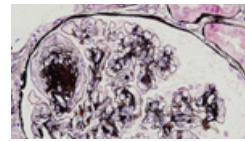




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# PATH BEAT

The Newsletter of the Department of Pathology  
University of Iowa Carver College of Medicine

No. 15 Fall 2013



## Department News

### New University of Iowa Pathology Chair and DEO: Nitin Karandikar M.D., Ph.D.

“His leadership style embraces the integrated approach to medical education and clinical care that we value so highly here at the UI.”

— Debra Schwinn, M.D.  
Dean of the UI Carver  
College of Medicine

Leaders with the University of Iowa Health Care have appointed Nitin Karandikar, M.D., Ph.D., as the new Chair and DEO of the Department of Pathology at the University of Iowa Roy J. and Lucille A. Carver College of Medicine. Dr. Karandikar also holds the Dr. Richard G. Lynch Chair in Experimental Pathology.

Dr. Karandikar joined the department coming from the University of Texas Southwestern (UTSW) Medical Center in Dallas, Texas, where he was Professor and Vice Chair of Pathology, held the Vernie A. Stembridge, M.D., Distinguished Chair in Pathology, and was a Professor of Neurology and Immunology.

“We are delighted that Dr. Karandikar has accepted the position as head of pathology. His leadership style embraces the integrated approach to medical education and clinical care that we value so highly here at the UI,” says Debra Schwinn, M.D., Dean of the UI Carver College of Medicine. “Dr. Karandikar is a nationally known researcher and educator with a proven track record of drawing together clinical practice, interdisciplinary research, and medical training to advance patient-focused care and develop the next generation of leaders in biomedicine. His

skills, passion, and dedication make him an ideal choice to lead the department.”

Dr. Karandikar expressed his enthusiasm about this move. “I am very excited about the opportunity of joining this world-class institution as Head of Pathology and collaborating with its illustrious leaders,” he says. “I look forward to working with my colleagues in pathology to further its excellence at the crossroads of clinical diagnostics, disease-based research, and fundamental biomedical education.”

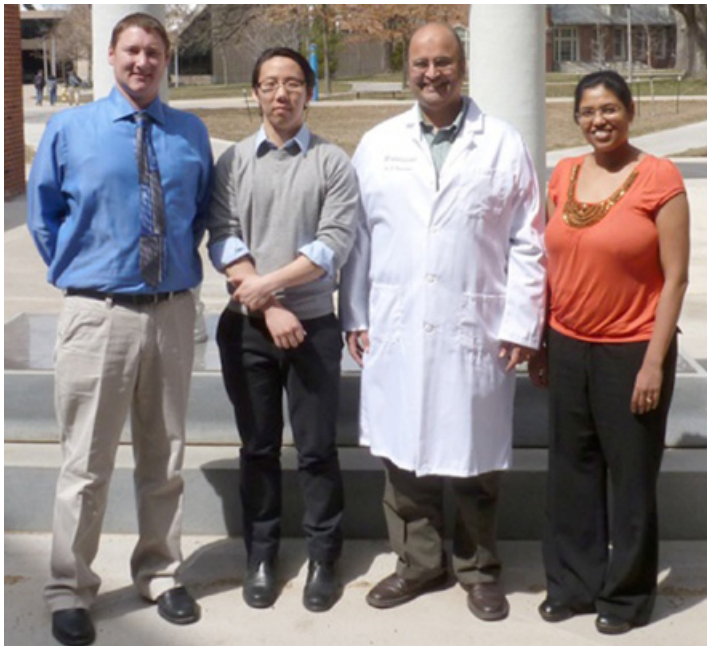
Dr. Karandikar is board-certified in clinical pathology and hematopathology by the American Board of Pathology and is a member of many national professional groups, including the American Society of Clinical Pathologists and the American Association of Immunology. Dr. Karandikar has been honored for his teaching and has been a lecturer and visiting professor in the U.S., Europe and India. He is primary or co-author on more than 100 publications and is a member of two editorial boards.

Dr. Karandikar received a medical degree from B.J. Medical College, University of Poona, India, where he also completed a residency in clinical and anatomic

*Continued on page 2*

pathology. During this residency, he had to complete a small thesis project, which he cites as the roots of his eventual interest in research. He received a doctoral degree in Immunology and Molecular Pathogenesis from Northwestern University Medical School in Chicago, Illinois. Dr. Karandikar followed with a Clinical Pathology Residency and a Hematopathology Fellowship at the University of Texas Southwestern Medical Center in Dallas, Texas. Dr. Karandikar's clinical expertise is the multi-modality diagnosis of hematolymphoid and immune disorders, including leukemias and lymphomas, particularly by applying multi-parameter flow cytometry.

Dr. Karandikar directed the UTSW Division of Hematopathology, served as the Medical Director of the UTSW Hospital and Reference Laboratories, and directed two clinical fellowship programs. He has been honored with several national awards, although the ones closest to his heart are the awards for teaching and mentorship given to him by his students and trainees.



Pictured: Research Team - Michael Crawford, Tommy Lee, Nitin Karandikar and Sushmita Sinha

### The Karandikar Research Laboratory

Dr. Karandikar is internationally known for his research into immune interactions that underlie disease progression and regulation of immune-mediated diseases, including multiple sclerosis (MS). He was recently presented with the prestigious Reingold Award from the National Multiple Sclerosis Society at a ceremony in New York. This award honors Dr. Karandikar's most outstanding research proposal entitled, "CNS-Specific Regulatory CD8+ T cells in Autoimmune Demyelination," and includes a 4-year grant award from the NMSS. Dr. Karandikar's

research is also supported by multiple grant awards from the National Institutes of Health.

His research has been investigating the role of a group of immune system cells in multiple sclerosis and other immune diseases and aims for new insights into MS immunopathology and new targeted therapeutic strategies. Through studies in human MS and its animal model, experimental autoimmune encephalomyelitis (EAE), his group is dissecting the role of autoreactive and immune regulatory CD8+ and CD4+ T-cells in the intrinsic as well as therapeutic modulation of disease. An additional intent of these studies is to unveil the regulatory components of the healthy immune system. His group is closely involved in several collaborative projects, including In Vitro allogenesis in hematopoietic stem cell transplantation to alleviate graft-versus-host disease, mechanistic dissection of immune therapy of asthma and clinical projects involving immunophenotypic characterization and multi-modality diagnostics of hematolymphoid disorders and the development and evaluation of newer diagnostic test technologies in cellular immunology and clinical flow cytometry.

On the personal front, Dr. Karandikar likes to spend most of his time with his wife, Ashwini, and 7-year old son, Ankur. His hobbies include swimming, music and drama. Over many years, he has performed, produced, written and directed multiple plays, and musicals, mainly in Indian forums [serving as a composer, playwright, actor, director and singer]. His most recent production was an invited, 90-minute musical play [which he wrote, composed and directed] performed at the Arie Crown Theater in Chicago by a team of 40 amateur artists from Dallas. Dr. Karandikar hopes to continue these pursuits in Iowa City and neighboring areas.

### Recent Publications

[Modulation of immune function occurs within hours of therapy initiation for multiple sclerosis.](#)

Ayers CL, Mendoza JP, Sinha S, Cunnusamy K, Greenberg BM, Frohman EM, **Karandikar NJ**.

Clin Immunol. 2013 May; 147(2):105-19. doi: 10.1016/j.clim.2013.02.015. Epub 2013 Mar 6.

