Innovation, Discoveries, and Entrepreneurship – *Ulysses J. Balis*

Overview

As background, I have been a contributing faculty member at the University of Michigan, as both a division director and as a computational scientist for over 8 years. During this time, I have continued a strong program of entrepreneurial and commercialization development activities, with the most recent effort, Verinata Health (originally Living Microsystems, where I served as one of its three founding scientists and bench level investigator) resulting in its acquisition by Illumina in 2012 for over $350M. Prior successful entrepreneurial activities resulting in financially successful commercial entities or acquisitions include: Idaho Technology (purchased by bioMerieux, 2013), Aperio Technologies (acquired by Leica, Inc., 2012) to name a few. Through the course of these activities, I have been an inventor of 19 patents or pending patent applications. At present, I serve as one of the University of Michigan Medical School Fast Forward Medical Innovation (FFMI) program's faculty champions, with my emphasis being imaging and health information technology. I have active research programs in both image-based and clinical lab results-based analytics and am the PI or co-PI of several commercialization/validation grants seeking to make multi-analyte assays with analytics (MAAAs) a clinically available technology, following vigorous prospective validation trials. I have served on numerous NIH peer review study sections, including my being a standing member and stand-in chair on the NIAID MID-B study section for the last 6 years. I have received multiple international awards for my work in computational pathology (including the CAP Lansky Award, in 2000 and appointment to the Dirac Foundation as its only physician member in 2009).

Sub-Millimeter Oxygen Tension measurement of Vmax and Km in Oxygen Consumption measurements of in vitro hepatocyte co-culture using Ruthenium sol-gel technology 450 nm light interrogation technology

During my first postdoctoral fellowship in tissue engineering (my second postdoc was in bioinformatics), my primary project was characterization of porcine hepatocytes in co-culture. Oxygen tension measurement technology at that time (ca. 1996) was dependent upon the use of the Clark Polarographic Electrode, which was highly prone to signal noise and baseline drift, making the accurate measurement of very low oxygen tensions (< 5 mmHg) very challenging. By incorporating a relatively new oxygen probe technology into a standard P60 measurement cell, it became possible to measure both V_{max} and K_m parameters with very high precision and accuracy. The accuracy attained in my tissue-engineering paper was the highest-ever reported at the date of publication, and represented a new paradigm in accurate in vitro oxygen tension measurement. Additionally, the technology was useful in confirming that porcine hepatocytes exhibited highest metabolic activity at 39.4 C, thus explaining why most culture experiments at 37 would either fail or lead to low metabolic activity. My resulting pilot data allowed Organogenesis Corporation to further develop their extracorporeal liver support program and additionally resulted in several patents for bioreactor design with me as a names co-inventor.

Quantitative Real-Time PCR (Qt-PCR):

Working with Carl Witter at the University of Utah, I was a core member of the team that developed and then initially reported the attainment of quantitative real-time PCR, using fluorescence resonance energy transfer as the underlying interrogation technique. This approach was complemented by the use of robotics technology and tailored embedded systems design software, to realize a true turnkey solution that could be readily deployed in either an investigational or clinical lab. The technology was licensed to Roche Medical Systems and since that time, Roche has placed over 10,000 systems worldwide. My participation with this team allowed me to share my robotics design and embedded systems design experience to the controller system, realizing true walk-away operation. I am one of the senior authors of the publication introducing this new technology in *Biotechniques*.

Creation of the first International Standard for Digital Image Exchange of Pathology image subject matter, using the DICOM 3.0 platform as the underlying exchange framework

Serving as Informatics Committee Chair of the College of American Pathologists, I commissioned a subcommittee (which I also chaired) to work on the emerging problem of image interoperability. After five years of effort, working with Lloyd Hildebrand and Louis Korman, and the ACR/NEMA/DICOM Working Group 5 we were successful in standing up in 1999 an extension to DICOM specifically designed for endoscopy, ophthalmology and pathology, known as the Visible Light (or VL) Image Object Definition (IOD). The VL standard later served as the foundational basis for the more contemporary Supplement 145, which is intended to support storage and exchange of whole-slide imaging. The College of American Pathologists recognized me in 2000 for this effort by their bestowing upon me the Lansky Award, one of their most prestigious awards. To my knowledge, I remain the youngest-ever recipient of the Lansky Award.

