Growth Hormone and Aging: Benefits of Endocrine Defects

Andrzej Bartke

Southern Illinois University School of Medicine

Springfield, Illinois USA

Our studies of giant transgenic mice over-expressing growth hormone

The animals:

Various lines expressing human or bovine GH under control of metallothionien-1 or PEPCK promoters (produced in the laboratory of Dr. Thomas Wagner).

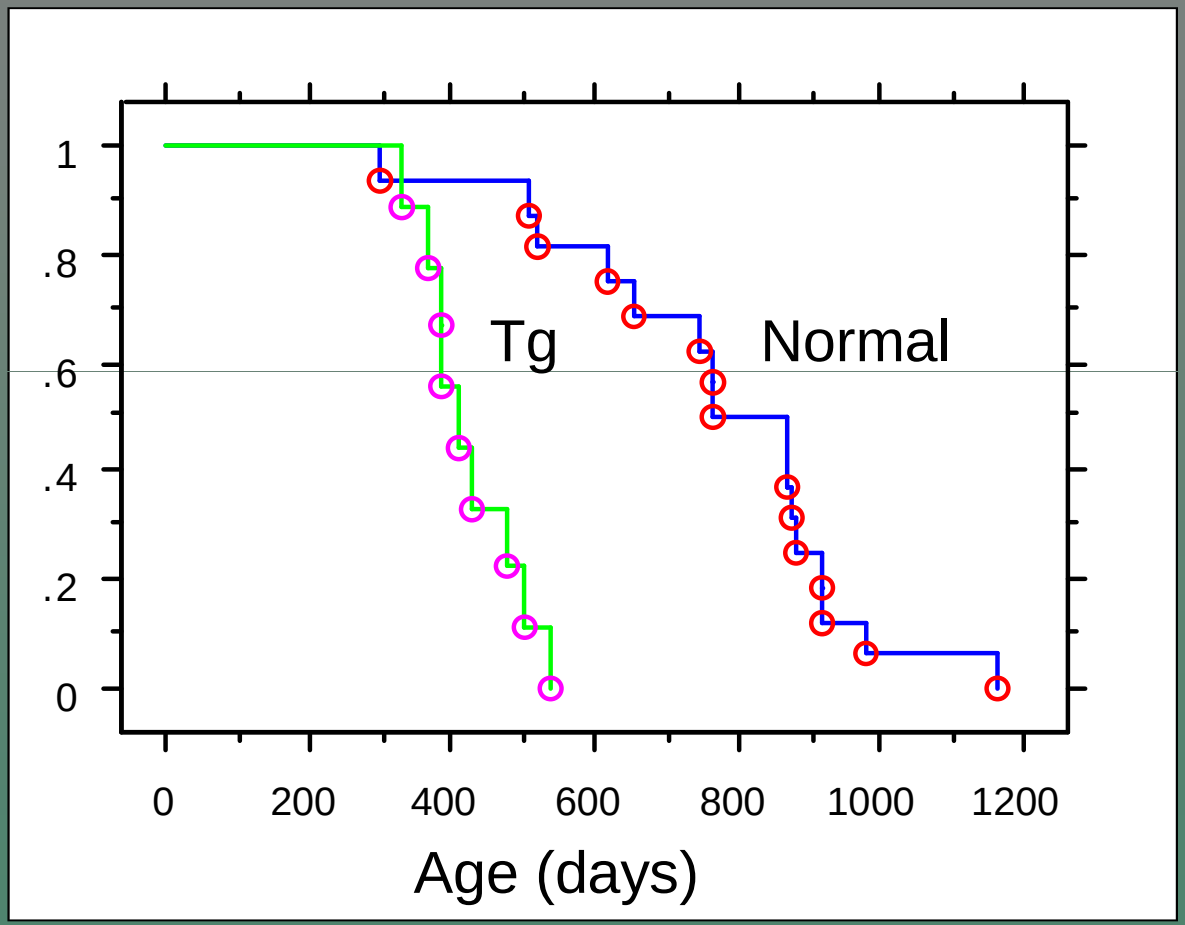
Their characteristics:

- Increased plasma levels of GH and IGF-1
- Increased growth, adult body size and percent of lean body mass
- Various reproductive deficits, particularly in females

Our objective:

To identify mechanisms of reduced fertility

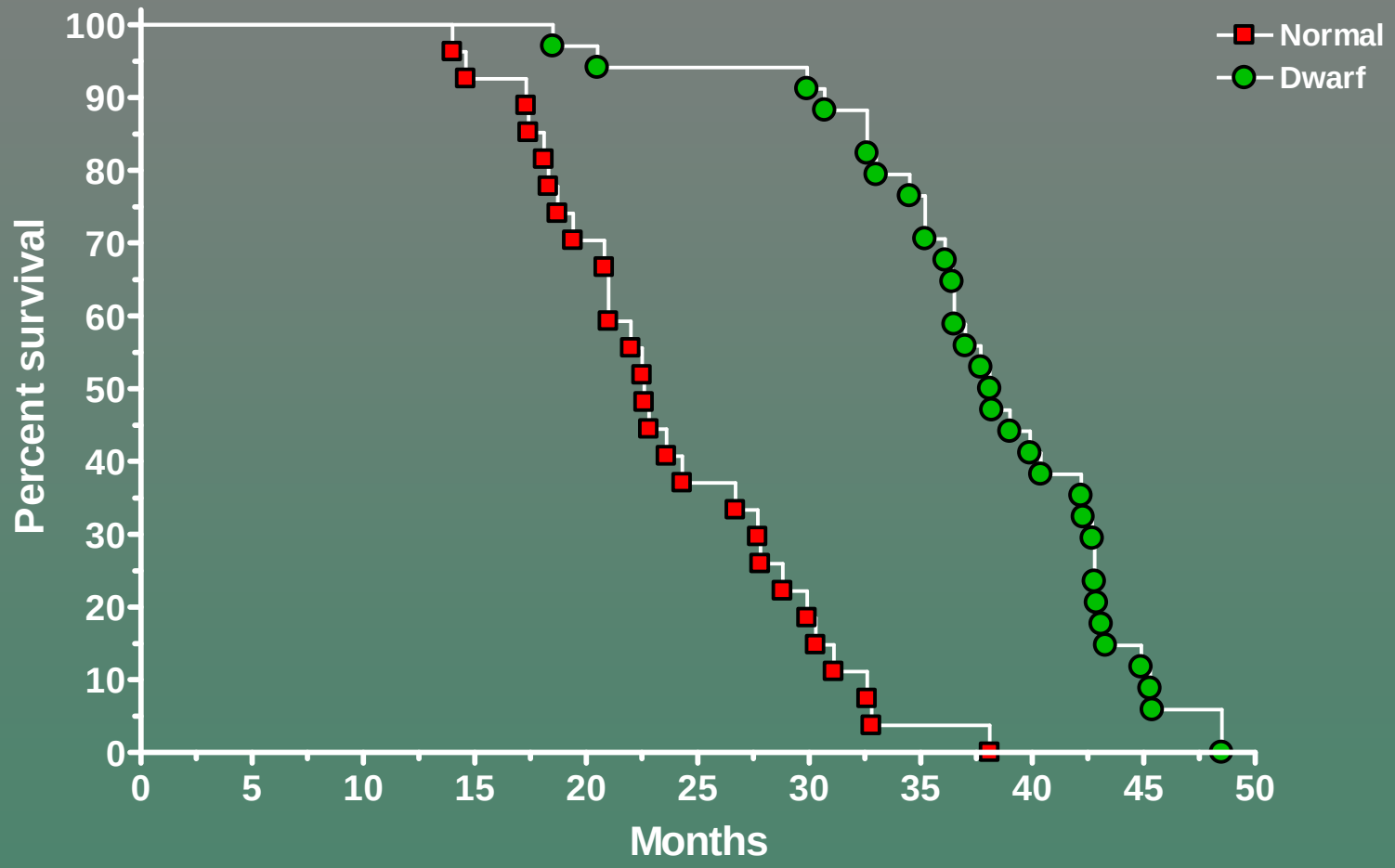
Survival plots of growth hormone transgenic (Tg) and normal male mice



Symptoms of premature aging in GH transgenic mice

- Scoliosis and weight loss
- Reduced replicative potential of fibroblasts in vitro
- Early decline of cognitive function
- Early decline of turnover rate of hypothalamic neurotransmitters, norepinephrine, and dopamine
- Advanced age-related glial activation in several brain regions
- Early loss of reproductive competence
- Early onset of age-related disease

