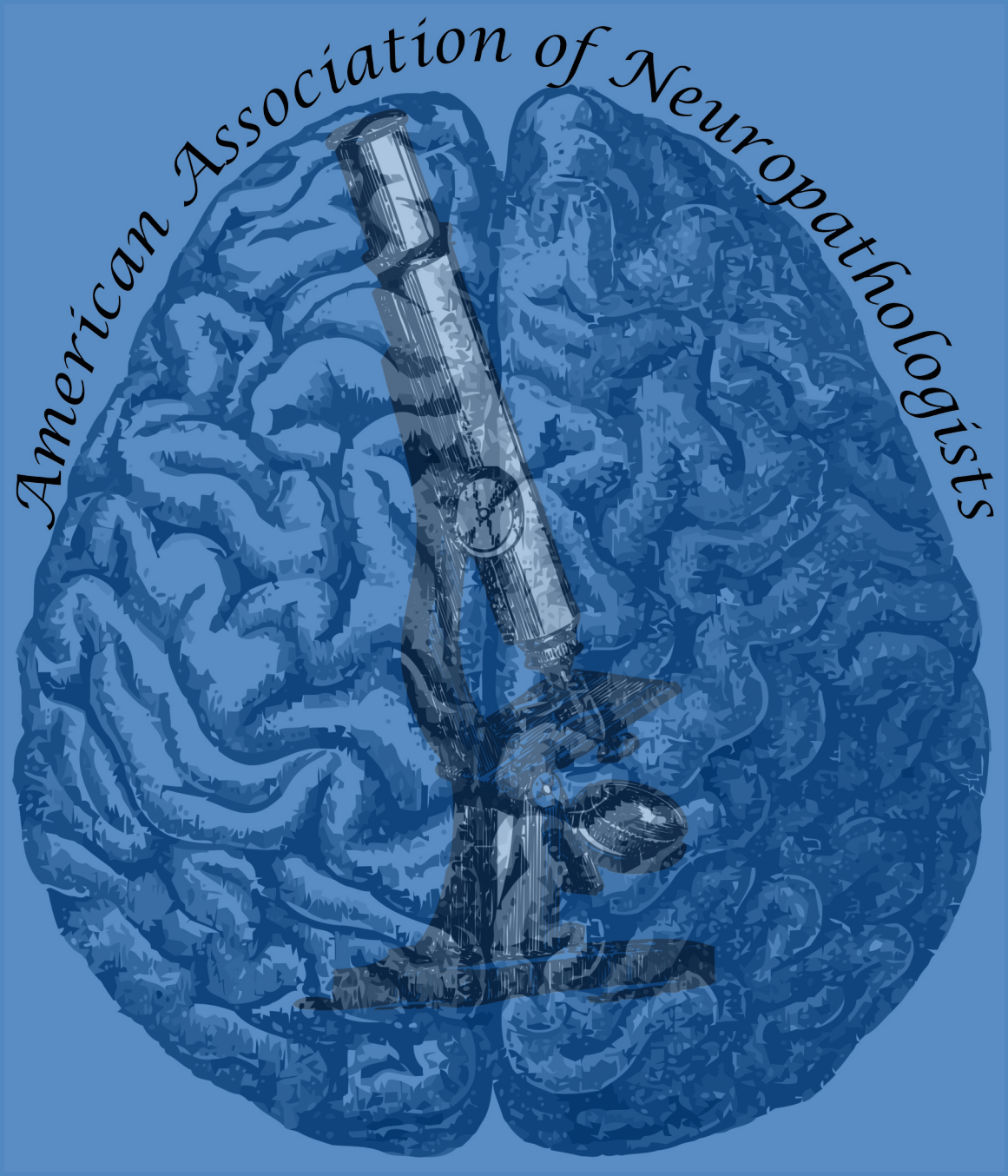
90th Annual Meeting

June 12-15, 2014

THE NINES HOTEL

Portland, Oregon



This activity is provided by the
American Association of Neuropathologists

For additional information about the accreditation of this program, please contact the AANP office at 440-793-6565 or aanpoffice@gmail.com

ALL MEETING SESSIONS WILL BE HELD AT
THE NINES HOTEL
525 SW Morrison
Portland, OR 97204
Phone: 1-877-229-9995

All platform presentations and general sessions (Special Lectures, Korey Lecture, DeArmond Lecture, Parisi Lecture, Business Meetings, Diagnostic Slide Session, and Presidential Symposium) will be held in the Fashion and Culture Ballrooms of the hotel.
All poster sessions will be held in the Prefunction area and Studio Ballroom.

PRE-REGISTRATION PICK-UP
Attendees pre-registered and pre-paid for the Special Course and/or Meeting will have their name badge, program booklets, June 2014 issue of JNEN with abstracts, reception ticket(s) and registration receipt ready for pick-up at the AANP Registration Desk, located in the prefunction area outside of the ballrooms. On-site registration and additional tickets for the Annual Reception will be available at the Desk.

REGISTRATION DESK	Prefunction Area
Wednesday, June 11	6:30 pm – 9:00 pm
Thursday, June 12	6:30 am - 12 noon
	6:30 pm – 9:00 pm
Friday, June 13	7:00 am - 12 noon
	5:30 pm – 6:00 pm
Saturday, June 14	7:00 am - 12 noon

PLEASE, wear your name badge!
Your name badge is required for admittance to any function of the Association, including the Special Course, all Friday, Saturday and Sunday sessions, and the Friday evening reception.

ABSTRACTS
Abstracts of the papers presented in the program are published in the June 2014 issue of the Journal of Neuropathology and Experimental Neurology.

This meeting is sponsored in part by generous contributions from

MEETING EXHIBITORS
Nikon
Wolters Kluwers Health
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RECEPTION PRIZE CONTRIBUTORS
Wolters Kluwers Health
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Please visit their displays and exhibits in the Prefunction area

Thursday, June 12	12:00 pm – 5:30 pm
Friday, June 13	7:00 am - 5:30 pm
Saturday June 14	7:00 am - 5:30 pm

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TARGET AUDIENCE

The educational design of AANP's Annual Meeting addresses the needs of physicians and scientists in the field of neuropathology who are involved in the diagnosis and/or treatment of patients with neurological disorders.

STATEMENT OF NEED

The purpose of this activity shall be to advance medical and scientific knowledge, understanding, and competence in the practice of neuropathology. The practice of neuropathology is understood to include diagnosis of diseases of the nervous system, scientific investigation into their causes, and teaching of neuropathology principles to colleagues and trainees.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

1. Cite new information on the underlying causes and mechanisms of neurologic diseases

2. Discuss research findings related to basic molecular pathways to better understand disorders of brain overgrowth and CNS neoplasia

3. Incorporate new knowledge into improving everyday clinical practice and teaching of neuropathology

DISCLAIMER

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented is this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed in this activity should not be used by clinicians without evaluation of patient conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

CME CREDIT

Physician Accreditation Statement

The American Association of Neuropathologists is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Physician Credit Designation Statement

The American Association of Neuropathologists designates this live educational activity for a maximum of *25.5 AMA PRA Category 1 Credits* ™ . Physicians should only claim credit commensurate with the extent of their participation in the activity.

In order to receive credit for this activity, the participant must complete the CME evaluation and credit application in the registration packet and return it to the Registration Desk or mail it to:

American Association of Neuropathologists
C/o Kate Pfanmiller
5575 S. Sycamore St., Suite 205
Littleton, CO 80120

The chart below details the maximum number of credit hours a physician can earn for each educational activity being certified for *AMA PRA Category 1 Credit™* at this year's Annual Conference.

Activity	CME Credit Hours
Special Course	7.25
Scientific Sessions	8
Korey Lecture	1
DeArmond Lecture	1
Parisi Lecture	1
What Every Pathologists Needs to Know	1
Diagnostic Slide Session	3
Presidential Symposium	3.25
Total	25.50

DISCLOSURE INFORMATION

Disclosure of Unlabeled Use

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The American Association of Neuropathologists do not recommend the use of any agent outside of the labeled indications.

Disclosure of Commercial Support

"In-kind" support through the donation of microscopes is being provided by Pacific Microsystems LLC.

The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of any organization associated with this activity. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings.

Disclosure of Conflict of Interest

The American Association of Neuropathologists requires instructors, planners, managers and other individuals who are in a position to control the content of this activity to disclose any real or apparent conflict of interest they may have as related to the content of this activity. All identified conflicts of interest are thoroughly vetted by AANP for fair balance, scientific objectivity of studies mentioned in the materials or used as the basis for content, and appropriateness of patient care recommendations. Complete disclosure information will be provided to learners on-site.The Planners and Managers reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

The following planners and managers have Nothing to Disclose:

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Thomas Beach

Consultant/Independent Contractor: GE Healthcare

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These faculty have the following to Disclose

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NOTES to PRESENTERS

Platform Presenters

1. The AV system uses Powerpoint 2010, so please be sure your presentation is saved in a compatible format.
2. Please include a conflict of interest slide.

*Please title the presentation with your name and date & time of presentation (NAME DATE TIME.PPT), and bring it on a USB flash drive
*Macintosh users, be sure to save your presentation as .ppt (NAME DATE TIME.PPT). If the ".ppt" extension is not present in the file name, the file will not be recognized by the PC computer.
*Please bring all content (photos, videos, etc.) so that if something isn't shown correctly, we can rebuild it from the original file..
*It is your responsibility to get your file to the AV staff prior to your presentation.
*The AV staff will be available to to load and test your presentation from 7:00 am – 7:45 am, during session breaks, and at the end of the evening sessions, ONLY (specifically NOT during lunch)
*For morning presentations, please try to have your presentation loaded on the evening preceding your talk.
*Diagnostic Slide Session presentations also may submit their files on Saturday from 6:30-7:45 pm in The Nines Ballroom.
*To avoid potential problems, you will not be allowed to use your own computer, although you may bring it as a backup.

Poster Presenters

Both poster sessions will be held in Prefunction Area and Studio Ballroom of the hotel. Approximately half the posters will be displayed all day Friday and the remainder all day Saturday. Posters should be up by 8:00 am on the morning of your presentation and taken down by 8:30 pm the same day. The poster board size is 8 ft wide x 4 ft high. Please plan your poster to be at least a few inches smaller in each direction. The poster board surface and construction should accommodate either Velcro or push pins. Push pins will be provided

To encourage interaction with interested attendees, authors must be present at their posters for discussion/questions during morning or afternoon refreshment breaks, at the following designated times:

	Friday, June 13	Saturday, June 14
EVEN Numbered Posters:	10:00 - 10:30 am	4:00 – 4:30 pm
ODD Numbered Posters:	4:00 – 4:30 pm	10:00 - 10:30 am

MICROSCOPE VIEWING ROOM	Meier Boardroom.
Thursday, June 12	7:00 am - 5:30 pm
Friday, June 13	7:00 am - 5:30 pm
Saturday June 14	7:00 am - 5:30 pm
BUSINESS MEETING	Fashion Ballroom
Friday, June 13	11:45 am - 12:45 pm
Saturday June 14	11:45 am – 12:45 pm

The awards for Meritorious Contributions to Neuropathology will be presented on Friday June 13th, 2014

SPECIAL MEETINGS BY INVITATION ONLY

Wednesday June 11		
NP Program Directors Meeting	5:00 pm	Design 1 Ballroom
Education Committee Meeting	7:00 pm	Gallery 1 Room
Thurs June 12		
Awards Committee Meeting	5:30 pm	Gallery 1 Room
Executive Council Meeting	6:00 pm	Gallery 3 Room
Fri June 13		
Trainee Luncheon	11:45 pm – 2:00 pm	Design Ballroom
Awards Committee Meeting	5:30 pm – 7:30 pm	Gallery 1 Room
Professional Affairs	5:30 pm – 7:30 pm	Gallery 2 Room
Saturday June 14		
JNEN Editorial Board Meeting	7:00 am – 8:00 am	Design 1 Ballroom
Awards Committee Meeting	5:30 pm - 7:30 pm	Gallery 1 Room
WebTech Committee	5:30 pm – 6:30 pm	Georgian Room
Presidential Reception	6:30 pm – 8:00 pm	Design Ballroom
Sun June 15		
Founders Breakfast	7:00 am – 8:00 am	Gallery 1 Room

ANNUAL RECEPTION

The annual reception will be 6:30 to 8:30 pm, Friday in the Prefunction Area and Design Ballroom. Registrants and guests of the AANP are welcome to attend. There will be a cash bar. Additional tickets are $20 each for guests of AANP attendees, and may be purchased at the time of registration or at the door. Several "prizes" will be awarded to trainees.

