“Turning Conversations into Tangibles”

Winston Patrick Kuo, DDS, SM, DMSc

February 19, 2015

“BioPharma Research Council Virtual Annual Meeting”

Topics covered today

Tangibles in all shapes and forms (throughout my career):

- Transitioning from academia to industry
- What we do and my role at IES Diagnostics
- Concluding remarks

IES DIAGNOSTICS LLC.

Graduate student to Assistant Professor

Vol 442|3 August 2006|doi:10.1038/nature04843 nature

LETTERS

The calmodulin pathway and evolution of elongated beak morphology in Darwin's finches

Arhat Abzhanov[1]†, Winston P. Kuo[1,2,3]†, Christine Hartmann[4], B. Rosemary Grant[5], Peter R. Grant[5] & Clifford J. Tabin[1]

A classic textbook example of adaptive radiation under natural selection is the evolution of 14 closely related species of Darwin's finches (Fringillidae, Passeriformes), whose primary diversity lies in the size and shape of their beaks[1–4]. Thus, ground finches have deep and wide beaks, cactus finches have long and pointed beaks (low depth and narrower width), and warbler finches have slender and pointed beaks, reflecting differences in their respective diets[4]. Previous work has shown that even small differences in any of the three major dimensions (depth, width and length) of the beak have major consequences for the overall fitness of the birds[5–7]. Recently we used a candidate gene approach to explain one pathway involved in Darwin's finch beak morphogenesis[8]. However, this type of analysis is limited to molecules with a known association with craniofacial and/or skeletogenic development. Here we use a less constrained, complementary DNA microarray analysis of the transcripts expressed in the beak primordia to find previously unknown genes and pathways whose expression correlates with specific beak morphologies. We show that calmodulin (CaM), a molecule involved in mediating Ca^{2+} signalling, is expressed at higher levels in the long and pointed beaks of cactus finches than in more robust beak types of other species. We validated this observation with in situ hybridizations. When this upregulation of the CaM-dependent pathway is artificially replicated in the chick frontonasal prominence, it causes an elongation of the upper beak, recapitulating the beak morphology of the cactus finches. Our results indicate that local upregulation of the CaM-dependent pathway is likely to have been a component of the evolution of Darwin's finch species with elongated beak morphology and provide a mechanistic explanation for the independence of beak evolution along different axes. More generally, our results implicate the CaM-dependent pathway in the developmental regulation of craniofacial skeletal structures.

To understand the genetic basis of the species-specific beak morphologies, we previously performed a comparative candidate gene analysis with developmental genes known to be associated with craniofacial development. We found that a broader and earlier domain of bone morphogenetic protein 4 (BMP4) expression in the distal neural-crest-derived mesenchyme correlated with the very deep and wide beak morphology of the ground finches[8]. This expression difference was shown to be functionally significant by misexpression analysis in chick embryos[8].

However, the candidate gene approach did not yield any candidates for pathways that could be involved in evolution of the longer beak morphology characteristic of the cactus finch species. To identify pathways involved in the evolution of long beaks, cDNA microarrays were used for a direct comparison of the gene expression profiles of several thousand transcripts in stage 26 frontonasal processes (which give rise to the upper beak) of five species of genus *Geospiza*: the sharp-beaked finch (*Geospiza difficilis*), the medium and large ground finches (*G. fortis* and *G. magnirostris*), and the cactus and large cactus finches (*G. scandens* and *G. conirostris*) (Fig. 1a; Methods). We first used hierarchical clustering to inspect whether the overall expression profiles clustered according to species (Methods). The resultant tree illustrates that most of the individual

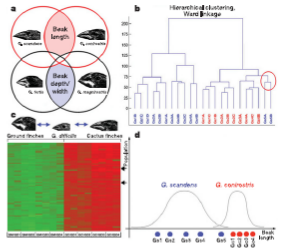


Figure 1 | Microarray analysis in different finch species. a, Clustering strategy to isolate transcripts whose expression correlated with beak morphology. **b**, The Ward linkage tree showed that most of the individual samples clustered by species. Each individual was sampled two to four times. The *y*-axis is euclidian distance between branches. **c**, The final clusters of transcripts, which were upregulated in the comparison between cactus finches and the sharp-beaked finch and were downregulated or remained unchanged in the ground finches compared with the sharp-beaked finch. **d**, Individual expression profiles clustered by species except for the occasional individual profile, probably reflecting a certain overlap in morphology or development between the species. Each spot represents the length of an individual beak.

