Se-Jin Lee

PERSONAL:

Birthplace: Seoul, South Korea (born October 20, 1958)
Citizenship: United States (naturalized 1977)
Spouse: Emily Lucy Germain-Lee, M.D.
Child: Benjamin Charles Germain Lee, Ph.D.

EDUCATION:

1981 AB, Harvard College (*summa cum laude*, Biochemical Sciences)
1989 MD and PhD, Johns Hopkins University School of Medicine
(Molecular Biology and Genetics; PhD advisor—Daniel Nathans)

PROFESSIONAL APPOINTMENTS:

1981 Medical Scientist Training Program, Johns Hopkins University School of Medicine
1989 Staff Associate, Carnegie Institution of Washington, Department of Embryology
1991 Assistant Professor, Johns Hopkins University School of Medicine, Department of Molecular Biology and Genetics
1997 Associate Professor, Johns Hopkins University School of Medicine, Department of Molecular Biology and Genetics
2001 Professor, Johns Hopkins University School of Medicine, Department of Molecular Biology and Genetics
2013 The Michael and Ann Hankin and Partners of Brown Advisory Professor in Scientific Innovation, Johns Hopkins University School of Medicine (endowed professorship)
2017 Professor Emeritus, Johns Hopkins University School of Medicine
2017 Presidential Distinguished Professor, University of Connecticut School of Medicine
2017 Professor, The Jackson Laboratory

HONORS:

1980 *Phi Beta Kappa* (Harvard College)
1981 *summa cum laude* (Harvard College)
2010 American Association for the Advancement of Science (AAAS) (elected Fellow)
2011 Senior Scholar in Aging (Ellison Medical Foundation)
2012 National Academy of Sciences (elected Member)
2013 Rolf Luft Award (Karolinska Institutet)
2013 Ho-Am Prize in Medicine (Samsung)
2015 National Academy of Inventors (elected Fellow)
2020 International Space Center Research and Development Conference Award
2023 Passano Award

SELECTED OTHER PROFESSIONAL ACTIVITIES:

2010 - 2015 Medical Advisory Committee, Muscular Dystrophy Association
2019 to date Senior Scientific Advisor to the Dean, University of Connecticut School of Medicine
2021 to date Search and Screen Committee, Medical Physiology, National Academy of Sciences
2021 - 2023 Member, NIH Skeletal Muscle and Exercise Physiology Study Section
2023 - 2025 Chair, NIH Skeletal Muscle and Exercise Physiology Study Section

CONSULTING ACTIVITIES WITH INDUSTRY:

1992 - 1994	Consultant, Cambridge Neuroscience, Inc.
1994 - 2011	Scientific founder and consultant, MetaMorphix, Inc.
2006 - 2009	Consultant, Merck and Co.
2011	Consultant, Eleven Biotherapeutics, Inc.
2011 - 2012	Consultant, NGM Biopharmaceuticals, Inc.
2012 - 2013	Consultant, Pfizer, Inc.
2013	Consultant, Teva Pharmaceuticals Inc.
2014	Consultant, Ascelegen, Inc.
2015	Consultant, Chugai Pharmaceutical Co., Ltd.
2016	Consultant, Akros Pharma, Inc.
2017	Consultant, Chugai Pharmaceutical Co., Ltd.
2017 - 2019	Member, Scientific Advisory Board, AliveGen, Inc.
2019	Member, Scientific Advisory Board, Eclode, Inc.
2022 to date	Consultant, Alnylam Pharmaceuticals, Inc.
2022 to date	Consultant, Biohaven Pharmaceuticals, Inc.

ISSUED U.S. PATENTS: 57 total

SELECTED PUBLICATIONS ON MYOSTATIN (ANNOTATED):

Alexandra C. McPherron, Ann M. Lawler, and **Se-Jin Lee** (1997) Regulation of skeletal muscle mass in mice by a new TGF-ß superfamily member. *Nature* 387:83-90.

> We report the discovery of myostatin and its function as a negative regulator of muscle mass. This paper launched the myostatin field. There are now over 3500 papers identified by a Pubmed search with the term “myostatin,” and according to Google Scholar, this is the most highly cited paper under the search term “skeletal muscle.” Eleven companies have tested myostatin inhibitors in clinical trials for a wide range of indications characterized by muscle loss and/or metabolic dysfunction, with 24 of these clinical trials having reached phase II or III.

Alexandra C. McPherron and **Se-Jin Lee** (1997) Double muscling in cattle due to mutations in the myostatin gene. *Proc. Natl. Acad. Sci., USA* 94:12457-12461.

> We report the cloning of the myostatin gene from 9 different mammalian, avian, and piscine species and the identification of naturally-occurring mutations in two heavily-muscled breeds of cattle. These findings demonstrate that the sequence and function of myostatin have been highly conserved through evolution.

Se-Jin Lee and Alexandra C. McPherron (2001) Regulation of myostatin activity and muscle growth. *Proc. Natl. Acad. Sci., USA* 98:9306-9311.

> This is the first description of each of the following: (i) myostatin exists in a latent complex bound to its propeptide, (ii) follistatin is a potent naturally-occurring inhibitor of myostatin, and (iii) myostatin signals through activin type II receptors. Drugs based on each of these findings have been or are currently being tested by pharmaceutical/biotechnology companies in phase II or III clinical trials.

Alexandra C. McPherron and **Se-Jin Lee** (2002) Suppression of body fat accumulation in myostatin-deficient mice. *J. Clin. Invest.* 109:595-601.

> We show that loss of myostatin can suppress total body fat accumulation and improve glucose metabolism in mouse models of obesity and type 2 diabetes.

Teresa A. Zimmers, Monique V. Davies, Leonidas G. Koniaris, Paul Haynes, Aurora F. Esquela, Kathy N. Tomkinson, Alexandra C. McPherron, Neil M. Wolfman, and **Se-Jin Lee** (2002) Induction of cachexia in mice by systemically administered myostatin. *Science* 296:1486-1488.

> We show that systemic overexpression of myostatin in mice induces a cachexia-like syndrome reminiscent of that seen in humans with a variety of different diseases, such as cancer, AIDS, and heart disease. We also show that myostatin circulates in the blood in a latent form.

Neil M. Wolfman, Alexandra C. McPherron, William N, Pappano, Monique V. Davies, Kening Song, Kathleen N. Tomkinson, Jill F. Wright, Liz Zhao, Suzanne M. Sebald, Daniel S. Greenspan, and **Se-Jin Lee** (2003) Activation of latent myostatin by the BMP-1/tolloid family of metalloproteinases. *Proc. Natl. Acad. Sci., USA* 100:15842-15846.

> We show that myostatin is activated from its latent state by proteolytic cleavage of the propeptide by the BMP/tolloid family of metalloproteases. This finding is the basis for drug development activities aimed at preventing myostatin activation.

Markus Schuelke, Kathryn R. Wagner, Leslie Stolz, Christoph Hubner, Thomas Riebel, Wolfgang Komen, Thomas Braun, James F. Tobin, and **Se-Jin Lee** (2004) Myostatin mutation associated with gross muscle hypertrophy in a child. *New Engl. J. Med*. 350:2682-2688.

> This is the first identification of a human with a myostatin mutation. This paper shows that myostatin plays a similar role in humans as in other species.