PROGRAM and SCIENTIFIC SESSIONS

SPECIAL COURSE — The Nines Ballroom
Thursday, June 12, 2014 — 8:00 am - 5:15 pm

Morning: *PI3K-AKT-mTOR and Brain Overgrowth: Too Much of a Good Thing*
Afternoon: *A Practical Approach to Pediatric Brain Tumors*
Directors: Robert Hevner, MD, PhD and Anthony Yachnis, MD

PLATFORM PRESENTATIONS — Fashion or Culture Ballrooms
Friday, June 13 — 8:00 am – 4:00 pm
Saturday, June 14 — 8:00 am – 4:00 pm

POSTER PRESENTATIONS — Prefunction and Studio Ballroom
Friday, June 13 — 8:00 am – 6:30 pm
Saturday, June 14 — 8:00 am – 6:30 pm

SAUL R. KOREY LECTURE — The Nines Ballroom
Friday, June 13 — 10:30 am - 11:30 am

Alzheimer's disease and related dementias
Thomas Montine, MD, PhD
University of Washington, Seattle, WA

DEARMOND LECTURE — The Nines Ballroom
Friday, June 13 — 4:30 pm – 5:30 pm

Prionic Loops, Dependence Receptors, and a New Approach to Alzheimer's Disease
Dale Bredesen, MD
Buck Institute for Research on Aging, Novato, CA

PARISI LECTURE — The Nines Ballroom
Saturday, June 14 — 10:30 am – 11:30 am

Human Parechovirus Encephalitis?
Clayton Wiley, MD, PhD
University of Pittsburgh Medical Center, Pittsburgh, PA

DIAGNOSTIC SLIDE SESSION — The Nines Ballroom
Saturday, June 14 — 8:00 pm -11:00 pm

PRESIDENTIAL SYMPOSIUM — The Nines Ballroom
Sunday, June 15 — 8:00 am – 12 noon

State of the Art: Brain Tumor Diagnosis

MEETING AT A GLANCE

THURSDAY June 12, 2014

SPECIAL COURSE
Morning: *PI3K-AKT-mTOR and Brain Overgrowth: Too Much of a Good Thing*
Afternoon: *A Practical Approach to Pediatric Brain Tumors*

FRIDAY June 13, 2014

8:00 -10:00 am	**Fashion Ballroom** *Predictive Glioma Markers*	**Culture Ballroom** *AD, CTE, Prions*
10:00 -10:30 am	REFRESHMENT BREAK	
10:30 -11:30 am	KOREY LECTURE	

Alzheimer's disease and related dementias
Thomas Montine, MD, PhD
University of Washington, Seattle, WA

11:45 -12:45 pm	BUSINESS MEETING I	
12:45 - 2:00 pm	LUNCH BREAK	
2:00 – 4:00 pm	**Fashion Ballroom** *Inflammatory, Ophthalmic*	**Culture Ballroom** *Developmental, Pediatric*
4:00 –4:30 pm	REFRESHMENT BREAK	
4:30 –5:30 pm	DEARMOND LECTURE	

Prionic Loops, Dependence Receptors, and a New Approach to Alzheimer's Disease
Dale Bredesen, MD
Buck Institute for Research on Aging, Novato, CA

6:30 - 8:30 pm ANNUAL RECEPTION

MEETING AT A GLANCE

SATURDAY June 14, 2014

8:00 -10:00 am	**Fashion Ballroom** *Tumors* *Molecular Phenotypes*	**Culture Ballroom** *Muscle, Nerve* *Infectious*
10:00 -10:30 am	REFRESHMENT BREAK	
10:30 -11:30 am	PARISI LECTURE *Human Parechovirus Encephalitis?* Clayton Wiley, MD, PhD University of Pittsburgh, Pittsburgh, PA	
11:45 -12:45 pm	BUSINESS MEETING II	
12:45 - 2:00 pm	LUNCH BREAK	
2:00 – 4:00 pm	**Fashion Ballroom** *Tumors 3*	**Culture Ballroom** *ALS, FTD, PD*
4:00 –4:30 pm	REFRESHMENT BREAK	
4:30-5:00 pm	What Every Neuropathologist Needs to Know I *10 Things every Neuropathologist needs to know about Prions* Mark L. Cohen, MD University Hospitals Case Medical Center, Cleveland, OH	
5:00 - 5:30 pm	What Every Neuropathologist Needs to Know II *Molecular Aspects of Metastatic Brain Tumors* Ronald L. Hamilton, MD University of Pittsburgh Medical Center, Pittsburgh, PA	
8:00 - 11:00 pm	DIAGNOSTIC SLIDE SESSION	

SUNDAY June 15, 2014

8:00 am - 12:00 pm	PRESIDENTIAL SYMPOSIUM *State of the Art: Brain Tumor Diagnosis*

THURSDAY, June 12, 2014

SPECIAL COURSE

Morning: *PI3K-AKT-mTOR and Brain Overgrowth: Too Much of a Good Thing*
Afternoon: *A Practical Approach to Pediatric Brain Tumors*
Directors: Robert Hevner, MD, PhD and Anthony Yachnis, MD

8:00 am – 8:10 am	*Welcome and CME Pre-test*	Anthony T. Yachnis, MD University of Florida College of Medicine, Gainesville, FL
8:10 am – 8:30 am	*Lhermitte-Duclos disease*	Anthony T. Yachnis, MD University of Florida College of Medicine, Gainesville, FL
8:30 am – 9:15 am	*PI3K-Akt-mTOR in Gliomas*	Craig Horbinski, MD University of Kentucky, Lexington, KY
9:15 am – 10:00 am	*Autism as a sequence*	Manuel F. Casanova, MD University of Louisville, Louisville, KY
10:00 am – 10:30 am	REFRESHMENT BREAK	
10:30 am – 11:15 am	*Size Matters: The Genetic Basis of Megalencephaly and Segmental Cortical Dysplasias*	William B. Dobyns, MD University of Washington, Seattle, WA
11:15 am – 12:00 pm	*Pathology of Hemimegalencephaly*	Robert Hevner, MD, PhD University of Washington, Seattle, WA
12:00 pm - 1:00 pm	LUNCH BREAK	
1:00 pm – 1:45 pm	*Focal Cortical Dysplasias*	Eleonora Aronica, MD Universtiy of Amsterdam, Netherlands
1:45 pm – 2:30 pm	*Tuberous Sclerosis* Complex	Harry Vinters, MD UCLA, Los Angeles, CA
2:30 pm – 3:15 pm	*Medulloblastomas and Other Embryonal Tumors*	Charles Eberhart, MD Johns Hopkins University, Baltimore, MD
3:15 pm - 3:45 pm	REFRESHMENT BREAK	
3:45 pm – 4:30 pm	*Pediatric Gliomas: A Survival Guide*	Tarik Tihan, MD, PhD UCSF, San Francisco, CA
4:30 pm – 5:15 pm	*AT/RT and Related Tumors*	Alexander Judkins MD, FRCP Children's Hospital Los Angeles, Los Angeles, CA

AANP 2014 Special Course

PI3K-AKT-mTOR and Brain Overgrowth: Too Much of a Good Thing

A Practical Approach to Pediatric Brain Tumors

Anthony T. Yachnis, MD
University of Florida College of Medicine, Gainesville, FL

Welcome to this year's Annual AANP Course! We will consider some neoplastic, hamartomatous, and malfomative conditions of brain overgrowth that share a common molecular pathogenesis involving defects of the PTEN-PI3kinase-Akt-mTOR pathway. A brief review of Lhermitte-Duclos will serve as an introduction to the first part of the course. Afternoon sessions will cover contemporary aspects of pediatric brain tumor diagnosis. Enjoy the course!

Special Course Objectives:

1. Identify the spectrum of genetic and neuropathologic conditions in which brain overgrowth occurs.
2. Relate morphologic and histologic features of brain overgrowth to molecular alterations in the PTEN-Akt-mTOR pathway
3. Assess the clinical and diagnostic utility of the new consensus classification of focal cortical dysplasias.
4. Review contemporary criteria for diagnosis and classification of pediatric embryonal and glial brain tumors.
5. Relate histological and molecular characteristics of childhood CNS neoplasms to current therapeutic strategies.

Lhermitte-Duclos disease: Circumscribed cerebellar cortical overgrowth with granule cell hypertrophy and altered PTEN/mTOR signaling

Anthony T. Yachnis, MD
Professor, Chief, Neuropathology Section
Department of Pathology, Immunology, & Lab Medicine
University of Florida College of Medicine

In 1920, Lhermitte and Duclos reported a 36 year-old man who died following an illness involving headache, nausea, ataxia, hearing loss, and cognitive disturbance. At autopsy, the cerebellum contained circumscribed regions of widened folia populated by large neurons. In 1969, Dr. Mary Ambler and colleagues reported that localized cerebellar cortical overgrowth is due, in large part, to hypertrophy of granule neurons in her classic JNEN paper. This paper also documented the first familial cases of the disease. An association between LDD and Cowden disease was initially recognized in the early 1990s. Onset of LDD in adulthood is now considered pathognomonic for Cowden disease, which is an autosomal dominant syndrome causing a variety of mucocutaneous lesions (facial trichilemmomas, acral keratoses, skin and oral papillomas, and hamartomatous mucosal polyps) and malignancies including carcinomas of the breast, thyroid, endometrium, and genitourinary tract. Both LDD and Cowden disease are linked to germline loss of function mutations of the PTEN gene on chromosome 10q23, which lead to hyperactivity of the mTOR (mammalian target of rapamycin) pathway that is known to regulate protein synthesis and cell size. Experimental models showed that deletion of PTEN impairs migration of granule neurons as well as deregulation of cell size leading to granule cell hypertrophy and dysplastic gangliocytoma-like alterations. Subsequent studies of human LDD studies confirmed activation of the mTOR pathway in many cases, suggesting its role in disease pathogenesis and as a potential therapeutic target. PTEN mutations may be absent in pediatric cases of LDD suggesting a differing pathobiology. Abnormal PTEN/AKT/mTOR signaling occurs in neoplasia and in brain overgrowth syndromes such as hemimegalencephaly, tuberous sclerosis, and even autism.

1. Ambler M, Pogacar S, Sidman R. Lhermitte-Duclos disease (granule cell hypertrophy of the cerebellum). Pathological analysis of the first familial cases. J Neuropathol Exp Neurol 1969;28:622-647.
2. Yachnis AT, Trojanowski JQ, Memmo M, Schlaepfer WW. Expression of neurofilament proteins in the hypertrophic granule cells of Lhermitte-Duclos disease. An explanation for the mass effect and the myelination of parallel fibers in the disease state. J Neuropathol Exp Neurology 1988;47;206-216.
3. Padberg, GW, Schot JD, Vielvoye GJ, et al. Lhermitte-Duclos disease and Cowden disease. A single phakomatosis. Annals of Neurology 1991;29:517-523.
4. Kwon C-H, Zhu X, Zhang J, et al. Pten regulates neuronal soma size: A mouse model of Lhermitte-Duclos disease. Nature Genetics 2001:29:404-411.
5. Abel TW, Baker SJ, Fraser MM, et al. Lhermitte-Duclos Disease: a Report of 31 Cases with Immunohistochemical Analysis of the PTEN/AKT/mTOR Pathway. J Neuopathol Exp Neurol. 2005;64:341-9.
6. Kresak, JL, Roper SN, Yachnis AT. Lhermitte-Duclos disease: Circumscribed cerebellar cortical overgrowth with granule cell hypertrophy and altered PTEN/mTOR signaling. Pathol Case Rev 2013;18:253-256.

Anthony T. Yachnis, M.D., has been a faculty member at the University of Florida College of Medicine for the past two decades. Thanks to some fantastic colleagues and trainees, he has co-authored more than 100 publications, including journal articles, book chapters and two books. He has given numerous invited national and local presentations; and has won national and local awards for research and teaching, including the Horatio T. Enterline Award in surgical pathology and the Moore and Rubinstein Awards from the American Association of Neuropathologists. Dr. Yachnis currently serves on the education committee of the USCAP and previously worked on the neuropathology committee of the CAP. He was the senior associate editor for the publication, Laboratory Investigation, from 2003 - 2008 and is currently still active on its editorial board. He is an associate editor for Histopathology and served on the editorial board for the Journal of Neuropathology and Experimental Neurology from 1998 - 2003. One of his favorite activities was moderating the annual Diagnostic Slide Session of the AANP from 2008 to 2013. Prior to his tenure at the UF College of Medicine, Dr. Yachnis completed pathology residency and a surgical pathology fellowship at the University of Pennsylvania from 1986 to 1991. He then received specialized training in pediatric neuropathology at Philadelphia Children's Hospital in 1993. He is honored to have served the AANP as President this year!

PI3K-Akt-mTOR in gliomas

Craig Horbinski, M.D., Ph.D.
Associate Professor
Director of Molecular Anatomic Pathology
Director of Markey Biospecimen and Tissue Procurement Shared Resource Facility
University of Kentucky

At the end of this activity learners should be able to:
1. Describe the general sequence of events leading from RTK activation through mTOR, including the major consequences of PI3K pathway activation.
2. List mechanisms by which gliomas activate the PI3K pathway, focusing on alterations of major genes in the pathway.
3. Describe which markers in the PI3K pathway are used in surgical neuropathology and how to apply them.
4. Discuss current therapeutic strategies aimed at the PI3K pathway, including successes and challenges.

The phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) pathway is one of the most powerful and important signaling pathways in animal cell biology. Because the PI3K pathway drives such critical phenomena as cell growth, it is no surprise that its machinery is co-opted by cancers. For example, the vast majority of gliomas have activation of the PI3K pathway. This occurs through a variety of mechanisms targeting multiple nodes in the pathway, including (but not limited to) RTK, PIK3CA, PTEN, and mTOR. Although evaluation of most components in the pathway is not routine in the clinical workup of gliomas, testing for 10q/PTEN deletion can be helpful in some circumstances. Drugs aiming to treat gliomas by blocking the PI3K pathway have had uneven success, depending on context and whether the tumor can muster resistance. Currently, mTOR antagonists and dual PI3K-mTOR antagonists show the most promise and are under intense investigation in the laboratory and the clinic. Since any truly revolutionary therapy for people with gliomas will likely have to deal with this powerful and far-reaching PI3K pathway, a cogent understanding of its significance is essential for all who care for these unfortunate patients.

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A native of Buffalo, N.Y., Dr. Horbinski did his undergraduate training in Biology at Canisius College and a combined M.D., Ph.D. at the State University of New York at Buffalo. He was nominated to the James A. Gibson Anatomical Honour Society in 1997. While a graduate student in the neurosciences, Dr. Horbinski studied the mechanisms of dendrite growth. After a one-year postdoctoral research fellowship studying Parkinson Disease at the University of Pittsburgh, Dr. Horbinski completed a three-year Anatomic Pathology residency at UPMC. During this time he changed his focus to oncology, specifically the development and evaluation of cutting-edge molecular diagnostics for tumors. Dr. Horbinski expanded this work while doing a two-year neuropathology fellowship at UPMC, focusing his research on both the molecular diagnostics of gliomas and mechanisms underlying gliomagenesis. In 2009 Dr. Horbinski won the O.T. Bailey-Helena Riggs Award for Best Presentation at the 50th annual Diagnostic Slide Session at the American Association of Neuropathologists Annual Meeting in San Antonio.

Upon completion of his neuropathology fellowship in July of 2009, Dr. Horbinski joined the faculty in the Department of Pathology and Laboratory Medicine at the University of Kentucky in Lexington. He is now a tenured Associate Professor with an NCI-funded research laboratory studying novel glioma therapies. Dr. Horbinski is the founder and director of the University of Kentucky Brain Tumor Bank, the founder and director of the Molecular Anatomic Pathology laboratory, and the Director of the Markey Cancer Center Biospecimen and Tissue Procurement Shared Resource Facility. To date he has published over 50 original papers and reviews, and has given over 30 invited lectures at national and international venues.

