

## Amgen Countermeasures for Bone and Muscle Loss in Space and on Earth



## Amgen-Sponsored Studies

- Commercial Biomedical Test Module (CBTM)
- CBTM-1
  - STS-108, 12-05-2001, 11 days 20 hours
  - Tested bone antiresorptive (Osteoprotegerin)
- CBTM-2
  - STS-118, 08-08-2007, 12 days 18 hours
  - Tested muscle growth promoter (Myostatin inhibitor)
- CBTM-3
  - STS-135, 07-08-2011, 12 days 18 hours
  - Tested bone growth promoter (Sclerostin inhibitor)

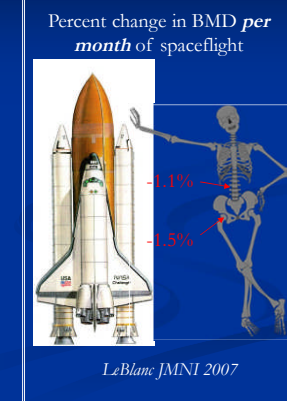


## Muscles and Bone Respond to Loading




- Transduction of mechanical loads
- Forces transmitted through hard and soft tissues
- Generate chemical signals between and within musculoskeletal tissues
- Alter cellular and intracellular processes to induce tissue growth

## Muscles and Bone Respond to Unloading



## Astronaut Musculoskeletal Fitness




1. *Reduce health risks to acceptable limits*
2. *Maximize crew time availability for mission*



- ISS crew expected to exercise a couple of hours/day, 7 days per week
  - Too much exercise can be a physical and psychological burden
- Crews should not have to rely on exercise
  - Crisis or emergency situations
  - Injury or illness

## Terrestrial Musculoskeletal Problems

- **Disease / genetics**
  - Post-menopause osteoporosis
  - Muscular dystrophy
  - Amyotrophic lateral sclerosis
  - Cancer / AIDS cachexia
  - Obesity / diabetes
- **Disuse**
  - Casting
  - Bedrest
  - Spinal cord or nerve injury
  - Surgery / rehab / disuse
- **Aging**
  - Male & female osteoporosis
  - Sarcopenia

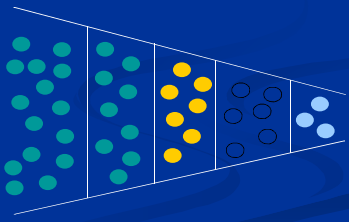




## Pharmaceutical Development

Early Target      Preclinical Research      Clinical Research      Commercialization

Discovery   Screen   HTL   Lead Opt   Preclinical   Phase 1   Phase 2   Phase 3   Filing   Launch/ Monitor

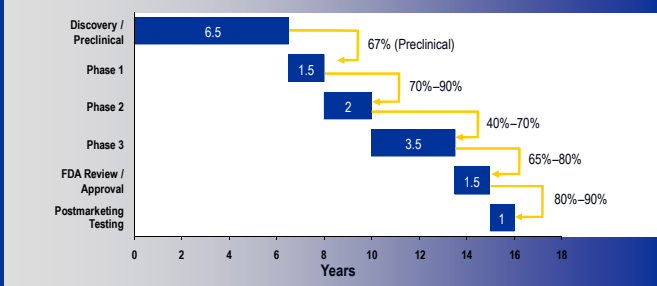
Review/Portals



- Identification of target and validation
- Molecule / therapy selection
- Study of toxicology and pharmacology
- Process development
- Delivery methods
- Demonstrate safety

## Biotech / Pharma R&D

- Biotech / Pharma industry spends > \$70B annually on R&D
- R&D process takes 12-15 years with 10%-30% success rate at a cost of ~\$1B per drug brought to market
- Failure of drugs can drive real cost to ~\$4B per successful drug



Phase	Duration (Years)	Success Rate
Discovery / Preclinical	6.5	67% (Preclinical)
Phase 1	1.5	70%-90%
Phase 2	2	40%-70%
Phase 3	3.5	65%-80%
FDA Review / Approval	1.5	80%-90%
Postmarketing Testing	1	

**Target Identification**

Early stage research targets are identified by mining information from various sources

- Internal discovery research — OPG
- Literature
- Scientific meetings — Myostatin
- Collaborations — Sclerostin
- Contacts in field
- Licensing opportunities

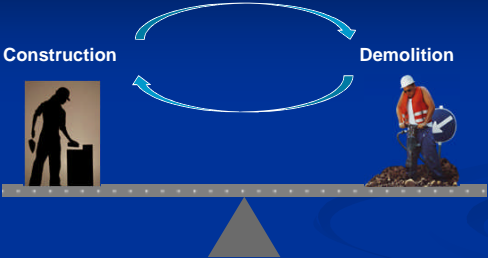
Once a potential target is identified it is assessed against many criteria

