MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA

THE PATHWAY

September 2017 Volume 8, Issue 3

What you don't know about your AGE level can kill you

Researcher explores link of people's AGE levels to risks for cancer and other diseases

This story was written by Dawn Brazell and is available through MUSC News at the link below:

http://academicdepartments.musc.edu/newscenter/2017/AGE-level-links-to-cancer-and-chronic-disease/index.html

Turner especially wants parents to know about the research because very simple changes they make in their kids' diets can significantly impact their future health.
Some general tips and a tip sheet (pdf) that can be downloaded:

http://academicdepartments.musc.edu/newscenter/pdf/Healthy-communities-pdf-accessible.pdf

Dr. Turner explores the link between tumor biology and lifestyle.

Steven L. Carroll, M.D., Ph.D., FASCP, FCAP

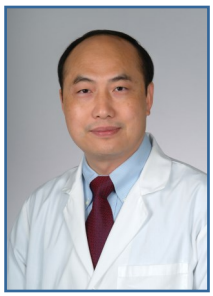
Department Chair

Inside this issue:

This newsletter is made possible from the generous contributions of MUSC's Pathology and Laboratory Medicine Faculty and Staff. The success of this publication is dependent upon this support. Thank you for your interest, time and information. For inquiries, suggestions or submission information please contact Lori Roten (roten@musc.edu).

ANNUAL SERVICE AWARDS

Dr. Rick Nolte - 10 years of service



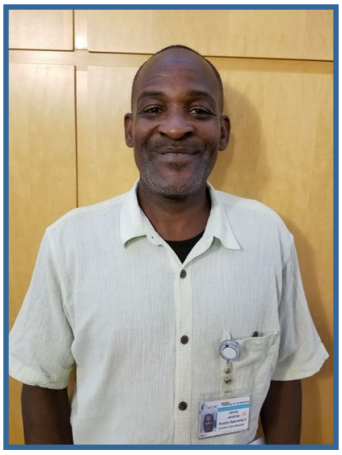
Dr. Gavin Wang - 10 years of service

Dr. Sally Self - 30 years of service

Jarvis Jenkins - 30 years of service

Jason Flamm - 10 years of service

JARVIS JENKINS



Supply Specialist II

Nomination: Always being there.

Other Nominees: Lisa Coulter, Raymond Edwards, Jason Flamm, Chad Fluharty, Karen Geroulis, Brent Grimball, Julie Haebig, Elizabeth Hansell, Dolly Hope, Sonya Jordan, Teresa Kennedy, LaQuantes Mack, Linda McCarson, Lori Roten, Margaret Romano, Nancy Smythe, Ashley Wooldridge, Iya Znoyko

CONGRATULATIONS!

TO: Dr. Steven L. Carroll and Family

IT'S A GRANDDAUGHTER!

Alice Joanna Wasieleski
Born on September 10, 2017
8 lbs., 6 ounces

TO: Beth Hansell and Family

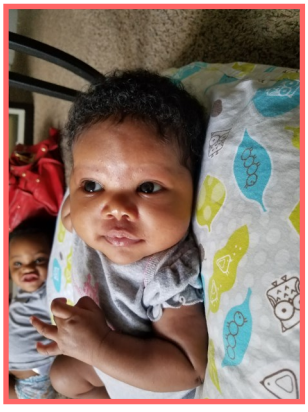
IT'S A GRANDDAUGHTER!

Elizabeth Ann Hansell
Born on August 3, 2017
6 lbs., 12 ounces

TO: Kenyaria Noble and her Husband

IT'S A GIRL!

Kaydence is two months old and her brother Domani (in the background is almost 2 years old.



RESEARCH DIVISION UPDATE

Statistics for the Division of Research from July through September Nine grant proposals were submitted requesting $2,280,881 in total first year costs. Also, during this period five grants was awarded totaling $520,552.

Congratulations and many thanks to everyone involved in obtaining these awards.