Se-Jin Lee, Lori A. Reed, Monique V. Davies, Stefan Girgenrath, Mary E.P. Goad, Kathy N. Tomkinson, Jill F. Wright, Christopher Barker, Gregory Ehrmantraut, James Holmstrom, Betty Trowell, Barry Gertz, Man-Shiow Jiang, Suzanne M. Sebald, Martin Matzuk, En Li, Li-fang Liang, Edwin Quattlebaum, Ronald L. Stotish, and Neil M. Wolfman (2005) Regulation of muscle growth by multiple ligands signaling through activin type II receptors. *Proc. Natl. Acad. Sci., USA* 102:18117-18122.

> We provide the first genetic evidence that myostatin signaling *in vivo* is mediated by the activin type II receptors. This paper is also the first description of the soluble form of one of these receptors as a potent inhibitor of myostatin *in vivo*. This soluble receptor, which is still the most potent muscle anabolic agent described to date, has been the focus of drug development activities by several companies. Furthermore, using this soluble receptor, we show that other ligands cooperate with myostatin to regulate muscle growth. In subsequent work, we identify activin A as the key cooperating ligand.

Se-Jin Lee (2007) Quadrupling muscle mass in mice by targeting TGF-ß signaling pathways. *PLoS ONE* 2:e789.

> I provide additional evidence that other TGF-ß family members cooperate with myostatin to limit muscle growth and reveal the extraordinary muscle growth (quadrupling of muscle mass) that can be induced by targeting multiple ligands simultaneously. These studies along with the soluble receptor studies are the basis for drug development strategies aimed at targeting other ligands in addition to myostatin to treat muscle loss.

Se-Jin Lee (2008) Genetic analysis of the role of proteolysis in the activation of latent myostatin. *PLoS ONE* 3:e1628.

> I provide genetic evidence showing that latent myostatin is activated by proteolytic cleavage of its propeptide *in vivo*.

Se-Jin Lee, Yun-Sil Lee, Teresa A. Zimmers, Arshia Soleimani, Martin M. Matzuk, Kunihiro Tsuchida, Ronald D. Cohn, and Elisabeth R. Barton (2010) Regulation of muscle mass by follistatin and activins. *Mol. Endocrinol.* 24:1998-2008.

We identify activin A as another TGF-ß family member that acts to limit muscle mass and show that follistatin normally acts to inhibit signaling by myostatin/activin A in muscle.

Se-Jin Lee, Thanh V. Huynh, Yun-Sil Lee, Suzanne M. Sebald, Sarah Wilcox-Adelman, Naoki Iwamori, Christoph Lepper, Martin M. Matzuk, and Chen-Ming Fan (2012) Role of satellite cells versus myofibers in muscle hypertrophy induced by inhibition of the myostatin/activin signaling pathway. *Proc. Natl. Acad. Sci., USA* 109:E2353-E2360.

We show that myofibers are the direct target for myostatin signaling and that muscle growth induced by myostatin inhibition does not require satellite cells. These findings have implications for targeting this pathway to treat conditions in which the satellite cell pool has been depleted, such as in aging.

Yun-Sil Lee and **Se-Jin Lee** (2013) Regulation of GDF-11 and myostatin activity by GASP-1 and GASP-2. *Proc. Natl. Acad. Sci., USA* 110:E3713-22

We show that both myostatin and GDF-11 are regulated by the inhibitory binding proteins, GASP-1 and GASP-2, *in vivo*.

Yun-Sil Lee, Thanh V. Huynh, and **Se-Jin Lee** (2016) Paracrine and endocrine modes of myostatin action. *J. Appl. Physiol.* 120:592-598

We provide genetic evidence that myostatin has both paracrine and endocrine modes of action.

Se-Jin Lee, Adam Lehar, Jessica U. Meir, Christina Koch, Andrew Morgan, Lara E. Warren, Renata Rydzik, Daniel W. Youngstrom, Harshpreet Chandok, Joshy George, Joseph Gogain, Michael Michaud, Thomas A. Stoklasek, Yewei Liu, and Emily L. Germain-Lee (2020) Targeting myostatin/activin A protects against skeletal muscle and bone loss during spaceflight. *Proc. Natl. Acad. Sci., USA* 117:23942-23951.

We report the results of our “Sending Mighty Mice to Space” project, in which we show that blocking myostatin/activin A signaling protects against skeletal muscle and bone loss in mice sent to the International Space Station.

Se-Jin Lee, Adam Lehar, Yewei Liu, Chi Hai Ly, Quynh-Mai Pham, Michael Michaud, Renata Rydzik, Daniel W. Youngstrom, Michael M. Shen, Vesa Kaartinen, Emily L. Germain-Lee, Thomas A. Rando (2020) Functional redundancy of type I and type II receptors in the regulation of skeletal muscle growth by myostatin and activin A. *Proc. Natl. Acad. Sci., USA* 117:30907-30917.

We report a comprehensive genetic analysis of type II (ACVR2 and ACVR2B) and type I (ALK4 and ALK5) receptors to show that myostatin and activin A utilize all possible receptor combinations to signal directly to myofibers to regulate muscle growth. We also show that targeting signaling in myofibers is sufficient to cause reduced overall body fat content and improved glucose metabolism, demonstrating that these result from the anabolic effects in muscle.

Yewei Liu, Adam Lehar, Renata Rydzik, Harshpreet Chandok, Yun-Sil Lee, Daniel W. Youngstrom, Joshy George, Martin M. Matzuk, Emily L. Germain-Lee, and **Se-Jin Lee** (2021) Local versus systemic control of bone and skeletal muscle mass by components of the transforming growth factor-ß signaling pathway. *Proc. Natl. Acad. Sci., USA* 118:e2111401118.

We report a detailed genetic analysis of the role of follistatin in regulating both muscle and bone and show that targeting the two type 1 receptors (ALK4 and ALK5) in osteoblasts leads to an approximate 10-fold increase in bone mass and density, revealing the extraordinary capacity for bone accrual that is normally kept in check by this regulatory system.

SELECTED REVIEW ARTICLES ON MYOSTATIN

Se-Jin Lee (2004) Regulation of muscle mass by myostatin. *Ann. Rev. Cell Dev. Biol.* 20:61-86.

> I review what is known about the myostatin regulatory system, and I propose that one of the reasons that the myostatin regulatory network has been so highly conserved through evolutionary selection is that it plays a critical role in regulating the overall metabolic balance between muscle and adipose tissue.

Se-Jin Lee (2021) Targeting the myostatin signaling pathway to treat muscle loss and metabolic dysfunction. *J. Clin. Invest*. 131(9):148372.

> I review the current state of efforts to target the myostatin pathway for clinical applications.

Se-Jin Lee (2023) Myostatin: a skeletal muscle chalone. *Annu. Rev. Physiol.* 85:269-291.

> I review the current state of knowledge of the myostatin signaling pathway, particularly in the context of the chalone theory for the control of tissue size by circulating feedback growth inhibitors.

