

Bjorn R. Olsen, MD, PhD and his colleagues published, Suppressed NFAT-dependent VEGFR1 expression and constitutive VEGFR2 signaling in infantile hemangioma in *Nature Medicine*.

The paper describes for the first time, a mechanism for the rapid growth of the benign blood vessel tumor known as infantile hemangiomas, which is the most common tumor found in children. The findings implicate gene mutations that facilitate the abnormal activity of a hormone called VEGF as a cause of the tumor's growth, and suggest that anti-VEGF therapies, already approved for other conditions, may be an effective treatment.

Infantile hemangiomas are localized and rapidly growing regions of disorganized angiogenesis. Dr. Olsen and his colleagues show that expression of vascular endothelial growth factor receptor-1 (VEGFR1) in hemangioma endothelial cells (hemECs) and hemangioma tissue is markedly reduced compared to controls. Low VEGFR1 expression in hemECs results in VEGF-dependent activation of VEGFR2 and downstream signaling pathways. In hemECs, transcription of the gene encoding VEGFR1 (FLT1) is dependent on nuclear factor of activated T cells (NFAT). Low VEGFR1 expression in hemECs is caused by reduced activity of a pathway involving b1 integrin, the integrin-like receptor tumor endothelial marker-8 (TEM8), VEGFR2 and NFAT. In a subset of individuals with hemangioma, they found missense mutations in the genes encoding VEGFR2 (KDR) and TEM8 (ANTXR1). These mutations result in increased interactions among VEGFR2, TEM8 and b1 integrin proteins and in inhibition of integrin activity. Normalization of the constitutive VEGFR2 signaling in hemECs with soluble VEGFR1 or antibodies that neutralize VEGF or stimulate b1 integrin suggests that local administration of these or similar agents may be effective in hemangioma treatment.

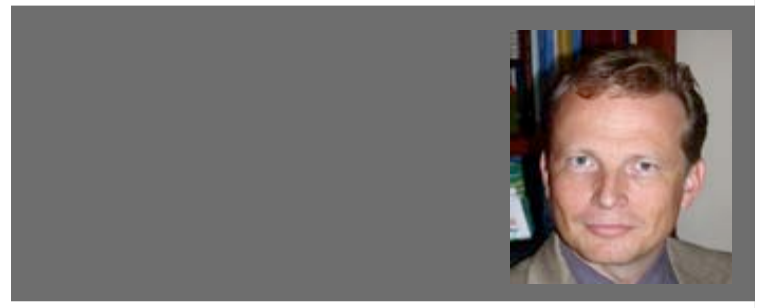
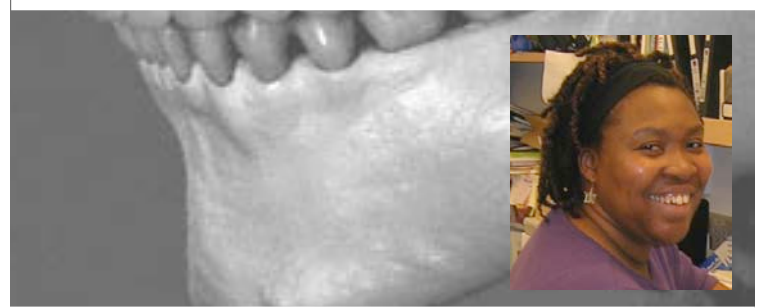
This work was supported by the John B. Mulliken Foundation and grants AR36820 and AR48564 from the National Institutes of Health.

HARVARD

SCHOOL OF DENTAL MEDICINE

OFFICE OF RESEARCH BULLETIN

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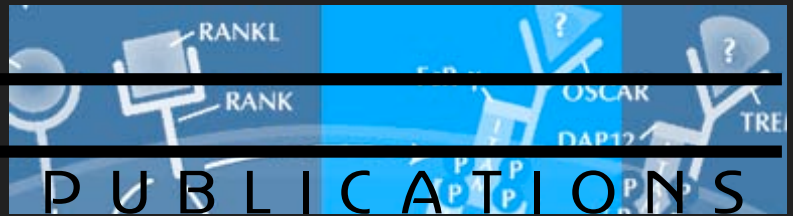
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LITT COMMUNICATIONS

