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

My laboratory focuses on skeletal development, leveraging insights from developmental biology to better understand skeletal diseases and identify potential new treatments.

Early in my career, I cloned the human PTH/PTHrP receptor and its gene, uncovering that gain-of-function mutations in this receptor are responsible for Jansen Metaphyseal Chondrodysplasia—a severe form of short-limbed dwarfism associated with hypercalcemia. Using mouse models carrying these mutations, I contributed to defining the PTH/PTHrP receptor's critical role in skeletal biology.

Subsequently, I pioneered the concept that oxygen gradients regulate tissue morphogenesis during skeletal development. Beyond serving as a key metabolic substrate in enzymatic reactions such as mitochondrial respiration, oxygen also functions as a regulatory signal. My laboratory investigates how hypoxia and hypoxia-driven pathways influence skeletal development, aiming to uncover novel mechanisms of cellular adaptation to low oxygen levels and identify therapeutic targets for cartilage and bone diseases.
To achieve these goals, we employ genetically modified mouse models and a wide array of in vivo, ex vivo, and in vitro approaches to analyze phenotypes and elucidate the underlying biology.

Active NIH award relevant to this application
1.R01 HD112003 (Schipani, PI) 01/04/23-31/03/28
NIH/NICHD
Role: PI
Title: *Hypoxia and Mitochondria in Spine Development and Congenital Scoliosis*
The goal of this study is to advance our understanding of how hypoxia,hypoxia-driven pathways, and bioenergetic metabolism control somitogenesis.

Pending NIH award relevant to this application
2.R01 AR084536 (Schipani, PI) 04/01/25-04/31/30
NIH/NIAMS

Role: PI
Title: *Mitochondrial Respiration and The Biology of Growth Plate Chondrocytes*
The goal of this study is to establish how oxidative phosphorylation controls chondrocyte hypertrophy in the murine developing growth plate.

Original Publication relevant to this application

1.Lanzolla G, Sabini E, Beigel K, Khan MP, Sherry Liu X, Wang D, Laslow B, Taylor D, Bellido T, Giaccia A, **Schipani E**. Pharmacological inhibition of HIF2 protects against bone loss in an experimental model of estrogen deficiency. **PNAS 2024**;121. **PMCID: in progress**

2.Khan MP, Sabini E, Beigel K, Lanzolla G, Laslow BM, Wang D, Merceron C, Giaccia A, Long F, Taylor DM, **Schipani E.** HIF1 safeguards cortical bone formation against impaired oxidatiyve phosphorylation. **JCI Insight 2024**; 9(18):e182330**.** PMCID: PMC11457864

3.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: PMC7255488

I have not published or created research products under another name.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

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
2015-2020	Professor of Cell and Developmental Biology, University of Michigan, School of Medicine, Ann Arbor, MI
2013-2020	Professor of Medicine, University of Michigan, School of Medicine, Ann Arbor, MI
2013-2020	Professor of Orthopedic Surgery (*with tenure*), University of Michigan, School of Medicine, Ann Arbor, MI
2011-2013	Professor of Anatomy and Cell Biology, Indiana University, School of Medicine, Indianapolis, IN
2011-2013	Professor of Medicine (*with tenure*), Indiana University, School of Medicine, Indianapolis, IN
2006-2011	Associate Professor of Medicine, Harvard Medical School, Boston, MA
1997-2006	Assistant Professor of Medicine, Harvard Medical School, Boston, MA
2008-2011	Associate in Biology, Massachusetts General Hospital, Boston, MA
1996-2008	Assistant in Biology, Massachusetts General Hospital, Boston, MA
1995-1996	Assistant Professor (*with tenure*), University of Pisa, Medical School of Pisa, Pisa, Italy
1993-1997	Instructor in Medicine, Harvard Medical School, Boston, MA
1990-1996	Research Fellow in Medicine, Massachusetts General Hospital, Boston, MA
1990-1993	Research Fellow in Medicine, Harvard Medical School, Boston, MA
1985-1988	Clinical Fellow-Medical School of Pisa, Pisa, Italy

Honors

2024-present	Consulting Editor of JCI Insight
2024	Associate Editor of Endocrinology
2022	Chair of the 2022 Bone and Teeth Gordon Research Conference
2020	Co-Chair of the 2020 Bone and Teeth Gordon Research Conference
2021-2022	Reviewing Editor of *eLife*
2021-2024	Associate Editor of *JCI Insight*
2021-2023	Editorial Board Member of *Journal of Bone and Mineral Research*
2020	Co-Chair of 2020 Bone and Teeth Gordon Research Conferences
2020	Guest Editor of *Bone*
2019-present	Fellow of the ASBMR
2019	ASBMR Esteemed Paula Stern Achievement Award
2017-2019	Member of the ASBMR Council
2016-2020	Editorial Board Member of *Endocrinology*
2015	Editor Scientific Reports (Nature Publishing Group)
2014-2015	Section Editor *Current Osteoporosis Reports*