COMPLETE LIST OF ORIGINAL RESEARCH PUBLICATIONS:

Daniel Linzer, **Se-Jin Lee**, Linda Ogren, Frank Talamantes, and Daniel Nathans (1985) Identification of proliferin mRNA and protein in mouse placenta. *Proc. Natl. Acad. Sci., USA* 82:4356-4359. [PMID: 3859868]

Se-Jin Lee and Daniel Nathans (1987) Secretion of proliferin. *Endocrinology* 120:208-213. [PMID: 3780559]

Se-Jin Lee and Daniel Nathans (1988) Proliferin secreted by cultured cells binds to mannose-6-phosphate receptors. *J. Biol. Chem.* 263:3521-3527. [PMID: 2963825]

Se-Jin Lee, Frank Talamantes, Elizabeth Wilder, Daniel Linzer, and Daniel Nathans (1988) Trophoblastic giant cells of the mouse placenta as the site of proliferin synthesis. *Endocrinology* 122:1761-1768. [PMID: 3359962]

Se-Jin Lee (1990) Expression of HSP86 in male germ cells. *Mol. Cell. Biol.* 10:3239-3242. [PMID: 2342473]

Se-Jin Lee (1990) Identification of a novel member (GDF-1) of the transforming growth factor-ß superfamily. *Mol. Endocrinol.* 4:1034-1040. [PMID: 1704486]

Se-Jin Lee (1991) Expression of growth/differentiation factor-1 in the nervous system: Conservation of a bi-cistronic structure. *Proc. Natl. Acad. Sci., USA* 88:4250-4254. [PMID: 2034669]

Alexandra C. McPherron and **Se-Jin Lee** (1993) GDF-3 and GDF-9: Two new members of the transforming growth factor-ß superfamily containing a novel pattern of cysteines. *J. Biol. Chem.* 268:3444-3449. [PMID: 8429021]

Elaine E. Storm, Thanh V. Huynh, Neal G. Copeland, Nancy A. Jenkins, David M. Kingsley, and **Se-Jin Lee** (1994) Limb alterations in *brachypodism* mice due to mutations in a new member of the TGF-ß superfamily. *Nature* 368:639-643. [PMID: 8145850]

Sharon A. McGrath, Aurora F. Esquela, and **Se-Jin Lee** (1995) Oocyte-specific expression of growth/differentiation factor-9. *Mol. Endocrinol.* 9:131-136. [PMID: 7760846]

Noreen S. Cunningham, Nancy A. Jenkins, Debra J. Gilbert, Neal G. Copeland, A. Hari Reddi, and **Se-Jin Lee** (1995) Growth/Differentiation Factor-10: A new member of the transforming growth factor-ß superfamily related to bone morphogenetic protein-3. *Growth Factors* 12:99-109. [PMID: 8679252]

Alexandra C. McPherron, Ann M. Lawler, and **Se-Jin Lee** (1997) Regulation of skeletal muscle mass in mice by a new TGF-ß superfamily member. *Nature* 387:83-90. [PMID: 9139826]

Aurora F. Esquela, Teresa A. Zimmers, Leonidas G. Koniaris, James V. Sitzmann, and **Se-Jin Lee** (1997) Transient down-regulation of inhibin-ßC expression following partial hepatectomy. *Biochem. Biophys. Res. Comm.* 235:553-556. [PMID: 9207194]

Alexandra C. McPherron and **Se-Jin Lee** (1997) Double muscling in cattle due to mutations in the myostatin gene. *Proc. Natl. Acad. Sci., USA* 94:12457-12461. [PMID: 9356471]

Alexandra C. McPherron, Ann M. Lawler, and **Se-Jin Lee** (1999) Regulation of anterior/posterior patterning of the axial skeleton by growth/differentiation factor-11. *Nature Genet*. 22:260-264. [PMID: 10391213]

Renbin Zhao, Ann M. Lawler, and **Se-Jin Lee** (1999) Characterization of GDF-10 expression patterns and null mice. *Dev. Biol.* 212:68-79. [PMID: 10419686]

Christopher T. Rankin, Tracie Bunton, Ann M. Lawler, and **Se-Jin Lee** (2000) Regulation of left-right patterning in mice by growth/differentiation factor-1. *Nature Genet.* 24:262-265. [PMID: 10700179]

Edward C. Hsiao, Leonidas G. Koniaris, Teresa A. Zimmers-Koniaris, Suzanne M. Sebald, Thanh Huynh, and **Se-Jin Lee** (2000) Characterization of growth/differentiation factor-15 (*Gdf15*): a TGF-ß superfamily member induced following liver injury. *Mol. Cell. Biol.* 20:3742-3751. [PMID: 10779363]

Se-Jin Lee and Alexandra C. McPherron (2001) Regulation of myostatin activity and muscle growth. *Proc. Natl. Acad. Sci., USA* 98:9306-9311. [PMID: 11459935]

Alexandra C. McPherron and **Se-Jin Lee** (2002) Suppression of body fat accumulation in myostatin-deficient mice. *J. Clin. Invest.* 109:595-601. [PMID: 11877467]

Teresa A. Zimmers, Monique V. Davies, Leonidas G. Koniaris, Paul Haynes, Aurora F. Esquela, Kathy N. Tomkinson, Alexandra C. McPherron, Neil M. Wolfman, and **Se-Jin Lee** (2002) Induction of cachexia in mice by systemically administered myostatin. *Science* 296:1486-1488. [PMID: 12029139]

Kathryn R. Wagner, Alexandra C. McPherron, Nicole Winik, and **Se-Jin Lee** (2002) Loss of myostatin attenuates severity of muscular dystrophy in mdx mice. *Ann. Neurol.* 52:832-836. [PMID: 12447939]

Aurora F. Esquela and **Se-Jin Lee** (2003) Regulation of metanephric kidney development by growth/differentiation factor 11. *Dev. Biol.* 257:356-370. [PMID: 12729564]

Neil M. Wolfman, Alexandra C. McPherron, William N, Pappano, Monique V. Davies, Kening Song, Kathleen N. Tomkinson, Jill F. Wright, Liz Zhao, Suzanne M. Sebald, Daniel S. Greenspan, and **Se-Jin Lee** (2003) Activation of latent myostatin by the BMP-1/tolloid family of metalloproteinases. *Proc. Natl. Acad. Sci., USA* 100:15842-15846. [PMID: 14671324]

Markus Schuelke, Kathryn R. Wagner, Leslie Stolz, Christoph Hubner, Thomas Riebel, Wolfgang Komen, Thomas Braun, James F. Tobin, and **Se-Jin Lee** (2004) Myostatin mutation associated with

gross muscle hypertrophy in a child. *New Engl. J. Med*. 350:2682-2688. [PMID: 15215484]

Se-Jin Lee, Lori A. Reed, Monique V. Davies, Stefan Girgenrath, Mary E.P. Goad, Kathy N. Tomkinson, Jill F. Wright, Christopher Barker, Gregory Ehrmantraut, James Holmstrom, Betty Trowell, Barry Gertz, Man-Shiow Jiang, Suzanne M. Sebald, Martin Matzuk, En Li, Li-fang Liang, Edwin Quattlebaum, Ronald L. Stotish, and Neil M. Wolfman (2005) Regulation of muscle growth by multiple ligands signaling through activin type II receptors. *Proc. Natl. Acad. Sci., USA* 102:18117-18122. [PMID: 16330774]

Se-Jin Lee (2007) Quadrupling muscle mass in mice by targeting TGF-ß signaling pathways. *PLoS ONE* 2:e789. [PMID: 17726519]

