University of Iowa Health Care

PathBeat

The Department of Pathology Alumni Newsletter

No.10/Summer 2009

VISION STATEMENT

To be an international leader in academic pathology and laboratory medicine

MISSION STATEMENT

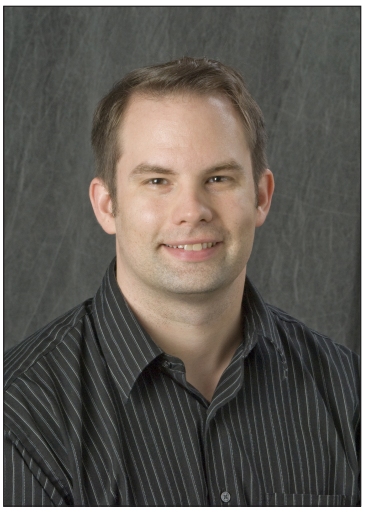
The Department of Pathology is committed to serving:

- Patients, by providing innovative care, excellent service, and exceptional outcomes, with pathology and laboratory medicine of the highest quality
- Current and future generations of health care providers and biomedical scientists, by providing opportunities to learn using innovative educational methods in a supportive environment
- Society, by using scientific discovery to develop a better understanding of human disease
- Our employees, by providing an environment and culture that supports continuous professional growth, respect for diversity, and acknowledges that their contributions are the foundation for our success

UI Department of Pathology Announces New Faculty:

Ryan Askeland, MD, Assistant Clinical Professor

Diagnostic Surgical and Cytopathology with focus in Breast Pathology



"I decided that pathology was an excellent career choice after my post-sophomore fellowship in pathology during my second year of medical school. The clinical and basic science knowledge base that pathologists must have to understand a wide variety of disease processes was very interesting to me."

We are proud to announce Ryan Askeland, M.D., will be joining the University of Iowa Pathology Department as Clinical Assistant Professor as of July 1, 2009. After completing his residency in Anatomic and Clinical Pathology, Dr. Askeland was a Surgical Pathology Fellow and has most recently completed his Fellowship in Cytopathology (2009) following his Surgical Pathology Fellowship at the University of Iowa Department of Pathology. He is a graduate of University of Iowa Carver College of Medicine.

Dr. Askeland's professional interests are diagnostic surgical and cytopathology with a special interest in breast pathology. He also enjoys teaching and working with medical students and resident physicians.

Dr. Askeland was raised in his hometown of Fort Dodge, Iowa. He initially became interested in science and medicine during his undergraduate years at the University of Northern Iowa (UNI). While attending classes at UNI, Dr. Askeland had classes in physiology and biochemistry which led him to consider a career in medicine.

When asked why he chose the University of Iowa, Dr. Askeland responded,

"The pathologists in the department are not only excellent laboratorians, diagnosticians, teachers and researchers, but also skillful communicators. It is great to be part of such a great tradition here at the University of Iowa."

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Dr. Askeland believes the benefits of working in an academic medical center are the variety and challenge of difficult cases, the ability to consult colleagues with extensive experience, the abundant interdisciplinary conferences, and the ease of collaboration with other departments. Dr. Askeland's career has been shaped by all of the Anatomic and Clinical pathology faculty at the University of Iowa at various points during his residency and fellowship training.

As a UI pathologist, he will work at the forefront of adopting and communicating new discoveries within basic science and translate them into information that is valuable towards patient care.

When Dr. Askeland is outside of work, his interests are in fishing, golfing, and Hawkeye sports. Dr. Askeland can be reached at his office by calling (319) 353-8986 or by email at ryan-askeland@uiowa.edu.

Honors and Awards

AOA Member
ASCP Award for Academic Excellence and Achievement, 2002

Previous Research Experience

Summer Research Fellowship Program, 2000

Publications, Posters, and Presentations

Askeland RW, Bromley C, Vasef MA. Detection of HER-2/neu Gene Amplification Using Chromogenic In Situ Hybridization and Tissue Microarray: Correlation with HER-2/neu Protein Expression Using Immunohistochemistry. J Histotechnol, 28(1); 11-14, March 2005.

Askeland RW, McGrane S, Levitt JS, Dane SK, Greene DL, Vandeberg JA, Walker K, Porcella A, Herwaldt LA, Carmen LT, Kemp JD. Improving Transfusion Safety: Implementation of a Comprehensive Computerized Barcode-Based Tracking System for Detecting and Preventing Errors. Transfusion, 48 (7); 1308-1317, July 2008.

Askeland RW, Bromley C, Vasef MA. Epidermal Growth Factor Receptor (EGFR) Protein, p53, and Cyclin D1 Expression in Colon Carcinoma: Correlation with EGFR Gene Amplification Using a Chromogenic In Situ Hybridization (CISH) Assay (Abstract 438). United States and Canadian Academy of Pathology Annual Meeting, San Antonio, TX, Poster Presentation, March 2005.

Askeland RW, DeYoung BR. Urothelial Carcinoma in Patients < 30 Years of Age: A Clinicopathologic Analysis of 8 Cases (Abstract 81). United States and Canadian Academy of Pathology Annual Meeting, Atlanta, GA, Poster Presentation, February 2006.

Askeland RW, McGrane S, Levitt JS, Dane SK, Greene DL, Vandeberg JA, Walker K, Porcella A, Herwaldt LA, Carmen LT, Kemp JD. Improving Transfusion Safety at an Academic Medical Center: Implementation of a Comprehensive Computerized Barcode-Based Tracking System. Pathology Research Day, Iowa City, IA, October 10, 2006.