Bradley Schulte, Ph.D., Vice Chair of Research

GRANT APPLICATIONS SUBMITTED - 7/1/2017-9/30/2017

Principal Investigator	Proposed Start Date	Title	Total 1st YR Dollars
Carroll, Steve	1/1/2018	Development of Effective Combinatorial Therapies that Target MPNST Heterogeneity	$274,696
Cheung, Hiu	2/1/2018	Developing a Combination Therapy Targeting Ovarian Cancer Stem Cells	$100,000
Mehrotra, Meenal	4/1/2018	Role of Hematopoietic Stem Cell-Derived Osteoblasts in Osteosarcoma Progression	$74,750
Spyropoulos, Demetri	4/1/2018	Investigation into a Inflammatory Promoter of Colorectal Cancer	$186,875
Spyropoulos, Demetri	1/1/2018	Genomic Analysis of the Stress Response and Microbiome in Peromyscus	$100,000
Ethier, Stephen	7/1/2018	Tandem duplicator Phenotype and Oncogenic Signaling in Triple Negative Breast Cancer	$777,100
Wang, Gavin	7/1/2018	Intracellular Signaling Network Analysis of Stress-Induced Stem Cell Senescence	$371,230
Wang Gavin	7/1/2018	MYC Inhibition-Induced Cancer Stem Cell depletion	$371,230
Fan, Hongkuan	11/1/2017	SCTR Microbiome Retreat: Targeting Gut Microbiota to Treat Sepsis	$25,000
Total Proposals	**9**		**$2,280,881**

GRANTS AWARDED - 7/1/2017-9/30/2017

Turner, David	7/1/2017 - 6/30/2018	AGEs Metabolites as Unifying Biological Mechanisms	$49,000
Turner, David	10/1/2017 - 9/30/2022	AGE Metabolites as a Unifying Biological Mechanism Linking Lifestyle, Metabolism and Cancer Disparity	$137,850
Findlay, Victoria	10/1/2017 - 9/30/2018	Lifestyle Associated Reactive Metabolites and their Negative Impact on breast Cancer risks	$60,000
Findlay, Victoria	10/1/2017 - 9/30/2022	AGE Metabolites as a Unifying Biological Mechanism Linking Lifestyle, Metabolism and Cancer Disparity	$77,627
Lazarchick, John	9/28/2017	An Open-Label Multicenter, Phase 1/2 Study of the Safety and Dose Escalation of BAX888, an Adeno-associated Virus Serotype 8 (AAV8) Vector Expressing B-Domain Deleted Factor VII (BDD-FVIII) in Severity	$196,075
Totals Awarded	**5**		**$520,552**

FACULTY FOCUS

By

Laura Spruill, M.D.

I was born in Rochester, NY, where I was raised in the suburbs with my younger sister, Dawn and my younger brother Matthew. We had a family dog, Shannon who lived nearly my entire childhood, and survived my mother who died when I was 13. Much of my childhood memories are related to the change in seasons: Fall was always my favorite and brought the Hilton Apple Festival, nose nipping crispness in the air and glorious changes in the maple leaves. Winter was cold and snowy and long, but I remember going sledding with my dad, whose patience for whining or inability to climb hills was limited, and snow days, the northern equivalent to hurricane days. Spring was always late, and I recall that the advertisements for cute short-sleeved Easter dresses always seemed absurd, but brought with it the lilacs and daffodils. Summer was short, especially for a kid, and consisted of bike rides, playing in the yard, dew covered clover in the morning, and hot summer nights baking under a fan in my second floor, shared bedroom.

I went to college at SUNY Geneseo, where I graduated with a BS in Biochemistry with a minor in Fine Art. Geneseo was the quintessential college town, and I have dreams of visiting my children at such a place when they are old enough to attend college. The summer before my senior year, I applied to a summer research program in Charleston, at the encouragement of some of my far more adventurous friends. I was wait-listed, but at the last minute accepted after I had already lined up a summer job at Kodak, where I had worked the two summers previous. After some debate, I accepted the opportunity and made the 16 hour drive south to MUSC with my dad and stepmom. I remember seeing the palmetto trees and thinking that I was definitely not in western NY anymore. The 97 degree days in May confirmed that observation. That summer was one of the defining seasons of my life. I was, to that point, staunchly set on attending medical school alone, a choice born after the death of my mother. However, that summer, I realized I had an interest in research. I also met my future husband Josh and I made great friends in Charleston and at MUSC who would help to get me back to Charleston.

