BIOGRAPHICAL SKETCH

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NAME: **ERNESTINA SCHIPANI**

eRA COMMONS USER NAME (credential, e.g., agency login): **schipani**

POSITION TITLE: **PROFESSOR (with tenure)**

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Medical School of Pisa, Pisa, Italy	M.D.	10/1985	
Medical School of Pisa, Pisa, Italy	Ph.D.	06/1989	Endocrinology
MGH-Harvard Medical School	Research Fellowship	11/1993	Endocrinology

A. PERSONAL STATEMENT

I have been studying skeletal development for the last twenty-five years. Early in my career, I cloned the human PTH/PTHrP receptor and its gene, and discovered that gain-of-function mutations of the PTH/PTHrP receptor cause Jansen Metaphyseal Chondrodysplasia, a severe form of short-limbed dwarfism associated to hypercalcemia. Analysis of mutant mice I generated using those mutations have contributed to shape up our current understanding of the role of the PTH/PTHrP receptor in skeletal development and homeostasis, and hematopoiesis.

Next, I pioneered the notion that gradients of oxygen control tissue morphogenesis during skeletal development. Oxygen is not only an essential metabolic substrate in numerous enzymatic reactions, including mitochondrial respiration, but also a regulatory signal. My laboratory studies the role of the hypoxia-driven pathways in skeletal development with the overall goal of unveiling both novel aspects of the cellular adaptation to hypoxia and new avenues for the treatment of cartilage and bone diseases. Our central hypothesis is that reprogramming of energy metabolism is a crucial mechanism to protect tissues that physiologically experience low oxygen tension from intracellular anoxia. We are testing the hypothesis in the developing skeleton of genetically modified mice using *in vivo* and *ex-vivo* assays.

B. POSITIONS AND HONORS

Positions

1985-1988 Clinical Fellow-Medical School of Pisa, Pisa, Italy
1990-1993 Research Fellow in Medicine, Harvard Medical School, Boston, MA
1990-1996 Research Fellow in Medicine, Massachusetts General Hospital, Boston, MA
1993-1997 Instructor in Medicine, Harvard Medical School, Boston, MA
1995-1996 Assistant Professor (with Tenure), University of Pisa, Medical School of Pisa, Pisa, Italy
1996-2008 Assistant in Biology, Massachusetts General Hospital, Boston, MA
2008-2011 Associate in Biology, Massachusetts General Hospital, Boston, MA
1997-2006 Assistant Professor of Medicine, Harvard Medical School, Boston, MA
2006-2011 Associate Professor of Medicine, Harvard Medical School, Boston, MA
2011-2013 Professor of Medicine (with tenure), Indiana University, School of Medicine, Indianapolis, IN.
2011-2013 Professor of Anatomy and Cell Biology, Indiana University, School of Medicine, Indianapolis, IN.

2013-2020 Professor of Orthopedic Surgery (with tenure), University of Michigan, School of Medicine, Ann Arbor, MI.
2013-2020 Professor of Medicine, University of Michigan, School of Medicine, Ann Arbor, MI.
2015-2020 Professor of Cell and Developmental Biology, University of Michigan, School of Medicine, Ann Arbor, MI.
2020-present William Wikoff Smith Professor Orthopedic Surgery, University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA.
2020-present Full Professor of Orthopedic Surgery (with tenure), University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA.

Honors

1985 M.D. Summa Cum Laude
1989 Ph.D. Summa Cum Laude
1994-1995 National Osteoporosis Foundation Fellowship
1995 Travel Award of the International Conference On Calcium Regulating Hormones
1996 Young Investigator Award (ASBMR)
2002-2007 Editorial Board of *Endocrinology*
2004-2015 Editorial Board of *Journal of Bone and Mineral Research*
2005-present ASCI Member
2007-present Editorial Board of *Bone*
2007-2011 IBMS council
2008-2011 Regular member SBSR NIH Study Section
2014-2018 Regular member MTE NIH Study Section
2014-2015 Editor Current Osteoporosis Reports
2016-present Editorial Board of *Endocrinology*
2016-present ASBMR Council
2018 Elected Co-Chair and Chair of 2022 Bone and Teeth of Gordon Conferences
2019 ASBMR Esteemed Paula Stern Achievement Award
2019 Fellow of the ASBMR
2020 Co-Chair of 2020 Bone and Teeth Gordon Conferences
2022 Chair of 2022 Bone and Teeth Gordon Conference