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



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

Endocrine characteristics of adult Ames dwarf mice

	Normal	Dwarf
Body weight (g)	38.5 ±1.8	12.9 ±0.6*
Plasma GH (ng/ml)	15.7 ±7.2	ND
Plasma IGF-1 (ng/ml)	165 ±10	ND
Plasma insulin (IU/ml)	78 ±11	46 ±3*
Plasma glucose (mg/ml)	1.58 ±0.09	1.06 ±0.08*

GHR/GHBP-KO (-/-) mice

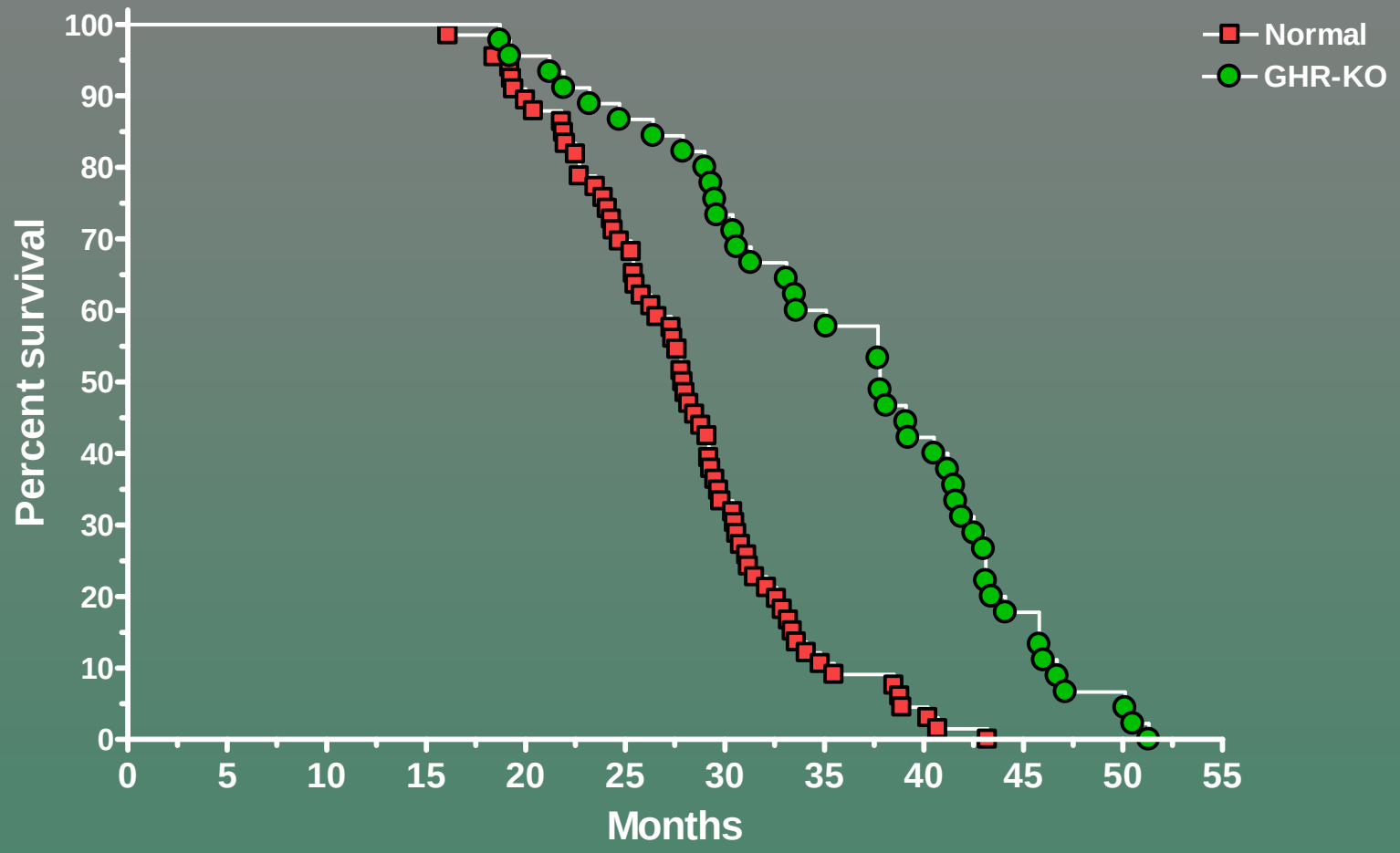
Phenotypic characteristics:

- severely reduced IGF-I levels
- reduced growth and adult body size
- delayed puberty
- reduced fertility
- reduced plasma insulin with reduced or normal glucose

Percent increase in mean lifespan:

40-55% (Coschigano et al., 2000)

