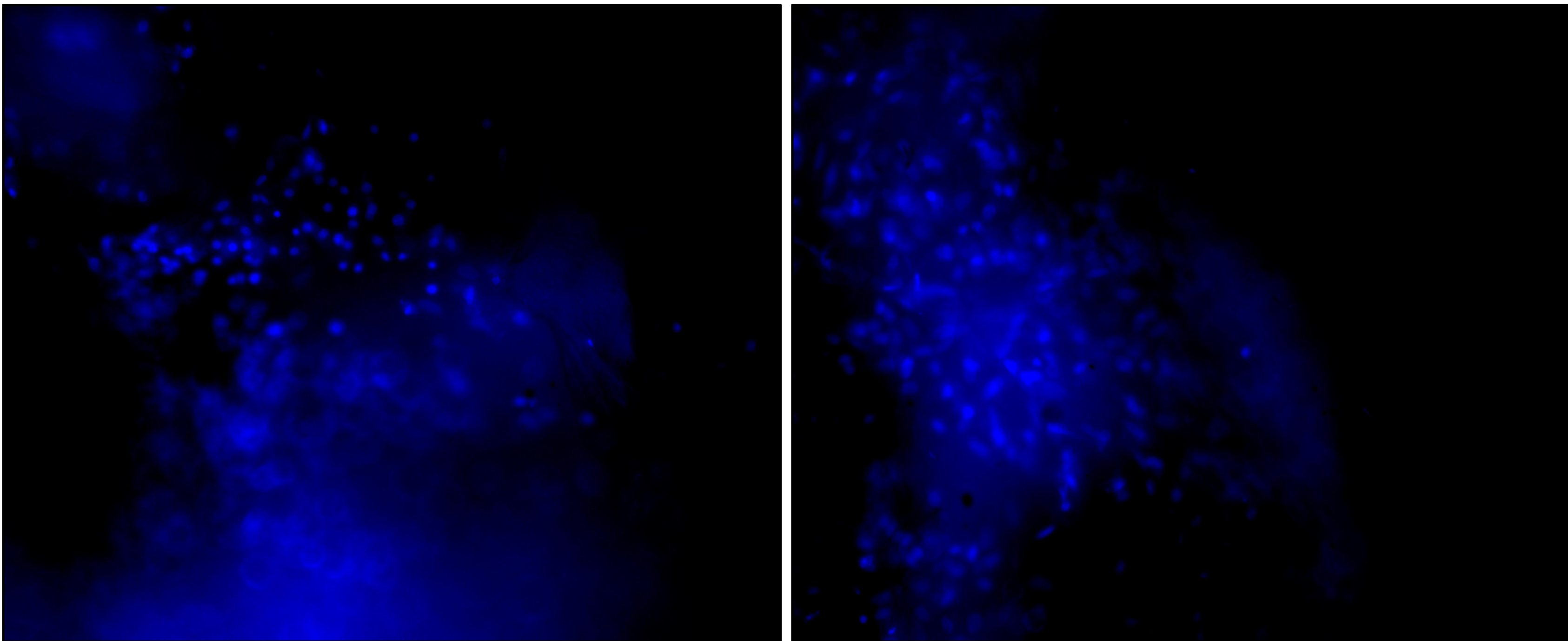
[Barrett et al. 2019](#)

