BIOGRAPHICAL SKETCH /CV

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NAME: Richard M. Levenson, M.D.

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

POSITION TITLE: Professor and Vice Chair of Strategic Technologies, Dept. of Pathology and Lab. Med.

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
Harvard University, Cambridge MA	B.A.	1974	History and Literature
University of Michigan School of Medicine, Ann Arbor	MD	1979	Medicine
Washington University, St. Louis, MO			
Board Certification, Anatomic Pathology)		1979-82 1989	Anatomic Pathology

A. Personal Statement

My background combines medical training and optical-based instrumentation development in the commercial sector. I obtained my MD degree at the University of Michigan, and trained in anatomic pathology at Washington University. A faculty position at Duke was followed by a CMU appointment to develop multispectral imaging approaches. In 2000, I entered the private sector to join CRI (now part of PerkinElmer) where I became VP of Research, and PI on federally funded projects to develop multispectral microscopy systems and software, three-dimensional small-animal imaging, optical dynamic contrast techniques, and birefringence microscopy. From 2009-2012, I worked as a consultant in areas such as quantitative pathology, optical brain thermometry, intraoperative surgical guidance, and pharmaceutical and medical device development, and in 2012 become Professor and Vice Chair for Strategic Technologies in the Dept. of Pathology & Laboratory Medicine, UC Davis Medical Center. Since arriving, I have become involved in advanced technology developments using secondary ion mass spectrometry to perform high-level multiplexing on pathology specimens, in UV-surface excitation microscopy, and polychromatic birefringence imaging. I have also been involved in exploratory work on tumor immunotherapy using glycated chitosan as an adjuvant, and have been working to bring up novel techniques for multiplexed immunofluorescence intended to characterize the tumor microenvironment.

B. Positions and Honors

2012-Present	Professor and Vice Chair for Strategic Technologies, Dept. of Pathology, UC Davis
2009-Present	Brighton Consulting, Boston, MA
1999-2009	Vice President Research, Cambridge Research and Instrumentation (CRI), Inc.
1998-1999	Adjunct Asst. Professor, Dept. of Pathology, Univ. of Pittsburgh
1996-1998	Special Faculty, Center for Light Microscope Imaging and Biotechnology, Carnegie Mellon University; Adjunct Asst. Professor, Department of Pathology, Univ. of Pittsburgh and Duke University; Consultant in imaging technologies.
1989-1996	Asst. Professor, Pathology Dept. and Adjunct Asst. Professor, Computer Science Dept., Duke University, Durham, NC, and Staff Physician and Investigator in the VA Geriatric Research, Education and Clinical Center, VA Medical Center, Durham, NC.
1987-1996	Assistant Professor, Departments of Pathology and Medicine, and Senior Associate, Howard Hughes Medical Institute, Duke University, Durham, NC.
1986-1987	Instructor, Departments of Medicine and Biochemistry, University of Rochester

1982-1986 Wilmot Cancer Research Fellow, Department of Medicine, Endocrinology Unit, University of Rochester.

1979-1982 Resident in Pathology, Assistant in Pathology, Trainee (NIEHS) in Pathology, Fellow in Medicine (Immunology) Barnes Hospital, Washington University Medical School, St. Louis, Missouri.

C. Contribution to Science

1. Multispectral imaging: I spent many years at the technology interface between pathology and advanced imaging methods, first at Carnegie Mellon University, where I began work on the Applied Spectral Imaging Sagnac interferometer-based spectral imaging module for microscopy, and followed that by moving to Cambridge Research and Instrumentation, Inc. (CRI, Woburn, MA) with the goal of developing the methods, reagents, instruments and software for commercial wide-field microscopy instrumentation. I became VP for Research, and served as PI for a number of large NIH (mostly SBIR) research awards, with collaborators at universities and medical schools across the country. Topics, in addition to multispectral imaging per se included novel total internal reflection microscopy optics, multimodal small-animal imaging using reflectance, fluorescence, structured illumination and fluorescence multiplexing, birefringence imaging for the detection of spindle formation in oocytes, and fluorescence dynamic contrast imaging in small animals. I organized a number of conferences at optics meetings, as well as serving on numerous imaging-centric NIH, NCI and NSF grant review panels. The methods that I helped develop have been successfully commercialized, and now form the basis of the PerkinElmer Nuance and Vectra product offerings. I hold a number of patents in this area.

