BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Varughese, Kottayil Iype

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

POSITION TITLE: Professor of Physiology and Biophysics

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
St. Berchman's College, Changanachery, Kerala, India	B.Sc	05/1966	Physics
Indian Institute of Technology, Madras, India	M.Sc	06/1968	Physics
University of Madras, Madras, India	Advanced Diploma	06/1969	Biophysics
University of Madras, Madras, India	Ph.D	06/1974	Crystallography

A. Personal Statement

I am a structural biologist, and I have been studying structure and function of biological molecules for more over 30 years. I received my initial training in crystallography at the laboratory of Prof. G. N. Ramachandran at the University of Madras and subsequently at the Roswell Park Cancer Institute in Buffalo, New York. I continued my career in the application of X-ray crystallography to solve fundamental and applied problems in structural biology, at the National Research Council, Canada; at the University of California, San Diego (UCSD); and at The Scripps Research Institute. At the Scripps Institute, I studied platelet interactions relevant to blood clotting, and I received initial funding and two periods of renewal from NHLBI for these studies. Additionally, I received initial funding and subsequent renewal to study protein interactions that lead to phosphorylation and signal transduction. In 2006, my coworkers and I moved to the University of Arkansas for Medical Sciences to establish and develop the X-ray Crystallography Center, the first of its kind in this University. I direct and help teach just one specialty course in crystallography for graduate students and postdoctoral fellows. I have published extensively in reputed journals such as Science, PNAS, Molecular Cell, Nature structural and Molecular Biology, Structure, JBC and Biochemistry. In summary, my lab had long been studying protein-protein interactions using crystallography techniques over the last three decades. For the last 7 years my laboratory has been employing structure-based drug design techniques to locate therapeutic agents to combat atherosclerosis, a project that received support from the American Heart association. We have succeeded in obtaining small molecule inhibitors with IC_{50} value in the range of 20-40nM. Additionally, I have been collaborating with Dr. Haibo Zhao for the last 6 years as a co-investigator in this R01 grant and as a CO-PI in an R21 in studies aimed at understanding the role of certain proteins in osteoporosis. This current project in collaboration with Dr. Maria Schuller is on also on the same path to design therapeutic inhibitors. Here our primary goal is to elucidate the structure of the complex between FoxO1 and β-catenin.

B. Positions and Honors

1974 – 1977 Research Associate/Project Assistant, Indian Institute of Science, Bangalore, India
1977 – 1981 Research Affiliate, Biophysics Department, Roswell Park Memorial Institute, Buffalo, NY
1981 – 1981 Visiting Associate, Institute for National Product Research, University of Georgia, Athens, GA

1982 – 1987 Research Associate, Division of Biological Science,
National Research Council of Canada, Ottawa
1987 – 1993 Assistant Research Biologist, Department of Biology, University of California, San Diego, CA
1993 – 1996 Associate Project Biologist, University of California, San Diego, CA
1996 – 2006 Associate Professor, Department of Molecular and Experimental Medicine,
The Scripps Research Institute, La Jolla, CA
2006–present Professor, Department of Physiology and Biophysics,
University of Arkansas for Medical Sciences, Little Rock, AR

C. Contribution to Science

1. ***Cyclic Peptides, cyclic AMP and cAMP Dependent Protein Kinase:*** Early in my carrier, as a small molecule crystallographer in Dr. Gopinath Kartha's laborotory at Roswell Park Memorial Institute, Buffalo, NY, I carried out structural analysis of cyclic peptides to characterize them and to understand the nature of metal ion bindings. Additionally I characterized the crystal structure of cAMP at high resolution. In an attempt to learn more on the function of cAMP, I collaborated with Dr. Susan Taylor and carried out the structural characterization of the regulatory subunit of the enzyme cAMP dependent protein kinase.

   a. **Varughese**, K.I., Kartha, G. and Kopple, K.D. Crystal structure and conformation of cyclo(glycyl-D-leucyl-L-leucyl)$_2$. *J. Am. Chem. Soc*. **103**, 3310-3313. (1981).