[1]Department of Genetics, Harvard Medical School, Boston, Massachusetts 02115, USA. [2]Decision Systems Group, Brigham and Women's Hospital, Harvard Medical School, 310 Thorn Building, 75 Francis Street, Boston, Massachusetts 02115, USA. [3]Department of Oral Medicine, Infection and Immunity, Harvard School of Dental Medicine, 188 Longwood Avenue, Boston, Massachusetts 02115, USA. [4]Institute of Molecular Pathology, Dr Bohr-Gasse 7, A-1030, Vienna, Austria. [5]Department of Ecology and Evolutionary Biology, Princeton University, Princeton, New Jersey 08544, USA. †Present address: Department of Developmental Biology, Harvard School of Dental Medicine, Boston, Massachusetts 02115, USA.

2006

nature biotechnology

A sequence-oriented comparison of gene expression measurements across different hybridization-based technologies

Winston Patrick Kuo[1,2,3,18], Fang Liu[4,18], Jeff Trimarchi[2], Claudio Punzo[2], Michael Lombardi[5], Jasjit Sarang[5], Mark E Whipple[6], Malini Maysuria[7], Kyle Serikawa[7], Sun Young Lee[8], Donald McCrann[9], Jason Kang[10], Jeffrey R Shearstone[11], Jocelyn Burke[2,12], Daniel J Park[2,12], Xiaowei Wang[1,12], Trent L Rector[2], Paola Ricciardi-Castagnoli[13], Steven Perrin[11], Sangdun Choi[14], Roger Bumgarner[7], Ju Han Kim[15], Glenn F Short III[2,12], Mason W Freeman[2,12], Brian Seed[2,12], Roderick Jensen[5], George M Church[2], Eivind Hovig[4], Connie L Cepko[2], Peter Park[16], Lucila Ohno-Machado[3] & Tor-Kristian Jenssen[17]

Over the last decade, gene expression microarrays have had a profound impact on biomedical research. The diversity of platforms and analytical methods available to researchers have made the comparison of data from multiple platforms challenging. In this study, we describe a framework for comparisons across platforms and laboratories. We have attempted to include nearly all the available commercial and 'in-house' platforms. Using probe sequences matched at the exon level improved consistency of measurements across the different microarray platforms compared to annotation-based matches. Generally, consistency was good for highly expressed genes, and variable for genes with lower expression values as confirmed by quantitative real-time (QRT)-PCR. Concordance of measurements was higher between laboratories on the same platform than across platforms. We demonstrate that, after stringent preprocessing, commercial arrays were more consistent than in-house arrays, and by most measures, one-dye platforms were more consistent than two-dye platforms.

Gene expression microarray technology has greatly matured over the past decade, and it is expected that the technology will extend its current role as an experimental tool for basic science research and become increasingly applied in clinical practice. Several large efforts to create standardized protocols for microarray experiments (from probe annotation to data analysis) have been initiated: the Minimum Information About a Microarray Experiment (MIAME) standards (http://www.mged.org/Workgroups/MIAME/miame.html), The External RNA Controls Consortium (ERCC) (http://www.cstl.nist.gov/biotech/Cell&TissueMeasurements/GeneExpression/ERCC.htm) and The MicroArray Quality Control (MAQC) project (http://www.fda.gov/nctr/science/centers/toxicoinformatics/maqc/). All these initiatives aim at improving the quality of microarray data through standardization.