**Key Individuals at Amgen**

**AMGEN**

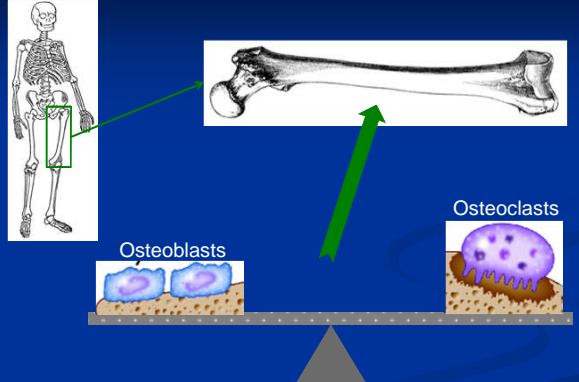
- David Lacey —
  - Former Director of Metabolic Disorders
  - Former Senior Vice President for Research
- Paul Kostenuick
  - Lead Amgen PI for osteoprotegerin study (STS-108)
- HQ Han
  - Lead Amgen PI for myostatin inhibitor study (STS-118)
- Chris Paszty
  - Lead Amgen PI for sclerostin antibody study (STS-135)

**Tissue Homeostasis**



Bone	Replaced about every 10 years
Muscle	Likely "replaced" even more frequently

**Bone Homeostasis**




**BioSERVE**  
TECHNOLOGIES


## Spaceflight Experiment Design

**AMGEN** **NASA** Ames Research Center

- Female, 9 week C57Bl/6 mice
  - Duration 12-13 days
- Mice flown in Animal Enclosure Modules (AEMs)
  - 24-30 mice in flight
  - 24-30 mice in ground controls
  - 12-15 mice as baseline controls
- Treatments
  - Flight vs. Ground
  - Drug therapeutic vs. vehicle ("placebo")
- Temperature, humidity and carbon dioxide matched as closely as possible between flight and ground




*Daily Crew Observations in Flight*



*Inside Orbital Environment Simulator at KSC*

**BioSERVE**  
TECHNOLOGIES

## Animal Enclosure Module (AEM)



Labels on the right side of the diagram:

- Air in
- Water Box
- Food Bars
- Water Lixit
- Air Out (filter underneath)

AEMs turned and kept in vertical position for ground controls

- Schedule offset from launch by ~48 hours
- Air flows from top to bottom, waste filter below "floor" on bottom

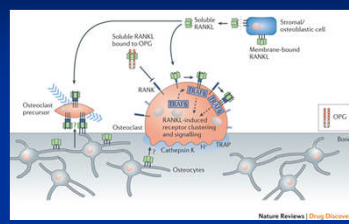
**BioSERVE**  
TECHNOLOGIES

## Discovery of Osteoprotegerin

- OPG was discovered and patented in 1997 through an Amgen genomics program that screened for novel genes and proteins
- OPG was identified as TNF receptor superfamily with surprising skeletal effects
- Discovery considered landmark event that enabled a new understanding of bone biology
- OPG Ligand was identified soon after in 1998 as a cytokine that regulated osteoclasts and induced bone resorption

**BioSERVE**  
TECHNOLOGIES


## OPG / RANK Signalling



Labels in the diagram:

- Soluble RANKL
- Soluble RANKL bound to OPG
- Strongly osteoclasts cell
- Membrane bound RANKL
- RANK
- RANKL induced receptor clustering and signaling
- Cartilage K
- IL-6
- IL-1
- IL-17
- IL-18
- IL-21
- IL-22
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- IL-99
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FROM:  
Nat Rev Drug Discov. 2012 May;11(5):401-19. doi: 10.1038/nrd3705.  
Bench to bedside: elucidation of the OPG-RANK-RANKL pathway and the development of denosumab. Lacey DL, Boyle WJ, Simonet WS, Kostenuik PJ, Dougall WC, Sullivan JK, San Martin J, Dansey R, Nat Rev Drug Discov. 2012 May;11(5):401-19.



Labels below the X-rays:

- Lack of OPG
- Normal OPG
- Extra OPG



## RANK Ligand Inhibitors

	Native OPG	PEG-OPG monomer	RANK-Fc	Fc-OPG	OPG-Fc (AMC9-2003)	Denosumab (AMC 163)
Expression (host)	E. coli/CHO	E. coli	CHO	E. coli	CHO	CHO
RANKL affinity	+++	++	+++	+++	++++	++++
In vitro activity	+++	++	+++	+++	+++	+++
In vivo potency	++	+	++	++	+++	++++
PK/PD	++	+	++	++	+++	++++

Legend: OPG-CHO, RANK-CHO, OPG-dimerization domain, Fc, Ig Fc domain, Ig variable domain

FROM: Nat Rev Drug Discov. 2012 May;11(5):401-19. doi: 10.1038/nrd3705. Bench to bedside: elucidation of the OPG-RANK-RANKL pathway and the development of denosumab. Lacey DL, Boyle WJ, Simonet WS, Kostenuik PJ, Dougall WC, Sullivan JK, San Martin J, Dansey R, Nat Rev Drug Discov. 2012 May;11(5):401-19.