HIGH THROUGHPUT GENOMICS CAPELLA IMAGER/ ARRAYPLATE/ qNPA™ TECHNOLOGY

The Capella Imager provides an imaging solution for research groups that expect to analyze fewer than 10 ArrayPlates per day. The imager uses night vision technology to image multiple panels of a 96 well plate. A typical full plate scan takes approximately 15 to 20 minutes to read; however, the instrument can be programmed to read smaller portions of the plate in order to save both time and reagents. The ArrayPlate is hybridized with Programming Linkers, which are DNA oligonucleotides with two distinct sequence domains. One half of the Programming Linker has homology to the anchor sequence attached to the surface of the plate. Each spot (shown in a different color above) has a different linker sequence, allowing the Programming Linker to be specifically targeted to each spot. The gene specific portion of the programming linker has sequence complementary to the protection oligonucleotide generated in the qNPA library step. miRNA can also be measured in the qNPA ArrayPlate. The qNPA™ Technology is a quantitative nuclease protection assay (qNPA) that allows researchers to quickly and accurately measure the gene expression levels in a wide range of mammalian, plant and bacterial cell types. The fast, automated protocol requires no RNA extraction, no RNA amplification, and no RNA labeling, leading to more reproducible results. qNPA™ Technology is uniquely suited to produce robust gene expression results from formalin-fixed paraffin embedded (FFPE) and other fixed tissues where RNA quality is an issue. These samples typically yield poor gene expression results due to RNA cross-linking and fragmentation. Due to the inaccessibility of the RNA, significant time and resources are required to prepare the samples.

SARTORIUS STEDIM BIOTECH MIKRO-DISEMBRATOR FOR SAMPLE SIZES

The Mikro-Dismembrator, a homogenization technology that utilizes laboratory ball mills used to grind rigid or frozen material. The Mikro-Dismembrator simplifies your sample preparation. Diverse samples such as teeth, bone, brain material, tumour tissue or dye pigments may be treated. High efficiency minimizes sample degradation, especially using liquid nitrogen. The samples are rapidly disintegrated resulting in a much faster isolation of involving manual grinding processes and thereby reducing the risk of sample degradation. In addition, the use of enzymes, which are often employed for cell lysis, can be avoided, thus replacing the introduction of foreign proteins, which may interfere with subsequent analysis. This is particularly advantageous in proteome research. Reproducibility of the disintegration process is guaranteed by digital control of shaking frequency and shaking time. This ensures comparable experimental conditions even within large series of experiments – another big advantage over any manual processes. A dual problem exists when attempting to study the cellular components of structural tissues. Hard and/or brittle materials of biological origin (bone, hair, teeth, cartilage, etc.) typically contain a low number of cells from which biological materials of interest, such as RNA, protein and DNA, can be extracted. The high proportion of structural or storage material in such samples, like collagen, keratin, starch or a calcified matrix, poses a barrier to the solubilization of the cells in extraction reagents and also to effective disruption and homogenization of such materials.

The mission of the Laboratory for Innovative Translational Technologies (LITT) is to enable HSDM and HMS research community to early access to new, enabling leading-edge genomic and proteomic technologies. LITT functions in a collaborative research mode that is essential for the translation of new technologies into practical biomedical applications. A part of LITT's mission is to stimulate translational research collaborations within HSDM and HMS communities. In addition, it will help researchers to reach their endpoint quicker, with less risk at a reduced cost. LITT currently has local, national and international collaborations in a wide variety of research areas, including bio-defense, biomarker detection in a variety of cancers samples, craniofacial development, emerging infectious diseases, stem cell research and orthopedics.

Please contact Winston Patrick Kuo if you have any questions to these technologies or other technologies at HC-LITT. In addition if there are technologies that you would like HC-LITT to evaluate, which can benefit your research please contact Winston directly (Winston_Kuo@hsdm.harvard.edu).

