GH and aging: Surprising benefits of endocrine defects

Andrzej Bartke

SIU School of Medicine

Springfield, Illinois USA

JAGIELLONIAN UNIVERSITY

Krakow, Poland

Founded in 1364

Collegium Maius

Permission to use images requested from Jagiellonian University

UNIVERSITY OF KANSAS

Lawrence, Kansas, U.S.A.

Strong Hall

Photos courtesy of KU Marketing Communications

Ames dwarf mice

Origin: Spontaneous recessive somatic mutation; Ames dwarf, df (Schaible & Gowen, 1961)

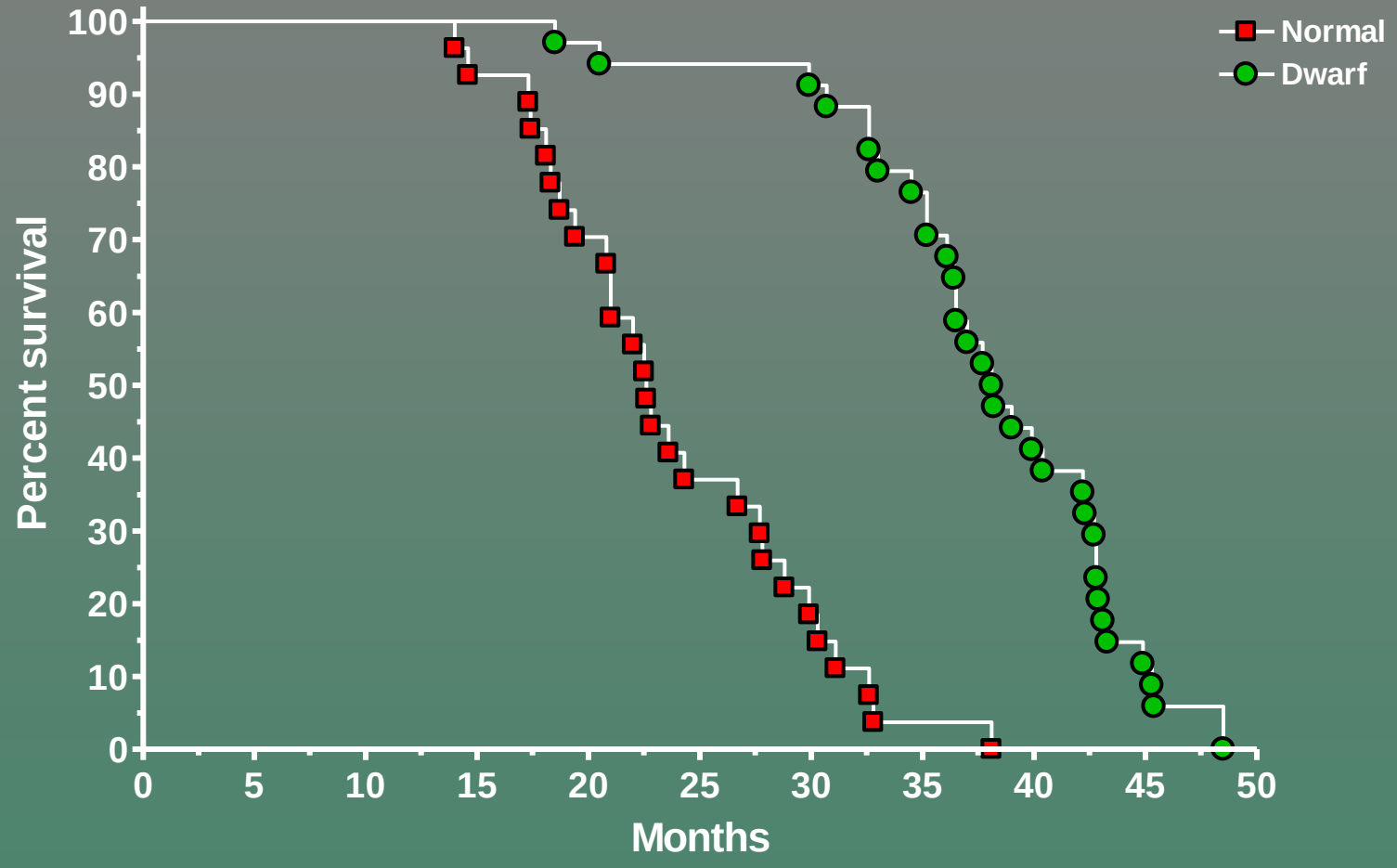
Cloning and characterization of the gene:

Prophet of pituitary factor 1; Prop-1^{df}

(Sornson et al., 1996)

Primary effects: Failure of differentiation of somatotrophs, lactotrophs and thyrotrophs; absence of GH, PRL and TSH

Survival plot for Ames dwarf (Prop-1^{df}) mice



In his book, *My Life in Science*, 2002 Nobel Prize winner Sydney Brenner made this observation:

"… you can always know too much. …being an experienced scientist in a particular field … can curtail creativity because you know too many reasons why something may not work. So I believe that it's people who come from the outside … who can see things a different way, who can take the new step."

GHR/GHBP-KO (-/-) mice

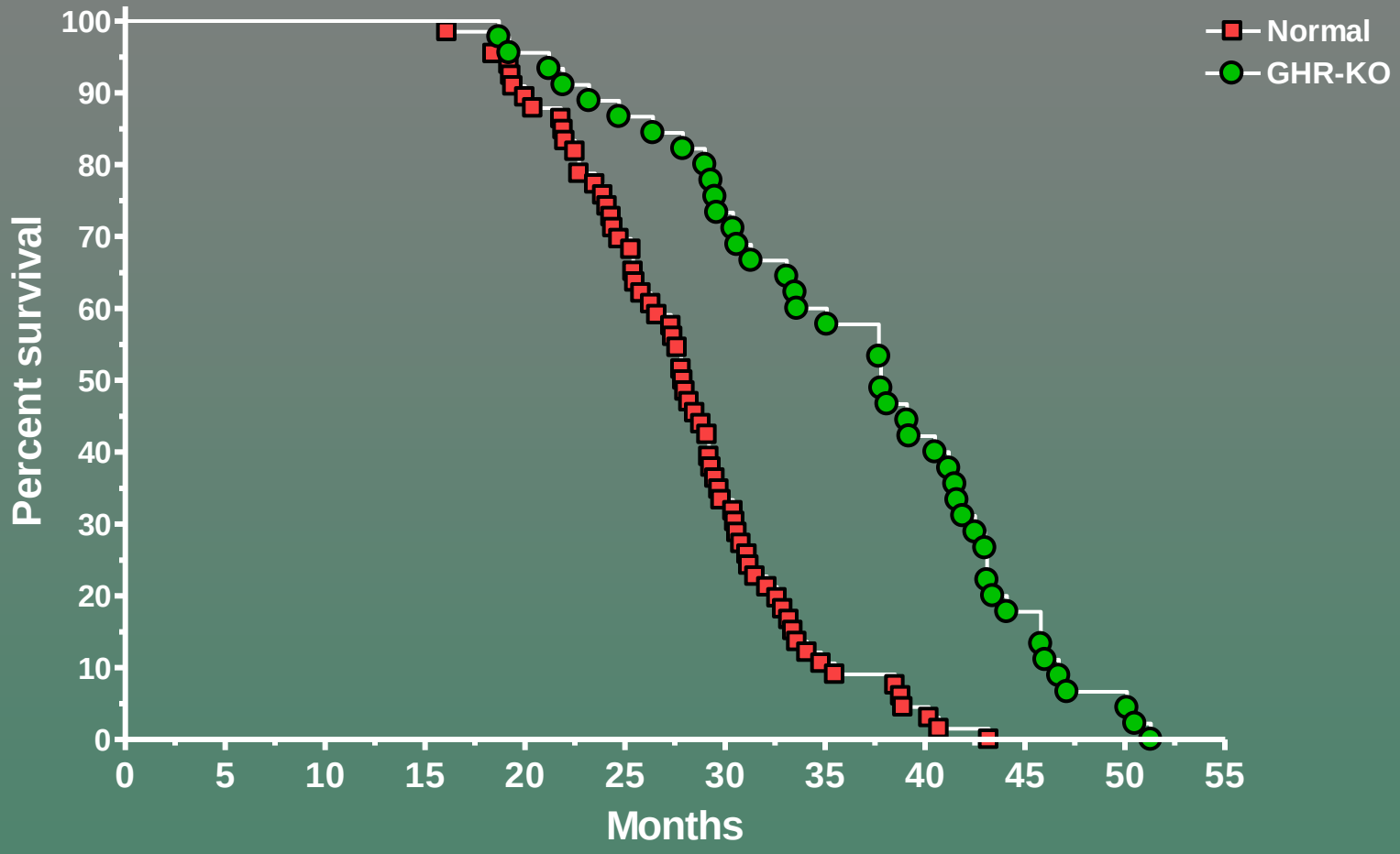
Origin:

Knockout of the GH receptor/GH binding protein gene; GHRKO (Zhou et al., 1997)

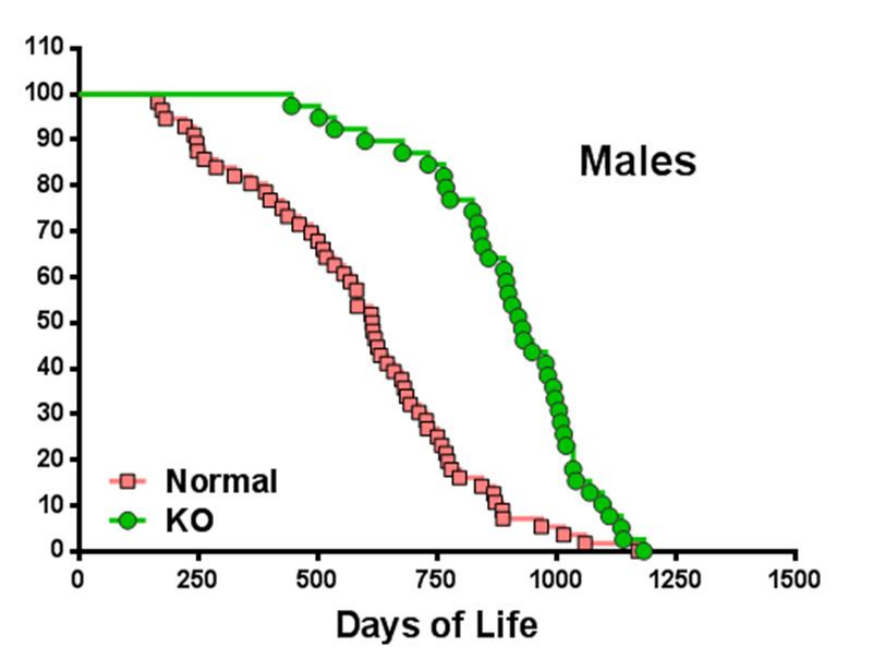
Primary effects:

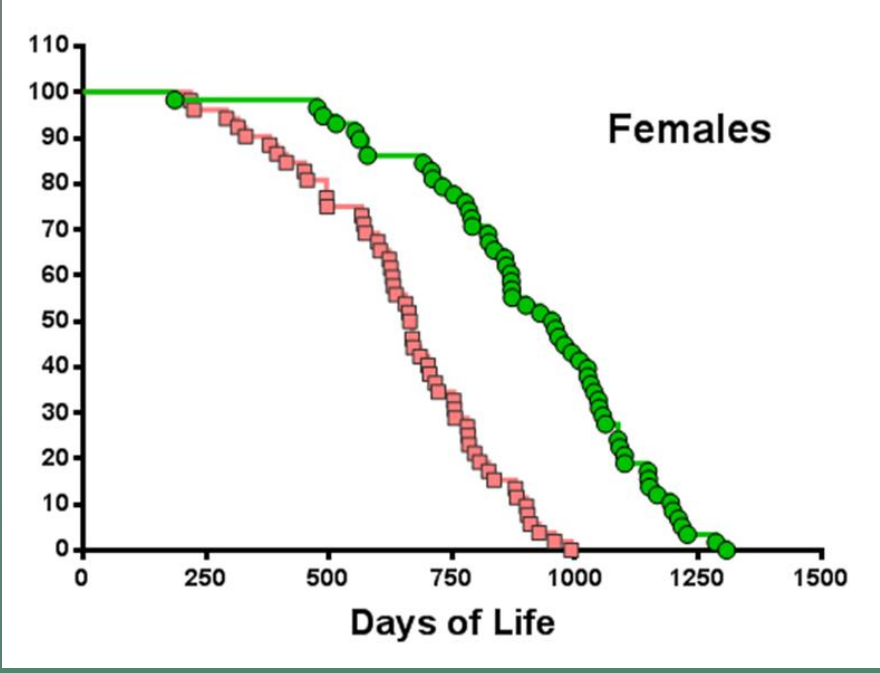
- absence of GH receptor
- absence of GH binding protein
- GH resistance