C. CONTRIBUTIONS TO SCIENCE (>150 publications)

1. I was member of the team who cloned the cDNAs encoding the rat and opossum parathyroid hormone (PTH)/PTH related peptide (PTHrP) receptors, and I cloned the human homolog of this receptor and its gene. My study solved a long-lingering question in the field by proving that the PTH/PTHrP receptors expressed in bone and kidney are identical proteins. Next, I demonstrated that, at odds with what had been for long time hypothesized, Pseudohypoparathyroidism type 1b, a rare endocrine disorder of calcium and phosphate homeostasis, is not caused by mutations in the PTH/PTHrP receptor gene. This finding prompted a wide genome search that eventually led to identification of the Gsalpha gene as the one responsible for Pseudohypoparathyroidism type 1b. More importantly, I discovered that gain-of-function mutations of the PTH/PTHrP receptor result in Jansen Metaphyseal Chondrodysplasia, a severe form of short-limbed dwarfism associated to hypercalcemia. Jansen Metaphyseal Chondrodysplasia has been one of the first examples in the literature of a human disease being caused by a constitutively active G-protein coupled receptor.

a. **Schipani E**, Karga H, Karaplis AC, Potts JT Jr, Kronenberg HM, Segre GV, Abou-Samra AB, Jüppner H. Identical complementary deoxyribonucleic acids encode a human renal and bone parathyroid hormone (PTH)/PTH-related peptide receptor. **Endocrinology 1993**;132(5):2157-2165.

b. **Schipani E**, Weinstein LS, Bergwitz C, Iida-Klein A, Kong XF, Stuhrmann M, Kruse K, Whyte MP, Murray T, Schmidtke J, van Dop C, Brickman AS, Crawford JD, Potts JT Jr., Kronenberg HM, Abou-Samra AB, Segre GV, Jüppner H. Pseudohypoparathyroidism type Ib is not caused by mutations in the coding exons of the human parathyroid hormone (PTH)/PTH-related peptide receptor gene. **J Clin Endocrinol Metab 1995**; 80:1611-1621.

c. **Schipani E**, Kruse K, Jüppner H. A constitutively active mutant PTH/PTHrP receptor in Jansen type metaphyseal chondrodysplasia. **Science** 1995; 268:98-100.

d. **Schipani E**, Langman CB, Parfitt AM, Jensen GS, Kikuchi S, Kooh SW, Cole WG, Jueppner H. Constitutively activated receptors for parathyroid hormone and parathyroid hormone-related peptide in Jansen's metaphyseal chondrodysplasia. **N Engl J Med** 1996; 335:708-14. Free Article

2. Taking advantage of the mutations I had identified in patients, I generated transgenic mice expressing a constitutively active PTH/PTHrP receptor (Jansen receptor) in chondrocytes and osteoblasts, respectively. Lessons from these transgenic mice have contributed to shape up our current understanding of the role of the PTH/PTHrP receptor in cartilage and bone development and homeostasis, and in hematopoiesis. Among the numerous findings, I provided experimental evidence that expression of the Jansen receptor in chondrocytes considerably delays hypertrophic terminal differentiation of these cells, and this most likely is the cause of the severe dwarfism observed in Jansen patients. Moreover, by expressing the same Jansen receptor in cells of the osteoblast lineage, I demonstrated that the osteoblastic PTH/PTHrP receptor is a crucial mediator of both bone forming and bone resorbing actions of PTH. I was also member of the team who discovered that activation of the PTH/PTHrP receptor in cells of the osteoblast lineage leads to a significant expansion of the pool of hematopoietic stem cells in vivo. In particular, I characterized the mouse transgenic line used for this investigation; this mouse line was instrumental for conceiving the project and for the overall design and success of the study. Lastly, I reported the presence in the normal bone marrow of cells that express both hematopoietic cell surface antigens and classical mesenchymal markers, and I showed that this bone marrow population is increased upon expression of the Jansen receptor in cells of the osteoblast lineage.