Levenson, R.M., A. Fornari and M. Loda (2008), "Multispectral imaging and pathology: seeing and doing more." **Expert Opinion in Medical Diagnostics** 2: 1067-1081

Levenson, R.M., D.T. Lynch, H. Kobayashi, J.M. Backer and M.V. Backer (2008), "Multiplexing with multispectral Imaging: From mice to microscopy." **ILAR J** 49: 78-88.

Taylor, C.R. and **R.M. Levenson** (2006), "Quantification of immunohistochemistry--issues concerning methods, utility and semiquantitative assessment II." **Histopathology** 49(4): 411-24.

Mansfield, J.R., K.W. Gossage, C.C. Hoyt and R.M. **Levenson** (2005), "Autofluorescence removal, multiplexing, and automated analysis methods for in-vivo fluorescence imaging." **J Biomed Opt** 10(4): 41207.

Gao, X., Y. Cui, **R.M. Levenson**, L.W. Chung and S. Nie (2004), "In vivo cancer targeting and imaging with semiconductor quantum dots." **Nat Biotechnol** 22(8): 969-76.

2. Image analysis: Imaging needs to be complemented by robust, reliable, and easy-to-use image analysis techniques that can provide quantitative data that can complement routine morphology assessment. While at CRI I helped develop machine-learning based tools that combined train-by-example neural-net segmentation with subcellular region detection and quantitation. The methods were implemented into CRI and PerkinElmer software, and I am an inventor on US patents 8,639,043, 8,379,962, and 7,555,155. While these techniques are now quite widely available in commercial and open-source software packages, for many years the CRI software tools were clear technology leaders in terms of performance, speed and simplicity.

Mansfield, J.R., K.W. Gossage, C.C. Hoyt and R.M. **Levenson** (2005), "Autofluorescence removal, multiplexing, and automated analysis methods for in-vivo fluorescence imaging." **J Biomed Opt** 10(4): 41207.

3. Highly multiplexed IHC via ion-beam imaging (MIBI). One of the primary challenges in pathology is to provide multiple simultaneous measurements of molecular expression while preserving tissue morphology. Stanford Professor Garry Nolan's work on mass-tag-enabled highly multiplexed flow cytometry appeared to be a promising approach. Dr. Nolan's group had figured out how to perform tissue imaging but lacked familiarity with relevant anatomic pathology. I brought that dimension to the project and the collaboration has so far yielded a paper recently published in Nature Medicine describing the route to 100-plex immunohistochemistry at better than light-microscope resolution. A companion opinion piece in Nature Methods hailed this and a related technique as "Next- Gen Pathology," and a review has been published in Laboratory Investigation. Further collaborative work is now funded by three grants, one from the U.S. Department of Defense and two from the NCI. Our goal for this technique is to enable major research discoveries in tissue-based studies, and as

equipment cost and performance metrics benefit from a redesign (now underway), it may ultimately become a standard diagnostic procedure.