Askeland RW, Clamon G, Weydert J. ERCC1 Protein Expression in Small Cell Carcinoma: An Immunohistochemical Study of 41 Primary and Metastatic Neoplasms. Pathology Research Day, Iowa City, IA, October 9, 2007.

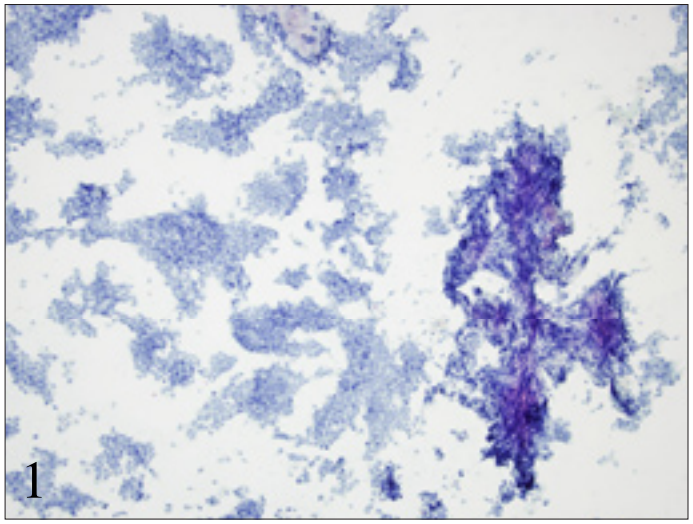
What is Your Diagnosis?

Ryan Askeland, MD, Assistant Clinical Professor of Pathology

Cytopathology Fellow 2008-2009
Pathology AP/CP Resident (Iowa), 2004-2008
MD, University of Iowa Carver College of Medicine 2000-2004

Patient Case

A 73 year old Caucasian male was seen in general surgery clinic with a palpable right subareolar breast mass. The patient did not report any nipple discharge, pain, or skin changes associated with the mass. Mammography demonstrated an ovoid 3 cm subareolar mass with slightly irregular contours and calcifications. Fine needle aspiration was requested and two aspirates yielded 1.5 ml of serosanguinous fluid. A pap stained aspirate smear is presented in Figure 1. Subsequently, the patient underwent modified radical mastectomy. Sentinel lymph node examination revealed no neoplasm. Gross examination demonstrated a 3 cm ovoid, encapsulated, tan-red and friable subareolar mass. Low and high power photomicrographs of the neoplasm are presented in Figures 2 and 3. **Diagnosis found on page 7.**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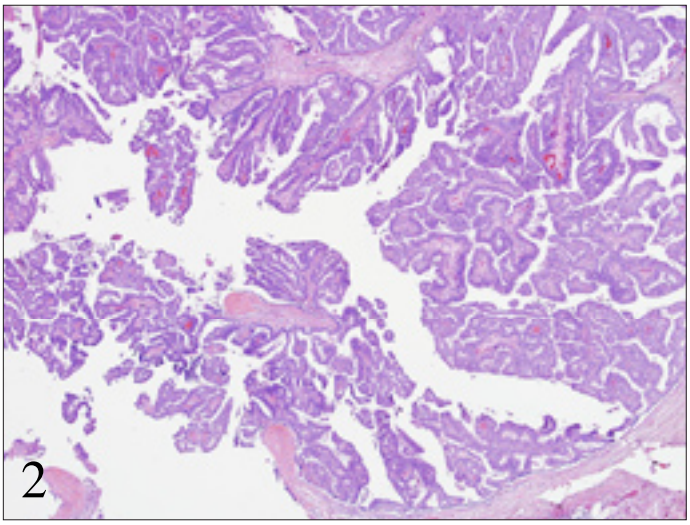
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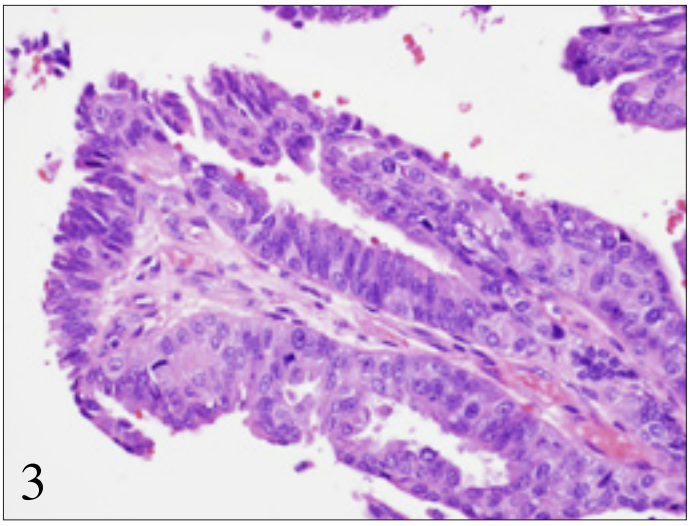
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Do you have the answer? The diagnosis can be found on page 7 ➔

UIDL Corner

Visit the new UI Diagnostic Laboratories website: www.healthcare.uiowa.edu/uidl

Recent Events

Nov 6-8, 2008

American Society of Nephrology (ASN) Renal Week 2008
Same-day Renal Biopsy Consultation Exhibit Booth #517
Pennsylvania Convention Center, Philadelphia, PA