Survival plot for GHR-KO mice



GHRH-KO (KO) mice live longer than control (Ct) mice



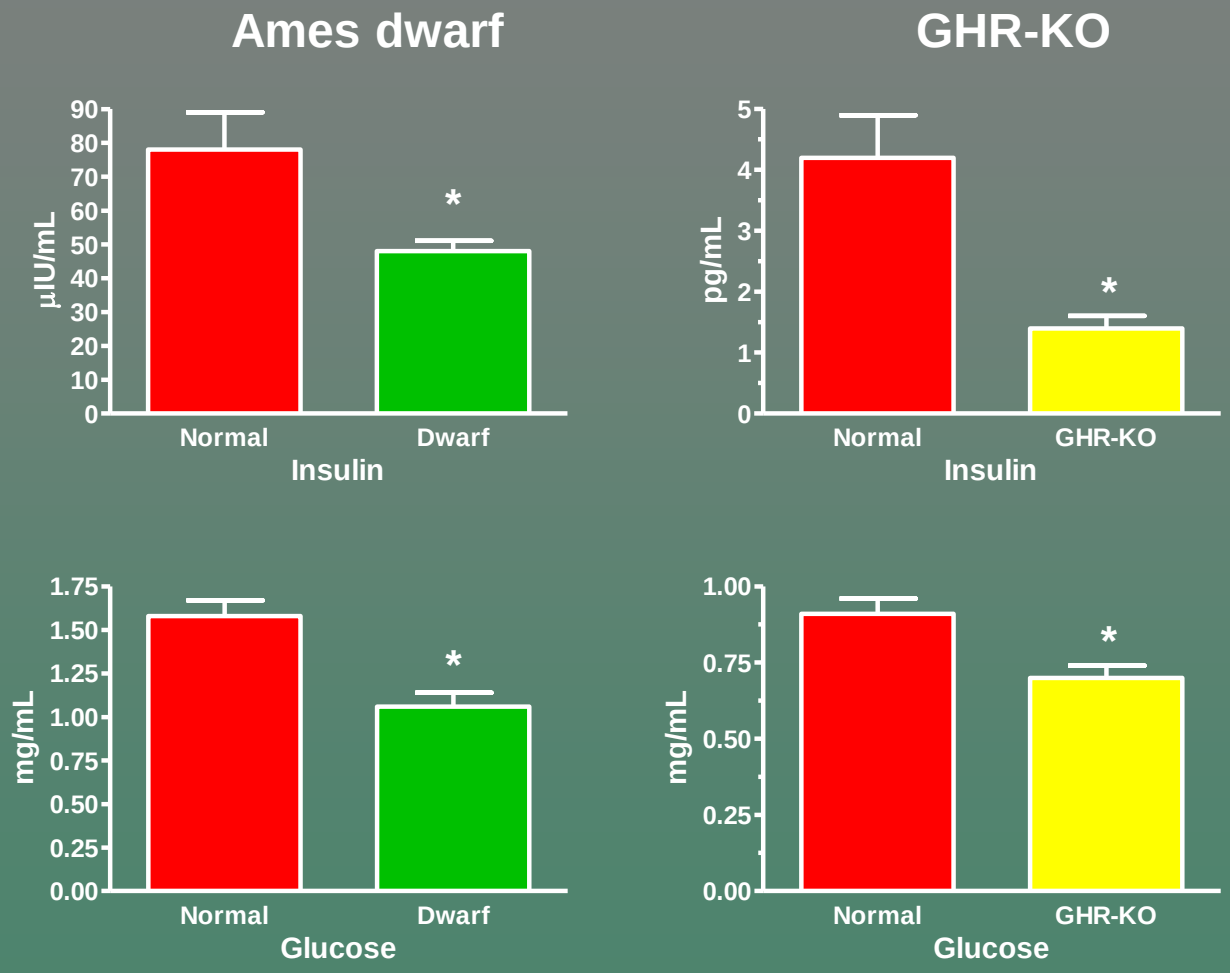


L. Sun et al., eLIFE 2013

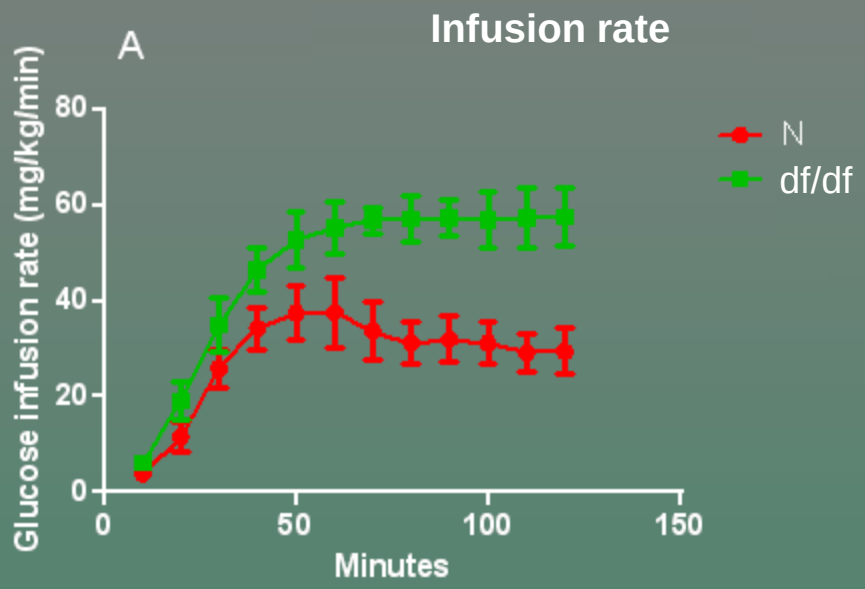
Long-lived mutant mice have longer "healthspan"

- Incidence of cancer is reduced
- Fatal diseases develop later in life
- Aging of the immune system is delayed
- Aging of collagen, joint cartilage, and development of osteoarthritis are all delayed
- ***Cognitive function (learning and memory) is maintained***
- ***Neuromusculoskeletal function (strength, balance, and coordination) is maintained***
- ***Insulin sensitivity (blood glucose mgmt.) is maintained***

Ames dwarf and GHR-KO mice have reduced levels of insulin and glucose

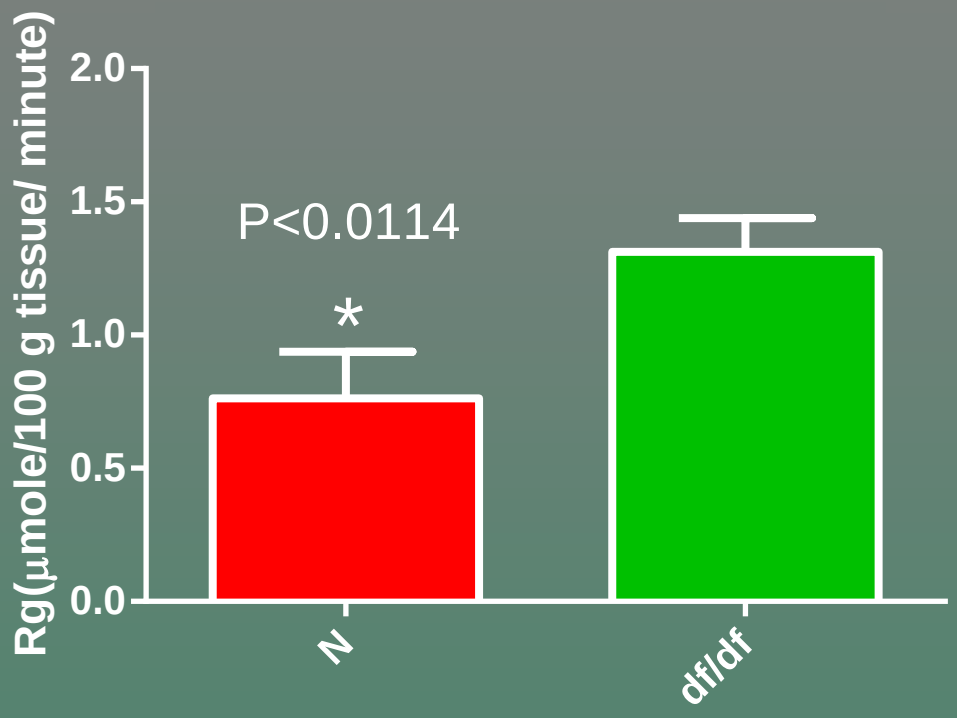


Ames dwarf mice are insulin sensitive



Wiesenborn DS, Ayala JE, King E, Masternak MM. Age (2014) 36:9709.

Fat glucose uptake



Wiesenborn DS, Ayala JE, King E, Masternak MM. Age (2014) 36:9709.

PubMed

Display Settings: Abstract

Full text links

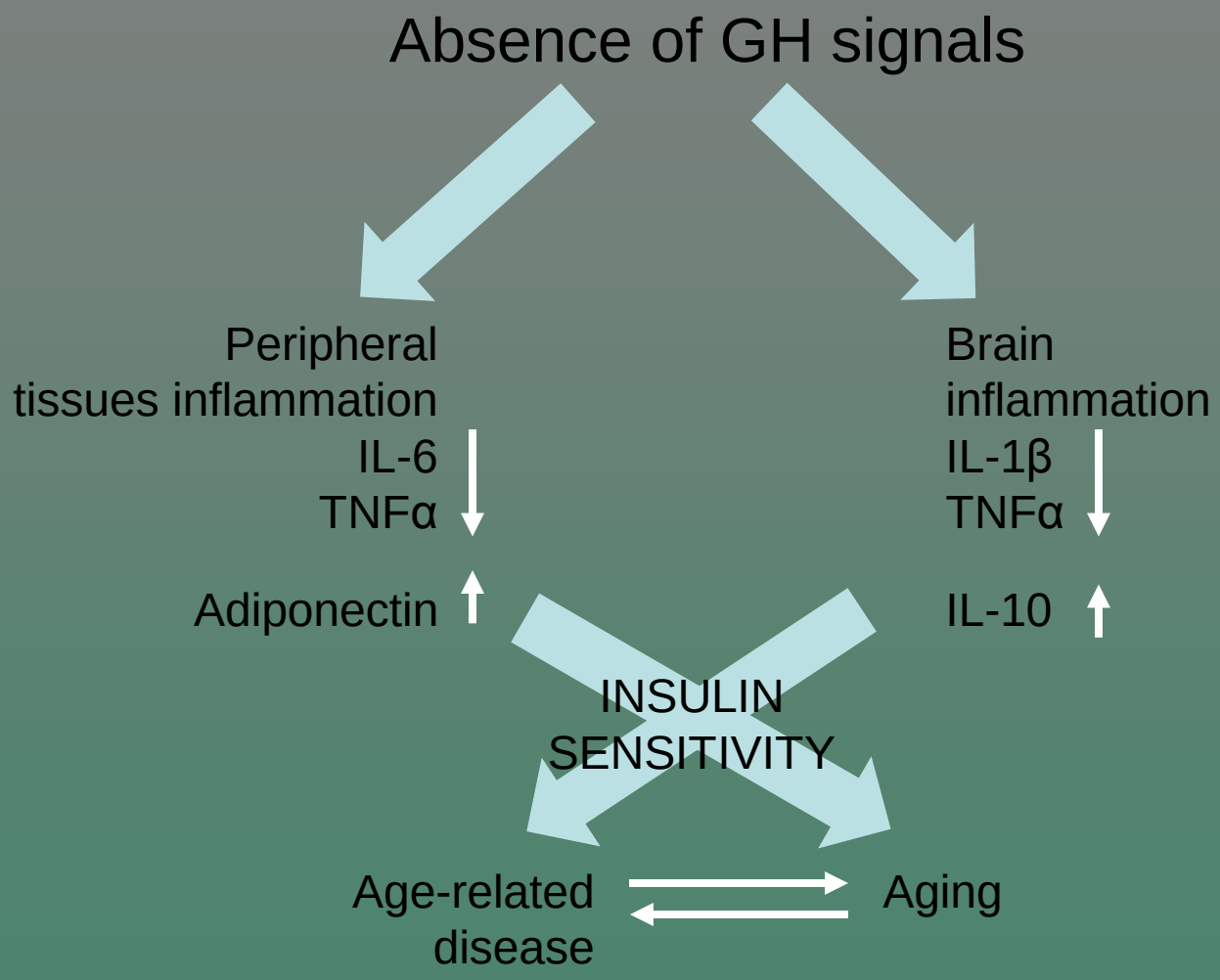
Full Text Online FREE WILEY

Aging Cell. 2014 Sep 20. doi: 10.1111/acel.12262. [Epub ahead of print]

Specific suppression of insulin sensitivity in growth hormone receptor gene-disrupted (GHR-KO) mice attenuates phenotypic features of slow aging.