a. **Schipani E**, Lanske B, Hunzelman J, Luz A, Kovacs CS, Lee K, Pirro A, Kronenberg HM, Jüppner H. Targeted expression of constitutively active receptors for parathyroid hormone and parathyroid hormone-related peptide delays endochondral bone formation and rescues mice that lack parathyroid hormone-related peptide. **Proc Natl Acad Sci USA** 1997; 94:13689-94. PMCID: PMC28367

b. Calvi ML, Sims NA, Hunzelman JL, Knight MC, Giovannetti A, Saxton JM, Kronenberg HM, Baron H, **Schipani E**. Activated parathyroid hormone/parathyroid hormone-related protein receptor in osteoblastic cells differentially affects cortical and trabecular bone. **J Clin Invest** 2001; 107: 277-286 (**Featured paper**). PMCID: PMC199196

c. Calvi LM, Adams GB, Weibrecht K, Weber JM, Olson DP, Knight MC, Martin RP, **Schipani E** *(I generated and characterized the mouse transgenic line used in the study)*, Divieti P, Bringhurst FR, Milner LA, Kronenberg HM, Scadden DT. Osteoblastic cells regulate the hematopoietic stem cell niche. **Nature 2003**; 425: 841-846.

d. Ohishi M, Ono W, Ono N, Khatri R, Marzia M, Baker EK, Root SH, Wilson TLS, Iwamoto Y, Kronenberg HM, Aguila HL, Purton LE, **Schipani E**. A novel population of cells expressing both hematopoietic and mesenchymal markers is present in the normal adult bone marrow and is augmented in a murine model of marrow fibrosis. **Am J Pathol 2012**;180:811-8 (***AJP Highlight***). PMCID: PMC3349873

3. Studying the fetal growth plate, I was intrigued by its avascularity; this simple observation led me to the discovery that hypoxia-signaling pathways are important in skeletal development. Oxygen is not only an indispensable metabolic substrate but also a regulatory signal. I pioneered the notion that gradients of oxygenation are crucial for tissue morphogenesis during skeletal development. Along these lines, I discovered that the murine fetal growth plate displays a gradient of oxygenation with an inner, hypoxic region. I generated the first conditional knockout model of hypoxia-inducible factor-1alpha (HIF1) reported in the literature, and I provided unequivocal evidence that HIF1 is a survival factor for hypoxic growth plate chondrocytes in vivo. In addition, I established that HIF-1 is essential for development of the nucleus pulposus, which, like the fetal growth plate, is an avascular tissue. The role of HIF-1 as a survival factor has been confirmed by other laboratories also in cancer cells. Furthermore, I proved that this transcription factor is necessary for timely differentiation of mesenchymal cells into chondrocytes and for joint development in vivo. In addition, I provided genetic evidence that, surprisingly, VEGF, which is both a survival factor for chondrocytes and a classical downstream target of HIF-1 transcriptional activity, has only a modest role in mediating the survival function of HIF1 in cartilage. Conversely, I demonstrated that HIF1-dependent reprogramming of metabolism is a critical event downstream of HIF1 as both a survival and differentiation factor in chondrocytes. Along those lines, I showed that HIF1-dependent suppression of mitochondrial respiration and thereby oxygen consumption has a key role in endochondral bone development because it protects growth plate chondrocytes that are physiologically hypoxic from lethal intracellular anoxia.