Major portals for deposition and retrieval of microarray data, such as the Gene Expression Omnibus (GEO)[1] and ArrayExpress[2], will be truly useful only if experiments are sufficiently reliable and annotated so that meaningful results can be extracted across platforms. The diversity of platforms and microarray data raise the questions of whether and how data from different platforms can be compared and combined. The results from previous cross-platform comparisons have been mixed and continue to be debated[3–10]. Although a body of information continues to develop, at least one of the following factors may have biased the results of previous comparative studies: (i) nonidentical samples on different platforms; (ii) samples not sufficiently distinct; (iii) samples processed using different protocols; (iv) lack of technical replicates; (v) data preprocessing steps not standardized; (vi) only a few types of platforms directly compared; (vii) measurements matched using probe annotations; (viii) 'agreement' not unambiguously quantified or (ix) insufficient biological validation. Although some of the above conditions may be reflective of the actual limitations of these platforms, in practice they complicate assessing the magnitude of disagreement attributable to the platforms.

[1]Department of Developmental Biology, Harvard School of Dental Medicine, 188 Longwood Ave., Boston, Massachusetts 02115, USA. [2]Department of Genetics, Harvard Medical School, Howard Hughes Medical Institute, Boston, Massachusetts, USA. [3]Decision Systems Group, Brigham and Women's Hospital, Boston, Massachusetts, USA. [4]Department of Tumor Biology, Institute for Cancer Research, The Norwegian Radium Hospital, Montebello, Oslo, Norway. [5]Department of Physics, University of Massachusetts Boston, Boston, Massachusetts, USA. [6]Department of Otolaryngology-Head and Neck Surgery, [7]Department of Microbiology, University of Washington, Seattle, Washington, USA. [8]Division of Biology, California Institute of Technology, Pasadena, California, USA. [9]Department of Biochemistry, Boston University School of Medicine, Boston, Massachusetts, USA. [10]Macrogen Inc., Seoul, Korea. [11]Research Molecular Discovery, Biogen Idec, Cambridge, Massachusetts, USA. [12]Department of Molecular Biology, Massachusetts General Hospital, Boston, Massachusetts, USA. [13]Department of Biotechnology and Bioscience, University of Milano-Bicocca, Milano, Italy. [14]Department of Molecular Science and Technology, Ajou University, Suwon, Korea. [15]Seoul National University Biomedical Informatics, Seoul National University College of Medicine, Seoul, Korea. [16]Childrens' Hospital Informatics Program, Harvard Medical School, Boston, Massachusetts, USA. [17]PubGene AS, Vindern, Oslo, Norway. [18]These authors contributed equally to this work. Correspondence should be addressed to W.P.K. (wkuo@genetics.med.harvard.edu).

Received 4 January; accepted 25 April; published online 2 July 2006; doi:10.1038/nbt1217

Sensory Ability in the Narwhal Tooth Organ System

MARTIN T. NWEEIA,[1,2,3]* FREDERICK C. EICHMILLER,[4] PETER V. HAUSCHKA,[5,6] GRETCHEN A. DONAHUE,[7] JACK R. ORR,[8] STEVEN H. FERGUSON,[9] CORTNEY A. WATT,[9] JAMES G. MEAD,[2] CHARLES W. POTTER,[2] RUNE DIETZ,[10] ANTHONY A. GIUSEPPETTI,[11] SANDIE R. BLACK,[12] ALEXANDER J. TRACHTENBERG,[13] AND WINSTON P. KUO[13,14]