Being accepted into the Medical Scientist Training Program (MSTP or MD/PhD) program at MUSC is one of the “God Moments” in life. Even many years later, I don’t understand how I got in, but I accept it as a gift from above to align my future to bring me to today. I completed my PhD thesis in Dr. Paul McDermott’s lab with a project looking at translational regulation of proto-oncogenes in the development of cardiac hypertrophy. At the time, I was using cutting edge technology and the concept of growth regulation at the level of the ribosomes was somewhat new. In the short 10 years after defending, it is all old news. But, in the years it took me to earn my PhD, I married Joshua Bunyan Spruill who worked in the department of Cell Biology and Anatomy, now the Department of Regenerative Medicine, in the Molecular Morphology and Imaging core as a computer expert. We had our first child Samantha Helen Spruill a few years later.

Returning to the wards as a lowly minion after having done the self directed work of completing a PhD was a humbling experience. But I had Josh’s support and the marvelous support of family, and it seemed that all the stars were aligning as we were rounding the corner toward the end of fourth year. I was pregnant with my second child and excited for new beginnings on many fronts. By that time I had decided that Pathology was the best choice for me. With the visual nature of the work and its behind-the-scenes impact on patient care, much like in research, it was well suited to my strongest skill set. Despite encouragement from career minded advisors to branch out to a different institution for residency, I knew that I would receive the strong training I wanted with the happy life I desired at MUSC. Josh was supportive of pathology and ecstatic to stay in Charleston.

Continuation of Faculty Focus by Dr. Laura Spruill

Luke Joshua Spruill was born February 9, 2008. His daddy died February 10. Josh had untreated epilepsy that manifested primarily as night-time tonic-clonic seizures. I was in the hospital after giving birth and couldn't be there to protect his airway.

At this point in my life, I relearned the definition of family. I had the picture of my family at graduation framed in my mind: smiling momma in cap and robe, hanging on to a wee babe while my husband smiled at my side holding Sam on a sunlit campus. The disappointment at the loss of that picture and all it represented was overwhelming. But, I gained, in this season of my life, an extended family to include my MUSC family, my church family, my daycare family and renewed and continuing support of all of my immediate and extended family. Josh's parents Ken and Gloria Spruill were, to that point, extremely supportive of both Josh and I, but became my greatest support and closest family after his death. Beginning residency as a newly single mom with a 4 month old and 3 year old was challenging. But again, God provided, and I had childcare help on busy months, supportive co-residents and supportive faculty mentors at work, and I had friends outside of work who were all in. Residency went quickly and children grew.

Fall of my third year of residency, I was set up with a radiology resident, Pal Suranyi. A quick search for a picture online showed a stern appearing eastern European and despite my trepidation, I sent the now infamous one line email: "My friend Roger and your friend Vanessa think we should meet." We talked on the phone and had our first date, lunch at the Wycliffe House. The stage was set, though the road was winding, for us to be married July 21, 2012, just a few weeks into my first fellowship in Surgical Pathology. Roughly 2 years later, with some strong advocacy by my colleagues and mentors, I joined the faculty at MUSC. With marriage came new challenges. I gained two beautiful stepchildren Kinga Salome Suranyi and Benett Samuel Suranyi. Being a stepmother has, surprisingly (to me) been one of the hardest challenges I've faced. In some respects, after 5 years, the hard work is paying off.

Currently, my children are 9, 12, 15 and 18, and are each thriving in their own way. All of them do well in school, though their grades vary based on effort and attention to detail. Luke, the youngest, is currently a yellow belt in Taekwondo and is learning to spar. He is my hope for one of my children to follow our footsteps into medicine. Samantha, the 12 year old, participated in swim team over the summer and is enjoying learning clarinet and is very artistic. Benett is my handsome 15 year old stepson and he plays the most beautiful French horn you've ever heard and spends his time focused on marching band, concert band and his girlfriend. Kinga has graduated high school and is currently taking a gap year, attempting to travel as much as possible while learning the responsibility of being an adult. Pal has recently become an American citizen and has taken the name Pal Spruill Suranyi as a show of respect to the family that has so completely supported us. He is an Associate Professor of Radiology at MUSC and loves teaching. In his spare time he is on the leadership team at our church, plays multiple instruments, and is bonding with our new kitten Figaro. I am an Assistant Professor in Surgical Pathology at MUSC and I'm trying to balance work, advancement and family with variable success. I love my job and I love the people I work with and I'm thankful for God's path to this time and place.