- Tested on mice flown on STS-108
- Developed into drug approved by the FDA in 2010

## STS-108 Results

Group	Total BMD (mg/cm³)
Ground VEH	~430
Flight VEH	~380
Flight OPG	~500

- Bone mineral density greater in flight treated mice than flight untreated OR ground controls
- Other measures also significantly improved in treated mice
  - Trabecular bone properties
  - Bone strength
  - Markers of bone resorption
  - Dry mass, mineral mass, % mineral composition
- Spaceflight increased bone resorption AND reduced formation. OPG did not affect bone formation parameters – effect exclusively through inhibiting resorption consistent with expectations

## STS-108: Muscle Fiber CSA

From Fitts, Riley and Widrick, (2000), J Appl Physiol, 89:823-839.

- Similar levels of muscle atrophy occur in mouse (12 days), rat (14 days) and human (17 days) soleus

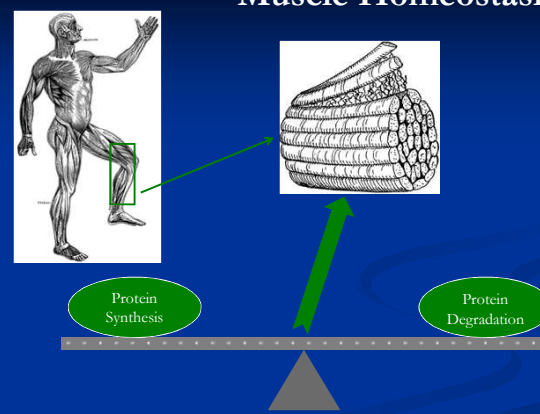
## CBTM-1 Publications

- Bateman, T.A., Morony, S., Ferguson, V.L., Simske, S.J., Lacey, D.L., Warmington, K.S., Geng, Z., Tan, H.L., Shalhoub, V., Dunstan, C.R. and Kostenuik, P.J. (2002) "Osteoprotegerin Mitigates Spaceflight-Induced Changes in Mouse Bone Mass, Density and Mineral Composition", *ASBMR* abstract.
- Kostenuik, P.J., Bateman, T.A., Morony, S., Warmington, K., Geng, Z., Adamu, S., Simske, S.J., Ferguson, V.L., Dunstan, C.R. and Lacey, D.L. (2002) "OPG Prevents Relative Osteopenia and Deficits in Skeletal Strength in Mice During a 12.5 Day Spaceflight", *ASBMR* abstract.
- Harrison BC, Allen DL, Stodieck LS, Kostenuik PJ, Bateman TA, Morony, S, Leinwand, LA (2003) "Skeletal muscle adaptations to microgravity in the mouse." *J Appl Physiol* 95:2462-2470.
- Dalton P, Gould M, Girtan B, Stodieck LS, Bateman TA (2003) "Preventing annoyance from odors in spaceflight: a method for evaluating the sensory impact of rodent housing." *J Appl Physiol* 95:2113-2121.
- Pecaut, MJ, Nelson, GA, Peters, LL, Kostenuik, PJ, Bateman, TA, Morony, S, Stodieck, LS, Lacey, DL, Simske, SJ, Gridley, DS Effect of spaceflight on immunity in the C57BL/6 mouse, Part I: Immune population distribution. In press for: *J Appl Physiol* 94:2085-2094; 2003.
- Gridley, DS, Nelson, GA, Peters, LL, Kostenuik, PJ, Bateman, TA, Morony, S, Stodieck, LS, Lacey, DL, Simske, SJ, Pecaut, MJ Effect of spaceflight on immunity in the C57BL/6 mouse, Part II: Activation, cytokines, erythrocytes, and platelets. *J Appl Physiol* 94:2095-2103; 2003.

