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## 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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MOUNT SINAI  
SCHOOL OF  
MEDICINE

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



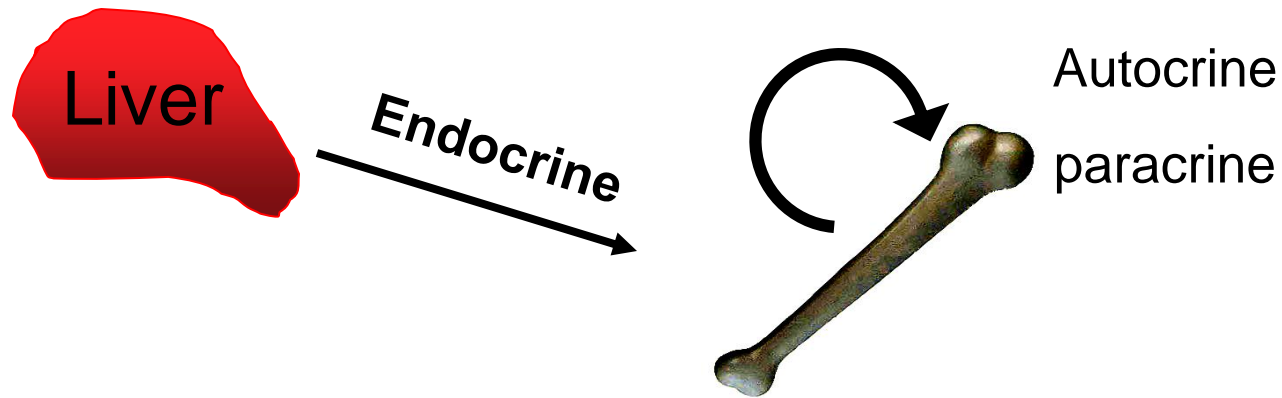
MOUNT SINAI  
SCHOOL OF  
MEDICINE

Sebastien Elis, Hayden-William Courtland,  
Yingjie Wu, Hui Sun, Karl J Jepsen and  
Shoshana Yakar

Mount Sinai School of Medicine  
Department of Medicine  
Division of Endocrinology, Diabetes and Bone Diseases

ENDO 09, Washington, 6.12.09

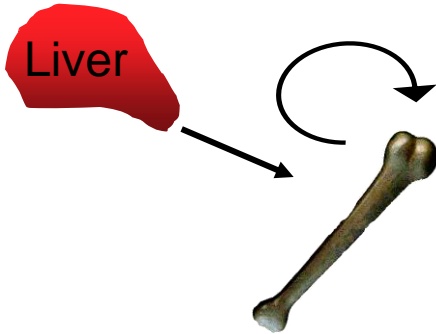
# IGF-1 is an endocrine, and autocrine/paracrine modulator of growth and metabolism



Aim:

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

## Control



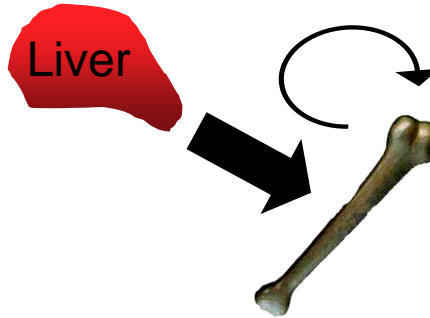
**Normal** serum IGF1 levels  
**Normal** tissue IGF1 levels

## HIT

Hepatic IGF-1 Transgene



TTR promoter



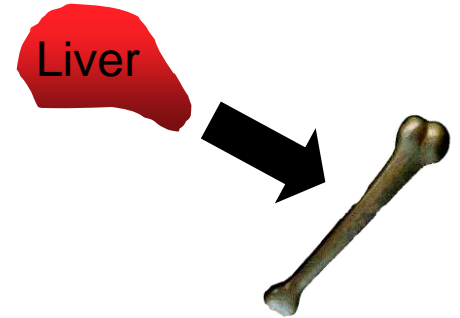
**High** serum IGF1 levels  
**Normal** tissue IGF1 levels