April 27, 2009

Cancer CME Conference
Presented by: Nancy Rosenthal, MD, Professor (Clinical) of Pathology, Section Director, Hematopathology, Vice Chair for Educational Affairs
Title: "What's New in the WHO: Classification of Acute Leukemia"
Trinity, Moline, IL

May 2-5, 2009

2009 Pediatric Annual Meeting (PAS)
Same-day Renal Biopsy Consultation Exhibit Booth #414
Baltimore Convention Center, Baltimore, MD

May 7-9, 2009

3rd Annual Anatomic Pathology/Cytology Combined Course
Speakers included: Bruce Wenig, MD (Head and Neck Pathology), Zsolt Argenyi, MD (Dermatopathology), and Kim Geisinger, MD (Cytopathology)
Hotel Vetro and Conference Center, Iowa City, IA

May 27, 2009

Neurology CME Conference
Presented by: Steven A Moore, MD, PhD, Professor, Neuropathology
Topic: Muscular Dystrophy
Genesis, Davenport, IA

August 17, 2009

Cancer CME Conference
Presenter: Frank Mitros, MD, Professor, Department of Pathology
Topic: Gastrointestinal Pathology
Trinity, Moline, IL

For further information to schedule a speaker, send specimens, order tests, or consult with a pathologist, please contact:

Lisa Rathjen
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New HPV DNA Testing

Aaron Bossler, MD, PhD
Assistant Professor and Director of the Molecular Pathology Laboratory and Molecular Infectious Disease Section

Cervical cancer is an important cause of preventable cancer-related death among women. It is the second most commoncancer among women worldwide and primarily affects women between 30 and 45 years of age. High risk human papillomavirus (HPV) infection has been associated with more than 99% of cases of cervical cancer. HPV type 16 is detected in 60-70% of all cervical cancer specimens, with HPV 18 at 15-20%, and HPV 31, 33, and 45 rounding out the five most common types. Other high risk types include HPV 35, 39, 51, 52, 56, 58, 59, 66, 68, 72, and 83.

The American Society of Colposcopy and Cervical Pathology (ASCCP) released consensus guidelines in 2006 for the use of HPV testing in the evaluation of women for cervical cancer and precursor lesions from cytologic specimens. (2006 Consensus Conference Guidelines et al. Am. J. Ob & Gyn, Oct. 2007). They recommend:

- Reflex HPV testing with atypical squamous cells of undetermined significance (ASC-US) result except for women less than 20 years of age
- All women 30 or more years old as screening
- All women with atypical glandular cells of undetermined significance
- Post colposcopy follow-up and post treatment follow-up if CIN2 or greater.

In March, 2009, the ASCCP released recommendations for the use of HPV 16 and 18 genotyping for those women 30 years and older who had negative cytology and a positive high-risk HPV DNA test. They recommended molecular genotyping for HPV 16 and 18 would be clinically useful for determining who should be referred for immediate colposcopy if 16 or 18 are positive, and who could be followed-up with repeat cytology and high-risk HPV testing in 12 months.

The Molecular Pathology Laboratory in the Department of Pathology at the University of Iowa Hospitals and Clinics (UIHC) provides HPV detection of high risk types using a signal amplification method, the Invader® HPV test from Hologic, Inc. The assay tests for the qualitative detection of HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 which are associated with cervical cancer and its precursor lesions. This is the same assay as the Cervista™ HPV assay from Hologic that was recently FDA approved. However, the submission only included the analysis of ThinPrep PreservCyt® liquid-based cytology specimens and thus required our laboratory to independently validate the use of SurePath liquid-based cytology specimens. The assay has also been validated by our lab for testing of formalin-fixed paraffin-embedded cancer tissue biopsy specimens.

Cells from specimens collected using the SurePath liquid-based Pap test are concentrated by centrifugation, lysed, digested, and then extracted from lysate using the BioRobot EZ1. The purified DNA is then used in the Hologic™ Invader® DNA Assay. UIHC only uses SurePath LBC at this time which is the explanation for the choice of specimen to validate initially.

Unlike many other molecular based assays, this one does not use polymerase chain reaction or PCR. The Hologic™ Invader® DNA Assay utilizes Cleavase® enzymes to recognize and cleave specific structures that are formed by the hybridization of a primary probe, and an Invader® oligonucleotide to a nucleic acid target. Two oligonucleotides hybridize in tandem to the target DNA to form an overlapping structure. The 5'-end of the primary probe includes a 5'-flap that does not hybridize to the target DNA. The 3'-end of the bound Invader® oligo overlaps the primary probe, but does not need to hybridize to the target DNA. The Cleavase® enzyme recognizes this overlapping structure and cleaves off the unpaired 5'-flap of the primary probe, releasing it as a target-specific product. The primary probe cycles on the target DNA isothermally, this allows for multiple rounds of primary probe cleavage for each target DNA.

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In the secondary reaction, each released 5'-flap can serve as an Invader® oligo on a fluorescence resonance energy transfer (FRET™) cassette to create another overlapping structure that is recognized and cleaved by the Cleavase® enzyme. When the FRET™ cassette is cleaved, the fluorophore and the quencher are separated generating a detectable fluorescence signal. Fluorescence is then detected by the TECAN GENios™ plate reader. The analysis program calculates the signal difference from the NDTS and internal control to determine the status of each patient reaction and the HPV result is reported on the summary page.