# Cell Culturing and Osseointegration Method

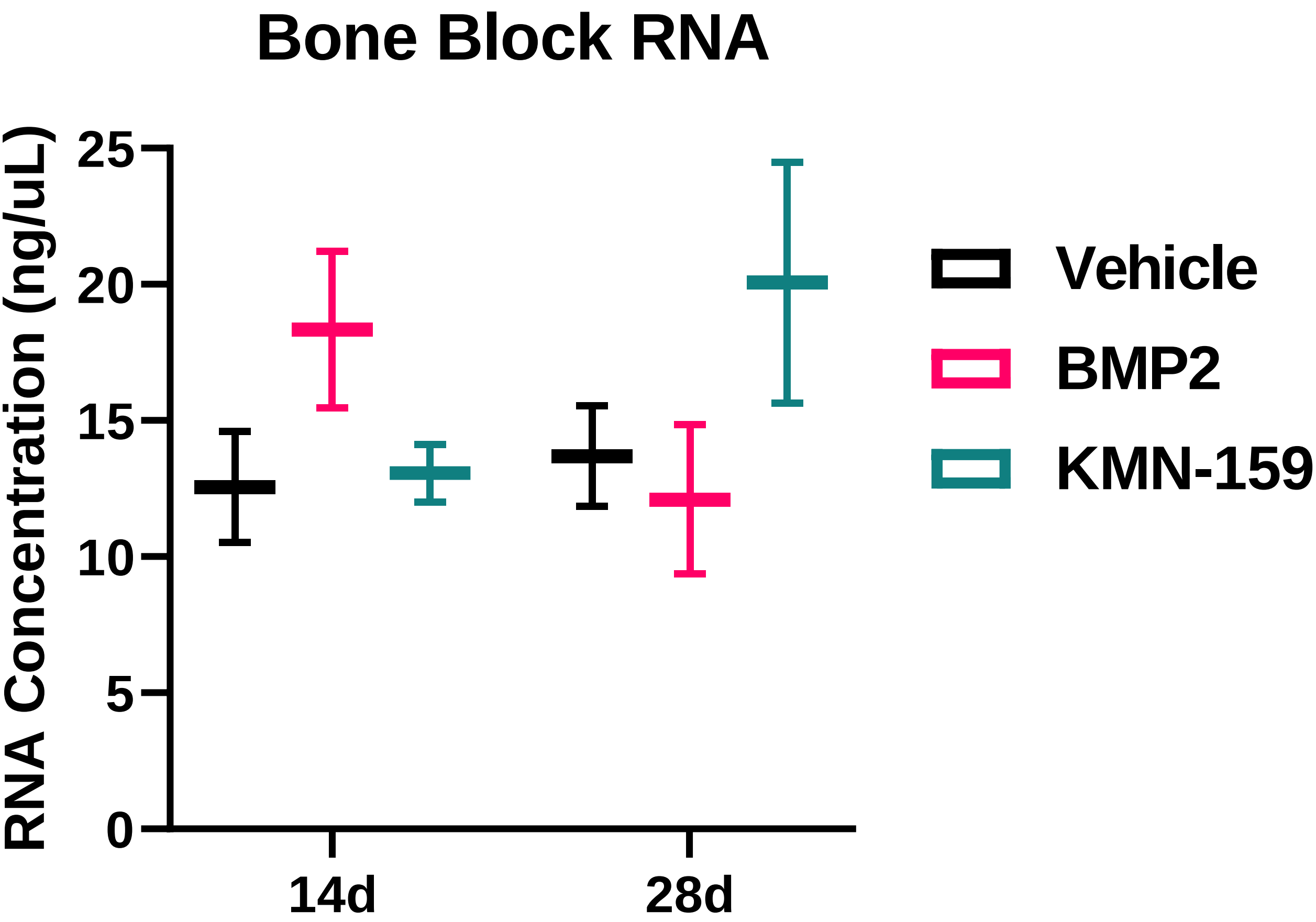


**3D *in vitro* model of osseointegration.** Rat bone marrow cells were harvested from tibiae and femurs and plated in culture flasks with KMN-159, BMP2, or vehicle for 7d, after which they were seeded onto 5x5x5 mm deproteinized bovine bone blocks. A defect was made and a collagen plug and implant inserted. Blocks were then cultured to endpoints.