Novel Role of HSC Derived Cells in Bone and Dental Tissues

by Meenal Mehrotra, Ph.D.

Bone is a dynamic organ that undergoes continuous regeneration. It consists of specialized cells, mineralized and unmineralized connective tissue matrix and spaces including the bone marrow cavity, vascular canals, canaliculi and lacunae. During development and growth, the skeleton is sculpted to achieve its shape and size by the removal of bone from one site and deposition at a different one; this process is called modeling. Once the skeleton has reached maturity, regeneration continues via periodic replacement of old bone with new at the same location. This process is called remodeling and is responsible for the complete regeneration of the adult skeleton every 10 years[1]. Remodeling is achieved by the sequential action of osteoclasts (which resorb bone) and osteoblasts (which lay down or form bone). A continuous supply of new osteoclasts and osteoblasts from their respective progenitors and stem cells in the bone marrow is essential to maintain normal bone turnover. Osteoblasts, whose specialized functions include synthesis and secretion of bone components, are believed to arise from stem cells via osteoprogenitor cells. Friedenstein[2] showed for the first time that, on transplantation of bone marrow under the renal capsule, new bone is formed from donor cells, demonstrating that whole bone marrow possesses a stem cell that can give rise to osteoblasts. The prevailing paradigm is that the bone marrow contained two distinct classes of stem cells: Mesenchymal Stem Cells (MSCs) and Hematopoietic Stem Cells (HSCs) and their repertoire of differentiation/ reconstituting potentials are distinct and separate from each other. Subsequent studies led to the general belief that osteoblasts are derived from MSCs[3,4]. But bone and bone marrow are closely aligned compartments, suggesting that these tissues may represent a single functional unit with a common progenitor that gives rise to both osteoblasts and hematopoietic cells. This is a relatively controversial topic in the field of bone biology but was suggested almost 40 years ago when it was shown that bone marrow and endochondral bone arose from the same vascular cells that invaded the initial cartilage molds of long bones[5,6,7]. Several studies in the past 10-15 years have kept reviving this discussion and challenging the current dogma that osteoblasts are derived solely from MSCs[8,9,10,11]. Olmsted-Davis *et al* found that a single adult hematopoietic cell ("side population" cell) could function as an osteoblast in mice[10] while Dominici *et al* transplanted marrow cells that had been transduced with GFP-expressing retroviral vector and observed a common retroviral integration site in clonogenic hematopoietic cells and osteoprogenitors from each of the recipient mice[11]. Most recently, Otsuru *et al* have shown that non-adherent cells from bone marrow (the fraction where HSCs reside) engrafted into bone and differentiated into osteoblasts far more efficiently than plastic-adherent MSCs[12] and Hofmann *et al* demonstrated that transplanted murine long-term repopulating hematopoietic cells can differentiate to osteoblasts in the marrow stem cell niche[13]. Along those lines, using mice transplanted with a clonal population derived from a single GFP$^+$ HSC, we showed, for the first time, that HSCs can give rise to osteo-chondrogenic cells[14].