Survival plot for GHR-KO mice

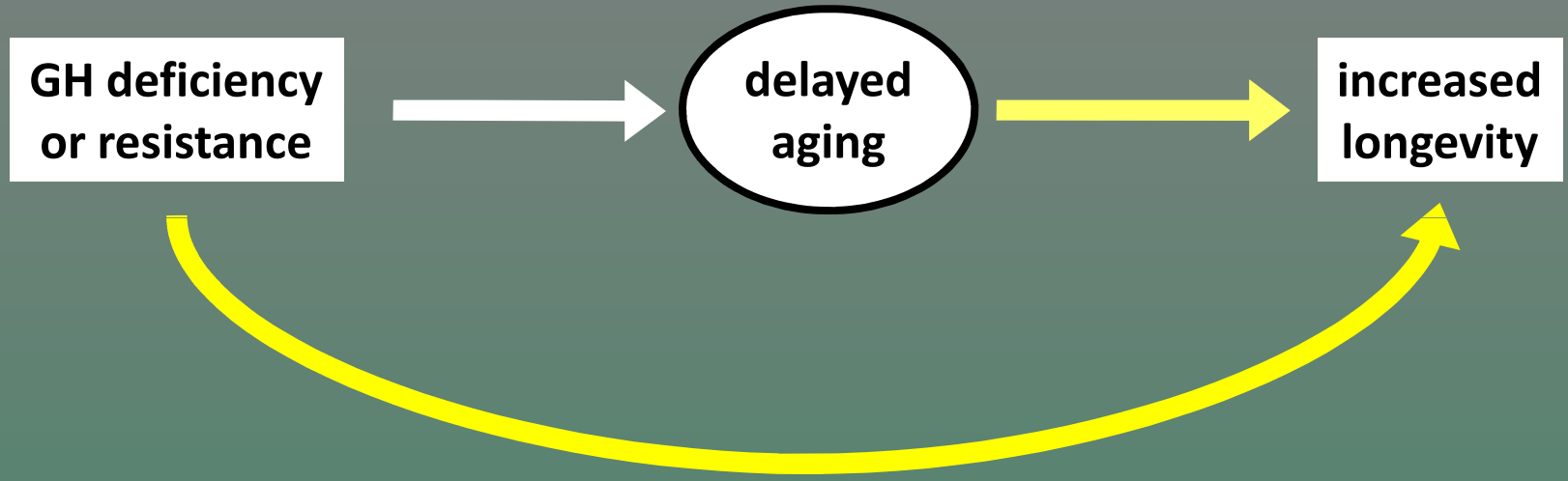


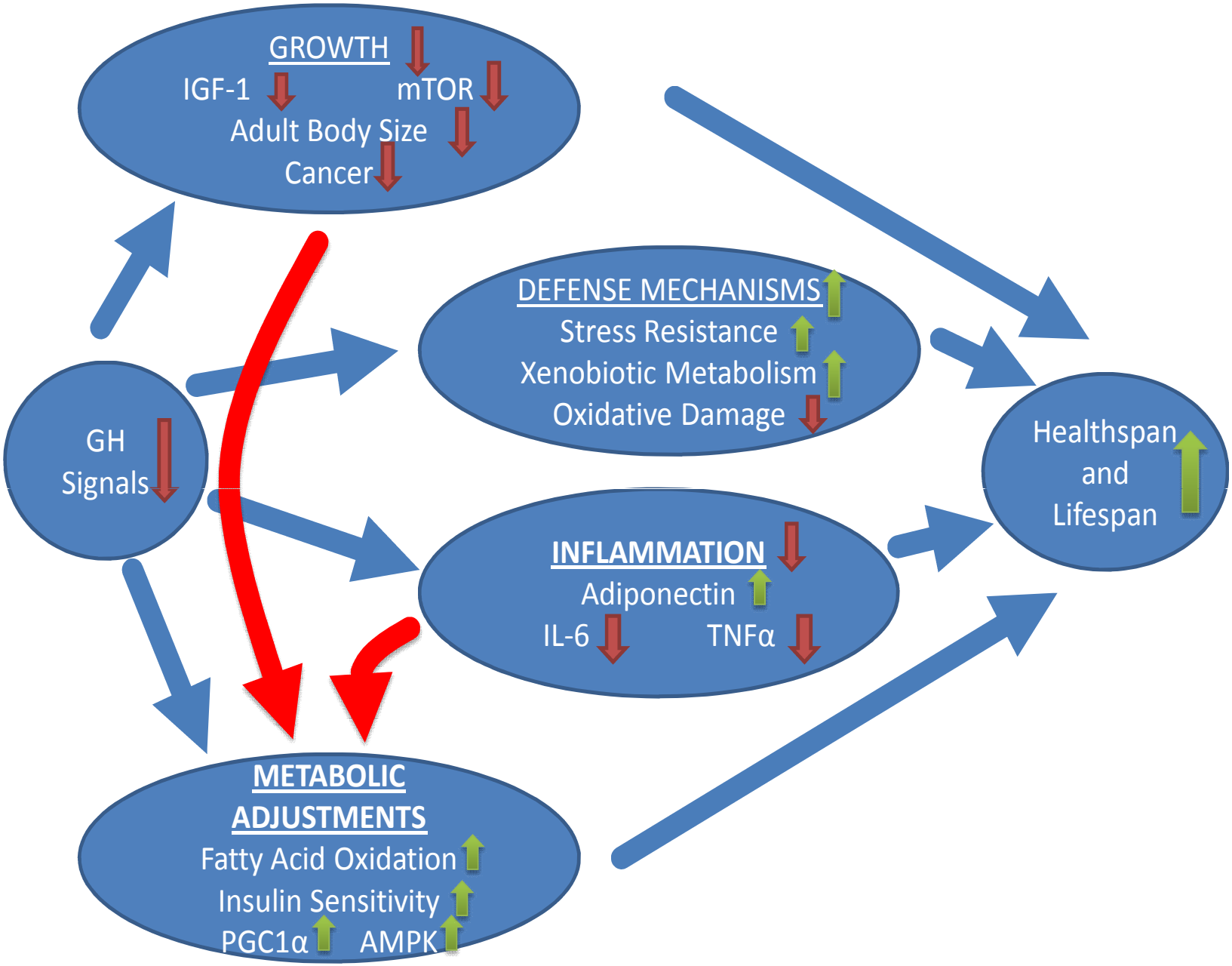
The world's oldest mouse?

Genotype:	**GHR-KO (-/-)**
Sex:	**Male**
Born:	**January 15, 1998**
Died:	**January 8, 2003**
Age:	**1819 days**
Bodyweight: (post-mortem)	**7.8 g**

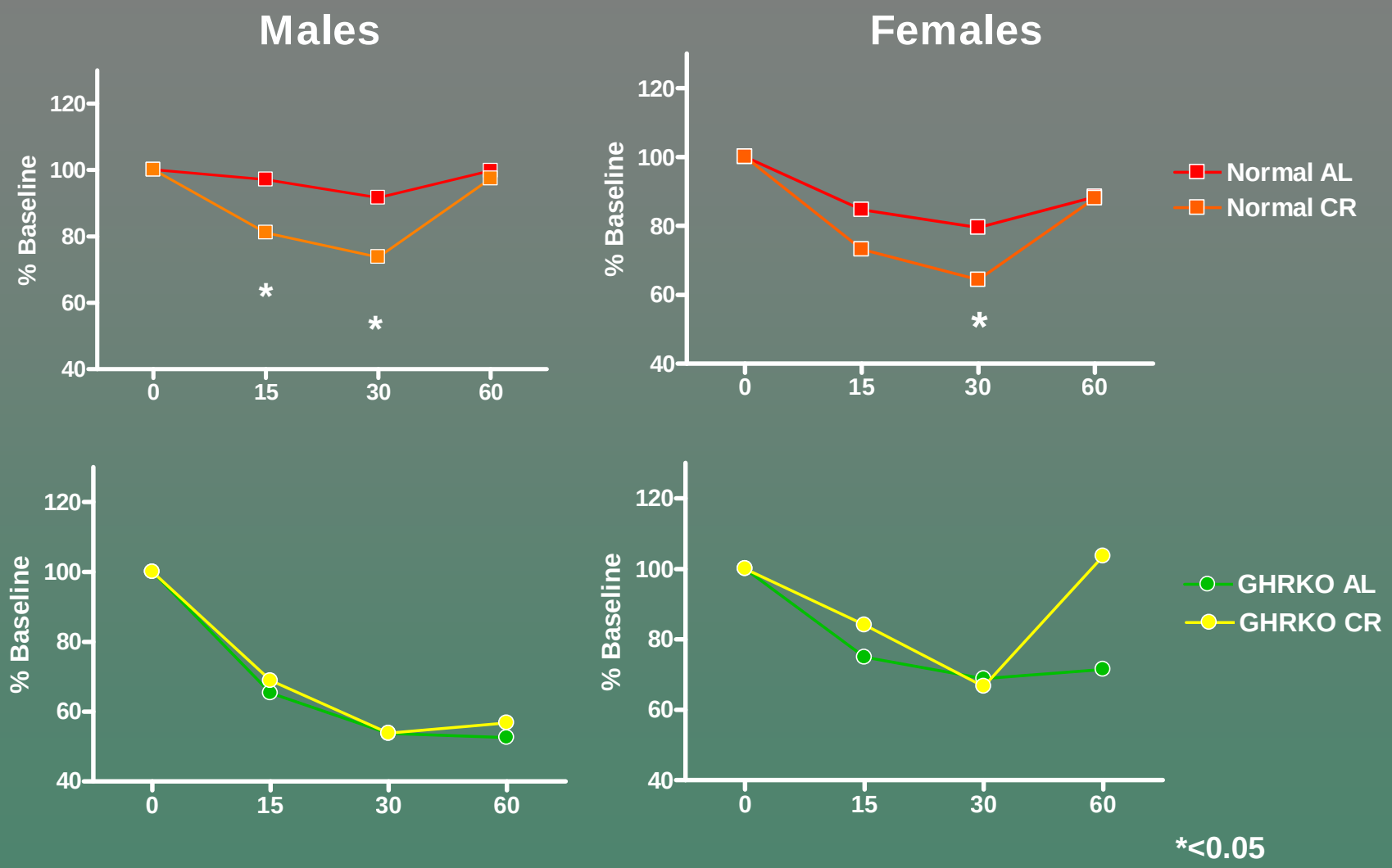
Long-lived mutant mice have longer "healthspan"

- 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***


GH deficiency or resistance
delayed aging
increased longevity

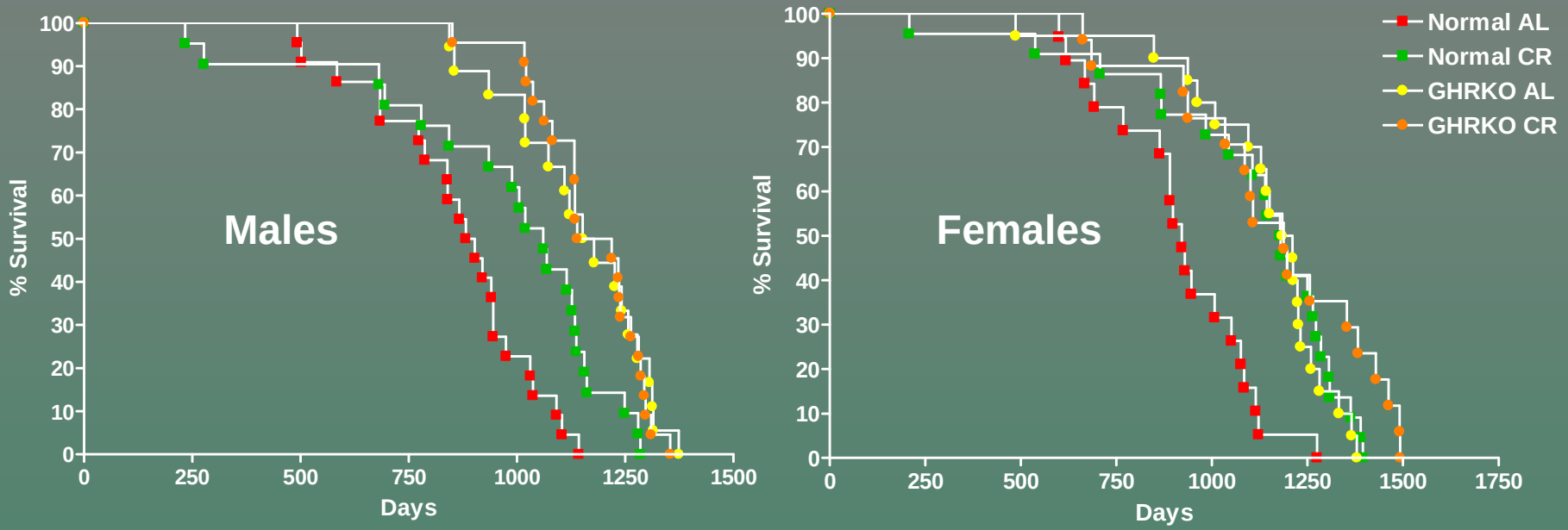

GROWTH
IGF-1
mTOR
Adult Body Size
Cancer
DEFENSE MECHANISMS
Stress Resistance
Xenobiotic Metabolism
Oxidative Damage
GH
Signals
Healthspan
and
Lifespan
INFLAMMATION
Adiponectin
IL-6
TNFα
METABOLIC
ADJUSTMENTS
Fatty Acid Oxidation
Insulin Sensitivity
PGC1α
AMPK