   b. Kartha, G., **Varughese**, K.I. and Aimoto, S. Conformation of cyclo (-L-Pro-Gly)$_3$ and its Ca^{2+} and Mg^{2+} complexes. *Proc. Natl. Acad. Sci. USA*, **79**, 4519-4522, 1982.

   c. **Varughese**, K.I., Lu, C.T. and Kartha, G. The crystal and molecular structure of cyclic adenosine 3'- 5' monophosphate sodium salt, monoclinic form. *J. Am. Chem. Soc.*, **104**, 3398-3401, 1982.

   d. Su Y., Dostmann W.R., Herberg F.W., Durick K., Xuong N.H., Ten E.L., Taylor S.S., and **Varughese K.I**. Regulatory subunit of protein kinase A: structure of deletion mutant with cAMP binding domains. *Science*, **269**, 807-813, 1995

2. **Phosphorylation induced Signal Transduction**: We have carried out structural characterization of the phosphorelay proteins that control sporulation in *Bacillus subtilis*. Our lab was the first to show how the components of the phosphorelay interact to exchange the phosphoryl moiety. We worked out the rules of interaction. Our studies became the basis for understanding the cross talk. In fact, we were the first to provide a structure based explanation for the phenomenon of cross-talk. Additionally we delineated the interactions between the transcription factor and DNA.

   a. **Varughese,** K.I., Madhusudan, Zhou, X.Z., Whiteley, J.M., and Hoch, J.A. Formation of a novel four-helix bundle and molecular recognition sites by dimerization of a response regulator phosphotransferase. *Mol. Cell.*, **2**, 485-493, 1998.

   b. Zapf, J., Sen, U., Madhusudan, Hoch, J.A., and **Varughese**, K.I. A transient interaction between two phosphorelay proteins trapped in a crystal lattice reveals the mechanism of molecular recognition and phosphotransfer in signal transduction. *Structure*, **8**, 851-862, 2000.

   c. Zhao H, Msadek T, Zapf J, Madhusudan, Hoch J, Varughese K. DNA complexed structure of the key transcription factor initiating development in sporulating bacteria. *Structure* 2002 10, 1041-1050.

   d. Howell, A., Dubrac, S., Noone, D., **Varughese**, K.I. and Devine, K. Interactions between the YycFG and PhoPR two-component system in *Bacillus subtilis*: the PhoR kinase phosphorylates the

non-cognate YycF response regulator upon phosphate limitations. *Mol. Microbiol*. 2006. 59:1199-215.

3. ***Adhesive Molecular Interactions in Platelet Function****:* Bleeding from damaged blood vessel is stopped by platelet adhesion and thrombus formation at the site of injury. Platelet adhesion starts when the subendothelial matrix is exposed to the blood stream and this process requires the binding of the platelet glycoprotein (GP) Ib-IX-V receptor complex to the A1 domain of von Willebrand Factor (vWF). As a part of our efforts to gain definitive information on the mechanism and regulation of this key process in hemostasis and thrombosis, we solved the three dimensional structure of the A1 domain and I546V A1 that causes a bleeding disorder. Additionally we have identified small molecule inhibitors that modulate vWF binding to platelets with the goal of developing anti-thrombotic agents. Thrombin bound to platelets contributes to arrest bleeding and, in pathological conditions, may cause vascular thrombosis. We have determined the structure of platelet glycoprotein Ibα (GpIbα) bound to thrombin. Three sulfated tyrosine residues of the glycoprotein play crucial roles in thrombin binding. We generated the GPIbα amino terminal domain (GPIbα-N) fully sulfated on three tyrosine residues and solved the structure of its complex with thrombin. There are two positively charged surfaces in thrombin which influence substrate binding. We have analyzed the involvement of both these surfaces in platelet glycoprotein binding with special emphasis on the role of the three sulfated tyrosine residues.