## KO-HIT

Total IGF-1 KO+  
Hepatic IGF-1 Transgene



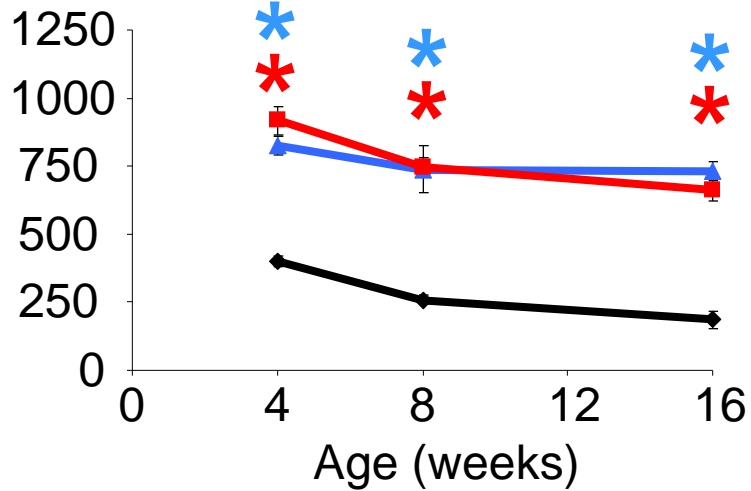
TTR promoter



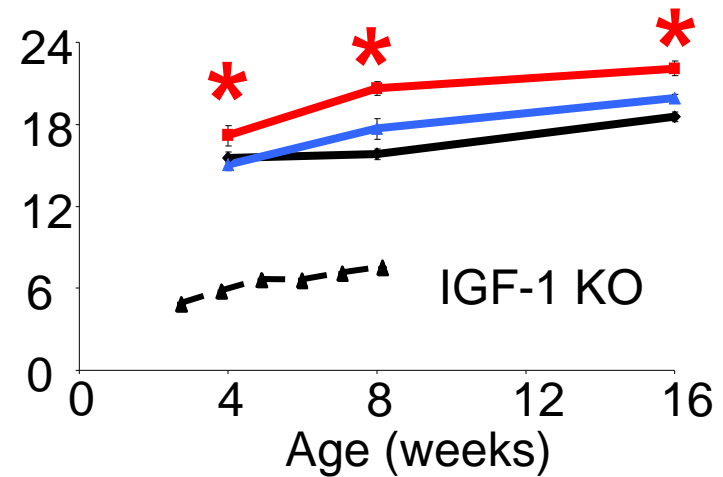
High serum IGF1 levels  
**NO** tissue IGF1

# 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

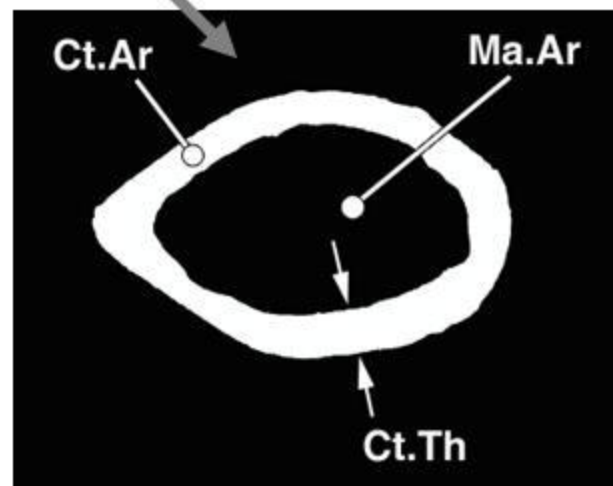


Morphology

Dynamic  $\mu$ CT

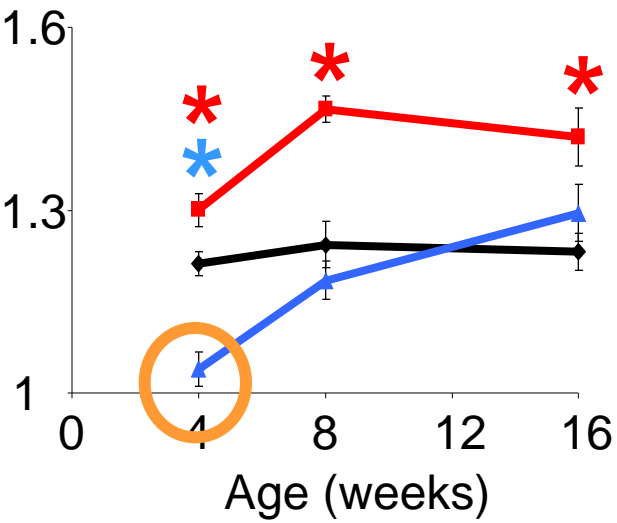
Midshaft of femur

Bone Compartment size

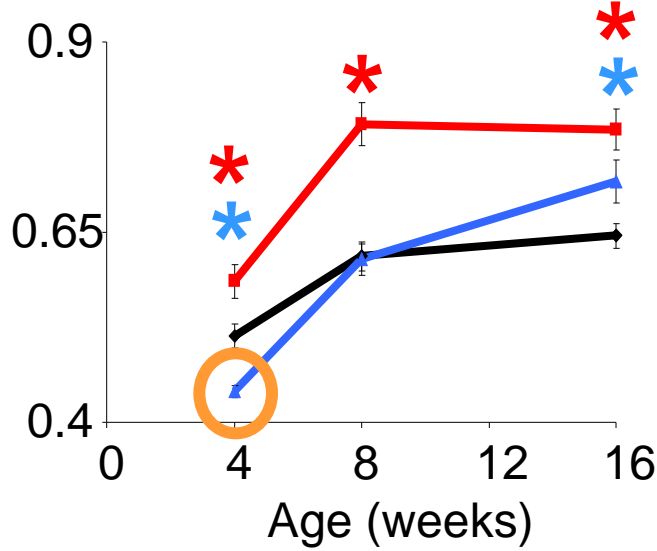


# Cortical bone

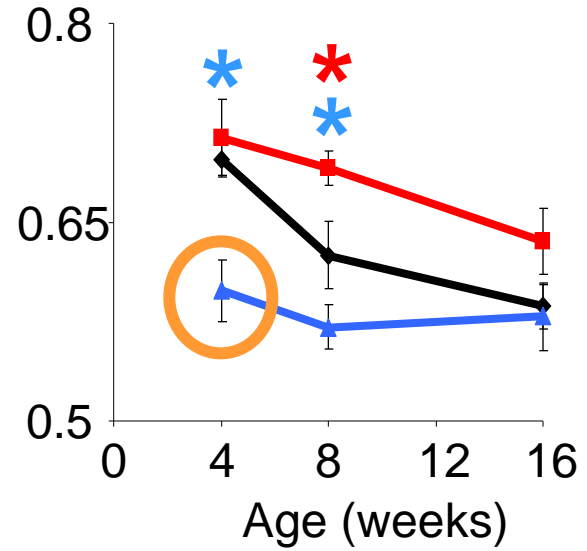
## Total Area (mm<sup>2</sup>)