[The Disease-Ameliorating Function of Autoregulatory CD8 T Cells Is Mediated by Targeting of Encephalitogenic CD4 T Cells in Experimental Autoimmune Encephalomyelitis.](#)

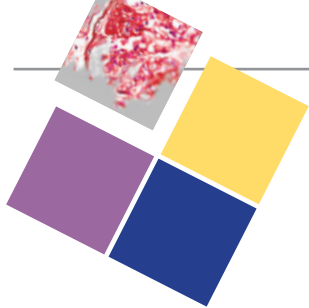
Ortega SB, Kashi VP, Tyler AF, Cunnusamy K, Mendoza JP, **Karandikar NJ**.

J Immunol. 2013 Jul 1;191(1):117-126. Epub 2013 Jun 3.

[CD8+ T Cells Are Required For Glatiramer Acetate Therapy in Autoimmune Demyelinating Disease.](#)

Tyler AF, Mendoza JP, Firan M, **Karandikar NJ**

PLoS ONE 8(6): e66772. doi:10.1371/journal.pone.0066772. 2013 June 21.



# UIDL Corner

A national reference laboratory of the Department of Pathology, University of Iowa Carver College of Medicine.

## New Tests

**Hepatitis C Virus Genotyping,**  
Plasma – 1a/1b subtyping

**Herpes Simplex Virus (HSV) 1 & 2**  
Type Specific IgG ABS (Glycoprotein G), Plasma

**HSV 1 & 2 Typing and VZV**  
Qualitative PCR, CSF, Vesicle Fluid, Surface Swab

**HSV Qualitative PCR, CSF, Vesicle Fluid,** Surface Swab

**HIV Antigen/Antibody Combo,**  
HIV Quant version 2.0 with dual target and lower limit of detection (20 copies/ml) on the Cobas

**Varicella Zoster Virus (VZV) IgG**  
Detection, Plasma

For detailed information about ordering these new tests, please go to our test directory at:  
[www.healthcare.uiowa.edu/uidl](http://www.healthcare.uiowa.edu/uidl)



UI Diagnostic Lab  
Department of Pathology  
200 Hawkins Drive 5231 RCP  
Iowa City IA 52242-1087  
Toll-free: 1-866-844-2522  
Website and Test Directory:  
[www.healthcare.uiowa.edu/uidl](http://www.healthcare.uiowa.edu/uidl)

## FASTER Core Lab Testing Now Available

Matthew Krasowski, M.D., Ph.D., Director of Clinical Pathology

The following tests are now performed in Core Laboratory and final reports can be faxed within **3-4 HOURS** of specimen receipt:

### CHEMISTRIES

Alpha-1-antitrypsin  
Angiotensin converting enzyme (ACE)  
Beta-2-microglobulin  
Ceruloplasmin  
Cystatin C  
Ferritin  
Folate  
NT-proBNP  
Prealbumin  
PSA, free  
Soluble transferrin receptor  
Vitamin B12  
Vitamin D (25-hydroxy)  
Luteinizing hormone (LH)  
Parathyroid hormone (PTH)  
Progesterone  
Prolactin  
T3 (triiodothyronine)  
T3 (triiodothyronine), free  
Testosterone  
Testosterone, free and total

### ENDOCRINOLOGY AND TUMOR MARKERS

Alpha-1-antitrypsin  
Angiotensin converting enzyme (ACE)  
Beta-2-microglobulin  
Ceruloplasmin  
Cystatin C  
Ferritin  
Folate  
Prealbumin  
PSA, free  
Soluble transferrin receptor

### FETAL TESTING

Lamellar body count (fetal lung maturity)  
OD450 on amniotic fluid

### INFECTIOUS DISEASE SEROLOGIES

CMV IgG antibodies  
CMV IgM antibodies  
EBV full panel (heterophile IgM, VCA IgG, VCA IgM, EBNA)  
EBV acute panel (heterophile IgM, VCA IgM)  
Hepatitis B virus surface antigen (HBsAg)  
Hepatitis B virus surface antibody (HBsAb)

### INFECTIOUS DISEASE (CONT'D)

Hepatitis A virus antibodies, IgM  
Hepatitis A virus antibodies, total  
Hepatitis B core antigen, total antibodies  
Hepatitis B core antigen, IgM antibodies  
Hepatitis C virus antibodies  
HIV antigen/antibody combo  
HSV-1 specific IgG  
HSV-2 specific IgG  
Measles IgG antibodies  
Mumps IgG antibodies  
Rubella IgG antibodies  
Rubella IgM antibodies  
Varicella-Zoster IgG antibodies

### THERAPEUTIC DRUG MONITORING

Acetaminophen  
Amikacin  
Carbamazepine  
Cyclosporine  
Digoxin  
Everolimus  
Levetiracetam (Keppra)  
Lamotrigine (Lamictal)  
Lidocaine  
Lithium  
Methotrexate  
Phenytoin  
Phenytoin, free  
Sirolimus (Rapamycin)  
Tacrolimus  
Theophylline  
Tobramycin  
Valproic acid

### TOXICOLOGY

Ethanol volatile panel (toxic alcohols)  
Ethylene glycol (rapid immunoassay)

### IMMUNOLOGY

Anti-CCP  
C3  
C4  
Kappa/lambda free light chains (serum)  
IgA  
IgE  
IgG  
IgM  
Rheumatoid factor



## Diabetic Nephropathy: Fighting a “Multi-Edged” Sword Reasoning behind performing renal biopsies “for a cause” in patients with long standing diabetes mellitus

**Dannie Holanda, M.D.**

Clinical Assistant Professor, Renal Pathology, Department of Pathology

### What you see is (*not always*) what you get...

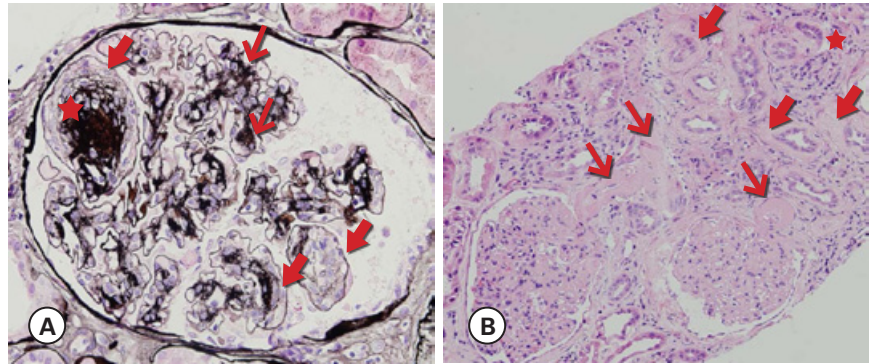
Diabetic nephropathy (DN) is the single most common disorder leading to renal failure in adults. It is also one of the most common causes of nephrotic range proteinuria and nephrotic syndrome in this population group.

DN develops as a consequence of diabetes mellitus (DM), both types 1 and type 2 (DM1 and DM2), and also in other types of DM (drug induced, gestational, etc.). Although the underlying pathologic mechanisms (e.g. autoimmune versus metabolic), genetic profiles, and age of onset vary among different types of DM patients, the renal biopsy findings of DN are usually the same in all DM types.