   a. Celikel, R., **Varughese, K.I**., Madhusudan, Yoshioka, A., Ware, J. and Ruggeri, Z.M. Crystal structure of the von Willebrand factor A1 domain in complex with function blocking NMC-4 Fab. *Nature Struc. Biol.*, **5**, 189-194, 1998.
   b. Celikel R., Ruggeri Z.M., and **Varughese K.I**. von Willebrand factor conformation and adhesive function is modulated by an internalized water molecule. *Nature Structural Biology,* **7**, 881-884, 2000.
   c. Celikel R., McClintock R.A., Roberts J.R., Mendolicchio G.L., Ware J., **Varughese K.I**., and Ruggeri Z.M. Modulation of alpha-thrombin function by distinct interactions with platelet glycoprotein Ibα. *Science* **301**, 218-221, 2003.
   d. Zarpellon A., Celikel R., Roberts J.R., McClintock R.A., Mendolicchio G.L., Moore K.L., Jing H., **Varughese K.I.**, and Ruggeri Z.M. Binding of α-thrombin to surface-anchored platelet glycoprotein Ibα sulfotyrosines through a two-site mechanism involving exosite I. *Proc Natl Acad Sci U S A,* **108**, 8628-8633, 2011. PMCID: PMC3102361

4. ***Anti-methamphetamine antibodies***: Methamphetamine (METH) is a major drug threat in the United States and worldwide. Monoclonal antibody (mAb) therapy for treating METH abuse is showing exciting promise and the understanding of how mAb structure relates to function will be essential for future development of these important therapies. We determined the crystal structures of a high affinity anti-(+)-METH therapeutic single chain antibody fragment (scFv6H4, K_D=10 nM) derived from one of the candidate mAb, in complex with METH and the (+) stereoisomer of another abused drug, 3,4-methylenedioxymethamphetamine (MDMA), known by the street name “ecstasy”. As a part of this ongoing study, we are designing mutants with higher potency. One of the designed mutants exhibited a 3-fold higher affinity for methamphetamine and 17-fold higher affinity for amphetamine compared to the wild-type antibody.

   a. Celikel R., Peterson E.C., Owens S.M., and **Varughese K.I.** Crystal structures of a therapeutic single chain antibody in complex with two drugs of abuse-Methamphetamine and 3,4-methylenedioxymethamphetamine. *Protein Science,* **18**, 2336-2345, 2009. PMCID: PMC2788288
   b. Peterson E.C., Celikel R., Gokulan K., and **Varughese** K.I. Structural characterization of a therapeutic anti-methamphetamine antibody fragment: oligomerization and binding of active metabolites. *PLoS ONE,* **8,** e82690. DOI:10.1371/journal.pone.0082690, 2013. PMCID: PMC3857803

c. Thakkar S., Nanaware-Kharade N., Celikel R., Peterson E.C., and **Varughese** K.I. Affinity improvement of a therapeutic antibody to methamphetamine and amphetamine through structure-based antibody engineering. *Sci. Rep.,* **4**, 3673, DOI:10.1038/srep03673, 2014. PMCID: PMC4070344

5. **Structure-based drug design for atherosclerosis:** Atherosclerosis is a disease in which plaque builds up inside the arteries limiting the flow of oxygen-rich blood to the organs and other parts of your body. Severe forms of atherosclerosis can lead to heart attack, stroke or even death. Cardiovascular diseases (CVD) continue to be a leading cause of mortality world-wide. The main medications used for treating atherosclerosis-related CVD are statins to reduce LDL levels in the blood; but there are several observations suggesting that the overall level of LDL may not be the cause of atherosclerosis. For example, half of the patients who suffer heart attacks have normal levels of LDL. Under oxidative stress, LDL gets oxidized and interacts with different receptors which do not recognize normal LDL. The scavenger receptor LOX-1 found on endothelial cells binds ox-LDL, triggering endothelial dysfunction initiating plaque formation in arteries. We have designed therapeutic inhibitors of LOX-1 to prevent/reduce the uptake of ox-LDL by endothelial cells and thereby reducing the damaging effects of ox-LDL on blood vessels. We have succeeded in obtaining small molecule inhibitors with EC_{50} value in the range of 20-40nM.