Arum O[1], Boparai RK, Saleh JK, Wang F, Dirks AL, Turner JG, Kopchick JJ, Liu JL, Khardori RK, Bartke A.

GH deficiency or resistance reduce inflammation

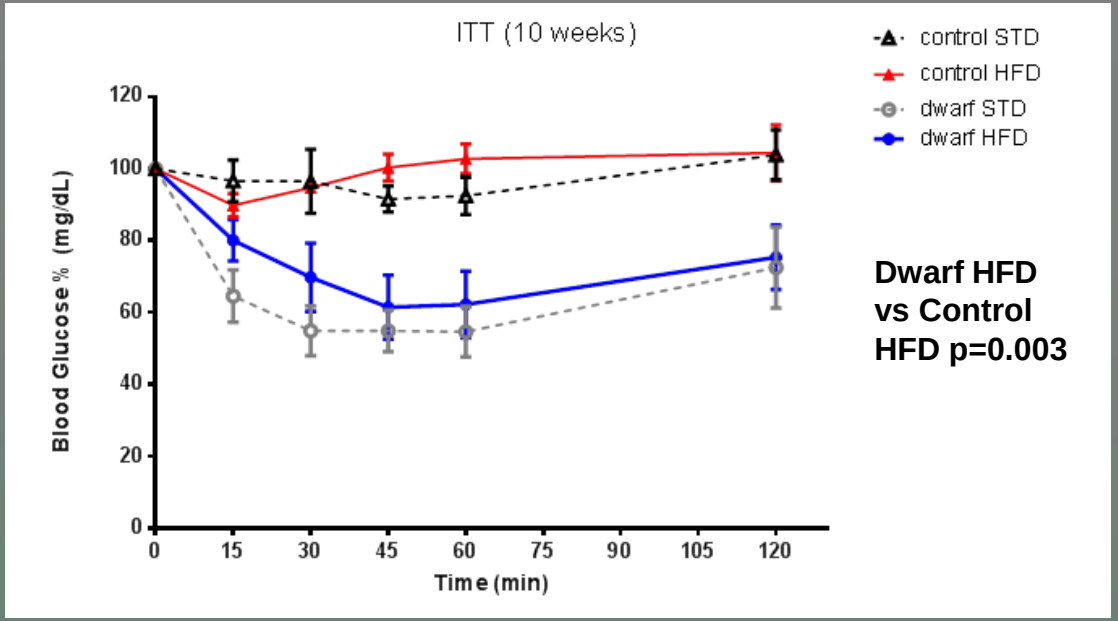


GH-resistant and GH-deficient mice challenged with a high-fat diet (HFD) remain insulin sensitive

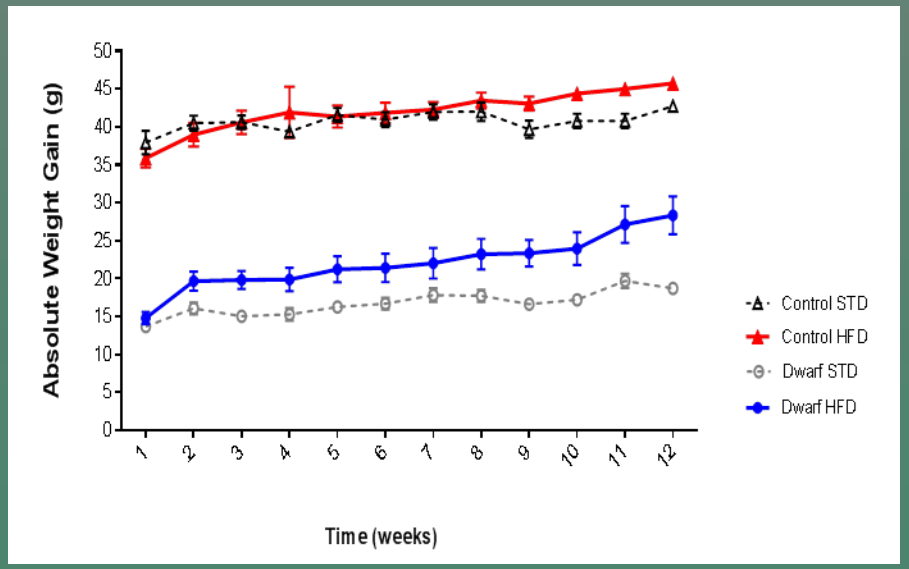
In GHR-/- mice, HFD produces further increase in obesity but no change in insulin sensitivity and little or no change in insulin levels (Berryman et al. 2005; Robertson et al. 2006).

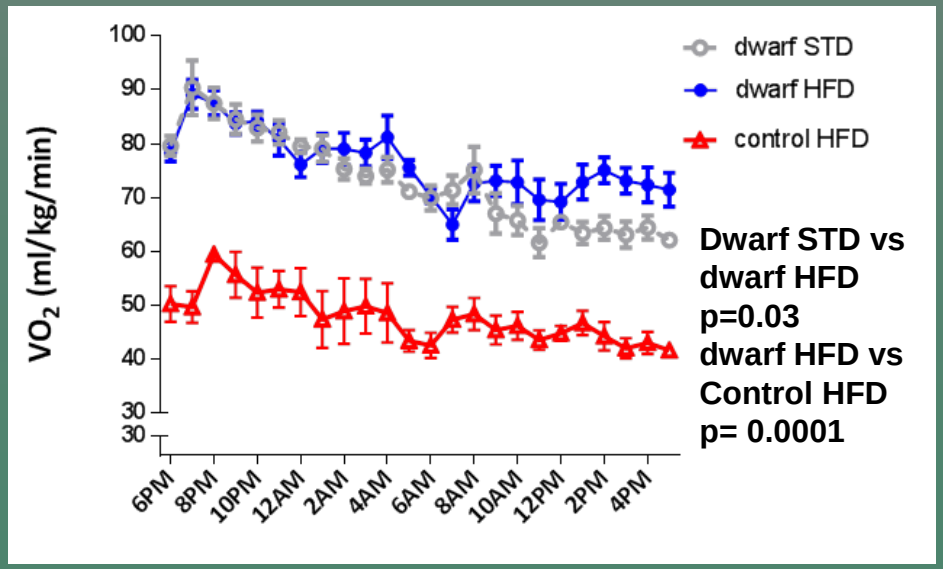
In Ames dwarf mice, HFD produces further increases in adiposity and lepin levels, but the animals remain insulin sensitive and are protected from the increase in plasma cholesterol and from suppression of locomotory activity and metabolic rate. (C. Hill, unpublished)

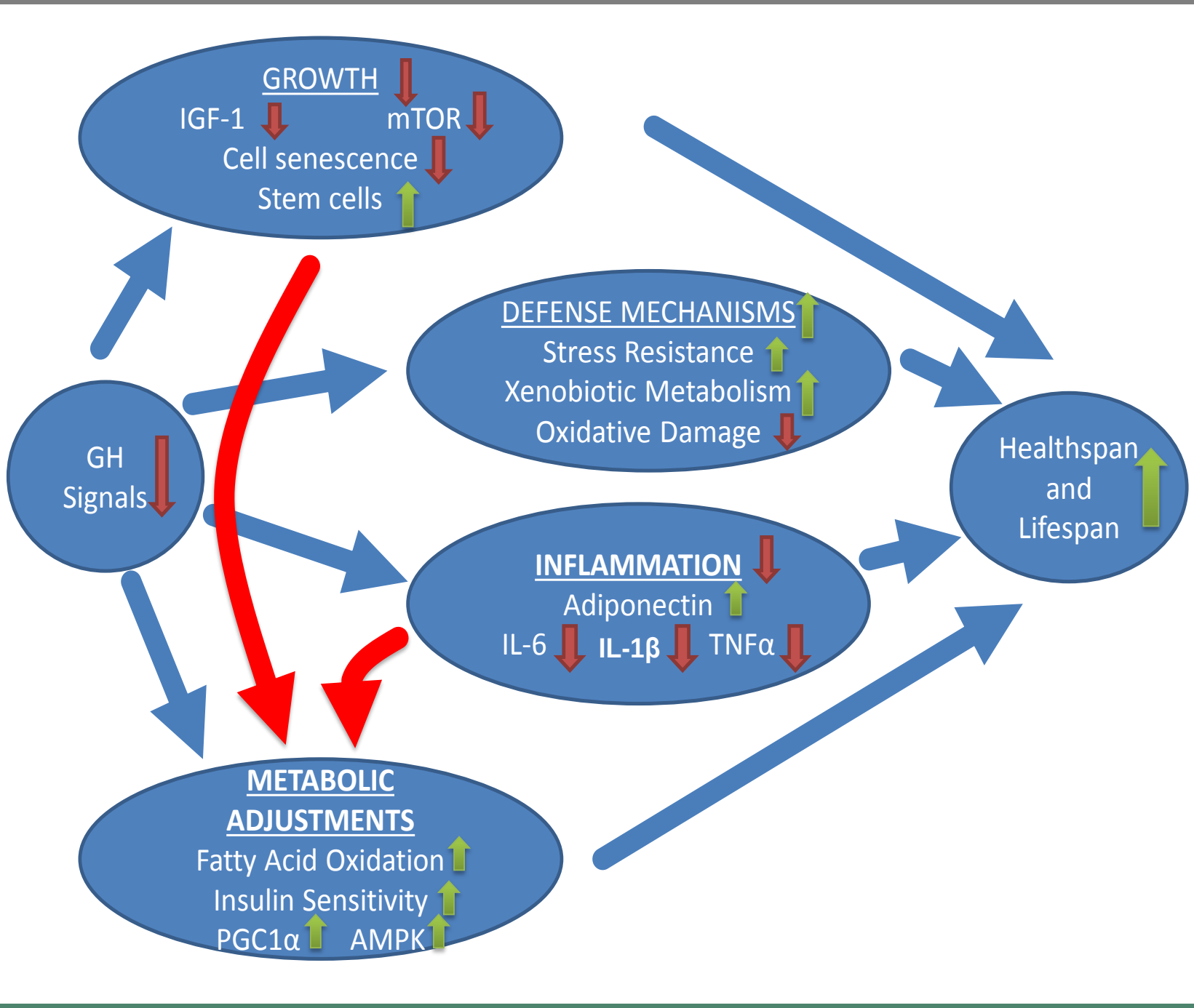
GH-deficient mice challenged with a high-fat diet (HFD) remain insulin sensitive



