IOWA DEPARTMENT OF PATHOLOGY, UNIVERSITY OF IOWA CARVER COLLEGE OF MEDICINE

PATHOLOGYBEAT

Volume 16
Spring 2015

Conference
May 1 – 2, 2015 @ UIHC

UIDL HEMATOPATHOLOGY
NEW FRONTIERS

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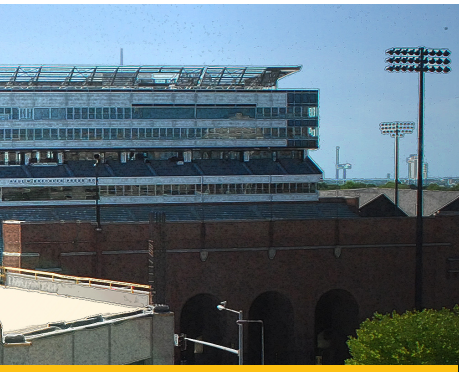

SPECIAL EVENT!

FRIDAY, MAY 1
KINNICK STADIUM PRESS BOX

Case Presentations

Wine, hors d'oeuvres, socializing and reminiscing

SATURDAY, MAY 2, 2015
East Room, 8th Floor
University of Iowa Hospitals and Clinics
10AM – 3:30PM UIHC FACULTY PRESENTATIONS:

The Saturday program has been approved for *AMA PRA Category 1 Credit*™

Shining a Fluorescent Light: 10-color Flow Cytometry and Cluster Analysis
Nitin Karandikar, MD, PhD, Chair and Department Executive Officer

Multidisciplinary Approach to Diagnosis, Risk Stratification, and Minimal Residual Disease Detection in Plasma Cell Neoplasms
Carol Holman, MD, PhD, Director of Leukemia Pathology
Holden Comprehensive Cancer Center

Cytogenetic Studies in Neoplastic Lymphoid Conditions
Ben Darbro, MD, PhD, Director, Shivanand R. Patil Cytogenetics and Molecular Laboratory

Prognostic Markers in B-cell Lymphomas
Sergei Syrbu, MD, PhD, Medical Director, Immunopathology Laboratory

Myeloid Neoplasms: Morphology and Beyond
Nancy Rosenthal, MD, Director of Hematopathology

Next Generation Sequencing for High Yield AML and MDS Analysis
Aaron Bossler, MD, PhD, Director, Molecular Pathology Laboratory

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University of Iowa Carver College of Medicine
University of Iowa Health Care

Munir Tanas, MD joins faculty from Cleveland Clinic
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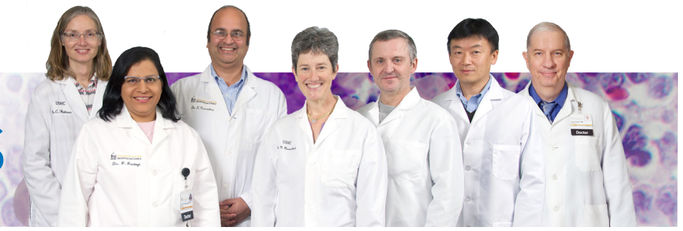


UIDL HEMATOPATHOLOGY:
NEW FRONTIERS
Conference Presentation Summaries

Shining a Fluorescent Light: 10-color Flow Cytometry and Cluster Analysis
Nitin Karandikar, MD, PhD, Chair and Department Executive Officer

This talk will cover the utility of flow cytometry in the diagnosis and management of hematolymphoid neoplasia. The advantages of the cluster analysis approach with 10-color flow cytometry will be demonstrated.

Multidisciplinary Approach to Diagnosis, Risk Stratification, and Minimal Residual Disease Detection in Plasma Cell Neoplasms
Carol Holman, MD, PhD, Director of Leukemia Pathology Holden Comprehensive Cancer Center

Plasma cell neoplasms span a wide spectrum of clinical presentations and outcomes. Therefore, correct classification is essential in order for the proper treatment to be started and the appropriate prognostic information to be conveyed to the patient. This session will review the current classification of plasma cell neoplasms, and describe the role of cytogenetic, FISH, and flow cytometric testing in the initial evaluation of these patients. The role of flow cytometry and CD138-enriched FISH to evaluate minimal residual disease following treatment will also be discussed. Case-based examples will be used throughout the presentation to illustrate key points.

Cytogenetic Studies in Neoplastic Lymphoid Conditions
Ben Darbro, MD, PhD, Director, Shivanand R. Patil Cytogenetics and Molecular Laboratory

Diagnosis, prognostication, and treatment decisions for neoplastic lymphoid conditions rely heavily on cytogenetics testing. Conventional cytogenetics (karyotype), fluorescence in situ hybridization (FISH), and now cytogenomic/chromosomal microarrays (CMA) can all be components of clinically appropriate cytogenetic studies on these diverse neoplasms. In this session, Dr. Darbro will be presenting the current state of the art of cytogenetic testing for acute and chronic lymphoid leukemias as well as non-Hodgkin lymphomas.

Prognostic Markers in B-cell Lymphomas
Sergei Syrbu, MD, PhD, Medical Director, Immunopathology Laboratory

Updates on prognostic markers in B-cell lymphoma (DLBCL, MCL and FL), which includes:

1. Clinical markers – IPI, MIPI and FLIPI scores
2. Tumor intrinsic markers – Cell of origin (GBC vs ABC type), FISH (cMYC, Bcl-2, and Bcl-6) and IHC for the expression/significance of Bcl-2, cMYC, Bcl-6, CD5, MIB1, p53/p21, etc.
3. Tumor microenvironment – Tumor associated histiocyte-macrophage cells (M1 vs M2 type)
4. Extra-tumoral markers – serum free immunoglobulin light chains, serum cytokines/chemokines (IL-1RA, IL-2Rα, IL-8, MIP-1β, and CXCL9), and absolute lymphocyte/monocyte count.

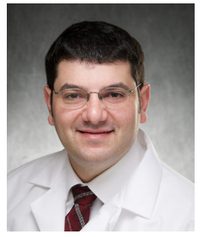
Myeloid Neoplasms: Morphology and Beyond
Nancy Rosenthal, MD, Director of Hematopathology

The diagnosis of acute myeloid leukemia can be difficult and the parameters by which we sub-classify these leukemias continues to evolve. In this session we will review clinical, morphologic, immunophenotypic and cytogenetic abnormalities that allow us to classify AML. We will also discuss new cytogenetic abnormalities that may be leukemia defining in the future. The clinical importance of morphologic versus cytogenetic abnormalities in AML with myelodysplasia related changes and the difficult diagnosis of acute erythroid leukemia will be presented. Finally, reactive mimics that may lead to the misdiagnosis of AML will be shown.

Next Generation Sequencing for High Yield AML and MDS Analysis
Aaron Bossler, MD, PhD, Director, Molecular Pathology Laboratory

This presentation will review the clinical utility and testing options for mutation profiling including common standard of care genetic changes and up and coming genetic biomarkers. Testing options available from the University of Iowa Molecular Pathology Laboratory will be discussed.

Munir Tanas, MD joins faculty from Cleveland Clinic



Munir Tanas, MD, joins us from Cleveland Clinic where he recently finished a bone and soft tissue pathology fellowship under the mentorship of Dr. Brian Rubin and Dr. John Goldblum. Working with Dr. Goldblum, Munir was involved in several clinico-pathological projects where he looked at the utility of fluorescence in situ hybridization (FISH) in the diagnosis of mesenchymal neoplasms. After his sarcoma pathology fellowship, he went on to do a post-doctoral research fellowship in the lab of Dr. Rubin, where he showed that a t(1;3)(p36;q25) translocation encodes a *WWTR1-CAMTA1* gene fusion in 90% of epithelioid hemangioendothelioma (EHE) and went on to dissect the function of the fusion protein.

Munir is excited to bring this experience to the Department of Pathology at University of Iowa which utilizes cutting-edge approaches to the diagnosis of sarcomas. In addition to histomorphological evaluation, patients will have their sarcomas evaluated with a sophisticated array of ancillary techniques. Immunohistochemistry is performed utilizing the newest antibodies available in the field. To identify chromosomal translocations, a wide variety of split-apart FISH probes are available. Translocations not amenable to evaluation by FISH will soon be evaluated utilizing an RNA-based next generation sequencing assay which can be used to detect more than 20 gene fusions including those present in some of the very rarest of sarcomas. Bone tumors are diagnosed in conjunction with an outstanding musculoskeletal radiology group. Munir is looking forward to assisting in any way possible with bone and soft tissue cases.

