



## **Autocrine/paracrine IGF-1 plays a critical role in determining bone size prenatally and early postnatally**

Sébastien Elis, Hayden-William Courtland, Yingjie Wu, Hui Sun, Karl J. Jepsen, Shoshana Yakar

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SCHOOL OF  
MEDICINE

# **Elevated levels of serum IGF-1 restore peak bone properties and mechanical functionality in the absence of autocrine/paracrine IGF-1**



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SCHOOL OF  
MEDICINE

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ENDO 09, Washington, 6.12.09

# IGF-1 is an endocrine, and autocrine/paracrine modulator of growth and metabolism



Aim:

To test whether elevated serum IGF-1 levels can support skeletal growth and integrity in the complete absence of tissue IGF-1

## Control



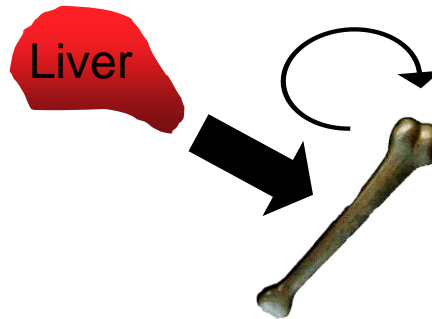
**Normal** serum IGF1 levels  
**Normal** tissue IGF1 levels

## HIT

Hepatic IGF-1 Transgene



TTR promoter



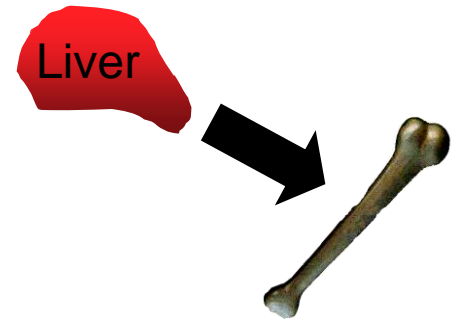
**High** serum IGF1 levels  
**Normal** tissue IGF1 levels

## KO-HIT

Total IGF-1 KO+  
Hepatic IGF-1 Transgene



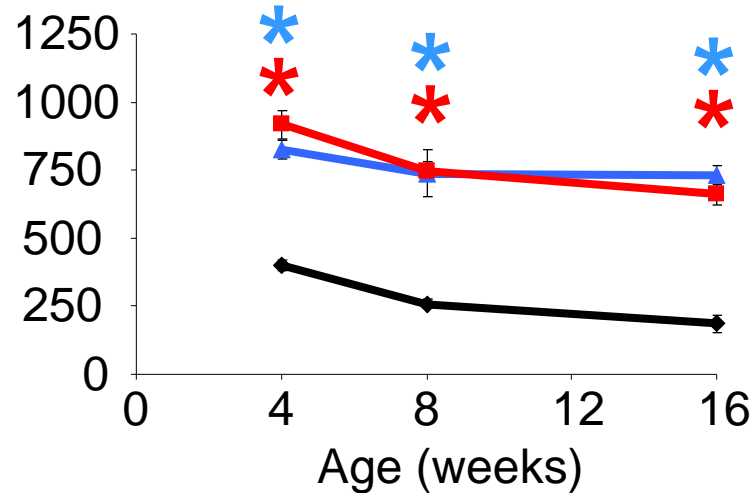
TTR promoter



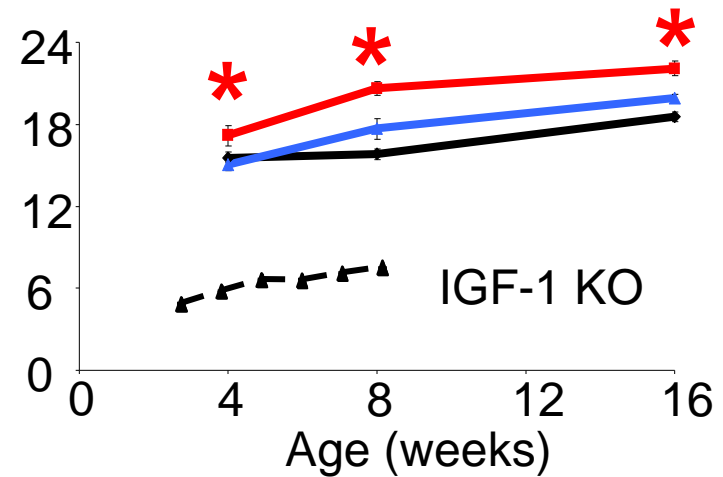
High serum IGF1 levels  
**NO** tissue IGF1




# High levels of endocrine IGF-1 increase body weight

Serum IGF-1 (ng/mL)