a. Thakkar S, Wang X, Khaidakov M, Dai Y, Gokulan K, Mehta JL, **Varughese** KI. Structure-based Design Targeted at LOX-1, a Receptor for Oxidized Low-Density Lipoprotein. Scientific reports. 2015; 5:16740. PubMed [journal] PMID: 26578342 PMCID: PMC4649741

b. Ding Z, Liu S, Wang X, Deng X, Fan Y, Shahanawaz J, Shmookler Reis RJ, **Varughese** KI, Sawamura T, Mehta JL. Cross-talk between LOX-1 and PCSK9 in vascular tissues. Cardiovascular research. 2015; 107(4):556-67. PubMed [journal] PMID: 26092101

c. Pothineni NVK, Karathanasis SK, Ding Z, Arulandu A. **Varughese** KI, Mehta JL: LOX-1 in Atherosclerosis and Myocardial Ischemia: Biology, Genetics, and Modulation. Journal of the American College of Cardiology 2017 6;69(22):2759-2768. doi: 10.1016/j.jacc.2017.04.010.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1Pas8bDA7dJ5L/bibliography/48217519/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

STAR Funding -Admin Supplement
Period: 03/01/2018 to 02/29/2020
Agency : NIH/NIAMS
Role: Co-investigator
PI: Maria Schuller
Effort 25% .
Major goals: Osteoporosis is one of the most common features of human aging, and is caused, at least in part by a deficiency in bone formation by the specialized cells that produce the bone matrix, called osteoblast. The work proposed in this application seeks to identify new drugs (cell penetrating peptides) that can promote bone formation. These drugs may prove useful to treat age-related osteoporosis and other degenerative disorders of aging.

Completed Research Support

R21 AR068509-01A1
Title: Structural and functional analyses of Rab7 binding to Plekhm1
Role: Co-PI
Agency: National Institutes of Health - National Institute of Arthritis and Musculoskeletal and Skin Diseases
Type: R21
Period: 04/01/16 – 03/31/18
The major goal is to study how Rab7 and plekhm1 interact in osteoclasts, and design therapeutic agents for the treatment of bone loss in metabolic bone diseases such as osteoporosis and arthritis.

13GRNT17240028: SWA Winter 2013 Grant-in-Aid
Agency: American Heart Association.
Title: Structure based drug design for atherosclerosis targeted at LOX-1, a rece*ptor for oxidized low-d*ensity lipoprotein
Role: Principal investigator:
Period 07/01/2013 to 06/30/2015 (No fund extension)
The primary goal of this project is to find therapeutic inhibitors of LOX-1.
Overlap: None

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: **Maria J. Almeida**

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

POSITION TITLE: **Professor**

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion year(s)	FIELD OF STUDY
University of Porto, Portugal	B.S.	1987	Marine Biology
Abel Salazar Institute of Biomedical Sciences, Porto, Portugal	Ph.D.	1997	Comparative Physiology
CNRS National Museum of Natural History, Paris, France	Postdoctoral	2001	Comparative Physiology
University of Arkansas for Medical Sciences, Little Rock	Postdoctoral	2005	Molecular Biology

A. Personal Statement

The overall goal of my research is to elucidate the cellular and molecular mechanisms responsible for the loss of bone with aging. I have more than 10 years of research experience in the area of biomineralization and an additional 15 years in the area of basic bone biology. Work from my lab has revealed critical mechanisms of action of the anti-aging FoxO transcription factors on the skeleton. Our extensive work using multiple models of conditional gain or loss of function of FoxOs, Sirt1 and mitochondrial reactive oxygen species in different populations of cells within the osteoblast and osteoclast lineage has elucidated that osteoblast progenitors expressing Osx1-Cre are critical targets of the effect of old age. In addition, as a co-investigator in several other grants, we elucidated seminal cellular targets of action of estrogens and androgens on bone. As a well-recognized, productive skeletal biologist with a strong record of R01 funding and mentorship, I have effectively managed a large NIH-supported research laboratory. In addition, during the last decade I have forged several fruitful collaborations with other investigators at UAMS and other institutions in the US and abroad. My productivity and expertise attest for my ability to successfully accomplish the work proposed in collaboration with Dr. Kottayil Varughese.