"At University of Iowa we are fortunate to have outstanding musculoskeletal radiology support, which is key to the accurate diagnosis of bone tumors."

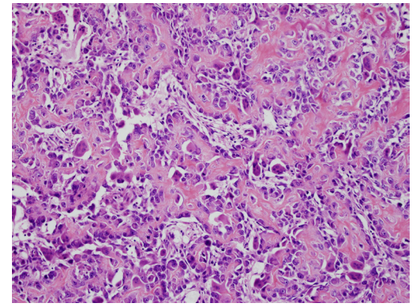


Figure 1. Osteoblastoma. Histological evaluation reveals a bone-forming lesion characterized by a proliferation of plump osteoblasts. Osteoblasts can be enlarged, imparting a hobnailing appearance to the lesion and mimicking a more aggressive neoplasm. However, cytological atypia is absent and correlation with radiology demonstrated a non-aggressive appearance to the lesion, supporting the diagnosis of osteoblastoma.

"Diagnosis of bone and soft tissue tumors is supported by a comprehensive immunohistochemical panel including STAT6 (solitary fibrous tumor/hemangiopericytoma), INI1 (renal rhabdoid tumor/malignant extrarenal rhabdoid tumor, epithelioid sarcoma, other epithelioid sarcomas), TLE1 (synovial sarcoma), MUC4 (low grade fibromyxoid sarcoma), NKI-C3 (cellular neurothekeoma), MDM2/CDK4 (well differentiated/dedifferentiated liposarcoma, and SOX-10 (neoplasms with neural or melanocytic differentiation)."

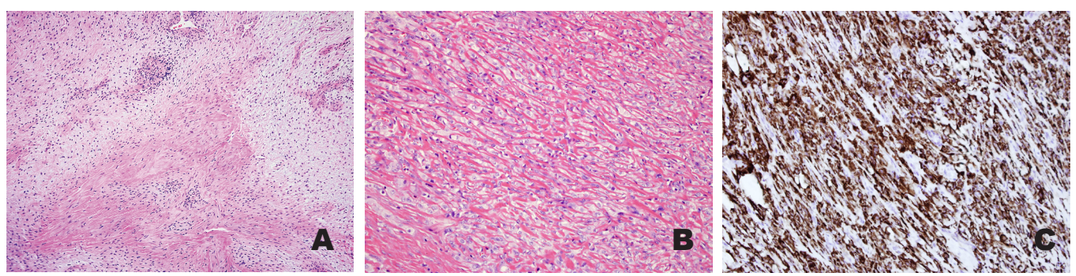


Figure 2. Low grade fibromyxoid sarcoma/sclerosing epithelioid fibrosarcoma. This hybrid sarcoma contains histological features of both low grade fibromyxoid sarcoma **(panel A)** and sclerosing epithelioid fibrosarcoma **(panel B)**. The diagnosis is supported by strong and diffuse immunoreactivity for MUC4 **(panel C)**, including the sclerosing epithelioid fibrosarcoma component (SEF). A subset of SEF, in particular those associated with low-grade fibromyxoid sarcoma (LGFMS) histology have been shown to harbor the same t(7;16) translocation seen in LGFMS, suggesting that these patterns represent the histological spectrum of the same entity.

Amyloidosis And Kidney Disease: A Brief Review

Prerna Rastogi, MD, PhD
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College of American Pathologists Immunohistochemistry Committee Member
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Amyloidosis comprises a group of disorders with an inherent defect in protein folding and extracellular deposition of low molecular weight fibrils. These are composed of soluble precursor proteins which have undergone conformational change. There is progressive organ dysfunction due to normal tissue replacement by amyloid.

Historic reference to amyloid can be found in the writings of Rudolf Virchow in 1853, who referred to tissue deposits of starch like material that stained in a similar manner to plant cellulose when exposed to iodine. He also described their amorphous and hyaline appearance on light microscopy. Subsequently with the use of polarized microscopy these deposits exhibited apple green birefringence with Congo red dye. Clinical manifestations depend upon the type, location, and the amount of deposition of these amyloid fibrils. However, initial symptoms may be non-specific and the diagnosis may be missed. Although the disease incidence is estimated at 8 cases/ million people per year in the United States, it may be underdiagnosed. Progress in the diagnosis and treatment of amyloidosis has led to efficacious clinical response and long-term survival can be achieved.

Amyloid deposition in a particular organ depends not only on the type of amyloid, but also on the extracellular matrix. The amyloid fibrils are characteristically described as having an antiparallel beta-pleated sheet configuration. The amyloid precursor protein undergoes conformational changes due to acidification or other chemical modifications, point mutations, deletions, premature stop codons or proteolytic cleavage. This results in protein misfolding and makes them fibrillogenic. The influence of the surrounding matrix also contributes to amyloid deposition, particularly in the setting of plasma cell dyscrasias or chronic inflammatory conditions. Protein misfolding may also occur in association with aberrant chaperone proteins and increased production of amyloidogenic precursors. Interaction of the aberrant proteins with extracellular matrix components including serum amyloid P-component (SAP), proteoglycans, and glycosaminoglycans influence the specific organ/tissue localization of amyloid deposits.

At least 30 different human and 10 different animal protein precursors of amyloid fibrils are now known. The nomenclature for amyloid deposits is based on the chemical structure of the fibril protein. The amyloid is represented by “A” followed by a suffix that is an abbreviated form of the precursor protein’s name. The principal types of amyloid found in humans are listed in Table 1 in this simplified list.

Table 1. Types of amyloid

Name	Amyloidogenic protein	Extent Systemic (S)/ Localized (L)	Clinical Syndrome	Treatment
AL	Immunoglobulin Light chain, heavy chain (AH) or both (ALH)	S, L	Plasma cell dyscrasia	Steroids, cyclophosphamide, melphalan, bortezomib, autologus stem cell rescue
AA	Serum amyloid A protein	S, rarely localized	Chronic inflammation	Treat underlying cause - antibiotics, cyclophosphamide, anti-IL-6 antibodies (Tocilizumab), heparin sulphate analogs (Eprodisate)
ATTR	Transthyretin	S, rarely localized	Familial hereditary amyloidosis	Liver transplant, tafamidis, diflunisal
A Fib	Fibrinogen	S	Involves kidney	Liver and kidney transplant
A LECT 2	Leucocyte chemotactic factor	S	Kidney	Under research
A beta-2 M	Beta-2 microglobulin	S, rarely localized	Sporadic, dialysis associated	Modified dialysis membranes, kidney transplant

IDENTIFICATION: A renal biopsy is performed to establish the presence and type of renal amyloid, which is important for prognosis and treatment. Various techniques are available to identify the type of amyloid deposits, including direct immunofluorescence on frozen tissue, immunohistochemistry on paraffin-embedded tissue via the commercially available immunoperoxidase or alkaline phosphatase detection kits, and laser microdissection/mass spectrometry (LMD/MS).

Although rarely performed, gross examination of kidneys involved by amyloid reveals enlarged kidneys with a pale, “waxy” cut surface. All renal compartments may be involved including glomeruli, tubules, interstitium and renal medulla where they may be seen around the vasa recta, loops of Henle, and collecting ducts.

On light microscopy amyloid appears as eosinophilic amorphous material that progressively replaces the glomerular mesangium on hematoxylin and eosin stain (Figure 1A). Examination of the biopsy may demonstrate periodic acid Schiff (PAS) stain negative (Figure 1C) and Jones silver stain (JMS) negative (Figure 1D) areas where normal mesangial matrix has been replaced by amyloid. The nodular glomerular mesangial expansion in case of amyloid must be carefully differentiated from diabetic nephropathy (silver and PAS positive) and other forms of nodular glomerulosclerosis. Similar deposits may be noted in arterioles (Figure 1B) and sometimes resemble hyalinosis. However, they have the characteristic staining properties with PAS, JMS and Congo red which can help distinguish the two.