**OPG Drug Development**

- Amgen selected Denosumab (fully human monoclonal antibody to RANK Ligand) as the drug to take into clinical trials
- FDA approved Denosumab in 2010
  - Initially for the treatment of postmenopausal osteoporosis (Prolia)
  - Subsequently for treatment of bone metastases (Xgeva)
- Sales for Prolia and Xgeva were in excess of \$1.2B in 2012
- Amgen conducting additional clinical trials for other indications
  - Prolia – rheumatoid arthritis
  - Prolia - glucocorticoid induced osteoporosis
  - Prolia – male osteoporosis
  - Xgeva – cancer related bone damage (multiple myeloma)
  - Xgeva – prevention of bone metastases in breast cancer
  - Xgeva – prevention of bone metastases in prostate cancer

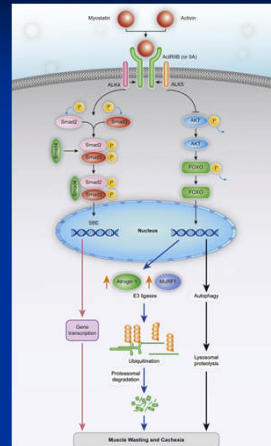
**Muscle Homeostasis**



**Discovery of Myostatin  
(a.k.a. GDF-8)**

- Discovered by Se-Jin Lee and Alexandra McPherron at Johns Hopkins University in 1997
  - Identified as a member of the TGF- $\beta$  superfamily of signaling proteins that regulates development and tissue homeostasis;
  - Myostatin found to be expressed almost exclusively in skeletal muscle and act as a negative regulator of muscle growth;
  - The myostatin gene is a highly conserved across multiple species
- Regulation of myostatin has been shown to be quite complex

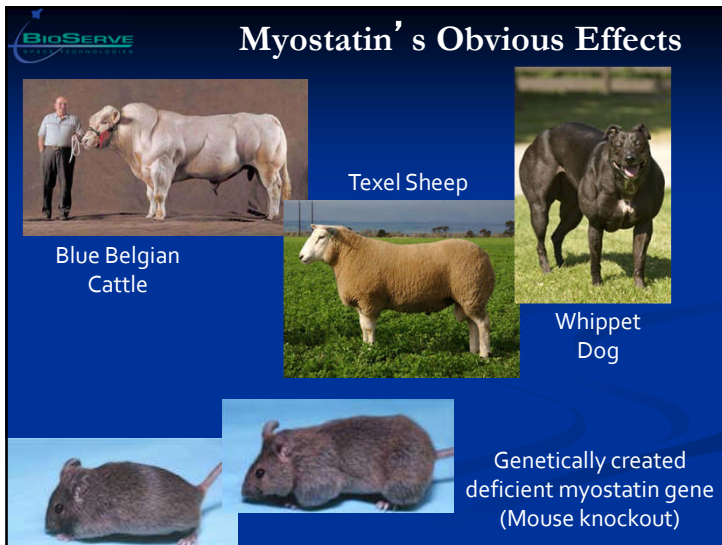
**Myostatin Signalling**



- Myostatin signals through activin Type II receptors
- Intracellular cascade ultimately leads to protein degradation and muscle wasting
- Variety of myostatin inhibitors have been studied

FROM:  
Myostatin/activin pathway antagonism: Molecular basis and therapeutic potential. Han HQ, Zhou X, Mitch WE, Goldberg AL. Int J Biochem Cell Biol, 2013.

## Myostatin's Obvious Effects



Texel Sheep

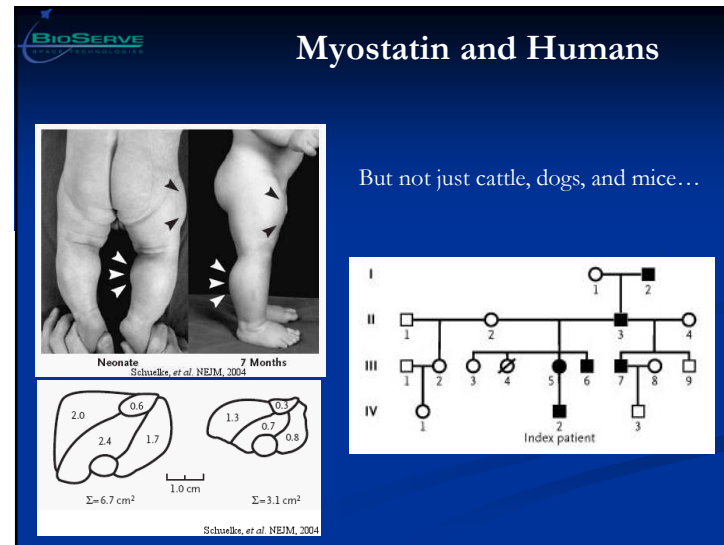
Blue Belgian Cattle

Whippet Dog

Genetically created deficient myostatin gene (Mouse knockout)

## Myostatin and Humans

But not just cattle, dogs, and mice...