# Model Validation

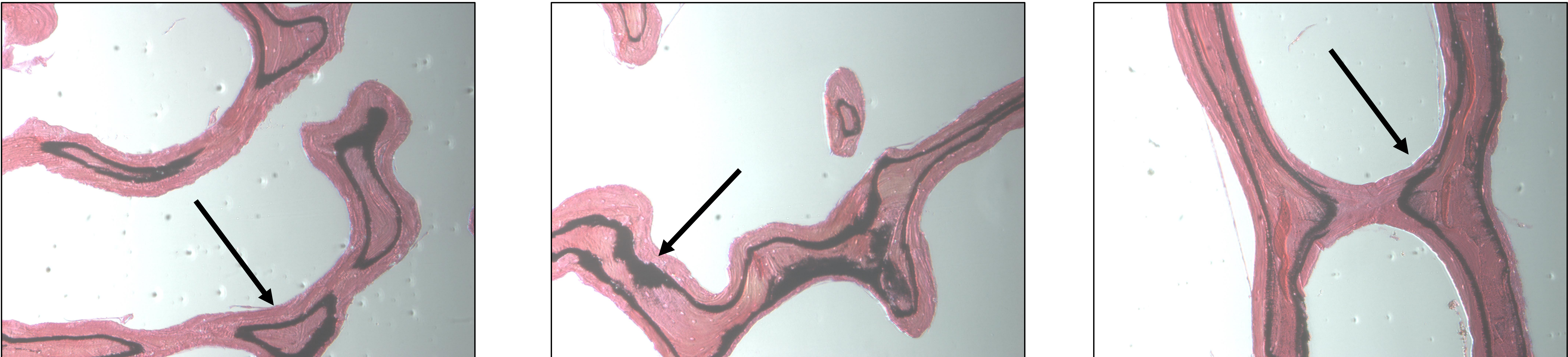


**Bone cells attach to bone block and survive for up to 28d in culture.** Representative images of slices of bone block stained for nuclei show cells within the trabeculae of the bone block.