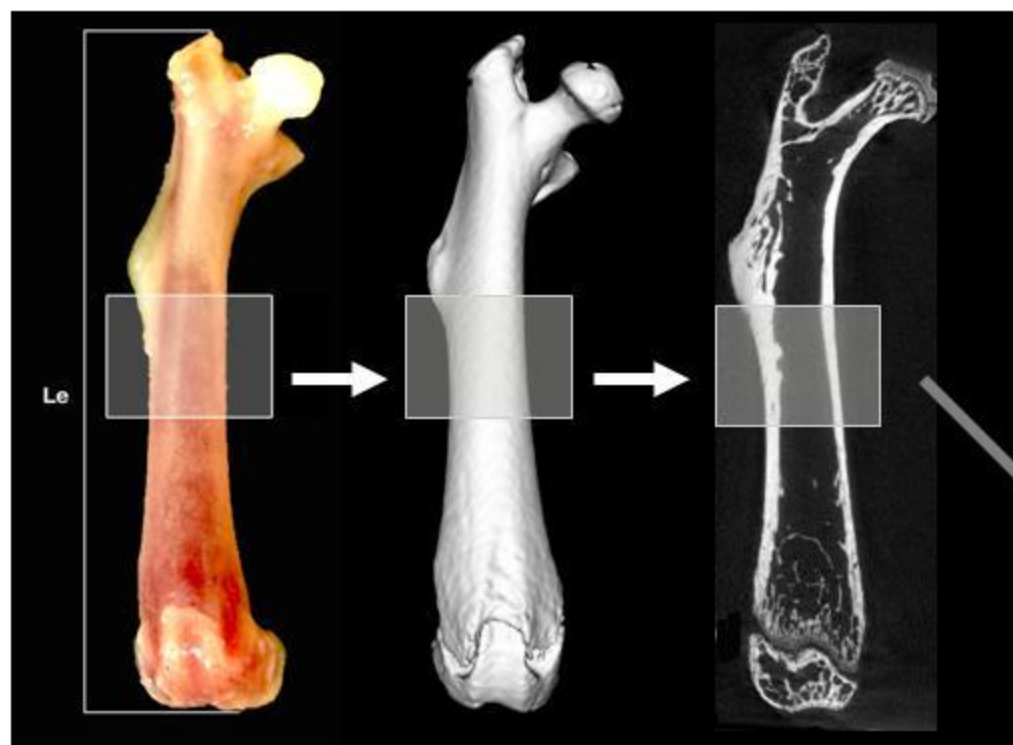


Body Weight (g)



Legend		Serum	Tissue
	Control	✓	✓
	HIT	✓	✓
	KO-HIT	✓	✗

# Micro Computational Tomography

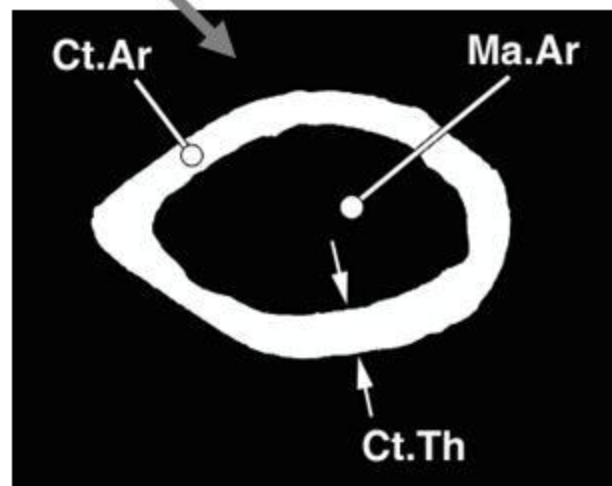


Morphology

Dynamic  $\mu$ CT

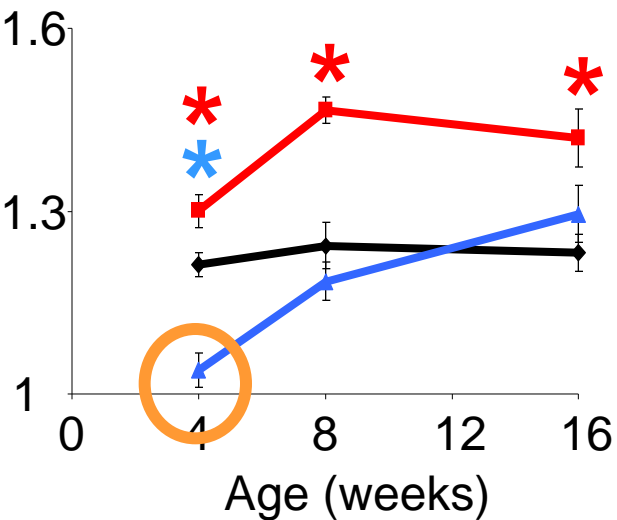
Midshaft of femur

Bone Compartment size

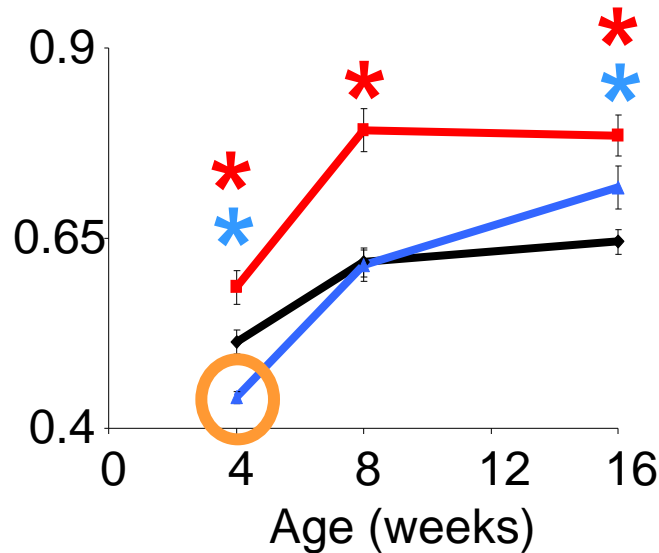


## Cortical bone

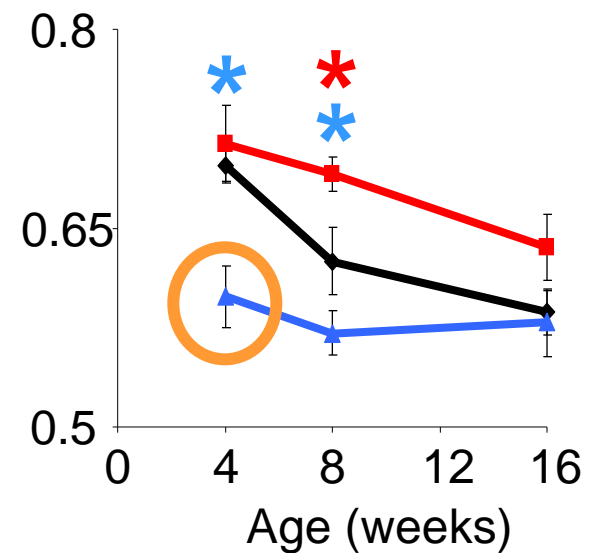
### Total Area (mm<sup>2</sup>)