Dr. Horbinski is board-certified in both Anatomic Pathology and Neuropathology, and is a member of the American Association of Neuropathologists, the American Association of Cancer Researchers, the United States and Canadian Academy of Pathology, and the Society for Neuro-Oncology. He is a regular reviewer for many journals, including PLoS One, Neuro Oncology, Clinical Cancer Research, and the Journal of Molecular Diagnostics, and is on the editorial boards of Acta Neuropathologica, Brain Pathology, and the Journal of Neuropathology and Experimental Neurology.

Autism as a sequence: From heterochronic germinal cell divisions to abnormalities of cell migration and cortical dysplasias

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Objectives:
1: Summarize the recent neuropathological literature on autism spectrum disorders.
2: Explain clinical symptoms of autism spectrum disorders based on known neuropathological findings.
3: Describe medical interventions for autism spectrum disorders based on known neuropathology.

The considerable heterogeneity in the number and severity of symptoms observed in autism spectrum disorders (ASD) has been regarded as an obstacle to any future research. It has been said that the concept of autism as a unitary disorder (i.e., one resulting from a common cause) is close to being abandoned. However, the guiding heuristic in science is to first disproof the explanation with the fewest assumptions. In this case the null hypothesis should be that autism is the result of symptom divergence where one pathophysiological mechanism stands at the root cause of the condition. In this lecture we will review neuropathological findings in both idiopathic and syndromic autism that suggest a single pathophysiological mechanism acting during brain development: the heterochronic division of germinal cells and subsequent migrational abnormalities of daughter cells to their target fields. In autism, abnormalities of cell migration are suggested from accounts of focal dysplasias, abnormalities in the thickness of the cerebral cortex, variations in neuronal density, minicolumnar alterations, the presence of supernumerary neurons in the molecular layer, irregular laminar patterns, poor differentiation of the gray/white matter interface, and heterotopias Multiple exogenous (e.g., viruses, drugs) and endogenous (e.g., genetic mutations) factors are known to disrupt the division of germinal cells and provide for an autism phenotype. The variety of endogenous and exogenous factors, their timing of action during brain development, and the genetic susceptibility of affected individuals (a Triple Hit hypothesis) may all account for the clinical heterogeneity of ASD.

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Dr. Manuel Casanova made his residency training in neurology at the University District Hospital in Puerto Rico and then spent 3 years doing a fellowship in neuropathology at The Johns Hopkins Hospital. During his stay at the Johns Hopkins Hospital, Dr. Casanova was in-charge of Pediatric Neuropathology, a fact that kindled his interest in developmental disorders of the brain. His clinical experience was enhanced by appointments as either a consultant or staff neuropathologist at Sinai Hospital (Maryland), the North Charles Hospital and the D.C. General Hospital. He spent several years as Deputy Medical Examiner for Washington, D.C.. His medical expertise was recognized by honorary appointments as a Scientific Expert for the Armed Forces Institute of Pathology (AFIP) and as a Professorial Lecturer for the Department of Forensic Science at George Washington University. Dr. Casanova spent 8 years helping to establish 2 of the most successful brain banks in this country: The Johns Hopkins Brain Resource Center and the Brain Bank Unit of the Clinical Brains Disorders Branch at the National Institutes of Mental Health. He came to the University of Louisville in 2003 as the Gottfried and Gisela Kolb Endowed Chair in Psychiatry.

Size Matters:
The Genetic Basis of Megalencephaly and Segmental Cortical Dysplasias

William B. Dobyns, MD, Professor
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Objectives:
1. Describe the fundamental developmental pathways that underlie abnormalities in brain size and related cortical development
2. Discuss the critical importance of the timing (growth curves) and associated abnormalities that contribute to the current classification of megalencephaly and segmental cortical dysplasia (including hemimegalencephaly and focal cortical dysplasia)
3. Describe the role of postzygotic (mosaic) mutations in the expression of developmental brain abnormalities
4. Discuss the relationships between dysregulation of critical growth regulatory pathways (especially PI3K-AKT signaling) and megalencephaly

Abnormal brain size occurs in many human developmental disorders, and recent work has discovered underlying defects in several critical intracellular signaling pathways, especially the PI3K-AKT pathway. This lecture will review the most common syndromes with abnormally large brain size or megalencephaly and partial forms such as focal cortical dysplasia, and review common neurological complications which include intellectual disability, autism, epilepsy, hydrocephalus and Chiari malformation. The remainder of the lecture will review the underlying genetic basis for several of these syndromes, and end with discussion of possible therapeutic interventions.

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William B. Dobyns is Professor of Pediatrics (Genetics) and Neurology (Pediatric Neurology) at the University of Washington, and Principal Investigator in the Center for Integrative Brain Research at Seattle Children's Research Institute. He obtained his medical degree at the Mayo Medical School in Rochester, Minnesota, and then completed training programs in Pediatric Neurology at Baylor College of Medicine in Houston, Texas and Medical Genetics at the Mayo Graduate School of Medicine in Rochester. He previously held faculty positions at the Medical College of Wisconsin, Indiana University School of Medicine, the University of Minnesota, and The University of Chicago. He is a physician-scientist who studies the nature and causes of human developmental brain disorders. While best known for studies of lissencephaly and other brain malformations, his work also involves intellectual disability, autism, and early childhood epilepsies. He has contributed to the discovery of 30-40 human disease genes including ARX, DCX, LIS1, PIK3CA, PIK3R2 and AKT3, all of which are important epilepsy genes, as well as the 17p13.3 deletion associated with Miller-Dieker syndrome, and the 16p11.2 deletion associated with autism.

Pathology of Hemimegalencephaly

Robert F. Hevner, MD, PhD
Professor, Department of Neurological Surgery, University of Washington

At the end of this activity learners should be able to:
1. Describe the principal macroscopic and histologic features and variations in hemimegalencephaly
2. Relate how heterogeneous pathologic features of hemimegalencephaly arise from diverse developmental disturbances in the PI3K-AKT signalling pathway
3. Recall that hemimegalencephaly sometimes occurs in the context of syndromes, such as Proteus syndrome

Hemimegalencephaly (HME) is a severe brain malformation characterized by asymmetrical overgrowth of the hemispheres and dyslamination of the cerebral cortex. The histopathology of HME is variable among cases, but frequently includes neuronal hypertrophy and dysplasia, leptomeningeal glioneuronal heterotopia, polymicrogyria, abnormal myelination, and nodular or microscopic heterotopia within the cortex or white matter. Numerous cases of HME have been linked to non-inherited, postzygotic mutations in genes such as AKT3 that enhance activity in the PI3K-AKT signaling pathway. The mosaic distribution of cells with the mutation accounts for asymmetric pathology. When tissues other than the brain are also affected, HME may occur in the context of syndromes, such as Proteus syndrome. Mouse models of HME are being developed and have begun to shed further light on the pathogenesis of HME.

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Dr. Hevner obtained his B.S. degree in Cellular & Molecular Biology from the University of Michigan (Ann Arbor), and M.D.-Ph.D. from the Medical College of Wisconsin (Milwaukee). He has maintained a dual career track since. After training in Anatomic Pathology (Brigham and Women's Hospital, Boston) and Neuropathology (Stanford), he began research in his current area of brain development as a postdoctoral fellow at UCSF. He joined the faculty at University of Washington (Seattle) in 2000, and has been Professor since 2008. Currently, he is neuropathologist at Seattle Children's Hospital, and has his research lab at Seattle Children's Research Institute.

Focal cortical dysplasias: a neuropathological and molecular perspective

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1. Explain the new consensus classification of distinct FCD subtypes based on histopathological features
2. Discuss the recently emerging hypotheses on the molecular pathogenesis of FCD
3. Explain the mechanisms of epileptogenesis in FCD

Focal cortical dysplasias (FCD) represent localised malformative brain lesions frequently encountered in surgical resection specimens from patients with chronic medically intractable epilepsy. The access to clinically well-characterized neurosurgical material has provided a unique opportunity to better define the neuropathological, neurochemical and molecular features of FCD. After the first description of the neuropathological features of FCD provided by Taylor in 1971, different FCD classification systems have been proposed. However, since the morphological spectrum of FCD is broad, the development of a unified and comprehensive classification represents a great challenge and requires continuous updates. A task Force of the Diagnostic Methods Commission of the International League Against Epilepsy (ILAE) has recently generated a new consensus classification of distinct FCD subtypes based on histopathological features. The ILAE classification represents the basis for clinical studies to better define specific clinical, electrophysiological and imaging features, but may also guide prospective studies addressing the molecular pathogenesis and epileptogenicity of different FCD variants.The cellular and molecular mechanisms underlying FCD are still unclear, in particular our knowledge concerning the pathogenesis of FCD I is still rather limited and animal models which precisely replicate the specific histopathological features of FCD variants are not yet available. However new hypotheses are recently emerging on the molecular pathogenesis of FCD II. The recent advances in the neuropathological classification of FCD will be presented and both emerging neuropathological and basic science evidence will be addressed highlighting the involvement of different, but often converging pathogenetic and epileptogenic mechanisms, which may create the basis for new therapeutic strategies in FCD and other related developmental disorders.

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5. Vezzani A. Before epilepsy unfolds: finding the epileptogenesis switch. Nat Med 2012; 18: 1626-1627.

Native of Italy (17-7-1965) Eleonora Aronica studied Medicine and Surgery at the University of Catania (Italy) where she graduated and completed the neurology residence program in 1993. After receiving a doctorate from the University of Amsterdam in The Netherlands, she had research associated appointments at the Wadsworth Center for Laboratories and Research, in Albany (NY, USA) and at the Albert Einstein College of Medicine, Department of Neuroscience in New York (1993-1996). In 1996 she moved to The Netherlands and after receiving the “Teding van Berkhout” fellowship on epilepsy research she joined the Department of Neuropathology of the Academic Medical Center (AMC) at the University of Amsterdam. Here she completed the Neuropathology residence program and is presently working as neuropathologist. She is actively involved in the different research lines, including epilepsy. In 2011 she was awarded the Michael Prize which is an international award for the best contribution to scientific and to clinical research and which promotes further development in epileptology. She is the author of more than 200 peer-reviewed original articles and reviewer for various scientific journals.

TUBEROUS SCLEROSIS COMPLEX & NEUROLOGIC DISEASE

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LEARNING OBJECTIVES:

1. *Cite the heterogeneous neurologic/neuropathologic manifestations of TSC.*
2. *Elucidate how the molecular genetics of TSC has revolutionized our understanding of normal and abnormal brain development.*
3. *Discuss the myriad components of cell metabolism that are influenced by tuberin and hamartin.*
4. *Discuss the role of 'corticectomy' in treating TSC-related seizures.*

Tuberous sclerosis complex (TSC) has been recognized as a neurocutaneous or familial tumor syndrome, since the late 1800s. It is an autosomal dominant disorder with an estimated incidence of 1 in 6000 live births. Afflicted individuals throughout the world are estimated to number 1 million, and TSC is encountered in all ethnic groups. Though it is a multisystem disorder, major manifestations---often its presenting feature(s)---involve the CNS, though heart, lung, skin & kidney are often involved. Commonly encountered neurologic manifestations include intractable epilepsy, cognitive disability, autism, focal neurologic deficits, hydrocephalus, and neurobehavioral abnormalities. Though it has been recognized for many decades, studies of TSC rapidly evolved after the discovery of the two main TSC genes, TSC2 (discovered in 1993) and TSC1 (1997). Finding a pathogenic mutation (defined as one that clearly inactivates the function of the TSC1 or TSC2 gene products, hamartin or tuberin) is sufficient to make the diagnosis. Clinical diagnostic criteria that support the diagnosis include three lesions of 'neurologic interest', cortical dysplasias (tubers), supependymal nodules (SENs), and subependymal giant cell astrocytoma (SEGA)—all considered 'major diagnostic criteria' in the recently revised and updated formulation of TSC diagnostic criteria (see Northrup et al, 2013). Subependymal nodules (SENs) may be precursors of SEGAs. Study of the function/ dysfunction of both TSC1 and TSC2 have provided cell, developmental and neurobiologists as well as cancer biologists with much fascinating data. Both genes interact with each other, but also with numerous proteins that mediate cell growth, transcription, translation, autophagy, maturation, and development. They interact with CDK1 and Cyclin A, B, with AKT, AMPK, Rabaptin-5, p27, SMAD2 or SMAD3, and the mTOR and B-Raf pathways. When there are pathogenic mutations in one of the TSC genes, their inhibitory effect on the mTOR pathway is lost, leading to pS6 overexpression within tubers; indeed, this can be used as an immunohistochemical marker to detect dysmorphic cells. mTOR itself is found within two structurally and functionally distinct protein complexes: mTORC1 and mTORC2. TSC2 acts as a GTPase-activating protein towards Ras homolog enriched in brain (Rheb), the proximate effect of which is inhibition of mTOR signaling. TSC1 protein stabilizes TSC2 by preventing its ubiquitination. Further details of these pathways will be explored during the lecture. Knockout mice have been developed, in the brains of which many of the neuropathologic features of 'tubers' are seen, though often not as a multifocal process.The Neuropathologist encounters TSC lesions (usually) as SEGAs (intraventricular neoplasms) or as 'tuberectomy' specimens, since tuber resection is now a widely accepted element of 'epilepsy surgery'. Tubers have a histopathologic appearance very similar to that of FCD ILAE type IIB, with 'balloon cells', dysmorphic neurons and neuronal cytomegaly and disorganization. Indeed, without the clinical information that a specimen originates from a TSC patient, a tuber may be indistinguishable from FCD. Though anti-hamartin and anti-tuberin antibodies are available, employing these does not help to confirm one or the other diagnosis, as the proteins are widely expressed within the CNS.

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Medulloblastomas And Other Embryonal Tumors: Current Classification and Diagnosis

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At the end of this activity learners should be able to:
1.Recognize morphological features associated with specific embryonal tumor subtypes.
2.Identify key molecular changes present in medulloblastoma and embryonal tumor subtypes
3.Explain how to use microscopic and molecular features to stratify medulloblastoma for therapy.