2014-2018 Regular Member MTE NIH Study Section
2007-2011 Regular Member SBSR NIH Study Section
2007-2011 Member of the IBMS council
2007-2021 Editorial Board Member of *Bone*
2005-present ASCI Member
2004-2015 Editorial Board Member of *Journal of Bone and Mineral Research*
2002-2005 Editorial Board Member of *Endocrinology*
1996 Young Investigator Award (ASBMR)
1995 Travel Award of the International Conference On Calcium Regulating Hormones
1989 PhD Summa Cum Laude
1985 MD Summa Cum Laude

C. Contributions to Science (>150 publications, *h* index 72)

1. **The PTH/PTHrP receptor in development and disease**

I cloned the human receptor for PTH and PTHrP (PTH/PTHrP receptor) and its gene, and I 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 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. Building on the mutations I identified in patients, I generated transgenic mice expressing a constitutively active PTH/PTHrP receptor (Jansen receptor) in chondrocytes and osteoblasts, respectively. These transgenic models have significantly advanced our understanding of the PTH/PTHrP receptor's role in cartilage and bone development, homeostasis, and hematopoiesis. Notably, my research demonstrated that expression of the Jansen receptor in chondrocytes markedly delays the terminal hypertrophic differentiation of these cells, likely explaining the severe dwarfism observed in Jansen patients. Additionally, by expressing the Jansen receptor in cells of the osteoblast lineage, I established that the osteoblastic PTH/PTHrP receptor is a key mediator of both the bone-forming and bone-resorbing actions of PTH. Currently, I am collaborating with my former mentor, Dr. Harald Jueppner, to explore potential therapeutic approaches for the treatment of Jansen patients.

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

c.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.

d.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**).

2. **HIF-1 and the reprogramming of metabolism in endochondral bone development**

While studying the fetal growth plate, we became intrigued by its avascular nature, which led us to uncover the critical role of hypoxia-signaling pathways in skeletal development. Oxygen, beyond being a vital metabolic substrate, also functions as a key regulatory signal. We were among the first to propose that oxygen gradients are essential for tissue morphogenesis during skeletal development. Through our research, we discovered that the murine fetal growth plate exhibits a gradient of oxygenation, with a hypoxic core region. To further investigate, we developed the first conditional knockout model of hypoxia-inducible factor-1 alpha (HIF-1), providing definitive evidence that HIF-1 acts as a survival factor for hypoxic chondrocytes in the growth plate in vivo. The role of HIF-1 as a survival factor has since been confirmed in a variety of settings, including cancer models. We also established that HIF-1 is crucial for the timely differentiation of mesenchymal cells into chondrocytes and for joint development in vivo. Furthermore, we provided genetic evidence that vascular endothelial growth factor (VEGF)—a classical downstream target of HIF-1 and a known survival factor for chondrocytes—plays only a modest role in mediating HIF-1's survival function in cartilage. Instead, we showed that HIF-1-dependent metabolic reprogramming is a critical downstream mechanism supporting chondrocyte survival and differentiation. Notably, we demonstrated that HIF-1 reduces mitochondrial respiration and oxygen consumption

in growth plate chondrocytes, a key adaptation ensuring their survival and proper differentiation under hypoxic conditions. Currently, we are investigating how the interplay between oxidative phosphorylation and HIF-1-mediated metabolic reprogramming governs skeletal development.

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***).

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***).

c.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).**

d.Khan MP, Sabini E, Beigel K, Lanzolla G, Laslow BM, Wang D, Merceron C, Giaccia A, Long F, Taylor DM, **Schipani E.** HIF1 safeguards cortical bone formation against impaired oxidative phosphorylation. **JCI Insight 2024**; 9(18):e182330*.*

3. HIF1 and the reprogramming of metabolism in somitogenesis

In collaboration with Dr. Mark Lewandoski at NCI, we recently established that HIF-1 is critical for spine development as its loss in the presomitic mesoderm impairs somitogenesis and causes spine and rib malformations that closely mimic those observed in patients with Jarcho-Levin Syndrome, a rare form of spondylothoracic dysplasia. A manuscript reporting those findings is in preparation.

We are currently investigating whether the impairment of somitogenesis secondary to loss of HIF-1 is due to dysregulation of glycolysis and mitochondrial function in the presomitic mesoderm.