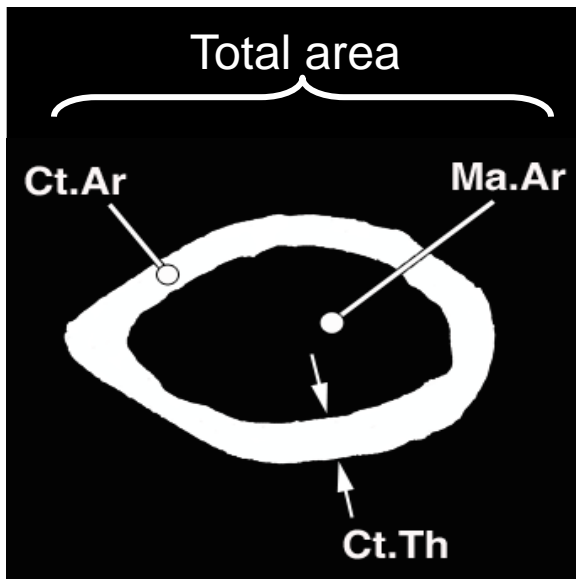
### Cortical Area



### Marrow Area



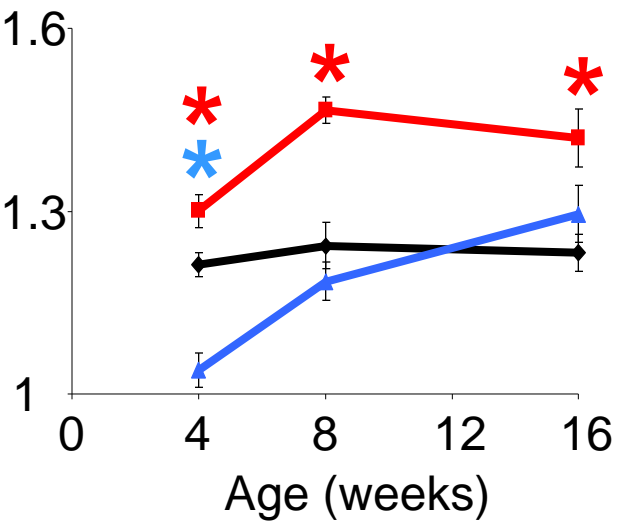
**Autocrine/paracrine IGF-1  
critical for early growth (before 4w)**



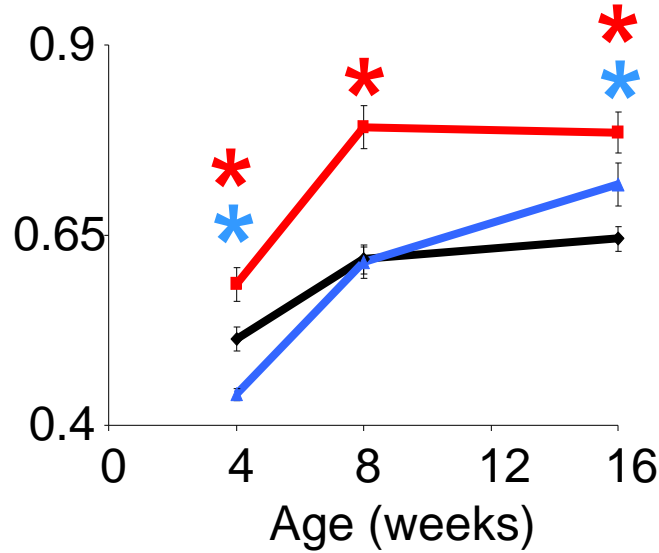
Legend		Serum	Tissue
—◆—	Control	✓	✓
—■—	HIT	✓	✓
—▲—	KO-HIT	✓	✗

# Cortical bone

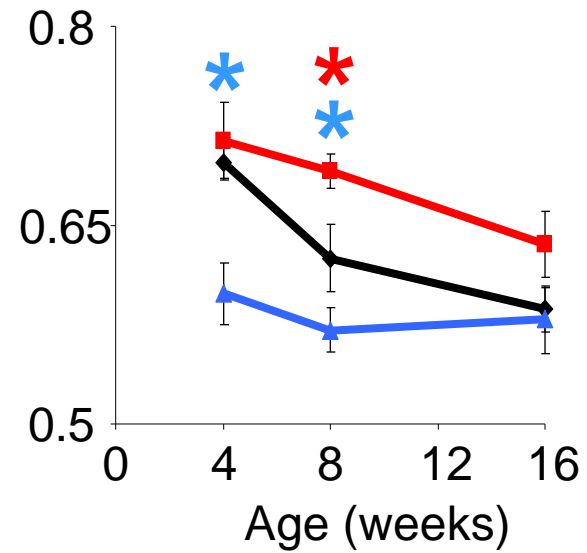
## Total Area (mm2)