Founder, Living Microsystems (LMS) and CellPoint Diagnostics, 2002

In 2002, I and four Harvard/MIT scientists founded Living Microsystems and CellPoint Diagnostics. The mission of these companies was to use microfluidic/microfabricated constructs to extract fetal cells from maternal blood, thus removing the need for either amniocentesis or chorionic villous sampling, and to detect rare circulating tumor cells (CTCs) in the peripheral circulation, respectively. Ten years later, the LMS (under a new branding of Verinata, Inc.) was acquired by Illumina for $350 million. My image analysis technology was fundamental to both the IP blocking strategy of the company as well as its ability to reliably detect rare events. Similarly, the image analysis technology that I developed for CellPoint became part of the $80 million package that was licenses to Johnson & Johnson in 2010. Additionally, I am a co-author on the first paper (in Nature) describing the use of microfluidics to reliably detect CTCs. Overall, these efforts have led to over 15 patents and patents pending.

Laboratory Information Digital Data Exchange (LIDDEX) Project

From 2008-2010, in my capacity as co-organizer of the Lab Infotech National Meeting, I organized a series of public demonstrations to showcase the feasibility of true cross-vendor lab results interoperability across actual vendor platforms on the meeting's exhibit area floor. My team reprised this demonstration, by invitation, at the 2010 caBIG National Meeting, for which it was the recipient of the 2010 caBIG Innovation award. The core technology of this federated architecture became the technical basis by which the current MTRAC-funded THIOMON effort is now supported.

THIOMON

Our group at the University of Michigan, a collaboration myself as a pathology informaticist with expertise in interoperability and inter-institutional electronic interface design, a gastroenterologist (Peter Higgins) with IBD and machine learning expertise and a statistician (Ji Zhu) with expertise in clinical assay validation, decided to explore the utility of extracting encoded data from routine laboratory results (e.g. a higher dimensional form of pattern recognition) and convert such data into medically actionable information, in the form of a formal automated clinical decision support system. Specifically, we used a large patient dataset and tested whether random forest statistical methods could identify a predictive pattern in the combined primary data set represented by complete blood counts (CBCs) and comprehensive serum chemistries (COMPs), to predict clinical response to thiopurine therapy. We found that this algorithm was 86% accurate, while in these same patients the conventional reference lab-based metabolite assay (priced at $200) was only 59% accurate. This set of algorithms, along with its clinical performance characteristics has been peer-reviewed and published, and additionally, the overall portfolio of algorithmic intellectual property enjoys strong domestic patent protection (patent held by the University of Michigan).

We have implemented these algorithms in support of direct clinical care, over the past 3 years at UMHS. These algorithms can and are being used to make clinical decisions for patients with inflammatory bowel disease. Unambiguously this test is more accurate than the existing metabolite test, costs less than the existing test, and returns results faster (24 hours vs. 2 weeks). Additionally, technology transfer is ongoing, via the carrying out of a split study, as enabled by MTRAC funding (see active Grants, below)

Technology Transfer Activities

AutoLeuk flow cytometry decision support tool for automated generation of leukemia flow cytometry reports: Transferred to ARUP Laboratories as a proprietary unpublished software application / trade secret, May 19, 1994.

LightCycler Robotics and microcontroller design. Transferred as non-published proprietary source code and engineering designs to Idaho Technology, Inc., 1996. Royalty terms: confidential one-time payment.

Vector Quantization image compression software. Transferred as non-published code to Aperio Technology, Inc., 2000. Royalty terms: (confidential; fully vested in 2007, option conversion to cash in 2012, upon purchase of Aperio by Leica Scientific).

Automated Barcode tracking system for Anatomic Pathology Workflow. Exclusively licensed to Impac Medical Systems by MGH Corporate Sponsored Licensing and Research, 2005. Royalty terms: $250,000.

Numerous image analysis detection technologies / patents for rare circulating cells transferred to Living Microsystems, Inc. (now Verinata Health, Inc.) for substantial equity ownership (terms confidential; fully vested 2005, stock conversion to cash as a result of Verinata's acquisition by Illumina in 2013).

Contribution to numerous microfluidic methods, as trade secrets, transferred to Living Microsystems, Inc. (now Verinata Health, Inc.) for substantial equity ownership (terms confidential; fully vested 2005, stock conversion to cash as a result of Verinata's acquisition by Illumina in 2013).

Spatially Invariant Vector Quantization (SIVQ). Disclosed to U-M Technology Transfer, 2010. Shared with at least seven collaborating academic groups, free of licensing terms. Licensing to multiple parties under investigation, with completion of non-royalty use to the National Cancer Institute for a new clinical trials Laser Capture Microdisection core lab.

Awarded Patents and Pending Patent Applications

WO 2000/078932 Cell culture systems and methods for organ assist devices. Cosman Maury D, Dimilla Paul A, Toner Mehmet, Yarmush Martin L, Balis Ulysses J, Tilles Arno W: The General Hospital December 2000.