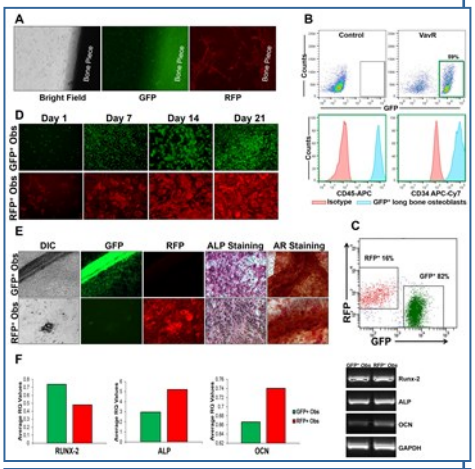


Fig. 1: Characterization of GFP$^+$ cells from the long bones of VavR mice. Cells were obtained from tibia and femur of VavR mice by explant culture. Both GFP$^+$ and RFP$^+$ cells can be seen migrating out of the bone piece **(A)**. Analyzing the GFP$^+$ population of cells cultured from long bone cells (59%) demonstrates that all the GFP$^+$ cells also expressed the hematopoietic markers CD45 and CD34 **(B)**. The GFP$^+$ and RFP$^+$ cells were sorted and replated under osteogenic conditions **(C)**. Observing the cells from day 1 to day 21 shows that GFP$^+$ cells, though smaller than the RFP$^+$ cells, do aggregate to form colonies **(D)**. Ob can be identified in both cultures by the presence of alkaline phosphatase staining. The Ob mineralized and laid down calcium in both cultures as evidenced by positive alizarin red staining in both cultures **(E)**. The GFP$^+$ Obs also expressed the various markers of the osteoblastic lineage such as RUNX-2, ALP and osteocalcin, measured both by real -time PCR and RT-PCR. The RFP$^+$ cells are shown as controls **(F)**. Bar=100μM.

My lab has further tried to confirm this by using a specific transgenic mice known as Vav-recombinant or VavR, described in a recent study by Suga et al[15] which has reported generation of a Cre-activated dual fluorescence mouse strain with Cre expressing mice under Vav-1 gene promoter. Vav-1 is a pan-hematopoietic marker expressed exclusively in hematopoietic system[16]. In these mice, all hematopoietic cells driven by Vav-1 are labeled with GFP after Cre-mediated excision of floxed RFP and non-hematopoietic cells with no Cre activity remain RFP labeled. Importantly, any cells that ever transcribed Vav-1 at any point during development are permanently labeled with GFP, eliminating the problem of transient expression of hematopoietic lineage markers[15]. Thus, this is an ideal model for our studies. Cells were obtained from bones of VavR mice by explant culture. Both GFP^+ and RFP^+ cells can be seen migrating out of bone **(Fig. 1A)**. Analyzing the GFP^+ population of cultured cells (59%) demonstrates that these cells also expressed hematopoietic markers CD45 and CD34, indicating their hematopoietic origin **(Fig. 1B)**. The cells were then sorted into GFP^+ and RFP^+ populations **(Fig. 1C)** and grown for 3 weeks in osteogenic media. The progression of cells in culture is shown in **Fig. 1D**. The GFP^+ cells, though smaller than RFP^+ cells, do aggregate to form colonies. Osteoblasts can be identified in GFP^+ cultures by presence of alkaline phosphatase (ALP) staining. These osteoblasts mineralized and laid down calcium as evidenced by positive alizarin red staining **(Fig. 1E)**. The GFP^+ osteoblasts also expressed various markers of osteoblastic lineage such as RUNX-2, ALP and osteocalcin (OCN) (**Fig. 1F)**. Thus, our data confirms that there exists a population of osteoblasts which have a hematopoietic origin.

Now that we have shown that HSCs can give rise to osteoblasts, our next question was if we can use HSCs in genetic diseases of bone with high turnover to bring about healing such as Osteogenesis imperfecta (OI). OI, an autosomal dominant disorder caused by a mutation in one of the two genes that encode type I collagen (COL1AI or COL1A2), is the most common hereditary bone disease. It is characterized by mild to severe reduction in the quantity of bone matrix that leads to repeated fractures, low bone mass and bone deformity. In the United States, the incidence of OI is estimated to be 1 per 20,000 live births. At present there is no cure for OI. Treatment is aimed at increasing overall bone strength to prevent fractures. Long-term treatment with the drugs has its own side effects; therefore several strategies are being tested experimentally in OI to enhance bone remodeling, one of them being the use of stem cells. Thus we are working on the hypothesis that HSCs could have a therapeutic value in OI by differentiating into osteoblasts, thereby replacing the affected osteoblasts by normal cells. We have previously shown that transplantation of an enriched population of HSCs can ameliorate the bone defects seen in OI mice[17]. Our recent data from OI mice transplanted with a clonal population derived from a single GFP^+ HSC demonstrates a significant improvement in the trabecular and the cortical parameters in engrafted mice **(Fig. 2 I)**. We also show that HSC transplantation leads to the formation of functional osteoblasts that deposited collagen and formed bone *in vivo* **(Fig. 2 II)**. We are currently working on characterizing the factors modifying bone reconstitution by HSCs in OI and also defining the molecular mechanisms regulating HSC differentiation to osteoblasts. Effect of factors on mobilization of HSCs and their differentiation to osteoblasts are also being studied. Findings from this study will be significant in that they can be applied to long-term studies to enhance and accelerate bone healing in OI.