Neonate

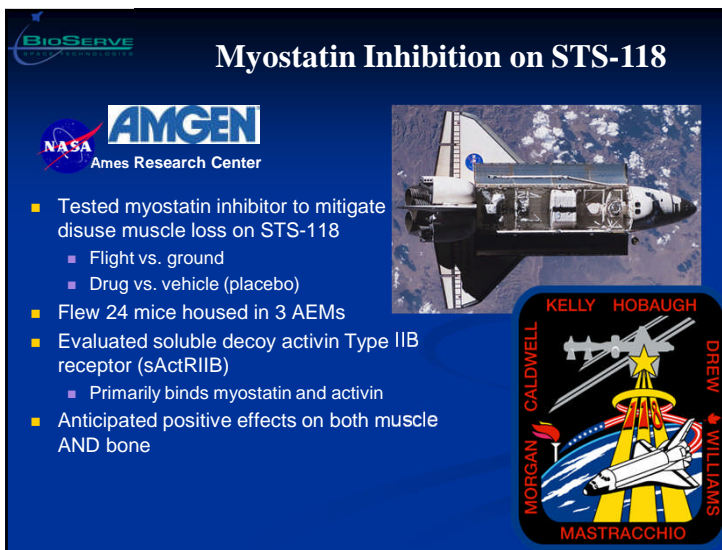
7 Months

Schuelke, et al. NEJM, 2004

Index patient

Schuelke, et al. NEJM, 2004

## Myostatin Inhibition on STS-118



NASA Ames Research Center

- Tested myostatin inhibitor to mitigate disuse muscle loss on STS-118
  - Flight vs. ground
  - Drug vs. vehicle (placebo)
- Flew 24 mice housed in 3 AEMs
- Evaluated soluble decoy activin Type IIB receptor (sActRIIB)
  - Primarily binds myostatin and activin
- Anticipated positive effects on both muscle AND bone

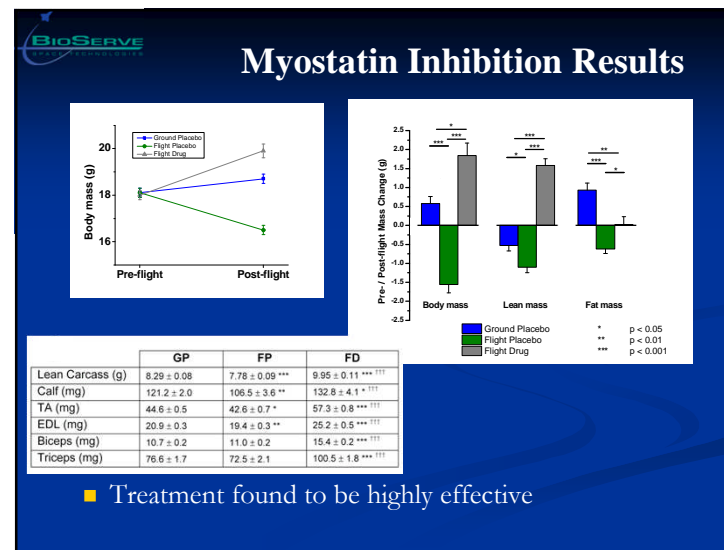
KELLY HOBAUGH

MORGAN CALDWELL

DREW WILLIAMS

MASTRACCHIO

## Myostatin Inhibition Results



Body mass (g)

Pre-flight

Post-flight

Pre- / Post-flight Mass Change (g)

Body mass

Lean mass

Fat mass

Ground Placebo

Flight Placebo

Flight Drug

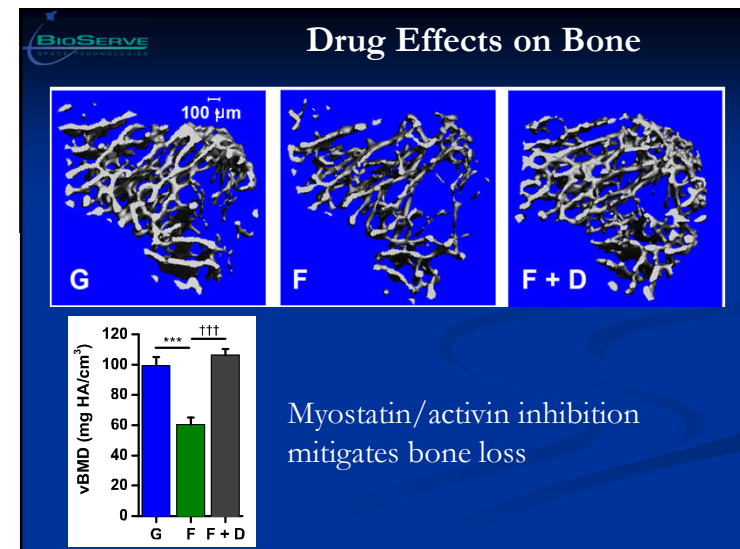
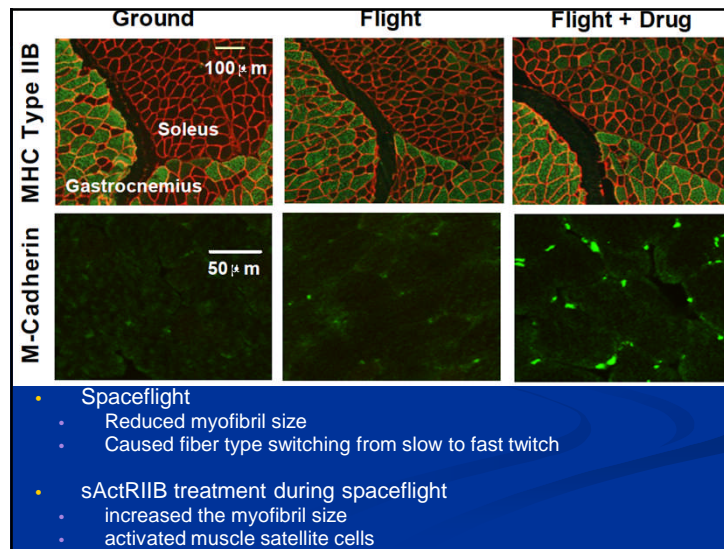
p < 0.05