[1]Department of Restorative Dentistry and Biomaterial Sciences, Harvard School of Dental Medicine, Boston, Massachusetts
[2]Department of Vertebrate Zoology, Smithsonian Institution, Washington, DC 20560
[3]Harvard Museum of Comparative Zoology, Boston, Massachusetts 02138
[4]Delta Dental of Wisconsin, Stevens Point, Wisconsin 54481
[5]Boston Children's Hospital, Orthopedic Research, Boston, Massachusetts 02115
[6]Harvard Medical School, Orthopaedic Surgery, Boston, Massachusetts 02115
[7]University of Minnesota, Carlson School of Management, Minneapolis, Minnesota 55455
[8]Fisheries and Oceans Canada, Winnipeg, MB, Canada
[9]Freshwater Institute, Fisheries and Oceans Canada, Winnipeg, MB, Canada
[10]Institute of Bioscience, Arctic Research Center, Aarhus University, Frederiksborgvej 399, Roskilde, Denmark
[11]National Institute of Standards and Technology, ADAF Paffenbarger Research Center, Gaithersburg, Maryland
[12]Calgary Zoo, Veterinary Services, Calgary, Alberta, Canada
[13]Harvard School of Dental Medicine, Catalyst Laboratory for Innovative Translational Technologies, Boston, Massachusetts
[14]Department of Developmental Biology, Harvard School of Dental Medicine, Boston, Massachusetts

ABSTRACT

The erupted tusk of the narwhal exhibits sensory ability. The hypothesized sensory pathway begins with ocean water entering through cementum channels to a network of patent dentinal tubules extending from the dentinocementum junction to the inner pulpal wall. Circumpulpal sensory structures then signal pulpal nerves terminating near the base of the tusk. The maxillary division of the fifth cranial nerve then transmits this sensory information to the brain. This sensory pathway was first described in published results of patent dentinal tubules, and evidence from dissection of tusk nerve connection via the maxillary division of the fifth cranial nerve to the brain. New evidence presented here indicates that the patent dentinal tubules communicate with open channels through a porous cementum from the ocean environment. The ability of pulpal tissue to react to external stimuli is supported by immunohistochemical detection of neuronal markers in the pulp and gene expression of pulpal sensory nerve tissue. Final confirmation of sensory ability is demonstrated by significant changes in heart rate when alternating solu-

Abbreviations used: CGRP – calcitonin gene-related peptide; ECG – electrocardiograph; FAME – fatty acid methyl esters; HSD – honest significant difference; HTO – hunters and trappers organization; SEM – scanning electron microscopy; TS – Tremblay Sound.

*Correspondence to: Martin T. Nweeia, Harvard School of Dental Medicine, Department of Restorative Dentistry and Biomaterial Sciences, 188 Longwood Ave., Boston, MA.
E-mail: Martin_nweeia@sdm.harvard.edu

Animal Care Animal Protocol, 04384. Office of Research Subject Protection, Harvard Medical School
Received 8 November 2013; Accepted 15 January 2014.
DOI 10.1002/ar.22886
Published online 00 Month 2014 in Wiley Online Library (wileyonlinelibrary.com).