C. Hill, unpublished

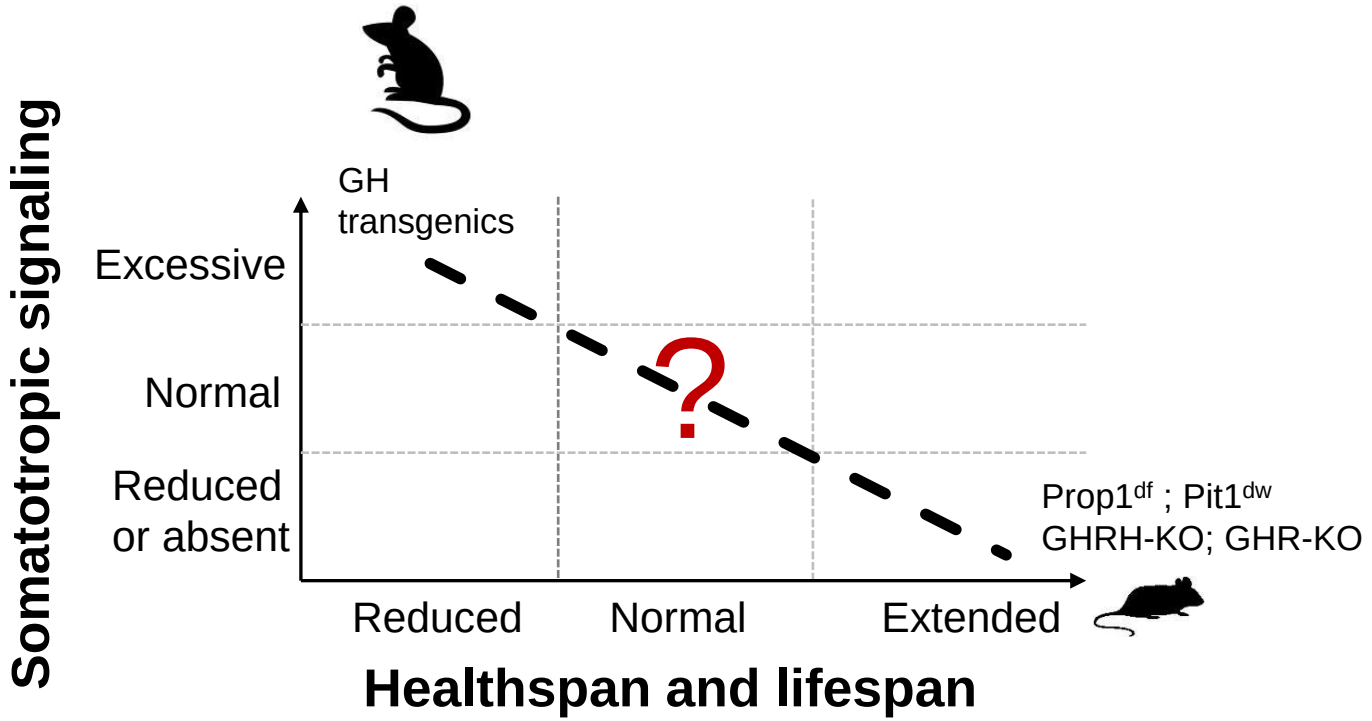




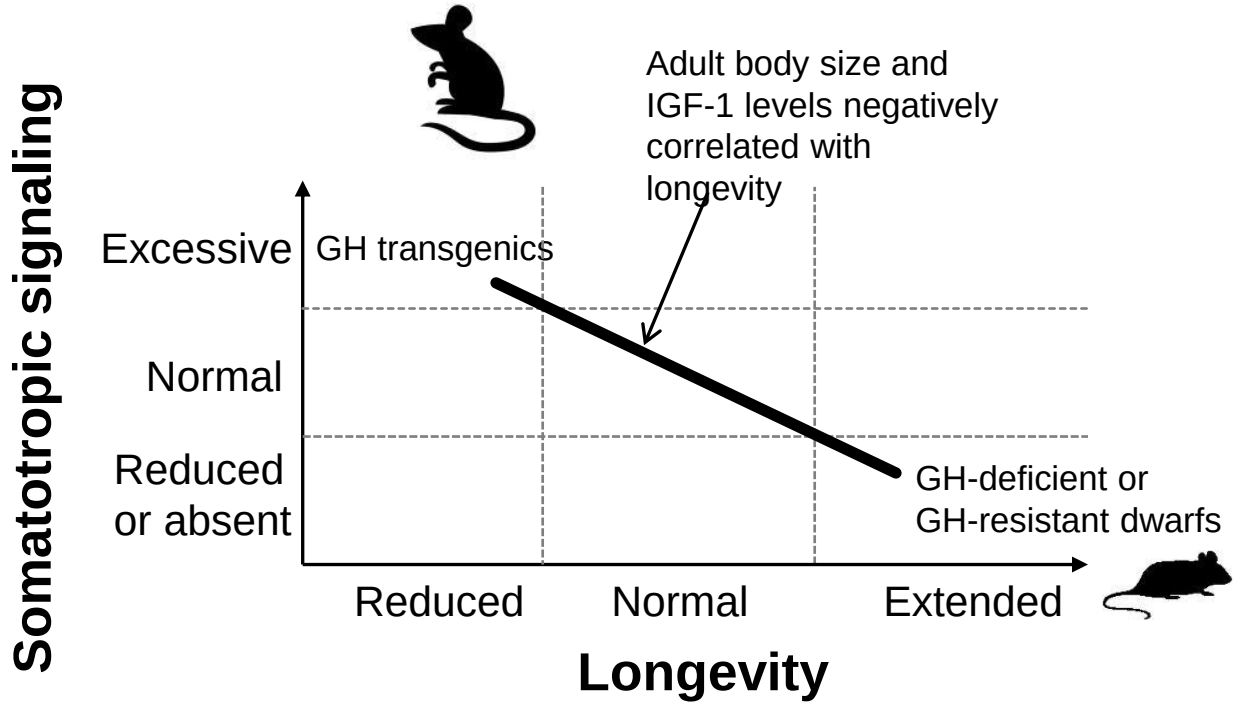

GROWTH
IGF-1
mTOR
Cell senescence
Stem cells
DEFENSE MECHANISMS
Stress Resistance
Xenobiotic Metabolism
Oxidative Damage
GH
Signals
Healthspan
and
Lifespan
INFLAMMATION
Adiponectin
IL-6
IL-1β
TNFα
METABOLIC
ADJUSTMENTS
Fatty Acid Oxidation
Insulin Sensitivity
PGC1α
AMPK

To what extent do results obtained in mutants and transgenics represent physiological relationships in genetically normal animals?

Aging and lifespan in mice with growth hormone (GH) excess, deficiency or resistance

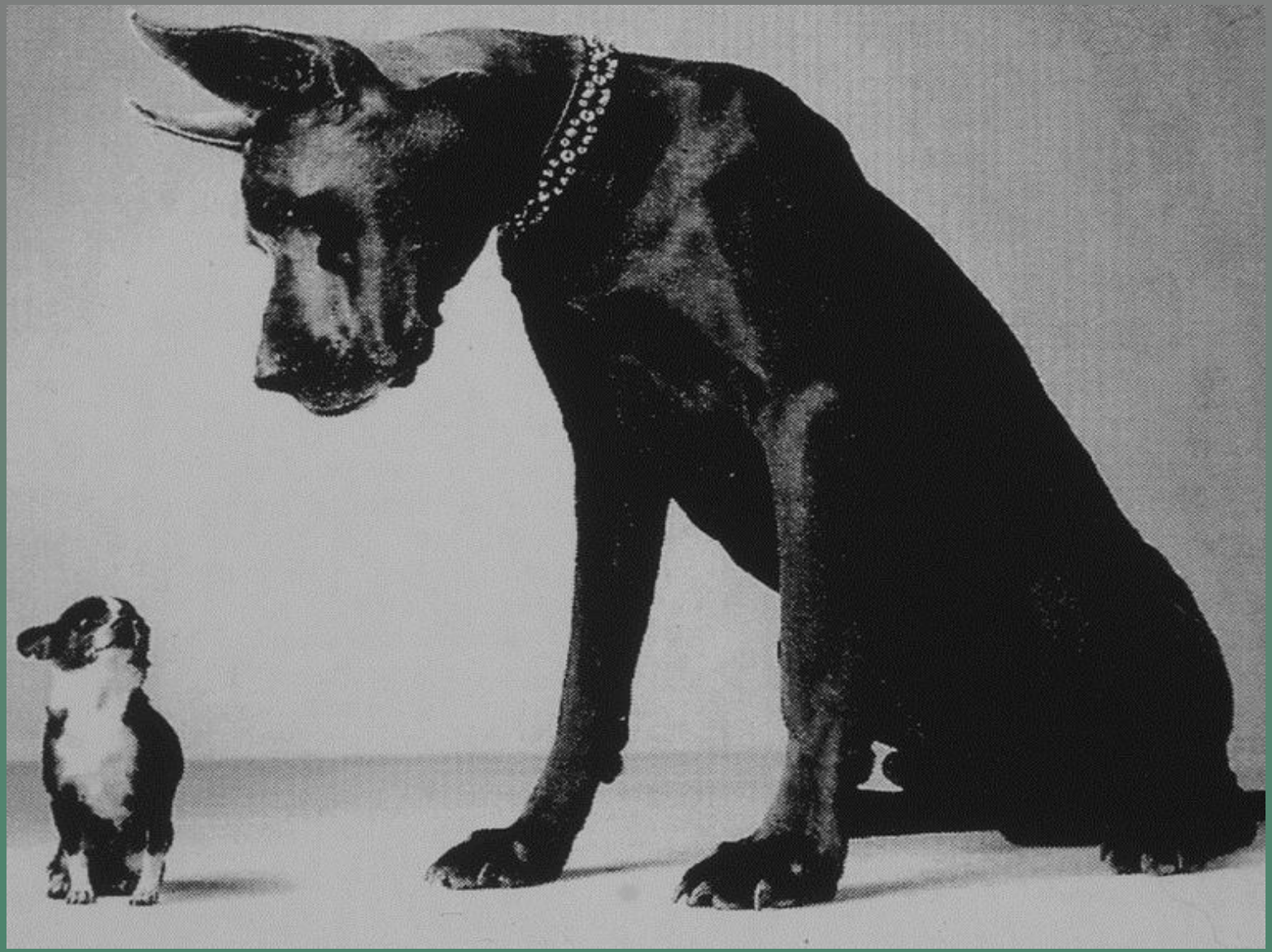


Relationship of somatotropic signaling to longevity in normal (wild type) mice



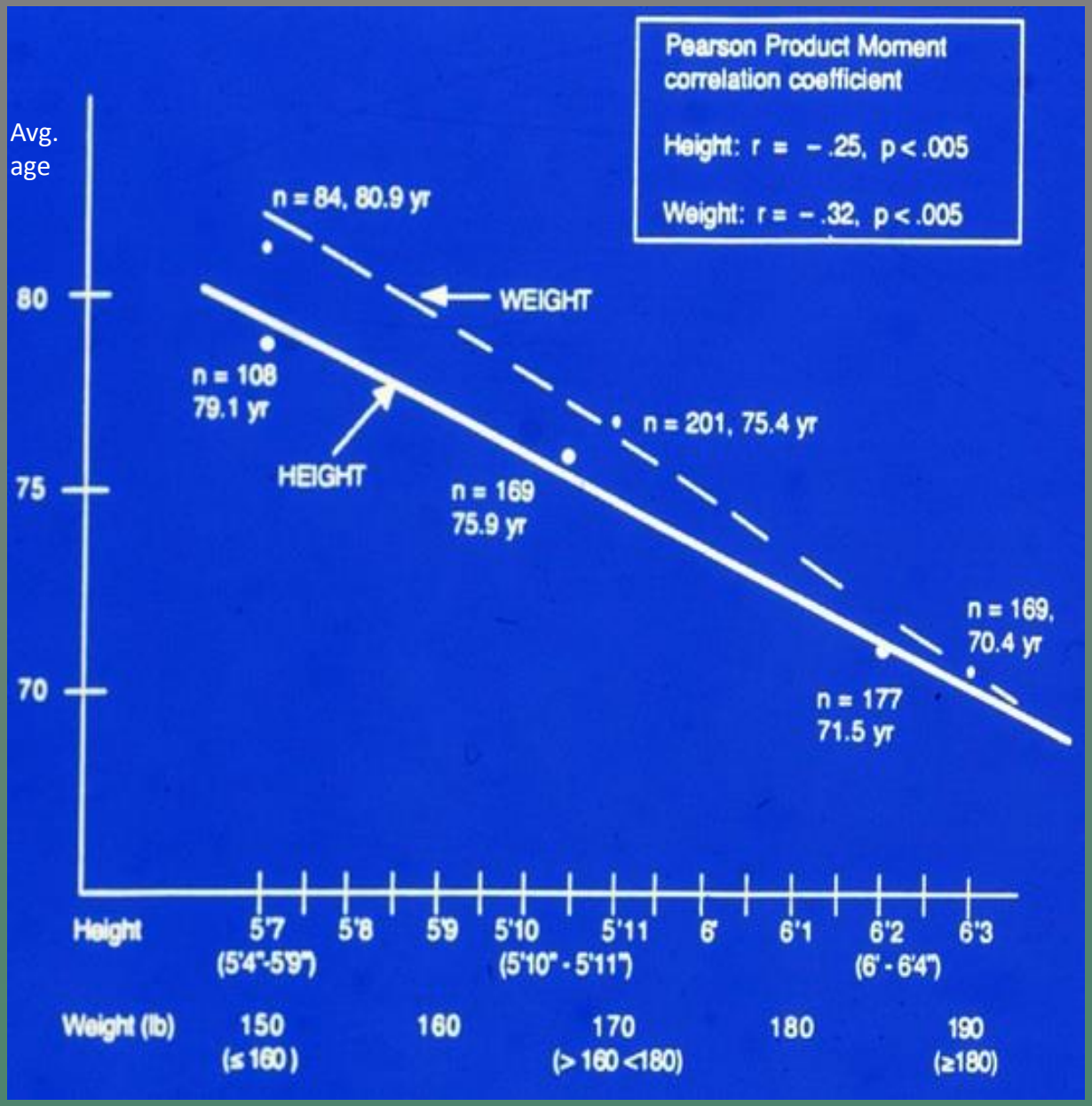
To what extent do results obtained in laboratory stocks of mice represent physiological relationships in other species?