p < 0.01

p < 0.001

	GP	FP	FD
Lean Carcass (g)	8.29 ± 0.08	7.78 ± 0.09 ***	9.95 ± 0.11 *** <sup>†††</sup>
Calf (mg)	121.2 ± 2.0	106.5 ± 3.6 **	132.8 ± 4.1 * <sup>††</sup>
TA (mg)	44.6 ± 0.5	42.6 ± 0.7 *	57.3 ± 0.8 *** <sup>†††</sup>
EDL (mg)	20.9 ± 0.3	19.4 ± 0.3 **	25.2 ± 0.5 *** <sup>†††</sup>
Biceps (mg)	10.7 ± 0.2	11.0 ± 0.2	15.4 ± 0.2 *** <sup>†††</sup>
Triceps (mg)	76.6 ± 1.7	72.5 ± 2.1	100.5 ± 1.8 *** <sup>†††</sup>

Treatment found to be highly effective



**CBTM-2 Publications**


- Han, HQ, Stodieck LS, Ferguson, VL, Zhou, XL, Lu, J, Hanson, AM, Young, MH, Jiao, E, Kwak, K, Rosenfeld, R, Boone, T, Simonet, W and Lacey, DL. (2008) "Pharmacological myostatin antagonism effectively mitigates spaceflight-induced muscle atrophy in mice", *ASGB abstract*.
- Ferguson, VL, Paietta, P, Stodieck, LS, Hanson, AM, Young, MH, Bateman, TA, Lemus, M, Kostenuik, PJ, Jiao, E, Zhou, XL, Simonet, W, Lacey, DL and Han, HQ (2009) Inhibiting Myostatin Prevents Microgravity Associated Bone Loss in Mice", *ASBMR abstract*.
- Baqai FP, Gridley DS, Slater JM, Luo-Owen X, Stodieck LS, Ferguson V, Chapes SK, Pecaut MJ (2009) "Effects of spaceflight on innate immune function and antioxidant gene expression", *J Appl Physiol*, 106(6):1935-42.
- Ortega MT, Pecaut MJ, Gridley DS, Stodieck LS, Ferguson VL, Chapes, SK (2009) "Shifts in Bone Marrow Cell Phenotypes Caused by Space Flight", *J Appl Physiol*, 106(2):548-55.
- Allen DL, Bandstra ER, Harrison BC, Thorng S, Stodieck LS, Kostenuik PJ, Morony S, Lacey DL, Hammond TG, Leinwand LL, Argraves WS, Bateman TA, Barth JL (2009) "Effects of Spaceflight on murine skeletal muscle gene expression", *J Appl Physiol*, 106(2):582-95.
- Gridley DS, Slater JM, Luo-Owen X, Rizvi A, Chapes SK, Stodieck LS, Ferguson VL, Pecaut MJ (2009) "Spaceflight effects on T lymphocyte distribution, function and gene expression", *J Appl Physiol*, 106(1):194-202.
- Lebsack, TW, Fa, V, Woods, CC, Gruener, R, Manziello, AM, Pecaut, MJ, Gridley, DS, Stodieck, LS, Ferguson, VL and Deluca, D (2010) "Microarray analysis of spaceflown murine thymus tissue reveals changes in gene expression regulating stress and glucocorticoid receptors", *J Cell Biochem*, March epub ahead of print.