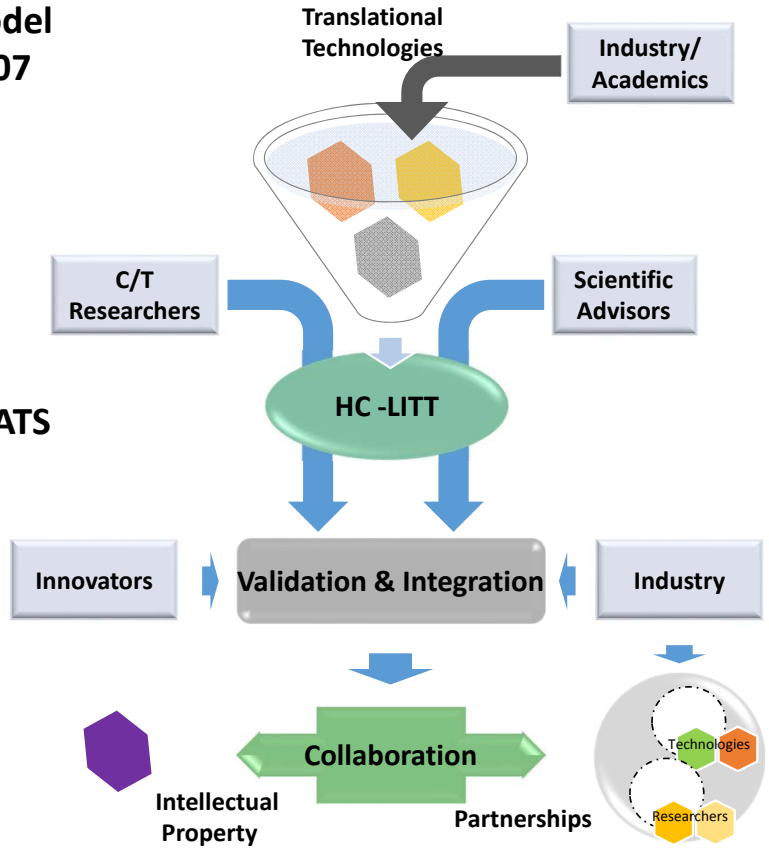
2014

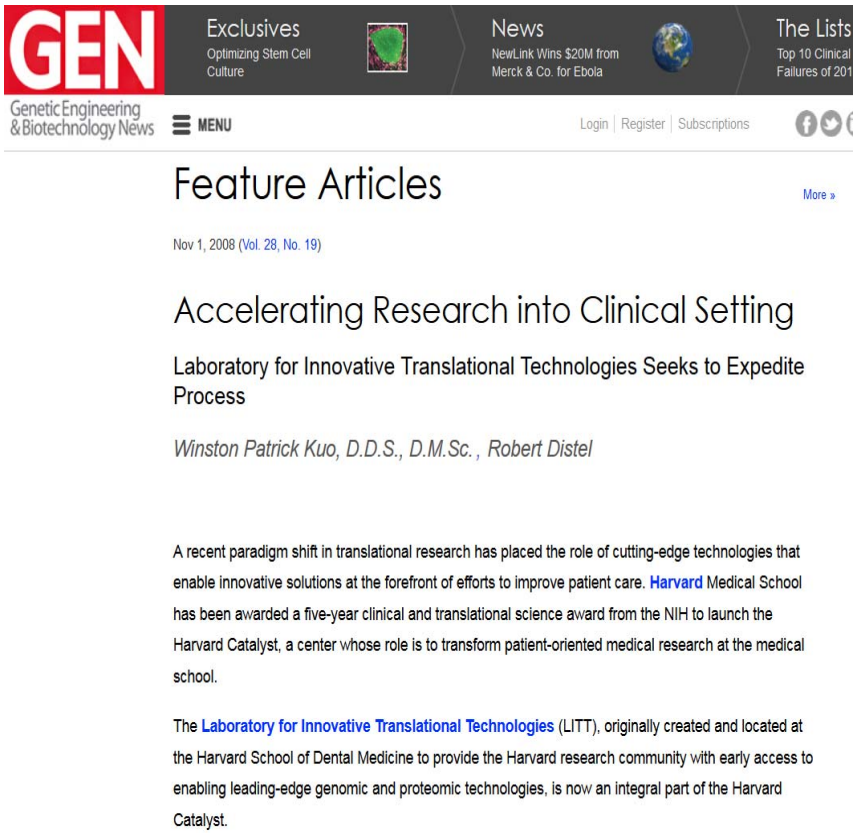
Harvard Medical School

Harvard Catalyst – Laboratory for Innovative Translational Technologies (2008-2013)

Innovative Model founded in 2007

Funded by NCATS





GEN Genetic Engineering & Biotechnology News

Exclusives: Optimizing Stem Cell Culture

News: NewLink Wins $20M from Merck & Co. for Ebola

The Lists: Top 10 Clinical Failures of 201

MENU | Login | Register | Subscriptions

Feature Articles

More »

Nov 1, 2008 (Vol. 28, No. 19)

Accelerating Research into Clinical Setting

Laboratory for Innovative Translational Technologies Seeks to Expedite Process

Winston Patrick Kuo, D.D.S., D.M.Sc. , Robert Distel

A recent paradigm shift in translational research has placed the role of cutting-edge technologies that enable innovative solutions at the forefront of efforts to improve patient care. Harvard Medical School has been awarded a five-year clinical and translational science award from the NIH to launch the Harvard Catalyst, a center whose role is to transform patient-oriented medical research at the medical school.