EVENTS @ HSDM

HSDM BASIC AND CLINICAL SCIENCE FORUM

NOVEMBER 21, 2008
12 - 1 PM REB AUDITORIUM

Douglas P. Mortlock, PhD

Assistant Professor of Molecular Physiology & Biophysics and Assistant Professor of Pediatrics Vanderbilt University Medical Center



MAPPING LONG-RANGE REGULATORY ELEMENTS AROUND BMP FAMILY GENES

DECEMBER 4, 2008
12 - 1 PM REB AUDITORIUM

René St-Arnaud, PhD

Professor of Medicine, Surgery, and Human Genetics at McGill University & Senior Investigator at the Canadian Shriners Hospital for Children



Most Thursdays from 12 to 1pm in the REB Auditorium, HSDM Postdoctoral Fellows present at the **Research In Progress Seminar Series**. If you are interested in learning more about this Seminar Series, or would like the schedule, please contact:

NATHANIEL GILL
(nathaniel_gill@hsdm.harvard.edu)

RESEARCH IN PROGRESS SEMINARS

HSDM TRANSLATIONAL RESEARCH JOURNAL CLUB



This journal club student series is aimed at bringing together dental students specifically clinical and research oriented. The basic aim is to present key articles that have successfully bridged the gap between basic science and a clinical application, be it diagnosis, prognosis or therapeutics. This series will be organized by students but is open to all members of the dental school, including post-docs and faculty members. Each meeting will be moderated by two key faculty members, one clinical and one from basic research, who will help the students dissect the finer details of the paper and emphasize the translational aspect and future impact on human health from these studies.

The meetings will be held once a month on a weekday evening at 5:30pm for about 1 to 1.5 hours followed by dinner for all attendees. We will soon compile a list of monthly themes, selected paper and invited faculty members. We welcome student volunteers to lead each session with help from senior students and faculty. A detailed curriculum and venue-times will be posted and circulated soon. Please address suggestions or comments to:

MALCOLM WHITTMAN
(mwhitman@hms.harvard.edu)

PRAVEEN ARANY
(arany@fas.harvard.edu)

HSDM STUDENT NEWS



Dr. Joel Stern
(PhD BSDM Nov '08)

This November, Joel will become the sixth graduate of the Biological Sciences in Dental Medicine Program, based at HSDM and offered through the Graduate School of Arts and Sciences of Harvard University. Joel's PhD dissertation, [Mechanisms of suppression of experimental autoimmune encephalomyelitis by synthetic compounds and fusion antibodies](#) was defended in September and was completed under the mentorship of Jack L. Strominger, MD, Higgins Professor of Biochemistry, Harvard University.



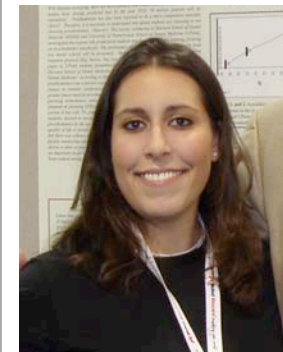
Kirsi Hakkinen
(DMD Class of 2010)

Kirsi Hakkinen was invited to present at the Hinman Student Research Symposium. Kirsi presented, [Comparing the morphology, migration, and adhesions of fibroblasts in three-dimensional extracellular matrices](#). Kirsi took a year off for research with a Howard Hughes scholarship and worked under the mentorship of Dr. Kenneth Yamada at the National Institutes of Dental and Craniofacial Research at the NIH in Bethesda, MD.



Dr. Brian Swann
(MPH June '08)

Brian Swann, DDS, MPH won the Albert Schweitzer Award at HSPH. Brian's project, [Invisible children: Access to oral health care for children with developmental disabilities from migrant farm worker families in a Northern California region](#) was completed under the mentorship of Dr. Saskia Estupian Day with the Pan American Health Organization, Dr. Joan Reed at HMS, and Dr. Chester Douglass at HSDM.



Marisa Zarchy
(DMD Class of 2010)

Marisa Zarchy was invited to present at the American College of Prosthodontics' meeting. Marisa presented, [A survey: Current trends and mentoring of dental students in prosthodontics at Harvard and University of Pennsylvania Schools of Dental Medicine](#). Marisa and her colleague, Matilda Dhima won first place for their poster presentation at the ACP in Nashville, TN. Faculty Mentors for the project were Vicki Petropoulos DMD, MS, and Robert F. Wright DDS.



Dr. Satheesh Elangovan
(DMSc Class of 2011)

Satheesh Elangovan won the prestigious Tarrson Regeneration Scholarship from the American Academy of Periodontology. Satheesh was one of two recipients of the \$38,000 scholarship for his research, [Non viral gene delivery strategies for periodontal regeneration](#) under the mentorship of Dr. Henry Margolis at The Forsyth Institute. Satheesh will receive funding in the amount of \$38,000 per year for his final three years of the DMSc Periodontology Program.