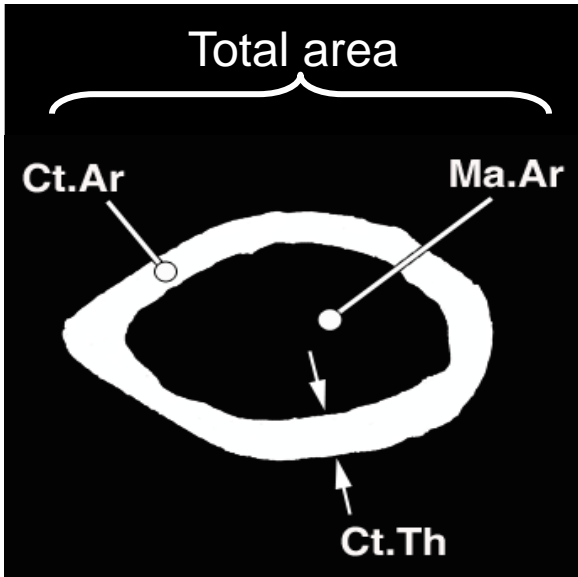
## Cortical Area



## Marrow Area



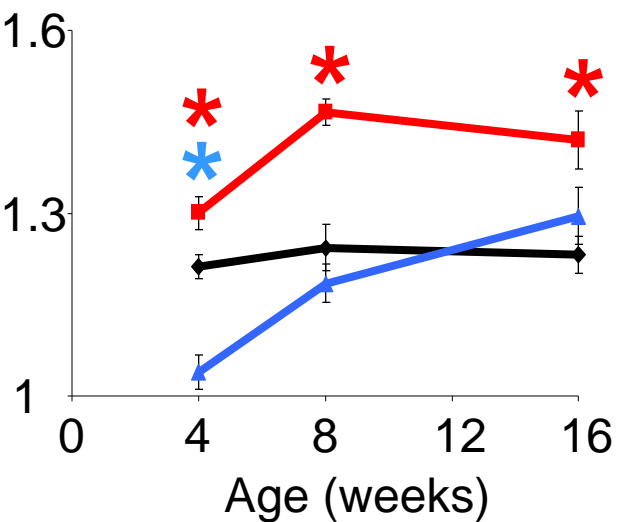
**Autocrine/paracrine IGF-1 critical for early growth (before 4w)**



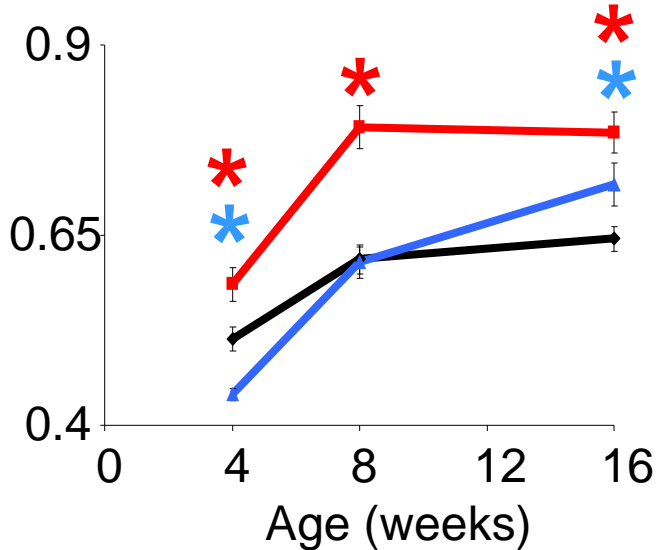
Legend		Serum	Tissue
—◆—	Control	✓	✓
—■—	HIT	✓	✓
—▲—	KO-HIT	✓	✗

# Cortical bone

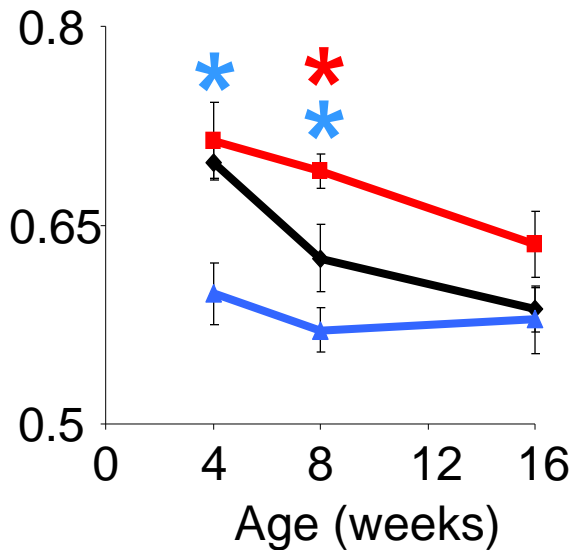
## Total Area (mm<sup>2</sup>)