Other special stains used include Thioflavin (T or S) fluorescent stain, which are highly sensitive, but relatively less specific as they may bind to other smaller oligomers, proteins with a higher beta sheet content etc. The gold standard for the diagnosis of amyloid is the Congo red stain. Amyloid deposits when stained with Congo red are “salmon pink” (Figure 2A) and exhibit “apple-green” birefringence (Figure 2B) when viewed under polarized light. The Congo red stained sections when viewed by ultraviolet light microscope with tetramethylrhodamine isothiocyanate (TRITC) filter will make the deposits stand out in bright red color.

Electron microscopy is used to identify amyloid fibrils. Glomerular amyloid spicules can result from parallel alignment of amyloid fibrils in the sub-epithelial zone perpendicular to the glomerular basement membrane (Figure 2C). The fibrils are described as rigid and non-branching, with an average diameter of 7 to 10nm (Figure 2D).

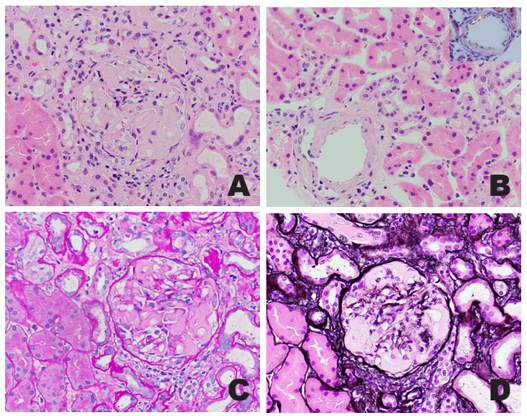

Figure 1. AL amyloidosis. A) Amorphous eosinophilic material expanding the mesangium and capillary loop basement membrane (H& E, 400x).B. Vessel wall with pale pink amyloid deposits (H & E, 400X), inset: apple green bi-refringence in the same vessel (Congo-red stain, 400x) C. Pale pink colored , PAS negative amyloid deposits (PAS, 400X). D. Silver stain negative amyloid deposits in the glomerulus (JMS, 400x).

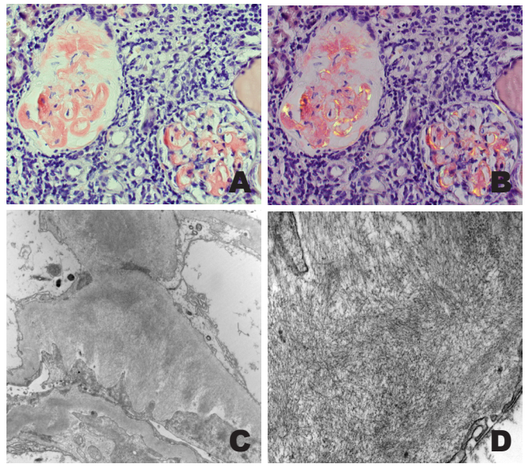

Figure 2. Amyloid AL. A) “Salmon – pink” deposits on Congo-red stain in the glomerular capillary loops (400X). B) “Apple green” birefringence under polarized light. C. Ultrastructural image of amyloid spicules, oriented perpendicular to the glomerular capillary loop basement membrane (Transmission electron microscopy, 12000X Direct Mag.). D. Random fibrils measured at 8.89 nm +/- 1.74 (SD) nm (Transmission electron microscopy, 50000x Direct Mag.).

TYPES OF AMYLOIDOSIS:

Light Chain amyloidosis (AL amyloid) – The disease affects mainly individuals with an average age of 65 years (range 23 to 91 years). Clinical manifestations include fatigue and weight loss. Patients usually present with nephrotic range proteinuria, edema, hepatosplenomegaly, cardiac failure and occasionally carpal tunnel syndrome. Renal involvement presenting with proteinuria is seen in 70% of patients. Cardiac involvement is seen in up to 60% of the cases and a subset of patients may also present with cardiac failure. AL amyloidosis usually occurs in association with plasma cell dyscrasias. Rarely, it may be associated with Waldenström

macroglobulinemia or non-Hodgkin lymphoma. Only 5% of the patients with AL amyloidosis will have overt multiple myeloma at the time of presentation. Rather, most present with monoclonal gammopathy of uncertain significance (MGUS). The deposits in immunoglobulin -derived amyloidosis in the vast majority of patients are composed of fragments of immunoglobulin light chains accounting for approximately 85% cases, followed by heavy chains and light chains (AHL) both or rarely fragments of heavy chains (AH) only.

Renal biopsy is of particular value in patients with monoclonal gammopathy of undetermined significance (MGUS) with accompanying renal dysfunction. These findings will usually trigger a cascade of further investigation often including imaging, serum and urine protein electrophoresis with immunofixation, bone marrow biopsy and serum free light-chain (sFLC) assay.

Appropriate clinical findings are a trigger for instituting aggressive therapy for an underlying plasma cell clone or lymphoplasmacytic disorder.

AA amyloidosis – AA amyloidosis is the second most common type of renal amyloidosis, accounting for 5% to 7% of cases. This is derived from the acute-phase reactant serum amyloid A protein (SAA). Under normal circumstances SAA plays a role in inflammation and defense functions. Up-regulation of SAA production (in the setting of inflammation), and protein misfolding together cause tissue deposits. In developing nations tuberculosis or other chronic infections cause AA amyloidosis, whereas in developed nations autoimmune diseases such as rheumatoid arthritis, ankylosing spondylitis, chronic juvenile arthritis, inflammatory bowel disease and familial Mediterranean fever (FMF) are thought to be responsible. Interestingly, hereditary auto-inflammatory diseases and periodic fever syndromes, including FMF carry an increased risk for the development of AA amyloidosis. In the setting of chronic infection or autoimmune disorders, proteinuria leading to nephrotic syndrome and renal insufficiency are suggestive of AA amyloidosis.

The renal deposits are similar to those described for the AL amyloid, and in the case of FMF involve small calibre vessels throughout the body. In the kidney they extensively deposit in the glomeruli, around the tubules and rarely may be more prominent in medulla. Patients may present with GI symptoms including malabsorption, intestinal pseudo-obstruction, diarrhea, or bleeding. They may also develop hepatosplenomegaly, gastrointestinal and adrenal insufficiency. However, cardiac, skin or soft tissue involvement is relatively uncommon.

It is important to remember that in patients with rheumatoid arthritis there may often be amyloid AA deposits with co-existing immune-complex disease. Hence a thorough investigation is warranted. Diagnosis depends on finding both clinical organ involvement and histological confirmation of amyloid deposits.

In contrast to AL amyloid where the emphasis is control of malignant cell clone, treatment options in AA amyloid address control/management of underlying predisposing disease. The objective is to decrease the acute phase reactant levels, including circulating serum SAA levels. Immunomodulatory drugs are being used in controlling the progression of amyloidosis-associated renal symptoms including proteinuria and improving long-term survival. Efficient anti-inflammatory therapy can delay or halt the development of AA amyloidosis and preserve organ function in patients with rheumatoid arthritis, chronic infection etc.

The category of non immunoglobulin associated non-AA and apparently sporadic amyloidosis types include dialysis related amyloidosis, A Lect-2 and ApoAIV associated amyloidosis.

Dialysis-related amyloidosis – In patients with renal failure who undergo chronic hemodialysis treatment, β2-microglobulin (β 2m) can form amyloid in osteoarticular structures. It helps in maintaining stability of the MHC1 molecules. The majority of this circulating β2m is filtered through the glomeruli into the tubules and reabsorbed by the proximal tubular cells. During hemodialysis the membrane molecular weight cut-offs are below or near the molecular weight of β2m, hence it does not get efficiently eliminated and accumulates within the patient. Patients with end stage kidney disease have uremia and require dialysis. The concentration of both heparin and urea is increased in such patients, and these two substances are known to accelerate fibrillogenesis. Patients complain of shoulder pain due to arthritis of the scapulohumeral joint and amyloid deposition in the rotator cuff. Physiological/ reactive rise in β2m levels occurs in conditions of increased cell turnover such as viral infections and hematopoetic malignancies, but is not associated with β2m amyloidosis.