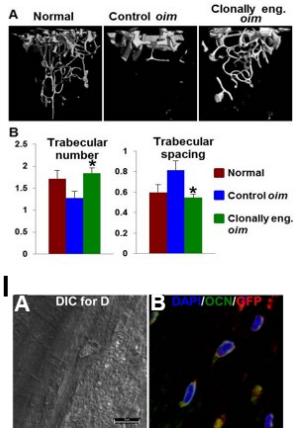


Fig 2: (I) (A) Representative ex vivo micro-CT pictures of proximal tibia below growth plate from normal, control OI and clonally engrafted OI mice. Markedly increased trabecular bone can be seen in clonally engrafted OI compared to control OI. **(B) Morphometric Analysis from ex-vivo micro-CT** from normal (n=3), control OI (n=3) and clonally engrafted OI (n=4) demonstrates an increase in trabecular number and a decrease in trabecular spacing similar to those seen in normal mice. *p<0.05 comparing clonally engrafted OI to control OI.

(II). Representative high magnification images of different regions of tibia from clonally engrafted OI mice taken at 6 months after TP. Differential interference contrast (DIC) images show cell morphology (A) and DAPI staining was used to identify the cell nuclei. Sections were stained with antibodies to Osteocalcin (green) and GFP (red). GFP expression (red) shows the presence of HSC derived cells within the bone. Merged images of GFP, osteocalcin and DAPI staining (B) show the presence of GFP^+ cells which expressed osteocalcin. Bar= 10 µM

Another area that we are working on is examining if these hematopoietic-derived osteoblasts play a role in the progression of osteosarcoma. Osteosarcoma is the most common primary malignant bone sarcoma and one of the leading causes of cancer-related death in the pediatric age group, but mechanisms underlying its progression remain elusive. Despite wide-margin surgery and intensification of chemotherapeutic treatment, overall survival rates have plateaued at 60%. Novel treatment modalities are therefore

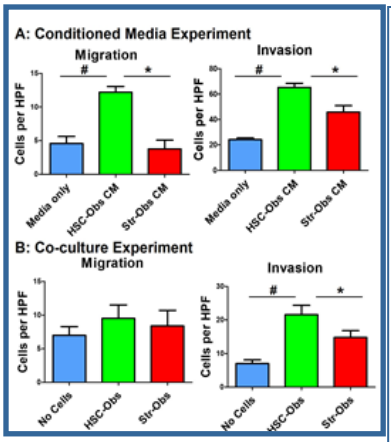


Fig. 3: HSC-Obs increased migration and invasion of OS cells to a greater extent when compared to MSC-Obs. Obs were obtained from pieces of tibia and femur from VavR mice by explant culture and sorted for GFP^+ (HSC) and RFP^+ (MSC) cells. These were grown for 3 weeks in osteogenic media. Equal number of cells were plated for all experiments and were counted after collection of CM to normalize it. Also after collection of CM, images were taken to confirm that no RFP^+ cells were seen in GFP cultures and vice versa. For collecting CM, serum-free media was added to the cells and incubated for 24h at 37°C with 5% CO_2, after which the CM was collected. **(A).** CM experiment: Migration (4h) and invasion (22h) were measured in OS cells against CM from HSC-Obs and MSC-Obs. There was a significantly greater increase in migration and invasion by HSC-Obs when compared to that seen with MSC-Obs. **(B).** Co-culture experiment: Equal number of HSC-Obs and MSC-Obs were plated in the bottom of the well for 24 h. Well with no cells (media only) was the control. Migration showed a trend while for invasion, there was a significant increase by HSC-Obs as compared to MSC-Obs.