Renal biopsy findings highly suggestive of DN in the glomeruli are: mesangial expansion (usually in a nodular configuration) and nodular glomerulosclerosis (figure A), which is usually positive for silver stain (“Kimmelstiel-Wilson lesion”). Nearly pathognomonic in the past, nodular mesangial expansion is not considered as specific of DN as it once was, and can be recognized in other conditions involving the kidney (e.g., in smokers, renal amyloidosis, chronic glomerulonephritis, among others) of non-diabetic individuals. Nonetheless, particularly if a positive history of DM is given, these glomerular changes remain extremely helpful in establishing a diagnosis of DN. Other common biopsy findings of variable specificity of DN in the glomeruli are: glomerular enlargement, which can be the only biopsy finding in very early stages of DN, and capillary loop alterations, with glomerular basement membrane increase in thickness and “remodeling.” Development of microangiopathic changes is also a feature of DN, and includes capillary loop “splitting,” micro-aneurysms (loss of capillary loop attachments to mesangium, leading to marked capillary loop dilatation, figure A), and “mesangial interposition,” which, in a simplified manner, is seen as “slippage” of mesangial cell portions into within the “split” glomerular capillary loops.

### A smoldering flame can always spit fire...

Advancing DN glomerulopathy ultimately progresses to global glomerulosclerosis. Changes involving renal compartments other than the glomeruli in advancing DN chronicity include hyaline deposition in renal arterioles, which can be quite remarkable



Figures A. and B. Diabetic nephropathy (DN). Figure A (Jones silver stain, 400x magnification). An enlarged glomerulus showing nodular glomerulosclerosis, or Kimmelstiel-Wilson (“K-W”) lesion, of diabetic nephropathy, which is positive for Jones silver stain (star). Also noted are nodular, also silver positive, mesangial expansion (arrowheads), and capillary microaneurysms, containing cellular elements, some in peripheral relation to the K-W lesion (thick arrows). Figure B (hematoxylin and eosin stain, 100x magnification). Severe hyalinosis of the arteriolar walls, which has a nodular pattern seen in some areas, quite remarkable at the glomerular hilum (arrowheads). Also noted at the top right (star), are interstitial fibrosis and tubular atrophy, with markedly thickened tubular basement membranes (thick arrows). Also note, the relatively acellular nodular mesangial expansion, as compared to markedly cellular glomeruli of acute post-infectious glomerulonephritis (PIGN) superimposed on DN, which are represented on figures D and E.

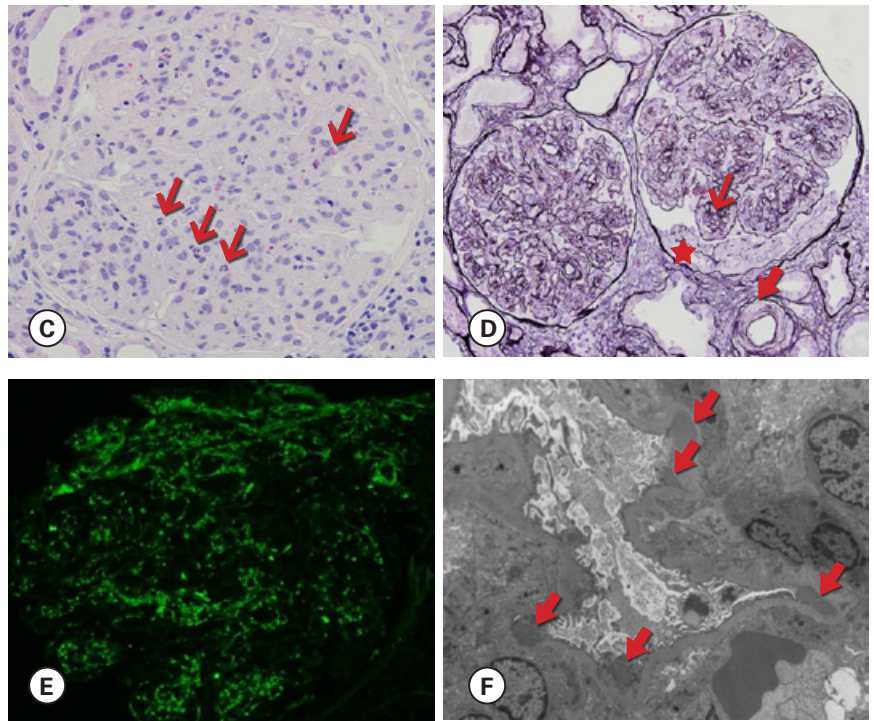
and occupy the entire arteriolar wall thickness (figure B), and interstitial fibrosis and tubular atrophy, or scarring of the tubulo-interstitium (figure B).

As seen structurally in renal tissue, adaptations and alterations in DN can also be analyzed functionally as a progressing process. And they generally tend to correlate with the glomerular changes seen on biopsy. In early phases of DM, (glomerular enlargement, regarded as an “adaptive phase”), there is an increase in glomerular filtration rate (GFR), called “hyperfiltration.” This mechanism is glucose-dependent, and can be corrected with good glycemic control. In this phase, an increase in the overall kidney size actually occurs. The mechanisms have been demonstrated, and elegantly described by Satriano and Vallon. In a simplified manner, vasoactive mediators promote afferent arteriolar dilation, causing glomerular hyperperfusion. Glucose, glucose-derived advanced glycation end products (AGEs) and Angiotensin II enhance the production of TGF- $\beta$  in mesangial cells (which may then proliferate and produce increased matrix) and podocytes. With podocyte involvement and disturbance of the foot process integrity, and tubular epithelial cell alterations, microalbuminuria (30-300 mg/day of albumin excretion in the urine) may develop, followed by proteinuria (albuminuria >300 mg/day). Although

variable, overt proteinuria can be observed by an average of 15 years after onset of DM. This is observed as progressive increase in protein spillage into the urine, to nephrotic range (>3- 3.5 g/day of protein in urine), along with progressive chronic kidney disease (CKD). According to Gall et al., if compared with the background population, mortality in patients with Type 1 diabetes and without proteinuria is elevated two-fold to three-fold; in contrast, it is increased 20- to 200-fold in patients with proteinuria.

A relatively well established correlation can be seen between the different clinical (functional) stages of DN and its structural (biopsy) findings. This correlation has been reliably studied by Mogesen et al., in DM1 patients but can also be observed, although not with such tight correlation, in DM2 patients, probably due to other microvasculature (hemodynamic) alterations taking place in DM2. According to this scheme, there can be several years of an otherwise relatively “compensated” (or “steadily declining”) renal function, along with a steady increase in proteinuria. It is during or after the advanced stages of DN that a more “downhill” decline in GFR can happen, with a somewhat sharp rise in proteinuria to well into, and even to way above the minimal ranges of nephrotic proteinuria. Experienced in our practice, is that proteinuria may be extremely high, and largely surpass the nephrotic mark, in advanced DN.

On one hand, this trending DN progression tendency gives a relative disease predictability and guidance towards the “what to expect” of DN progression clinically. But it may also be right around the advanced stages of DN (“sharp decline” of GFR plus a “sharp increase” in proteinuria), especially in patients that for various reasons may have an irregular or a difficult follow up, that concerns may rise regarding the potential causes. DN patients may be biopsied to rule out acute or ongoing coexisting causes for renal decompensation other than DN. In addition, if hematuria and red blood cell (RBC) casts are present in the urine in this setting, they may arise as an even more diagnostically problematic setback in deciding clinically if the picture is of solely progressing DN. Hematuria, and even erythrocyte casts in the urine, although much less common than proteinuria, can also occur in DN without association with any other apparent causes. A correlation study by O’Neill and Walker et al. described hematuria in up to 30%, and RBC casts in up to 13% of patients with DN and no other causes of glomerulonephritis. Another study by Matsumura et al. observed that when present without other co-existing causes of glomerulonephritis (e.g., immune-complex glomerulonephritis), hematuria in DN is usually accompanied by overt proteinuria, and suggests advanced stages of the disease. Also noted in this study was that, in patients with DM and hematuria, biopsies showing glomerular capillary microaneurysms occur more often in patients with than without hematuria.