This assay is an analyte specific reagent, developed by Third Wave (now owned by Hologic). The probes are designed to detect a portion of the L1 gene in family specific combinations. The three families of HPV detected are the A9 (HPV-16, -31, -33, -35, -52, and -58), A7 (HPV-18, -39, -45, -68, and -59) and A5/A6 (HPV -51, -66, and -56) families. Each reaction also includes primers and probe for detecting human histone gene (H2BE) as a control for adequate DNA and specimen cellularity. Appropriate HPV family positive control DNA for each family is included in the assay. The assay also includes No DNA Template Solution (NDTS) which is used to determine the baseline level of fluorescent signal, and a positive and negative control cell specimen for extraction and signal amplification quality control.

The assay has been validated by the Molecular Pathology Laboratory for detection of HPV in cervical cytology specimens with an analytic sensitivity of ~2500 copies/reaction and on formalin-fixed paraffin-embedded specimens.

Questions may be directed to Aaron Bossler, M.D., Ph.D. Director of the Molecular Pathology Laboratory, 391-384-9566, or e-mail: aaron-bossler@uiowa.edu.

Rosenthal Named Vice-Chair for Education

Congratulations to Nancy Rosenthal, MD, Director Hematopathology, Director of Hematopathology Fellowship Program, and Director of the Hematology portion of resident education, who has been recently appointed as Vice Chair for Educational Affairs.

M2 Teacher of the Year

Congratulations to Ramesh Nair, MD, Director of Renal Pathology, who is this year's M2 Teacher of the Year! The other two nominees were Jo Benda MD and Hans House MD (Director of FCP III, ER physician).

2008 Guide to America's Top Pathologists

Please help us congratulate Jo Benda MD who was included in the 2008 Edition of the "Guide to America's Top Pathologists" as she was inadvertently omitted from our last issue in which her colleagues Michael Cohen, MD, Barry DeYoung, MD, and Frank Mitros, MD were mentioned.

Clinical Achievement Award

This award recognizes a clinical and an anatomic pathology faculty member for significant achievement in the creation and delivery of clinical services. The 2008 winners are: Annette Schlueter, MD, PhD (Clinical Pathology) and Marcus Nashelsky, MD (Anatomic Pathology).

L-R: John Kemp, MD, Annette Schlueter, MD, PhD, Marcus Nashelsky, MD, Michael Cohen, MD

Diagnosis: Encapsulated (Intracystic) Papillary Carcinoma

(continued from page 3, "What is Your Diagnosis?")

- Encapsulated (intracystic) papillary carcinoma (EPC) is an uncommon breast malignancy (<2% of breast carcinomas) that typically occurs in women in their mid 60's. A slightly higher percentage of male breast carcinomas are papillary.
- EPC is often subareolar and may present as a palpable mass with or without nipple discharge.
- Breast imaging typically demonstrates a round, circumscribed, solitary mass with or without calcifications.
- Fine needle aspiration often yields a cellular aspirate containing papillary or cribriform clusters within a cystic hemorrhagic background. Naked nuclei and single columnar epithelial cells are also present in the background. Myoepithelial cells are not observed in the aspirate. Differentiation from other papillary neoplasms of the breast is extremely difficult on an aspirate.
- Histologically, EPC may exhibit a variety of patterns. At low power, a circumscribed papillary neoplasm within a cystically dilated duct surrounded by a rim of fibrous tissue may be observed. At high power, the papillae are covered by hyperchromatic, stratified monomorphic columnar cells with variable mitotic activity.
- Myoepithelial cells are not present within the papillae. Recent studies have demonstrated no myoepithelial cells at the periphery of EPC. Smooth muscle myosin heavy chain immunohistochemistry performed in this case revealed no myoepithelial cells within and surrounding the neoplasm.
- EPC has historically been viewed as a variant of ductal carcinoma in situ (DCIS) but the absence of myoepithelial cells at the periphery of the neoplasm suggests that it may be a low grade invasive carcinoma with expansile growth.
- Clinically, EPC is managed as DCIS and is associated with an excellent prognosis with local therapy alone.
- Breast tissue adjacent to EPC demonstrates DCIS in 50% of cases and is associated with increased risk of local recurrence. Invasive carcinoma (usually invasive ductal carcinoma, NOS) is identified in 33% of cases and should be clearly present beyond the fibrous rim of EPC. Only the clearly invasive foci should be measured for staging purposes to avoid overtreatment.

2008-2009 Resident Program Awards

Resident Teaching Award

Congratulations to Jamie Weydert, MD, Assistant Professor, Surgical Pathology. This award is given in appreciation by the Pathology Residents to a faculty member who has put forth exceptional effort toward the teaching and education of students, residents and fellows.

George D. Penick Award

Congratulations to Elizabeth Manion, MD and, Nathan Lueck, MD (Co-Chief Residents). This award is given to residents who display the highest level of achievement in educating medical students, clinical colleagues, paramedical personnel and others.

Best Wishes to Our 2009 Graduates!