A-Lect2 amyloidosis – This is derived from leukocyte chemotactic factor 2, and is a recently identified form of amyloidosis, with a predilection for kidney disease. This is seen in individuals of Mexican heritage or those from the northern Indian subcontinent of Punjab. These cases are associated with renal failure and variable amounts of proteinuria. It may involve liver, spleen and colon. Treatment strategies for this condition are not yet well established.

Apolipoprotein AIV – It is derived from apolioprotein ApoAIV, a glycoprotein that is important for lipid metabolism.There is no mutation evident in the *APOA4* gene. Of the cases reported in literature the renal involvement was predominantly medullary with almost no involvement of glomeruli or vessels. Thus far, there is no evidence of family history or mutation in the *APOA4* gene.

Heritable amyloidoses – Hereditary (familial) forms are associated with mutations in the amyloid precursor protein transthyretin (TTR), a carrier protein for thyroid hormone and also a retinol binding protein. It is synthesized in the liver as a 127 amino acid long chain, which form tetramers. There is extracellular misfolding and aggregation of the quaternary structures.

In United States 85% of familial amyloidosis is due to ATTR. The rest include amyloidosis derived from transthyretin (ATTR), fibrinogen (AFib), apolipoproteins AI and AII (AApoAI and AApoAII), lysozyme (ALys), gelsolin (AGel), and cystatin (ACys).The presentation of these forms is widely variable. Despite these mutations being inherited as autosomal dominant traits, different penetrance may allow for vastly different clinical manifestations.

ATTR is typically associated with cardiac involvement, peripheral neuropathy and rarely nephropathy, ophthalmopathy and central nervous system (CNS) amyloidosis. Familial amyloidosis is associated with the aggregation of one of over 100 TTR mutations. There may be tissue specific deposition eg: familial amyloid polyneuropathy (FAP) in the nerves, familial amyloid cardiomyopathy (FAC) in the heart and familial leptomeningeal amyloidosis in the brain meninges.

AFib amyloidosis – This is derived from fibrinogen, a 610 amino acid protein, produced exclusively by the liver which plays a critical role in clotting. There is characteristic renal involvement, which manifests itself as nephrotic syndrome and hypertension. Variants of fibrinogen A alpha-chain (AFib) cause one of the most common types of hereditary amyloidosis in Europe. The protein consists of two identical sets of three polypeptide chains (a, b and g). Up to six autosomal dominant amyloidogenic mutations have been described in fibrinogen structure and have variable penetrance (level of expression). There is deposition of a fibrinogen variant in vascular walls and in atheromatous plaques. Nephrotic syndrome with hyperlipidemia and hypertension can further accelerate the plaque formation and in susceptible patients give rise to Afib amyloid.

Usually these patients have no previous family history of kidney disease. They develop different phenotypes depending on the mutation. AFib is associated with a relatively slow progression of amyloid deposition in the kidney, compared to AL amyloid.

Age-related (senile) systemic amyloidosis – It is important to note that the wild type transthyretin has extensive β-pleated sheet structure and with age can undergo spontaneous aggregation and deposition in the myocardium. This is referred to as systemic senile amyloidosis (SSA). This may manifest as congestive heart failure or arrhythmia in the seventh decade. These patients have longer survival compared to patients with cardiac involvement from AL amyloidosis (75 versus 11 months). Renal involvement is rare in this entity. This may be occasionally confused with late-onset cardiomyopathy due to mutant TTR. To confound the matters even more, a family history may not be apparent, and a mutation screen may be necessary to distinguish the two causes of cardiomyopathy in older adults.

In summary amyloid nephropathy is common in AA and AL type amyloidosis, and relatively rare in ATTR, ALECT-2, A-fibrinogen and A- apolipoproteins (AI, AII, and AIV) amyloidosis. After the introduction of mass spectrometry however, the rarer subtypes of amyloidosis, ALECT2 in particular, are being increasingly reported.

DIAGNOSIS – Purely clinical symptom based diagnosis of amyloidosis type is not possible. The presence of amyloidosis may often but not always be suggested by the history and clinical manifestations (eg, nephrotic syndrome in a patient with multiple myeloma or long-standing, active rheumatoid arthritis) or on imaging. The treatments are markedly different and may range from cytotoxic drugs for AL amyloidosis to immunomodulatory drugs for AA or liver transplantation for A-fibrinogen amyloid (Table 1).

Extensive clinical evaluation should include family history, imaging, serum protein electrophoresis, urine electrophoresis, and bone marrow biopsy as required. In systemic amyloidosis, a fat pad biopsy, when appropriately performed, has excellent diagnostic sensitivity. Immunohistochemistry and immunofluorescence on frozen sections are rapid and efficient methods for amyloid typing.

In cases that are inconclusive or negative, evaluation by a reference laboratory, using more sophisticated methods such as DNA studies or mass spectrometry (MS) may be employed. MS identifies with precision the unique protein sub-structure present in hereditary and familial forms of amyloid. In addition, it can be performed on archival paraffin embedded tissue and obviates the need for fresh or frozen specimens. Currently, MS is available through specialized reference labs. The findings must be interpreted with caution and with a full awareness of technique/instrument limitations and pitfalls.

Clearly accurate identification of the amyloid type is the key to appropriate patient management. More entities/ mutations are likely to emerge as research into this field continues, as are targeted therapies. The ultimate goal would be utilizing an appropriate combination of clinical skills, laboratory investigations and targeted therapy to reverse the disease course and ameliorate patient suffering.

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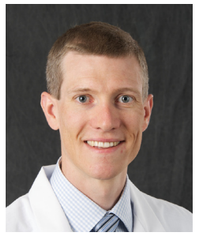

MALDI-TOF in Clinical Microbiology

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Clinical Assistant Professor, Pathology
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Species-level identification of bacteria and yeast is one of the primary activities of the clinical microbiology laboratory. Biochemical techniques were developed during the first century of clinical microbiology that allowed presumptive identification of a few common microbes within minutes and more definitive identification within 8 hours to a day. This system has low resolution for closely-related species and often fails with inert or metabolically similar organisms such as non-glucose-fermenting Gram-negative rods and Gram-positive rods. Delay and uncertainty over identification are two common outcomes of failed or limited biochemistry that have historically delayed the initiation of effective, narrow-spectrum antibiotic treatment for pathogens and, for contaminants and commensal organisms, may result in unnecessary treatment and distraction from alternative diagnoses.

Another major activity of the laboratory, susceptibility testing of bacteria, is predicated on having at least a presumptive identification before testing is performed and reported, making rapid identification by means other than biochemistry an even more attractive proposition.

The main historical alternative to biochemical identification, 16S (for bacteria) and 18S (for fungi) rDNA sequencing, is available to the UIHC Microbiology Laboratory and is expensive ($80 for in-house sequencing), low throughput, and takes at least two days but is almost always definitive. Because differences in ribosomal sequence can be used in this manner to identify bacteria and fungi and up to 50% of the dry weight of a growing bacterial cell consists of ribosomes, a proteomic technique that weighs the major components of cells has the potential to identify virtually any bacterium or fungus without being dependent on biochemistry. Matrix-Assisted Laser Desorption Ionization / Time-of-Flight Mass Spectrometry (MALDI-TOF MS) is capable of doing this for organisms that have been recovered in culture in minutes instead of hours or days. A MALDI-TOF mass spectrum is generated as described in Figure 1 and contains the precise weights of each component of the cell that can be easily ionized within the mass range of 2-20kDa where most ribosomal components fall.