Insulin tolerance tests

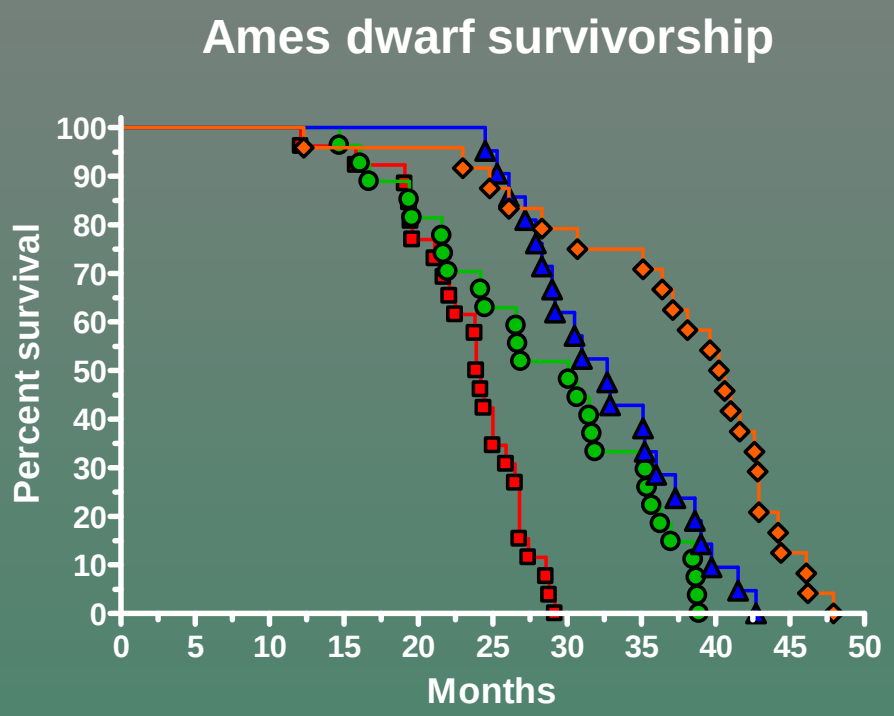


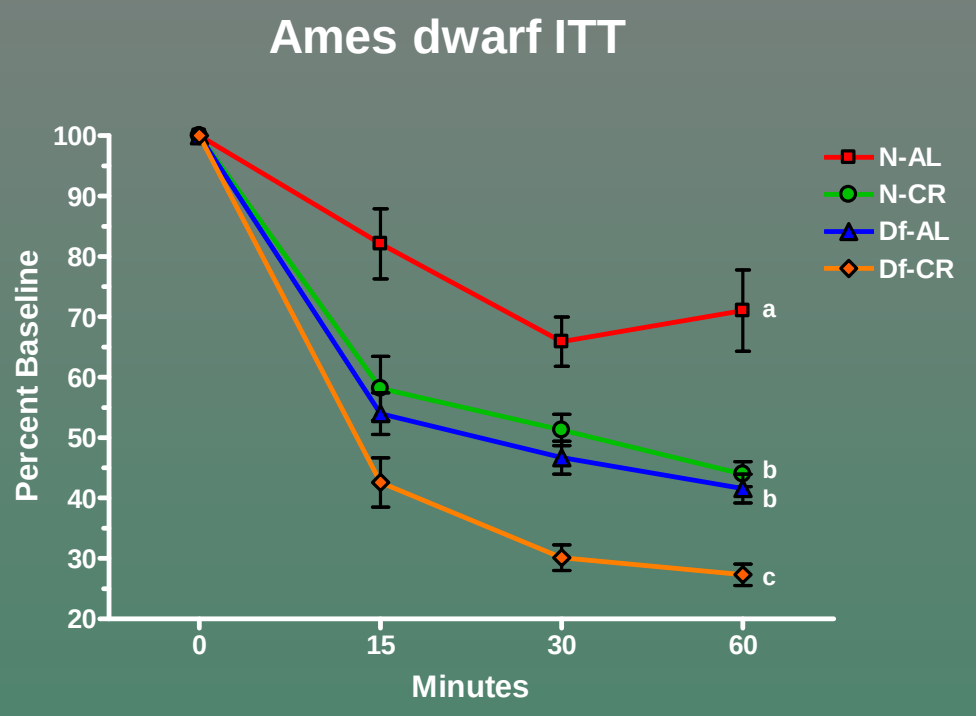
M. Bonkowski et al., *PNAS* 2006

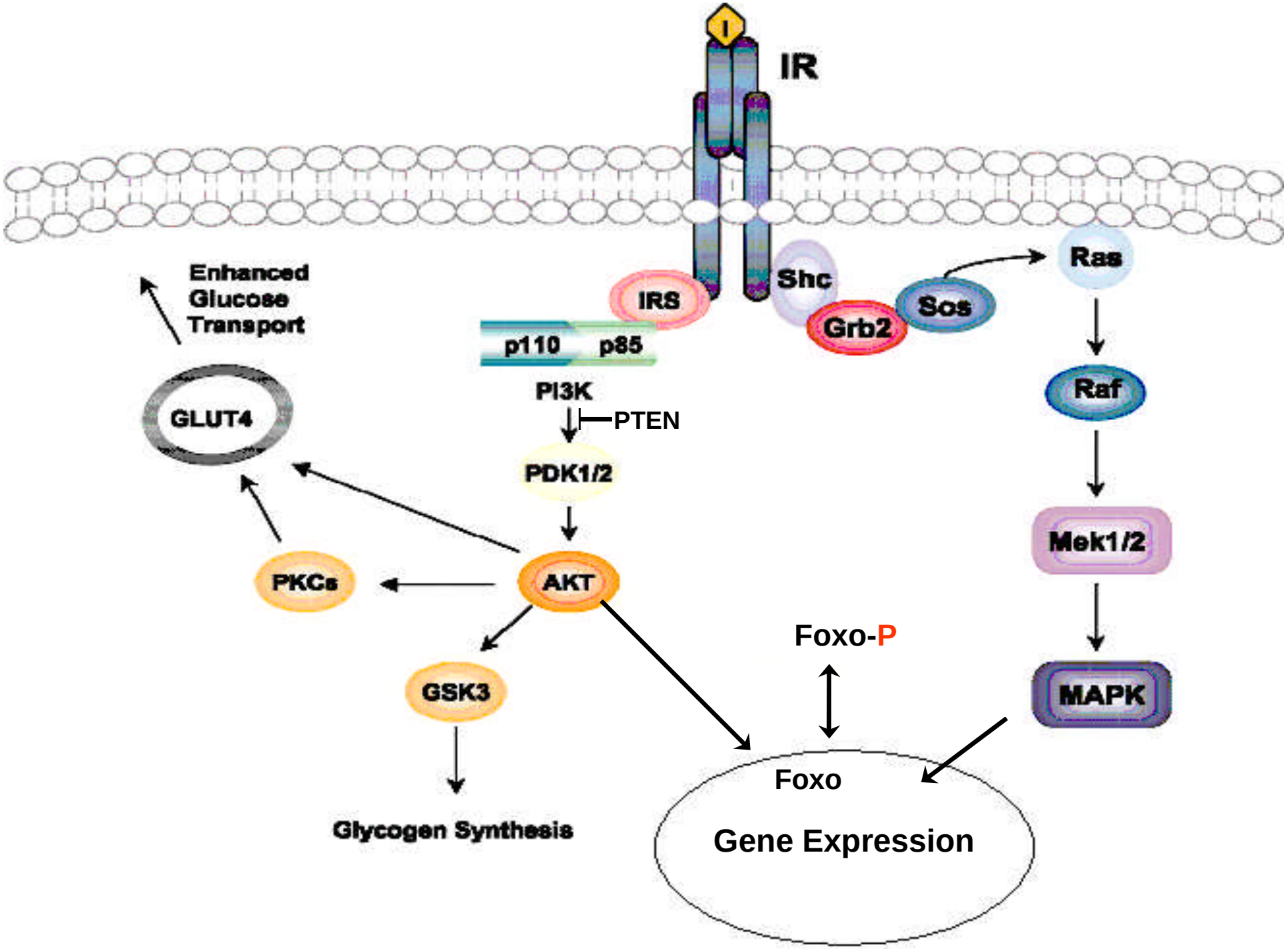
Response of GHR-KO mice to calorie restriction