It is becoming increasingly clear that the various embryonal tumors harbor distinct genetic abnormalities, and these are associated with altered prognosis and potentially different responses to the same treatment regimens. Because of this, more precise microscopic and molecular classification of medulloblastoma and related tumors is now a prominent feature of current and planned clinical trials (1,2). CNS embryonal tumors listed in the WHO classification include medulloblastoma, medulloepithelioma, ependymoblastoma, ATRT and CNS PNET (3). However, specific variants exist within these groups. Medulloblastoma variants include desmoplastic/nodular and large cell/anaplastic tumors, and these are now linked to a well-established molecular classification scheme which contains four main groups (4,5,6). Medulloblastoma in which the WNT pathway is active generally have classic histology and are associated with very good clinical outcomes. Hedgehog pathway activity is typically found in desmoplastic/nodular tumors, and is most frequently identified in either infants or young adults. Group 3 medulloblastoma are often large cell/anaplastic, characterized by increased MYC expression, and associated with very short survival. Group 4 medulloblastoma have an intermediate prognosis and are not associated with a single defining molecular pathway. The molecular features of CNS PNET are just beginning to come into focus. However, discrete subtypes such as Embryonal Tumors with Abundant Neuropil and True Rosettes (ETANTR) showing specific clinical, pathological and molecular features are now recognized within this group (7,8,9). In addition, molecular diagnostic studies suggest that pediatric GBM and AT/RT have in the past sometimes been misdiagnosed as CNS PNET.

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Charles Eberhart received his M.D. and Ph.D. degrees from UT Southwestern in 1997, with post-graduate clinical training in Anatomical Pathology and Neuropathology at Johns Hopkins Hospital. Dr. Eberhart has been a member of the Johns Hopkins University School of Medicine faculty since 2001, and currently directs the divisions of Neuropathology and Ophthalmic Pathology. Much of his research centers on how signalling pathways involved in normal development, such as Notch and Hedgehog, drive tumor growth through regulation of stem cell phenotypes. Dr. Eberhart is on the editorial boards of the Journal of Neuropathology and Experimental Neurology, Neurooncology, and Brain Pathology. He has published over 170 original research articles on diseases of the brain and eye.

PEDIATRIC GLIOMAS: A SURVIVAL GUIDE FOR NEUROPATHOLOGISTS

Tarik Tihan, MD PhD
Professor of Pathology, UCSF School of Medicine

At the end of this activity learners should be able to:
1.Describe at least four typical histological features and two typical genetic alterations associated with pilocytic astrocytomas
2.List at least four typical histological and clinical characteristics of pilomyxoid astrocytomas
3.Define at least three cardinal findings in pleomorphic xanthoastrocytomas and learn the definition of pleomorphic xanthoastrocytoma with anaplastic features
4.Define at least four clinicopathological and genetic features for low and high grade diffuse astrocytomas in the pediatric population
5.List at least three differences between pediatric and adult infiltrating gliomas

Two distinct groups of tumors will be discussed in this lecture on gliomas in children; Pilocytic Astrocytoma (PA) on the benign or indolent end, and infiltrating low and high grade gliomas on the other. The most aggressive form of infiltrating glioma, obviously is the pediatric glioblastoma. The critical issue obvious to the pathologists, neurooncologists and the neurosurgeons, is that circumscribed gliomas such as PA are distinct from infiltrating gliomas genetically and histologically. The molecular pathological advances in the characterization of these tumors have also shed light into their diagnosis, treatment and prognostication. PAs are "surgical" tumors for which gross total resection often results in cure. These tumors were found to harbor unique genetic aberrations in the MAPK pathway, and nearly all PAs seem to have an aberration in this pathway, the most common of which is the BRAF gene duplication resulting in the KIAA1549:BRAF fusions. Other alterations such as BRAF, NF1 and KRAS gene mutations described in PAs also highlight the importance of this pathway for the genesis of PAs. The variants and patterns within the PA group have also identified some of the more aggressive tumors in this category. Infiltrating gliomas in the pediatric population are distinct not only from PA, but also from the adult infiltrating gliomas. The genetic aberrations found in adult infiltrating gliomas are extremely rare among pediatric tumors. There is an accelerated effort to define the biology and genetics of infiltrating gliomas, since these tumors have far worse prognosis than the former group. Future studies will surely uncover genetic aberrations peculiar to infiltrating gliomas in the pediatric age group, and point to better management strategies.

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1986-89:PhD Studies, University of Vienna, Department of Medical Chemistry, Vienna, Austria. 1990-91:Postdoctoral Research Associate, University of South Florida, Department of Internal Medicine & H. Lee Moffitt Cancer Center, Tampa, FL. 1991-92: House officer, Beth Israel Medical Center, Department of Neurosurgery, New York, NY and Manager of the Recanati Research Laboratory. 1992-94:Resident in Pathology, Beth Israel Medical Center, Department of Pathology, New York, NY. 1994-95: Fellow in Oncologic Pathology, Memorial Sloan-Kettering Cancer Center, Department of Pathology. New York, NY.1995-97:Fellow in Neuropathology, State University of New York at Stony Brook, Department of Pathology. Stony Brook, NY.1997-99:Clinical Instructor, Johns Hopkins Medical School, Department of Pathology, Baltimore, MD. 1999-2002:Assistant Professor, Johns Hopkins Medical School, Department of Pathology, Baltimore, MD.2002-07:Associate Professor, and 2008-present: Professor, UCSF School of Medicine, Department of Pathology.

AT/RT and Related Tumors: Pathology and Diagnosis of SMARCB1-deficient Neoplasms

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Children's Hospital Los Angeles & Keck School of Medicine of USC, Los Angeles, CA.

1. Discuss the role of SMARCB1 expression in the differential diagnosis of tumors with rhabdoid differentiation
2. identify other CNS and non-CNS tumors that may show inactivation of SMARCB1
3. Estimate the prevalence of germline SMARCB1 abnormailites in patients with isolated CNS rhabdoid tumors.

Atypical teratoid/rhabdoid tumors (AT/RT) are highly aggressive and lethal tumors encountered primarily in the pediatric age group. Histologically, these tumors are variable in their appearance and show a spectrum of features, including characteristic rhabdoid cells and immunohistochemical evidence of polyphenotypic differentiation. AT/RT are defined by mutations and deletions in the SMARCB1 (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1) gene (also referred to as SNF5/BAF47/INI1) or, in very rare cases, other genes related to the SWI/SNF chromatin remodeling compelx. Tumors with identical histopathological features occur in the kidneys (renal rhabdoid) and soft tissues (soft tissue rhabdoid) locations. At the molecular/genetic level, all these tumors demonstrate SMARCB1 inactivation. A number of other tumors have been reported to show evidence of SMARCB1 inactivation. This raises the question: what does it mean when you have a newly diagnosed patient with SMARCB1 inactivation?

1. Biegel JA, Rorke LB, Emanuel BS (1989) Monosomy 22 in rhabdoid or atypical teratoid tumors of the brain. N Engl J Med 321:906.
2. Rorke LB, Packer RJ, Biegel JA. (1996) Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood: definition of an entity. J Neurosurg. 85:56-65.
3. Burger PC, Yu IT, Tihan T, et al.(1998) Atypical teratoid/rhabdoid tumor of the central nervous system: a highly malignant tumor of infancy and childhood frequently mistaken for medulloblastoma: a Pediatric Oncology Group study. Am J Surg Pathol 22:1083-1092.
4. Versteege I, Sevenet N, Lange J, Rousseau-Merck MF, Ambros P, Handgretinger R, Aurias A, Delattre O (1998) Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. Nature 394:203-206.
5. Judkins AR, Mauger J, Ht A, Rorke LB, Biegel JA. (2004) Immunohistochemical analysis of hSNF5/INI1 in pediatric CNS neoplasms. Am J Surg Pathol. 28:644-50.
6. Judkins AR, Burger PC, Hamilton RL, et al. (2005) INI1 protein expression distinguishes atypical teratoid/rhabdoid tumor from choroid plexus carcinoma. Journal of neuropathology and experimental neurology 64:391-397..
7. Hasselblatt M, Gesk S, Oyen F, Rossi S, Viscardi E, Giangaspero F, Giannini C, Judkins AR, Fruhwald MC, Obser T, Schneppenheim R, Siebert R, Paulus W (2011) Nonsense Mutation and Inactivation of SMARCA4 (BRG1) in an Atypical Teratoid/Rhabdoid Tumor Showing Retained SMARCB1 (INI1) Expression. Am J Surg Pathol 35:933-935.
8. Eaton KW, Tooke LS, Wainwright LM, Judkins AR, Biegel JA. (2011) Spectrum of SMARCB1/INI1 mutations in familial and sporadic rhabdoid tumors. Pediatr Blood Cancer. 56:7-15.
9. Sullivan LM, Folpe AL, Pawel BR, Judkins AR, Biegel JA (2013) Epithelioid sarcoma is associated with a high percentage of SMARCB1 deletions. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc 26:385-392.
10. Wang X, Haswell JR, Roberts CW. (2014) Molecular pathways: SWI/SNF (BAF) complexes are frequently mutated in cancer--mechanisms and potential therapeutic insights. Clin Cancer Res. 20:21-7.

Dr. Judkins received a bachelor's degree (1991) from State University of New York Geneseo, graduating Summa Cum laude. He received his medical degree (1996) from the University of Rochester School of Medicine in New York. Dr. Judkins trained at the Hospital of the University of Pennsylvania, where he completed residency training in anatomic pathology (1996-99), and served as chief resident (1998-99). He completed fellowships in neuropathology (1999-2001, the Hospital of the University of Pennsylvania) and forensic pathology (2001-2002, Philadelphia Office of the Medical Examiner and MCP Hahneman University). Dr. Judkins is board certified in anatomic pathology, neuropathology and forensic pathology. He joined the faculty of the University of Pennsylvania School of Medicine as an Assistant Professor in the Department of Pathology and Laboratory Medicine and the staff of CHOP as a Neuropathologist in 2002. While there, he developed immunohitochemcal staining for INI1/BAF47/SMARCB1 as a routine marker for pediatric brain tumors. Since 2010, he has been Pathologist-in-Chief at Children's Hospital Los Angeles, Associate Professor (Clinical Scholar) and Vice Chair of Pathology at Keck School of Medicine of USC.

Notes

	Predictive Glioma Markers Arie Perry & Craig Horbinski Fashion Ballroom	**AD, CTE, Prions** Peter Nelson & Julia Kofler Culture Ballroom
8:00- 8:15	1. *Predicting the Likelihood of an IDH1 or IDH2 Mutation in Patients Diagnosed with Infiltrative Gliomas* - Craig Horbinski, MD, PhD	9. *Pyroglutamylated Amyloid-B Correlates with Hyperphosphorylated Tau and Severity of Alzheimer's Disease*- Johannes Attems, MD
8:15- 8:30	2. *Glutamine Based PET Imaging Facilitates Enhanced Metabolic Detection of Gliomas in vivo* - Sriram Venneti, MD, PhD	10. *TDP-43 Influences Cognition, Memory Loss and Hippocampal Atrophy in Alzheimer's Disease* - Keith Josephs, MD
8:30- 8:45	3. *Simplified Grading System for WHO Grade II-III Gliomas Based on 1p/19q Status, IDH 1/2 Mutation Status, and Nestin Expression* - Kimmo Hatanpaa, MD, PhD	11. *Novel Fluid Biomarkers for Brain Amyloid in Presymptomatic Alzheimer Disease* - Richard J. Perrin, MD, PhD
8:45- 9:00	4. *Loss of CDKN2A/p16 is Associated with Shortened Overall Survival in Grade II and III Glioma* - Gerald Reis, MD, PhD	12. *Beclin1/BECN1 Interacts with Surface APP and Facilitates its Internalization and Sorting for Autophagosomal Degradation* - Edward Plowey, MD, PhD
9:00- 9:15	5. *Biopsy Site has Important Prognostic Implications in Gliomas* - Marta Couce, MD, PhD	13. *Beta-Amyloid Accumulation in Chronic Traumatic Encephalopathy* - Thor Stein, MD, PhD
9:15- 9:30	6. *Is hTERT Immunohistochemistry Predictive of 1p/19q Co-deletion in Grade II-III Diffuse Gliomas?* - Christina Appin, MD	14. *Single Episode of Severe Axonal Injury in Humans Can Lead to Tau Pathology Resembling Chronic Traumatic Encephalopathy* - Daniel Perl, MD
9:30- 9:45	7. *TERT Promoter Mutation is Associated with Older Age at Diagnosis, Independent of Glioma Grade, Histology and IDH1/2 Status* - Melike Pekmezci, MD	15. *Glycans Modulate the Transmissibility of PrPSc and the sCJDMM2 and sFI Phenotypes* - Laura Cracco, PhD
9:45- 10:00	8. *Efficacy of Mono and Dual PI3K and MAPK Inhibition in Glioblastoma and Triple-Negative Breast Cancer Brain Metastasis Models* - Robert McNeill, BS	16. *Postmortem Neostriatal Neurop Transmissibility and Propagation of Co-Existing Prions of Sporadic Creutzfeldt-Jakob Disease into Humanized Transgenic Mice Athology in Early Huntington Disease* - Ignazio Cali, MS

10:00 - 10:30 am — REFRESHMENT BREAK

10:30 – 11:30 am — KOREY LECTURE

Update on the 2012 NIA-AA Alzheimer Disease Diagnostic Criteria

Thomas Montine, MD, PhD

University of Washington, Seattle, WA

11:45 am – 12:45 pm — Business Meeting I (Fashion Ballroom)

12:45 – 2:00 pm — Lunch Break

The Saul R. Korey Lectureship

The Korey Lectureship was established by Dr. Robert D. Terry in honor of Dr. Saul R. Korey, the founder and first Chair of the Department of Neurology at Albert Einstein College of Medicine. Dr. Korey's vision of an interdisciplinary approach to the study of neurological diseases by basic and clinical scientists has inspired generations of colleagues and trainees. Dr. Terry, a close collaborator and colleague of Dr. Korey, was the first recipient of the prestigious Potamkin Prize for Pick's and Alzheimer's Disease in 1988, in recognition of his seminal observations of the pathological changes in Alzheimer disease. Dr. Terry generously contributed a portion of the prize funds to endow the Korey Lectureship, to be administered by the American Association of Neuropathologists, with the lecturer to be chosen annually by the President in conjunction with the Nominating Committee and the Chair of the Program Committee.