Small dogs outlive big dogs



Shorter baseball players live longer
(T. Samaras, 2003)

Sources: Townsend letter for Doctors & Patients, October 1996, and The Baseball Encyclopedia, 9th Edition, Joseph Reichler, ed., Macmillan, NY, 1993



Shorter men live longer: Association of height with longevity and FOXO3 genotype in American men of Japanese ancestry

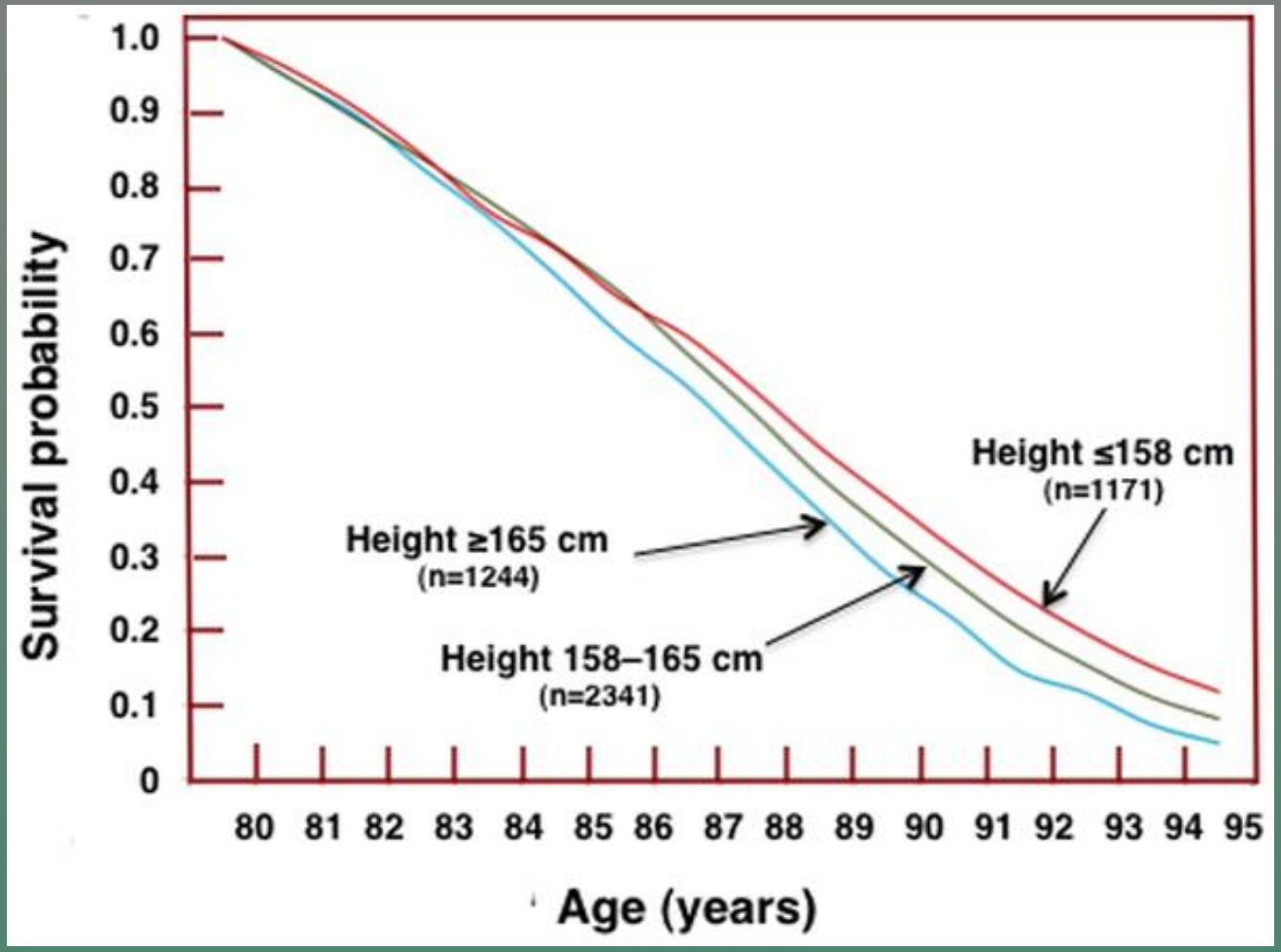
Baseline height was positively associated with all-cause mortality.

RR=1,007 (95% Cl 1,003-1,011
P=0.002

Height was also associated with FOXO3 genotype and (positively) with fasting blood insulin levels.

He Q, Morris BJ, Grove JS, Petrovitch H, et al. (2014) Shorter Men Live Longer: Association of Height with Longevity and FOXO3 Genotype in American Men of Japanese Ancestry. PLoS ONE 9(5): e94385

In American men of Japanese ancestry, height is inversely associated with longevity



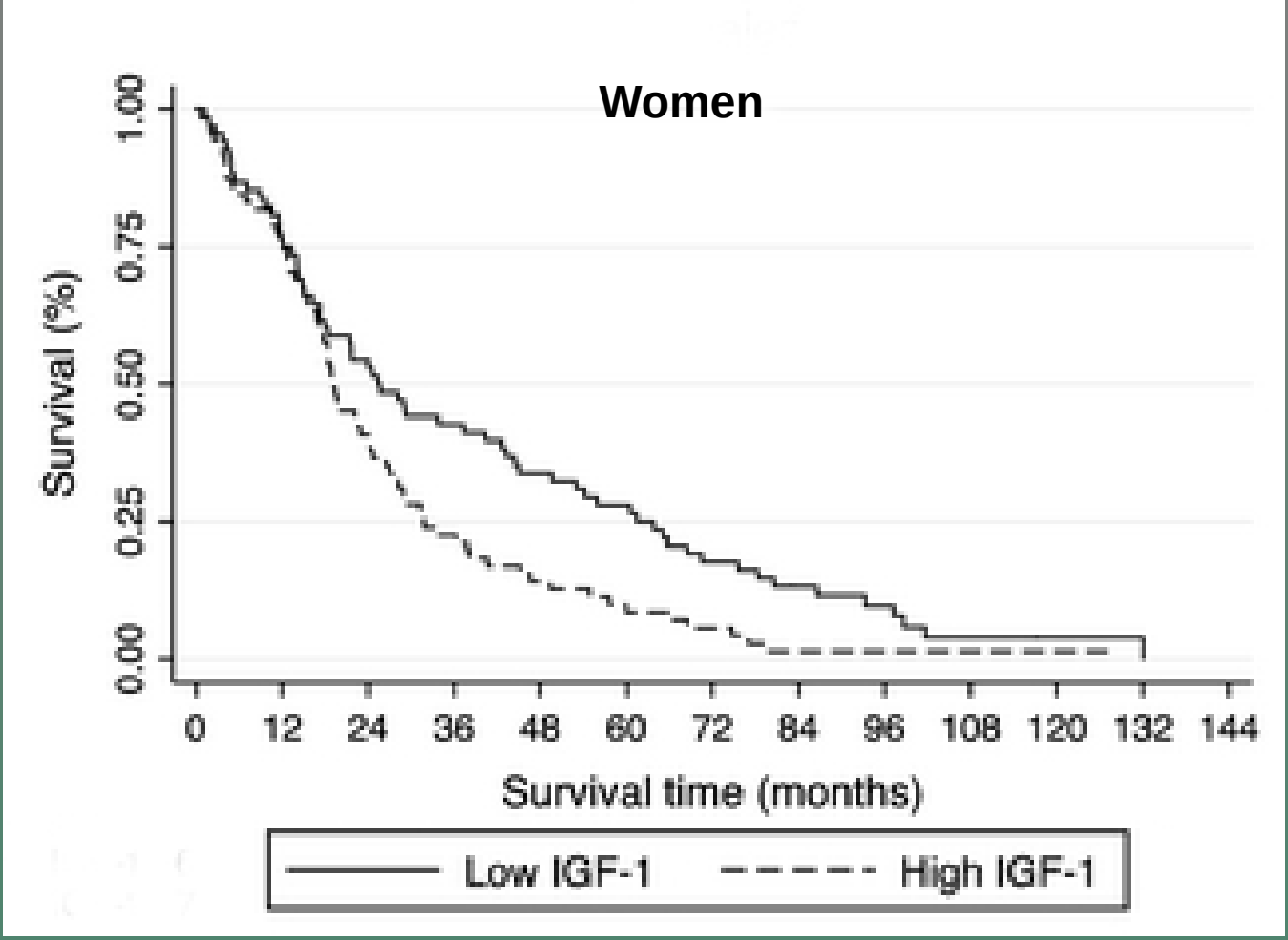
He Q, Morris BJ, Grove JS, Petrovitch H, et al. (2014) Shorter Men Live Longer: Association of Height with Longevity and FOXO3 Genotype in American Men of Japanese Ancestry. PLoS ONE 9(5): e94385.

PLOS | ONE

Single-nucleotide polymorphisms (SNPs) related to somatotropic and insulin signaling and associated with extension of human longevity

Gene	*Phenotype*	*Reference*
IGF-IR	low free plasma IGF-1	Bonafe et al., 2003
IGF-IR	IGF-1 resistance; short stature ♀	Suh et al., 2008
GH-1	short stature ♀	VanHeemst et al., 2005
AKT-1 ∗	?	Pawlikowska et al., 2009
FOXO3A ∗	?	Wilcox et al., 2008; Flachsbart et al., 2009; Pawlikowska et al., 2009; Li et al., 2009; Anselmi et al., 2009
∗ Consistent in three unrelated cohorts ♀ In women only		

Low insulin-like growth factor-1 level predicts survival in humans with exceptional longevity



Milman S, Atzmon G, Huffman DM, Wan J, Crandall JP, Cohen P, Barzilai N. Aging Cell, 2014 Aug;13(4):769-71

Impact of growth hormone (GH) resistance on the incidence of diabetes and cancer

	Individuals with GH receptor deficiency	Unaffected relatives	General population in Ecuador
Incidence of diabetes	0%	6% of all disease	5%
Death from diabetes	0%	5%	Similar to values in unaffected relatives
Incidence of cancer	1 of 99	17% of all disease	
Death from cancer	0%	20%	

Based on data from 152 GHR-deficient subjects and 1606 unaffected relatives; Guavara-Aguirre et al., 2011

Insulin signaling and human longevity

(results from Leiden Longevity Study; diabetics excluded)

In comparison to their partners, middle-aged offspring of nonagenarian siblings had the following characteristics:

- Lower fasted and non-fasted glucose;
- Lower fasted insulin;
- Higher HOMA score;
- Improved glucose tolerance;
- Higher insulin-mediated glucose disposal rate during hyperinsulinemic-euglycemic clamp.

Rozing et al., 2009, 2010; Wijsman et al., 2011

Questions we are now addressing

- Role of systemic and hypothalamic inflammation in mediating the effects of GH on insulin signaling and aging;

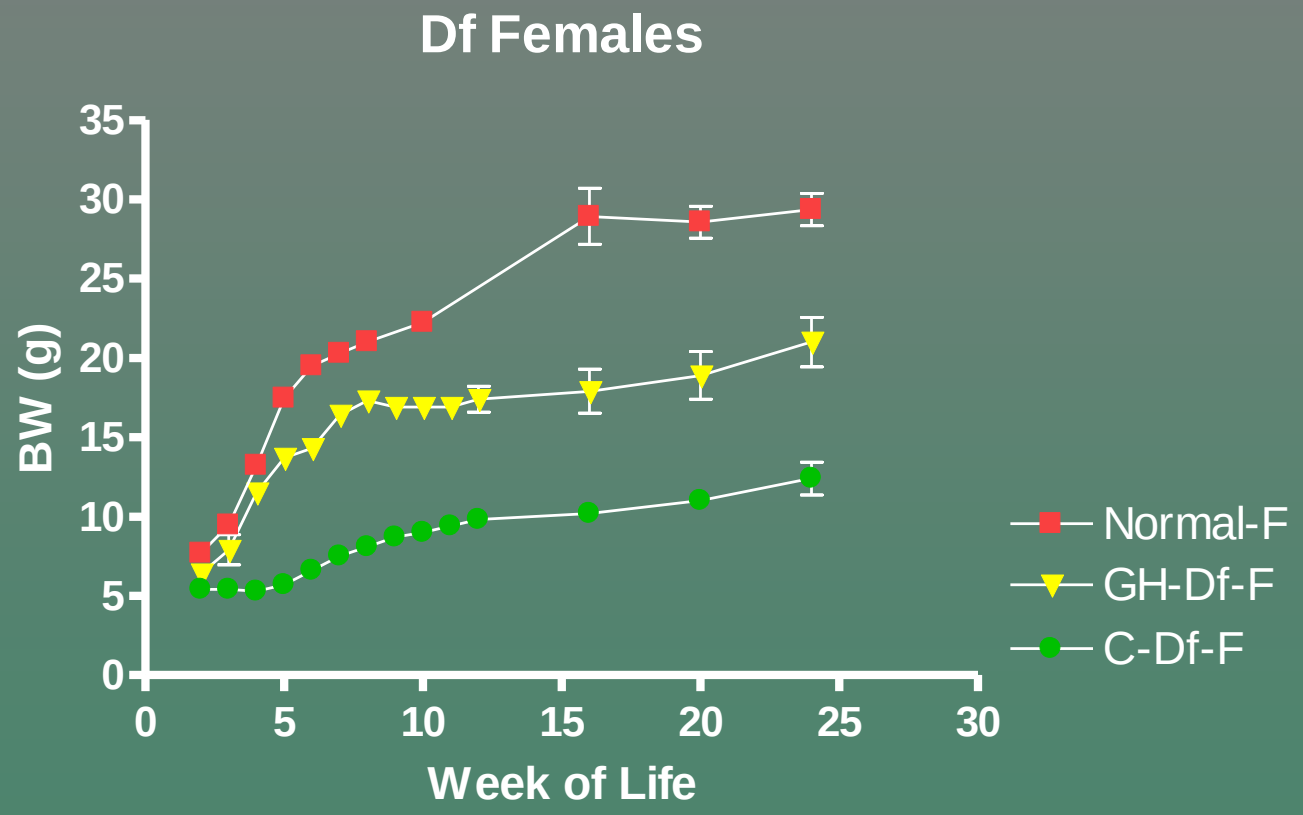
- Role of thermogenesis in inducing metabolic adaptations that promote healthy aging;

- Role of GH signaling during development in the control of aging and longevity.