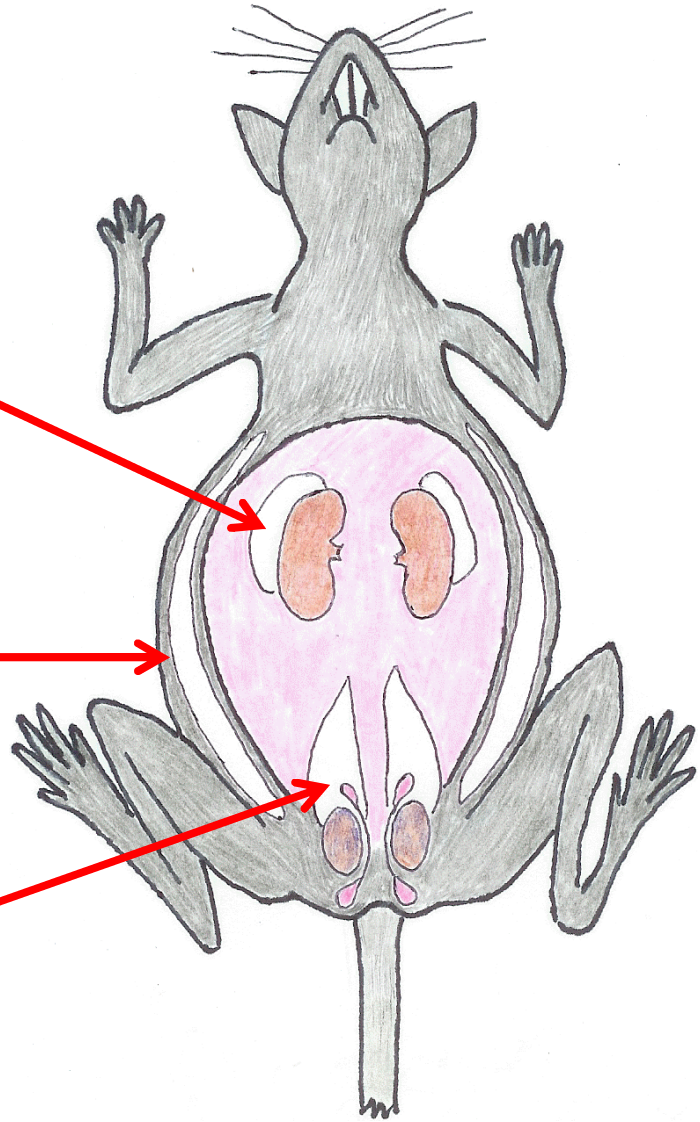
Interaction of Ames dwarfism with calorie restriction (CR)



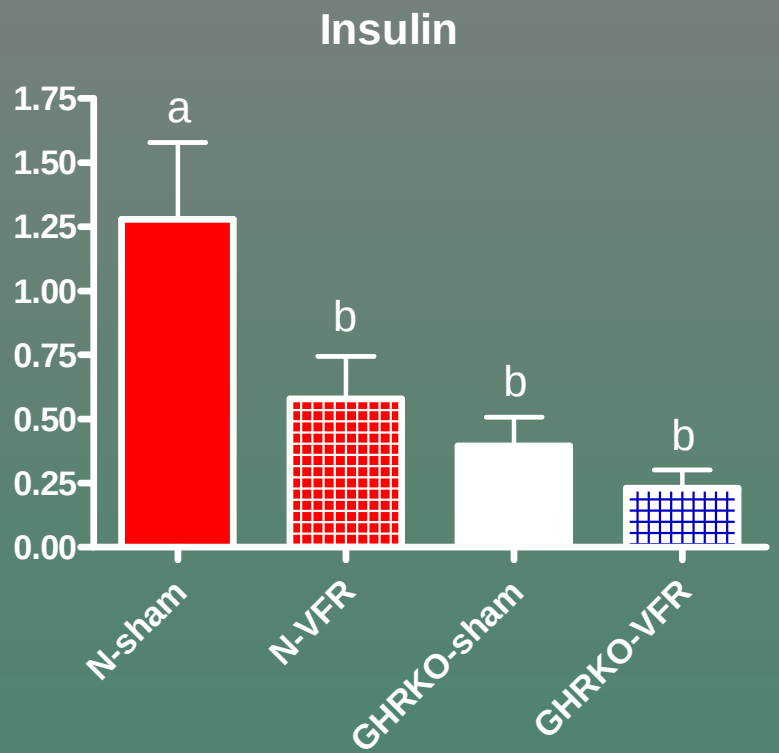


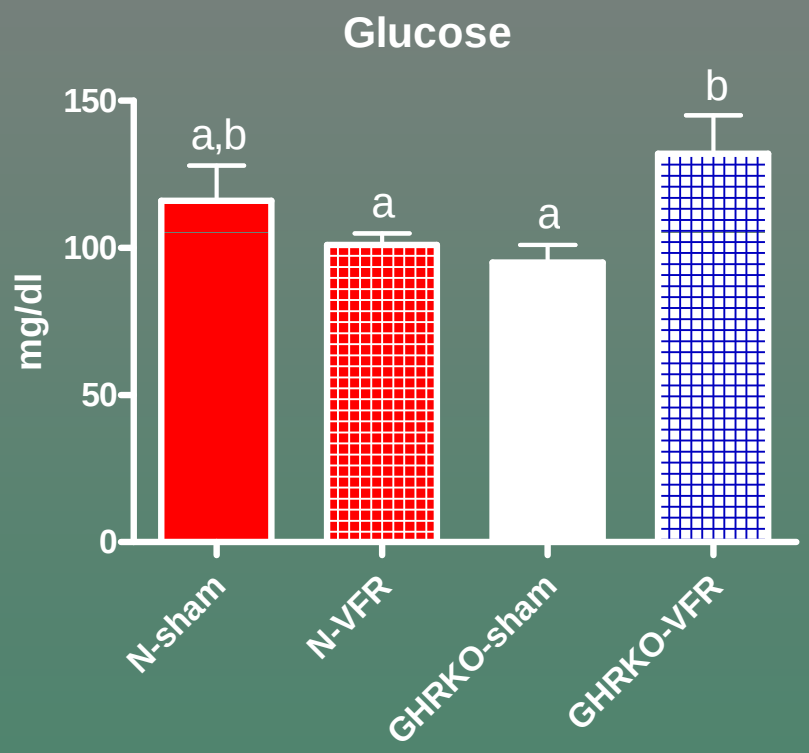

IR
Enhanced
Glucose
Transport
GLUT4
IRS
p110
p85
PI3K
PTEN
PDK1/2
AKT
PKCs
GSK3
Glycogen Synthesis
Shc
Grb2
Sos
Ras
Raf
Mek1/2
MAPK
Foxo-P
Foxo
Gene Expression