Figures C, D, E and F: acute post infectious glomerulonephritis (PIGN). Figure D (Hematoxylin and eosin stain, 400x magnification). “Proliferative” glomerulus, showing a lobulated appearance, and increased circulating neutrophils and eosinophils (arrowheads). Figure E (Jones silver stain, 200x magnification). Although some findings might be attributed to underlying diabetes involving the kidney, with arteriolar wall hyalinosis (arrow), and, to some extent a nodular glomerular mesangial expansion (arrowhead), when compared with the glomerulus of figure A (from diabetes nephropathy), which does not have global endocapillary hypercellularity, these glomeruli show evidence of active glomerulonephritis, and a cellular crescent (star). Figure F (direct immunofluorescence antibody staining to complement C3). Granular and “chunky” bright positive glomerular staining for C3. Figure G (electron microscopy, 3000x direct magnification): Glomerular subepithelial “hump-like” immune complex mediated type electron dense deposits of PIGN.

On the other hand, it is exactly because of such well-established disease relationship progression, that an assumption may take place clinically that, when a faster than steady renal decompensation and severe proteinuria take place, they can be explained as decompensation from “the natural course of DN.” An expected, but not always correct clinical diagnosis of solely DN may then ensue as a cause, while other potential causes for glomerular diseases, could be “masked” by these otherwise expected DM clinical findings. Immune-complex glomerulonephritis, membranous nephropathy, some “rapidly progressing” variants of focal segmental glomerulosclerosis (e.g., collapsing or cellular variants), or renal amyloidosis are some examples.

### The “Lernaean Hydra”

Far from being a novelty statement, it is known that patients with DM have increased susceptibility to bacterial infections. Not uncommonly, patients with poorly controlled DM are hospitalized due to difficult to treat infections, such as cellulitis and osteomyelitis. When found to have renal failure, proteinuria, hematuria and RBC casts in urine, such patients may be biopsied during hospitalization, to rule out, for example, post-infectious glomerulonephritis (PIGN). As real clinico-pathological correlation examples, biopsy figures A and B represent the glomeruli and vessels of a 60 year-old male patient with DM for several years, hospitalized for management of a difficult

continued on page 8

# Updates in Diagnostic Immunohistochemistry: Expanded Offerings from the University of Iowa Immunopathology Laboratory



## **Andrew M. Bellizzi, M.D.**

Clinical Assistant Professor, Department of Pathology; Co-Director of Immunopathology Laboratory; Associate Director of Surgical Pathology Fellowship Program; Co-Director of GI Pathology, Holden Comprehensive Cancer Center; College of American Pathologists Immunohistochemistry Committee Member

Phone: 319-356-4436

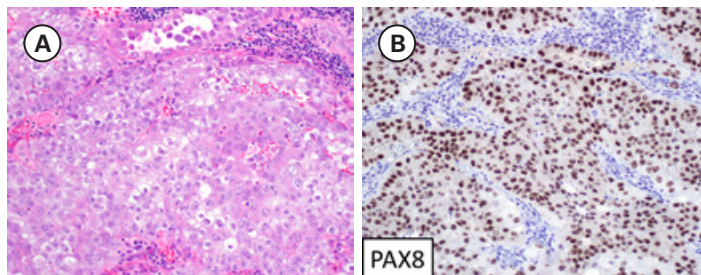
Email: [andrew-bellizzi@uiowa.edu](mailto:andrew-bellizzi@uiowa.edu)

### **Introduction:**

The purpose of this column is to describe newly implemented diagnostic immunohistochemical tests now available at the University of Iowa Hospitals and Clinics. The intention is for this column to run in each issue of PathBeat during an anticipated period of test expansion. For each protein, the biologic and diagnostic relevance will be discussed and an illustrative case(s) provided. In the last issue I reviewed the mismatch repair proteins, MLH1, PMS2, MSH2, and MSH6. Since that time we have adopted testing for the following: PAX8; HHV-8; IgG4 and IgG; MDM2 and CDK4. Themes to be stressed are that the expansion of one's test menu to include antibodies of greater specificity allows for improved diagnostics and may *decrease* the number of immunostains ordered in an individual case. The impetus behind this test menu expansion is the opportunity to bring a golden age of developmental biologic and molecular genetic discovery to paraffin.

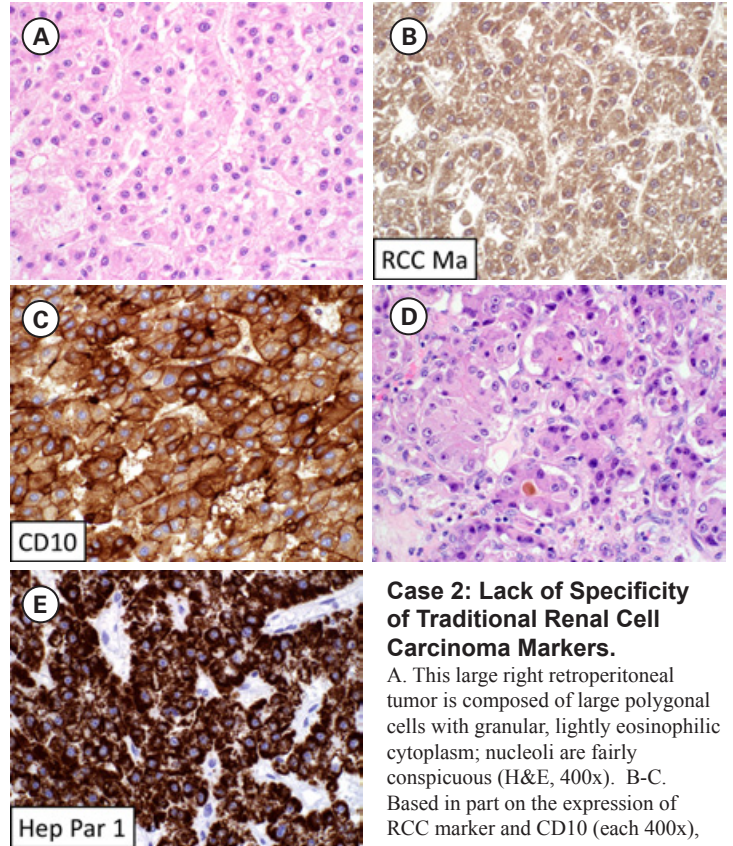
### **Paired Box Gene 8 (PAX8):**

**Background:** *PAX8*, one of 9 paired-box genes, encodes a transcription factor involved in thyroid, kidney, and Müllerian tract development. It is especially critical in the thyroid, with germline mutations resulting in congenital hypothyroidism. *PAX8* has emerged as a key diagnostic tool to identify carcinomas of the thyroid, kidney (see Case 1), and Müllerian tract. An advantage, compared to some traditional diagnostic markers, is relatively good retention of expression in anaplastic thyroid carcinoma and sarcomatoid renal cell carcinoma. In kidney, it overcomes the lack of specificity of markers like RCC Ma, CD10, and vimentin (see Case 2) and functions well as a "stand alone" marker. *PAX8* is also expressed by parathyroid and thymic tumors. Polyclonal *PAX8* (but not monoclonal



### **Case 1: PAX8 Immunohistochemistry in Renal Cell Carcinoma.**

A. This 13 cm tumor involved the upper kidney and adrenal gland and at least focally expressed CD10, melan-A, and inhibin. It was considered indeterminate for a renal vs. adrenal cortical primary (H&E, 200x). B. The tumor diffusely, strongly expresses PAX8, supporting a renal origin (200x).