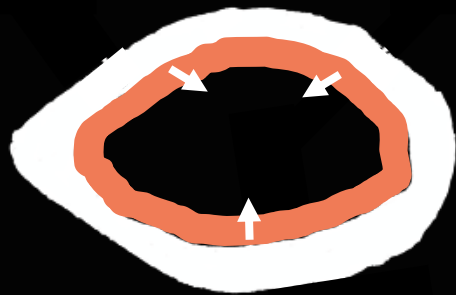
## Cortical Area



## Marrow Area



## Marrow infilling



## Control

Serum Tissue

✓ ✓

## Legend

Control  
HIT  
KO-HIT

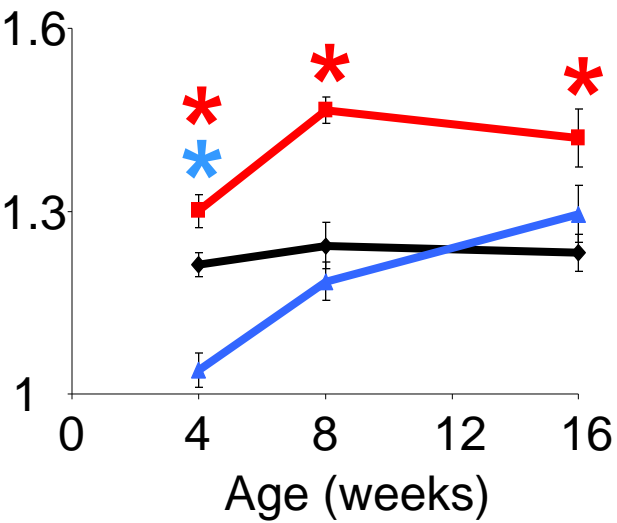
## Serum Tissue

✓ ✓  
✓ ✓  
✓ ✗

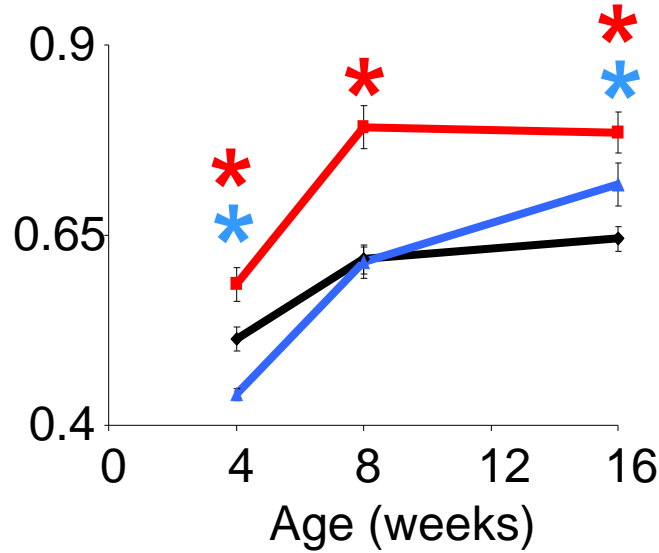


# Cortical bone

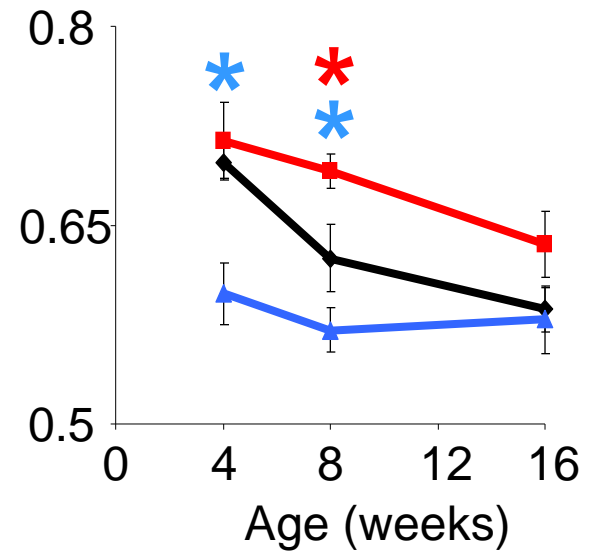
## Total Area (mm2)