Se-Jin Lee (2008) Genetic analysis of the role of proteolysis in the activation of latent myostatin. *PLoS ONE* 3:e1628. [PMID: 18286185]

Alexandra C. McPherron, Thanh V. Huynh, and **Se-Jin Lee** (2009) Redundancy of myostatin and growth/differentiation factor 11 function. *BMC Dev. Biol.* 9:24. [PMID: 19298661]

Yuichi Oshima, Noriyuki Ouchi, Masayuki Shimano, David R. Pimentel, Kyriakos N. Papanicolaou, Kalyani D. Panse, Kunihiro Tsuchida, Enrique Lara-Pezzi, **Se-Jin Lee**, and Kenneth Walsh (2009) Activin A and follistatin-like 3 determine the susceptibility of heart to ischemic injury. *Circulation* 120:1606-1615. [PMID: 19805648]

Kevin J. Morine, Lawrence T. Bish, Joshua T. Selsby, Jeffrey A. Gazzara, Klara Pendrak, Meg M. Sleeper, Elisabeth R. Barton, **Se-Jin Lee**, and H. L. Sweeney (2010) Activin IIB receptor blockade attenuates dystrophic pathology in a mouse model of Duchenne muscular dystrophy. *Muscle Nerve* 42:722-730. [PMID: 20730876]

Se-Jin Lee, Yun-Sil Lee, Teresa A. Zimmers, Arshia Soleimani, Martin M. Matzuk, Kunihiro Tsuchida, Ronald D. Cohn, and Elisabeth R. Barton (2010) Regulation of muscle mass by follistatin and activins. *Mol. Endocrinol.* 24:1998-2008. [PMID: 20810712]

Young Jae Lee, Alexandra McPherron, Susan Choe, Yasuo Sakai, Roshantha A. Chandraratna, **Se-Jin Lee**, and S. Paul Oh (2010) Growth differentiation factor 11 signaling controls retinoic acid activity for axial vertebral development. *Dev. Biol.* 347:195-203. [PMID: 20801112]

Saskia C.A. de Jager, Beatriz Bermúdez, Ilze Bot, Rory R. Koenen, Martine Bot, Annemieke Kavelaars, Vivian de Waard, Cobi J. Heijnen, Francisco J.G. Muriana, Christian Weber, Theo J.C. van Berkel, Johan Kuiper, **Se-Jin Lee**, Rocio Abia, and Erik A.L. Biessen (2011) Growth differentiation factor 15 deficiency protects against atherosclerosis by attenuating CCR2-mediated macrophage chemotaxis. *J. Exp. Med.* 208:217-225. [PMID: 21242297]

Masayuki Shimano, Noriyuki Ouchi, Kazuto Nakamura, Yuichi Oshima, Akiko Higuchi, David R. Pimentel, Kalyani D. Panse, Enrique Lara-Pezzi, **Se-Jin Lee**, Flora Sam, and Kenneth Walsh (2011) Cardiac myocyte-specific ablation of follistatin-like 3 attenuates stress-induced myocardial hypertrophy. *J. Biol. Chem.* 286:9840-9848. [PMID: 21245136]

Nicolas Ricard, Delphine Ciais, Sandrine Levet, Mariela Subileau, Christine Mallet, Teresa A. Zimmers, **Se-Jin Lee**, Marie Bidart, Jean-Jacques Feige, and Sabine Bailly (2012) BMP9 and BMP10 are critical for postnatal retinal vascular remodeling. *Blood* 119:6162-6171. [PMID: 22566602]

Yi Liu-Chittenden, Bo Huang, Joong Sup Shim, Qian Chen, **Se-Jin Lee**, Robert A. Anders, Jun O. Liu, and Duojia Pan (2012) Genetic and pharmacological disruption of the TEAD-YAP complex suppresses the oncogenic activity of YAP. *Genes Dev*. 26:1300-1305. [PMID: 22677547]

Se-Jin Lee, Thanh V. Huynh, Yun-Sil Lee, Suzanne M. Sebald, Sarah Wilcox-Adelman, Naoki Iwamori, Christoph Lepper, Martin M. Matzuk, and Chen-Ming Fan (2012) Role of satellite cells versus myofibers in muscle hypertrophy induced by inhibition of the myostatin/activin signaling pathway. *Proc. Natl. Acad. Sci., USA* 109:E2353-E2360. [PMID: 22869749]

Yang A. Roby, Michael A. Bushey, Li E. Cheng, Heather M. Kulaga, **Se-Jin Lee**, and Randall R. Reed (2012) *Zfp423/OAZ* mutation reveals the importance of Olf/EBF transcription activity in olfactory neuronal maturation. *J. Neurosci.* 32:13679-13688a. [PMID: 23035080]

Raouia Fakhfakh, **Se-Jin Lee**, and Jacques P. Tremblay (2012) Administration of a soluble activin type IIB receptor promotes the transplantation of human myoblasts in dystrophic mice. *Cell Transplant.* 21:1419-1430. [PMID: 22449443]

Sandrine Levet, Delphine Ciais, Galina Merdzhanova, Christine Mallet, Teresa A. Zimmers, **Se-Jin Lee**, Fabrice P. Navarro, Isabelle Texier, Jean-Jacques Feige, Sabine Bailly, and Daniel Vittet (2013) Bone Morphogenetic Protein 9 (BMP9) controls lymphatic vessel maturation and valve formation. *Blood*, 122:598-607. [PMID: 23741013]

Yun-Sil Lee and **Se-Jin Lee** (2013) Regulation of GDF-11 and myostatin activity by GASP-1 and GASP-2. *Proc. Natl. Acad. Sci., USA* 110:E3713-22. [PMID: 24019467]

Yasuhiro Yoshimatsu, Yulia G. Lee, Yuichi Akatsu, Luna Taguchi, Hiroshi I. Suzuki, Sara I. Cunha, Kazuichi Maruyama, Yuka Suzuki, Tomoko Yamazaki, Akihiro Katsura, S. Paul Oh, Teresa A. Zimmers, **Se-Jin Lee**, Kristian Pietras, Gou Young Koh, Kohei Miyazono, and Tetsuro Watabe (2013) Bone morphogenetic protein-9 inhibits lymphatic vessel formation via activin receptor-like kinase 1 during development and cancer progression. *Proc. Natl. Acad. Sci., USA* 110:18940-18945. [PMID: 24133138]

Alison M. Muir, Yinshi Ren, Delana H. Butz, Nicholas A. Davis, Robert D. Blank, David E. Birk, **Se-Jin Lee**, David Rowe, Jian Q. Feng, and Daniel S. Greenspan (2014) Induced ablation of *Bmp1* and *Tll1* produces osteogenesis imperfecta in mice. *Hum. Mol. Genet.* 23:3085-3101. [PMID: 24419319]

Elizabeth M. MacDonald, Eva Andres-Mateos, Rebeca Mejias, Jessica L. Simmers, Ruifa Mi, Jae-Sung Park, Stephanie Ying, Ahmet Hoke, **Se-Jin Lee**, and Ronald D. Cohn (2014) Denervation atrophy is independent from Akt and mTOR activation and is not rescued by myostatin inhibition. *Dis. Model. Mech.* 7:471-481. [PMID: 24504412]