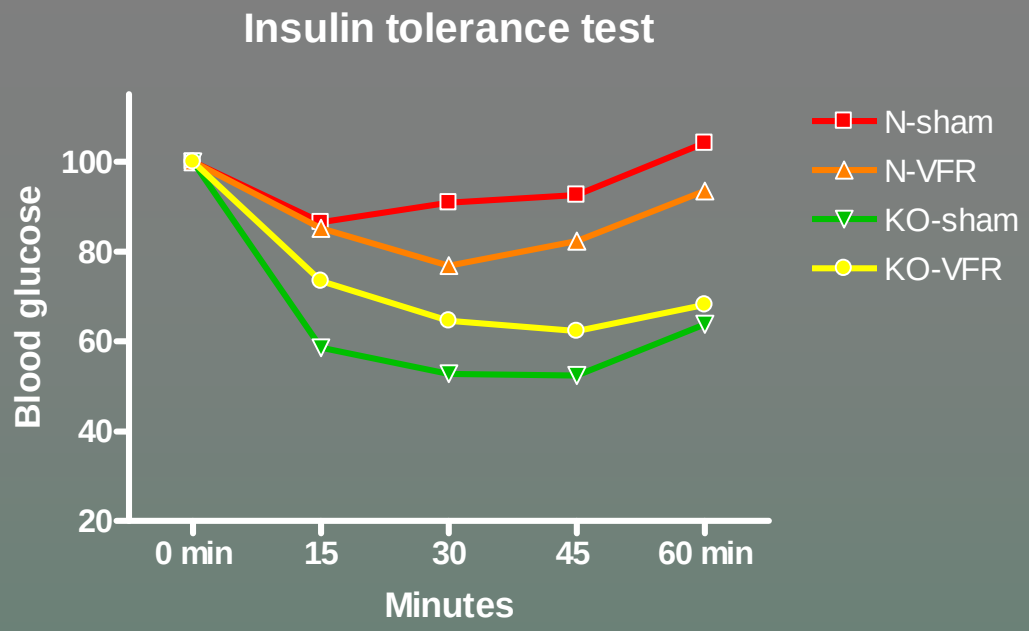
Major fat depots in a male mouse

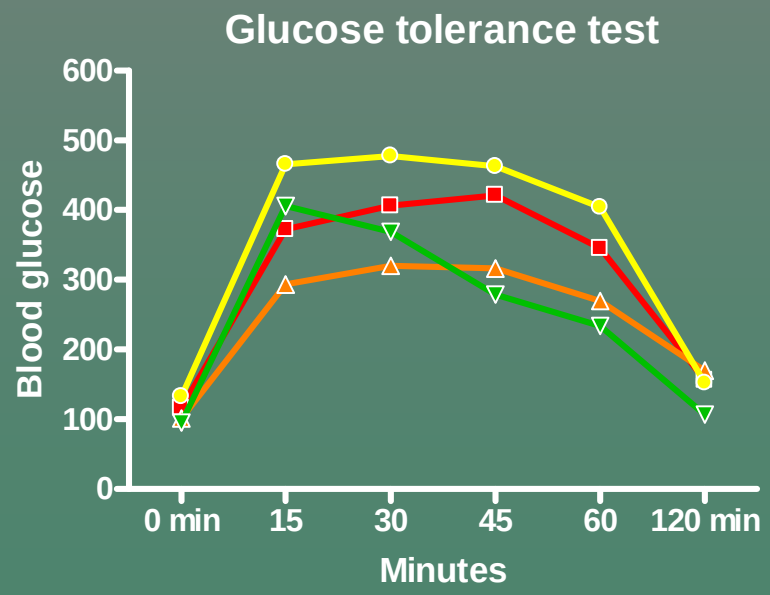


Peripheral insulin and glucose levels following visceral fat removal (VFR) or sham surgery in GHR-KO and normal mice