## Cortical Area



## Marrow Area



Marrow infilling



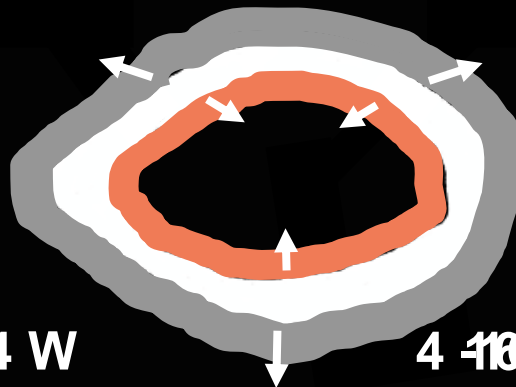
16W

Control

Serum Tissue



periosteal apposition



4 W

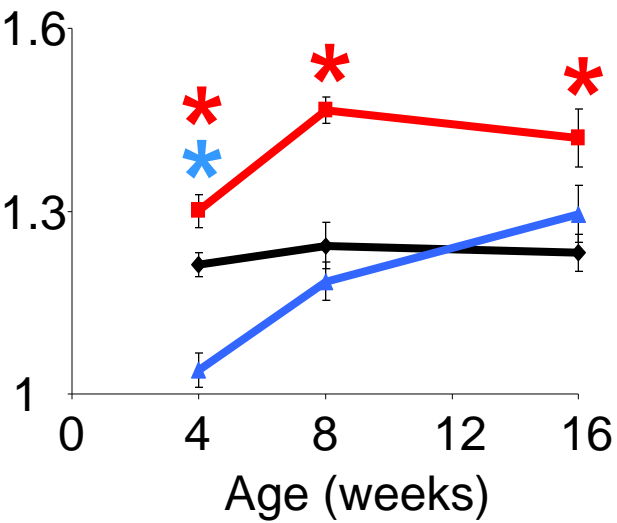
HIT

Serum Tissue

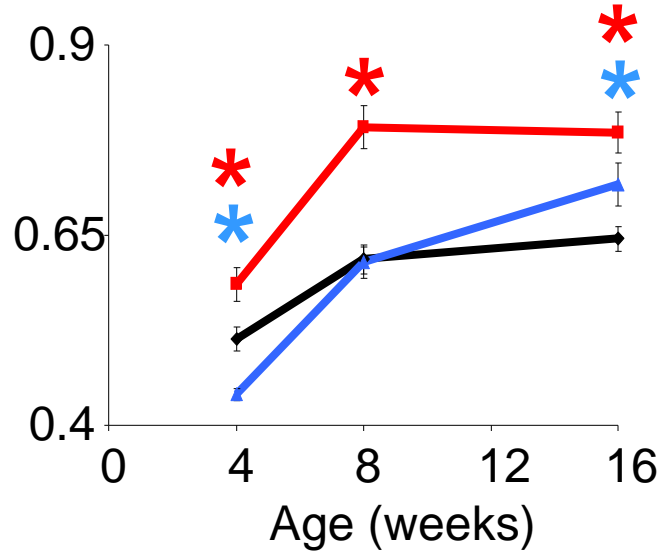


# Cortical bone

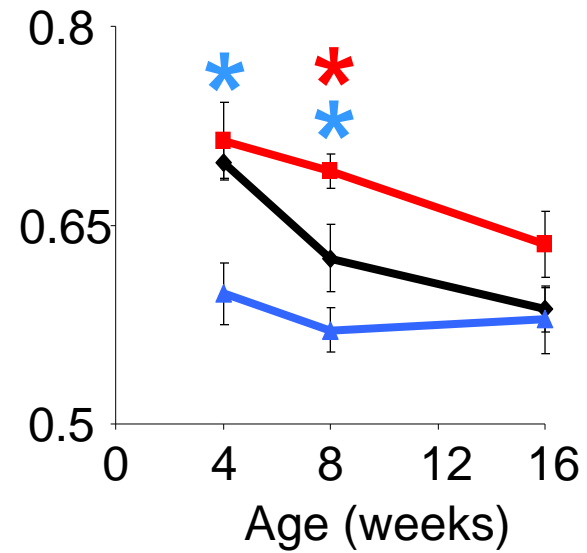
## Total Area (mm<sup>2</sup>)



## Cortical Area



## Marrow Area

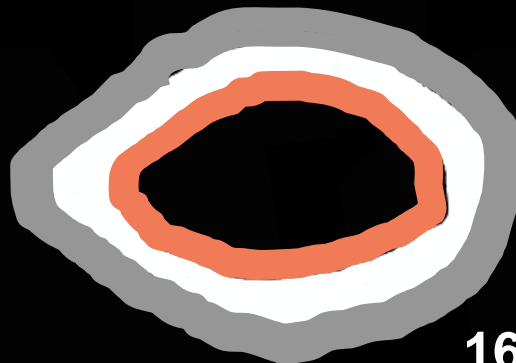


## Marrow infilling



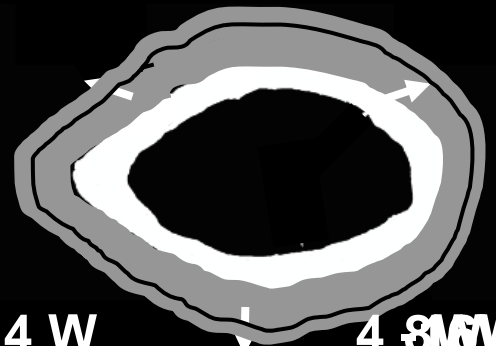
16W

## Periosteal apposition



16W

## Periosteal apposition



4 W

4 8W

Control

Serum Tissue



HIT

Serum Tissue



KO-HIT

Serum Tissue

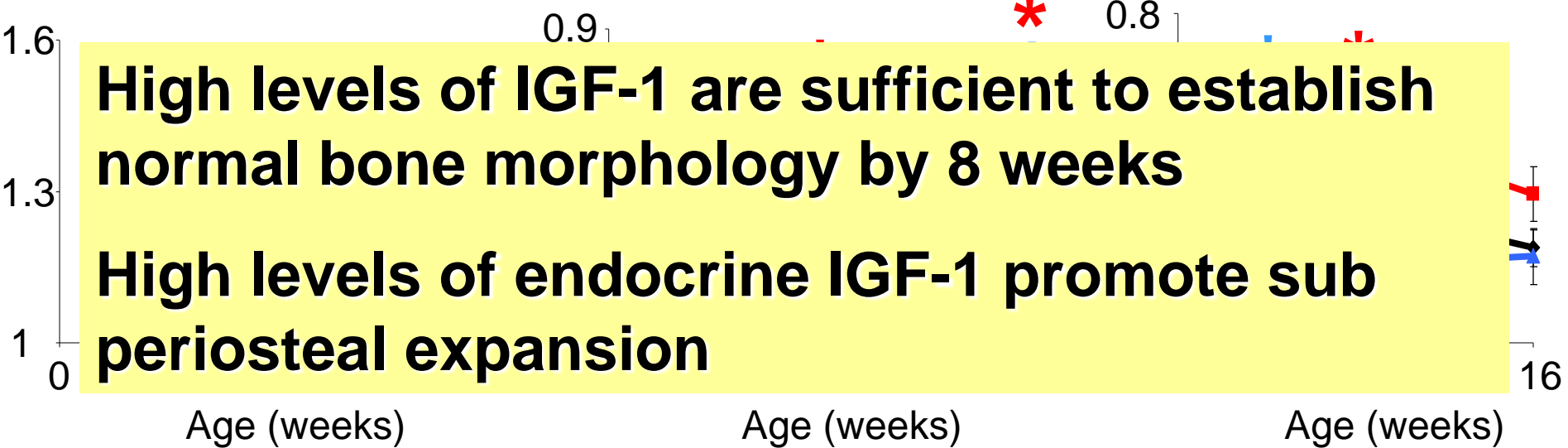


# Cortical bone

Total Area (mm<sup>2</sup>)