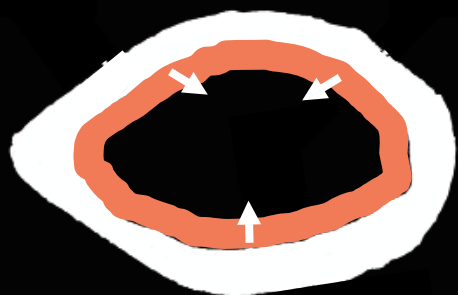
## Cortical Area



## Marrow Area



**Marrow infilling**



4 W

16 W

**Control**

**Serum Tissue**

✓ ✓

**Legend**

**Serum Tissue**

—◆— **Control**

✓ ✓

—■— **HIT**

✓ ✓

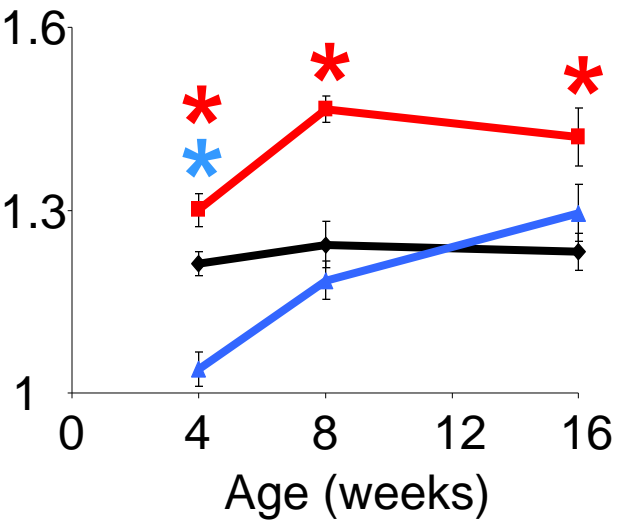
—▲— **KO-HIT**

✓ ✗

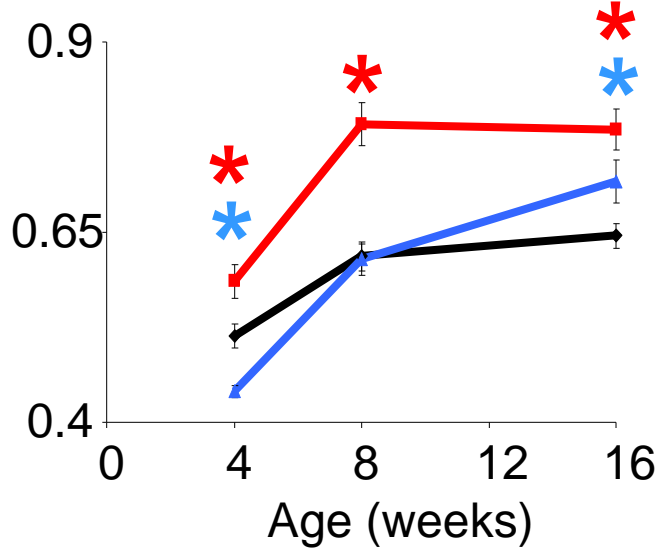


# Cortical bone

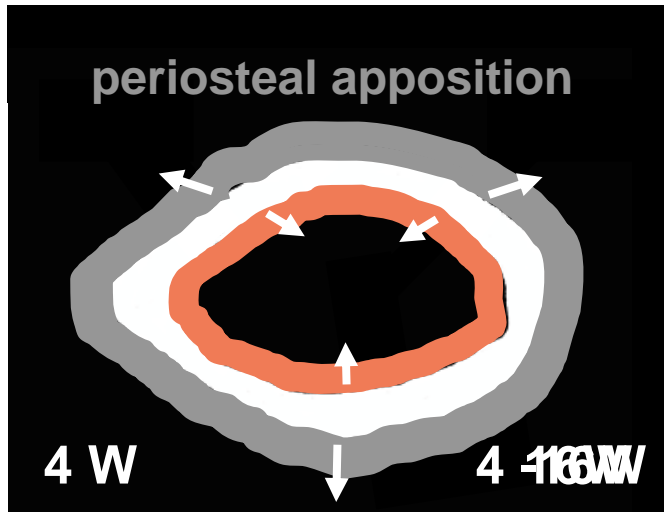
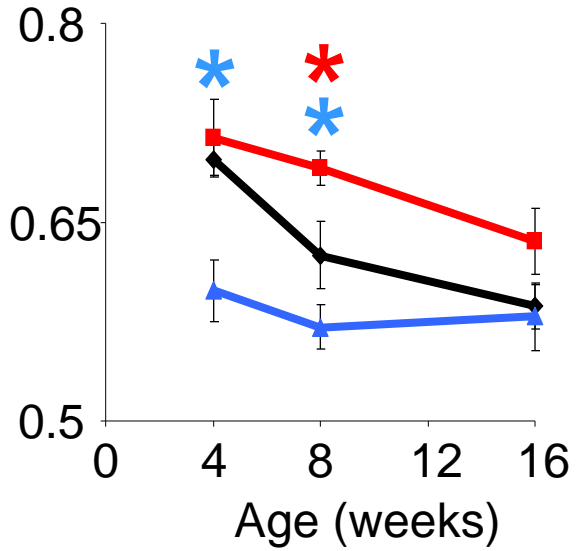
## Total Area (mm<sup>2</sup>)