4. HIF-2 and the control of bone mass accrual and homeostasis

A gradient of oxygenation exists within the bone marrow, despite its high vascularization. This phenomenon underscores the complexity of the bone marrow microenvironment, where localized hypoxia plays critical roles in cellular function. In collaboration with Dr. Amato Giaccia at Stanford, we demonstrated that osteoblasts have the remarkable ability to produce and secrete erythropoietin (EPO), a hormone essential for erythropoiesis, when hypoxia-inducible factor-2 (HIF-2), another transcription factor central to the hypoxic response, is activated in those cells. Our findings suggest that transient pharmacological activation of the hypoxia signaling pathway in osteoblasts could serve as a therapeutic approach to enhance EPO production, especially in conditions characterized by EPO deficiency, such as chronic kidney disease. In addition to its role in EPO production, HIF-2 has distinct effects on skeletal development. Unlike HIF-1, HIF-2 plays a less critical role in growth plate development. Interestingly, however, our research uncovered that reducing or inhibiting HIF-2 in mesenchymal progenitors and their descendants during development leads to the formation of stronger bones with increased trabecular bone mass. This improvement is driven by the expansion of mesenchymal progenitor cells within the bone marrow, which subsequently differentiate into osteoblasts. By increasing the pool of these progenitors, we effectively enhanced bone-forming capacity. A particularly exciting breakthrough involved the testing a HIF-2 inhibitor, PT2399, which was originally developed to treat clear cell renal carcinoma. In mouse models of menopause (characterized by estrogen deficiency), this drug prevented bone loss and promoted bone formation by expanding the pool of early osteoblast precursors. These findings highlight a promising therapeutic avenue for addressing osteoporosis and other bone loss conditions by targeting HIF-2. Currently, our research employs unbiased methodologies, including transcriptomic analyses, to elucidate the molecular mechanisms underlying the expansion of mesenchymal progenitor cells when HIF-2 activity is pharmacologically suppressed. These studies aim to identify novel pathways that can be leveraged to optimize bone health therapeutics.

a.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.

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.

c.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.

d.Lanzolla G, Sabini E, Beigel K, Khan MP, Sherry Liu X, Wang D, Laslow B, Taylor D, Bellido T, Giaccia A, **Schipani E.** Pharmacological inhibition of HIF2 protects against bone loss in an experimental model of estrogen deficiency. **PNAS 2024;121.**

5. HIFs in the pathogenesis of fibroblastic tumors of the soft tissue and cartilage regeneration

Our laboratory has demonstrated that continuous activation of the hypoxia signaling pathway in mesenchymal progenitor cells of the limb bud may have detrimental effects on skeletal development. Specifically, this persistent activation leads to aggressive fibrosis in synovial joints, the development of fibroblastic tumors in soft tissue, and dwarfism by disrupting both the proliferation and hypertrophic differentiation of growth plate chondrocytes. These findings underscore the critical role of tightly regulated hypoxia signaling in maintaining skeletal health and normal development. Notably, we also discovered that activation of the hypoxia signaling pathway in mesenchymal progenitors results in the formation of ectopic cartilage in the soft tissues surrounding the growth plate and promotes matrix accumulation in the developing growth plate. These findings suggest that increased activity of the hypoxia signaling pathway may be sufficient to drive cartilage formation under certain conditions. Taken together, if appropriately controlled, *transient* activation of hypoxia signaling could be harnessed to promote cartilage regeneration. By stimulating chondrogenesis while inhibiting hypertrophy, this strategy could enable cartilage repair in vitro and in vivo without inducing adverse outcomes, such as synovial fibrosis or fibroblastic tumor formation, provided the activation is carefully timed and transient. Our current research focuses on two main objectives: 1. Investigating the role of the hypoxia signaling pathway in the initiation and progression of fibroblastic tumors of the soft tissue; 2. Attempting to appropriately exploit the hypoxia signaling pathway for regenerating cartilage.These efforts aim to elucidate the dual role of hypoxia signaling in both pathology and regeneration, offering insights into novel therapeutic strategies for conditions involving fibroblastic tumors and cartilage repair.

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.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.

c.Mangiavini L, Merceron C, Araldi E, Khatri R, Gerard-O'Riley R Wilson TLS, Sandusky G. Abadie J, Lyons LM, Giaccia AJ and **Schipani E**. Fibrosis and HIF-1a-dependent tumors of the soft tissue upon loss of VHL in mesenchymal progenitors. **AJP 2015;** 185:3090-101.

https://www.ncbi.nlm.nih.gov/myncbi/ernestina.schipani.1/bibliography/public/

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 homolog.