Douglas J. DiGirolamo, Vandana Singhai, Xiaoli Chang, **Se-Jin Lee**, and Emily L. Germain-Lee (2015) Administration of soluble activin receptor 2B increases bone and muscle mass in a mouse model of osteogenesis imperfecta. *Bone Res.* 3:14042. [PMID: 26161291]

Ryan G. Walker, Elizabeth B. Angerman, Chandramohan Kattamuri, Yun-Sil Lee, **Se-Jin Lee**, and Thomas B. Thompson (2015) Alternative binding modes identified for Growth and Differentiation Factor-associated Serum Protein (GASP)-family antagonism of myostatin. *J. Biol. Chem.* 290:7506-7516. [PMID: 25657005]

Yun-Sil Lee, Adam Lehar, Suzanne Sebald, Min Liu, Kayleigh A. Swaggart, C. Conover Talbot, Jr, Peter Pytel, Elisabeth R. Barton, Elizabeth M. McNally, and **Se-Jin Lee** (2015) Muscle hypertrophy induced by myostatin inhibition accelerates degeneration in dysferlinopathy. *Hum. Mol. Genet.* 24:5711-5719. [PMID: 26206886]

Lori R. Bernstein, Amelia C.L. Mackenzie, **Se-Jin Lee**, Charles L. Chaffin, and Istvan Merchenthaler (2016) Activin decoy receptor ActRIIB:Fc lowers FSH and therapeutically restores oocyte yield,

prevents oocyte chromosome misalignments and spindle aberrations, and increases fertility in midlife female SAMP8 mice. *Endocrinology* 157:1234-1247. [PMID: 26713784]

Yun-Sil Lee, Thanh V. Huynh, and **Se-Jin Lee** (2016) Paracrine and endocrine modes of myostatin action. *J. Appl. Physiol.* 120:592-598. [PMID: 26769954]

Alison M. Muir, Dawiyat Massoudi, Ngon Nguyen, Douglas R. Keene, **Se-Jin Lee**, David E. Birk, Jeffrey M. Davidson, M. Peter Marinkovich, and Daniel S. Greenspan (2016) BMP1-like proteinases are essential to the structure and wound healing of skin. *Matrix Biol.* 56:114-131. [PMID: 27363389]

Benjamin V. Park, Zachary T. Freeman, Ali Ghasemzadeh, Michael A. Chattergoon, Alleluiah Rutebemberwa, Jordana Steigner, Matthew E. Winter, Thanh V. Huynh, Suzanne M. Sebald, **Se-Jin Lee**, Fan Pan, Drew M. Pardoll, and Andrea L. Cox (2016) TGFß1-Mediated SMAD3 Enhances PD-1 Expression on Antigen-Specific T Cells in Cancer. *Cancer Discov*. 6:1366-1381. [PMID: 27683557]

Nikolas M. Eleftheriou, Jonas Sjölund, Matteo Bocci, Eliane Cortez, **Se-Jin Lee**, Sara I. Cunha, and Kristian Pietras (2016) Compound genetically engineered mouse models of cancer reveal dual targeting of ALK1 and endoglin as a synergistic opportunity to impinge on angiogenic TGF-β signaling. *Oncotarget* 7:84314-84325. [PMID: 27741515]

Hyo Kyun Chung, Dongryeol Ryu, Koon Soon Kim, Joon Young Chang, Yong Kyung Kim, Hyon-Seung Yi, Seul Gi Kang, Min Jeong Choi, Seong Eun Lee, Saet-Byel Jung, Min Jeong Ryu, Soung Jung Kim, Gi Ryang Kweon, Hail Kim, Jung Hwan Hwang, Chul-Ho Lee, **Se-Jin Lee**, Christopher E. Wall, Michael Downes, Ronald M. Evans, Johan Auwerx, and Minho Shong (2017) Growth differentiation factor 15 is a myomitokine governing systemic energy homeostasis. *J. Cell Biol.* 216:149-165. [PMID: 27986797]

Rajan Singh, Melissa Braga, Srinivasa T. Reddy, **Se-Jin Lee**, Meher Parveen, Victor Grijalva, Laurent Vergnes, and Shehla Pervin (2017) Follistatin Targets Distinct Pathways To Promote Brown Adipocyte Characteristics in Brown and White Adipose Tissues. *Endocrinology* 158:1217-1230. [PMID: 28324027]

Katja Breitkopf-Heinlein, Christoph Meyer, Courtney König, Haristi Gaitantzi, Annalisa Addante, Maria Thomas, Eliza Wiercinska, Chen Cai, Qi Li, Fengqi Wan, Claus Hellerbrand, Nektarios A. Valous, Maximilian J. Hahnel, Christian Ehlting, Johannes G. Bode, Stephanie Müller-Bohl, Ursula Klingmüller, Jutta Altenöder, Iryna Ilkavets, Marie-José Goumans, Lukas J. A. C. Hawinkels, **Se-Jin Lee**, Matthias Wieland, Carolin Mogler, Matthias P. Ebert, Blanca Herrera, Hellmut G. Augustin, Aránzazu Sánchez, Steven Dooley, and Peter ten Dijke (2017) BMP-9 interferes with liver regeneration and promotes liver fibrosis. *Gut* 66:939-954. [PMID: 28336518]

Brian C. Goh, Vandana Singhal, Angelica J. Herrera, Ryan E. Tomlinson, Soohyun Kim, Marie-Claude Faugere, Emily L. Germain-Lee, Thomas L. Clemens, **Se-Jin Lee**, and Douglas J. DiGirolamo (2017) Activin receptor type 2A (ACVR2A) functions directly in osteoblasts as a negative regulator of bone mass. *J. Biol. Chem.* 292:13809-13822. [PMID: 28659341]

Hadi Khalil, Onur Kanisicak, Vikram Prasad, Robert N. Correll, Xing Fu, Tobias Schips, Ronald J. Vagnozzi, Ruijie Liu, Thanh Huynh, **Se-Jin Lee**, Jason Karch, and Jeffery D. Molkentin (2017) Fibroblast-specific TGF-β–Smad2/3 signaling underlies cardiac fibrosis. *J. Clin. Invest.* 127:3770-3783. [PMID: 28891814]

Marie K. Bondulich, Nelly Jolinon, Georgina F. Osborne, Edward J. Smith, Ivan Rattray, Andreas Neueder, Kirupa Sathasivam, Mhoriam Ahmed, Nadira Ali, Agnesska C. Benjamin, Xiaoli Chang, James R.T. Dick, Matthew Ellis, Sophie A. Franklin, Daniel Goodwin, Linda Inuabasi, Hayley Lazell, Adam Lehar, Angela Richard-Londt, Jim Rosinski, Donna L. Smith, Tobias Wood, Sarah J. Tabrizi,

Sebastian Brandner, Linda Greensmith, David Howland, Ignacio Munoz-Sanjuan, **Se-Jin Lee**, and Gillian P. Bates (2017) Myostatin inhibition prevents skeletal muscle pathophysiology in Huntington's disease mice. *Sci. Rep.* 7:14275. [PMID: 29079832]

Rajan Singh, Shehla Pervn, **Se-Jin Lee**, Alan Kuo, Victor Grijalva, John David, Laurent Vergnes, and Srinivasa Reddy (2018) Metabolic profiling of follistatin overexpression: a novel therapeutic strategy for metabolic diseases. *Diabetes Metab. Syndr. Obes.* 11:65-84. [PMID: 29618935]