a. **Almeida M**, O'Brien CA. 2013. Basic Biology of Skeletal Aging: Role of Stress Response Pathways. Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 68(10):1197-208. PMCID: PMC3779633
b. **Almeida M**, Laurent M, Dubois V, Claessens F, O'Brien CA, Bouillon R, Vanderschueren D, Manolagas SC. 2017. Estrogens and Androgens in Skeletal Physiology and Pathophysiology. *Physiol Rev* 97(1):135-187. PMCID: PMC5539371
c. Farr J, **Almeida M** 2018. The spectrum of fundamental basic science discoveries contributing to organismal aging. J Bone Miner Res 33(9):1568-1584. PMCID: PMC6327947

d. **Almeida M**, Porter RM 2019. Sirtuins and FoxOs in Osteoporosis and Osteoarthritis. Bone 121:284-292. PMID: 30738214

B. Positions and Honors

Positions and Employment

2005-2007 Research Assistant Professor, Department of Medicine, Division of Endocrinology and Metabolism, Center for Osteoporosis and Metabolic Bone Disease, University of Arkansas for Medical Sciences, Little Rock, AR

2007-2011 Assistant Professor, Department of Medicine, Division of Endocrinology and Metabolism, Center for Osteoporosis and Metabolic Bone Disease, University of Arkansas for Medical Sciences, Little Rock, AR

2011-2018 Associate Professor (tenure track), Department of Internal Medicine, Division of Endocrinology and Metabolism, Center for Osteoporosis and Metabolic Bone Disease, University of Arkansas for Medical Sciences, Little Rock, Arkansas

2016-2018 Associate Professor (tenure), Department of Orthopaedic Surgery, University of Arkansas for Medical Sciences, Little Rock, AR

2018-Present Professor (tenure), Department of Internal Medicine, Division of Endocrinology and Metabolism, Center for Osteoporosis and Metabolic Bone Disease, University of Arkansas for Medical Sciences, Little Rock, AR

2018-Present Professor (tenure), Department of Orthopaedic Surgery, University of Arkansas for Medical Sciences, Little Rock, AR

Other Experience and Professional Memberships

2002-present Member, American Society for Bone and Mineral Research (ASBMR)

2004-present Member, Endocrine Society

2011-2015 Reviewer, NIAMS Small Grant Program for New Investigators (R03)

2015-present Ad-hoc reviewer NIH/SBSR Study Section (R01)

2016-present Ad-hoc reviewer NIH/SBDD Study Section (R01)

Honors

1989-1991 Advanced Formation on Human Resources award for undergraduate studies by the Portuguese National Institute of Scientific Research (JNICT/European Community Fund)

1991-1996 Ph.D. studies award by JNICT/European Community Fund

1997-2002 Post-Doctoral Fellowship award by JNICT/European Community Fund

2006 Award for Outstanding Research in the Pathophysiology of Osteoporosis by the American Society for Bone and Mineral Research