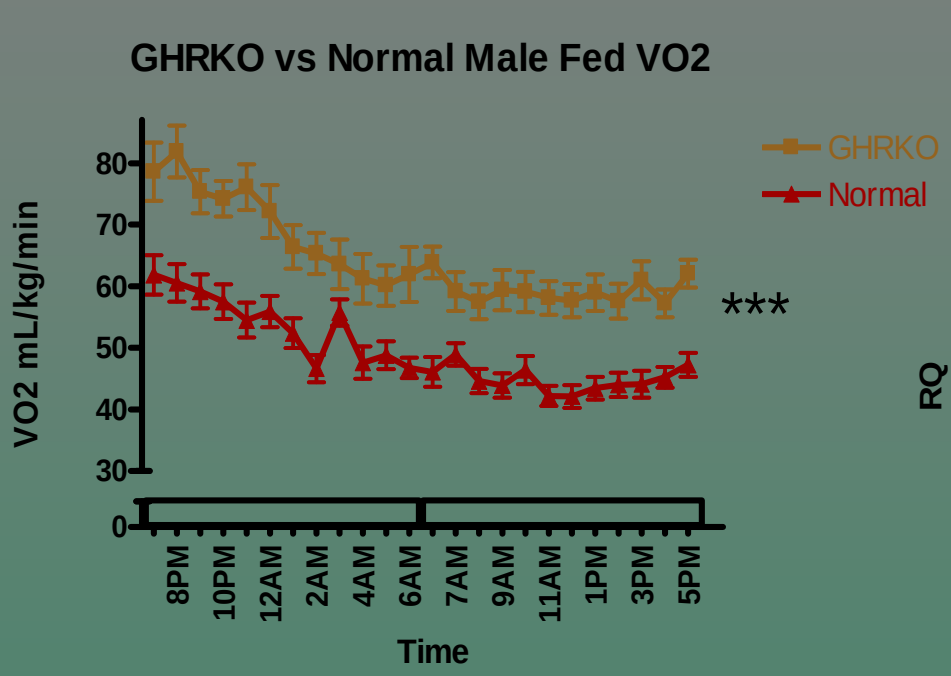


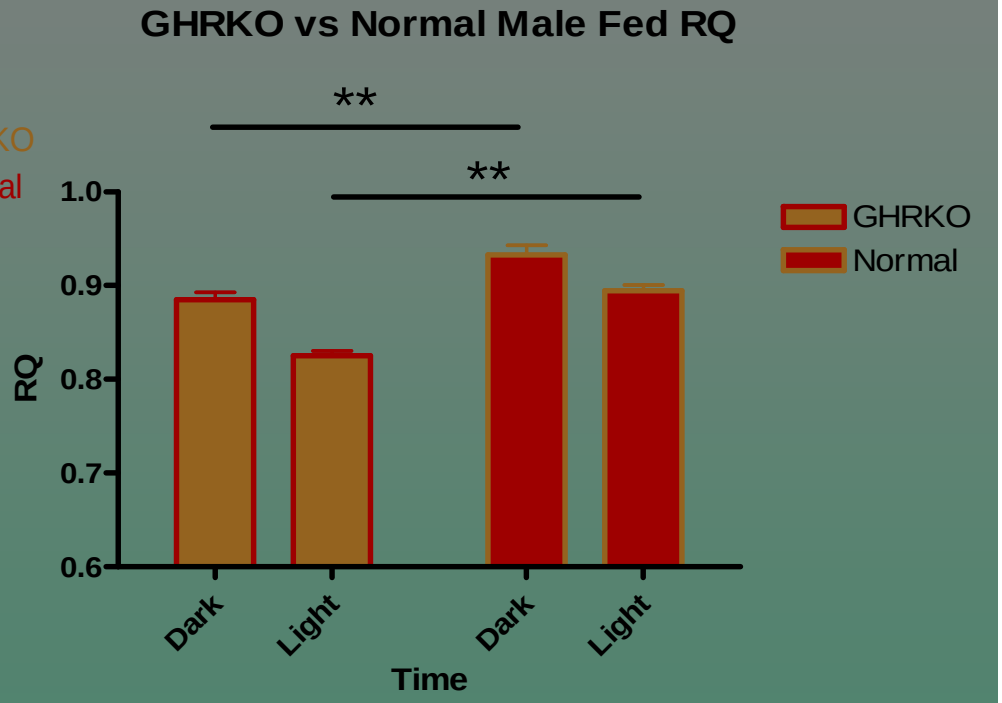






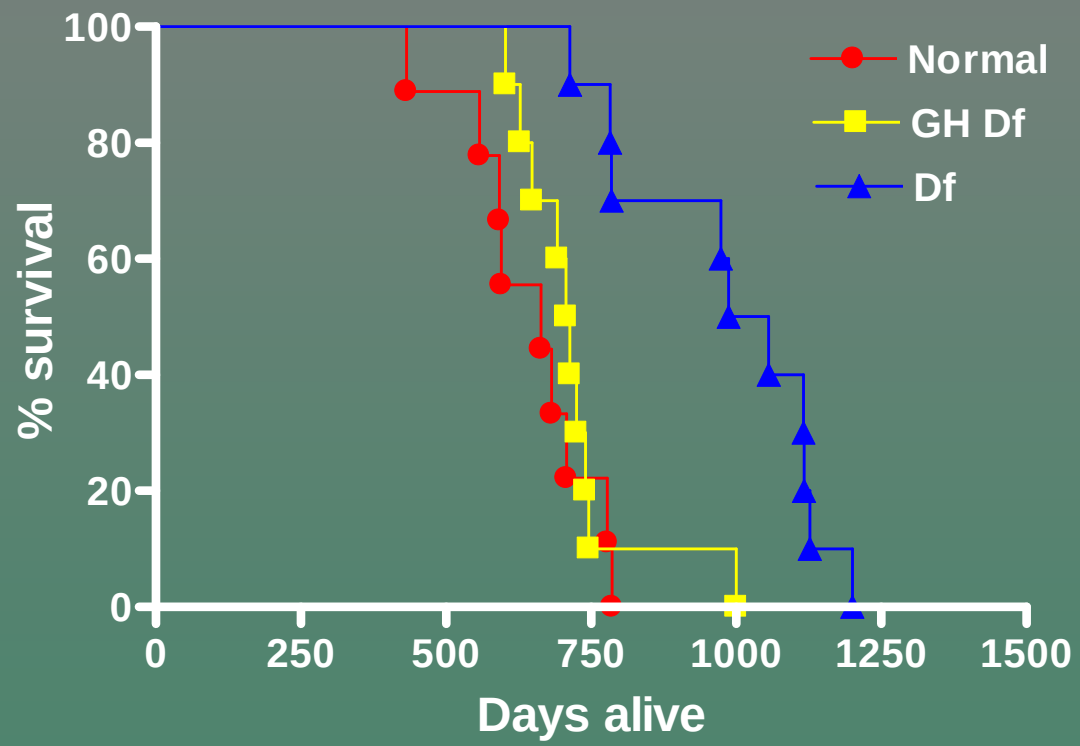
Insulin and glucose tolerance following visceral fat removal (VFR) or sham surgery in GHR-KO and normal mice


GHRKO vs Normal Male Fed VO2
VO2 mL/kg/min
80
70
60
50
40
30
0
8PM
10PM
12AM
2AM
4AM
6AM
7AM
9AM
11AM
1PM
3PM
5PM
Time
GHRKO
Normal
***


GHRKO vs Normal Male Fed RQ
**
**
RQ
1.0
0.9
0.8
0.7
0.6
Dark
Light
Dark
Light
Time
GHRKO
Normal

Ames dwarf mice

Survival plot of Ames dwarf mice, normal siblings and Ames dwarfs given GH replacement therapy

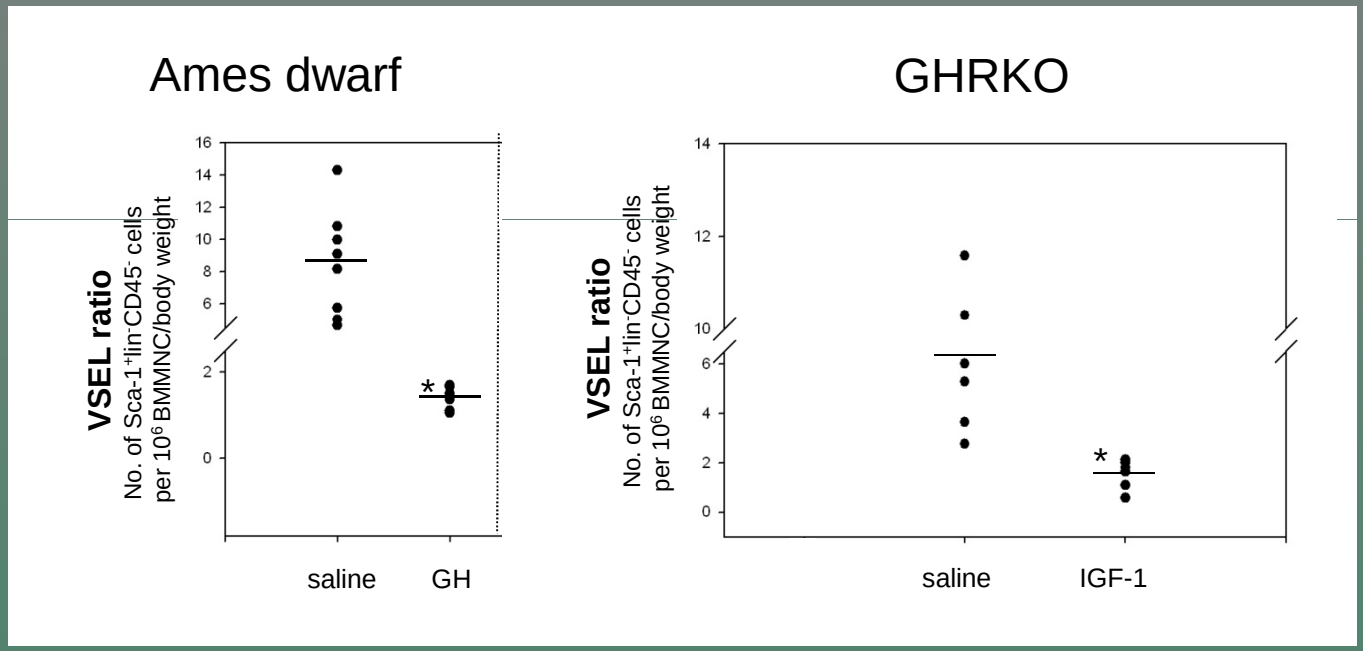


Number of VSELs in long-lived mice

Collaboration with Dr. M.Z. Ratajczak

Effects of hormone replacement therapy on the number of VSELs in long-lived mice

Collaboration with Dr. M.Z. Ratajczak



Advantages of long-lived mutants for the study of mechanisms of aging

1. Increased (or reduced) life expectancy can be traced to a known product of a single gene;

2. Young and healthy animals which we know will live long can be studied and compared to normal animals with the same genetic background and raised under identical conditions.