Graduate	New Position and Location
Cory Bernadt, MD, Resident	Surgical Pathology Fellowship, University of Iowa
Nathan Lueck, MD, Resident	Surgical Pathology Fellowship, University of Minnesota
Elizabeth Manion, MD, Resident	Breast Pathology Fellowship, Brigham & Women's Hospital, Boston
Matthew Zieske, MD, Resident	Cytopathology Fellowship, University of Iowa
Ryan Askeland, MD, Cytopathology Fellow	Assistant Professor, University of Iowa
Adam Bell, MD, Surgical Pathology Fellow	Hematopathology Fellowship, University of Iowa
Michelle Bleile, MD, Hematopathology Fellow	Surgical Pathology Fellowship, University of Iowa
Alan Junkins, PhD, Medical Microbiology Fellow	Chief of Microbiology Norton Healthcare, Louisville, KY
Elizabeth Moyle, MD, Surgical Pathology Fellow	Cytopathology Fellowship, University of Iowa
Michel Nasr, MD, Molecular Genetics Fellow	Assistant Professor, Hematopathology Health Sciences Ctr, University of Manitoba
Dean-Yar Tigrani, MD, Cytopathology Fellow	Private Practice, Great Lakes Pathologists, West Allis, WI

A Warm Welcome to Our Incoming 1st Year Residents!

Eric T. Hanson, M.D., Medical College of Wisconsin, 2009
James A. Kuzman, M.D., Ph.D., University of South Dakota, Sanford School of Medicine, 2009
Emilian ("Emil") V. Racila, M.D., Universitatea de Medicina Si Farmacie Carol Davila, 1988
Lori L. Sinclair, M.D., University of Iowa Roy J. and Lucille A. Carver College of Medicine, 2009
Thomas C. Wilson, M.D., University of Illinois College of Medicine, 2009

A Warm Welcome to Our Incoming Transfusion Medicine Fellow!

Daniel R. Walker, M.D., F. Hebert School of Medicine-Uniformed Services University, 1999

2009-2010 Pathology Residents

Shannon Gabriel-Griggs, MD Co-Chief Resident	R4
Leana Guerin, MD Acting Fellow in Surgical Pathology	R4
Sara (“Beth”) Kilborn, MD	R4
Benjamin Koch, MD	R4
Megan Samuelson, MD Co-Chief Resident	R4
Melissa Meier, MD	R3
Joseph Mitros, MD	R3
Martin Potash, MD	R3
Rebecca Wilcoxon, MD	R3
John Blau, MD	R2
Michael Gailey, DO	R2
Brian Linert, MD	R2
Joel Miron, MD	R2
Eyglo Thordardottir, M.D.	R2
Johnathon Yost, M.D.	R2
Eric Hanson, M.D.	R1
James Kuzman, M.D.	R1
Emilian (“Emil”) Racila, M.D.	R1
Lori Sinclair, M.D.	R1
Thomas Wilson, M.D.	R1

2009-2010 Pathology Externs

Paul Abrams	M3
Talitha Brown	M2
Phillip Chen	M3
Suzanne Crumley	M3
Stephanie Fischer	M3
Bryan Steussy	M4

2009-2010 Co-Chief Residents

Shannon Gabriel-Griggs, MD

Megan Samuelson, MD

Thank you to Liz Manion, MD and Nate Lueck, MD for serving as this past year’s co-chiefs.

2009-2010 Pathology Fellows

Elizabeth Moyle, M.D.
Cytopathology Fellow
Matthew Zieske, M.D.
Cytopathology Fellow
Adam Bell, M.D.
Hematopathology Fellow
Sophie Arbefeville, M.D.
Microbiology Fellow
Benjamin Darbro, M.D. PhD
Molecular Genetics Pathology Fellow
Cory Bernadt, M.D.
Surgical Pathology Fellow
Michelle Bleile, M.D.
Surgical Pathology Fellow
William (“Nick”) Rose, M.D.
Transfusion Medicine Fellow
Daniel Walker, M.D.
Transfusion Medicine Fellow

Residency Program Director

Leslie Bruch, MD

Associate Professor
Neuropathology Director
5232A RCP
(319) 384-8871
leslie-bruch@uiowa.edu

Recent Publications

Mechanisms of prostate cancer cell survival after inhibition of AR expression.
Cohen MB, Rokhlin OW.
Department of Pathology, The University of Iowa, Iowa City, Iowa 52242, USA.
Recent reports have shown that the AR is the key determinant of the molecular changes required for driving prostate cancer cells from an androgen-dependent to an androgen-independent or androgen depletion-independent (ADI) state. Several recent publications suggest that down-regulation of AR expression should therefore be considered the principal strategy for the treatment of ADI prostate cancer. However, no valid data is available about how androgen-dependent prostate cancer cells respond to apoptosis-inducing drugs after knocking down AR expression and whether prostate cancer cells escape apoptosis after inhibition of AR expression. This review will focus on mechanisms of prostate cancer cell survival after inhibition of AR activity mediated either by androgen depletion or by targeting the expression of AR by siRNA. We have shown that knocking down AR expression by siRNA induced PI3K-independent activation of Akt, which was mediated by calcium/calmodulin-dependent kinase II (CaMKII). We also showed that the expression of CaMKII genes is under AR control: active AR in the presence of androgens inhibits CaMKII gene expression whereas inhibition of AR activity results in an elevated level of kinase activity and in enhanced expression of CaMKII genes. This in turn activates the anti-apoptotic PI3K/Akt pathways. CaMKII also express anti-apoptotic activity that is independent from the Akt pathway. This may therefore be an important mechanism by which prostate cancer cells escape apoptosis after androgen depletion or knocking down AR expression. In addition, we have found that there is another way to escape cell death after AR inhibition: DNA damaging agents cannot fully activate p53 in the absence of AR and as a result p53 down stream targets, for example, microRNA-34, cannot be activated and induce apoptosis. This implies that there may be a need for re-evaluation of the therapeutic approaches to human prostate cancer.