2018 STAR award NIH/NIAMS

C. Contributions to Science

1. **FoxOs in skeletal homeostasis**. Wnt/β-catenin signaling is a seminal regulator of bone mass in animals and humans and compromised Wnt signaling plays a pathogenetic role in the development of the acquired forms of osteoporosis. My work has elucidated that ROS attenuates osteoblastogenesis by promoting the binding of FoxO transcription factors to β-catenin and sequestration of β-catenin away from TCF-mediated transcription. We have also elucidated that FoxOs exert antioxidant and pro-survival actions in mature osteoblasts. Furthermore, suppression of FoxOs by RANKL to allow for H2O2 accumulation is a critical requirement for osteoclastogenesis and bone resorption, under both physiologic and pathologic conditions.
   a. Ambrogini E*, **Almeida M***, Martin-Millan M, Payk JH, DePinho R, Han L, Goellner J, Weinstein RS, Jilka RL, O'Brien CA, Manolagas SC. 2010. FoxO-mediated defense against oxidative stress in osteoblasts is indispensable for skeletal homeostasis in mice. *Cell Metabolism* 11(2):136-46. *Contributed equally. PMCID: PMC2819984.
   b. Iyer S, Ambrogini E, Bartell SM, Han L, Roberson PK, de Cabo R, Jilka RL, Weinstein RS, O'Brien CA, Manolagas SC, **Almeida M** 2013. FoxOs attenuate bone formation by suppressing Wnt signaling. *J Clin. Invest.* 123(8):3409-3419. PMCID: PMC3726166.
   c. Bartell SM, Kim HN, Ambrogini E, Han L, Iyer S, Ucer SS, Rabinovitch P, Jilka RL, Weinstein RS, Zhao H, O'Brien CA, Manolagas SC, **Almeida M**. 2014. FoxO proteins restrain osteoclastogenesis

and bone resorption by attenuating H2O2 accumulation. Nature Communications 5:3773. PMCID: PMC4015330.

d. Iyer S, Han L, Ambrogini E, Yavropoulou M, Fowlkes J, Manolagas SC, **Almeida M**. 2017. Deletion of FoxO1, 3 and 4 in osteoblast progenitors attenuates the loss of bone mass in a model of type 1 diabetes. *J Bone Miner Res.* 32(1):60-69. PMCID: PMC5492385.

2. **Sirt1 is a therapeutic target for skeletal aging.** Sirt1 counters the development of aging-associated diseases, including osteoporosis, in mammals. Work from my lab has elucidated that Sirt1 stimulates bone formation and inhibits bone resorption via deacetylating FoxOs. Further, in collaboration with the group of Rafael de Cabo at the NIA, we found that synthetic small molecule activators of Sirt1 attenuate the loss of bone mass caused by disuse or aging. Our findings strongly support the notion that a Sirt1/FoxO axis is a reasonable target for the treatment and prevention of osteoporosis.
   a. Iyer S, Han L, Bartell SM, Kim HN, Gubrij I, de Cabo R, O'Brien CA, Manolagas SC, **Almeida M**. 2014. Sirtuin1 (Sirt1) Promotes Cortical Bone Formation by Preventing beta (β)-Catenin Sequestration by FoxO Transcription Factors in Osteoblast Progenitors. *J Biol Chem* 289(35):24069-78. PMCID: PMC4148840.
   b. Merken EM, Mitchell SJ, Martin-Montalvo A, Minor RK, **Almeida M**, Gomes AP, Scheibye-Knudsen M, Palacios HH, Licata JJ, Zhang Y, Becker KG, Khaiwesh H, Gonzalez-Reyes JA, Villalba JM, Baur JA, Vlasuk GP, Ellis JL, Sinclair DA, Bernier M, de Cabo R. 2014. SRT2104 extends survival of mice on a standard diet and preserves bone and muscle mass. *Aging Cell* 13:787-96. PMCID: PMC4172519.
   c. Kim HN, Han L, Iyer S, de Cabo R, Zhao H,. O'Brien CA, Manolagas SC, and **Almeida M**. 2015. Sirtuin1 suppresses osteoclastogenesis by deacetylating FoxOs. *Mol. Endocrinol.* 29(10):1498-509. PMCID: PMC4588729.

