Jack Layton Annual Lecture

The Surgical Pathology Lab of the Future

Thomas M. Grogan, M.D.
Founder, Ventana Medical Systems, Inc.
Professor Emeritus of Pathology, University of Arizona

Dr. Grogan has disclosed that he is a founder and Chief Scientific Advisor of Ventana Medical Systems, a company that develops, manufactures, and markets immunohistochemical systems that demonstrate tissue and cellular biomarkers of disease. He is also a member of the FDA Planning Committee, which determined that the presentation gave a well-balanced, evidence-based, and unbiased approach to diagnostic and therapeutic options related to quality patient care.

Conflict of Interest

- Ventana Medical Systems, a Roche company
- Founder & Scientific Advisor

Objectives

- Tribute to Jack Layton
- Describe the technical developments defining the "Lab of the Future"

The Ventana Story (thanks to Jack Layton)

Past

Founded in 1986 as a spin-off from the Department of Pathology, University of Arizona

Today

A 1,500 employee company in Tucson, Arizona, focused on new tools to advance the practice of pathology

Ventana spinoff from the University of Arizona

Key formative factors

- Medical practice-informed
- Departmental support: Jack
- "Science 1" university
- Community support
- Financial support
- Legal assistance

The early challenges: creative or criminal? (Jack saves the day)
Financial support: a quest for capital

- Equity, not debt
- Raised capital in 1989 after a year of rejection (39 rejections)
- Winning over skeptical investors

Venture capital:
Crabtree Ventures, LLC
- Long term: 5-10 years
- Willing to invest $10M

1990 - First Instrument - 320

Milestones & major accomplishments
1985 - 2003

Milestones & major accomplishments
2004 - present

Roche acquires Ventana in 2008

- Roche makes bold move amidst global economic turmoil

Where we are going ...

We are leaving the world of commoditized diagnostic (what is it) and going to higher value tests linked to therapy (what to do).
Leading the Way in Companion Diagnostics
189 collaborations projects with 40+ partners

What the Future Looks Like:
- New tools to aid therapy
- Next generation rabbit monoclonal directed at targets of therapy:
  - ALK1, BRAF V600E
- Next generation detection:
  - Multi-chromope
  - Hyper-sensitive
  - Multiplexed
- New cytology applications:
  - Cervical: CINtec PLUS
  - CTCs

New Rabbit Monoclonals
Rabbit monoclonal to mutated EGFR

Progesterone receptor is a significant factor associated with clinical outcomes and effect of adjuvant tamoxifen therapy in breast cancer patients.
- 4,046 invasive early stage breast carcinoma patients evaluated for PR status by 1E2 rabbit monoclonal antibody by IHC.
- 1E2 found 8% more sensitive than predicate
- PR positive tumors had a 34% higher survival including ER+ cases treated with tamoxifen.

PR Related Survival

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**p16 A Driver Event in Cervical Disease**

*HCp16 IHC on cervical biopsy, p16/4047 Dual stain on cervicitis cytology*

**Cervical Cancer Portfolio**

*Screening and Diagnosis*

- cobas® HPV Test
  - High sensitivity
  - High NPV - Rule out
- CINtec PLUS
  - High specificity, without losing sensitivity
  - High PPV - Rule in
- CINtec Histology
  - Colposcopy & Biopsy sampling
  - Accurate tissue diagnosis

**Diagnosis of an EML4-ALK-Positive**

*Non-Small-Cell Lung Cancer in a Single Representative Patient*

**Next Generation IHC Detection (Remote Sensing)**

**Next Generation of IHC Staining for ALK-1 in Lung Cancer**

**BRAF**

- Protein kinase involved in MAPK signaling pathway that regulates proliferation, differentiation and apoptosis
- 40-60% of melanomas and 10-15% of CRC possess somatic BRAF mutations.
- V600E represents 80-94% and 99.8% of mutation in melanomas and CRC, respectively.
- V600E activity is ~500 fold > than WT.
- BRAF and V-600E mutations are mutually exclusive.
**BRAF V600E Colorectal (3+ intensity)**

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**Hapten Library Enables High Level Multiplexing**

**New Chromogens Span the Spectrum**

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**Novel Brightfield Multiplexed IHC Tests**
- Deposition of novel chromogenic dyes has been enabled in FFPE tissue

**3-Color Immune Panel**

- CD3 (Positive T-cells)
- CD8 (Negative T-cells)
- Ki67 (Proliferation)

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**4-Color Chromogenic Multiplexing in DLBCL**

- CD3: Membranous; Brown
- CD4: Membranous/Dysplastic; Red
- CD20: Membranous; Blue
- Factor VIII: Nuclear; Black
Neutralizing Tumor-Promoting Chronic Inflammation: A Magic Bullet?


What the Future Looks Like:
- Next generation in-situ hybridization (ISH):
  - Gene copy number
  - Translocations
  -スーパー敏感なRT-PCR
  - Gene plus protein
- Next generation platforms:
  - FISH, IHC/ISH
  - Pre-Analytics
  - Integrated Pathology Work Station
  - Medical Cockpit

Enabling Single Gene Assays p53 Deletion in CLL

Enabling Sensitive mRNA Expression Assays
- The sensitivity of these chromogens provide anatomic pathologists with assays that currently require flow cytometry or RT-PCR

Bringing DNA Rearrangements to “Light”
- The spectral properties of these new chromogens enable two colors to combine to create a unique, third color

Turquoise + Magenta = Dark Blue
Yellow + Blue = Green
Yellow + Purple = Red

KAPPA mRNA + LAMBDA mRNA in Tonsil
Dual Color Kappa/Lambda mRNA Assay in Lymphoma

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Patient Safety: The Blueprint for Product Innovation
- Individual slide staining for H&E
- Automated, individualized IHC
- Barcode-driven workflow management
- Precise assay scoring with digital pathology
- Sensitive & specific optimized assays

Individualized Staining

Contamination in the H&E Process
Study shows every dip-&-dunk stainer is contaminated
- 73 labs analyzed — 100% showed reagent bath contamination
- Up to 36.4% of blank decracks slides contaminated with foreign tissue
- Up to 3.91% tissue fragments found in representative samples of reagent bath fluids
- Reagent turnover (flushing/changing) does not seem to mitigate rate of contamination
- For a lab that processes 250,000 slides/year, 99% quality means:
  - 279 errors/year, 23 errors/month, 6 errors/week, 1 patient at risk every day for misdiagnosis

Pre-analytic platform

Automated tissue preservation

Sources: Coif, A./Pensar, L./Innovation, 392, 2013. 139-139
Manduca rustica on Tecoma stans

Identical sequence...
Different functional morphology

Next Generation Cell Signaling Assays

Colon cancer

Secondary Adaptive Epigenetic Events

Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR

Colon cancer: Preservation of activation status of cell signaling molecules

Horizontal lines represent the median values of each biomarker

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  - Integrated Pathology Work Station
  - Medical Cocker
New Machine Vision

Automated HER2 D-ISH

Medical Cockpit

Integrated Pathologist Workstation
Revolutionary Workstation for Pathologists

The Medical Cockpit

- Data collection
- Data analysis
- Report generation

The “Lab of the Future”

Ideal Future

- Multi-parameter, multiplex results with morphology, phenotype and genotype with full definition of all therapeutic targets, communicated in a same-day patient report integrating all findings from pathology, radiology, surgery, and oncology
- Results communicated by a physician pathologist who serves as a diagnostician, lab director, information integrator, and communicator
- By these means, pathologists will deliver the highest level of personalized healthcare
Doing now what patients need next