Annalisa Addante, Cesareo Roncero, Laura Almale, Nerea Lazcanoiturburu, Maria Garcia-Alvaro, Margarita Fernandez, Julian Sanz, Seddik Hammad, Zeribe Nwosu, **Se-Jin Lee**, Isabel Fabregat, Steven Dooley, Peter ten Dijke, Blanca Herrera, and Aranzazu Sanchez (2018) Bone morphogenetic protein 9 as a key regulator of liver progenitor cells in DDC-induced cholestatic liver injury. *Liver Int.* 38:1664-1675. [PMID: 29751359]

Jason Roh, Ryan Hobson, Vinita Chaudhari, Pablo Quintero, Ashish Yeri, Mark Benson, Chunyang Xiao, Daniel Zlotoff, Vassilios Bezzerides, Nicholas Houstis, Colin Platt, Federico Damilano, Brian R. Lindman, Sammy Elmariah, Michael Biersmith, **Se-Jin Lee**, Christine E. Seidman, Jonathan G. Seidman, Robert E. Gerszten, Estelle Lach-Trifilieff, David J. Glass, Anthony Rosenzweig (2019) Activin type II receptor signaling in cardiac aging and heart failure. *Sci. Transl. Med.* 11. pii: eaau8680. [PMID: 30842316]

Qingnian Goh, Tajeong Song, Michael J Petrany, Alyssa AW Cramer, Chengyi Sun, Sakthivel Sadayappan, **Se-Jin Lee**, Douglas P Millay (2019) Myonuclear accretion is a determinant of exercise-induced remodeling in skeletal muscle. *eLife* 8. pii: e44876. [PMID: 31012848]

Joonho Suh, Je-Hyun Eom, Na-Kyung Kim, Kyung Mi Woo, Jeong-Hwa Baek, Hyun-Mo Ryoo, **Se-Jin Lee**, and Yun-Sil Lee (2019) Growth differentiation factor 11 locally controls anterior-posterior patterning of the axial skeleton. *J. Cell. Physiol*. June 10. doi: 10.1002/jcp.28904 [PMID: 31183862]

Joonho Suh, Na-Kyung Kim, Seung-Hoon Lee, Je-Hyun Eom, Youngkyun Lee, Joo-Cheol Park, Kyung Mi Woo, Jeong-Hwa Baek, Jung-Eun Kim, Hyun-Mo Ryoo, **Se-Jin Lee**, and Yun-Sil Lee (2020) GDF11 promotes osteogenesis as opposed to MSTN, and follistatin, a MSTN/GDF11 inhibitor, increases muscle mass but weakens bone. *Proc. Natl. Acad. Sci., USA* 117:4910-4920. [PMID: 32071240]

Yael Eshed-Eisenbach, Jerome Devaux, Anna Vainshtein, Ofra Golani, **Se-Jin Lee**, Konstantin Feinberg, Natasha Sukhanov, Daniel S. Greenspan, Keiichiro Susuki, Matthew N. Rasband, and Elior Peles (2020) Precise Spatiotemporal Control of Nodal Na+ Channel Clustering by Bone Morphogenetic Protein-1/Tolloid-like Proteinases. *Neuron* 106:806-815. [PMID: 32209430]

Gauthier Schang, Luisina Ongaro, Hailey Schultz, Ying Wang, Xiang Zhou, Emilie Brûlé, Ulrich Boehm, **Se-Jin Lee**, and Daniel J. Bernard (2020) Murine FSH production depends on the activin type II receptors ACVR2A and ACVR2B. *Endocrinology* 161:1-17. [PMID: 32270195]

Se-Jin Lee, Adam Lehar, Jessica U. Meir, Christina Koch, Andrew Morgan, Lara E. Warren, Renata Rydzik, Daniel W. Youngstrom, Harshpreet Chandok, Joshy George, Joseph Gogain, Michael Michaud, Thomas A. Stoklasek, Yewei Liu, and Emily L. Germain-Lee (2020) Targeting myostatin/activin A protects against skeletal muscle and bone loss during spaceflight. *Proc. Natl. Acad. Sci., USA* 117:23942-23951. [PMID: 32900939]

Se-Jin Lee, Adam Lehar, Yewei Liu, Chi Hai Ly, Quynh-Mai Pham, Michael Michaud, Renata Rydzik, Daniel W. Youngstrom, Michael M. Shen, Vesa Kaartinen, Emily L. Germain-Lee, and Thomas A. Rando (2020) Functional redundancy of type I and type II receptors in the regulation of skeletal muscle growth by myostatin and activin A. *Proc. Natl. Acad. Sci., USA* 117:30907-30917. [PMID: 33219121]

Irina Kramerova, Masha Marinov, Jane Owens, **Se-Jin Lee**, Diana Becerra, and Melissa J. Spencer (2020) Myostatin inhibition promotes fast fibre hypertrophy but causes loss of AMP-activated protein kinase signaling and poor exercise tolerance in a model of limb-girdle muscular dystrophy. J. Physiol 598:3927-3939. [PMID: 33460149]

Diana Monsivais, Takashi Nagashima, Renata Prunskaite-Hyyryläinen, Kaori Nozawa, Keisuke Shimada, Suni Tang, Clark Hamor, Julio E. Agno, Fengju Chen, Ramya P. Masand, Steven L. Young, Chad J. Creighton, Francesco J. DeMayo, Masahito Ikawa, **Se-Jin Lee**, and Martin M. Matzuk (2021) Endometrial receptivity and implantation require uterine BMP signaling through an ACVR2A-SMAD1/SMAD5 axis. *Nat. Commun.* 12:3386. [PMID: 34099644]

Yewei Liu, Adam Lehar, Renata Rydzik, Harshpreet Chandok, Yun-Sil Lee, Daniel W. Youngstrom, Joshy George, Martin M. Matzuk, Emily L. Germain-Lee, and **Se-Jin Lee** (2021) Local versus systemic control of bone and skeletal muscle mass by components of the transforming growth factor-ß signaling pathway. *Proc. Natl. Acad. Sci., USA* 118:e2111401118. [PMID: 34385332]

Se-Jin Lee, Adam Lehar, Renata Rydzik, Daniel W. Youngstrom, Shalendar Bhasin, Yewei Liu, and Emily Germain-Lee (2022) Functional replacement of myostatin with GDF-11 in the germline of mice. *Skelet. Muscle* 12:7. [PMID: 35287700]

Guanlan Xu, Junqin Chen, SeongHo Jo, Truman B. Grayson, Sasanka Ramanadham, Akio Koizumi, Emily L. Germain-Lee, **Se-Jin Lee**, and Anath Shalev (2022) Deletion of *Gdf15* reduces ER stress-induced beta-cell apoptosis and diabetes. *Endocrinology* 163:bqac030. [PMID: 35290443]

Marianne E. Emmert, Parul Aggarwal, Kritton Shay-Winkler, **Se-Jin Lee**, Qingnian Goh, and Roger Cornwall (2022) Sex-specific role of myostatin signaling in neonatal muscle growth, denervation atrophy, and neuromuscular contractures. *eLife* 11:e81121. [PMID: 36314781]