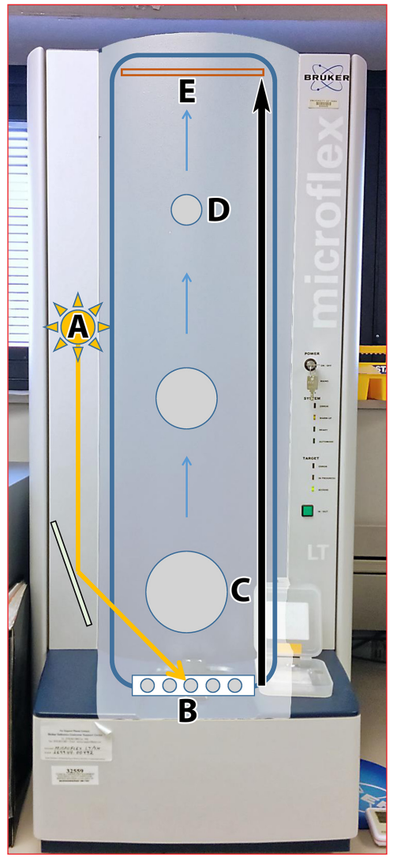

Figure 1: Bruker MALDI-TOF instrument

Because MALDI-TOF mass spectra are compared to a database of reference organisms' spectra to make an identification, organisms must first be grown in pure culture before spectra are collected and an identification is made. If multiple organisms are present the extra mass peaks render no spectrum in the database a good match and the identification fails. Because blood culture bottles typically (90% of the time) contain a large number of bacteria of a single species, a commercial purification system (the Bruker SepsiTyper system [1][2]) has been devised that can separate bacteria from blood and liquid culture media, resulting in a rate of identification of about 86% directly from blood culture bottles [3]. A species-level identification with the SepsiTyper saves at minimum one day for most aerobes and at least two days for anaerobes vs. a standard MALDI-TOF ID by bypassing culture in plate-format media. This has the potential to narrow the spectrum of antibiotic coverage, convert a patient to an oral drug instead of an IV drug, and/or identify the bacterium as a contaminant that can be ignored. Pathology, in collaboration with Internal Medicine, Pharmacy, and the Infectious Disease service, identified opportunities for improved patient care, cost avoidance and decreased length of stay if the Sepsityper system were implemented [4][5][6][7].

The laboratories at the Iowa City Veterans' Administration (VA; directed by Dr. Stacey Klutts) and the University of Iowa Hospitals and Clinics (UIHC; directed by Dr. Bradley Ford) are the only hospitals in Iowa that have implemented MALDI-TOF mass spectrometry for routine microbial identifications. UIHC currently performs about 2,000 identifications per month by MALDI-TOF MS. Hiring of personnel to perform SepsiTyper testing was recently completed and validation of the test and construction of a collaborative network of physicians and pharmacists to manage the data is a current work in progress.

The Iowa City Veterans' Administration and the University of Iowa Hospitals and Clinics are the only hospitals in Iowa that have implemented MALDI-TOF mass spectrometry for routine microbial identifications.

Figure 1: Collection of a MALDI-TOF spectrum on the Bruker MALDI-TOF instrument at UIHC. A) A laser light source is applied to B) a spot on a stainless steel target containing organisms overlaid with α-Cyano-4-hydroxycinnamic acid (HCCA) matrix which desorb such that the larger components [C] accelerate more slowly than the smaller components [D] in a high voltage (arrow) across an evacuated tube. A detector [E] measures the time of flight between desorption and detection, which is used to calculate a mass spectrum.

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[4] J. L. Nagel, A. M. Huang, A. Kunapuli, T. N. Gandhi, L. L. Washer, J. Lassiter, T. Patel, and D. W. Newton, "Impact of Antimicrobial Stewardship Intervention on Coagulase-Negative Staphylococcus Blood Cultures in Conjunction with Rapid Diagnostic Testing," *J. Clin. Microbiol.*, pp. JCM.00682–14, May 2014.

[5] D. Martiny, F. Debaugnies, D. Gateff, M. Gérard, M. Aoun, C. Martin, D. Konopnicki, A. Loizidou, A. Georgala, M. Hainaut, M. Chantrenne, A. Dediste, O. Vandenberg, and S. Van Praet, "Impact of rapid microbial identification directly from positive blood cultures using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry on patient management," *Clin. Microbiol. Infect.*, vol. 19, no. 12, pp. E568–E581, Dec. 2013.

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Updates in Diagnostic Immunohistochemistry, Part III: Further Offerings from the University of Iowa Immunopathology Laboratory

Introduction:

The purpose of this column is to discuss and illustrate the diagnostic immunohistochemical tests validated by the Immunopathology Laboratory since the last issue of PathBeat (see Table). All six markers are lineage-specific transcription factors and thus exemplars of next-generation immunohistochemistry.

Table: Recently Validated Immunohistochemical Stains at a Glance

Marker	Principal Diagnostic Application(s)
ERG	Vascular tumors; highlighting lymph-vascular space invasion by carcinoma
STAT6	Solitary fibrous tumor
SALL4	Germ cell tumors
SOX10	Melanoma; malignant peripheral nerve sheath tumor
ISL1	Pancreatic origin of neuroendocrine tumor
PAX6	Pancreatic origin of neuroendocrine tumor

ERG:

Background: The ETS-family transcription factor ERG (ETS-related gene) is constitutively expressed by endothelial cells and related neoplasms, and *ERG* gene fusions are identified in 40-50% of prostate cancers (*TMPRSS2-ERG*) and a smaller number of acute myeloid leukemias and Ewing sarcomas (10%).

ERG has emerged as the preferred marker of endothelial differentiation (Images 1A-D), compared to alternative markers including CD34, CD31, factor VIII-related antigen, and FLI1. Advantages include its high sensitivity and specificity and, as a transcription factor, ease of interpretation of staining. ERG has also been suggested as a secondary prostate cancer marker, either in the setting of small foci in core biopsies or a metastatic carcinoma of unknown origin.

Miettinen and colleagues examined ERG expression in a large set of vascular (n=250), other mesenchymal (n=973), and epithelial tumors (n=657). ERG was expressed by all hemangiomas, lymphangiomas, and Kaposi sarcomas; 96% of angiosarcomas; and 98% of epithelioid hemangioendotheliomas. Among other mesenchymal tumors, expression was restricted to 7 of 10 myeloid sarcomas (70%) and 2 of 29 (7%) Ewing sarcomas. Thirty of sixty-six (45%) prostate cancers were ERG-positive. ERG-positivity was only noted in 2 of 591 (0.3%) non-prostatic epithelial tumors with expression noted to be focal in each, as opposed to the diffuse, strong expression typical in the aforementioned tumor types. ERG expression has subsequently been reported in 41 of 109 (38%) epithelioid sarcomas, which were shown not to harbor oncogenic *ERG* gene fusions.

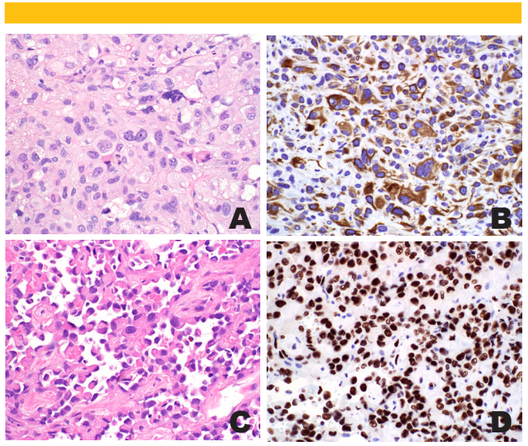


Image 1: ERG Staining in Epithelioid Angiosarcoma. (A) 31-year-old man with a lung mass undergoes endobronchial biopsy, which demonstrates a pleomorphic malignant neoplasm. A diagnosis of poorly differentiated non-small cell carcinoma is rendered based on a (B) positive pan-keratin immunostain (S-100, CD45, PLAP, TTF-1, p63, CD30, KIT, and CD5 are negative). (C) The patient subsequently undergoes a thoracoscopic biopsy, which in areas demonstrates a vasoformative lesion; (D) ERG-positivity supports a diagnosis of epithelioid angiosarcoma (each 400x)

Key Reference: Miettinen M, et al. ERG transcription factor as an immunohistochemical marker for vascular endothelial tumors and prostatic carcinoma. *Am J Surg Pathol.* 2011;35:432-441.

STAT6:

Background: An intrachromosomal gene fusion between the *NAB2* and *STAT6* loci on chromosome 12 has recently been identified by several groups as the defining molecular genetic signature of solitary fibrous tumor. The fusion protein replaces a NAB2 repressor domain with a STAT6 transactivation domain, resulting in transcriptional activation. Due to the proximity of *NAB2* and *STAT6* on chromosome 12, this fusion is not amenable to detection by conventional cytogenetics or fluorescence in situ hybridization.

STAT6 has emerged as a sensitive and specific marker of solitary fibrous tumor (Images 2A-D). Up to now solitary fibrous tumor has had a non-specific immunophenotype, with the most characteristically expressed marker (CD34; seen in 95%) also typically expressed by histologic mimics including soft tissue perineurioma, dermatofibrosarcoma protuberans (DFSP), and spindle cell lipoma.