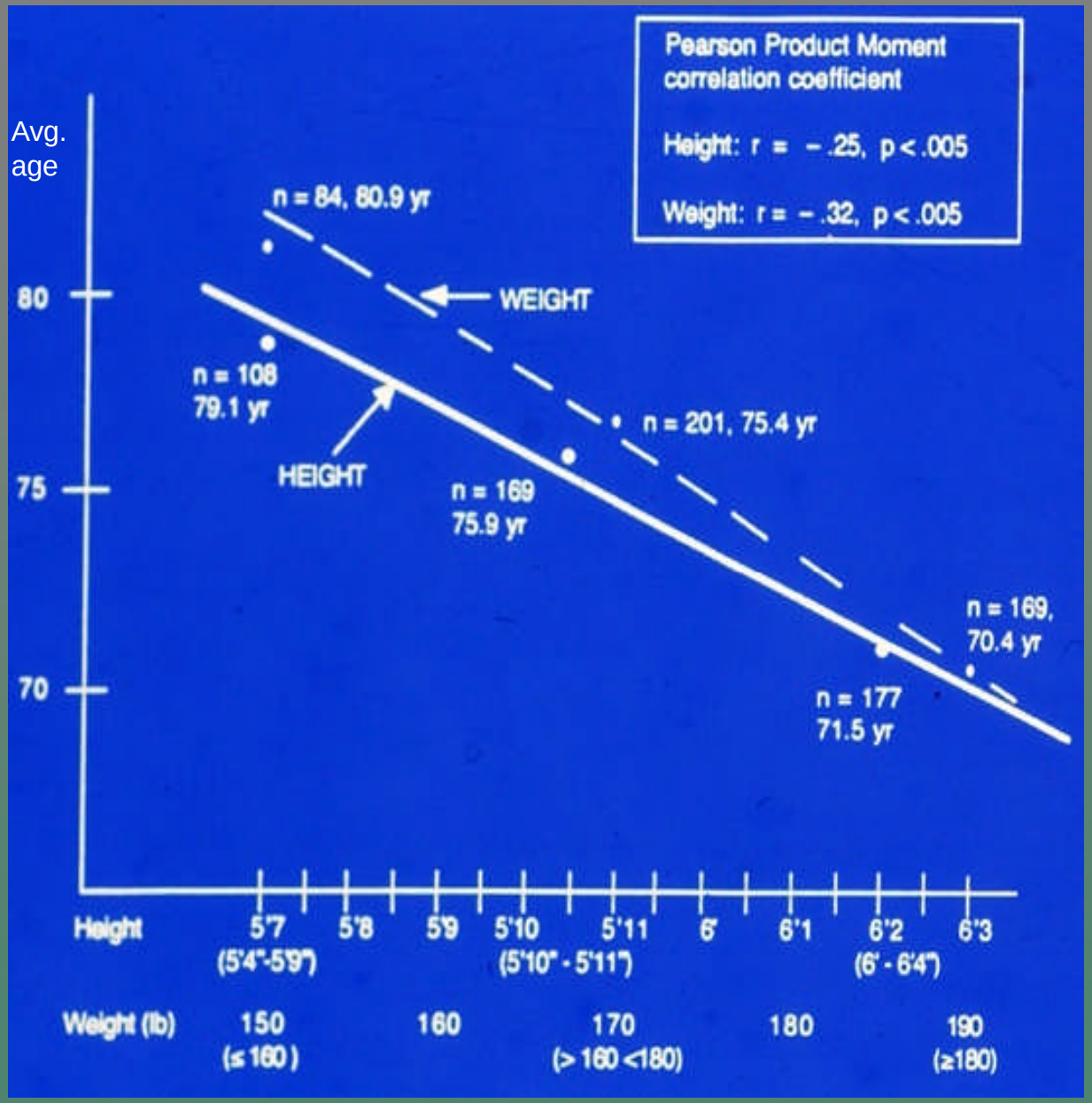
SIU

Southern Illinois University School of Medicine

Springfield, Illinois USA

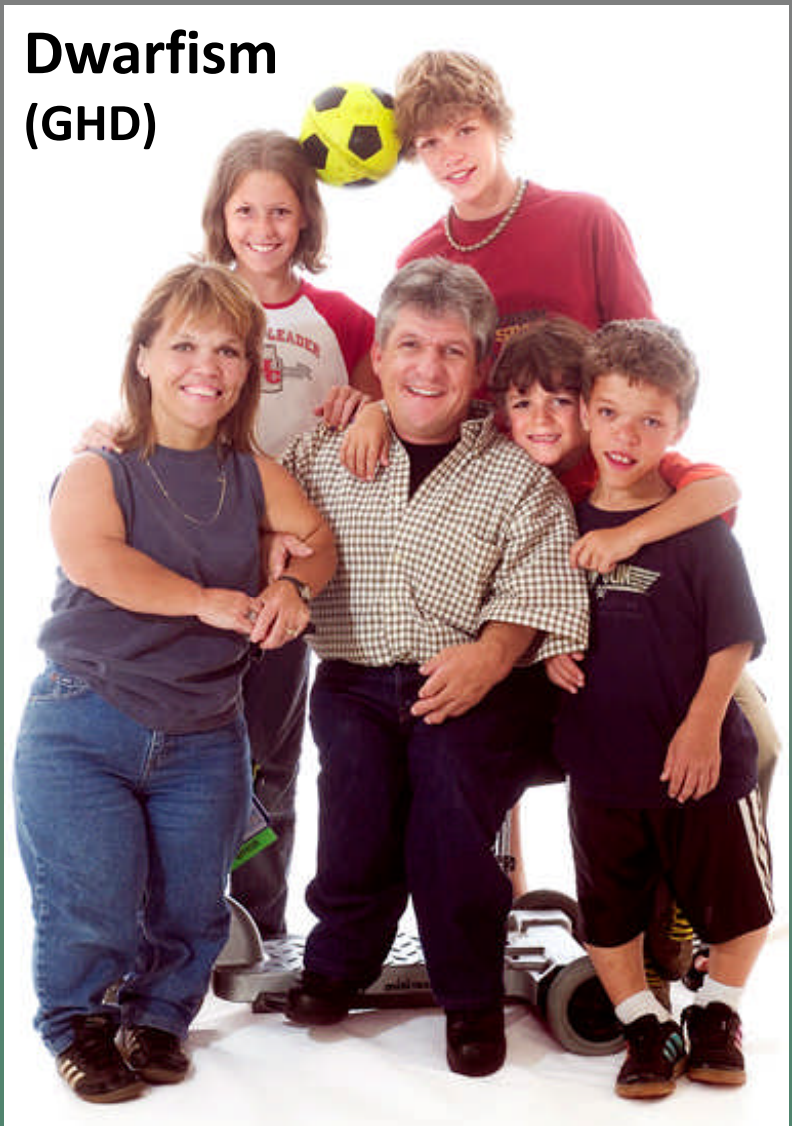
Average lifespan of pro baseball players vs. body size (mortality period 1976-92)

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



Human syndromes

Dwarfism
(GHD)



(c/o TLC's 'Little People, Big World')

Laron dwarfism

(Ecuador Institute of Endocrinology c/o ABC News)

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

Effects of growth hormone (GH) during different life stages

GH

- Somatic growth
- Sexual maturation
- Physical stamina
- Fertility
- Insulin resistance
- Rate of aging
- Reduced stress resistance?
- Cancer

EARLY / Beneficial

LATE / Detrimental

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Oge Arum

Michal S. Bonkowski

Holly Brown-Borg

Kurg Borg

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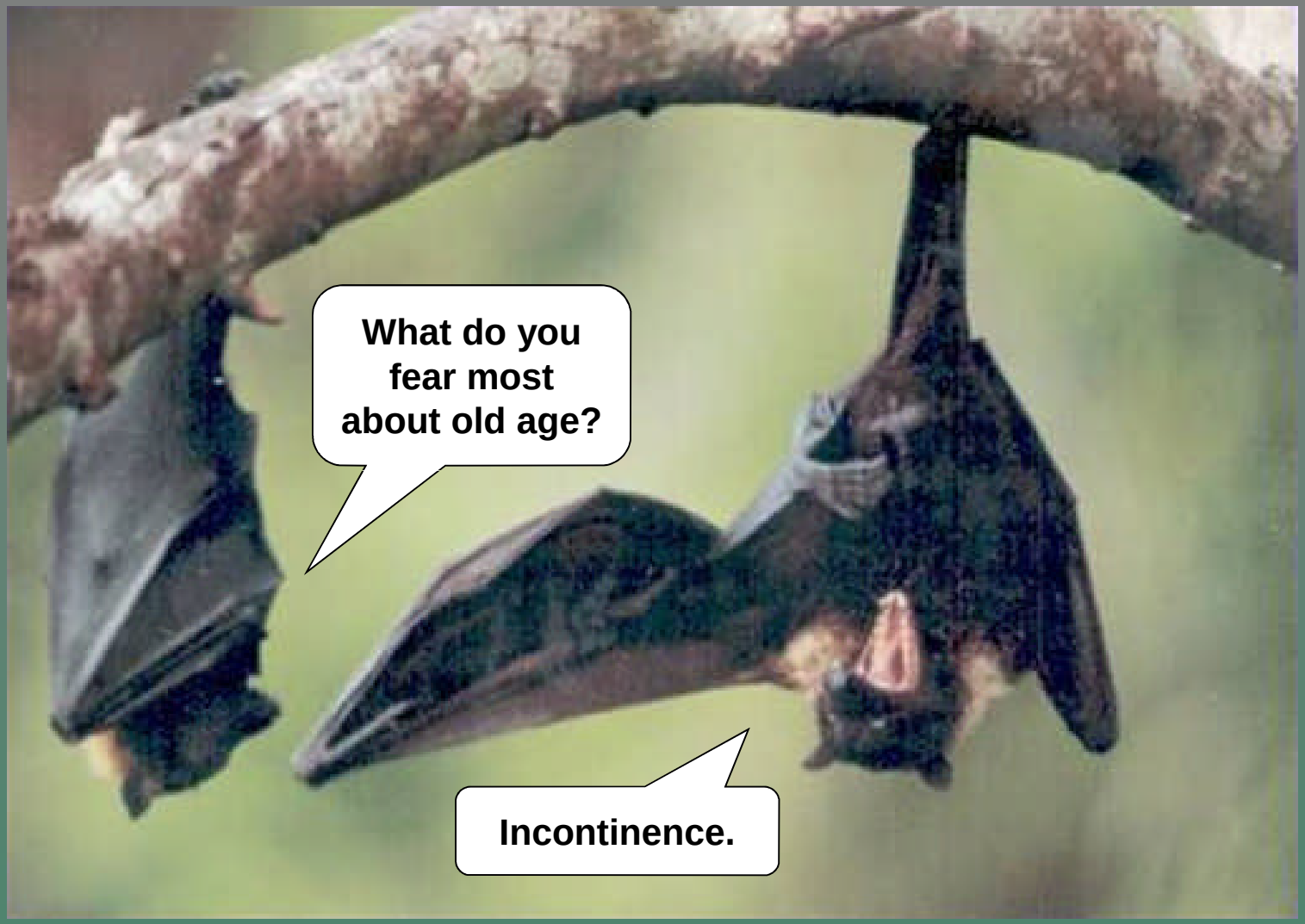
What do you fear most about old age?
Incontinence.

THANK YOU