Cortical Area

Marrow Area



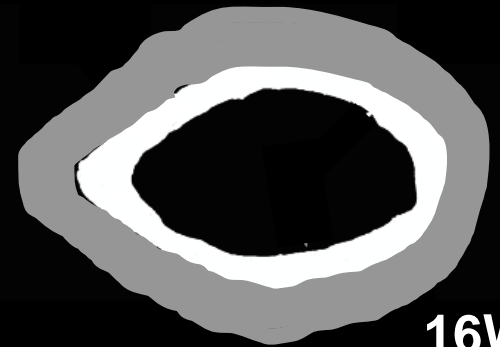
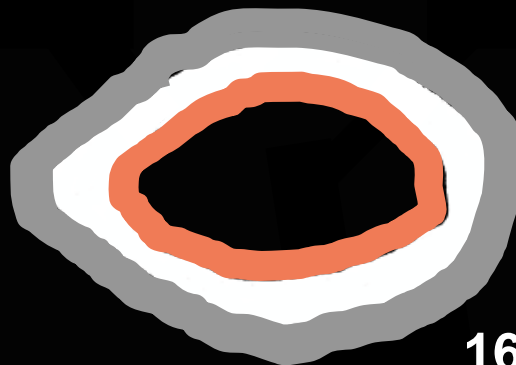
High levels of IGF-1 are sufficient to establish normal bone morphology by 8 weeks