Mandatory second opinion in cytopathology.
Cancer Cytopathol. 2009 Apr 25;117(2):82-91
Lueck N, Jensen C, Cohen MB, Weydert JA.
Department of Pathology, University of Iowa Carver College of Medicine, Iowa City, IA 52242, USA.
BACKGROUND: Mandatory review of outside pathologic material is intended to detect interpretive errors that may have a clinically significant impact on patient care. Prior to definitive treatment of referred patients, the University of Iowa Carver College of Medicine requires a review of pertinent pathologic material previously obtained at outside institutions. The aims of this study were to determine if this local standard of practice has a measurable impact on patient care. METHODS: The pathologic diagnoses of 499 second opinion cytology cases seen at the University of Iowa Carver College of Medicine were studied. Each second opinion was classified as “no diagnostic disagreement”, “minor disagreement”, or “major disagreement” with respect to the originating institution’s interpretation. The clinical impact of major disagreement cases was determined by pathologic and clinical follow-up via chart review. RESULTS: Second opinion cytology resulted in 37 cases (7.4% of total cases) with major diagnostic disagreements. Clinical and pathologic follow-up was available in 30 of the major disagreement cases; second opinion diagnosis was better supported in 22 of these cases compared to the outside diagnosis. The second opinion in 6 major disagreement cases prompted changes in clinical management. CONCLUSIONS: Major disagreements in second opinion cytology are common, likely reflective of the challenges inherent in the interpretation of cytologic specimens. Although mandatory second opinion of outside cytologic material prompted changes in clinical management in only a small fraction of cases (1.2%), this rate was similar to those previously published for surgical pathology second opinion. These findings support the notion that mandatory second opinion policy as an important part of patient care. (c) 2009 American Cancer Society.

Recommendations for the reporting of surgically resected thymic epithelial tumors.
Weydert JA, De Young BR, Leslie KO; Association of Directors of Anatomic and Surgical Pathology.
Department of Pathology, The University of Iowa Carver College of Medicine, Iowa City, IA 52242, USA. jamie-weydert@uiowa.edu
Thymic epithelial tumors include thymoma and thymic carcinoma. Histologic findings and extent of disease are key determinants of prognosis and help guide postoperative management in patients with thymic epithelial tumors. Given the relative rarity of these tumors, the use of tumor guidelines and checklists can facilitate accurate and comprehensive pathologic reporting in this setting. Diagnostic nomenclature (World Health Organization, Suster-Moran classifications) and staging criteria (modified Masaoka system) are emphasized.

Fetal exposure to ethanol has long-term effects on the severity of influenza virus infections.

McGill J, Meyerholz DK, Edsen-Moore M, Young B, Coleman RA, Schlueter AJ, Waldschmidt TJ, Cook RT, Legge KL.
Department of Pathology, University of Iowa, Iowa City, IA 52242, USA.

Alcohol use by pregnant women is a significant public health issue despite well-described risks to the fetus including physical and intellectual growth retardation and malformations. Although clinical studies are limited, they suggest that in utero alcohol exposure also results in significant immune deficiencies in naive neonates. However, little is known about fetal alcohol exposure (FAE) effects on adult infections. Therefore, to determine the long-term effects of FAE on disease susceptibility and the adult immune system, we infected FAE adult mice with influenza virus. In this study, we demonstrate that mice exposed to ethanol during gestation and nursing exhibit enhanced disease severity as well as increased and sustained pulmonary viral titers following influenza virus infection. Secondary exposure to alcohol as an adult further exacerbates these effects. Moreover, we demonstrate that FAE mice have impaired adaptive immune responses, including decreased numbers of virus-specific pulmonary CD8 T cells, a decreased size and frequency of pulmonary B cell foci, and reduced production of influenza-specific Ab following influenza infection. Together, our results suggest that FAE induces significant and long-term defects in immunity and susceptibility to influenza virus infection and that FAE individuals could be at increased risk for severe and fatal respiratory infections.

Extracellular Matrix 1 (ECM1) Expression Is a Novel Prognostic Marker for Poor Long-Term Survival in Breast Cancer: A Hospital-Based Cohort Study in Iowa.

Lal G, Hashimi S, Smith BJ, Lynch CF, Zhang L, Robinson RA, Weigel RJ.
Department of Surgery, University of Iowa, Iowa City, IA, USA, geeta-lal@uiowa.edu.

INTRODUCTION: Previous work in a small, unselected series showed that up to 83% of breast carcinomas overexpress ECM1 by immunohistochemistry (IHC) and that tumors with lymph node metastases are more likely to be ECM1-positive. We sought to further evaluate ECM1 expression and its effect on prognosis in an unselected cohort of patients with breast cancer. METHODS: ECM1 expression was examined by IHC in 134 women diagnosed with invasive breast cancer between 1986 and 1989 and correlated with clinical parameters and outcomes, including disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS) using Cox proportional hazards regression. RESULTS: During follow-up, 83 of 134 (66%) patients died. The median follow-up was 211 (range, 183-245) months for surviving patients. Based on a previously described cutoff of 10% staining, 47% of breast cancers were ECM1-positive. ECM1-positive tumors were associated with increasing patient age ($P = 0.01$). In multivariate analyses, while controlling for age, ER status, tumor grade, stage, and treatment, ECM1 expression emerged as a significant predictor of DSS (hazard ratios, 4.16 ($P = 0.009$) and 11.6 ($P = 0.01$) at 10 and 15 years, respectively) and DFS (hazard ratio, 3.08 ($P = 0.03$) at 15 years) with ECM1 overexpression predicting poorer survival. CONCLUSIONS: ECM1 was overexpressed in approximately half of invasive breast carcinomas and is an important prognostic marker, particularly for predicting poorer DSS, with its predictive value increasing with time from diagnosis. Further work is needed to confirm these findings and determine whether ECM1 expression is predictive of response to specific therapy.