**Other Indications for Myostatin Inhibitors**

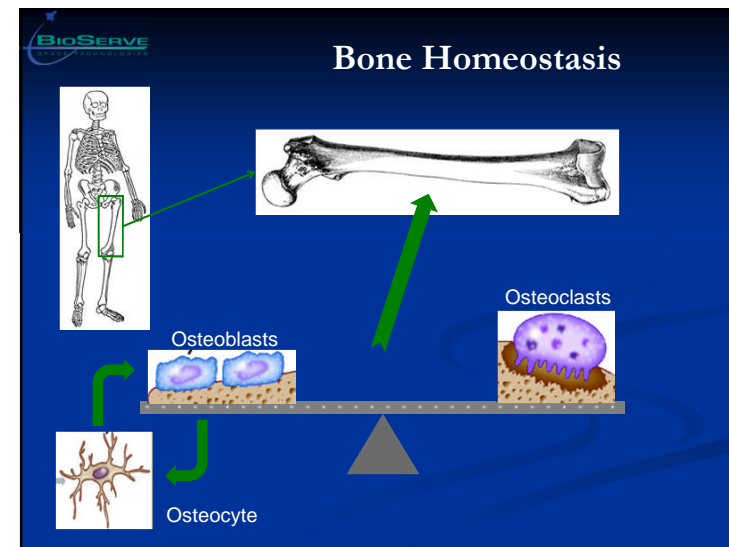
- Cancer cachexia
  - "Reversal of cancer cachexia and muscle wasting by ActRIIB antagonism leads to prolonged survival", (2010), X Zhou *et al*, *Cell*, 142:531-543.
- Chronic kidney disease
  - "Pharmacological inhibition of myostatin suppresses systemic inflammation and muscle atrophy in mice with chronic kidney disease", (2011), L. Zhang *et al*, *FASEB J*, 25(5):1653-1663.
- Also, Chronic obstructive pulmonary disease (COPD), glucocorticoid-induced muscle wasting and Type II diabetes



## Myostatin Inhibitor Drug Development




Company	Drug	Target Disease	Stage	Status
Amgen	AMG-745 (Peptibody)	Cancer	Ph I (BioServe Led)	Licensed to Atara
Wyeth	MYO-029 (decoy receptor)	Various MDs	Ph II	Stopped, acquired by Pfizer
Accelaron	ACE-031 (antibody)	Duchenne MD	Ph II	Stopped, acquired by Shire
Eli Lilly	LY2495655 (antibody)	Cancer	Ph II	Active
Pfizer	PF-06252616 (antibody)	Various MDs	Ph I	Active
Milo Biotechnology	Follistatin gene therapy	Various MDs	Ph II	Active



## Discovery of Sclerostin

- Sclerostin was first described in 2001 associated with research on patients suffering from sclerosteosis causing bone overgrowth
- Osteocytes exhibit mechanosensory function and are thought to underlie bone growth stimulatory responses to loading
- Sclerostin is secreted by osteocytes and inhibits osteoblasts – thus, inhibiting bone formation



*Li et al. JBM, 2008, 23(6):860-869.*

## Sclerostin Antibody


(McClung, ASBMR, 2012)

- Sclerostin naturally inhibits bone formation
- AMG 785 (sclerostin antibody) chosen as lead molecule for development (collaboration with UCB Pharmaceuticals)
- Block sclerostin (*via* sclerostin antibody; SclAB)
  - Inhibit the inhibition bone formation = bone formation
  - Infrequent dosing
  - Minimal side effects
- Administration of sclerostin antibody increases bone mass, decreases fracture risk, and improves fracture healing in multiple species
- At 1 year, spine bone mineral density (BMD) increased by:
  - 4% with alendronate (Fosamax)
  - 7% with teriparatide (Forteo)
  - 11.3% with sclerostin antibody

**Sclerostin Antibody on STS-135**

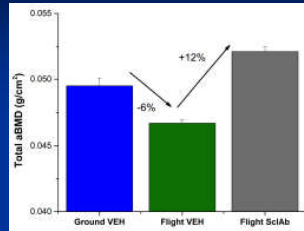
NASA AMGEN ucb Pharma

- Tested sclerostin antibody (mouse version) to mitigate bone loss on STS-135
  - Flight vs. ground
  - Drug vs. vehicle (placebo)
- Flew 30 mice housed in 3 AEMs. Ground controls housed in AEMs in environment simulator.
- Single injection of SclAb (100mg/kg) or vehicle given to mice
- Work supported by Amgen, UCB, NASA Johnson Space Center and NASA Ames Research Center
- Collaboration included Univ. of Colorado, Univ. of North Carolina and Harvard School of Medicine



**STS-135 Results**

- Bone mineral density greater in flight treated mice than flight untreated OR ground controls
- Other measures also significantly improved in treated mice
  - Microarchitecture bone properties
  - Bone strength and stiffness
  - Markers of bone formation
- Spaceflight increased bone resorption AND reduced formation.
- SclAb clearly increased bone formation, despite unloading, and completely prevented the negative effects of spaceflight on skeletal tissues.



