Se-Jin Lee

CONTACT INFORMATION:

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PERSONAL:

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

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

HONORS:

1980 *Phi Beta Kappa*, Harvard College
1981 *summa cum laude*, Harvard College
2010 Fellow, American Association for the Advancement of Science (AAAS)
2012 Member, National Academy of Sciences (Medical Physiology and Metabolism)
2013 Rolf Luft Award (Karolinska Institutet)
2013 Ho-Am Prize in Medicine
2013 The Michael and Ann Hankin and Partners of Brown Advisory Professorship in Scientific Innovation

OTHER PROFESSIONAL ACTIVITIES:

1992—1994	Consultant, Cambridge Neuroscience, Inc.
1994—2011	Scientific founder and consultant, MetaMorphix, Inc.
2006—2009	Consultant, Merck and Co.
2010—date	Member, Medical Advisory Committee, Muscular Dystrophy Association
2011	Consultant, Eleven Biotherapeutics, Inc.
2011—2012	Consultant, NGM Biopharmaceuticals, Inc.
2012—2013	Consultant, Pfizer, Inc.
2013	Consultant, Teva Pharmaceuticals Inc.

KEY PUBLICATIONS:

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.

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

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.

Markus Schuelke, Kathryn R. Wagner, Leslie Stolz, Christoph Hubner, Thomas Riebel, Wolfgang Komen, Thomas Braun, James F. Tobin, and **Se-Jin Lee** (2004) Gross muscle hypertrophy in a child associated with a myostatin (GDF-8) mutation. *New Engl. J. Med*. 350:2682-2688.

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.

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: 107—179]

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) Gross muscle hypertrophy in a child associated with a myostatin (GDF-8) mutation. *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(8):e789. doi:10.1371/journal.pone.0000789 [PMID: 17726519]

Se-Jin Lee (2008) Genetic analysis of the role of proteolysis in the activation of latent myostatin. *PLoS ONE* 3(8):e1628. doi:10.1371/journal.pone.0001628 [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. doi:10.1186/1471-213X-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 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. doi:10.1073/pnas.1206410109. [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. doi: 10.1073/pnas.1309907110. [PMID: 24019467]

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. *Skeletal 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.

ISSUED U.S. PATENTS: 53 total

INVITED LECTURES:

Scientific Conferences and Symposia:

Gordon Research Conference: Lysosomes (1988)
Gordon Research Conference: Animal Cells and Viruses (1990)
36th Annual Southeast Regional Developmental Biology Conference (1994)
1st International Conference on Bone Morphogenetic Proteins (1994)
15th Annual Congress of the Korean Society of Medical Genetics—plenary speaker (1995)
2nd International Conference on Fibrodysplasia Ossificans Progressiva (1995)
8th Annual TGF-ß Symposium (Japan)—plenary speaker (1997)
Gordon Research Conference: Myogenesis (1998)
Gordon Research Conference: Myogenesis (2001)
FASEB Summer Research Conference: The TGF-ß Superfamily—Signaling and Development (2001)
Keystone Symposium: Molecular Control of Adipogenesis and Obesity/Diabetes Mellitus—Molecular Mechanisms, Genetics, and New Therapies (2002)
American Physiological Society: Myostatin—symposium chair (2002)
Poultry Science Association: Genetic Technology Applied to Poultry Production (2002)
American Association for Cancer Research: The TGF-ß Superfamily—Roles in the Pathogenesis of Cancer and Other Diseases (2003)
FASEB Summer Research Conference: The TGF-ß Superfamily—Signaling and Development (2003)
Society for Developmental Biology, 62nd Annual Meeting—plenary speaker (2003)
Developmental Biology Day, University of Alabama at Birmingham (2004)
Life Sciences Research Foundation, guest speaker (2005)
Spring Symposium of the Korean Society of Endocrinology—plenary speaker (2006)
Endocrine Society: Normal and Oncogenic Roles of Activin, Inhibin, and Other TGF-ß Related Ligands (2007)
Poultry Performance Workshop (2007)
Partnership for Biotechnology Research (Huntsville, Alabama), 9th Annual BioRetreat—keynote

speaker (2007)
Banbury Center Conference: Molecular Mechanisms Modulating Skeletal Muscle Mass and Function (2008)
2nd Annual Dysferlin Conference (2008)
Institute of Myology workshop: Current Advances in the Development of Therapies for Neuromuscular Disorders Based on Myostatin Signaling (2008)
Washington University School of Medicine, Department of Pediatrics Retreat—keynote speaker (2009)
3rd Annual Dysferlin Conference (2009)
Therapeutic Targets in the Congenital Muscular Dystrophies (2009)
The Nature Colloquia on Biomedicine: Colloquium on Frailty—organizer (2010)
Parent Project Muscular Dystrophy (2010)
6th Annual Dysferlin Conference (2013)
ASBMR Symposium: Cutting Edge Discoveries in Muscle Biology, Disease, and Therapeutics (2013)

Universities/Research Institutes:

Carnegie Institution of Washington (1988)
Massachusetts Institute of Technology (1988)
Harvard Medical School (1990)
Fox Chase Cancer Center (1990)
Harvard University (1990)
Johns Hopkins University School of Medicine (1990)
SUNY Stony Brook (1991)
Stanford Medical School (1991)
Massachusetts Institute of Technology (1991)
University of Texas Southwestern Medical Center (1991)
Columbia College of Physicians and Surgeons (1991)
National Institutes of Health (1991)
Vanderbilt Medical School (1991)
Jackson Lab (1991)
National Institutes of Health (1992)
Carnegie Institution of Washington (1993)
Tokyo Medical and Dental University (1997)
University of Virginia Medical School (1998)
University of Cincinnati Medical School (1998)
Harvard Medical School, Massachusetts General Hospital (1998)
Roslin Institute (1998)
Carnegie Institution of Washington (1998)
University of Texas Southwestern Medical Center (1998)
University of Maryland Medical School (1999)
Center for Advanced Biotechnology and Medicine (2001)
University of Michigan School of Medicine (2002)
Mount Sinai School of Medicine (2003)
Marshall Space Flight Center (2003)
University of Pennsylvania (2003)
Boston Obesity Nutrition Research Center (2004)
University of Florida (2004)
SUNY Stony Brook (2004)
Joslin Diabetes Center (2005)
New York University Medical Center (2005)
Karolinska Institutet (2006)
University of Wyoming (2007)
Boston University School of Medicine (2007)

University of Miami School of Medicine (2008)
Boston Biomedical Research Institute (2008)
University of Maryland School of Medicine (2010)
Sanford-Burnham Medical Research Institute (2010)
University of Pennsylvania (2011)
Children's National Medical Center (2011)
Karolinska Institutet (2013)
Gachon University (2013)
Samsung Medical Center (2013)

Companies:

Genentech, Inc. (1990)
Genentech, Inc. (1991)
Creative Biomolecules, Inc. (1991)
Cambridge Neuroscience, Inc. (1991)
Creative Biomolecules, Inc. (1993)
Amgen, Inc. (1993)
ARES Advanced Technologies (1993)
Genetics Institute, Inc. (1994)
Proscript, Inc. (1997)
Hoechst Marion Roussel—Japan (1997)
Eli Lilly and Company (1998)
Pfizer, Inc. (1999)
Amgen, Inc. (2002)
Novartis Biomedical Research Institute (2005)
Merck Research Laboratories (2005)
Amgen, Inc. (2005)
Pfizer, Inc. (2005)
Merck Research Laboratories (2006)
Acceleron, Inc. (2007)
Merck Research Laboratories (2010)
NGM Biopharmaceuticals, Inc. (2010)
Eleven Biotherapeutics, Inc. (2011)
Pfizer, Inc. (2012)

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 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. Our findings have not only identified such a regulator but have also raised the possibility that myostatin may be responsible directly or indirectly for the regulation of muscle growth by a variety of other stimuli, including hormones and exercise. Moreover, our discovery of myostatin has revived some archaic theories about the regulation of tissue growth in general. Over 30 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 muscle chalone. 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. 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 community to exploit the biological properties of myostatin for both agricultural and human therapeutic applications. With respect to agricultural applications, our discovery suggested that blocking myostatin activity in livestock species could be an effective strategy for dramatically improving meat yields to help meet the shrinking world

food supply. 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 [2]. 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 as it does in mice and in cattle [3].

Since our original discovery of myostatin, one 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 have shown using a mouse model of Duchenne muscular dystrophy that loss of myostatin not only can cause increased muscle mass and strength in the setting of muscle degeneration but can also slow the development of fibrosis, suggesting that targeting myostatin activity may enhance muscle growth and muscle regeneration in patients with muscle degenerative diseases [4]. We also showed that administration of high levels of myostatin protein to mice can induce a dramatic wasting process similar to the cachexia seen in patients with diseases such as cancer and AIDS [5]. These findings raised the possibility that altered regulation of myostatin activity may play a role in the etiology of cachexia, which is a major cause of mortality in patients with cancer and yet is poorly understood at the mechanistic level. Whether or not altered signaling through this pathway underlies or contributes to the cachexia seen in these patients, our findings raise the possibility that targeting myostatin activity may be an effective strategy for counteracting the wasting process. Finally, we have shown that human therapeutic applications may not be limited just to muscle degenerative and wasting diseases. In particular, we showed that loss of myostatin can suppress fat accumulation and improve glucose metabolism in genetic and diet-induced models of obesity in mice [6]. 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 balance between muscle and fat [7, 8]. 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.

In order to pursue these types of applications, we have focused most of our recent research effort on understanding the biology of myostatin at the molecular and cellular level. 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:

- the identification of activin type II receptors as the receptors mediating myostatin signaling *in vivo* [9, 10]

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- 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 [9, 11, 12]

- the identification of naturally-occurring myostatin binding proteins, including follistatin, and the demonstration that these play important roles in regulating myostatin activity *in vivo* [5, 9, 13, 14, 15]

- the development of engineered myostatin inhibitors capable of increasing muscle growth when administered systemically to adult mice [10, 11].

- the demonstration that other TGF-ß family members cooperate with myostatin to limit muscle growth [10, 13, 14].

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.

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 1500 papers, and at least seven biotechnology and pharmaceutical companies have initiated clinical trials with agents targeting myostatin signaling to treat patients with debilitating muscle loss.

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