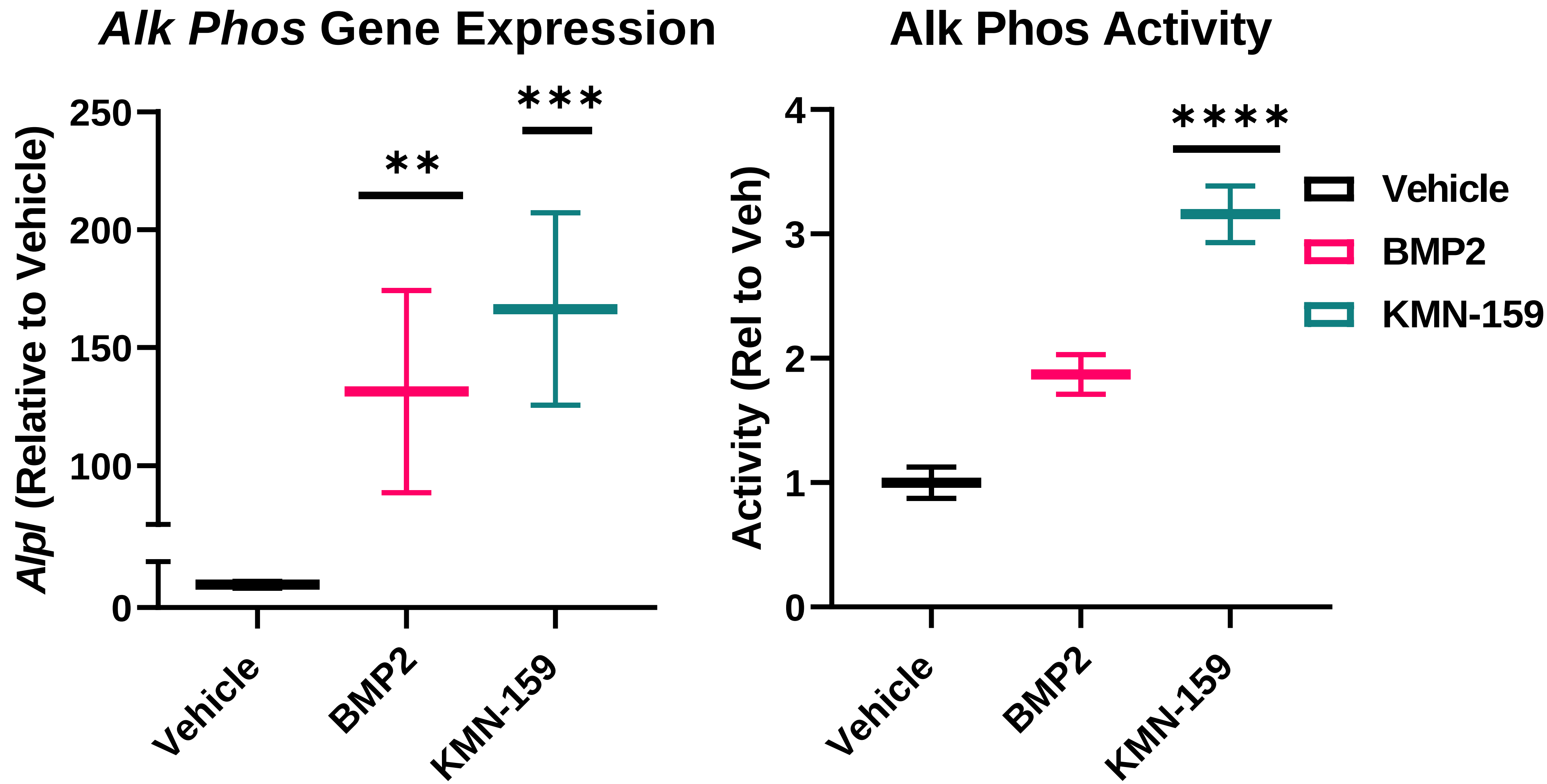


**Bone blocks seeded with bone cells and treated with collagen plugs produce mRNA suitable for downstream analysis.** Bone blocks (n=8 per group per time point) were homogenized and RNA isolated. Bars show average ± SEM.

# Bone Blocks Support Differentiation Toward Bone Producing Phenotype



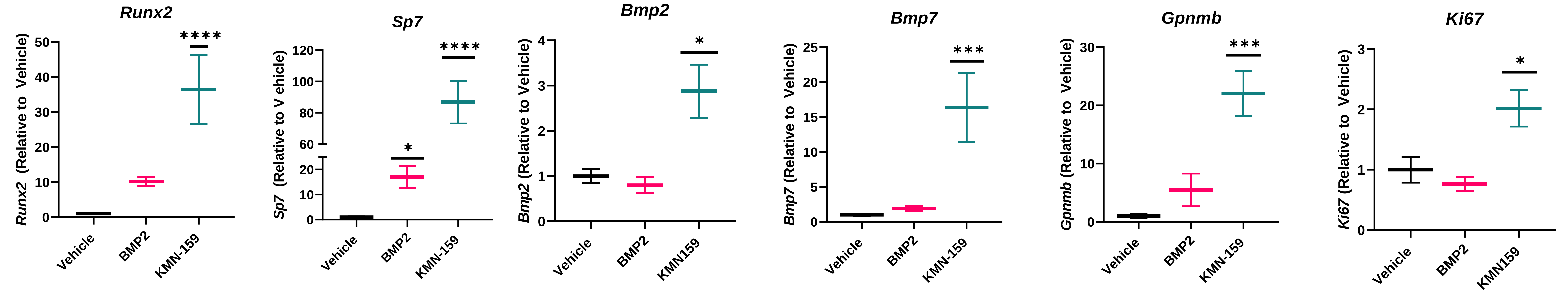
**Bone blocks display calcium deposition within bone fibers.** Bone blocks (28d) were sectioned and underwent Von Kossa staining for mineralization. Black staining (arrows) shows mineralization by differentiated osteoblasts.