Unrecognized Acute Phosphate Nephropathy in a Kidney Donor with Consequent Poor Allograft Outcome.

Agrawal N, Nair R, McChesney LP, Tuteja S, Suneja M, Thomas CP.
Department of Internal Medicine, Carver College of Medicine, University of Iowa, Iowa City, IA.

Acute phosphate nephropathy following a large phosphate load is a potentially irreversible cause of kidney failure. Here, we report on the unfavorable graft outcome in two recipients of deceased donor kidneys from a donor who had evolving acute phosphate nephropathy at the time of organ procurement. The donor, a 30-year-old with cerebral infarction, developed hypophosphatemia associated with diabetic ketoacidosis and was treated with intravenous phosphate resulting in a rise in serum phosphorus from 0.9 to 6.1 mg/dL. Renal biopsies performed on both recipients for suboptimal kidney function revealed acute tubular injury and diffuse calcium phosphate microcrystal deposits in the tubules, which were persistent in subsequent biopsies. A retrospective review of preimplantation biopsies performed on both kidneys revealed similar findings. Even though initial renal histology in both recipients was negative for BK virus, they eventually developed BK viremia with nephropathy but both had a substantive virologic response with therapy. The first patient returned to dialysis at 6 months, while the other has an estimated glomerular filtration rate of 12 mL/min, 17 months following his transplant. We conclude that unrecognized acute phosphate nephropathy in a deceased donor contributed substantially to poor graft outcome in the two recipients.

DNA-like class R inhibitory oligonucleotides (INH-ODNs) preferentially block autoantigen-induced B-cell and dendritic cell activation in vitro and autoantibody production in lupus-prone MRL-Faslpr/lpr mice in vivo.

Lenert P, Yasuda K, Busconi L, Nelson P, Fleenor C, Ratnabalasuriar RS, Nagy PL, Ashman RF, Rifkin IR, Marshak-Rothstein A.
Departments of Internal Medicine and Pathology, Carver College of Medicine, The University of Iowa, Iowa City, C312GH, 200 Hawkins Drive, IA 52242, USA. petar-lenert@uiowa.edu.

ABSTRACT: INTRODUCTION: B cells have many different roles in systemic lupus erythematosus (SLE), ranging from autoantigen recognition and processing to effector functions (for example, autoantibody and cytokine secretion). Recent studies have shown that intracellular nucleic acid-sensing receptors, Toll-like receptor (TLR) 7 and TLR9, play an important role in the pathogenesis of SLE. Dual engagement of rheumatoid factor-specific AM14 B cells through the B-cell receptor (BCR) and TLR7/9 results in marked proliferation of autoimmune B cells. Thus, strategies to preferentially block innate activation through TLRs in autoimmune B cells may be preferred over non-selective B-cell depletion. METHODS: We have developed a new generation of DNA-like compounds named class R inhibitory oligonucleotides (INH-ODNs). We tested their effectiveness in autoimmune B cells and interferon-alpha-producing dendritic cells in vitro and in lupus-prone MRL-Faslpr/lpr mice in vivo. RESULTS: Class R INH-ODNs have 10- to 30-fold higher inhibitory potency when autoreactive B cells are synergistically activated through the BCR and associated TLR7 or 9 than when stimulation occurs via non-BCR-engaged TLR7/9. Inhibition of TLR9 requires the presence of both CCT and GGG triplets in an INH-ODN, whereas the inhibition of the TLR7 pathway appears to be sequence-independent but dependent on the phosphorothioate backbone. This difference was also observed in the MRL-Faslpr/lpr mice in vivo, where the prototypic class R INH-ODN was more effective in curtailing abnormal autoantibody secretion and prolonging survival. CONCLUSIONS: The increased potency of class R INH-ODNs for autoreactive B cells and dendritic cells may be beneficial for lupus patients by providing pathway-specific inhibition yet allowing them to generate protective immune response when needed.

2008 Emily Cooley Memorial Lecture: lessons learned from pediatric transfusion medicine clinical trials . . . a little child shall lead them.