## Cortical Area



## Marrow Area

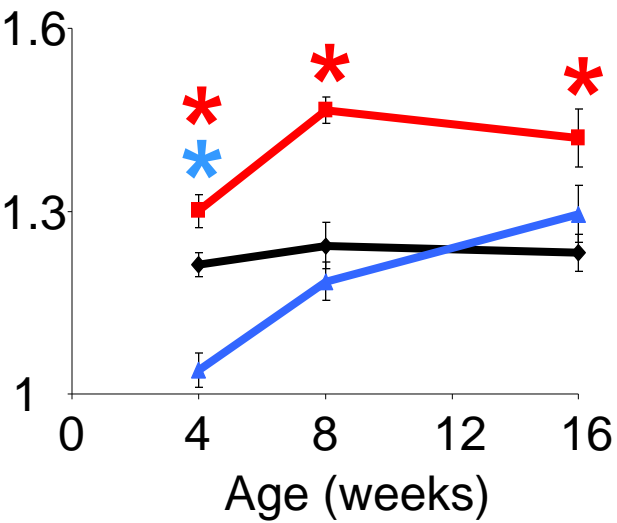


**Control**  
Serum Tissue  
✓      ✓

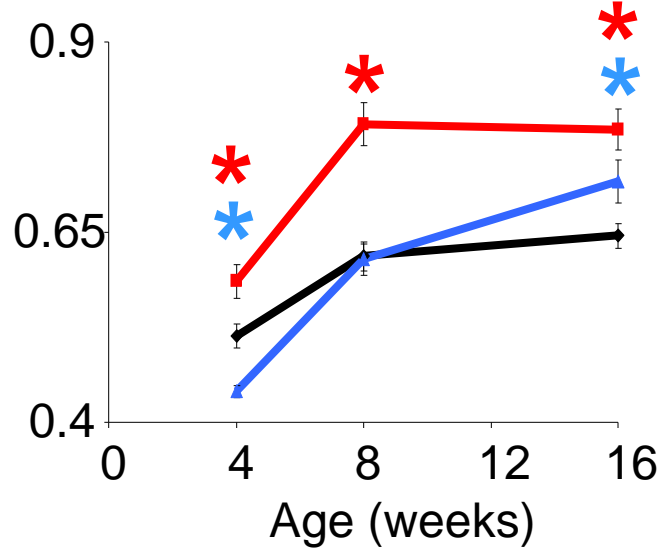
**HIT**  
Serum Tissue  
✓      ✓

# Cortical bone

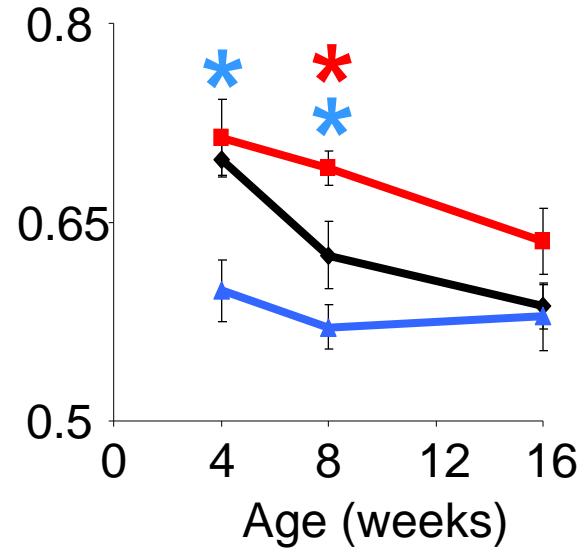
## Total Area (mm<sup>2</sup>)