Dr. Terry has summarized the qualities of the Korey lecturer as someone who has "been an active member of the Association, a working MD or MD/PhD neuropathologist, responsible for diagnostic work as well as teaching and research. The lecture should be aimed at the members of the Association, and the lecturer might well serve as a role model for younger members."

We are pleased to have **Thomas Montine, MD, PhD**, join our list of distinguished speakers.

1989 Nicholas K. Gonatas	*MG-60, a Novel Sialoglycoprotein of Medial Cisternae of the Neuronal Golgi Apparatus: Implications and Applications*
1990 Henry M. Wisniewski	*Amyloidosis in Alzheimer's Disease and the Spongiform Encephalopathies*
1991 Robert D. Terry	*Alzheimer's Disease as Seen by a Lucky Morphologist*
1992 Henry de Forest Webster	*Formation and Regeneration of Myelin*
1993 Kunihiko Suzuki	*Molecular Genetics of Tay-Sachs and Related Disorders:*
1994 No Lecture	*The Legacy of Saul Korey*
1995 Blas Frangione	*Amyloid Genes and Chaperones in Alzheimer Disease*
1996 Floyd Gilles	*The 3R's of Neuro-oncology – Recording, Reliability and Reporting*
1998 Sandra H. Bigner	*Molecular Genetics of Medulloblastoma*
1999 William F. Hickey	*Key Participants in the Initiation of Inflammation in the Central Nervous System*
2000 Mary E. Case	*Neuropathology and Forensic Pathology: A Natural Synergism*
2001 Paul H. Kleihues	*Molecular Biology of Brain Tumors*
2002 James E. Goldman	*Astrocytes, Intermediate Filaments, Cellular Stress and Neuropathology*
2003 Samuel K. Ludwin	*Pathology and Pathogenesis in Multiple Sclerosis*
2004 James M. Powers	*The Road Not Taken*
2005 Bernardino Ghetti	*Deciphering Hereditary Presenile Dementias: Neuropathology at the Crossroads of Neuropsychiatry and Molecular Genetics*
2006 Donna M. Ferriero	*Molecular Mechanisms of Hypoxic-Ischemic Injury in the Developing Nervous System*
2007 Dennis W. Dickson	*Neuropathology and Genetics of Parkinsonism*
2008 David N. Louis	*Brain Tumor Classification: Little Steps and Big Jumps*
2009 Stephen J. DeArmond	*Mechanisms of Neurodegeneration in Prion Disease Originating from the Neuronal Plasma Membrane*
2010 Peter C. Burger	*A Long-Term Perspective on Pediatric CNS Tumors*
2011 Hans H. Goebel	*Protein Aggregate Myopathies*
2012 Michael Norenberg	*Astrocyte Pathobiology*
2013 Harry Vinters	*Gain and Pain from Cerebral Microvessels – Adventures in Vascular Neuropathology*
2014 Thomas Montine	*Alzheimer's disease and related dementias*

Alzheimer's disease and related dementias

Thomas J. Montine, MD, PhD

At the end of this activity learners should be able to:
1. Explain the incidence and prevalence of Alzheimer's disease and related dementias
2. Review the co-morbidity of Alzheimer's disease and related dementias in older individuals
3. Discuss the development and application of revised NIA-AA guidelines for neuropathologic evaluation of Alzheimer's disease

1. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach.
Montine TJ, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Trojanowski JQ, Vinters HV, Hyman BT; National Institute on Aging; Alzheimer's Association. Acta Neuropathol. 2012 Jan;123(1):1-11
2. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Thies B, Trojanowski JQ, Vinters HV, Montine TJ. Alzheimers Dement. 2012 Jan;8(1):1-13
3. Ecology of the aging human brain. Sonnen JA, Santa Cruz K, Hemmy LS, Woltjer R, Leverenz JB, Montine KS, Jack CR, Kaye J, Lim K, Larson EB, White L, Montine TJ. Arch Neurol. 2011 Aug;68(8):1049-56
4. Montine, TJ, et al. Alzheimer's disease–related dementias: research challenges and opportunities. Final Report 2013.
http://www.ninds.nih.gov/funding/areas/neurodegeneration/workshops/adrd2013/ADRD_2013_ Report-and-Memorandum_508comp.pdf

Dr. Montine received his education at Columbia University (BA in Chemistry), the University of Rochester (PhD in Pharmacology), and McGill University (MD and CM). His postgraduate medical training was at Duke University, and he was junior faculty at Vanderbilt University where he was awarded the Thorne Professorship in Pathology. Currently, Dr. Montine is the Alvord Endowed Chair in Neuropathology and Chair of the Department of Pathology at the University of Washington where he is Professor of Pathology and Adjunct Professor of Neurological Surgery; he also is Adjunct Professor of Neurology at Oregon Health & Science University. UW Pathology is consistently among the top departments in NIH funding, is a regional reference laboratory for the Pacific Northwest, and is the Pathology training program for the Washington, Wyoming, Alaska, Montana, and Idaho (WWAMI) partnership. UW Pathology is home to the Center for Precision Diagnostics and the Center for Heart Regeneration, enterprise-wide efforts that bridge from fundamental research to clinical applications.

Dr. Montine is the Director of the Pacific Northwest Udall Center and is the Director of the University of Washington Alzheimer's Disease Research Center. Both of these national centers perform focused basic, translational, and clinical research including trials. The focus of the Montine Laboratory is on the structural and molecular bases of cognitive impairment. Our goal is to define key pathogenic steps and thereby identify new therapeutic targets. The Montine Laboratory addresses these prevalent, unmet medical needs through a combination of neuropathology, biomarker development and application, and experimental studies that test hypotheses concerning specific mechanisms of neuron injury and approaches to neuroprotection in the brain.

Awards for Meritorious Contributions to Neuropathology

The Award for Meritorious Contributions to Neuropathology recognizes members who have made significant contributions to the advancement of knowledge in neuropathology and provided service to the American Association of Neuropathologists. Candidates for this award may be nominated by any active member of the Association. The annual awardees are selected by the Nominating Committee in conjunction with the President and Vice President of the Association.

The qualities of outstanding scientific achievement and service are embodied in this year's recipients, **Drs. Floyd Gilles and Françoise Gray.** They join the rich roster of distinguished former award recipients.

1959	Armando Ferraro
	Arthur Weil
1960	Joseph H. Globus
	George B. Hassin
1968	Abner Wolf
	Paul I. Yakovlev
	Harry M. Zimmerman
1970	Webb E. Haymaker
1971	James W. Kernohan
1972	George A. Jervis
1979	Raymond D. Adams
	David Cowen
	Matthew T. Moore
1981	Richard Lindenberg
1983	Orville T. Bailey
1984	Margaret Murray
1985	Kenneth M. Earle
	Nathan Malamud
	Leon Roizin
1986	Martin G. Netsky
1987	No Award Presented
1988	Edward P. Richardson, Jr.
	F. Stephen Vogel
1989	Lucien J. Rubinstein
	Robert D. Terry
1991	Lysia K. S. Forno
1992	John Moossy
	Gabriele M. ZuRhein
1993	Peter W. Lampert
	Elias E. Manuelidis
1994	Murray B. Bornstein
	Samuel P. Hicks
	Lowell W. Lapham
1995	Amico Bignami
	Asao Hirano
1996	Pasquale A. Cancilla
	Franz Seitelberger
1997	Henryk M. Wisniewski
1998	Richard L. Davis
	Wolfgang Zeman
1999	Lucy B. Rorke
2000	William R. Markesbery
2001	John J. Kepes
	Henry de Forest Webster
2002	Dikran S. Horoupian
	Fusahiro Ikuta
	Kurt A. Jellinger
2003	Bernardino F. Ghetti
2004	Michael N. Hart
2005	E. Tessa Hedley-Whyte
	Suzanne S. Mirra
2006	Joseph E. Parisi
	Jeannette J. Townsend
2007	James M. Powers
	Cedric S. Raine
2008	Kinuko Suzuki
	Margaret G. Norman
2009	Peter C. Burger
	Pierluigi Gambetti
	Nicholas K. Gonatas
2010	Stephen J. DeArmond
	Samuel K. Ludwin
2011	William W. Schlaepfer
	Leroy R. Sharer
2012	Bernd W. Scheithauer
	Donald L. Price
2013	Reid Heffner
	Dawna Armstrong
2014	Floyd Gilles
	Francoise Gray

American Association of Neuropathologists Award for Meritorious Services to Neuropathology 2014. Dr. Floyd Gilles

Dr. Floyd Gilles obtained his undergraduate degrees, BA and BS, as well as his MD from the University of Chicago. In subsequent years he was awarded an honorary AM from Harvard when he was tenured. After Neurology training at Johns Hopkins and a subsequent NIH Special Fellowship in Neuropathology with Richard Lindenberg he obtained Board Certification in Neurology and Neuropathology. Floyd was inspired towards Pediatric Neuropathology by Dr. David Clark, who was a Pediatric Neurologist at John Hopkins.

Dr. Gilles was head of pediatric neuropathology at Boston Children's Hospital Medical Center and on the Harvard University faculty from 1962-1983. Three of Floyd's trainees while he was at Children's in Boston became Professors at Harvard and are also distinguished Neuropathologists (Dr. Alan Leviton, Dr. Hannah Kinney and Dr. E. Tessa Hedley-Whyte). Another became Chairman of Pathology at Seoul National University (Dr. Je Geun Chi). Several Neurology residents from Boston City Hospital and New England Medical Center spent a year of Neuropathology with Floyd.

Of his Harvard Trainees, Alan Leviton probably had the greatest impact on Floyd's career. Alan was also pursuing a Masters in Public Health while also a fellow in Neuropathology and stimulated Floyd's interest in the power of statistics in medical research. The latter influenced much of his subsequent highly cited work, whether it was on Perinatal Telencephalic Leukoencephalopathy, the Collaborative Perinatal Project of the NINCDS, or the Childhood Brain Tumor Consortium. It is interesting to look back on the bemusement of the Neuropathologists when Floyd presented them with 'Cluster Analysis' of the data from the Childhood Brain Tumor Consortium and now it is the generally accepted basis for analyzing high throughput molecular genetics!

In 1983 he took the Burton E Green Chair of Pediatric Neuropathology Children's Hospital Los Angeles and became Professor of Pathology, Neurological Surgery, and Neurology Keck School of Medicine University of Southern California 1983-2012. There, he continues his long-standing interests in normal in utero development of human brain and its adversities, in pathologist's diagnostic reproducibility in brain tumors, and in brain tumor histologic feature quantitation. Dr. Gilles has admirably served our Association in many ways including (but not inclusive) as Assistant Secretary Treasurer, Vice-President, and Korey Lecturer. The AANP is delighted to celebrate Floyd's many contributions and accomplishments in neuropathology with the Meritorious Service award.

American Association of Neuropathologists Award for Meritorious Services to Neuropathology 2014.

Françoise Gray, MD, PhD
University of Paris VII (Denis Diderot)

President Yachnis; Members and Guests:

Dr Umberto De Girolami and I are delighted to make some brief remarks on the occasion of the bestowal of the American Association of Neuropathologists's "Award for Meritorious Services to Neuropathology" to Professor Françoise Gray.
Umberto very much regrets that he is not present at this ceremony as, before learning of it, he had made arrangements to vacation in Europe.

Dr. Gray was born in Normandy and obtained her MD degree from the University of Rouen (graduating with the "silver medal"). In 1964 and 1965 she was an Externe/Interne des Hôpitaux at the University of Paris (post- graduate training in Internal Medicine) and then was a resident in Neurology and Pathology (Neuropathology) at the Salpêtrière. In 1983 she earned a PhD in Biology from the University of Paris.

After completion of training, Dr. Gray worked principally at four University Hospitals in central Paris, first at the Salpêtrière under Professor Raymond Escourolle followed by the Hôpital Henri Mondor and the Hôpital Poincaré and for the past twenty years she has been affiliated with the Hôpital Lariboisière, where she recently retired as Chair of the Pathology Department. At the University of Paris, she rose through the ranks to Full Professor, with a particularly keen interest in teaching vascular, degenerative and infectious diseases of the nervous system.

Dr. Gray's primary research interests have been in the area of the neuropathology of AIDS, prion diseases, and degenerative diseases, and in medico-legal Neuropathology, where she was appointed as expert witness to the Versailles courthouse. To support her research she has had continuous research funding from the INSERM (French equivalent to the NIH) and other granting agencies for the past thirty-five years. . She was "project leader" of two consecutive European Concerted Actions (1993-1996) on the Neuropathology of AIDS which allowed for research collaboration in this field with specialists around the World.

She has had numerous leadership and administrative roles locally, nationally and internationally. To name a few, at Lariboisière she was the administrative director of a large hospital unit (Pôle) which comprised four other departments, besides Pathology; also she was representative to the French National University Council, President of the French Society of Neuropathology, and President of the International Society of Neuropathology (2003-2006) Dr Gray is an active member of many neurologic professional societies, including the AANP, where she has been a faithful attendee at our Annual Meeting and is currently on the editorial board of 12 journals (including the "Advisory Board" of the JNEN).

Professor Gray's Curriculum Vitae includes more than 340 original peer-reviewed articles in French and English. The list of publications encompasses the full range of research inquiry in neurologic disease, particularly emphasizing "medical" Neuropathology of degenerative, hereditary/acquired metabolic, vascular, prion, HIV, and other infectious diseases. She has supervised more than 50 theses.

Francoise joined Jaques Poirier for the third Edition of the classic monograph "Escourolle and Poirier's Manual of Basic Neuropathology" and one of us (UdeG) has been privileged to participate with Dr Gray as a contributing editor to the Fourth and Fifth Editions of this book originally conceived and authored by Professors Raymond Escourolle and Jacques Poirier and published in French in 1971 and translated into English by Lucien Rubinstein, in 1978.