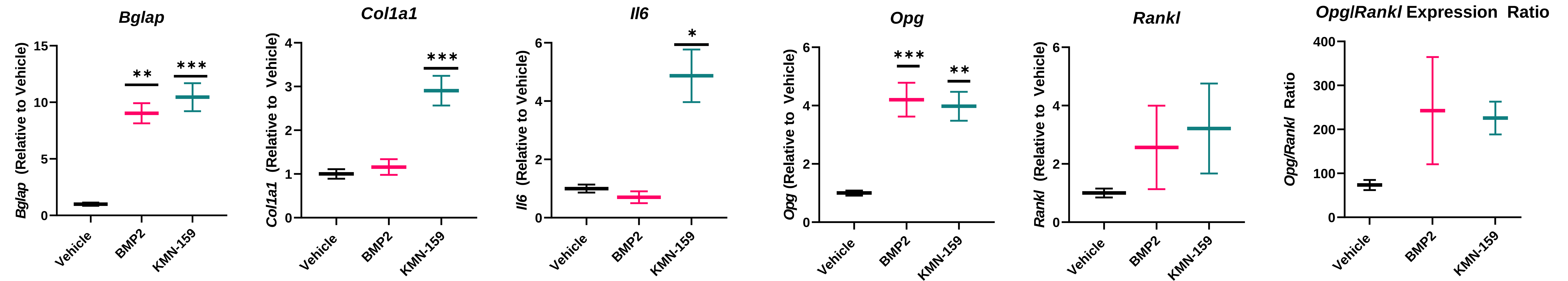
**KMN-159 increases both expression and activity of alkaline phosphatase.** The expression of alkaline phosphatase in bone blocks after 14d in culture and activity of alkaline phosphatase in cultured bone marrow cells after 14d was significantly elevated compared to vehicle.

\*= p<0.05, \*\*= p<0.01, \*\*\*= p<0.001, \*\*\*\*= p<0.0001 compared to vehicle

# KMN-159 Induces Osteoblast Differentiation Factors



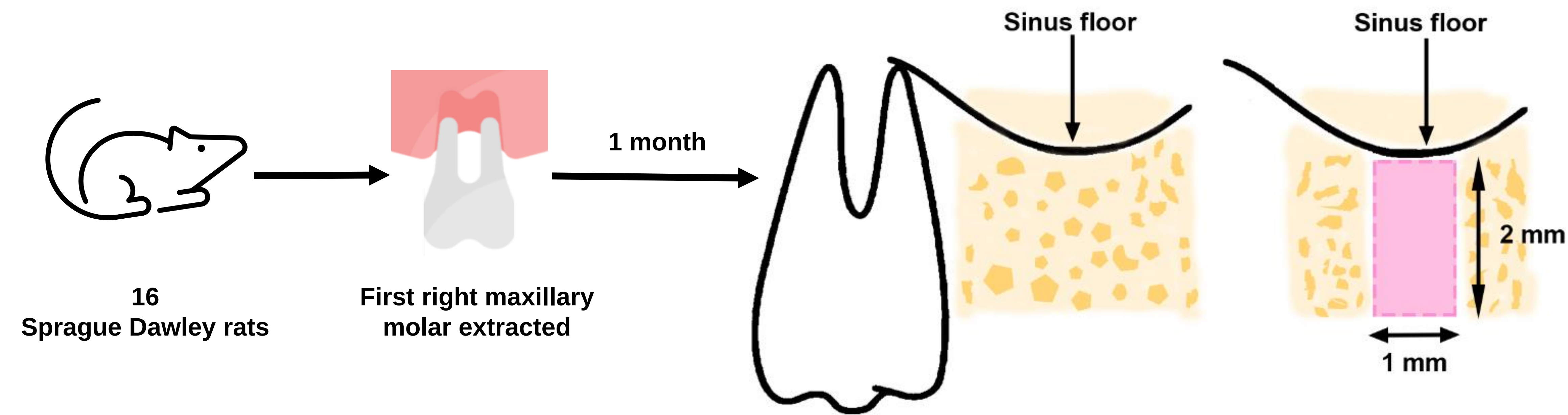
# KMN-159 Induces Mature Osteoblast and Bone Remodeling Genes



\*= p<0.05, \*\*= p<0.01, \*\*\*= p<0.001, \*\*\*\*= p<0.0001 compared to vehicle