Hyunwoo Choi, Bo-Gyeong Kim, Yong Hwan Kim, **Se-Jin Lee**, Young Jae Lee, and S. Paul Oh (2023) BMP10 functions independently from BMP9 for the development of a proper arteriovenous network. *Angiogenesis* 26:167-186. [PMID: 36348215]

Anne B. Newman, Sheena Patel, Jorge R. Kizer, **Se-Jin Lee**, Shalender Bhasin, Peggy Cawthon, Nathan LeBrasseur, Russell P. Tracy, Peter Ganz, and Steven Cummings. (2023) Evaluation of Associations of Growth Differentiation Factor-11, Growth Differentiation Factor-8 and their Binding Proteins Follistatin and Follistatin-like protein-3 with Dementia and Cognition. *J Gerontol A Biol Sci Med Sci*. Jan 20:glad019. doi: 10.1093/gerona/glad019. Epub ahead of print. PMID: 36660892

Peggy M. Cawthon, Sheena Patel, Anne B. Newman, Shalender Bhasin, Liming Peng, Russell Tracy, Jorge R. Kizer, **Se-Jin Lee**, Luigi Ferrucci, Peter Ganz, Nathan K. LeBrasseur, and Steve Cummings (2023) Evaluation of Associations of Growth Differentiation Factor-11, Growth Differentiation Factor-8 and their Binding Proteins Follistatin and Follistatin-like protein-3 with Measures of Skeletal Muscle Mass, Muscle Strength and Physical Function in Older Adults. *J Gerontol A Biol Sci Med Sci*. Feb 8:glad045. doi: 10.1093/gerona/glad045. Epub ahead of print. PMID: 36752218

INVITED REVIEWS AND COMMENTARIES:

Alexandra C. McPherron and **Se-Jin Lee** (1996) The transforming growth factor-ß superfamily. *In* Growth Factors and Cytokines in Health and Disease, vol. 1B. D. LeRoith and C. Bondy, eds. JAI Press, Inc., Greenwich, CT, pp. 357-393.

Se-Jin Lee and Alexandra C. McPherron (1999) Myostatin and the control of skeletal muscle mass.

Curr. Opin. Genet. Dev. 9:604-607. [PMID: 10508689]

Se-Jin Lee (2004) Regulation of muscle mass by myostatin. *Ann. Rev. Cell Dev. Biol.* 20:61-86. [PMID: 15473835]

Se-Jin Lee (2007) Sprinting without myostatin: a genetic determinant of athletic prowess. *Trends Genet.* 23:475-477. [PMID: 17884234]

Se-Jin Lee (2010) Speed and endurance: you can have it all. *J. Appl. Physiol.* 109:621-622. [PMID: 20538843]

Se-Jin Lee (2010) Extracellular regulation of myostatin: a molecular rheostat for muscle mass. *Immun., Endoc. & Metab. Agents in Med. Chem.* 10:183-194. [PMID: 21423813]

Se-Jin Lee and David J. Glass (2011) Treating cancer cachexia to treat cancer. *Skelet. Muscle* 1:2. [PMID: 21798080]

Se-Jin Lee (2012) Myostatin: regulation, function, and therapeutic applications. In Joseph A. Hill and Eric N. Olson (Eds.), *Muscle: Fundamental Biology and Mechanisms of Disease* (pp. 1077-1084). Academic Press.

Se-Jin Lee (2021) Targeting the myostatin signaling pathway to treat muscle loss and metabolic dysfunction. *J. Clin. Invest*. 131:148372. [PMID: 33938454]

Se-Jin Lee (2023) Myostatin: a skeletal muscle chalone. *Annu. Rev. Physiol.* 85:269-291. [PMID: 36266260]

Se-Jin Lee, Shalender Bhasin, Lloyd Klickstein, Venkatesh Krishnan, and Daniel Rooks (2023) Challenges and Future Prospects of Targeting Myostatin/Activin A Signaling to Treat Diseases of Muscle Loss and Metabolic Dysfunction. *J. Gerontol. A Biol. Sci. Med. Sci.* 78:S32-S37. [PMID: 36738276]

RESEARCH SUMMARY:

The overall focus of my research program has been to understand the molecular and cellular mechanisms underlying tissue growth and tissue regeneration with the long-term goal of developing new strategies for treating human diseases. For virtually my entire career, I have been interested in understanding the roles of extracellular signals in regulating embryonic development and adult tissue homeostasis, and almost all of that effort has focused on the superfamily of secreted proteins related to transforming growth factor-ß (TGF-ß). At the time that I became interested in this group of proteins when I was a Staff Associate at the Carnegie Institution of Washington's Department of Embryology, thirteen members of the TGF-ß family had been described in mammals. Many of these had been shown to play important regulatory roles during embryogenesis and in adult tissues, and many had shown promise for clinical applications, particularly with respect to tissue repair and tissue regeneration. Working on the assumption that many additional family members were yet to be identified and that these would also have biological activities that could be exploited for applications in regenerative medicine, I initiated a screen for new TGF-ß family members by taking advantage of the sequence homologies among the known family members. From this screen, which we continued after I moved my laboratory to the Johns Hopkins University School of Medicine, we identified a large number of novel TGF-ß family members that we have designated GDFs (growth/differentiation factors). Currently, the TGF-ß family in mammals encompasses over 35 distinct genes, and about one-third of these were discovered by my laboratory either solely or, in some cases, concurrently with

other laboratories. Because many of these GDFs turned out to have highly tissue-specific and cell type-specific expression patterns, understanding their precise biological functions has become the focus of intensive study both by my laboratory and by many others.

Without question, the most significant work of my laboratory has been the discovery of myostatin (GDF-8) and its role as a negative regulator of skeletal muscle mass [1]. We showed that myostatin is expressed almost exclusively in skeletal muscle tissue both during embryogenesis and in adult animals and that mice in which we knocked out the myostatin gene have a dramatic and widespread increase in skeletal muscle mass. We showed that individual muscles of myostatin knockout mice weigh about twice as much as corresponding muscles from normal mice and that the increase in mass results from a combination of muscle fiber hyperplasia and hypertrophy. Based on these and subsequent studies, it is clear that myostatin performs two functions, one to regulate the number of muscle fibers that are formed during development and a second to regulate the growth of individual muscle fibers postnatally. Our discovery of myostatin and its *in vivo* function uncovered a completely novel mechanism by which skeletal muscle mass is regulated. Prior to this discovery, there had been no evidence for the existence of a negative regulator of muscle growth. Moreover, our discovery of myostatin has revived some age-old theories about the regulation of tissue growth in general. Over 50 years ago, it was hypothesized that the size of a given tissue is controlled by the activity of a negative growth regulator (termed a chalone) that is produced specifically by that tissue and that acts to inhibit the growth of that tissue. Despite extensive efforts to obtain experimental support for this hypothesis, however, no molecules having the essential properties of a chalone have ever been isolated. Based largely on work from my laboratory, it is now clear that myostatin is, in fact, a skeletal muscle chalone [2]. Our work has shown that negative growth regulation is an important mechanism for limiting skeletal muscle mass and has raised the possibility that negative regulators of this type may exist for other tissues as well. Indeed, in very recent work [3], we have shown that targeting key receptors in osteoblasts can lead to increases in bone volume and density by approximately 10-fold, suggesting that bone mass may also be regulated by this type of mechanism. Hence, the mechanism of action of myostatin may prove to be a paradigm for how tissue growth and tissue size may be regulated throughout the body.