High levels of endocrine IGF-1 promote subperiosteal expansion

Marrow infilling

periosteal apposition

periosteal apposition



Control

Serum Tissue



HIT

Serum Tissue

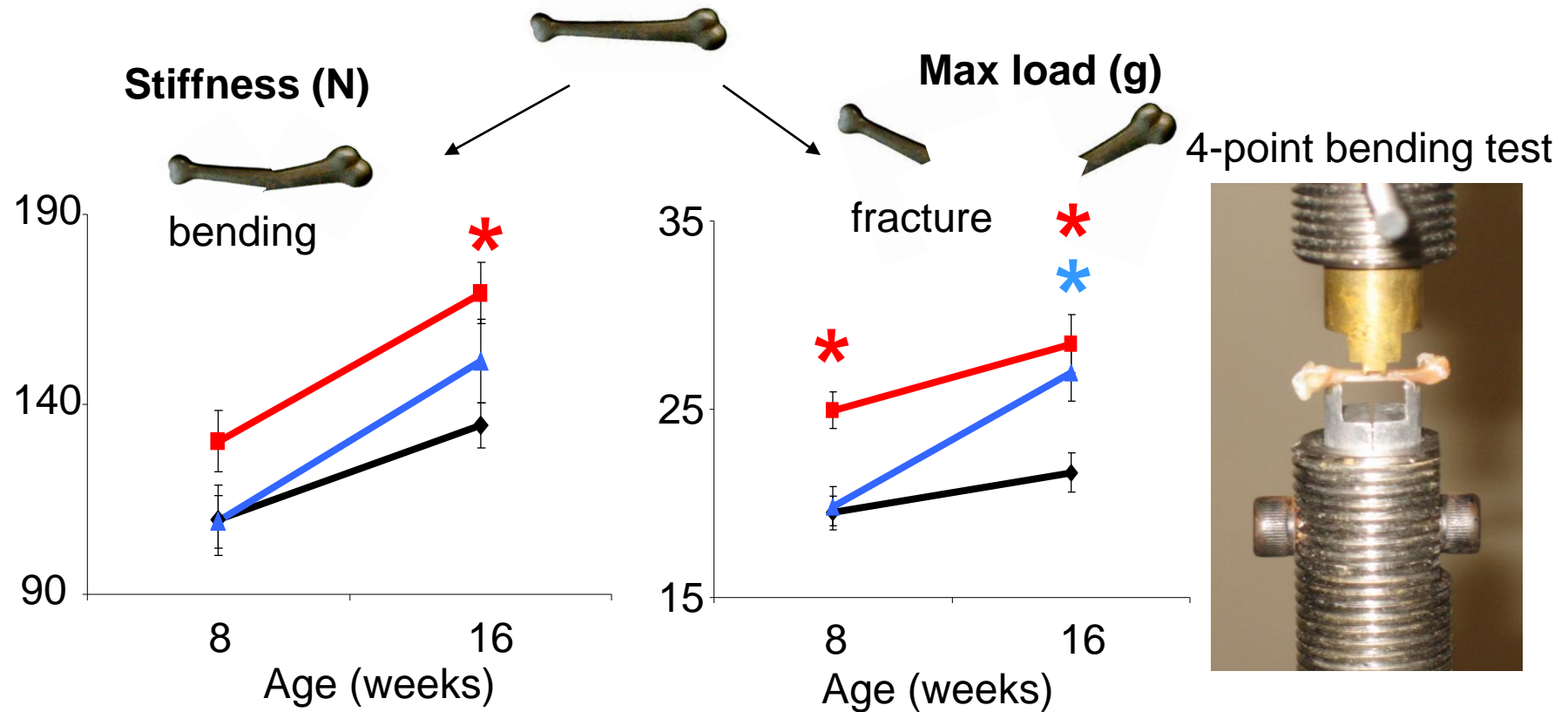


KO-HIT

Serum Tissue



# Mechanical properties



**8 weeks :**

HIT

cortices



max load



KO-HIT

cortices

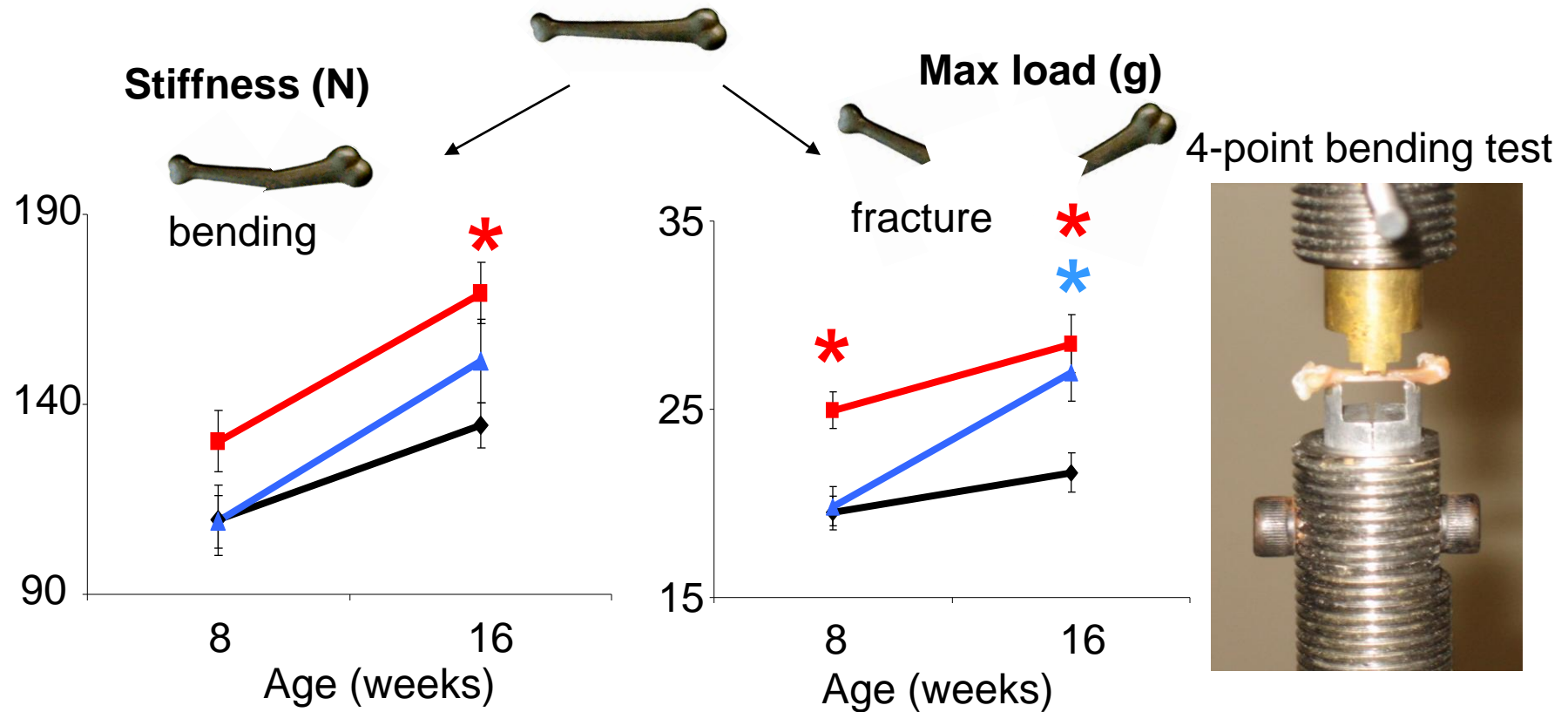


max load



Legend		Serum	Tissue
	Control	✓	✓
	HIT	✓	✓
	KO-HIT	✓	✗

# Mechanical properties



**16 weeks :**

HIT

cortices



max load



KO-HIT

cortices

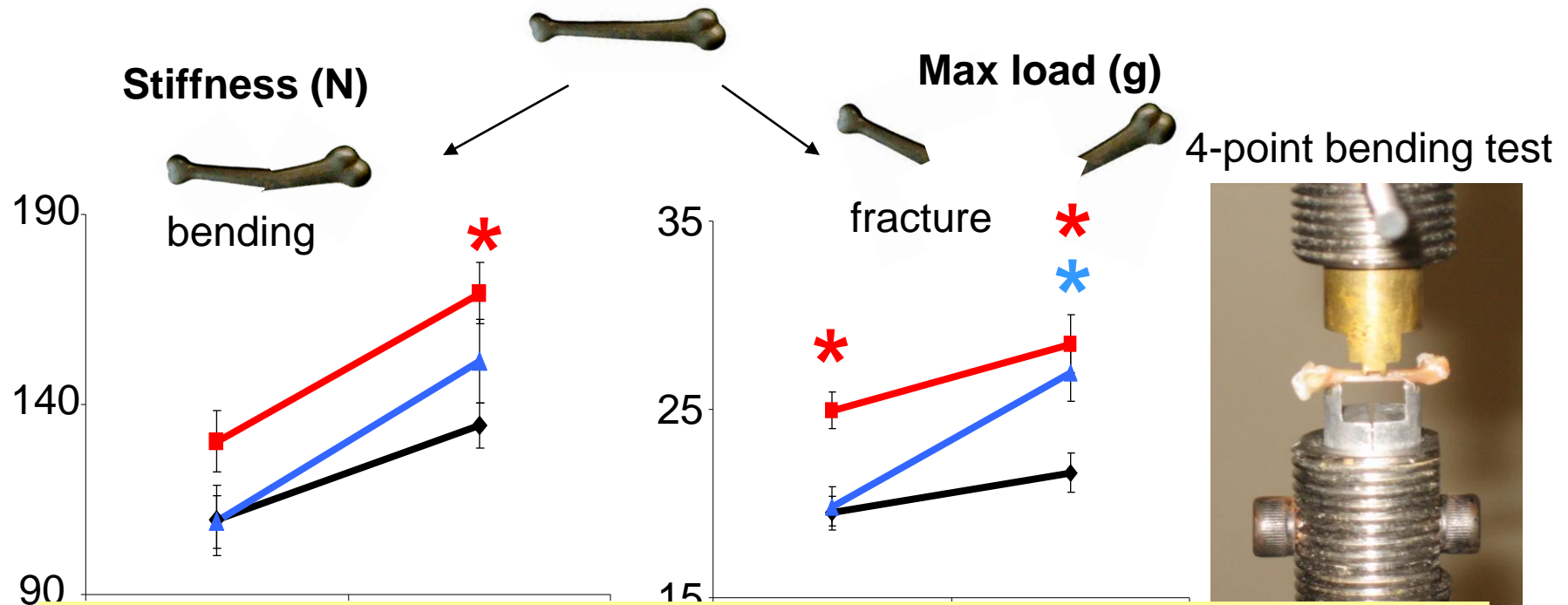


max load



Legend		Serum	Tissue
	Control	✓	✓
	HIT	✓	✓
	KO-HIT	✓	✗

# Mechanical properties



**Elevated levels of IGF-1 in serum increase bone mechanical properties**

**Elevated levels of IGF-1 compensate for a lack of local IGF-1 both morphologically and mechanically**

issue

✓

✓

✗

# Summary

**Postnatally, elevated serum IGF-1 levels :**

- increase in body weight.
- increase bone morphological traits
- increase in mechanical properties.