## Cortical Area



## Marrow Area



### Marrow infilling



16W

**Control**  
Serum ✓ Tissue ✓

### Periosteal apposition



16W

**HIT**  
Serum ✓ Tissue ✓

### Periosteal apposition



4 W

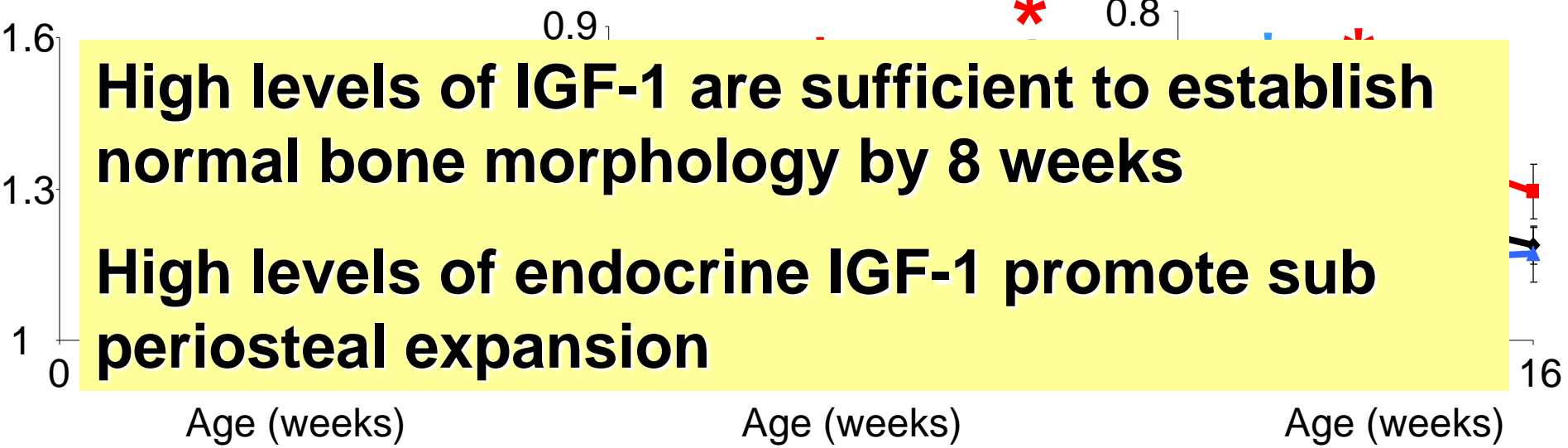
**KO-HIT**  
Serum ✓ Tissue ✗

# Cortical bone

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

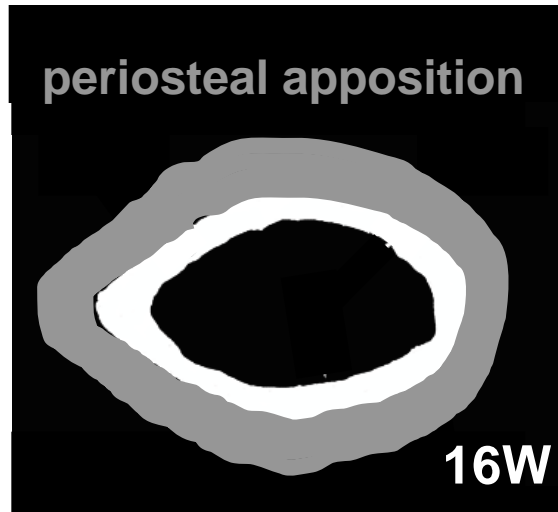
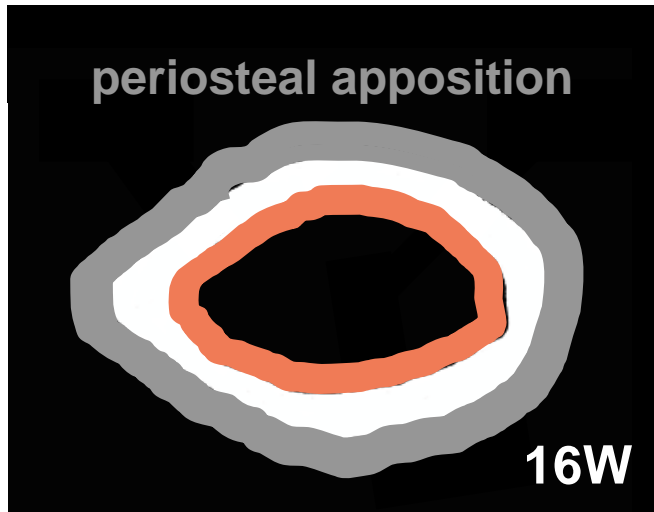
Cortical Area