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BACKGROUND: Many clinical practices in transfusion medicine are controversial and/or lack definitive guidelines established by sound clinical trials. Although recommendations based on results of clinical trials performed using infants and children may not always be applied directly to adults-and vice versa-lessons learned from pediatric trials can be useful when critically assessing the design/results/conclusions of adult trials. STUDY DESIGN AND METHODS: Four randomized clinical trials (RCTs) studying pediatric patients were critically reviewed. They addressed two red blood cell (RBC) transfusion issues: 1) transfusion guidelines by which RBC transfusions are “triggered” by liberal (LIB; high pretransfusion patient hematocrit [Hct] levels) versus being “triggered” by restricted (RES; low pretransfusion Hct levels) and 2) transfusion of fresh RBCs (</=7 days’ storage) versus RBCs (up to 42 days’ storage). RESULTS: Findings established by primary outcomes generally were firm (e.g., fewer RBC transfusions were given to infants/children managed by RES guidelines; transfusing small volumes of RBCs stored up to 42 days to preterm infants diminished allogeneic donor exposures and were equally efficacious and safe as fresh RBCs stored </=7 days). Findings based on secondary outcomes, subset, and post hoc analyses were inconsistent (e.g., clinical outcomes were equivalent after LIB or RES transfusions in only two of three RCTs; in the third, more neurologic problems were found in neonates given RES transfusions). CONCLUSIONS: Clinical practices should be based on data pertaining to the primary outcomes of RCTs, because trials are designed and statistically powered to address these issues. Clinical practices suggested by analysis of secondary outcomes, subsets of patients, and post hoc analyses should be applied cautiously until studied further-ideally, as primary outcomes in subsequent RCTs.

Upcoming Presentations

Robert A. Robinson, Edward B. Stelow, Diagnosing Salivary Gland Neoplasia, College of American Pathologists (CAP) ’09 Meeting, Washington DC, October 11-14, 2009.

Robert A. Robinson, Steven D. Vincent, Oral and Maxillofacial Pathology for the Practicing Pathologist, USCAP short course, Washington DC, March 20-26, 2010.

Laila Dahmoush, Robert A. Robinson, Common Diagnostic Problems in Head and Neck Tumors: A Combined Cytologic and Surgical Pathology Approach, USCAP short course, Washington DC, March 20-26, 2010.

Diekema, DJ; Pfaller, MA, 49th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 12-15, 2009. Posters:

1. Geographic Variation in the Frequency of Isolation and Fluconazole (FLU) and Voriconazole (VOR) Susceptibilities of Candida glabrata: an Assessment from the ARTEMIS DISK Global Antifungal Surveillance Program

2. Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2007: a 10.5-Year Analysis of Susceptibility of Candida Species to Fluconazole (FLU) and Voriconazole (VOR),

3. Comparison of Results of Fluconazole (FLU) and Voriconazole (VOR) Disk Diffusion Testing for Candida with Results from a Central Reference Laboratory in the ARTEMIS DISK Global Antifungal Surveillance Program

4. Wild Type Minimum Inhibitory Concentration (MIC) Distribution and Epidemiological Cutoff Values (ECVs) for Aspergillus fumigatus and Triazoles using Clinical and Laboratory Standards Institute (CLSI) method

5. In Vitro Susceptibility of Clinical Isolates of Aspergillus spp. to Anidulafungin, Caspofungin, and Micafungin: a Head-to-Head Comparison Using CLSI Broth Microdilution

6. Variation in Fluconazole-Susceptibility of Candida glabrata Bloodstream Isolates in the United States, 2001-2007

7. Wild-type Minimum Effective Concentration (MEC) Distributions and Epidemiological Cutoff Values (ECVs) for Caspofungin and Aspergillus Species

Links of Interest

Resident & Fellows Pictures: http://www.healthcare.uiowa.edu/pathology/site/residents/index.html

Pathology Department: http://www.healthcare.uiowa.edu/pathology/index.html

Laboratory Services Handbook for PDA or PocketPC: http://www.healthcare.uiowa.edu/path_handbook/pda/index.html

UIDL: http://www.healthcare.uiowa.edu/uidl/index.html

Research Awards and Information

Dr. Aaron Bossler along with Dr. Aloysius Klingelhutz in Microbiology have received a new collaborating research contract with Dr. John Lee from Sanford Research/USD. The title of this project is Mechanisms of Invasion for an HIV Related Head and Neck Cancer. This collaboration through June 30, 2012 will bring an estimated support in the amount of $194,992 for this collaborative effort.

Dr. Michael Cohen has received a continuation of a collaborating research contract with Dr. Pradip Roy-Burman from the University of Southern California. The title of this project is Pathogenesis and Progression of Prostate Cancer. The continuation will extend this collaboration through May 31, 2013 and will bring an estimated additional support in the amount of $398,067 for this collaborative effort.

Dr. Daniel Diekema has a new research contract negotiated with Astellas Pharma, Inc. for a research project titled Global Antifungal Surveillance: An International Surveillance Program for Invasive Mycoses, 2008. The contract total is $198,125. This contract is for the period of January 26, 2009 through January 22, 2010.

Dr. Steven Moore received two awards to fund a Congenital Muscular Dystrophy Workshop at the University of Iowa. The primary goal of this workshop is to bring together members of the clinical and basic science communities with an interest in CMDs to assess the current state of knowledge in the field and to foster future collaborative efforts. Dr. Moore was awarded $13,216 from the Muscular Dystrophy Association and $36,280 from the National Institutes of Health. A total of $49,496 was awarded to fund this workshop.

Dr. Peter Nagy received a notice of R01 funding from the National Institutes of Health. The title of the project is Pathogenesis of Neurodegenerative Diseases Caused by Mutations in Senataxin. This award is for the period of September 25, 2008 through July 31, 2012. The amount of this award is $1,312,500.

Dr. Sandra Richter has a new research contract negotiated with Becton Dickinson & Company for a research project titled Timing study of the Phoenix/Phoenix AP and Vitek 2 Panel Preparation. The contract total is $26,900. This contract is for the period of December 30, 2008 through May 1, 2009.

PathBeat is published for alumni and friends of the Department of Pathology, University of Iowa Carver College of Medicine.

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