**Tissue IGF-1 is critical for neonatal and early postnatal growth (before 4w).**

**Elevated serum IGF-1 levels fully compensate for a postnatal absence of tissue IGF-1 :**

**Morphologically & Mechanically**



# Acknowledgments

## Endocrinology division, Mount Sinai School of Medicine



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Clifford  
Rosen



Valerie Williams



Karl J Jepsen

**Orthopaedics department, Mount Sinai School  
of Medicine**



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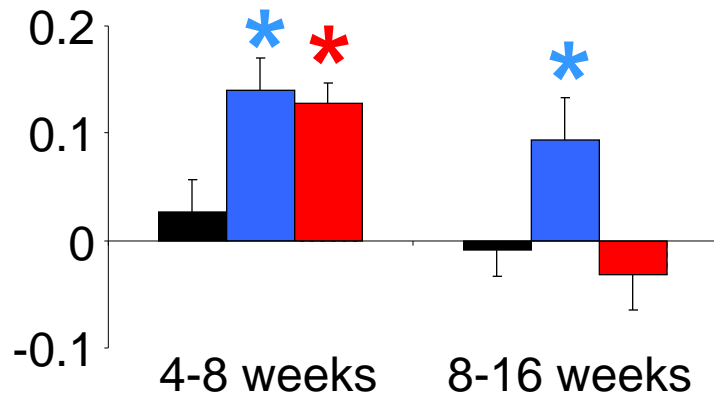
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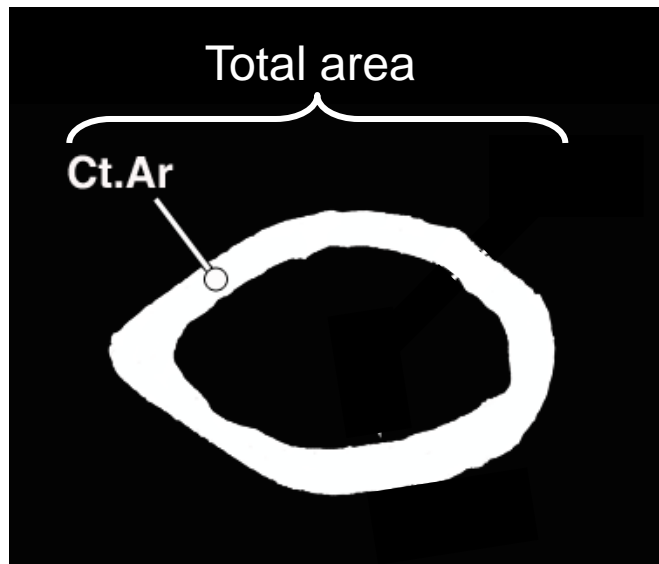
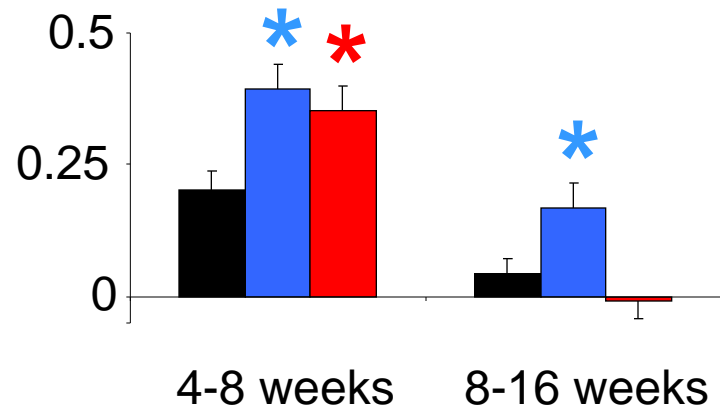
**THANK YOU**

# Increased serum IGF-1 levels accelerate growth rate

Growth rate of TtAr



Growth rate of CtAr



Legend		Serum	Tissue
<span style="display:inline-block; width:15px; height:15px; background-color:black;"></span>	Control	✓	✓
<span style="display:inline-block; width:15px; height:15px; background-color:red;"></span>	HIT	✓	✓
<span style="display:inline-block; width:15px; height:15px; background-color:blue;"></span>	KO-HIT	✓	x