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



**Control**

Serum Tissue



**HIT**

Serum Tissue

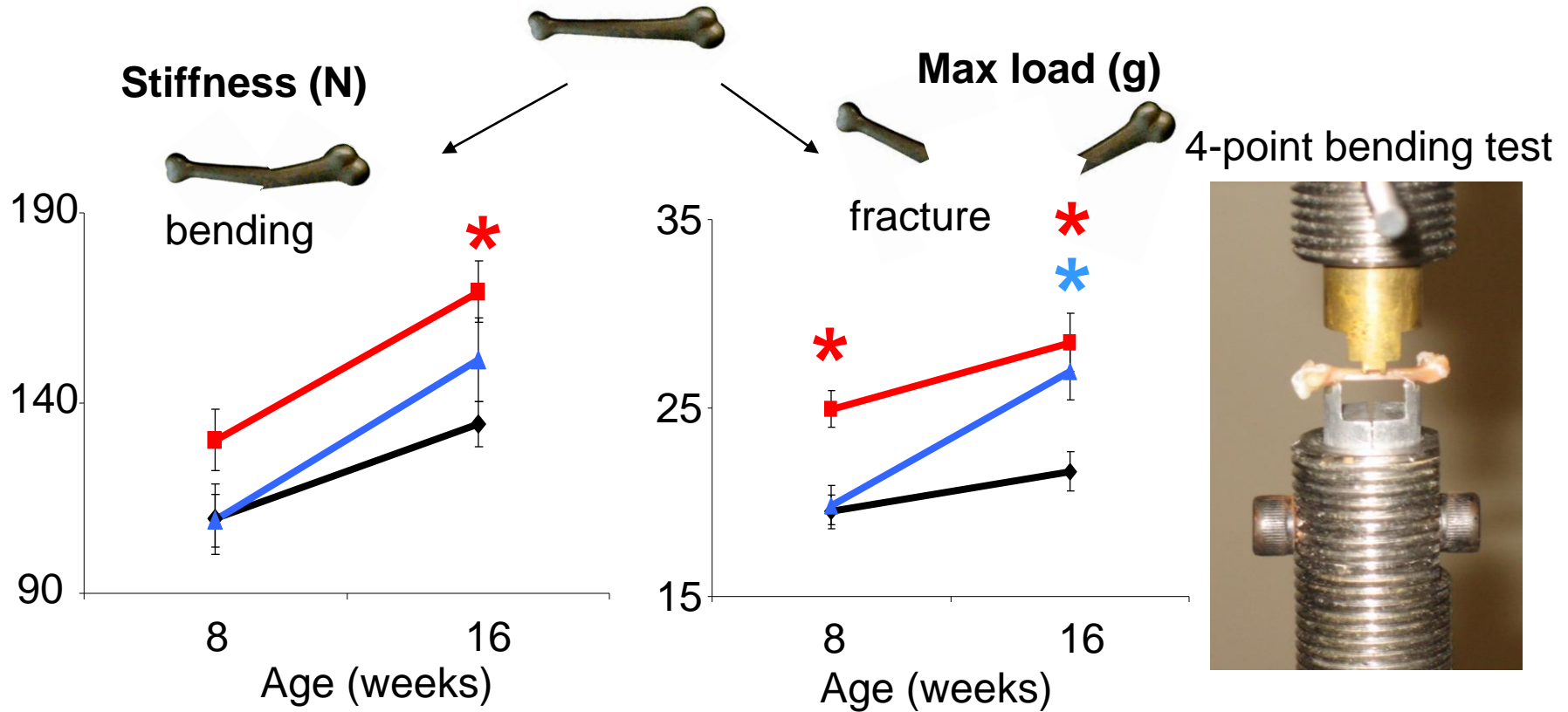


**KO-HIT**

Serum Tissue



# Mechanical properties



**8 weeks :**

HIT

cortices



max load



KO-HIT

cortices

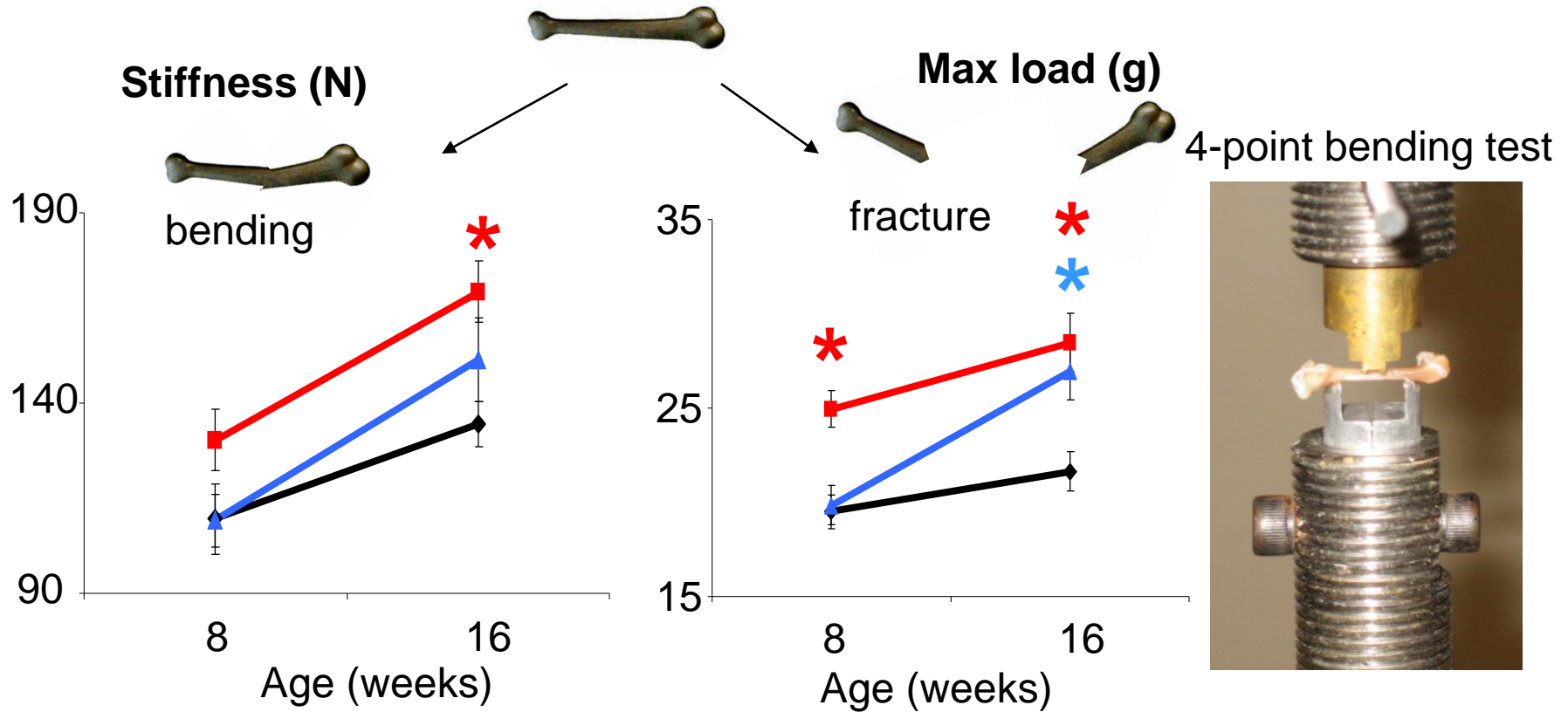


max load



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

# Mechanical properties

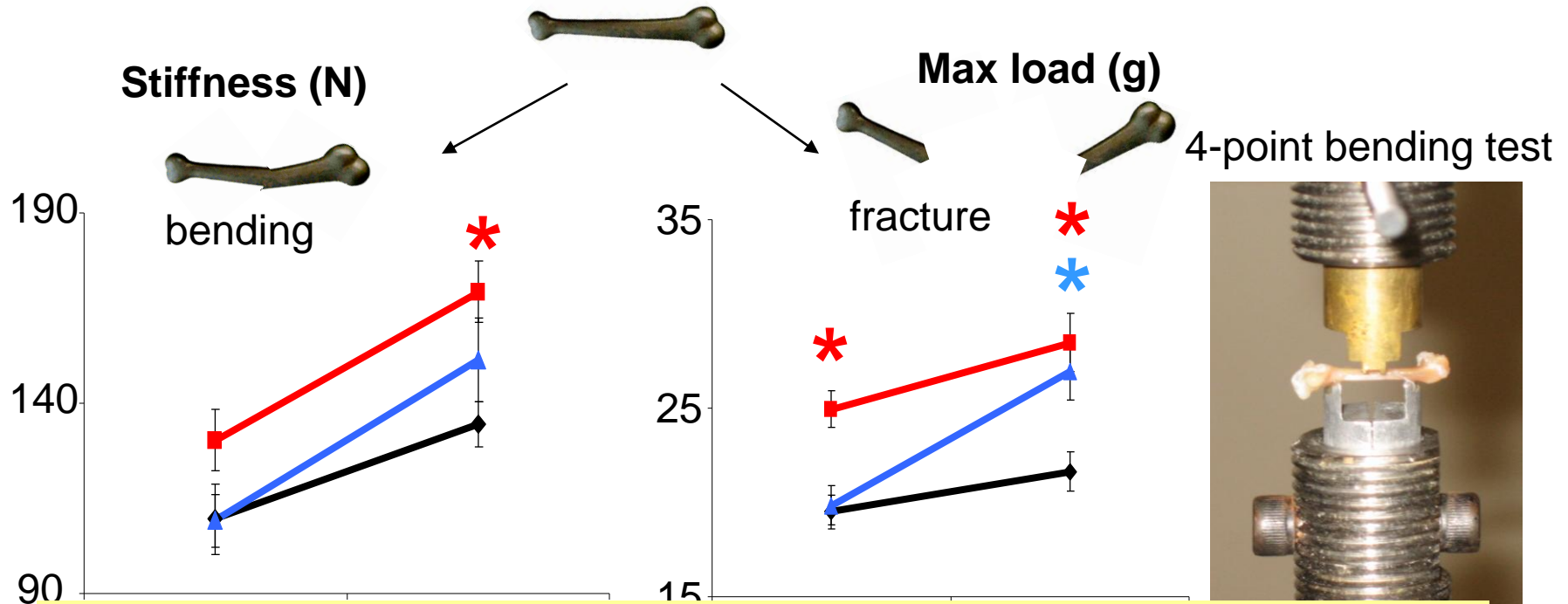


**16 weeks :**

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**

tissue

✓

✓

✗