### **Case 2: Lack of Specificity of Traditional Renal Cell Carcinoma Markers.**

A. This large right retroperitoneal tumor is composed of large polygonal cells with granular, lightly eosinophilic cytoplasm; nucleoli are fairly conspicuous (H&E, 400x). B-C. Based in part on the expression of RCC marker and CD10 (each 400x), a diagnosis of clear cell renal cell carcinoma was rendered. Based on gross features, this diagnosis was questioned, and D. re-examination of the tumor revealed apparent bile formation (H&E, 400x). E. The presence of hepatocellular differentiation is confirmed with Hep Par 1 staining (400x).

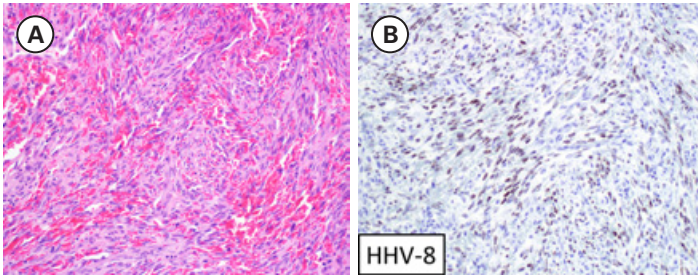
*PAX8*) is positive in about half of pancreatic neuroendocrine tumors (NETs), attributable to cross-reactivity with *PAX6* and *PAX4*, and is not positive in midgut NETs. We adopted a polyclonal *PAX8* antibody because of this "added value" application, which comes without sacrificed sensitivity in thyroid, kidney, and Müllerian carcinomas. Immunohistochemistry (IHC) for *PAX2* is also commercially available, but in head-to-head comparisons with *PAX8*, the latter has proven more sensitive in renal and Müllerian carcinomas, and *PAX2* is not expressed in the thyroid.

**Key Reference:** Ordonez NG. Value of PAX 8 immunostaining in tumor diagnosis: a review and update. *Advances in Anatomic Pathology*. 2012;19(3):140-51.

### Human Herpesvirus 8 (HHV-8):

**Background:** HHV-8, also known as Kaposi sarcoma (KS)-associated herpesvirus, was discovered by Patrick Moore and Yuan Chang (the same husband-and-wife team that described Merkel cell polyomavirus; discussed in the last issue of PathBeat), who performed “representational difference analysis” on KS tissues and non-lesional tissues from the same HIV-infected patients. In their landmark *Science* paper they reported finding HHV-8 sequences in 93% of 27 KS samples from AIDS patients, 15% of 39 lymph nodes and lymphomas from AIDS patients, and 0% of 36 lymph nodes and lymphomas from non-AIDS patients. In addition to its etiologic link to KS, HHV-8 is also detected in most cases of multicentric Castleman disease, as well as plasmablastic and primary effusion lymphomas. We adopted HHV-8 IHC as a supportive marker for these diagnoses (see Case 3). The antibody is directed against the virus’s latent nuclear antigen.

**Key Reference:** Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, Moore PS. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi’s sarcoma. *Science*. 1994;266(5192):1865-9.



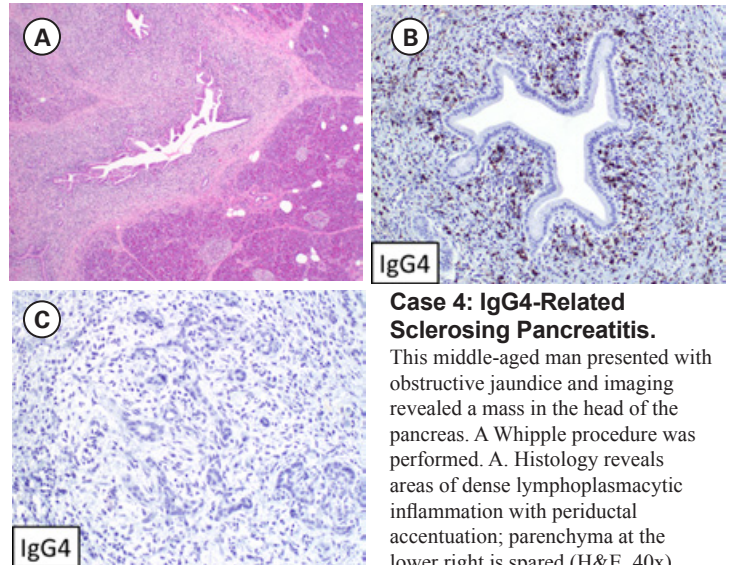
### Case 3: HHV-8 Immunohistochemistry in Kaposi Sarcoma.

An older woman from the Middle East presented with two subcentimeter violaceous papules on the calf and foot. She had been seen for similar lesions 5-years ago. HIV-testing was negative. A. The sections show a cellular spindle cell lesion disposed as haphazardly arranged fascicles with sieve-like vascular spaces. There is only minimal cytologic atypia (H&E, 200x). B. Kaposi sarcoma universally expresses HHV-8, regardless of clinicoepidemiologic features (200x).

### Immunoglobulin G4 (IgG4) and IgG:

**Background:** IgG4 is the least frequent IgG subclass, representing ~5% of total IgG. A family of diseases, of which autoimmune pancreatitis (AIP) type I represents the most familiar example, is typified by marked tissue infiltration by IgG4-expressing plasma cells and, histologically, by lymphoplasmacytic inflammation, follicular lymphoid hyperplasia, storiform fibrosis, sclerosis, and obliterative phlebitis (see Case 4). Other commonly affected sites/diseases include the extrahepatic biliary tree, gallbladder, liver, lacrimal gland, periorbital soft tissue, submandibular gland (Kuttner tumor), retroperitoneum (some cases of retroperitoneal fibrosis), mesentery, mediastinum (some cases of sclerosing mediastinitis), aorta, lung, pleura, breast, kidney, urinary tract, skin, central nervous system, thyroid (Reidel thyroiditis; some cases of Hashimoto thyroiditis), and lymph node. These have been unified under the rubric of “IgG4-related sclerosing disease.” Involvement of multiple organ sites, either synchronously or metachronously, is very common.

In addition to the total number of IgG4-expressing plasma cells, the ratio of IgG4-positive:total IgG-positive plasma cells is of interest, based on the premise that, if IgG4 normally represents



### Case 4: IgG4-Related Sclerosing Pancreatitis.

This middle-aged man presented with obstructive jaundice and imaging revealed a mass in the head of the pancreas. A Whipple procedure was performed. A. Histology reveals areas of dense lymphoplasmacytic inflammation with periductal accentuation; parenchyma at the lower right is spared (H&E, 40x).

B. IgG4 staining revealed up to 75 positive plasma cells per high-power field (150x). The IgG4:IgG ratio approached 100% (not depicted). C. By comparison, this obstructive chronic pancreatitis from a patient with an adjacent carcinoma is totally negative for IgG4 (200x).