Doyle and colleagues detected STAT6 expression in 98% of 60 solitary fibrous tumors (generally diffuse and strong), 14% of 21 dedifferentiated liposarcomas (DDLPS), and 10% of 10 deep fibrous histiocytomas and not in any of 140 other potential histologic mimics including cellular angiofibroma, desmoid fibromatosis, DFSP, gastrointestinal stromal tumor, low-grade fibromyxoid sarcoma, malignant peripheral nerve sheath tumor, monophasic synovial sarcoma, sarcomatoid mesothelioma, Schwannoma, soft tissue perineurioma, and spindle cell lipoma. STAT6 expression in a subset of DDLPSs has more recently been shown to be due to STAT6 amplification (the gene is at 12q13, nearby to 12q15, the latter consistently amplified in DDLPS).

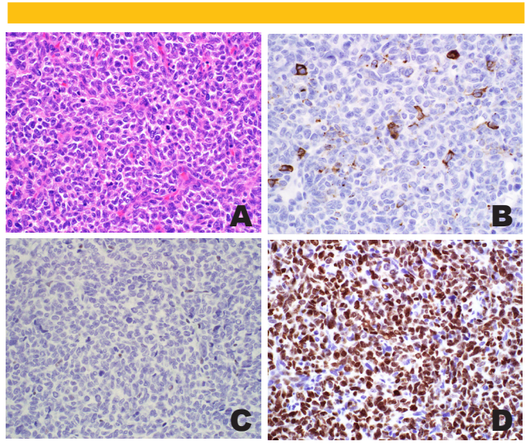


Image 2: STAT6 Staining in Malignant Solitary Fibrous Tumor (Hemangiopericytoma). (A) 71-year-old man with a T1-T2 spinal lesion composed of plump single cells with brisk mitotic activity. A diagnosis of synovial sarcoma is rendered, at least in part based on (B) scattered keratin-positive cells. (C) The tumor is TLE1-negative, though, and (D) expresses STAT6, supporting a diagnosis of malignant solitary fibrous tumor (this tumor type is still typically referred to as hemangiopericytoma in the brain and spinal cord) (each 400x).

Key Reference: Doyle LA, et al. Nuclear expression of STAT6 distinguishes solitary fibrous tumor from histologic mimics. *Mod Pathol.* 2014;27:390-395.

SALL4:

Background: The embryonic transcription factor SALL4 (sal-like protein 4) is a key regulator of pluripotency. While in the 10-week embryo SALL4 is expressed by germ cells, intestine, kidney, and some hepatocytes, in adult tissues SALL4 expression is limited to germ cells.

SALL4 has emerged as a highly sensitive marker of germ cell tumors (Images 3A-B), similar to placental alkaline phosphatase (PLAP). As SALL4 is a transcription factor, an advantage over PLAP is ease of interpretation. Additionally, SALL4 has superior sensitivity to PLAP in yolk sac tumor. It is variably expressed in choriocarcinoma and teratoma.

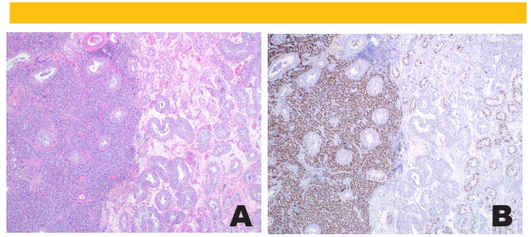


Image 3: SALL4 Staining in Seminoma and Intratubular Germ Cell Neoplasia. (A) Low-power photomicrograph of the interface of a seminoma with adjacent seminiferous tubules; (B) SALL4 highlights not only the invasive tumor but also intratubular germ cell neoplasia (right-hand side of image) (each 40x).

Miettinen and colleagues examined SALL4 expression in a set of 3,215 human tumors. As expected, SALL4 was expressed by all seminomas (n=85), embryonal carcinomas (n=30), and yolk sac tumors (n=9) and by most choriocarcinomas (6/7;

86%); it was also expressed (typically focally) by mature components of 6 of 10 teratomas (60%). SALL4 was also expressed by 5.7% of 2,393 non-germ cell epithelial neoplasms, with expression especially frequent in serous carcinoma, gastric adenocarcinoma, urothelial carcinoma, small cell lung carcinoma, and cholangiocarcinoma (each ranging from ~20-30%); expression was uncommon at other primary sites. Of note, neither OCT4 nor NANOG were co-expressed in a subset of examined SALL4-positive non-germ cell tumors. Expression was rare in 680 mesenchymal and neuroectodermal tumors with the notable exceptions of Wilms tumor (11/18; 61%) and rhabdoid tumor (3/3; 100%).

SALL4 is a highly sensitive and fairly specific marker of germ cell tumors. Expression is typically diffuse and strong, while expression in non-germ cell tumors is often focal (though occasionally diffuse, strong). SALL4-positivity in these latter tumors may reflect an embryonic stem cell phenotype.

SOX10:

Background: SOX10 (sex-determining region Y-related high mobility group box 10) is a transcription factor essential for neural crest development and phenotype maintenance. In normal tissues it is expressed by Schwann cells, melanocytes, and myoepithelial cells. *SOX10* inactivating mutations cause Waardenburg syndrome, type IVc, characterized by deafness, hypopigmentation, and Hirschsprung disease. Activating mutations have been identified in some melanomas.

SOX10 has emerged as a highly sensitive marker of Schwannian and melanocytic differentiation, similar to S-100 (Images 4A-B). Compared to S-100, SOX10 boasts both superior sensitivity (see below) and specificity, with S-100 also labeling dendritic cells, fat, cartilage, and a subset of carcinomas. It is significantly more sensitive than other specific markers of melanocytic differentiation, including melan A, HMB-45, MiTF, and tyrosinase.

Nonaka and colleagues reported SOX10-positivity in 97% of 78 melanomas, 49% of 77 malignant peripheral nerve sheath tumors, and 100% of 5 clear cell sarcomas, while S-100 was positive in 91%, 30%, and 60%, respectively. In this same study, SOX10 was not expressed by 269 other soft tissue tumors. Similar to S-100, SOX10 highlights sustentacular cells (e.g., in pheochromocytoma) and salivary gland tumors with myoepithelial differentiation (e.g., pleomorphic adenoma). Finally, SOX10 is often expressed by some gliomas, including oligodendrogliomas and astrocytomas.

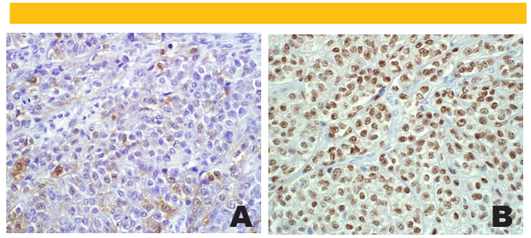


Image 4: S-100 vs. SOX10 Staining in a Clear Cell Sarcoma. (A) S-100; (B) SOX10 (each 400x). Transcription factors often demonstrate diffuse, strong staining in foci that only show weak, patchy staining with traditional differentiation markers.

Key Reference: Nonaka D, et al. Sox10: a pan-Schwannian and melanocytic marker. *Am J Surg Pathol.* 2008;32:1291-1298.

Willis BC, et al. SOX10: A Useful Marker for Identifying Metastatic Melanoma in Sentinel Lymph Nodes. *Appl Immunohistochem Mol Morphol.* 2014 Oct 29. [Epub ahead of print]

Islet 1 and PAX6:

Background: The homeodomain-containing transcription factor Islet 1 (ISL1) is expressed in the islets of Langerhans, cells in the anterior and intermediate lobes of the pituitary, parafollicular cells in the thyroid, chromaffin cells in the adrenal medulla, and in subsets of neurons. An ISL1 knockout mouse demonstrates a complete absence of differentiated islet cells.

PAX6, 1 of 9 paired box genes, is a transcription factor critical in eye, brain, and islet of Langerhans development. A PAX6 knockout mouse lacks glucagon-producing α-cells.

Islet 1 and PAX6 have emerged as sensitive and specific markers of pancreatic (well-differentiated) neuroendocrine tumors (NET), especially in their distinction from midgut NETs (Images 5A-D).