Levenson, R., Borowsky, A, Angelo, M. (2015), Immunohistochemistry and mass spectrometry for highly multiplexed cellular molecular imaging . **Lab Invest**, **95,** 397–405. doi:10.1038/labinvest.2015.2

Angelo, M., Bendall, S.C., Finck, R., Hale, M.B., Hitzman, C., Borowsky, A.D., **Levenson, R.M**., Lowe, J.B., Liu, S.D., Zhao., S. Natkunam, Y., Nolan, G.P. (2014), Multiplexed ion beam imaging (MIBI) of human breast tumors, **Nature Med**, 20: 436-42. doi:10.1038/nm.3488

4. Advances in slide-free microscopy (MUSE). Most recently, another major research area has been the development of a new kind of microscope that could replace conventional frozen-section analysis and potentially accelerate histological and molecular analyses. About 10 years ago, Stavros Demos from Lawrence Livermore, in collaboration with UC Davis pathologists, described a novel approach to *in-vivo* microscopy. Now, working with Dr. Stavros and my postdoctoral fellow, Dr. Farzad Fereidouni, we have extended this technique to the imaging of *ex-vivo* tissues. Microscopy with UV Surface Excitation **(MUSE)** rapidly generates striking diagnostic-quality. Advantages of the approach include:

a) fresh tissue can be stained and imaged within about 3 minutes—faster than frozen sections;
b) instrumentation costs can be low—possibly a few thousand dollars; and
c) the method can be adapted to work on cell-phone-like platforms, for potential global health applications.

MUSE may make histology available where there are no histology laboratories, and could provide diagnoses (via telepathology) even in remote areas. An introductory description was published as part of an optics conference proceedings, and a major manuscript is currently being prepared for submission to a significant peer-reviewed journal.

Fereidouni, F., Datta Mitra, A. Demos, S., **Levenson, R**.(2015) Microscopy with UV surface excitation (MUSE) for slide-free histology and pathology imaging. **Proc. SPIE** 9318, Optical Biopsy XIII: Toward Real-Time Spectroscopic Imaging and Diagnosis, 93180F, doi: 10.1117/12.2080408

5. Vision and medical perception research. Most recently, a paper on pigeons as potential surrogate medical image observers was published in PLoS ONE, and was widely covered in the popular and scientific press.

Levenson RM, Krupinski EA, Navarro VM, Wasserman EA (2015) Pigeons (Columba livia) as Trainable Observers of Pathology and Radiology Breast Cancer Images. PLoS ONE 10(11): e0141357. doi:10.1371/journal.pone.0141357

Bibliography: http://1.usa.gov/1O2wy3G

D. Ongoing and recent research support

Cancer histology and QC via MUSE: Sample-sparing UV surface-excitation microscopy 2017-2020
1 R33 CA202881-01 (**Levenson, PI**)
Validate the utility of MUSE technically as a precursor step before downstream molecular tests and develop improved sample handling methodology

Highly multiplexed ion-beam tissue RNA in situ imaging with sub-micron resolution
1 R21 CA183660-01 (**Levenson, PI)** 2014-2016
Develop reagents, methodology and software for RNA-in-situ using imaging mass spectrometry and lanthanide-based labeling (no-cost ext)

Next-generation molecular histology using highly multiplexed ion beam imaging (MIBI) of breast cancer tissue specimens for enhanced clinical guidance
BC132309 –DoD BCRP (Borowsky, PI; Levenson**, co-Investigator** 2014-2017

Develop and validate breast-cancer-informed marker panels of protein and nucleic-acid based panels for lanthanide-based multiplexed imaging

Highly multiplexed ion-beam tissue molecular imaging with sub-micron resolution

1 R33 CA183654-01 (Nolan, PI; **Levenson, Subcontractor PI**) 2014-2017

Develop reagents, methodology and software for antibody-based immuno-histochemistry using lanthanide labeling

Microscopy with ultraviolet sectioning excitation for realtime pathology

UC Davis Science Translation and Innovation Research (STAIR) grant, **Levenson, PI** 2015-2016

Develop and evaluate commercial prototypes of the MUSE microscope system for pathology diagnostics.

Phasor-based real-time spectral imaging software and hardware

UC Davis Science Translation and Innovation Research (STAIR) grant, **Levenson, PI** 2016-2017

Develop and test novel instrumentation to perform computationally efficient spectral imaging using novel hardware and phasor-based software analysis