needed. Recently, tumor-promoting roles for cells of the tumor microenvironment, specifically fibroblasts, have been described. But in osteosarcoma, which grows frequently in the long bones, the role for osteoblasts in the tumor stroma has not yet been extensively investigated. Conditioned media as well as co-culture experiments demonstrated that there was a greater increase in migration and invasion of osteosarcoma cells when exposed to HSC-derived osteoblasts as compared to MSC-derived ones **(Fig. 3 A&B)**. We are currently working on defining the factors or the mechanisms by which the hematopoietic-derived osteoblasts promote tumorigenesis in osteosarcoma. Our long-term objective is to identify mechanisms regulating the contribution of hematopoietic-derived osteoblasts to the osteosarcoma microenvironment and thereby, targeting those cells as a means to limit tumor progression by developing potential anti-tumor therapies.

Another project that we are working on is to examine the contribution of HSCs to the dental tissues such as pulp, periodontal ligament (PDL) and alveolar bone (AvB). Recent studies have shown that bone marrow cells can differentiate into pulp cells and regenerate PDL and AvB. While earlier studies have suggested that cells with hematopoietic markers (CD34, CD45) can be found in dental tissues, it has yet to be established that HSCs can differentiate into cells in pulp, PDL and AvB. Our data shows, for the first time, using mice transplanted with a clonal population derived from a single GFP^+ HSC as well as VavR mice that hematopoietic-derived cells are indeed present in all the three tissues **(Fig. 4)** and their percentage increases during ligature induced periodontitis and also during recovery. We are currently working on characterizing these hematopoietic-derived cells and also examining if a similar population is present in human dental tissues. This finding has opened new avenues of therapy for a number of dental diseases and injuries through the use of this novel cell source.

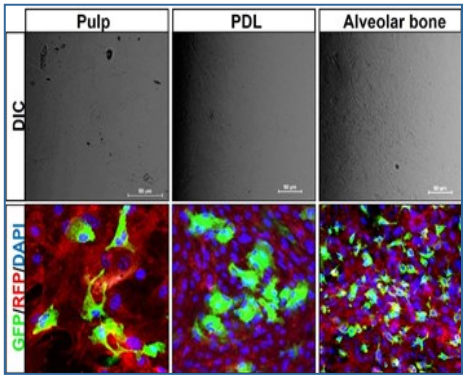


Fig. 4: Presence of hematopoietic-derived cells in dental tissues in transgenic mice: Cells from pulp, PDL and AvB were obtained from VavR mice, cultured and analyzed by immunofluorescence. GFP^+ cells (indicating their hematopoietic origin) can be appreciated among the RFP^+ cells in cultures from all three dental tissues. Hoechst shows the nuclear staining (blue) while DIC images show that morphology. Bar= 50µm.

Thus, the contribution of HSCs to mineralized tissue such as bone and teeth is a new and exciting field of research. Future studies will be aimed at understanding the functions of these cells in disease and cancer, and elucidating the factors and signaling pathways effecting the differentiation and actions of these cells.

References:

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UPCOMING MEETINGS

Holiday Celebration
South Carolina Aquarium
December 8, 2017

USCAP
Vancouver, Canada
March 17-23, 2018

Pathology Spring Symposium
East Beach Conference Center
Kiawah Island
April 17-21, 2018

Experimental Biology Annual Meeting
San Diego, CA
April 21-25, 2018

Association for Pathology Chairs
Coronado, CA
July 16-19, 2018

American Society for Clinical Pathology
Baltimore, MD
October 3-5, 2018

MUSC Department *of* Pathology & Laboratory Medicine Mission Statement:

To serve patients, health care providers, research scientists, scholars, and society by providing excellence and innovation in diagnostic services and educational resources in a respectful, professional and culturally diverse atmosphere.

Vision:

To become a preeminent leader in academic anatomic and clinical pathology while translating basic science discovery to improved clinical care.

www.musc.edu/pathology