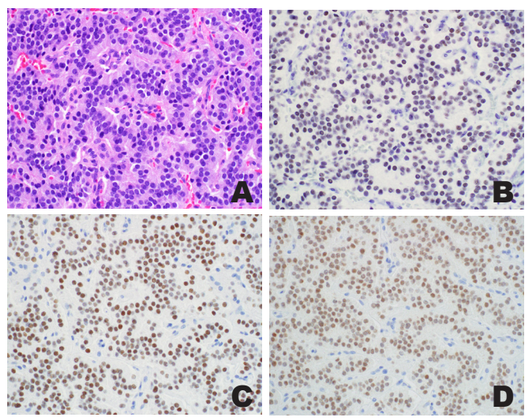


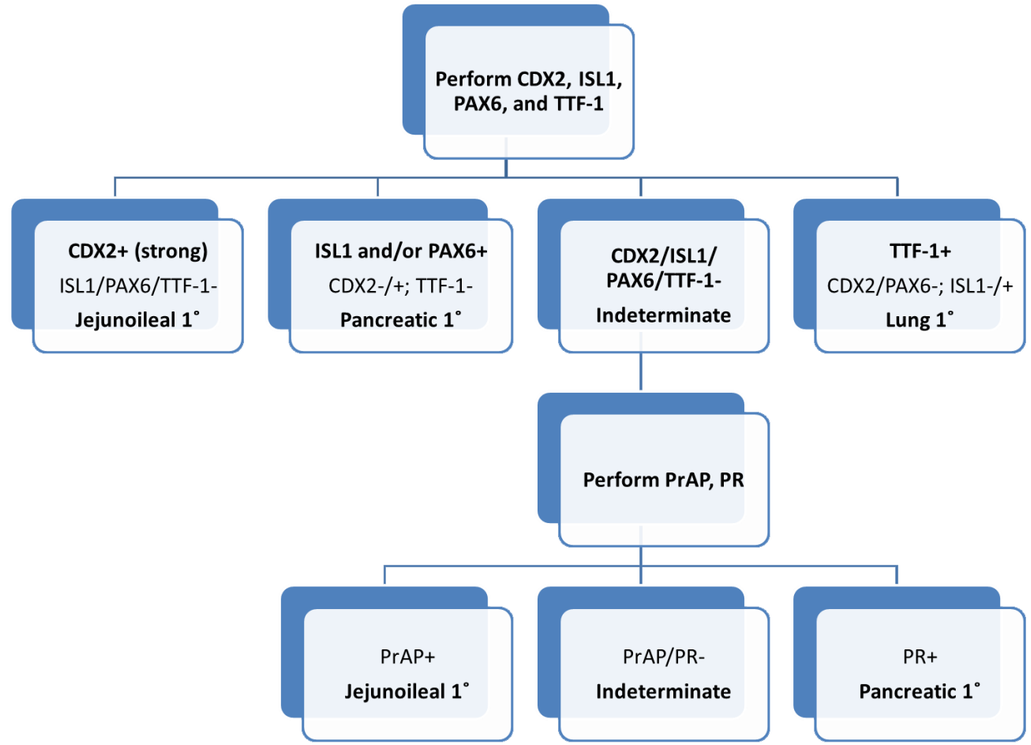
Image 5: ISL1 and PAX6 Staining in a Metastatic Neuroendocrine Tumor (NET) of Unknown Primary (A) 63-year old man with a well-differentiated NET of unknown origin metastatic to a lower portal vein lymph node. The tumor demonstrates (B) modest, though fairly diffuse CDX2 staining, as well as diffuse, strong (C) ISL1 and (D) PAX6 staining (each 400x). ISL1 and/or PAX6 staining of any intensity in a NET of occult origin suggests a pancreatic origin.

Stashek and colleagues detected ISL1 expression in 91% of 57 primary and 85% of 13 metastatic pancreatic NETs and in only 2% of 107 jejunoileal tumors. It was also expressed by 82% and 87% of duodenal and rectal tumors, respectively, although, of note, tumors from these sites rarely present as metastases of unknown origin. In the same study, PAX6 was expressed by 79% of 57 primary and 69% of 13 metastatic pancreatic NETs and by none of 107 jejunoileal tumors. It was also expressed by 62% and 56% of duodenal and rectal tumors.

Maxwell and colleagues subsequently found that an immunohistochemistry (IHC) classifier including the pancreatic NET markers ISL1, PAX6, PR, NESP55, and PDX1 and the midgut NET markers CDX2 and PrAP successfully assigned a pancreatic or midgut origin in 94% of 123 NETs. Of note, ISL1 and/or PAX6-positivity was detected in 90% of 51 pancreatic NETs, positioning these two markers in the first-tier, along with CDX2, of the IHC classifier.

Key Reference: Stashek KM, et al. Extensive Evaluation of Immunohistochemistry to Assign Site of Origin in Well-Differentiated Neuroendocrine Tumors: A Study of 10 Markers in 265 Tumors. *Mod Pathol.* 2014;27 Suppl 2:160A.

Maxwell JE, et al. A practical method to determine the site of unknown primary in metastatic neuroendocrine tumors. *Surgery.* 2014 Dec;156(6):1359-65;



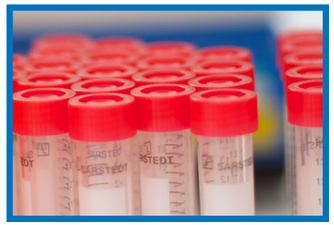
Iowa Neuroendocrine Tumor (NET) Site of Origin IHC Classifier. The site of origin of a well-differentiated NET of unknown origin can be determined with a panel of immunostains. Tier 1 markers include CDX2, ISL1, PAX6, and TTF-1. For "quadruple negative" tumors, the Tier 2 immunostains PrAP and PR can be performed.

DEPARTMENT OF PATHOLOGY, UNIVERSITY OF IOWA CARVER COLLEGE OF MEDICINE

NEW and ACTIVE RESEARCH AWARDS

NEW Research Awards

Dr. Vladimir Badovinac received a Co-PI grant funding with Dr. John Harty from the Department of Microbiology. The grant was awarded from the National Institutes of Health/National Institute of Allergy and Infectious Diseases (NIH/NIAID). The title of this project is *Memory CD8 T cell localization and protection from influenza*. This funding total is $1,900,000 and is for the period of November 1, 2014 through October 31, 2019.



Dr. Vladimir Badovinac received an Oberley Seed Grant from the University of Iowa, Holden Comprehensive Cancer Center. The title of this project is *Enhancing anti-tumor CD8 T cell responses for immunotherapy*. The award is in the amount of $50,000.

Dr. Leslie Bruch received a Medical Student Interest Group (MSIG) award from the Intersociety Council for Pathology Information, Inc. (ICPI). This 2014 MSIG award is a useful mechanism to encourage outstanding medical students to consider a career in pathology. The award is in the amount of $1,000.

Dr. Nitin Karandikar received a notice of grant funding from the National Multiple Sclerosis Society. The title of this project is *Role of CNS-Specific Autoreactive CD8+ T Cells in MS*. The amount of this award is $712,800 and is for the period of April 1, 2013 through March 31, 2017.

Dr. Nitin Karandikar received grant funding from the National Institute of Health/National Institute of Allergy and Infectious Diseases (NIH/NIAID). The title of this project is *CNS-specific regulatory CD8+ T cells in autoimmune demyelination*. The total direct costs for this award are$1,125,000. The period for this project is May 1, 2011 through April 30, 2016.

Dr. Nitin Karandikar received grant funding from National Institute of Health/National Institute of Allergy and Infectious Diseases (NIH/NIAID). The title of this project is *Dissecting the immunologic basis of health and disease*. The total direct costs for this award are $845,020. The period for this project is March 1, 2009 through February 28, 2015.

Dr. C. Michael Knudson received funding under the Carver College of Medicine Internal Funding Opportunity for High Throughput Screening. The award is in the amount of $10,000.

Dr. Kevin Legge and Dr. Thomas Waldschmidt received research funding from Iowa State University for the project with the title of *Adaptive immunity and protection generated to nanoparticle-based vaccination against influenza virus*. The award is in the amount of $18,230.