a. **Schipani E**, Ryan HE, Didrickson S, Kobayashi T, Knight M and Johnson RS. Hypoxia in cartilage: HIF-1a is essential for chondrocyte growth arrest and survival. **Genes Dev 2001**; 15: 2865-2876. (***Discussion on this paper in a "Research Roundup " in Journal of Cell Biology, 2001, 155, 693***). PMCID: PMC312800

b. Provot S, Zinyk D, Gunes Y, Khatri R, Le Q, Longaker MT, Giaccia AJ, **Schipani E**. Hif-1a regulates differentiation of limb bud mesenchyme and joint development. **J Cell Biol 2007;** 177:451-464 (***Cover Figure and Commentary in the same issue***). PMCID: PMC2064828

c. Maes C, Araldi E, Haigh K, Khatri R, Van Looeveren A, Giaccia AJ, Haigh JJ, Carmeliet G, **Schipani E**. VEGF-independent cell –autonomous functions of HIF-1alpha regulating oxygen consumption in fetal cartilage are critical for chondrocyte survival. **JBMR** 2012; 27:596-609. PMCID in progress

d. Yao Q, Parvez Khan M, Merceron C, LaGory E, Tata Z, Mangiavini L, Hu J, Vemulapalli K, Chandel NS,

Giaccia AJ, **Schipani E**. Suppressing mitochondrial respiration is critical for hypoxia tolerance in the fetal growth plate. **Developmental Cell 201;**49: 748-763 (**Preview in the same issue; featured in Science Signaling 2019; 12).** PMCID: in progress

4. I demonstrated that differently from HIF-1, HIF-2 another member of the HIF family of transcription factors is not as critical for endochondral bone development. More importantly, I established that the E3 ubiquitin ligase Von Hippel Lindau (VHL) responsible for degradation of HIFs is an essential regulator of endochondral bone development.
a. Pfander D, Kobayashi T, Knight MC, Zelzer E, Chan DA, Olsen BR, Giaccia AJ, Johnson RS, Haase V, **Schipani E**. Deletion of V*hlh* in chondrocytes reduces cell proliferation and increases matrix deposition during growth plate development. **Development 2004**; 131:2497-2508.
b. Araldi E, Khatri R, Giaccia AJ, Simon MC, **Schipani E**. Lack of Hif-2alpha in limb bud mesenchyme causes only a modest and transient delay of endochondral bone development. **Nature Medicine 2011;**17: 25-26. PMCID: PMC3215585
c. Aro E, Khatri R, Gerard-O'Riley R, Myllyharju J and **Schipani E**. Hypoxia-inducible factor-1 (HIF-1) but not HIF-2 is essential for hypoxic induction of collagen prolyl 4-hydroxylases in mouse epiphyseal growth plate chondrocytes. **JBC 2012;** 287:37134-44. PMCID: PMC3481313
d. Mangiavini L, Merceron C, Araldi E, Khatri R, Wilson TLS, Gerard-O'Riley R, Rankin EB, Giaccia AJ and **Schipani E**. Loss of VHL in mesenchymal cells of the limb bud alters multiple steps of endochondral bone development. **Dev Biol 2014;** 393(1):124-36. PMCID: PMC4335807