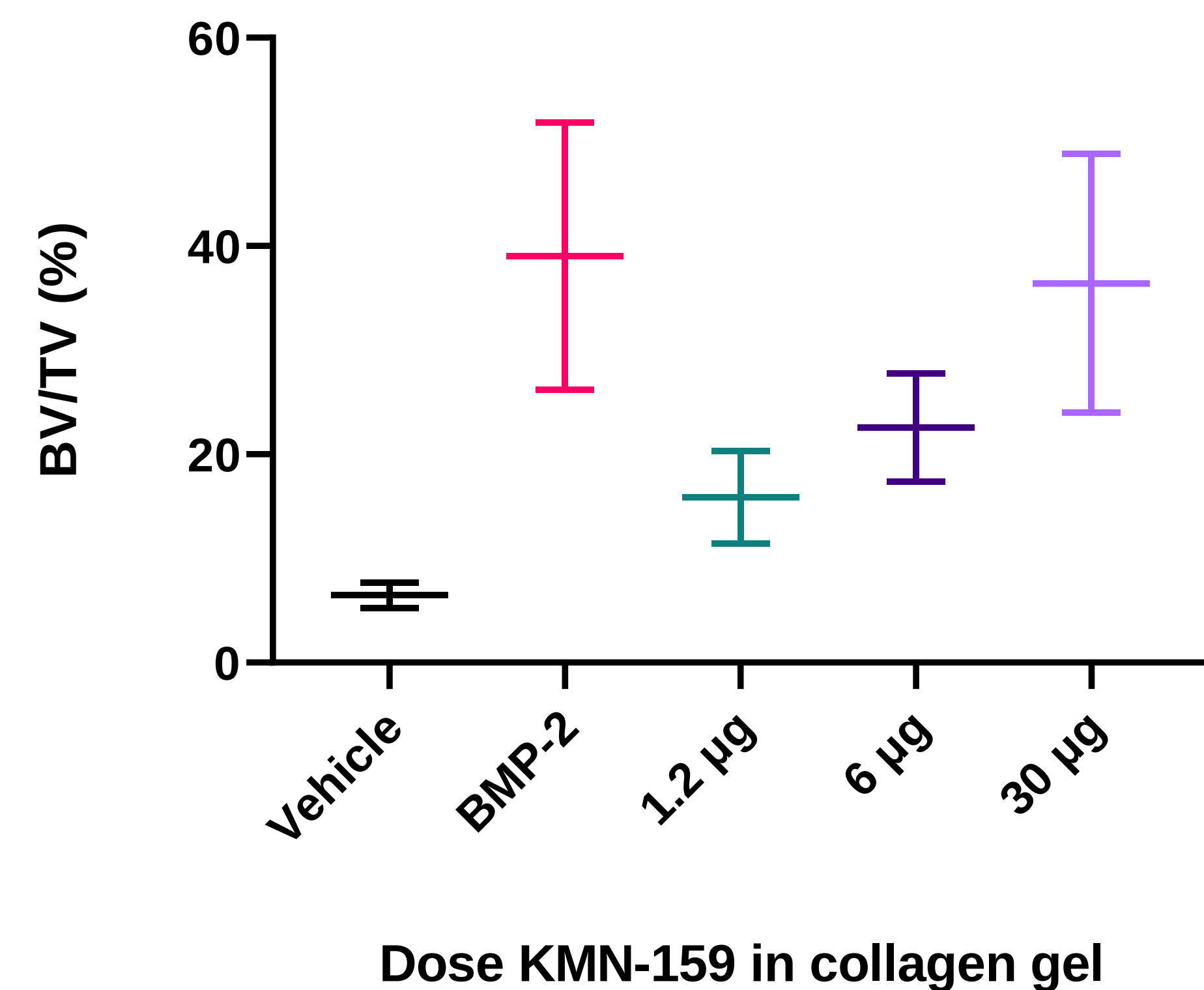
# *In vivo* Rat Efficacy and Safety Model