3. **Cellular senescence in aged bone**. Using a murine model with labeled osteoprogenitors, we have recently shown that age-related bone loss is associated with decreased number of osteoprogenitors and that in old mice these cells exhibit markers of senescence and increased capacity to support osteoclast formation. Senescence markers are also increased with age in osteocytes and associated with increased endosteal and intracortical bone remodeling. Elimination of senescent osteoclast lineage cells does not impact age-related bone loss, suggesting that senescence of osteoblast lineage cells contribute to skeletal aging.
   a. Kim HN, Chang J, Shao L, Han L, Iyer S, Manolagas SC, O'Brien CA, Jilka RL, Zhou D, **Almeida M**. 2017. DNA damage and senescence in osteoprogenitors expressing Osx1 may cause their decrease with age. *Aging Cell.* 16(4):693-703. PMCID: PMC5506444.
   d. Piemontese M, **Almeida M**, Robling AG, Kim HN, Xiong J, Thostenson JD, Weinstein RS, Manolagas SC, O'Brien CA, Jilka RL 2017. Old age causes de novo intracortical bone remodeling and porosity in mice. *JCI Insight* 2(17):e93771. PMCID: PMC5621920.
   c. Kim HN, Chang J, Iyer S, Han L, Campisi J, Manolagas SC, Zhou D, **Almeida M**. 2019. Elimination of senescent osteoclast progenitors has no effect on the age-associated loss of bone mass in mice. *Aging Cell* 18(3):e12923. PMCID: PMC6516158.

4. **Oxidative stress in pathological bone loss**. Work that I initiated has elucidated aging and sex steroid deficiency increases the generation of reactive oxygen species in bone. In addition, we have shown that reactive oxygen species in mesenchymal lineage cells and in osteoclast contributes to the loss of bone mass with age and estrogen deficiency, respectively. We have also elucidated that estrogens and androgens protect trabecular and cortical bone via different cellular targets revealing an unanticipated intricate mechanism of action of sex steroids on the skeleton.
   a. **Almeida M**, Han L, Martin-Millan M, Plotkin LI, Stewart SA, Roberson PK, Kousteni S, O'Brien CA, Bellido T, Parfitt AM, Weinstein RS, Jilka RL, Manolagas SC. 2007 Skeletal involution by age-associated oxidative stress and its acceleration by loss of sex steroids. *J Biol Chem* 282(37):27285-97. PMCID: PMC3119455.

b. Martin-Millan M, **Almeida M**, Ambrogini E, Han L, Zhao H, Weinstein RS, Jilka RL, O'Brien CA, Manolagas SC. 2010. The estrogen receptor α in osteoclasts mediates the protective effects of estrogens on cancellous but not cortical bone. *Mol Endocrinol.* 24(2):323-34. PMCID: PMC2817608.

c. **Almeida M**, Iyer S, Martin-Millan M, Bartell SM, Han L, Ambrogini E, Onal M, Xiong J, Weinstein RS, RL Jilka, CA O'Brien, SC Manolagas. 2013 Estrogen receptor-α signaling in osteoblast progenitors stimulates cortical bone accrual. *J Clin. Invest.* 123(1):394-404. PMCID: PMC3533305.

d. Ucer S, Iyer S, Kim HN, Han L, Rutlen C, Allison K, Thostenson JD, de Cabo R, Jilka RL., O'Brien C, **Almeida M***, Manolagas SC*. 2017. The effects of aging and sex steroid deficiency on the murine skeleton are independent and mechanistically distinct. *J Bone Miner Res*. 32(3):560-574. PMCID: PMC5340621. * Contributed equally

Complete List of Published Work
https://www.ncbi.nlm.nih.gov/sites/myncbi/maria.almeida.1/bibliography/45253025/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

R01 AR056679-06 (M Almeida, PI) 12/01/08-01/31/21
NIH/NIAMS $220,000
Role of FoxOs in Skeletal Homeostasis
The theme of this grant is that Sirt1 increases osteoblastogenesis and decreases osteoclastogenesis by deacetylating FoxOs in the respective progenitors. The age dependent decrease in Sirt1 activity contributes to the pathogenesis of involutional osteoporosis by tilting the balance between bone formation and resorption in favor of the latter. Activation of Sirt1 can ameliorate these effects and may thus represent a rational therapeutic target for the management of osteoporosis. The beneficial effect of Sirt1 on osteoblastogenesis is amplified by increased ATP production.