5. A gradient of oxygenation is also present in the bone marrow, despite its high degree of vascularization. Along these lines and in close collaboration with Dr. Thomas Clemens, we discovered that activation of the HIF signaling pathway in osteoblasts augments bone marrow angiogenesis. These findings provided clear experimental evidence that an HIF- dependent osteoblast-blood vessel coupling exists in vivo. In addition, Dr. Giaccia and I demonstrated that osteoblasts are able to produce and secrete erythropoietin (EPO), and thus modulate erythropoiesis, and that HIF-2 controls osteoblastic production of EPO. Lastly, we discovered that osteoblastic HIF-2 is an inhibitor of osteoblastogenesis and bone mass accrual. HIF2 can be selectively inhibited by small molecules that are currently in clinical trials in patients with renal carcinoma. Inhibiting HIF2 could represent a therapeutic approach for the treatment of the low bone mass observed in osteoporosis and aging.
a. Wang Y, wan C, Ximeng L, Bouxsein ML, Faugere MC, Guldberg RE, Johnson RS, Haase VH, Gerstenfield LC, **Schipani E**, Clemens TL. The hypoxia inducible factor pathway couples angiogenesis to osteogenesis during skeletal development **J Clin Invest** 2007, 117: 1616-1626 (**Featured paper and Cover Figure**). PMCID: PMC1878533
b. Rankin EB, Wu C, Khatri R, Wilson TLS, Rankin AL, Kuo CJ, **Schipani E,** Giaccia AJ. HIF signaling in osteoblasts regulates erythroid progenitors through EPO. **CELL** 2012; 149: 63-74. PMCID: PMC3408231
c. Wu C, Rankin EB, LaGory EL, Andersen R, Rhodes SD, Wilson TLS, Mohammed KS, Castillo A, Guise TA, **Schipani E**, Giaccia AJ. Selective inactivation of osteoblastic HIF prolyl hydroxylases regulates bone homeostasis through the regulation of OPG. **Genes Dev 2015**; 29: 791-802. PMCID: PMC4403258
d. Merceron C, Ranganathan K, Wang E, Tata Z, Makkapati S, Kahn MP, Mangiavini L, Yao QA, Castellini L, Levi B, Giaccia AJ, **Schipani E.** Hypoxia-inducible factor 2alpha is a negative regulator of osteoblastogenesis and bone mass accrual. **Bone Research 2019;**7:7. PMCID: in progress.

Patents
Patent: 5,840,853 Date: Nov 24, 1998. Parathyroid Hormone receptor and DNA encoding this receptor. I was member of the team who cloned the rat and opossum PTH/PTHrP receptors, and I then cloned the human homology.

D. Research Support

Ongoing Research Support

R01 AR073022 (Schipani, PI) 01/11/19-12/31/23
NIH/NIAMS
Role: PI
Title: *HIF-2alpha, a Novel Regulator of Osteoblastogenesis*

The goal of this study is to determine the role of HIF2 in the regulation of bone mass and osteoblastogenesis.

R01 AR074079 (Schipani, PI) 07/15/19-11/30/24
NIH/NIAMS
Role: PI
Title: *Mitochondria and TFAM in osteoblast biology*
The goal of this study is to establish the role of mitochondrial respiration in osteoblast biology.

R01 AR075770 (Schipani, PI) 09/23/20-01/31/26
NIH/NIAMS
Role: PI
Title: *Regenerating Hyaline Cartilage Using Nanofibrous Hollow Microspheres and Synergizing TGF-beta and HIF*
The goal of this study is to establish a novel approach to promote chondrogenesis and prevent chondrocyte hypertrophy.

R01 DK113039 (Jueppner, PI) 09/15/18-06/30/23
NIH/NIDDK
Role: Co-Investigator
Title: *PTH Inverse Agonists as Therapy for Jansens' Disease*
The goal of this study is the identification of therapeutic avenues for the treatment of Jansen Metaphyseal Chondrodysplasia.

Past Research Support (last three years)

P30 AR069620 (Jepsen, PI) 08/01/16-07/31/20
NIH/NIAMS
Role: Histology Core Director
Title: *Michigan Integrative Musculoskeletal Health Core Center*
The Michigan Integrative Musculoskeletal Health Core Center (MiMHC) will enable vertically integrative, multi-scale musculoskeletal science from molecular mechanisms to organismal function by increasing access to critical, specialized resources and expertise that are fundamental to the musculoskeletal research programs of 59 center investigators.

RO1 (Schipani, PI) 09/26/13-08/31/19
NIH/NIAMS
Role: PI
Title: HIF-1alpha, a survival and differentiation factor for cartilage.

R21 AR067330 (Schipani, PI) 07/01/15-06/30/18
NIH/NIAMS
Role: PI
Title: Exploring the physiological roles of osteoblastic EPO and osteoblastic EPOR.
the major goal of this project is to study the role EPO in bone development