Besides her brilliant professional career Françoise and her husband have four sons and eleven grandchildren. She also enjoys horses, breeding dogs, sailing, and swimming among other activties. Françoise and her husband have been the consummate gracious hosts, organizing magnificent dinner parties for many of our Members at their lovely home in the suburbs of Paris.

The AANP is proud to confer upon you the American Association of Neuropathologists's Award for Meritorious Services to Neuropathology.

Congratulations!

Umberto De Girolami and Tessa Hedley-Whyte
June13/14, 2014

TRAINEE LUNCHEON

11:45 pm – 2:00 pm
Design 1 Ballroom

The Transition from Fellowship to Independence
(Not Offered for CME Credit)

Sponsored by the
Journal of Neuropathology and Experimental Neurology

Michael Lawlor
Medical College of Wisconsin

Eddie Lee
University of Pennsylvania

Craig Horbinski
University of Kentucky

Pavan Auluck
Biogen Idec

Matija Snuderl
NYU

Marie Rivera-Zengotita
University of Florida

Aaron Wagner
Orlando Regional Hospital

Ray Sobel
Stanford

	Inflammatory, Ophthalmic Charles Eberhart & David Munoz Fashion Ballroom	**Developmental/Pediatric** Alex Judkins & Christopher William Culture Ballroom
2:00- 2:15	17. *Transient Receptor Potential Melastatin 4 Expression in Human Cerebral Infarcts*- Mehta Rupal, MD	25. *Development of the Hippocampal Formation in Human: Part I-Pyramidal Cell Layer*- Homa Adle-Biassette, MD, PhD
2:15-2:30	18. *Lymphocytic Hypophysitis: A Single Centre Experience of 11 Cases* - Marc Del Bigio, MD, PhD	26. *Fetal Nucleus/Fasciculus Solitarius: Synaptophysin Maturation* - Harvey Sarnat, MD
2:30- 2:45	19. *Myelin Loss in Adult-onset Leukoencephalopathy/Leukodystrophy with Axonal Spheroids is Secondary to Axonal Loss* - Murad Alturkustani, MD	27. *Radial Glia Defects and the Pathogenesis of Germinal Matrix Hemorrhage* - Jennifer Cotter, MD
2:45- 3:00	20. *Characteristic of Neural Tissue in Ovarian Teratomas Associated to Anti-NMDA Receptor Encephalitis (ANMDARE)* - David Munoz, MD	28. *A Century of Brain Hemorrhages in Autopsied Premature Infants at a Tertiary Pediatric Hospital* - Marco Hefti, MD
3:00- 3:15	21. *Astrocytic Regulation of Synaptic NMDA Receptors* - Marta Margeta, MD, PhD	29. *Hippocampal Anomalies in Sudden Unexplained Death in Young Children: An Extended Series* - Marco Hefti, MD
3:15- 3:30	22. *A Novel Telomere Phenotype In Human Retinal Photoreceptors* - William Bell, MD	30. *Construction of a Single Adenoviral Vector Carrying Both ZFN and Donor for the Treatment of Lysosomal Storage Diseases* - Qinwen Mao, MD, PhD
3:30- 3:45	23. *Intraocular Medulloepitheliomas in Children and Adults Show Markers of Retinal Development and Glioneuronal Differentiation* - Matthew Rose, MD, PhD	31. *The KCa3.1 blocker TRAM-34 Reduces Activated Microglia and ASD Like Behavior in a Rat Model of Neonatal HI Brain Injury* - Mirna Lechpammer, MD, PhD
3:45- 4:00	24. *Opthalmological Abnormalities in CTE* - Ann McKee, MD	32. *Developmental Synaptic Plasticity Defects in a Mouse Model of Down Syndrome* - Christopher William, MD, PhD

4:00 - 4:30 pm — REFRESHMENT BREAK

4:30 – 5:30 pm — DeArmond Lecture

Prionic Loops, Dependence Receptors, and a New Approach to Alzheimer's Disease

Dale Bredesen, MD

Buck Institute for Research on Aging, Novato, CA

6:30 – 8:30 pm — Annual Reception

Prefunction Area and Design Ballroom

The DeArmond Lecture

The DeArmond lecture was established in recognition of Stephen J. DeArmond's excellent leadership and organization of the scientific program for the 2006 International Congress of Neuropathology. This successful meeting garnered significant support intended for the future advancement of the mission of the American Association of Neuropathologists. To continue these intended goals and recognize Dr. DeArmond's contributions, the American Association of Neuropathologists has honored him by establishing the DeArmond Lecture. Dr. DeArmond is a leading authority on prion disease, where his work has been fundamental in demonstrating mechanisms of transmission and routes to therapeutics. The DeArmond Lecture focuses on honoring those making major advances in the field of neurodegeneration and aging with a particular emphasis on translating these findings to patient care.

We are pleased to have **Dale Bredesen, MD** join our list of distinguished speakers.

2008
Virginia M.–Y. Lee
TDP-43, A New Class of Proteinopathies in Neurodegenerative Diseases

2009
Rudy Tanzi
Decoding Alzheimer's Disease Gene by Gene

2010
Todd Golde
Alzheimer's Disease: Models and Therapeutics

2011
Beverley L. Davidson
Emerging Therapies for Neurogenetic Diseases

2012
Krystof Bankiewicz
New Therapies for Parkinson Disease

2013
Stanley Prusiner
A Unifying Role for Prions in Neurodegenerative Diseases

2014
Dale Bredesen
Prionic Loops, Dependence Receptors, and a New Approach to Alzheimer's Disease

Prionic Loops, Dependence Receptors, and a New Approach to Alzheimer's Disease

Dale E. Bredesen, M.D.
Augustus Rose Professor of Neurology Director, Mary S. Easton Center for Alzheimer's Disease Research at UCLA Director, Alzheimer's Disease Program Director, Neurodegenerative Disease Research David Geffen School of Medicine at UCLA

i.Discuss new mechanisms involved in Alzheimer's disease and mild cognitive impairment
ii.Describe a novel, integrative therapeutic approach to AD and MCI
iii.Review clinical trial results and therapeutic strategies in AD and MCI

Alzheimer's disease (AD) represents a major healthcare problem, affecting over 5 million Americans and approximately 30 million globally, at an annual cost of over $200 billion nationally. Despite the well-characterized neuropathology of AD, the underlying pathogenesis remains incompletely defined, and there is still no truly effective therapy. In studies of the basic mechanisms of neural cell death, we identified a novel type of receptor, dubbed dependence receptors (Mehlen et al., 1998; Rabizadeh et al., 1993); these receptors induce programmed cell death when their respective trophic ligands are withdrawn, and thus create cellular states of dependence on trophic factors, hormones, extracellular matrix, and other supportive ligands. Over 20 such receptors have been identified to date, including the beta-amyloid precursor protein, APP (Lu et al., 2000). APP functions as a molecular switch: interaction with the trophic ligand netrin-1 enhances cleavage at the alpha-cleavage site, producing sAPPalpha and alphaCTF, which mediate neurite extension, caspase inhibition, and the inhibition of Abeta peptide formation (Lourenço et al., 2009). Conversely, interaction of APP with Abeta itself leads to cleavage of APP at three sites, producing four peptides—sAPPbeta (from which N-APP is derived), Abeta, Jcasp, and C31—that mediate neurite retraction, caspase activation, and synaptic reorganization (Bredesen, 2009). Thus Abeta may function as an anti-trophin, and since the Abeta-APP interaction increases Abeta production, this pair forms a prionic loop; in contrast, netrin-1 has an anti-prionic effect. These alternative APP-mediated signals can be manipulated genetically, e.g., in transgenic mice, with a marked reduction in the Alzheimer's phenotype (Galvan et al., 2006); or pharmacologically, again with a reduction in the AD phenotype (Spilman et al., 2014). Furthermore, ApoE4, the most important genetic risk factor for AD, alters this critical balance in favor of the pro-AD signaling, at least in part via a reduction in SirT1 (Theendakara, 2013). These results, in the aggregate, suggest a model in which AD results from a chronic imbalance between synaptoblastic signaling and synaptoclastic signaling (Bredesen and John, 2013), amplified by prionic loops such as APP-Abeta. Since this balance is affected by many different factors in the environment—the same supportive factors whose reduction is associated with increased risk of AD—we have created an extensive therapeutic program that alters the balance to favor synaptoblastic signaling, instead of attempting to treat AD with a monotherapy that fails to address the many members of the underlying network.

Bredesen, D.E. 2009. Neurodegeneration in Alzheimer's disease: caspases and synaptic element interdependence. Mol Neurodegener. 4, 27.
Bredesen, D.E.John, V. 2013. Next generation therapeutics for Alzheimer's disease. EMBO Mol Med. 5, 795-8.
Galvan, V., Gorostiza, O., Banwait, S., et al. 2006. Reversal of Alzheimer's-like pathology and behavior in human APP transgenic mice by mutation of Asp664.Proc Natl Acad Sci 103, 7130-5.
Lourenço, F., Galvan, V., Fombonne, J., et al. 2009. Netrin-1 interacts with amyloid precursor protein and regulates amyloid-beta production. Cell Death and Differentiation. 16, 655-63.
Lu D.C., Rabizadeh S., et al., 2000. A second cytotoxic proteolytic peptide derived from amyloid beta-protein precursor. Nat Med. 6, 397-404.
Mehlen P., Rabizadeh S., Snipas S.J., et al., 1998. The DCC gene product induces apoptosis by a mechanism requiring receptor proteolysis. Nature. 395, 801-4.
Rabizadeh S., Oh J., Zhong L.T., et al. 1993. Induction of apoptosis by the low-affinity NGF receptor. Science. 261, 345-8.
Spilman P., Descamps O., Gorostiza O., et al., 2014. The multi-functional drug tropisetron binds APP and normalizes cognition in a murine Alzheimer's model. Brain Res. 1551, 25-44.
Theendakara V., Patent A., Peters-Libeu C., et al., 2013. Neuroprotective sirtuin ratio reversed by ApoE4. Proc Natl Acad Sci U S A.

Dr. Dale Bredesen's research focuses on the mechanisms of neurodegenerative diseases such as Alzheimer's disease. He earned his undergraduate degree at Caltech, his MD at Duke, and completed neurology residency at UCSF. He was NIH Fellow in the laboratory of Nobel Laureate Stanley Prusiner. In 1989 he joined the faculty at UCLA, where he was awarded the Elizabeth R. and Thomas E. Plott Chair. In 1994, he was recruited to the Burnham Institute to direct the Program on Aging, and then in 1998 became the Founding President and CEO of the Buck Institute for Research on Aging, the nation's only independent institute devoted to research on aging and age-associated disease. He held faculty positions at UCSF, UCLA and the University of California, San Diego. He recently completed a term as a member of the National Advisory Council on Aging. Dr. Bredesen's research has led to a new approach to Alzheimer's disease therapeutics. In December, 2013, Dr. Bredesen took a new position as Augustus Rose Professor and Director of the Easton Center for Alzheimer's Disease Research at UCLA.

Poster Session I

(Not Offered for CME Credit)

33. *An Interesting Case Of Sarcoid Myopathy*

Luis Gonzalez-Cuyar, Desiree Marshall, Nina Bozinov, Zackary Hoffer, Michael Weiss, B. Distad, C. Keene

34. *Neuromuscular Pathology of Bannayan-Riley-Ruvalcaba Syndrome: A Rare Case Report and Review of Literature*

Keng-Chih Su, Negar Khanlou, Anthony Verity, Jennifer Yi

35. *Novel Homozygous Cofilin-2 (CFL2) Mutation Causing a Congenital Form of Nemaline Myopathy with Filamentous Inclusions*

Leslie Bruch, Sheraden Mundy, Natalie Hauser, Joseph Shen

36. *Diagnostic Pitfall with Use of Alpha-dystroglycan Immunostain in Perimortem Muscle Biopsies*

Amanda Kan and Sophelia Chan

37. *Unusual Pathologic Features in a Patient with Laing Early Onset Distal Myopathy*

Marta Margeta, Grant de la Motte, Nigel Laing

38. *Granulomatous Fungal Myositis Presenting as Isolated Unilateral Myalgia: A Case Report*

Osama Elkadi and Jiang Qian

39. *Regional Necrotic Myopathies: Border Zone Muscle Fiber Necrosis Associated with Dermatomyositis Syndromes and Neoplasms*

Chunyu Cai, Rati Choksi, Ali Alshehri, Alan Pestronk

40. *Unusual Presentation of Hereditary Sensory Autonomic Neuropathy*

Armine Darbinyan, Kenneth Hughes, Mary Fowkes

41. *Paraneoplastic Sensory Neuronopathy In A 63-year-old Man Without A Demonstratable Underlying Malignancy*

Jenny Smith and Jeremy Deisch

42. *Expression of SERPING1 is Increased in Reactive Astrogliosis Associated with Neuroinflammation*

Amber Nolan, Nicole Croom, Han Lee, Marta Margeta

43. *Two Cases of Fatal Cerebral Edema with CNS Angiitis*

Denise Ng and Harry Vinters

44. *Autoimmune Polyglandular Syndrome Type 1 with Calcification in the Cortical Gray and White Matter and the Basal Ganglia*

Fahad Bafakih, Paul Benson, M. Beatriz Lopes

45. *Comparative Analysis of Neuronal Vulnerability of the Anterior Cingulate Cortex in Hereditary and Sporadic Tauopathies*

Adrian Oblak, Jill Murrell, Rose Richardson, Francine Epperson, Bernardino Ghetti

46. *Brainstem Pathology in Frontotemporal Degeneration Associated with the MAPT P301L Mutation*

Melissa Gener, Jill Murrell, Adrian Oblak, Bernardino Ghetti

47. *Effect Of Salvadora Persica Leaf Extract In Transgenic Drosophila Model Of Parkinson's Disease*

Yasir Siddique, Tanveer Beg, Falaq Naz, Smita Jyoti

48. *Effect Of Gingerol On The Oxidative Stress In The Brains Of Transgenic Drosophila Model Of Parkinson's Disease*