## Maxillary Extraction Model



## Results

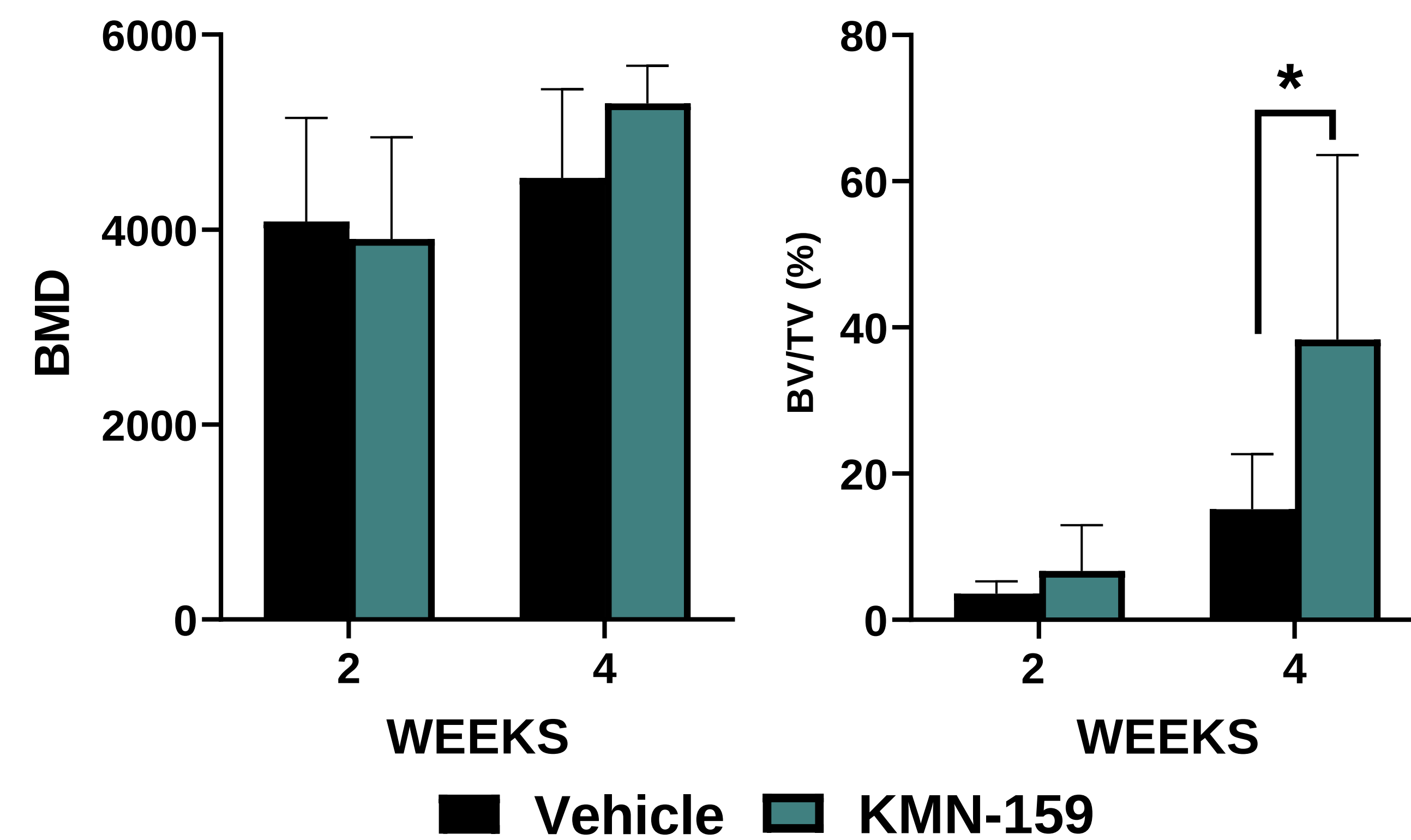
Rat Dental Implant Bone Volume Fraction



µCT analysis of bone formation in rat jaw following maxillary molar extraction 21d following placement of dental implant.

Pilot study data, n=7-10 per group

Rat Maxillary Molar Extraction µCT Analysis



µCT analysis of bone formation in rat jaw following maxillary molar extraction at 2- and 4-weeks post-implantation.

n=4 animals per group per time point

\* = p<0.05 compared to vehicle

## Conclusions

- We developed a novel *in vitro* model for studying osseointegration and testing of osteogenic compounds
- We validated our model by demonstrating that cells differentiate towards osteoblast phenotype within bone block
- We found that KMN-159 promoted expression of osteoblastic differentiation factors after 14d, osteoblast function and bone remodeling at 28d in bone block model
- KMN-159 treatment led to elevated *Opg:Rankl* ratio *in vitro*, indicating shift toward bone formation



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