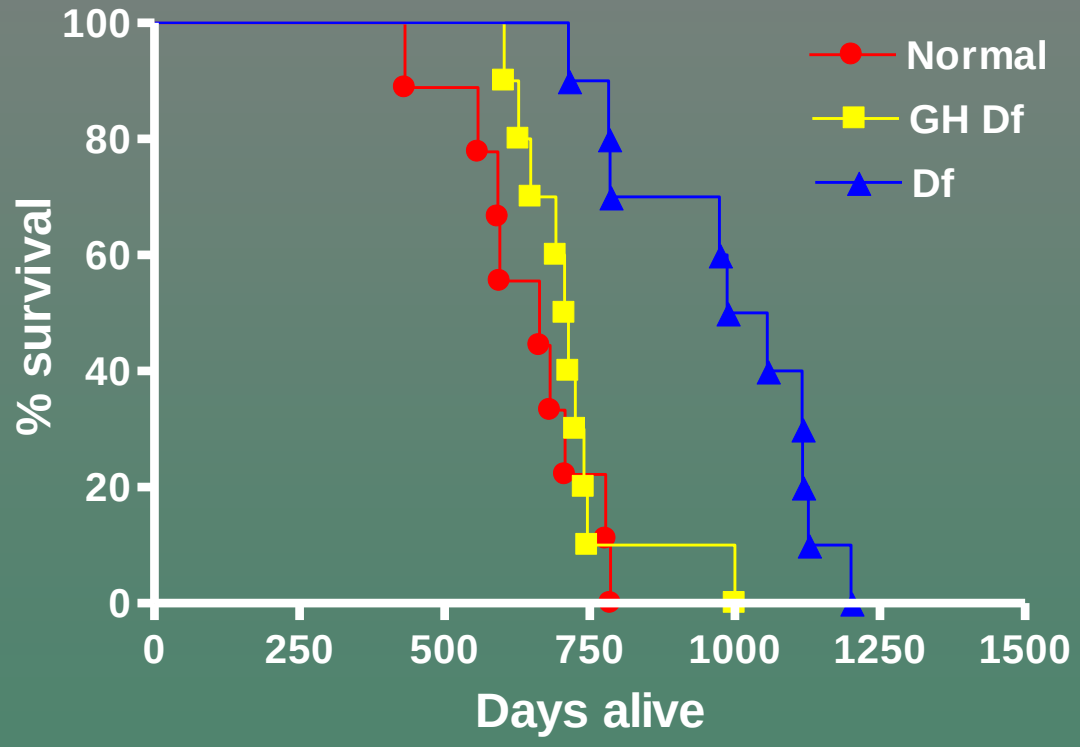
Ames dwarf mice

GH treatment of juvenile female dwarf mice leads to permanent changes in body weight

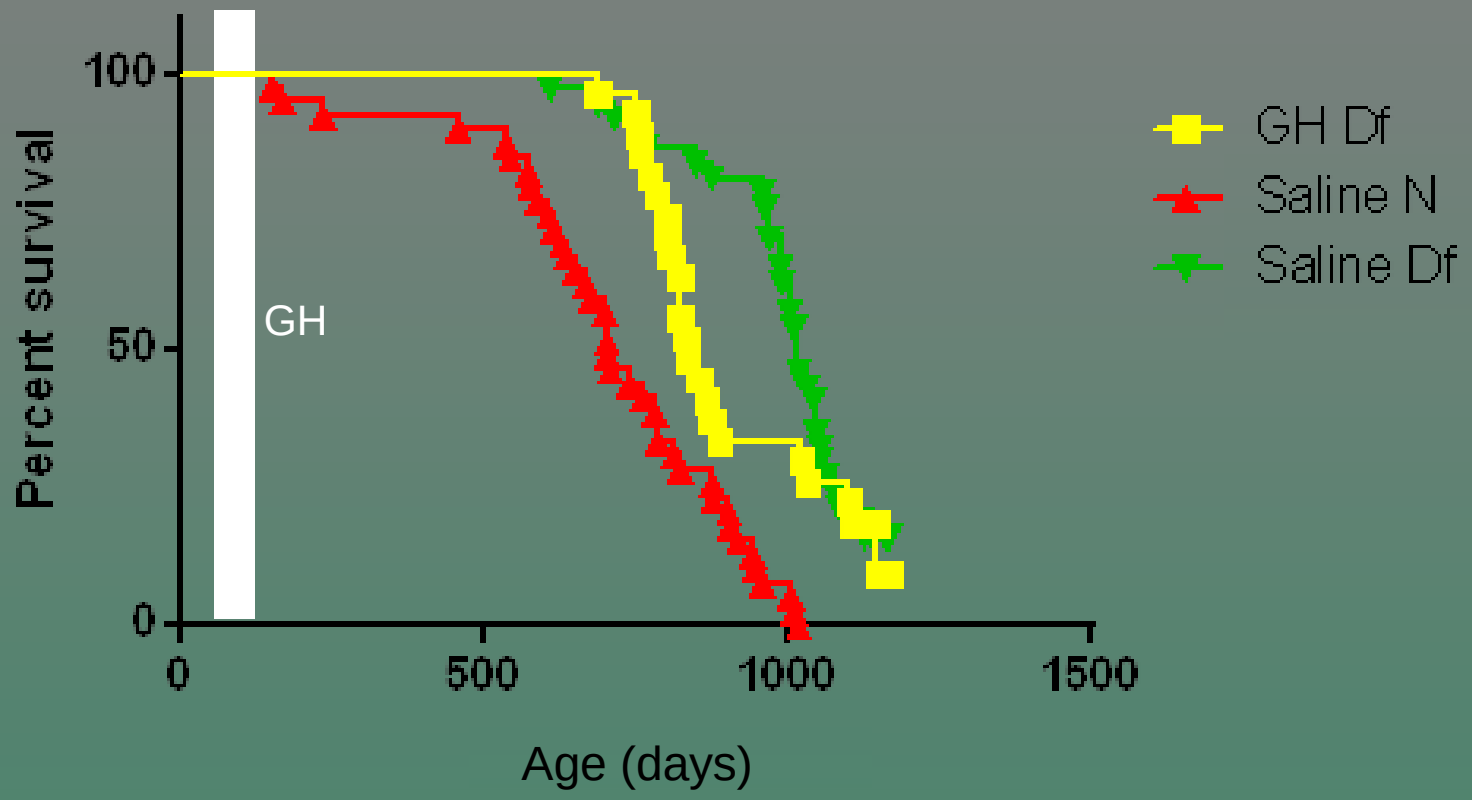
(bGH injections [twice daily] weeks 2 – 8)



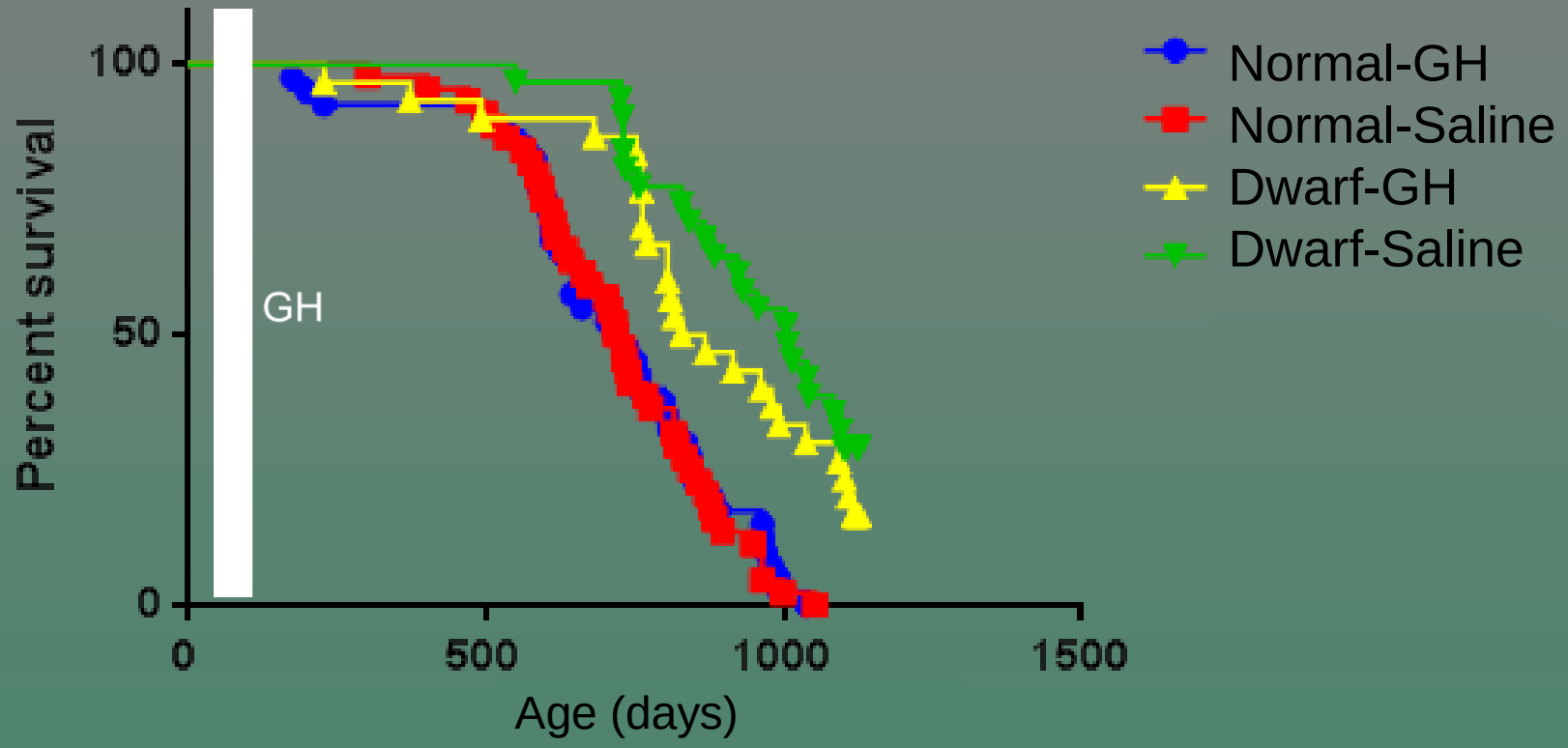
GH replacement therapy reduces longevity of Ames dwarf mice



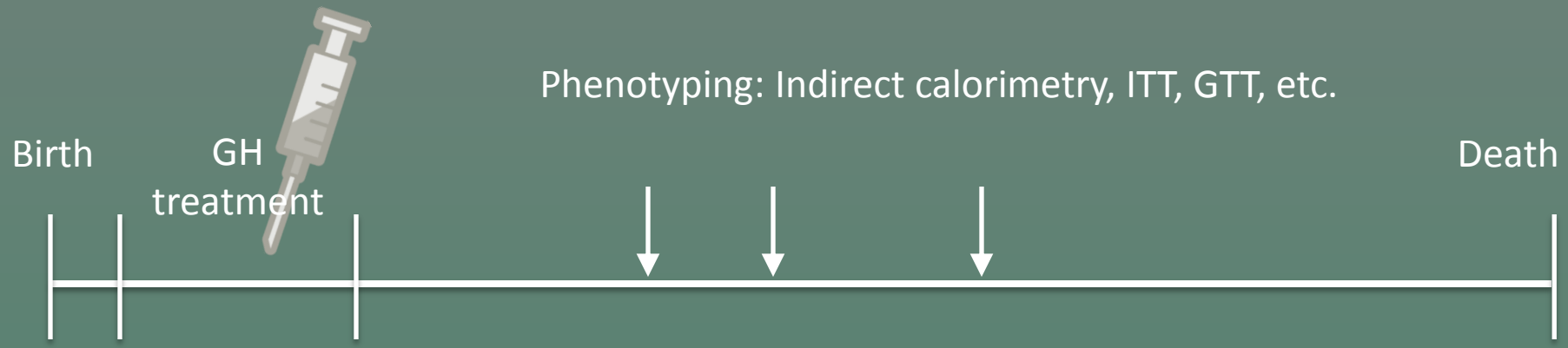
Treatment with GH between 2 and 8 weeks of age reduces longevity of Ames dwarf mice