Tanveer Beg, Yasir Siddique, Smita Jyoti, Falaq Naz, Rahul Sachdev

49. *Apigenin Extends Lifespan And Improves The Activity Pattern Of Parkinson's Disease Model Flies*

Yasir Siddique, Tanveer Beg, Falaq Naz, Smita Jyoti, Rahul Sachdev

Poster Session I

(Not Offered for CME Credit)

50. *Death of Neurons in the Substantia Nigra Prior to Incidental Lewy Body Disease*

Eric Richfield, Kavita Prasad, John Hedreen

51. *Effect of Lewy Bodies on Substantia Nigra Dopaminergic Neuron Cell Health*

Knarik Arkun, Ann Rice, Essie Komlada, James Bennett

52. *Evaluation of Lewy Pathology in Enteric Neurons from Living Patients*

Annie Hiniker, Ryan Gill, Chadwick Christine, Robert Nussbaum

53. *Hippocampal sclerosis in Lewy body disease*

Naoya Aoki, Melissa Murray, Kotaro Ogaki, Shinsuke Fujioka, Owen Ross, Dennis Dickson

54. *Flow Cytometry Analysis of Synaptosomes from Human Brain Reveals Changes Specific to Lewy Body and Alzheimer's Disease*

Nadia Postupna, C Keene, Caitlin Latimer, Emily Sherfield, Rachel Van Gelder, Jeffrey Ojemann, Thomas Montine, Martin Darvas

55. *Coincident Alzheimer's Disease Modifies Alpha-synuclein Pathology in Lewy body Disease*

Pallavi Gopal, Jon Toledo, Kevin Raible, Erin Abner, David Irwin, Johannes Brettschneider, Steven Arnold, Howard Hurtig, Peter Nelson, Charles Adler, Thomas Beach, John Trojanowski

56. *Clinicopathologic Correlations of FTLD-TDP Type B with High and Low Burden of TDP-43 Positive Inclusions in the Dentate Gyrus*

Esther Bit-Ivan, Anne Koronkiewicz, Melanie Peterson, Alfred Rademaker, Mallory Ward, Qinwen Mao, Sandra Weintraub, Nailah Siddique, Teepu Siddque, M. Marsel Mesulam, Eileen Bigio

57. *Clinicopathologic report of ocular involvement in ALS patients with C9ORF72 Mutation*

Eileen Bigio, Amani Fawzi, Esther Bit-Ivan, Joseph Simonett, Patryk Purta, Heather Moss, Nailah Siddique, Nicholas Volpe, Teepu Siddque

58. *Incidental, Insidious and Late Onset Neuronal Intermediate Filament Inclusion Disease in an 85-Year-Old Male – a Case Report*

Jason Chiang, Lananh Nguyen, Nigel Cairn, Oscar Lopez, Julia Kofler

59. *Adult-Onset Alexander Disease in a Paraplegic African-American Male with a Rare D138N Mutation in the GFAP Gene*

Ki-Eun Chang, Nancy Edwards, Bibhuti Mishra, Mark Hallett, Abhik Ray-Chaudhury

60. *GABA-ergic and Glycinergic Synaptic Deficit in Friedreich Ataxia*

Arnulf Koeppen, R Ramirez, Alyssa Becker, Joseph Mazurkiewicz

61. *Neuropathologic Features of Spinocerebellar Ataxia 5 (Lincoln's Ataxia.)*

Margaret Flanagan, Luis Gonzalez-Cuyar, Jake Hemingway, Zachary Hoffer, Thomas Montine, Thomas Bird, C. Keene

62. *Neuropathological Features of Early Onset Huntington's Disease with Marked Cerebellar Atrophy*

Caitlin Latimer, Patrick Cimino, Zachary Hoffer, Louis Gonzalez-Cuyar, Thomas Montine, Thomas Bird, C Keene

63. *Neurodegeneration in Bipolar Disorders*

Ayako Shioya, Kunimasa Arima, Yukio Kakuta, Takefumi Yuzuriha, Akira Tamaoka, Shigeo Murayama, Yuko Saito

64. *Brain Biopsy in Dementia or Neurologic Decline of Unknown Etiology*

Shino Magaki, William Yong, Negar Khanlou, Harry Vinters

65. *An Autopsy Case of Granulomatous Amoebic Meningoencephalomyelitis Caused by Balamuthia Mandrillaris in Japan*

Hajime Miyata, Kenju Hara, Ken Saitoh, Masae Ryufuku, Haruka Ouchi, Ken Shibano, Kenji Yagita, Hideaki Ishiguro

66. *A 29-year-old Pregnant Woman with Worsening Left Hemiparesis, Encephalopathy, and Hemodynamic Instability: A Case of SSPE*

Gerald Reis, Jana Ritter, William Bellini, Andrew Bollen

Poster Session I

(Not Offered for CME Credit)

67. *Balamuthia Amoebic Encephalitis, Diagnostic Challenges from Surgical Pathology to Autopsy: A Case Report*

Keng-Chih Su, Harry Vinters, Negar Khanlou, William Yong, Annie Wu, Wun-Ju Shieh, Dianna Blau, Atis Muehlenbachs

68. *Fatal Seronegative Rickettsia rickettsii Meningoencephalitis in an Infant*

Hope Richard and Christine Fuller

69. *Amebic Meningoencephalitis with Acanthamoeba spp.*

Stewart Neill, Christina Appin, Daniel Brat, Jeannette Guarner

70. *Lack of Findings to Support a Role for HPV in a Cohort of Focal Cortical Dysplasia, Type IIB*

Declan McGuone, Kevin Shapiro, Kevin Staley, Anat Stemmer-Rachamimov

71. *A Tissue Microarray Approach to the Immunohistochemical Characterization of Pituitary Adenoma*

William McDonald, Nilanjana Banerji, Joel Money, Kelsey McDonald

72. *CD1a Immunohistochemistry in Pituitary Lesions*

David Pisapia and Ehud Lavi

73. *Pituitary Adenomas: VUV (Very Unusual Variants)*

Bette Kleinschmidt-DeMasters, T Cummings, M Lopes

74. *Stellate Amyloid Deposition in a Densely Granulated-Somatotroph Type Pituitary Adenoma*

Nitin Agarwal, Priyanka Singh, Jean Eloy, James Liu, Ada Baisre

75. *Sellar Atypical Teratoid Rhabdoid Tumor (AT/RT)–A Rare Tumor of Middle Aged Women*

Derick Aranda, Mark Jentoft, Joseph Parisi

76. *Salivary Gland Rests in Rathke Cleft Cysts. A Review of the Literature*

Dibson Gondim, Gregory Bosh, Atul Agarwal, Daniel Fulkerson, Jose Bonnin

77. *A Rare Craniopharyngioma Recurred 21 years Later in Lumbosacral Dura, with Multiple Local and Cerebral Ectopic Recurrences*

Osama Elkadi and Jiang Qian

78. *Pineoblastomas in Adults: Outcomes in a Series of Twelve Patients*

Melissa Gener, Aaron Cohen-Gadol, Jamie Van Gompel, Jeremy Cardinal, Fredric Meyer, Mohammad Ariai, Mark Jentoft, Jose Bonnin

79. *Lack of BRAF-V600E Mutation in Papillary Tumor of the Pineal Region (PTPR)*

Patrick Cimino, Joseph Corbo, Arie Perry, Sonika Dahiya

80. *Bifocal Papillary Tumor of the Pineal Region (PTPR) with Unusual Cytogenetic Features*

Murat Gokden, Bret Mobley, Warren Sanger, Hilary Nickols

81. *The Utility of OCT4, CD117, and PLAP in Diagnosing Germinoma with Crush Artifact in the Central Nervous System*

Zhe Piao, Daniel Won, Eric Stiner, Todd Goldenberg

82. *Aggressive Juvenile Xanthogranuloma of Posterior Cranial Fossa and Temporal Bone: A Case Report*

Nishant Tiwari, Viviana Lorda Seijo, Guy Marshall, Frank Gannon

83. *Non-Psammomatous Melanotic Schwannoma in Meckel's Cave*

Zachary Hoffer, Gordana Juric-Sekhar, Caitlin Latimer, Jing Zhang, Lia Halasz, Manuel Ferreira, C. Dirk Keene, Luis Gonzalez-Cuyar

84. *Salivary Duct Carcinoma Presenting as a CP Angle Mass*

Stewart Neill, Kelly Magliocca, Patricia Hudgins, Matthew Schniederjan

Poster Session I

(Not Offered for CME Credit)

85. *Radiation-Induced Atypical Meningiomas Exhibit Higher Recurrence Rates Than Sporadic Meningiomas of the Same Grade*

Sarah Martin and Eyas Hattab

86. *WHO Grade I Meningiomas with Atypical Features: Correlation of Histopathology with Clinical Outcome*

Declan McGuone, Ariel Marciscano, Andrzej Niemierko, William Curry, Fred Barker II, Robert Martuza, Kevin Oh, Jay Loeffler, Helen Shih, Anat Stemmer-Rachamimov

87. *Rhabdoid-Like Meningioma: A Case Report*

Caterina Giannini, Jonathan Fratkin, Josephine Wyatt-Ashmead, Patrice Abell Aleff

88. *Leptomeningeal Melanomatosis With Signet-Ring Cell Features Mimicking Leptomeningeal Carcinomatosis: A Postmortem Examination*

Sarah Martin, Andrew Fabiano, Robert Fenstermaker, Richard Cheney, Jingxin Qiu

89. *Primary Malignant Melanoma of the Leptomeninges with GNA11 (Q209L) Mutation: Case Report and Literature Review*

Michael Lynch, G. Timothy Reiter, Joseph Drabick, Charles Specht

90. *Analysis of Select Angiogenic Markers in Melanoma Brain Metastases*

Dimitri Trembath, Stergios Moschos, Anna Snavely, Evan Bradler, Nana Nikolaishvilli-Feinberg, Bentley Midkiff, Jonette Werley, Michal Krauze, Ronald Hamilton

91. *Epithelioid Schwannoma of a Spinal Nerve Root*

Rachael Vaubel, Howard Chang, Karen Fritchie, Mark Jentoft

92. *Intracranial Angiolipoma in a 23 year Old Male with Sturge-Weber Syndrome*

Christopher Jones, Aaron Wagner, Gary Pearl

93. *Intracranial Osteosarcoma Arising in Fibrous Dysplasia*

Christine James, Darnell Josiah, Patrick Bacaj, Charles Rosen, Kymberly Gyure

94. *Epstein-Barr Virus-Positive Primary CNS Lymphomas Associated with Intracranial Mass Lesions in Immunocompetent patients*

Yasuo Sugita, Koichi Ohshima, Jun Masuoka, Yoshizo Kimura, Koichi Higaki, Susumu Nakashima

95. *An Unusual Case of an EBV-positive CNS Lymphoma in an Immunocompetent Adult*

Brian Bockelman, Cristina Vincentelli, Vathany Sriganeshan, Amilcar Castellano-Sanchez

96. *Lymphomas in Intraoperative Consultations (IOC) in Neuropathology*

Murat Gokden and Melody Harrison

97. *Divergent Glioneuronal Differentiation in Metastatic Intracranial Neuroendocrine Carcinomas*

Boleslaw Lach, Suhita Joshi, Naresh Murty, Nasim Huq

98. *Experimental Photothrombotic White Matter Infarct with Marked Motor Deficit: A New Animal Model*

Min-Cheol Lee, Hyoung-Ihl Kim, Kyung-Wha Lee, Young Kim, Hyung-Sun Kim

99. *Cerebral Biopsies in Posterior "Irreversible" Encephalopathy Syndrome (PIES)*

Hannes Vogel, Jennifer Ziskin, Gregory Moes

100. *Histopathological Features of Intracranial Vascular Involvement in Neurofibromatosis Type I, Ehlers-Danlos Type IV, and FMD*

Bette Kleinschmidt-DeMasters1, Seth Lummus

	Molecular Phenotypes Joanna Phillips & Sriram Venneti Fashion Ballroom	**Muscle, Nerve, Infectious** Marta Margeta & Michael Lawlor Culture Ballroom
8:00- 8:15	101. *Chromosome Band 7q34 Deletions Resulting in KIAA1549-BRAF and FAM131B-BRAF Fusions in Pediatric Low Grade Gliomas* - Jacquelyn Roth, PhD	109. *Motor Nerve Biopsy* - Arthur Hays, MD
8:15- 8:30	102. *A Clinicopathologic Study of Hypothalamic Pediatric Low-Grade Gliomas with BRAF V600E Mutation* - Cheng-Ying Ho, MD, PhD	110. *Treatment with ActRIIB-mFc Improves Lifespan, Behavior and Pathology in the Acta1 H40Y Murine Model of Nemaline Myopathy* - Michael Lawlor, MD, PhD
8:30- 8:45	103. *Identification of Molecular and Pathologic Subsets of Low Grade Gliomas and Glioneuronal Tumors by microRNA profiling* - Heather Ames, MD, PhD	111. *Keap1/Nrf2 Stress Response Pathway in Autophagic Vacuolar Myopathies* - Marta Margeta, MD. PhD
8:45- 9:00	104. *Cytogenetic Progression of Oligodendroglioma Assessed Using Single Nucleotide Polymorphism Array* - David Nauen, MD, PhD	112. *A Novel MTM1 Mutation in a Case of X-linked Myotubular/Centronuclear Myopathy* - Nitin Agarwal
9:00- 9:15	105. *Next Generation Sequencing and Immunohistochemistry for EGFR, p53 and Mutant IDH1 in High-Grade Gliomas* - Lyndsey Emery, MD, PhD	113. *Congenital Myasthenic Syndrome with Vacuolar Changes and Tubular Aggregates Caused by Mutations in DPAGT1* - Carolyn Rysgaard, MD
9:15- 9:30	106. *Evaluation of Targeted Next Generation Sequencing (NGS) for Assessment of Variations in Gliomas* - Ada Baisre, MD	114. *Identification of a Novel Polyomavirus in a Pancreatic Transplant Recipient with Retinal Blindness and Vasculitic Myopathy* - Phyllis Faust, MD, PhD
9:30- 9:45	107. *Differential Expression of Genes in Primary and Recurrent GBM Suggests a Transition Toward More Aggressive Molecular Subtype* - Gerald Reis, MD, PhD	115. *Neisseria Elongata Encephalitis Presenting as an Enhancing Brain Mass* - Jennifer Cotter, MD
9:45- 10:00	108. *Reprogramming Cell Circuits in Glioblastoma* - Mario Suva, MD, PhD	116. *Pathology of HTLV-1 Infection in the Brain* - Jiancong Liang, MD, PhD

10:00 - 10:30 am — REFRESHMENT BREAK

10:30 - 11:30 — PARISI LECTURE

Human Parechovirus Encephalitis?