Sara Hahn
(DMD Class of 2011)

Sara Hahn was invited to present at the American College of Prosthodontics' meeting. Marisa presented, [Determining the relationship between volume of impression material and closure of double arch impressions](#). Sara won third place for her poster presentation at the ACP in Nashville, TN. Faculty Mentors for the project were Philip Millstein DMD, MS, and Robert F. Wright DDS.

Forsyth Scientists Trigger Cancer-Like Response from Embryonic Stem Cells

Biophysical Switch Provides New Clues for both Cancer and Development Biology

Scientists from The Forsyth Institute, working with collaborators at Tufts and Tuebingen Universities, have discovered a new control over embryonic stem cells' behavior. The researchers disrupted a natural bioelectrical mechanism within frog embryonic stem cells and triggered a cancer-like response, including increased cell growth, change in cell shape, and invasion of the major body organs. This research shows that electrical signals are a powerful control mechanism that can be used to modulate cell behavior.

The team of Forsyth scientists, led by Michael Levin, PhD, Director of the Forsyth Center for Regenerative and Developmental Biology, have identified a new function for a potassium (KCNQ1) channel, mutations of which are known to be involved in human genetic diseases such as Romano-Ward and Jervell-Lange-Nielsen syndromes. The team interrupted the flow of potassium through KCNQ1 in parts of the *Xenopus* frog embryo. This resulted in a striking alteration of the behavior of one type of embryonic stem cell: the pigment cell lineage of the neural crest. When mutated, these pigment cells over-proliferate, spread out, and become highly invasive of blood vessels, liver, heart, and neural tube, leading to a deeply hyper-pigmented tadpole.

The body's natural biophysical signals, driven by ion transporter proteins and resulting in endogenous voltage gradients and electric fields, have been implicated in embryonic development and regeneration. The data in this study, which will be published in the *Proceedings of the National Academy of Sciences*, have not only elucidated a novel role for the KCNQ1 channel in regulating key cell behaviors, but for the first time have also revealed the molecular identity of a biophysical switch by means of which neoplastic-like properties can be conferred upon a specific embryonic stem cell sub-population. These data reveal that key properties of embryonic stem cells can be controlled through bioelectrical signals, identify transmembrane voltage potential as a novel regulator of neural crest function in embryonic development, and demonstrate that potassium flows can be an important aspect of cellular environment, which is known to regulate both cancer and stem cells.

This work was supported by grants from The National Institutes of Health, The American Heart Association, The National Highway Traffic Safety Administration and the March of Dimes.



Scientists Identify Genes Capable of Regulating Stem Cell Function

Animal Model Provides Insight on Pathways Used for Adult Tissue Maintenance and Regeneration; System for Studying Relationship between Stem Cells and Cancer

Abnormal stem cell proliferation in planarians is induced by genetic manipulation of conserved cellular signaling pathways. These abnormal cells can be specifically targeted without disturbing normal stem cell functions that support adult tissue homeostasis and regeneration. Importantly, this type of analysis could not be achieved in more traditional adult invertebrate model systems such as the fruit fly *Drosophila* and the nematode *C. elegans*. This research will be published in the journal *Disease Models & Mechanisms* available online on August 30. According to the paper's lead author, Dr. Néstor J. Oviedo, an Assistant Research Investigator in the Forsyth Center for Regenerative and Developmental Biology, this work provides new opportunities to expand knowledge of this regulatory molecule and the role it plays in cancer and tissue regeneration. "Our findings demonstrate that important signaling pathways regulating adult stem cell proliferation, migration and differentiation are evolutionarily and functionally conserved between planarians and mammals. Planarians are poised to not only advance the understanding of how diverse adult tissues are functionally maintained *in vivo*, but also will enhance our capabilities to identify, prevent, and remediate abnormal stem cell proliferation."

This study was funded in part by grants from The National Science Foundation National Institute of General Medical Sciences, National Institute of Human Development and US Department of Transportation.

QUESTIONS? COMMENTS? SUGGESTIONS?

Please contact Dawn M. DeCosta at 617.432.1121 (or) dawn_decosta@hdsf.harvard.edu