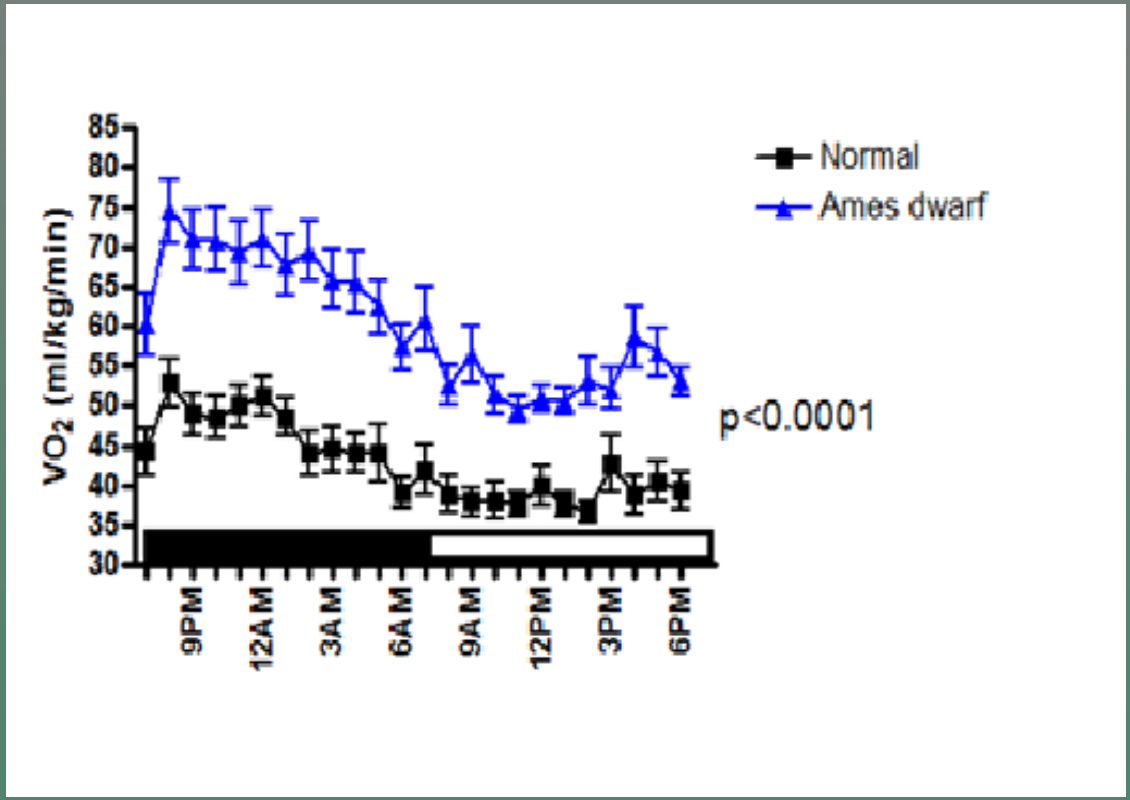
Treatment with GH between 1 and 7 weeks of age reduces longevity of Ames dwarf mice but not normal mice



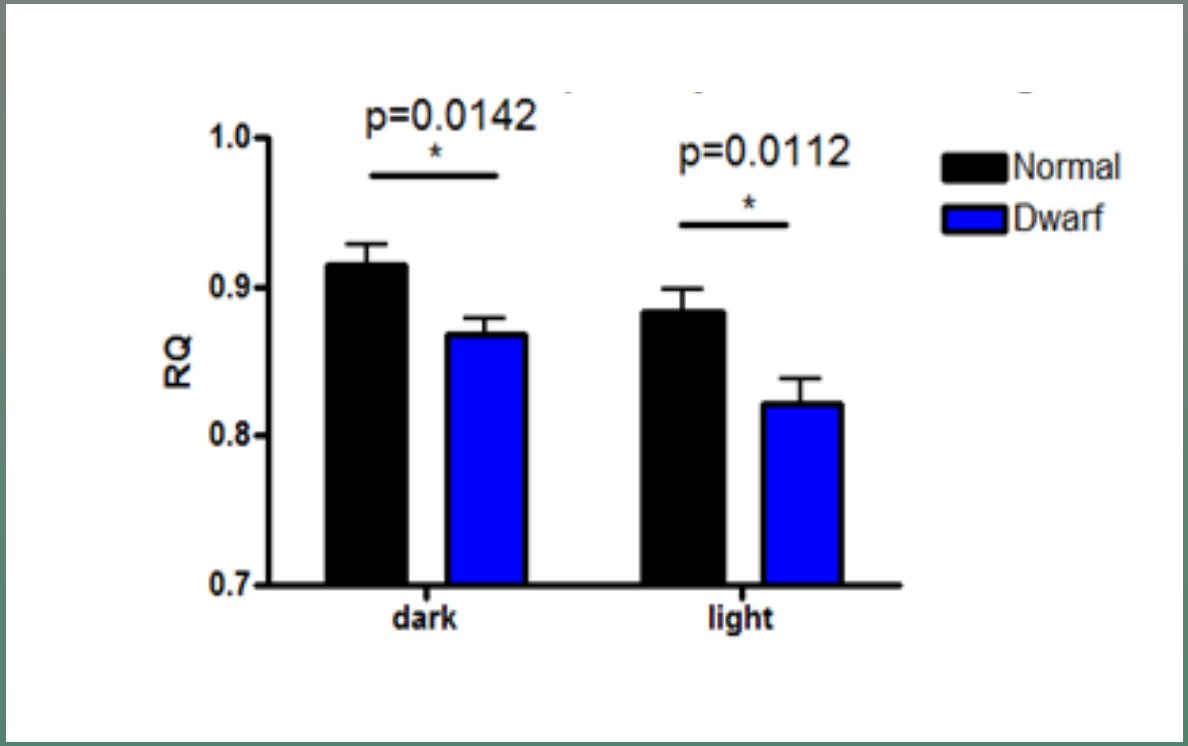
Study design of GH replacement therapy's early life impact on aging and longevity



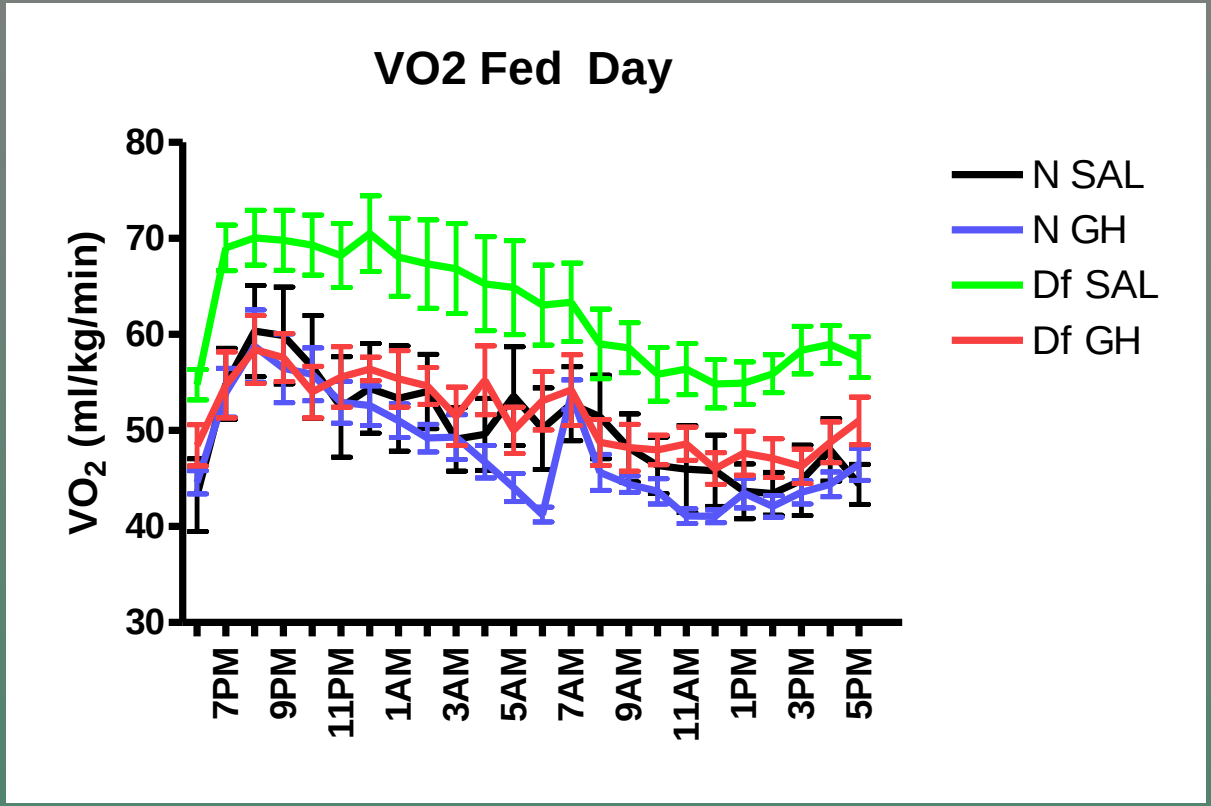
Oxygen consumption per gram body weight is increased in Ames dwarf mice



Respiratory quotient is reduced in Ames dwarf mice

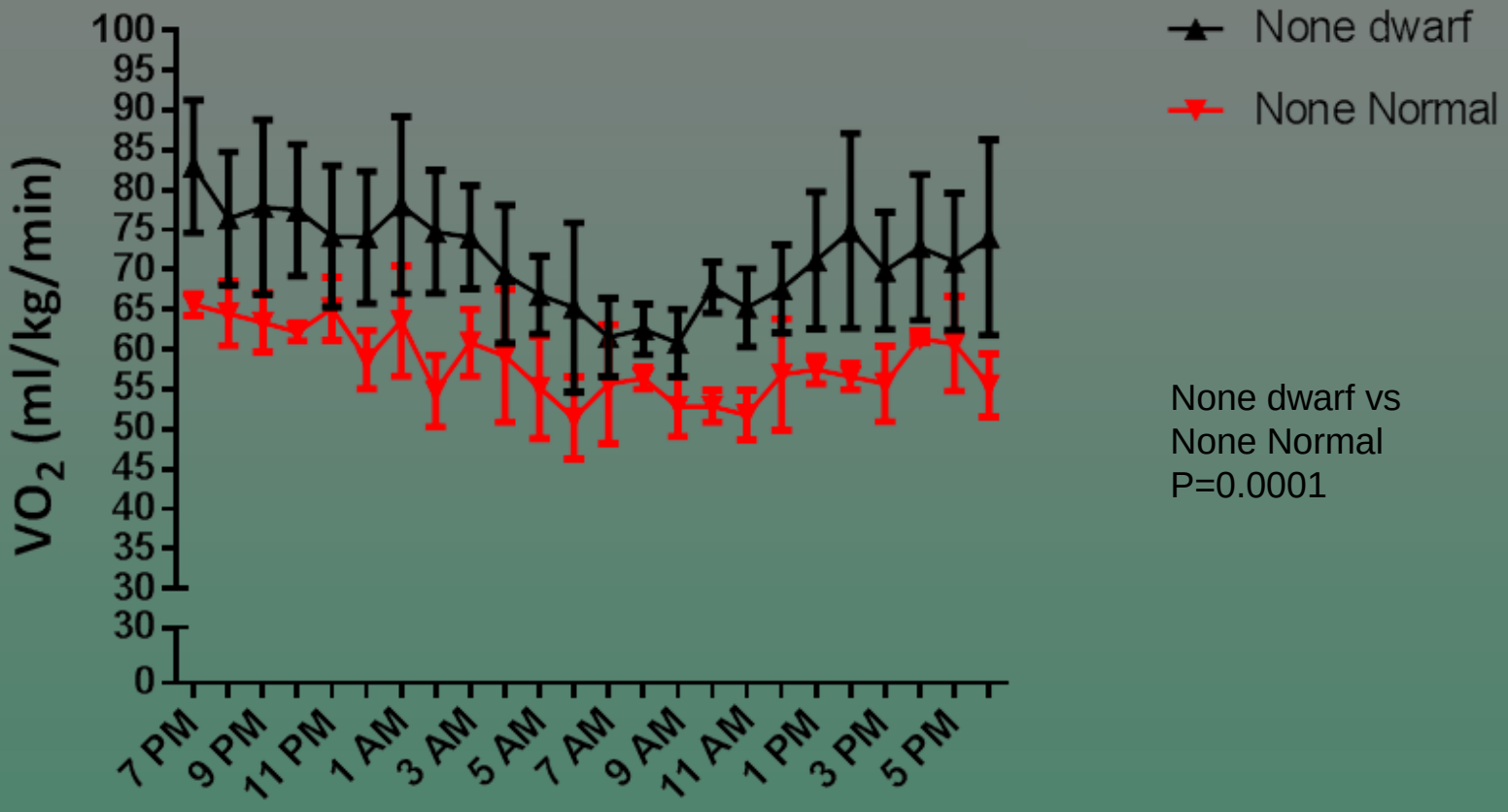


Growth hormone (GH) treatment early in life (weeks 2-8) normalizes oxygen consumption (VO_2) of Ames dwarf mice measured 7 months later