3R01AR056679 (M Almeida, PI) 3/1/2018 – 2/29/2020
NIH/NIAMS $150,000
STAR Funding - Admin Supplement
The goal of the work proposed in the STAR application is to develop specific cell-penetrating peptides to interfere with the interaction of FoxOs with β-catenin and, by this means, stimulate bone formation.

P20 GM125503-01 (O'Brien, PI) 12/01/2017 - 11/30/2022
NIH/NIGMS $1,500,000
Center for Musculoskeletal Disease Research
Role: Associate Director, Co-Leader Core 1, Mentor
The goal of this application is to establish a Center for Biomedical Excellence (COBRE) to be named the Center for Musculoskeletal Disease Research (CMDR) at the University of Arkansas for Medical Sciences (UAMS). This center will provide multidisciplinary development and unique research opportunities to young investigators and support them to the point of independence.

VA Merit (SC Manolagas, PI) 10/01/16-09/30/20
Estrogen, Androgen, Aging and Bone Loss in Males $150,000
Role: Co-Investigator
The goals of this project are to establish the similarities or differences of the contribution of the cell autonomous effects of androgens versus cell autonomous effects of estrogens and their respective receptors on osteoblasts and osteoclasts to the skeletal homeostasis of male mice. Specifically, the hypotheses to be tested is that the protective effect of androgens on cancellous bone is mediated primarily via the osteoclast AR and results from decreased osteoclastogenesis and shortened osteoclast lifespan secondary to increased apoptosis; while the protective effect of androgens on cortical bone is mediated via both the AR and the ERα.

Completed Research Support

P01 AG013918-16 (SC Manolagas, PI) 05/01/12-05/30/17
NIH/NIA

Molecular and Cellular Mechanisms of Osteoporosis

The central theme of the grant is that loss of bone with age is due to multiple factors including increased ROS, elevated oxidized lipids, relative glucocorticoid excess, and decreased physical activity. The goal of Project 1 is to test the hypothesis that increased ROS levels with advancing age is a fundamental mechanism of the age-dependent decline of bone strength and mass, and loss of estrogens exaggerates the adverse effects of aging on bone by decreasing defense against ROS, thereby, contributing perpetually to the loss of bone mass and strength that persists for decades after menopause, and is associated with old age.
Role: Co-Investigator in Projects 1 and 2

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Das, Bhaba Krishna

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

POSITION TITLE: Post Doctoral Fellow

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
Dibrugarh University, Dibrugarh, Assam, India	B.Sc	10/2004	Zoology
Madurai Kamaraj University, Tamil Nadu, India	M.Sc	08/2009	Biotechnology
ICGEB-Jamia Hamdard, New Delhi, India	Ph.D	10/2016	Structural Biology

A. Personal Statement

B. Positions and Honors

Honors

- CSIR-NET JRF/SRF scholarship from 2009-2014
- Prof. S. Krishnaswamy Memorial Endowment Prize, 2009.
- Prof. E.R.B. Shanmugasundaram Endowment Medal, 2009.
- Thiru K Ayyamperumal Pillai Endowment Medal, 2009
- Secured 1st position during Masters (M.Sc Biotechnology), 2009
- Qualified CSIR-JRF-NET, December 2008
- Qualified DBT-JRF-NET, April 2009
- Qualified GATE, 2009
- DBT Scholarship from 2007-2009
- Secured 3rd position during Graduation (B.Sc Zoology), 2004

C. Contributions to Science

- **Das, B.K., Kumar, A., Maindola, P., Mahanty, S., Jain, S.K., Reddy, M.K., Arockiasamy, A.** Non-native ligands define the active site of Pennisetum glaucum (L.) R. Br dehydroascorbate reductase. **Biochem. Biophys. Res. Commun.** 473(4) 1152-1157 2016

- **Kashyap, M., Jagga, Z., Das, B.K., Arockiasamy, A., Bhavesh, N.S.** ^{1}H, ^{13}C and ^{15}N NMR assignments of inactive form of P1 endolysin Lyz. **Biomol. NMR Assign.** 6(1): 87-89 2012.

D. Additional Information: Research Support and/or Scholastic Performance