In addition to the scientific significance of this work, our discovery of myostatin has launched a widespread effort in both the academic and pharmaceutical communities to target myostatin signaling for both agricultural and human therapeutic applications. With respect to agricultural applications, our discovery suggested that blocking myostatin activity in livestock and aquatic species could be an effective strategy for dramatically improving meat/fish yields. Indeed, we showed that the myostatin gene has been highly conserved through evolution, and, simultaneously with two other research groups, we demonstrated that mutations in the myostatin gene are the cause of the enhanced muscling seen in certain breeds of cattle that have been described as double-muscled by cattle breeders [4]. Since then, other laboratories have shown that either engineered or naturally-occurring mutations in the myostatin gene can also cause increased muscling in sheep, dogs, rabbits, rats, swine, and goats. With respect to human therapeutic applications, our discovery raised the possibility that inhibiting myostatin activity may represent a new strategy for increasing muscle growth and regeneration in the context of disease states characterized by muscle degeneration or wasting. This possibility was bolstered by a collaborative study that we carried out with Dr. Markus Schuelke and his colleagues in Germany in which we characterized a myostatin mutation in a child with about twice the normal muscle mass, thereby providing the first clear evidence that myostatin plays a similar role in humans [5].

In order to pursue these types of applications, we have focused much of our effort on elucidating the molecular, cellular, and physiological mechanisms underlying myostatin activity. Our general strategy has been to attempt to identify key regulatory components using biochemical methods and then to validate the roles of these components using genetic approaches in mice. In this regard, we believe that we have made considerable progress in terms of understanding some of the basic mechanisms underlying myostatin signaling and regulation. Some of our contributions in this regard include: (i) the identification of receptors mediating myostatin signaling [6-9]; (ii) the

demonstration that myostatin exists in a latent, inactive complex with its propeptide and the elucidation of the mechanisms by which myostatin is activated from this latent complex [6, 10-12]; (iii) the identification of naturally-occurring myostatin binding proteins, including follistatin, and the demonstration that these play important roles in regulating myostatin activity *in vivo* [3, 6, 10, 13-15]; (iv) the development of engineered myostatin inhibitors capable of increasing muscle growth when administered systemically to adult mice [7, 11]; (v) the demonstration that other TGF-ß family members, including activin A, cooperate with myostatin to limit muscle growth [3, 7, 13-14]; (vi) the demonstration that muscle growth induced by myostatin inhibition does not involve muscle stem cell activation [8]; and (vii) the discovery of the myostatin-related protein, GDF-11, and its biological functions [1, 15, 16-19]. Some of this work would not have been possible without the valuable contributions of close collaborators, most notably Dr. Neil Wolfman's group at Wyeth.

Another major focus of our research effort has been to explore the potential beneficial effects of targeting this pathway in the context of diseases affecting skeletal muscle. For example, we showed that high levels of myostatin expression in mice can induce a dramatic wasting process [10] similar to the cachexia seen in patients with diseases such as cancer, AIDS, and heart failure, raising the possibility that targeting myostatin activity may be an effective strategy for combating muscle wasting. Another example is a recent study in which we showed that blocking this signaling pathway could mitigate muscle and bone loss in mice that we sent to the International Space Station, which could have implications for combating muscle and bone loss seen not only in astronauts during extended space travel but also as a result of disuse, such as in people who are bedridden or wheel chair-bound or in the elderly [20]. Finally, we have shown that human therapeutic applications may not be limited just to muscle degenerative and wasting conditions. In particular, we showed that loss of myostatin can suppress fat accumulation and improve glucose metabolism in genetic models of obesity in mice [21]. In this respect, I have speculated that the reason that the myostatin regulatory system has evolved to include such a complex regulatory network of regulatory proteins is that its primary physiological role is to regulate the overall metabolic balance between muscle and fat [2, 22]. Whatever the primary role of myostatin may be, our findings have raised the possibility that inhibition of myostatin activity may be a novel strategy for the prevention or treatment of metabolic diseases, such as obesity and type II diabetes. Indeed, one of most exciting prospects is that targeting this signaling pathway may provide a general strategy to combat both metabolic dysfunction and frailty during aging.

Throughout the past two decades, I have worked extensively with both the academic and biotechnology/pharmaceutical research communities to explore potential clinical applications for our work. Indeed, I believe that our past work on myostatin has played a major role in stimulating the enormous effort directed at understanding the control of muscle growth by this signaling mechanism. A PubMed search with the term "myostatin" now lists over 3600 papers, and according to Google Scholar, our *Nature* paper in 1997 reporting the discovery of myostatin has over 5000 citations, making it the most highly cited paper under the search term "skeletal muscle." At least 11 biotechnology and pharmaceutical companies have initiated clinical trials with agents targeting myostatin signaling, with 24 of these clinical trials having reached phase II or III [23]. Collectively, these agents have been tested in patients with debilitating muscle loss, including patients with muscular dystrophy, inclusion body myositis, spinal muscular atrophy, muscle atrophy following hip fracture surgery, age-related sarcopenia, and cachexia due to chronic obstructive pulmonary disease, end stage renal disease, and cancer, as well as in patients with metabolic diseases. Several recent trials have shown promising results in improving muscle function in patients with SMA and reducing fat content and improving glucose metabolism in obese patients with type 2 diabetes, which have led to 3 new phase III trials targeting SMA as well as additional trials targeting obesity.

1. *Nature* 387:83-90, 1997.
2. *Annu. Rev. Physiol.* 85:269-291, 2023.
3. *Proc. Natl. Acad. Sci., USA* 118:e2111401118, 2021.
4. *Proc. Natl. Acad. Sci., USA* 94:12457-12461, 1997.
5. *New Engl. J. Med*. 350:2682-2688, 2004.

6. *Proc. Natl. Acad. Sci., USA* 98:9306-9311, 2001.
7. *Proc. Natl. Acad. Sci., USA* 102:18117-18122, 2005.
8. *Proc. Natl. Acad. Sci., USA* 109:E2353-E2360, 2012.
9. *Proc. Natl. Acad. Sci., USA* 117:30907-30917, 2020.
10. *Science* 296:1486-1488, 2002.
11. *Proc. Natl. Acad. Sci., USA* 100:15842-15846, 2003.
12. *PLoS ONE* 3(8):e1628, 2008.
13. *PLoS ONE* 2(8):e789, 2007.
14. *Mol. Endocrinol.* 24:1998-2008, 2010.
15. *Proc. Natl. Acad. Sci., USA* 110:E3713-22, 2013.
16. *Nature Genet*. 22:260-264, 1999.
17. *Dev. Biol.* 257:356-370, 2003.
18. *BMC Dev. Biol.* 9:24, 2009.
19. *Skelet. Muscle* 12:7, 2022.
20. *Proc. Natl. Acad. Sci., USA* 117:23942-23951, 2020.
21. *J. Clin. Invest.* 109:595-601, 2002.
22. *Ann. Rev. Cell Dev. Biol.* 20:61-86, 2004.
23. *J. Clin. Invest.* 131:148372, 2021.