Group	Total aBMD (g/cm³)	% Change
Ground VEH	0.050	-
Flight VEH	0.047	-6%
Flight SclAb	0.052	+12% (vs Flight VEH)

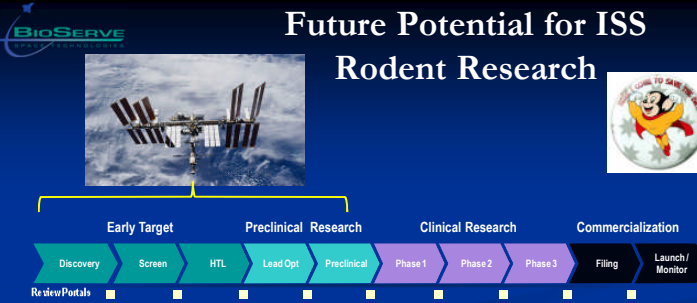
**CBTM-3 Publications**

- Bouxsein, ML, Bateman, TA, Hanson, AH, Pruitt, T, Livingston, E, Lemur, M, Louis L., Ellman, R, Spatz, J, Warmington, K, Tan, HL, Hill, D, Dwyer, D, Ortega, A, Maurya, S, Stolina, M, Lotinun, S, Baron, R, Paszty, C, Stodieck, LS and Ferguson, VL (2012), "Sclerostin Antibody Treatment Improves Bone Mass, Microarchitecture and Mechanical Properties in Mice Exposed to Microgravity: Results from the STS-135 Shuttle Mission", *ASBMR* and *NASA-HRP IWG* abstracts.
- Ellman, R, Ferguson, VL, Livingston, E, Lemus, M, Louis, L, Spatz, J, Warmington, K, Tan, HL, Hill, D, Stolin, M, Dwyer, D, Lotinun, S, Baron, R, Paszty, C, Stodieck, LS, Bouxsein, M, (2012), "Site- and Compartment-specific Effects of Microgravity on the Skeleton in Mice Flown on the STS-135 Shuttle Mission", *ASBMR* and *NASA-HRP IWG* abstracts.
- Lau, A, Ortega, A, Bouxsein, Bateman, TA, Hanson, AH, Pruitt, T, Livingston, Smith, C., de Rosa, A, Lai, E, Bowman, L, Stodieck, LS, Ellman, R, Spatz, J, Warmington, K, Tan, HL, Hill, D, Maura, S., Cureton, A, Lotinun, S, Paszty, C and Ferguson, VL, (2012), "Effects of Spaceflight and a Sclerostin Antibody Countermeasure on the Mechanical Properties of Bone in Mice", *ASBMR* abstract.
- Additional abstracts and publications from biospecimen sharing program are starting to appear.

**Sclerostin Antibody Drug Development**

- Amgen/UCB selected Romosozumab (fully human monoclonal antibody to sclerostin) to evaluate in clinical trials
  - Phase II trials have looked at doses up to 210mg and relatively infrequent treatments (up to 3 months between injections)
  - Drug appears safe and well tolerated
- Amgen/UCB are now conducting a Phase III clinical study for postmenopausal osteoporosis
  - Actively enrolling 5,000 patients as test subjects for study
  - Study will assess new fractures at 1 year after treatment
  - Results expected in ~2015
- If approved by the FDA (expected in ~2017), Romosozumab could become the clinical gold standard for treatment of postmenopausal osteoporosis.

## Future Potential for ISS Rodent Research



The diagram illustrates the future potential for ISS Rodent Research. It features a central timeline of drug development stages: Early Target (Discovery, Screen, HTL), Preclinical Research (Lead Opt, Preclinical), Clinical Research (Phase 1, Phase 2, Phase 3), and Commercialization (Filing, Launch/Monitor). Above the timeline is an image of the International Space Station (ISS) and a circular logo with a mouse and the text 'RODENT TO SPACE'. Below the timeline, a list of key findings is provided.

- These studies have shown the value of the spaceflight mouse models in testing novel musculoskeletal therapeutics
- Current efforts by NASA and CASIS will make it possible to study mice exposed to long-duration microgravity
- Would enable studies of extreme disuse that mimic severe neuro-degenerative disorders (e.g., ALS, neuropathies, spinal injury, etc.)
- Discovery of new drug targets and therapeutic compounds is possible

## Acknowledgements



The acknowledgements section includes a collage of images: a group photo of the STS-108, 118, 135 Musculoskeletal Research Teams, the Space Life Sciences Lab building, and various mission patches (KELLY-HORBAUGH, STS-108, STS-118, STS-135, STS-108, 118, 135). The text lists funding sources and research teams.

**Funding Sources:**

- Amgen
- NASA Space Product Development
- NASA Human Research Program
- NASA ISS National Lab
- NASA Ames Research Center
- NSBRI
- BioServe Space Technologies

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- Secondary science teams
- STS-108, 118, 135 crews