N SAL vs Df SAL p=0.003
Df SAL vs Df GH p =0.007

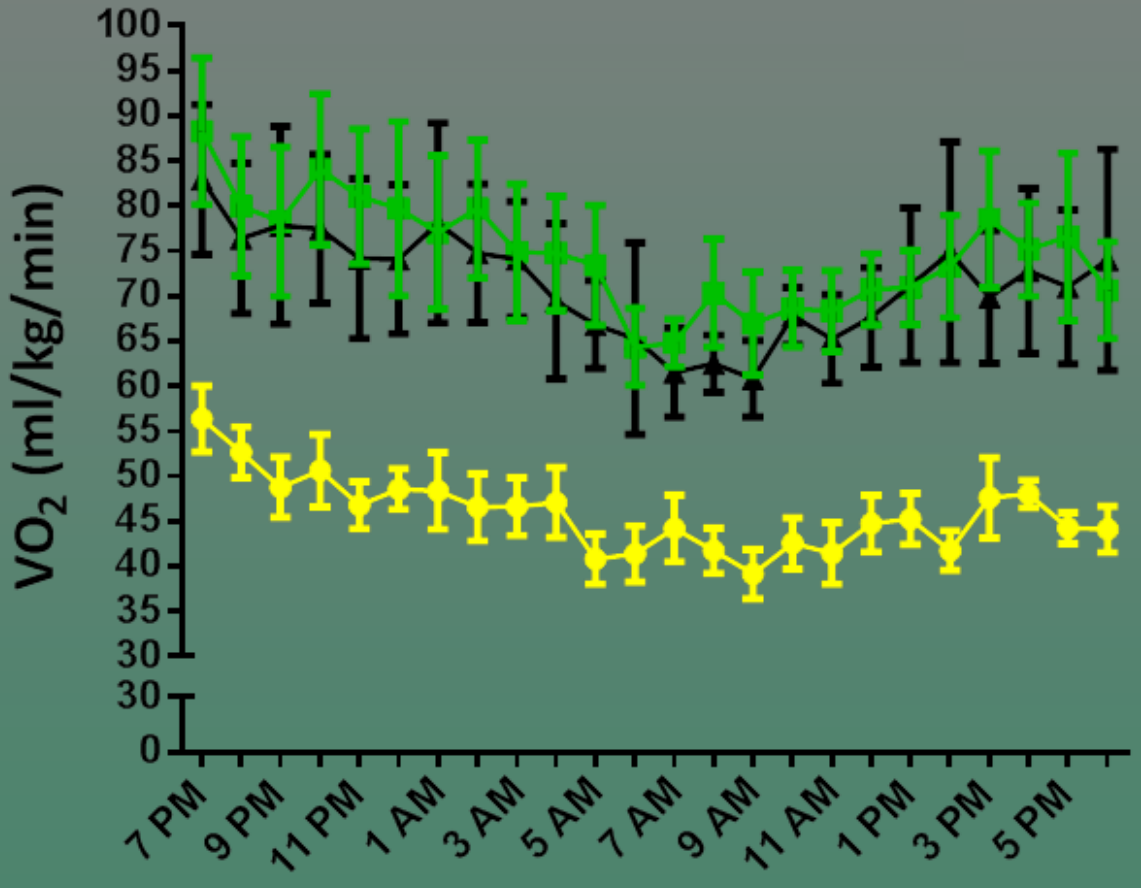
Oxygen consumption is increased in Ames dwarf mice



None dwarf vs
None Normal
P=0.0001

C. Hill, unpublished

Growth hormone treatment of juvenile Ames dwarf mice reduces adult oxygen consumption

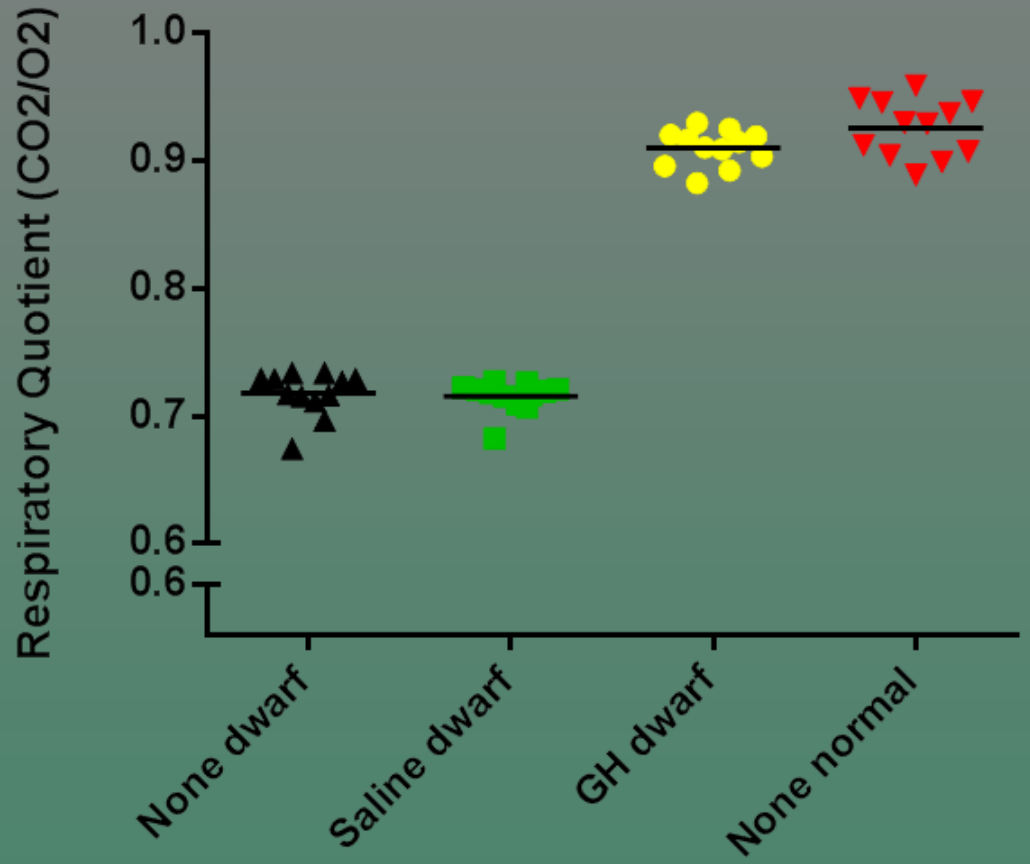


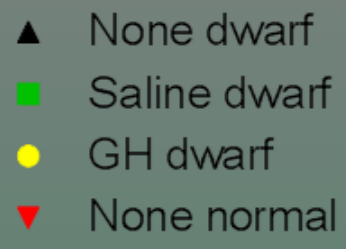
Saline dwarf vs None dwarf P=0.056

Saline dwarf vs GH dwarf P=0.0001

C. Hill, unpublished

Growth hormone treatment of juvenile Ames dwarf mice increases adult respiratory quotient



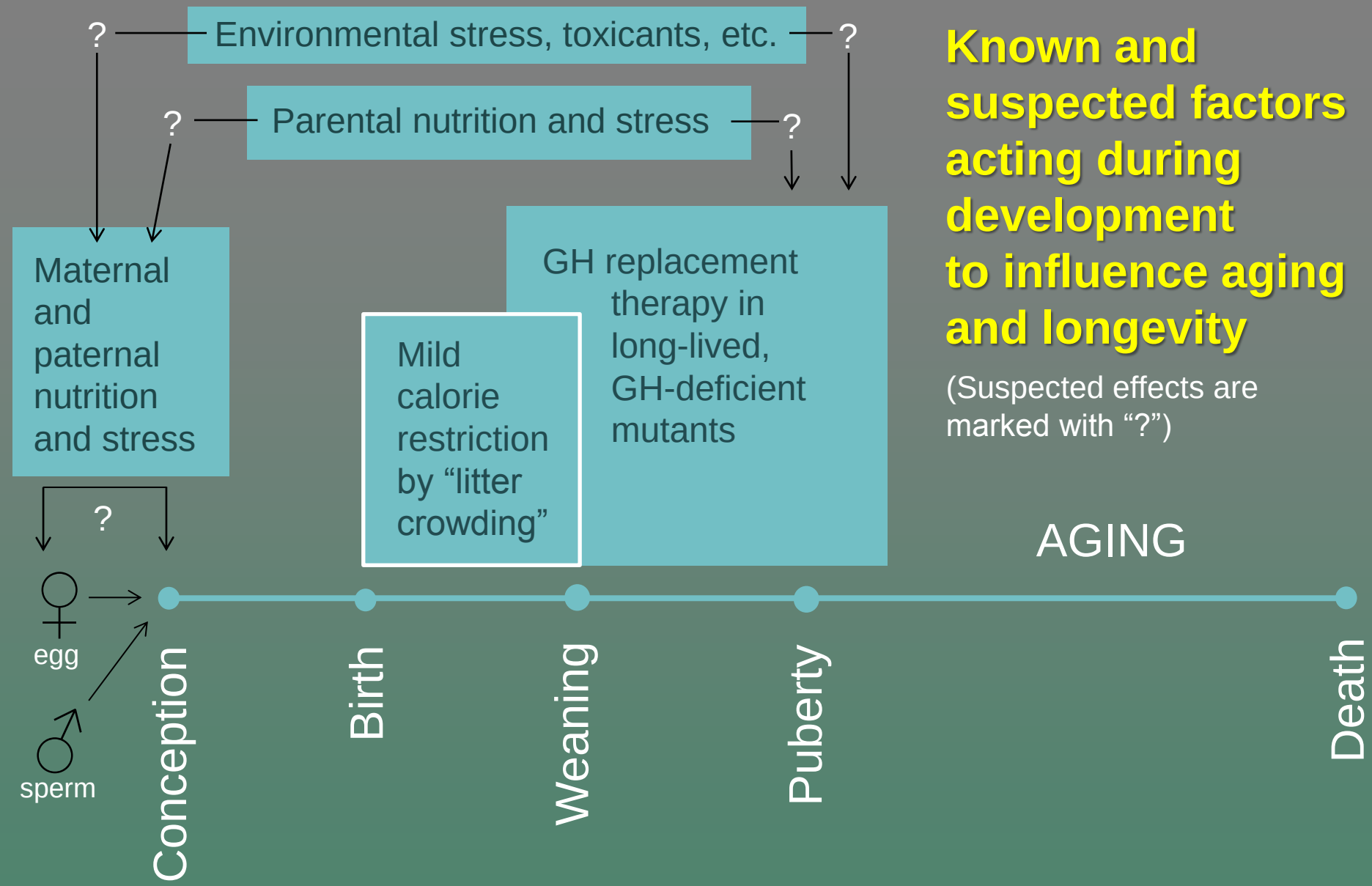


Saline dwarf vs None dwarf NS, P=0.6928

Saline dwarf vs GH dwarf P= 0.0001

GH dwarf vs None Normal NS, P=0.0541

C. Hill, unpublished



Known and suspected factors acting during development to influence aging and longevity

(Suspected effects are marked with "?")

Support: NIA, Illinois CFAR, the Ellison Medical Foundation and the Glenn Foundation

SIU: Khalid Al-Regaiey, Oge Arum, Michael S. Bonkowski, Holly Brown-Borg, Kurt Borg, Varadaraj Chandrashekar, Steven Hauck, Cristal Hill, William Hunter, Beth Kinney, Michal Masternak, Julie Mattison, Charles Meliska, Jacob Panici, Juliana Rocha, Liou Sun, Peggy Wang, Reyhan Westbrook, Chris Wright, Denise Zaczek

UNIVERSITY OF MICHIGAN:
Richard Miller, Jim Harper

OHIO UNIVERSITY:
John Kopchick, Darlene Berryman, Ed List

UNIVERSITY OF TEXAS:
Yuji Ikeno, Dave Sharp

UNIVERSITY OF BUENOS AIRES:
Daniel Turyn, Fernando Dominici, Johanna Miquet

MAYO CLINIC:
Jim Kirkland, Tamar Tchkonia, Tamara Pirtskhalava

THANK YOU