5% of total IgG, in tissues very densely infiltrated by plasma cells the number of IgG4-positive plasma cells may be “falsely” increased in the absence of an IgG4-related sclerosing disorder. Various thresholds for a “positive” test exist. The commonly used Mayo Clinic HISORt (histology, imaging, serology, other organ involvement, response to steroid therapy) criteria refer to the presence of  $\geq 10$  IgG4-positive plasma cells per high-power field (HPF) as “diagnostic” of AIP. In an incredibly comprehensive review of the histopathology of this class of lesions, Wah Cheuk and John Chan present their much stricter diagnostic criteria, in which cases must show 1. typical histology, 2.  $>50$  IgG4-positive cells per HPF, and 3. IgG4:IgG  $>40\%$  (2 and 3 are calculated as an average of the 3 most densely positive fields).

We have adopted IgG4 and IgG IHC, since the early recognition of this steroid-responsive class of diseases directs therapy, allaying disease complications and in some cases preventing a major surgery. Although serum IgG4 testing is available, it may be normal in up to 30% of cases and mildly elevated in other conditions.

**Key Reference:** Cheuk W, Chan JK. IgG4-related sclerosing disease: a critical appraisal of an evolving clinicopathologic entity. *Advances in Anatomic Pathology*. 2010;17(5):303-32.

### Mouse Double Minute 2 Homolog (MDM2) and Cyclin-Dependent Kinase 4 (CDK4):

**Background:** Liposarcoma can be broadly divided into 3 groups: 1. atypical lipomatous tumor (ALT)/well-differentiated liposarcoma (WDLPS) and dedifferentiated liposarcoma (DDLPS), 2. myxoid/round cell liposarcoma (characterized by *DDIT3* rearrangement), 3. pleomorphic liposarcoma (a cytogenetically complex high-grade sarcoma in which scattered lipoblasts are found). The first group of tumors is most common. The term ALT is used in the extremities and trunk (surgically amenable sites), while WDLPS is applied in the retroperitoneum, mediastinum, and spermatic cord, where recurrences are almost the rule. Neoplastic progression manifests as transformation to DDLPS. While ALT/WDLPS

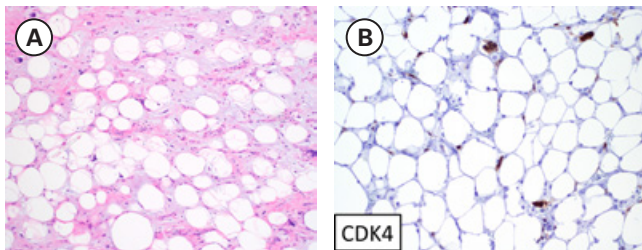
continued on page 8

## Diagnostic Immunohistochemistry *continued*

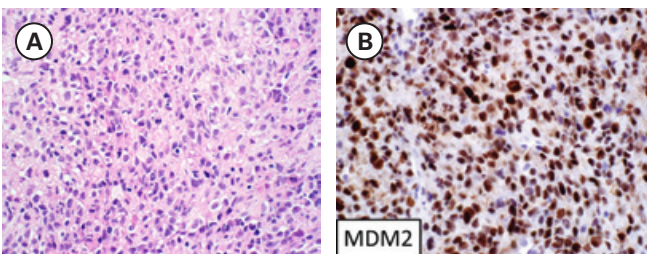
is a non-metastasizing lesion, progression to DDLPS denotes metastatic risk, on the order of 15%.

Karyotypically, ALT/WDLPS/DDLPS are characterized by the presence of giant marker and/or supernumerary ring chromosomes. These are composed of amplified genetic material from 12q14-15, which contains the *MDM2* and *CDK4* loci. While the former is nearly universally amplified, *CDK4* is not in up to 15% of ALT/WDLPS. These proteins are pathogenetically relevant, with *MDM2* and *CDK4* overexpression leading to p53 and Rb inactivation, respectively. Overexpression can be detected immunohistochemically. *MDM2* and *CDK4* IHC are useful in distinguishing ALT/WDLPS from benign lipomas (with reactive changes) and other well-differentiated adipocytic tumors (see Case 5) and DDLPS from other high-grade malignant neoplasms (see Case 6). IHC results must be interpreted in context, as *MDM2*-positivity may also be seen in a fraction of other tumor types, including malignant peripheral nerve sheath tumor, myxofibrosarcoma, and rhabdomyosarcoma. Positivity for both *MDM2* and *CDK4* improves specificity.

**Key Reference:** Binh MB, Sastre-Garau X, Guillou L, de Pinieux G, Terrier P, Lagace R, et al. *MDM2* and *CDK4* immunostainings are useful adjuncts in diagnosing well-differentiated and dedifferentiated liposarcoma subtypes: a comparative analysis of 559 soft tissue neoplasms with genetic data. *The American Journal of Surgical Pathology*. 2005;29(10):1340-7.



**Case 5: *MDM2/CDK4* Immunohistochemistry in Well-Differentiated Lipogenic Tumors.** A. Incisional biopsy of this 9 cm spermatic cord tumor was originally diagnosed as myxoid liposarcoma based on the presence of myxoid areas and a somewhat delicate branching vascular pattern. Note the scattered bizarre stromal cells, which suggest the correct diagnosis of well-differentiated liposarcoma (WDLPS) (H&E, 100x). B. In this diagnostic context, diffuse, strong staining of the atypical cells for *CDK4* and *MDM2* (not depicted) confirms the diagnosis of WDLPS (200x).



**Case 6: *MDM2/CDK4* Immunohistochemistry in Dedifferentiated Liposarcoma.** A. Core biopsy from a 40 cm retroperitoneal tumor demonstrates an undifferentiated neoplasm composed of sheets of epithelioid cells with brisk mitotic activity (H&E, 400x). After performing 17 immunostains a diagnosis of “malignant neoplasm,” indeterminate for sarcoma, carcinoma, and even lymphoma was rendered. B. This clinicopathologic scenario is typical of dedifferentiated liposarcoma and diffuse, strong *MDM2* and *CDK4* (not depicted) expression strongly suggested that diagnosis (400x). On the subsequent resection a small residual well-differentiated component was identified, firmly securing the diagnosis.

## Diabetic Nephropathy *continued*

to treat methicillin-resistant staphylococcus aureus (MRSA) infection of the foot. During his hospital course he was found to have 7g of proteinuria, hematuria, RBC urine casts, and “acute-on-chronic” renal failure. The biopsy performed to rule out glomerulonephritis showed DN with typical nodular glomerulosclerosis, severe arteriolar hyalinosis, and up to 40% tubulo-interstitial scarring. There was no evidence for an “active” immune-complex glomerulonephritis by light, immunofluorescence or electron microscopy, and a Congo red stain for amyloid was negative. In contrast, figures D, E and F show the biopsy of a 54 year-old female patient, with DM for several years, hospitalized for treatment of pseudomonas osteomyelitis of the leg, and found during hospitalization to have low GFR, nephrotic range proteinuria, hematuria and urine RBC casts. Clinically, although suspicion was that these could be due to the patient’s DM, given that a baseline creatinine was not known, and to exclude other potential causes for the clinical picture, a biopsy was performed, and showed acute PIGN, superimposed on findings of DN.