Dr. Steven Moore received funding for a study in collaboration with Sarepta Therapeutics, Inc. The research funding is in the amount of $334,191.

Dr. Andrean Simons-Burnett received grant funding from the National Institutes of Health/National Institute of Dental & Craniofacial Research (NIH/NIDCR). The title of this project is *Role of inflammation in resistance to EGFR inhibitors in head and neck cancer*. This funding total is $1,878,808 and is for the period of July 2, 2014 through April 30, 2019.

Dr. Munir Tanas received Sarcoma Pilot Funding from the University of Iowa, Melanoma and Sarcoma Program. The title of this project is *Towards the clinical application of WWTR1 and the hippo pathway in breast cancer: a translational proposal*. The award is in the amount of $30,000.

Dr. Weizhou Zhang received a V Scholar Grant Award from the V Foundation for Cancer Research. The title of this project is *Metformin and Nlrc4-inflammasome in obesity-associated cancer progression*. The award is in the amount of $200,000.

Dr. Weizhou Zhang received an Oberley Seed Grant from the University of Iowa, Holden Comprehensive Cancer Center. The title of this project is *TREM-1 facilitates pulmonary metastasis of breast cancer*. The award is in the amount of $50,000.

ACTIVE Research Awards

Dr. Marina Ivanovic received one of the first small Thoracic MOG research grants at the University of Iowa. The title of this project is *Metastasis-associated protein 1 expression in lung adenocarcinoma*. The award is in the amount of $15,000.

Dr. C. Michael Knudson received a Donald D. Dorfman Research Award from the Holden Comprehensive Cancer Center at the University of Iowa Health Care. This award is for the best research paper in lymphoma published in 2012 or 2013. The title of the paper is *2-deoxyglucose-induced toxicity is regulated by Bcl-2 family members and is enhanced by antagonizing Bcl-2 in lymphoma cell lines*. The award is in the amount of $2,500.

Dr. Kevin Legge received grant funding from the National Institutes of Health/National Institute of Alcohol Abuse and Alcoholism (NIH/NIAAA). The title of this project is *Chronic ethanol consumption and pulmonary immune suppression*. This funding total is $396,376 and is for the period of September 5, 2013 through August 31, 2015.

Dr. Deqin Ma received research funding from the Carver College of Medicine, Holden Comprehensive Cancer Center at the University of Iowa. The title of this project is *Molecular studies of leiomyosarcoma – identification of potential targets for personalized medicine*. The award is in the amount of $10,000.

FACULTY RESEARCH PUBLICATIONS

Loss of SOD3 (EcSOD) expression promotes an aggressive phenotype in human pancreatic ductal adenocarcinoma. O'Leary BR, Fath MA, **Bellizzi AM**, Hrabe JE, Button AM, Allen BG, Case AJ, Altekruse SF, Wagner B, Buettner GR, **Lynch CF**, Hernandez BY, Cozen W, Beardsley RA, Keene J, **Henry MD**, **Domann FE**, Spitz DR, Mezhir JJ. Clin Cancer Res. 2015 Jan 29. PMID: 25634994

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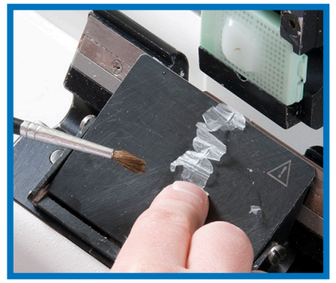
Impact of prostate inflammation on lesion development in the POET3(+) Pten(+/-) mouse model of prostate carcinogenesis. Burcham GN, Cresswell GM, Snyder PW, Chen L, Liu X, Crist SA, **Henry MD**, Ratliff TL. Am J Pathol. 2014 Dec;184(12):3176-91. PMID: 25455686

TRAIL activates JNK and NF-κB through RIP1-dependent and -independent pathways. Zhang L, Dittmer MR, Blackwell K, Workman LM, Hostager B, **Habelhah H**. Cell Signal. 2015 Feb;27(2):306-14. PMID: 25446254



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DEPARTMENT OF PATHOLOGY, UNIVERSITY OF IOWA CARVER COLLEGE OF MEDICINE

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Pathology Welcomes Dr. Prerna Rastogi

Monday, November 10, 2014

Dr. Prerna Rastogi received her medical training in India. She then moved to the United States where she pursued her doctoral studies at St. Louis University, St. Louis, MO in the lab of Dr. Jane McHowat, where she published several manuscripts, reviews and book chapters. She also received the American Heart Association pre-doctoral fellowship award. After receiving her PhD degree in 2008 she began her residency training in anatomic and clinical pathology at St. Louis University (2009-2013). Besides actively participating in medical and dental student teaching she served as the chief resident (2012-2013). Dr. Rastogi then joined the hematopathology fellowship at Moffitt Cancer Center in Tampa, FL in 2013, followed by specialized training in renal pathology at Nephropath in Little Rock, AR. She will participate on renal pathology and hematopathology services. She is married to Dr. Rahul Rastogi, a pain management physician, who will also be joining the UI Department of Anesthesia. They have 2 boys, Paarin (11 years) and Praneel (6 years). In her "me time" Dr. Rastogi likes to paint and drink tea. As a family they love to travel, her last visit being to Argentina.

Laila Dahmoush, MBChB, was appointed the University of Iowa Representative to the IAP (Iowa Association of Pathologists) board

Tuesday, December 02, 2014

Laila Dahmoush, MBChB, was appointed the University of Iowa Representative to the IAP (Iowa Association of Pathologists) board. Dr. Dahmoush replaces Robert A. Robinson, MD, PhD who has been the university's IAP representative for five years. The Iowa Association of Pathologists is the leading statewide organization serving pathologists, patients and the public. Nationally, IAP is affiliated with the College of American Pathologists.

The Department of Pathology celebrated recent faculty promotions at a faculty meeting on August 12, 2014. Congratulations to Vladimir Badovinac, PhD, who has been promoted to Associate Professor of Pathology and to Andrew Bellizzi, MD, who has been promoted to Clinical Associate Professor of Pathology, effective July 1, 2014.

Outstanding Achievement in Service and Performance

The National Marrow Donor Program (NMDP) has recognized the DeGowin Blood Center with two achievement awards! The awards recognize our center for outstanding achievement in service and performance, as well as collecting more than 25 hematopoietic stem cell products for NMDP in 2013.

Thanks to our outstanding staff in the Blood Center and the Iowa Marrow Donor Program. Your hard work and dedication have made us a leader in the field.

Front Row: Kate Ties, Gail Nelson, Kim Engler, Laura Collins
Middle Row: Amber O'Shogay, Luann Link, Jan Alrichs-Hanson, Annette Schlueter
Back Row: Beth Alden, Mikhail Arey, Al Andersen, Dave Huling, Shari Evans

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A Letter from UI Foundation

Forever Building a Strong Future

For nearly 125 years, the University of Iowa Department of Pathology has been providing comprehensive diagnostic and treatment services to patients, as well as integrating clinical and scientific expertise with research. Each day, it's evident that the UI Department of Pathology changes lives through education, patient care, and research.

What we do at the UI Department of Pathology wouldn't be possible without alumni and friends like you. Your generous contributions—which allow us to maintain state-of-the-art facilities and keep pressing forward on numerous research endeavors—are now more important than ever. As state funding continues to decrease and National Institute of Health funding proves to be even more difficult to secure, your support allows us to continue our tradition of excellence, expand our opportunities for crucial research, and educate future generations of pathologists.

I look forward to my new role as Associate Director of Development for Major Gifts at the Roy J. and Lucille A. Carver College of Medicine. Together, we can collaborate with the UI Department of Pathology as it continues to excel in compassionate care, education, and research. It's an honor to build upon the success of an exceptional program that is transforming the future of healthcare for generations to come.

To learn more about how your private support can change lives and support a department that is a recognized leader in pathology, please contact John Dwyer at john-dwyer@uiowa.edu or at (319) 467- 3861.

John Dwyer

Associate Director of Development for Major Gifts for the Carver College of Medicine, University of Iowa Hospitals and Clinics, the University of Iowa Foundation

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Each day, it's evident that the UI Department of Pathology changes lives through education, patient care, and research.