The Laboratory for Innovative Translational Technologies (LITT), originally created and located at the Harvard School of Dental Medicine to provide the Harvard research community with early access to enabling leading-edge genomic and proteomic technologies, is now an integral part of the Harvard Catalyst.

IES Diagnostics

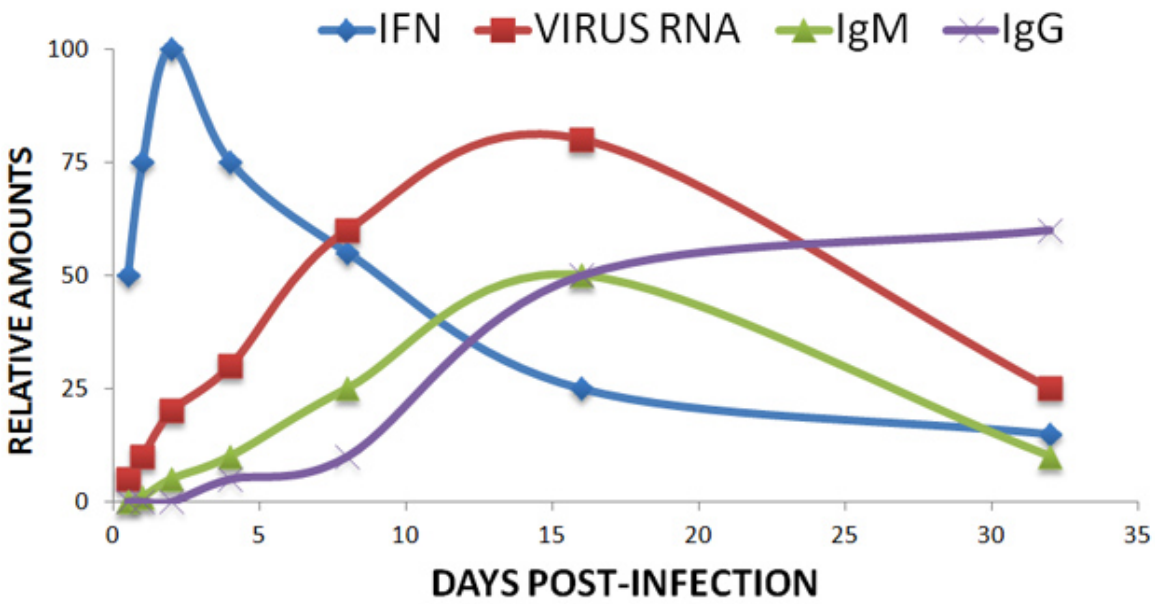
- Molecular diagnostics company with a proprietary, patent protected interferon assay/test that was developed at the U.S. FDA
- Licensed exclusively to IES Diagnostics by the NIH
- REACTIMMUNE an interferon-based assay that is capable of detecting the complete Interferon Expression Signature for a variety of diseases

http://iesdiagnostics.com/

Interferons –why important?

- Interferons, a family of cytokines, constitutes a first line of innate defense against viral infections, more specifically, type I IFNs, including IFNα and IFNβ, activating both toll-like receptors and non-TLR signaling cascades
- Body's immune system produces proteins called interferons to combat illnesses and diseases
- Each disease triggers our immune system to engage a distinctive combination of different types of interferons
- Accurately and reliably determine the IFN Signature for a variety of diseases.
- Shorten the drug discovery process for interferon based therapies,