### “Bending” the blades...

Diagnosing DN solely based on clinical grounds can be extremely challenging, as DN may overlap with or “complicate” other causes of glomerular diseases. DN itself can also “decompensate” clinically, after several years of disease, giving the erroneous impression of acute renal failure due, for example, to rapidly progressing glomerulonephritis. Positive laboratory findings in these patients (e.g., marked decrease in GFR over a short period of time, “sudden” marked worsening of proteinuria, and presence of hematuria and RBC casts), although helpful in triaging which patients should be biopsied, may bear difficulties in establishing a clinical diagnosis. Deciding a specific treatment regimen on clinical grounds only becomes difficult, especially given that immunosuppressive corticosteroid therapy, usually a frequent treatment of choice for glomerulonephritis, is relatively contraindicated and can worsen diabetes. Renal biopsy remains extremely helpful in establishing a diagnosis of DN and is also a valuable tool to exclude or diagnose co-existence, as well as disease activity and tractability of other causes of nephropathy in patients with DM with or without DN, such as immune-complex glomerulonephritis, FSGS, renal amyloidosis, among others.

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# Active Research Awards

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[Dr. Vladimir Badovinac](#) has a new collaborating research agreement with Dr. Thomas Griffith from the Minneapolis VA Health Care System. The title of this project is *Suppression of T cell immunity during sepsis*. The contract total is \$108,523. This contract is for the period of October 1, 2012 and should be complete by September 30, 2014.

[Dr. Daniel Diekema](#) has a new research contract negotiated with bioMerieux, Inc. for a research project titled *VITEK 2 and VITEK 2 Compact AF03 Antifungal Susceptibility Tests*. The contract total is \$79,225. This contract is for the period of July 1, 2012 through July 1, 2013.

[Dr. Daniel Diekema](#) has a continuation of research contract negotiated with Cerexa, Inc. for a research project titled *Tracking Resistance in Streptococcus pneumoniae (TRISP II)*. The contract total is \$334,500. This contract is for the period of June 26, 2012 through August 15, 2013.

[Dr. Carol Holman](#) received a University of Iowa and Mayo Clinic SPORC Career Development Award. The title of the project is *Immunohistochemical methods for predicting outcome of patients with post-transplant lymphoproliferative disorder-diffuse large B-cell lymphoma*. The amount of this award is \$48,726. The period for this project is December 1, 2012 through November 30, 2013.

[Dr. Siegfried Janz](#) received a notice of Shared Instrumentation (S10) funding from the National Institutes of Health. The title of the project is *Leica LMD 7000 Laser Capture Microdissection Microscope*. This award is for the period of July 1, 2013 through July 10, 2014. The amount of this award is \$216,933.

[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. The period for this project is April 1, 2013 through March 31, 2017.

[Dr. Nitin Karandikar](#) received grant funding for a one year continuation from the National Institute of Health/National Institute of Allergy and Infectious Diseases (NIH/NIAID). The title of this project is *Role of T cells in the immunomodulation of MS*. The total direct costs for this award are \$127,397. The period for this project is February 1, 2013 through January 31, 2014.

[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, 2014.

[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](#) received a notice of R56 funding from the National Institutes of Health to continue his project with the title of *Role of Dendritic Cells in Immunity to Pulmonary Influenza Virus Infections*. This additional funding total is \$335,471 and is for the period of April 10, 2013 and should be complete by March 31, 2014.

[Dr. Deqin Ma](#) has a new research contract negotiated with Ventana Medical Systems, Inc. for a research project titled *CINtec Histology Study*. The contract total is \$15,000. This contract is for the period of October 8, 2012 and should be complete by December 31, 2013.

[Dr. Andrean Simons-Burnett](#) received an American Cancer Society (ACS) Seed Grant Award from the Holden Comprehensive Cancer Center at the University of Iowa. The title of the project is *NOX4-mediated autophagy and glucose metabolism associated with resistance to Erlotinib in HNSCC*. The amount of this award is \$30,000. The period for this project is July 1, 2012 through June 30, 2013.

[Dr. Weizhou Zhang](#) received a notice of R00 funding from the National Institutes of Health. The title of the project is *Myofibroblasts, T Cells and Malignant Cells Interplay in Breast Cancer Metastasis*. This award is for the period of July 1, 2012 through June 30, 2015. The amount of this award is \$735,752.



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[Deficiency of Nox2 prevents angiotensin II-induced inward remodeling in cerebral arterioles.](#) Chan SL, **Baumbach GL.** *Front Physiol.* 2013 Jun 26;4:133.

[Sleep disturbance, distress, and quality of life in ovarian cancer patients during the first year after diagnosis.](#) Clevenger L, Schrepf A, Degeest K, Bender D, Goodheart M, Ahmed A, **Dahmouh L**, Penedo F, Lucci J 3rd, Thaker PH, Mendez L, Sood AK, Slavich GM, Lutgendorf SK. *Cancer.* 2013 Jun 24.

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[The Disease-Ameliorating Function of Autoregulatory CD8 T Cells Is Mediated by Targeting of Encephalitogenic CD4 T Cells in Experimental Autoimmune Encephalomyelitis.](#) Ortega SB, Kashi VP, Tyler AF, Cunnusamy K, Mendoza JP, **Karandikar NJ.** *J Immunol.* 2013 Jun 3.

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## Faculty

# AWARDS AND RECOGNITIONS



### Dr. Karandikar Receives the 2012 Stephen C. Reingold Award

**Nitin Karandikar, M.D., Ph.D.**, (pictured on right) received the **2012 Stephen C. Reingold Award** in June by the National Multiple Sclerosis (MS) Society. This award honors Dr. Karandikar's most outstanding research proposal entitled CNS-specific Regulatory CD8+ T cells in Autoimmune Demyelination.

The National MS Society is a driving force of MS research and treatment to stop disease progression, restore function, and end MS forever.

Congratulations, Dr. Karandikar!

Photo Credit: Paul Schneiderman

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### Dr. Robinson Receives the 2013 Frank A. Mitros Excellence in Teaching and Clinical Service Award



**Robert Robinson, M.D., Ph.D.**, Professor of Pathology was presented with the “**Frank A. Mitros Excellence in Teaching and Clinical Service Award**” at a recent faculty meeting.

This award is presented annually to a clinical faculty member who provides outstanding performance in both the clinical and educational missions of the Department after nomination by peers.

The award was presented to Dr. Robinson by Dr. Mitros himself, who said “**Bob, you are truly deserving of this recognition for all that you have done for the members of this department, the medical school, and the community**”.

During the nominating process, one of Dr. Robinson's nominators wrote: “I'd nominate Bob Robinson.

**Clinical Mission:** Obviously an expert in Head and Neck Pathology but I also consider him the best anatomic pathologist in our Department. You can consult him on virtually anything including zebra cases at any general surgical path site, an unusual autopsy finding, cytology, dermatology, immunology workup, and molecular tests that might be helpful. Despite his heavy clinical workload and administrative duties, he is efficient...he gets his cases signed-out and doesn't leave his patients/clinicians/clients waiting in the lurch for his diagnosis. As far as dealing with sticky situations, he has the best approach I've seen as a junior faculty. He is calm, professional, and says the right things that pretty much always defuse the situation.

**Educational Mission:** I think residents/fellows consider him one of their favorite faculty to sign-out with on service. He teaches in a variety of courses in addition to his usual great teaching at the scope and in Surg Path/Cyto conferences. He always has useful advice when we are evaluating residents/fellows. He is stepping up to take over as Surgical Pathology Director with Barry's departure. Oh, and he wrote a Head and Neck book that our residents use everyday... I can't think of anyone more deserving in our department.”