# 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

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Karl J Jepsen

**Orthopaedics department, Mount Sinai School  
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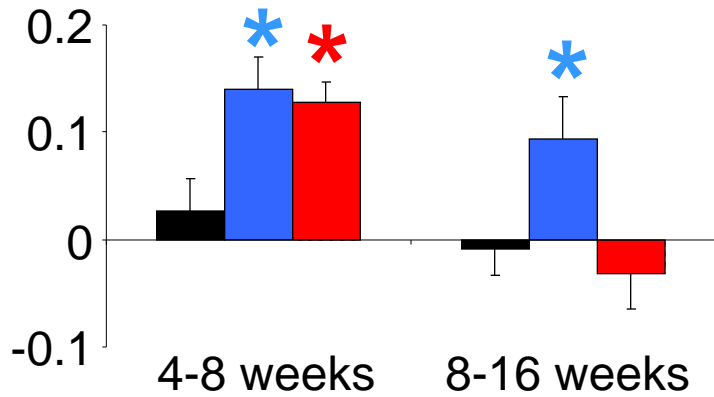
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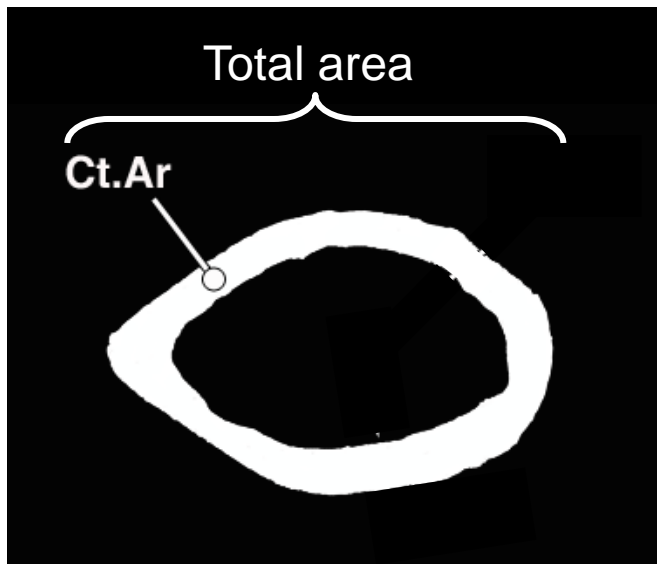
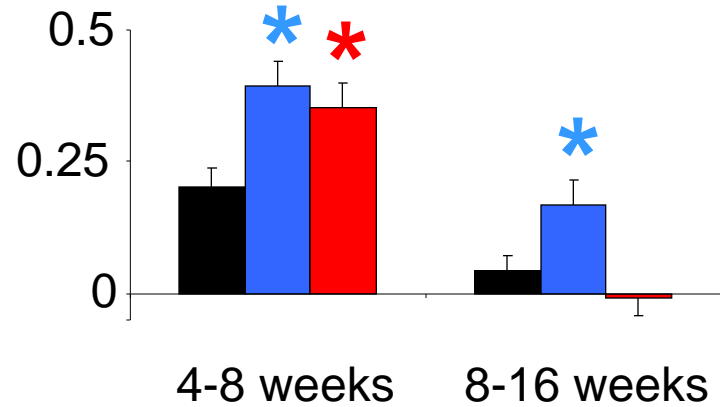
**THANK YOU**

# Increased serum IGF-1 levels accelerate growth rate

## Growth rate of TtAr



## Growth rate of CtAr



Legend		Serum	Tissue
■	Control	✓	✓
■	HIT	✓	✓
■	KO-HIT	✓	x