Interferons and Ebola Virus

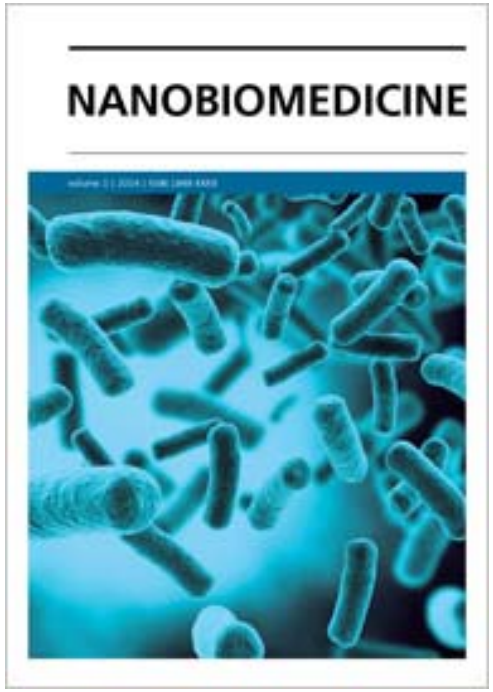


Graphical representation of the relationships between the innate immune response by IFNs and the adaptive immune response by IgM and IgG in response to a virus infection and resulting viral RNA levels.

http://pulse.embs.org/november-2014/path-extinguishing-ebola/

http://www.prweb.com/releases/2014/12/prweb12361334.htm

Building Communities via Journals



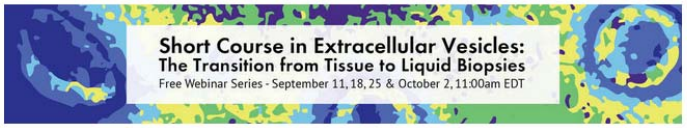
2012 → **2015**

http://www.intechopen.com/journals/

BRC partners with InTech Publishers

BRC

HOME EVENTS PARTNERS NEWS ABOUT BRC CONTACT



Short Course in Extracellular Vesicles:
The Transition from Tissue to Liquid Biopsies

Downloadable Handout

Summary Article Reprinted from The Journal of Circulating Biomarkers 2014

Session 1- September 11, 2014
Overview
Click to View Recording
Click to View Slides

Jan Lötvall
ISEV President
Professor Krefting Research Centre
University of Gothenburg, Sweden

Session 2- September 18, 2014
Applications
Click to View Recording
Click to View Slides

Johan Skog
Chief Scientific Officer
Exosome Diagnostics

Session 3- September 25, 2014
Commercialization
Click to View Recording
Click to View Slides

Sasha Vlassov
Senior Staff Scientist, Group Leader
ThermoFisher Scientific

Session 4- October 2, 2014 Panel on Regulatory and Funding Issues
Click to View Recording

Click to View Slides

Angel Ayuso Sacido, Ph.D.
Director of the Thoracic and Brain
Tumor Laboratory
CIOCC-IMMA
Fundacion Hospital de Madrid, Spain

Click to View Slides

Eva Rohde, MD
Head of the Transfusion Medicine
Department and Director of the
GMP-Laboratory
Paracelsus Medical University
Salzburg, Austria

Hosted By

Winston Kuo
COO
IES Diagnostics

Journal of Circulating Biomarkers

OPEN ACCESS
ARTICLE

Short Course in Extracellular Vesicles – The Transition from Tissue to Liquid Biopsies

Meeting Dispatch

Jan Lötvall[1], Johan Skog[2], Alexander V. Vlassov[3], Angel Ayuso Sacido[4], Eva Rohde[5,6], Joanne Gere[7] and Winston Patrick Kuo[8*]

1 Department of Internal Medicine, Gothenburg University, Gothenburg, Sweden
2 Exosome Diagnostics, Cambridge, MA, USA
3 Thermo Fisher Scientific, Austin, TX, USA
4 Thoracic and Brain Tumour Laboratory, CIOCC-IMMA, Fundacion Hospital de Madrid, Madrid, Spain
5 Spinal Cord Injury and Tissue Regeneration Center, Salzburg, Austria
6 Transfusion Medicine Department, Paracelsus Medical University, Salzburg, Austria
7 BioPharma Research Council, Tinton Falls, NJ, USA
8 IES Diagnostics, Inc., Cambridge, MA, USA
* Corresponding author(s) E-mail: winston@iesdiagnostics.com

DOI: 10.5772/60053

Questions

My contact information:
Email: wkuo@iesdiagnostics.com
Skype: wpkuo1
WeChat: TINNOVATOR
Telephone: 857-222-4363