Congratulations, Dr. Robinson!

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## Dr. Holanda Joins Renal Pathology Faculty



The Department of Pathology welcomes **Danniele Gomes Holanda, M.D.** as our newest faculty member. Dr. Holanda started on May 1, 2013, as Clinical Assistant Professor of Pathology and will mainly focus on running our renal pathology service.

After obtaining her M.D. from Universidade Federal do Ceara

in Brazil, Dr. Holanda completed her pathology residency training at the University of Maryland School of Medicine, followed by renal pathology, and transplantation pathology fellowships and a research scholarship in pathology at the Johns Hopkins University, the University of Pittsburgh Montefiore Hospital, and at the University of Iowa Hospitals and Clinics, respectively.

Dr. Holanda's main areas of interest in pathology are related to medical and allograft kidney, specifically mechanisms of glomerular podocyte injury, renal amyloidosis, and immune complex mediated glomerulonephritis. She also has a special interest in mechanisms of rejection in allograft kidneys and pancreas.

Dr. Holanda is married to Nuno Almeida, who is a political scientist, and has a six year-old son, Luis. She enjoys spending time with her family, dog Zoe, reading, writing, photography and listening to Brazilian Bossa Nova. She is best known in our Department as "Danni".

## Dr. Kirby Receives 2013 Resident Teaching Award



Congratulations to **Pat Kirby, FRCPath**, recipient of the **2013 Resident Teaching Award**. This award is given annually to a faculty member in the Department of Pathology who displays exemplary teaching and mentoring skills while working with the residents.

Presenting the award to Dr. Kirby at the recent Resident and Fellow Farewell Dinner, co-chief resident

Brittany Pakalniskis, M.D. offered the following perspectives of her resident colleagues:

*“She is remarkably passionate about her discipline and continues to amaze me in her breadth of knowledge and I can only hope to emulate her later on in my career....I think my next research project would be to work on cloning her. She's a phenomenal pathologist and a joy to work with....I love her one on one teaching - Dr. Kirby does a great job of tailoring teaching to my level. She makes even the most regular placenta interesting!”*



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## George D. Penick Award for Excellence in Education Presented to Dr. Steussy

Bryan Steussy, M.D., is the 2013 recipient of the **George D. Penick Award for Excellence in Education**. This award is presented annually to a Pathology Resident who displays excellence in and commitment to the education and teaching of medical students, peers, and clinical colleagues.

Dr. Steussy received the award at the Pathology Resident and Fellow Farewell Dinner held on May 10, 2013.

Congratulations, Bryan!

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The UI Pathology Department welcomes our  
**2013-2014 INCOMING CLASS OF RESIDENTS:**

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**Craig Dunseth, MD**  
B.A. Drury University, 2009  
M.D. University of Missouri-Columbia, 2013



**Thomas Keeney, MD**  
B.S. Creighton University, 2008  
M.D. Loma Linda University, 2013



**Sydney Rooney, MD**  
B.S. University of Pittsburgh, 2008  
M.D. University of North Dakota, 2013



**Katie Schouweiler, MD**  
B.S. University of North Dakota, 2008  
M.D. University of North Dakota, 2013

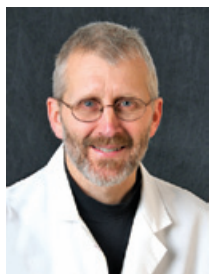


**Angela Wu, MD**  
B.S. University of California, Berkeley, 2008  
M.D. University of Minnesota, 2013

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## RESIDENCY LEADERS

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**Residency Program Director**

**Chris Jensen, MD**  
Clinical Professor  
Surgical Pathology  
Director of Cytopathology

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319-356-3217



**Assistant Residency Program Director**

**Leana A. Guerin, MD**  
Clinical Assistant Professor  
Surgical Pathology

[leana-guerin@uiowa.edu](mailto:leana-guerin@uiowa.edu)  
319-356-4432

For more information about our residency program, please contact:



**Pathology Residency Coordinator**

**Janet Delwiche, MA**  
Phone: 319-467-5193  
Email: [pathGMEcoord@uiowa.edu](mailto:pathGMEcoord@uiowa.edu)

Website: [www.medicine.uiowa.edu/pathology](http://www.medicine.uiowa.edu/pathology)

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## 2013–2014 PATHOLOGY STAFF ROSTER

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<b>Michelle Kurt MD, Co-Chief Resident</b>	R4
<b>Brittany Pakalniskis MD, Co-Chief Resident</b>	R4
Erica Savage MD	R4
Johanna Savage MD	R4
Bryan Steussy MD	R4

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Anna Dolezal MD	R3
Stephanie Fischer MD	R3
Omar Jaber MD	R3
Marisa Jacob MD	R3
Carolyn Rysgaard MD	R3
Stephanie Stauffer MD	R3

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Deema Alkapalan MD	R2
Ava Bhattarai MBBS	R2
Gagan Mathur MBBS	R2
Enas Yassin MBChB	R2

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Craig Dunseth MD	R1
Thomas Keeney MD	R1
Sydney Rooney MD	R1
Katie Schouweiler MD	R1
Angela Wu MD	R1

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## PATHOLOGY FELLOWS

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### Cytopathology

Michael Gailey DO  
James Lozano MD

### Hematopathology

Douglas Lynch MD

### Molecular Genetics

Ling Gao MD

### Surgical Pathology Fellows

Stacy Hitt MD  
Lori Sinclair MD  
Bryan Steussy MD  
Thomas Wilson MD

## PATHOLOGY EXTERNS

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Jonathan Davick	M3
Ipar (Zeynep) Demir	M2
Neha Dhungana	M2
Benjamin Dilger	M2
Renee Eigsti	M2
Emily McMullen	M2

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# Thank you!

The department thanks **Tom Wilson** and **Bryan Steussy** for their service over the past year as Co-Chief Residents. They have had numerous roles, including recruiting and scheduling, and have been active behind the scenes in maintaining and improving the quality of the program. We hope that the leadership skills they gained during this past year will serve them well in their future careers.

## Introducing the 2013-14 Chief Residents

Brittany Pakalniskis (left) and Michelle Kurt-Mangold (right) have been selected to serve as the University of Iowa Pathology Department's 2013-14 Co-Chief residents. Recently we asked each of them to share their thoughts about why they chose to become pathologists, and what they like best about their program:

### **Brittany:**

*I am a nerd at heart - in the best way possible! I have always enjoyed the more basic science-y part of medicine and my favorite component of caring for patients is making the diagnosis. Cancer biology is never boring, and I love how cerebral and behind-the-scenes pathology is.*

*The faculty and the residents here are intelligent, kind, collaborative, and a real pleasure to work with. After completing this program I feel confident that I will be as well prepared as possible for my first job thanks to all of these people who have contributed to my education.*

### **Michelle:**

*I chose pathology because it seemed to come naturally to me. After taking a histology course in undergraduate, I still remembered the microscopic appearance of tissues three years later when I took Pathology in medical school. At that point, I didn't necessarily know what a pathologist was, but I knew I liked what they did. For me, it's a great balance of interacting with clinicians and solitude at the microscope. I love the challenge it brings and can't imagine practicing any other type of medicine!*

*The best thing about our program is the camaraderie among the residents and staff. It is a great (and fun!) working environment that is mutually focused on education and patient care.*



Photo courtesy of Janet Delwiche