CA 2375505 Cell culture systems and methods for organ assist devices. / Systemes de culture cellulaire et procedes pour dispositifs d'assistance aux organes. Cosman Maury D, Dimilla Paul A, Toner Mehmet, Yarmush Martin L, Balis Ulysses J, Tilles Arno W: The General Hospital December 2000.

WO 2000/078920 Methods and devices for cell culturing and organ assist systems. Toner Mehmet, Yarmush Martin L, Balis Ulysses J, Tilles Arno W: The General Hospital December 2000.

EP1203075 Cell culture systems and methods for organ assist devices. Cosman Maury D, Dimilla Paul A, Toner Mehmet, Yarmush Martin L, Balis Ulysses J, Tilles Arno W: Gen Hospital May 2002.

US 6465252 Cell culture systems and methods for organ assist devices. Mehmet Toner, Arno W Tilles, Ulysses J Balis, Martin L Yarmush, Maury D Cosman, Paul A Dimilla: The General Hospital October 2002.

US 20030017142 Cell culture systems and methods for organ assist devices. Mehmet Toner, Arno W Tilles, Ulysses J Balis, Martin L Yarmush, Maury D Cosman, Paul A Dimilla: The General Hospital a Massachusetts January 2003:

US 6562616 Methods and devices for cell culturing and organ assist systems. Mehmet Toner, Martin L Yarmush, Ulysses J Balis, Arno W Tilles: The General Hospital May 2003.

US 6759245 Cell culture systems and methods for organ assist devices. Mehmet Toner, Arno W Tilles, Ulysses J Balis, Martin L Yarmush, Maury D Cosman, Paul A Dimilla: The General Hospital July 2004.

WO 2005/084380 System for delivering a diluted solution. Cosman Maury D, Kapur Ravi, Carvalho Bruce L, Barber Tom, Balis Ulysses J, Toner Mehmet, Huang Lotien Richard, Gray Darren S: The General Hospital September 2005.

WO 2005/084374 Magnetic device for isolation of cells and biomolecules in a microfluidic environment. Cosman Maury D, Kapur Ravi, Carvalho Bruce L, Barber Tom, Balis Ulysses J, Toner Mehmet, Huang Lotien Richard: The General Hospital September 2005.

US 20050282293 System for delivering a diluted solution. Maury D Cosman, Ravi Kapur, Bruce L Carvalho, Tom Barber, Ulysses J Balis, Mehmet Toner, Lotien R Huang, Darren S Gray: December 2005.

HK 1102296 傳送稀釋液體的系統. / System for delivering a diluted solution. Cosman Maury D, Kapur Ravi, Carvalho Bruce L, Barber Tom, Balis Ulysses J, Toner Mehmet, Huang Lotien Richard, Gray Darren S: The General Hospital November 2007.

EP1765503A2 System for delivering a diluted solution. Cosman Maury D, Kapur Ravi, Carvalho Bruce L, Barber Tom, Balis Ulysses J, Toner Mehmet, Huang Lotien Richard, Gray Darren S: Gen Hospital. March 28, 2007.

EP1776449 Magnetic device for isolation of cells and biomolecules in a microfluidic environment. Cosman Maury D, Kapur Ravi, Carvalho Bruce L, Barber Tom, Balis Ulysses J, Toner Mehmet, Huang Lotien Richard: Gen Hospital, April 25, 2007.

CN 200580006643 Magnetic device for isolation of cells and biomolecules in a microfluidic environment. Cosman Maury D, Kapur Ravi, Carvalho Bruce L, Barber Tom, Balis Ulysses J, Toner Mehmet, Huang Lotien Richard: Gen Hospital March 2008.

EP1931800 Systems and methods for enrichment of analytes. Kapur Ravi, Toner Mehmet, Gray Darren, Schmidt Martin, Walsh John, Huang Lotien Richard, Barber Tom, Carvalho Bruce, Balis Ulysses, Grisham Michael: Gen Hospital June 2008.

CN101310025 Systems and methods for enrichment of analytes. Ravi Kapur [US]; Mehmet Toner [US]; Richard Huang Lotien [US]; Tom Barber [US]; Bruce Carvalho [US]; Darren Gray [US]; Ulysses Balis [US]; John Walsh [Us]; Michael Grisham [US]; Ron Tompkins [US]; Martin Schmidt [US]. November 2008.

HK 1116516 用於微流體環境中的細胞和生物分子分離的磁力裝置. / Magnetic device for isolation of cells and biomolecules in a microfluidic environment.

Cosman Maury D, Kapur Ravi, Carvalho Bruce L, Barber Tom, Balis Ulysses J, Toner Mehmet, Huang Lotien Richard: The General Hospital December 2008.

US 20100273675 Methods for detecting fetal abnormality. Ulysses J Balis, Mehmet Toner, Ravi Kapur, John Walsh: October 2010.