Clayton Wiley, MD, PhD

University of Pittsburgh, Pittsburgh, PA

11:45 am – 12:45 pm — Business Meeting II (Fashion Ballroom)

12:45 – 2:00 pm — Lunch Break

The Parisi Lecture

The Parisi Lecture was established in 2007. The lecture was named the Parisi Lectureship in honor of one of the American Association of Neuropathologists' exceptional members, Dr. Joseph E. Parisi. He has published seminal neuropathological studies on a wide range of diseases affecting the nervous system, with particular focus on neurodegenerative diseases and multiple sclerosis. He has held virtually every office of the Society, including President, and has served on several AANP committees. In 2006, his dedication and generosity were recognized with the Award for Meritorious Contributions to Neuropathology. He is considered by many the heart and soul of the association and a man worth emulating.

We are pleased to have **Clayton Wiley, MD, PhD,**
join our list of distinguished speakers.

2008
Claudia Lucchinetti

The Spectrum of CNS Inflammatory Demyelinating Diseases: From Pathology to Pathogenesis

2009
Hans Lassmann

Inflammation Induced Mitochondrial Injury: A Major Mechanism of Neurodegeneration

2010
Joseph Dalmau

Autoimmune Synaptic Encephalitis

2011
Steven S. Scherer

Molecular Pathologies at the Nodes of Ranvier

2012
Bruce D. Trapp

Neuronal Damage in Multiple Sclerosis

2013
Albee Messing

GFAP: Friend or Foe

2014
Clayton Wiley

Human Parechovirus Encephalitis?

Human Parechovirus Encephalitis?

Clayton A. Wiley MD/PhD

At the end of this activity learners should be able to:
1.Describe the importance of Picornavirus infections in mediating severe CNS disease in the newborn.
2.Review the spectrum of histopathological changes that accompany enteroviral infection in the newborn and how they mimic those seen in periventricular leukomalacia (PVL).
3.Explain the importance of maternal humoral immunity and newborn exposure to adult enteroviral infections in the outcome of viral encephalitis.

Human Parechoviruses (HPeV) belong to the single-stranded positive-sense family of Picornaviruses. Originally classified as enteroviruses 22 and 23, they were reclassified in 1999 into their own genus on the basis of nucleotide sequence analysis. Currently 16 genotypes of HPeV are recognized. They are prevalent infectious agents, however, most infections are asymptomatic. Serological studies have suggested early seroconversion with a mean age of 14.6, 6.3 and 0.7 months for HPeV1, HPeV2 and HPeV3 respectively. HPeV3 was first reported in 2004 and genetic analysis suggests it may be a recently evolved (emergent) agent. Nevertheless it is a common cause of neonatal sepsis and meningitis in particular. Infection of preterm and term infants with HPeV3 is associated with seizures and periventricular white matter lesions. Despite unremarkable and "sterile" cerebrospinal fluid (CSF), HPeV3 nucleic acids can be amplified from CSF and occasionally throat and rectal swabs. We report the pathological findings in the first 2 autopsied cases of HPeV3 encephalitis. Both children were born approximately one month premature and neurologically intact but after a few weeks developed seizures and radiological evidence of white matter lesions. Neuropathology demonstrated classical periventricular leukomalacia (PVL) in the absence of an immune response. HPeV3 sequences were identified in nucleic acid extracted from brain, serum and CSF. Immunohistochemical and in situ hybridization probes were used to detect HPeV infection of neuroglial cells surrounding the PVL and in stem elements of the germinal matrix. While neonatal HPeV3 infections are common and frequently subclinical, they are usually diagnosed only in the presence of neurological damage. The robust viral neurotropism suggests that subclinical infections could manifest more subtle neurological damage.

Human Parechovirus Infection of the CNS

Harvala H, Simmonds P. Human parechoviruses: biology, epidemiology and clinical significance. J Clin Virol 2009; 45:1-9.
Stanway G, Joki-Korpela P, Hyypia T. Human parechoviruses--biology and clinical significance. Rev Med Virol 2000; 10: 57-69.
Verboon-Maciolek MA, Groenendaal F, Hahn CD, et al. Human parechovirus causes encephalitis with white matter injury in neonates. Ann Neurol 2008; 64:266-73.
Levorson RE, Jantausch BA. Human parechoviruses. Pediatr Infect Dis J 2009; 28(9): 831-2.

Human Picornavirus infection of CNS

Tyler KL, Martin JB. Infectious diseases of the central nervous system. Philadelphia, F.A. Davis, 1993.
Dotta F, Censini S, van Halteren AG, et al. Coxsackie B4 virus infection of beta cells and natural killer cell insulitis in recent-onset type 1 diabetic patients. Proceedings of the National Academy of Sciences of the United States of America. 2007; 104: 5115-20.
Palacios G, Oberste MS. Enteroviruses as agents of emerging infectious diseases. Journal of neurovirology. 2005; 11: 424-33.
Brokhman I, Pomp O, Fishman L, et al. Genetic modification of human embryonic stem cells with adenoviral vectors: differences of infectability between lines and correlation of infectability with expression of the coxsackie and adenovirus receptor. Stem Cells Dev. 2009; 18: 447-56.
Feuer R, Mena I, Pagarigan RR, et al. Coxsackievirus B3 and the neonatal CNS: the roles of stem cells, developing neurons, and apoptosis in infection, viral dissemination, and disease. The American journal of pathology. 2003; 163: 1379-93.
Wong KT, Munisamy B, Ong KC, et al. The distribution of inflammation and virus in human enterovirus 71 encephalomyelitis suggests possible viral spread by neural pathways. Journal of Neuropathology and Experimental Neurology. 2008; 67: 162-9.
Lafaille FG, Pessach IM, Zhang SY, et al. Impaired intrinsic immunity to HSV-1 in human iPSC-derived TLR3-deficient CNS cells. Nature. 2012; 491: 769-73.
Zhang SY, Jouanguy E, Ugolini S, et al. TLR3 deficiency in patients with herpes simplex encephalitis. Science. 2007; 317: 1522-7.

Dr. Wiley did his undergraduate training at the University of Chicago and his MD/PhD training in Neurosciences at the University of California San Diego. This was followed by Anatomical Pathology residency at University of California San Francisco and Neuropathology fellowship back at UCSD. In 1985 Dr. Wiley was appointed Assistant Professor of Pathology at UCSD where he advanced to the rank of full professor. In 1993 he was recruited to the University of Pittsburgh Medical Center as Director of the Division of Neuropathology and its fellowship program. Through out his professional career he has been actively involved in educating physician scientists at both pre- and postgraduate stages. From 1997 to 2012 Dr. Wiley served as Director of the Pittsburgh Medical Scientist Training Program and Associate Dean in the University of Pittsburgh School of Medicine. Throughout this time he was actively involved in the National Association of MD/PhD Programs and the MD/PhD Section of the GREAT group in the AAMC where he served as President and Chair respectively. He also served on the AAMC Council of Academic Societies Task Force on Dual Degree Programs. Dr. Wiley has maintained an active NIH funded research program investigating the pathogenesis of viral mediated neurodegeneration. He has published over 200 peer-reviewed publications and was elected a Fellow of the American Association for the Advancement of Science in 1997. Currently his research is focused on the role of innate and adaptive immunity in protecting the brain from viral infections. Dr. Wiley is an active member of the Pittsburgh Center for Vaccine Research where he is currently collaborating on developing vaccine strategies to prevent viral encephalitis.

	Tumors 3 Bette K. DeMasters & Fausto Rodriguez Fashion Ballroom	**ALS, FTD, PD** Eileen Bigio & Edward B. Lee Culture Ballroom
2:00- 2:15	117. WITHDRAWN	125. *Incidental Brain Pathologies in Prospectively Followed Normal Elderly Brain Bank Volunteers* - Brittany Dugger, PhD
2:15-2:30	118. *Aberrantly Expressed ErbB4 Promotes Malignant Peripheral Nerve Sheath Tumor Pathogenesis* - Stephanie Brosius, BA	126. *Neuropathologic Analysis Of 59 Centenarian Brains* - Masaki Takao, MD
2:30- 2:45	119. *Succinate Dehydrogenase (SDH) Deficiency in Non-familial Pituitary Adenomas* - Mark Curtis, MD, PhD	127. *Association Between Hippocampal Sclerosis of Aging (HS-Aging) Pathology and Sulfonylurea Drug Exposure in NACC* - Peter Nelson, MD, PhD
2:45- 3:00	120. *Immune Cell Infiltrates in Sparsely Granulated and Densely Granulated Growth Hormone Pituitary Adenomas* - Jian-Qiang Lu, MD, PhD	128. *The Role of the Unfolded Protein Response in Sporadic and Lrrk2-Driven Parkinson's Disease* - Annie Hiniker, MD, PhD
3:00- 3:15	121. *Histological Predictors of Progression and Radiosensitivity in Cranial Atypical Meningioma after Total or Subtotal Resection* - Chunyu Cai, MD, PhD	129. *The Basal Forebrain and Hypothalamus are Involved in a Subset of Patients with Amyotrophic Lateral Sclerosis (ALS)* - Matthew Cykowski, MD
3:15- 3:30	122. *Meningiomas That Meet Grade II by 3 Criteria Have an Increased Rate of Recurrence* - Christina Appin, MD	130. *Methylation of RAN Translated Glycine-Arginine Dipeptide Repeats in C9ORF72 FTLD and ALS* - Dennis Dickson, MD
3:30- 3:45	123. *NHERF1/EBP50 is a Marker of Ependymoma* - Maria-Magdalena Georgescu, MD, PhD	131. *C9orf72 Hypermethylation Influences Repeat Expansion Associated Pathology in ALS/FTD* - Edward B. Lee, MD, PhD
3:45- 4:00	124. *A Novel Medulloblastoma Model Mimicking Human Disease* - Guo Zhu, MD, PhD	132. *A Loss of Function Mutation in the C9ORF72 Mouse Ortholog Results in Motor System Degeneration* - Daniel Mordes, MD, PhD

4:00 - 4:30 pm — REFRESHMENT BREAK

4:30 – 5:00 pm — What Every Neuropathologist Needs to Know I

10 Things Every Neuropathologist Ought to Know about Prions

Mark L. Cohen, MD

University Hospitals Case Medical Center, Cleveland, OH

5:00 – 5:30 pm — What Every Neuropathologist Needs to Know II

Molecular Testing of Metastatic Brain Tumors

Ronald L. Hamilton, MD

University of Pittsburgh Medical Center, Pittsburgh, PA

10 THINGS EVERY NEUROPATHOLOGIST OUGHT TO KNOW ABOUT PRIONS

Mark Cohen, M.D.
University Hospitals Case Medical Center

At the end of this activity learners should be able to:
1.List 3 presenting features that suggest diagnoses other than Jakob-Creutzfeldt disease.
2.Explain the value of a positive CSF-tau result in the differential diagnosis of Jakob-Creutzfeldt disease.
3.Compare and contrast protein misfolding cyclic amplification (PMCA) with real-time quaking induced conversion (RT-QuIC).
4.List 5 brain regions that must be examined to adequately characterize human prion disease.

Although most neuropathologists do not need to be overly concerned with the histopathological features of prion diseases (mostly because our laboratories refuse to process the tissue), we are often called upon to be "content experts", especially when prion disease is suspected clinically (either rightly or wrongly). This 30 minute presentation will attempt to address the most common questions that neuropathologists are likely to be asked regarding this uncommon and poorly understood group of diseases.

1.Is it CJD or JCD?
2.How common is sporadic JCD?
3.Which clinical features should (and should not) suggest JCD?
4.What is the utility of CSF studies in JCD diagnosis?
5.What is PMCA? RT-QuIC?
6.Which tissues are potentially infectious, and what can be done to eliminate infectivity?
7.What are prion strains?
8.What's going on with variant CJD?
9.Is chronic wasting disease transmissible to humans?
10.How can I help with prion surveillance?

1.Klug GM, Wand H, Simpson M, et al. Intensity of human prion disease surveillance predicts observed disease incidence. J Neurol Neurosurg Psychiatry. 84:1372-7, 2013.
2.Takada LT, Geschwind MD. Prion diseases. Semin Neurol. 33:348-56, 2013
3.Hamlin C, Puoti G, Berri S, et al. A comparison of tau and 14-3-3 protein in the diagnosis of Creutzfeldt-Jakob disease. Neurology. 79:547-52., 2012
4.Belay ED, Blase J, Sehulster LM, et al. Management of neurosurgical instruments and patients exposed to Creutzfeldt-Jakob disease. Infect Control Hosp Epidemiol. 2013 Dec;34:1272-80.
5.Barria MA, Balachandran A, Morita M, et al. Molecular barriers to zoonotic transmission of prions. Emerg Infect Dis. 20:88-97, 2014

Mark Cohen is Professor of Pathology & Neurology at University Hospitals Case Medical Center and Histopathologist for the National Prion Disease Pathology Surveillance Center. His presence in this program is a testament to Churchill's maxim that success consists of going from failure to failure without loss of enthusiasm, as well as material evidence in support of the existence of the dopeler effect (the tendency of stupid ideas to seem smarter when they come at you rapidly).

WHAT EVERY NEUROPATHOLOGIST SHOULD KNOW: MOLECULAR TESTING OF BRAIN METASTASES

Ronald L. Hamilton, M.D
Associate Professor of Neuropathology
University of Pittsburgh

At the end of this activity learners should be able to:
1) Discuss contemporary molecular testing for the major CNS metastases: lung, breast, and melanoma.
2) Review specific mutations found in subtypes of these malignancies.
3) Describe how molecular testing is now used by clinicians to stratify patients for specific therapies of brain metastases.

Insertions and/or deletions within the EGFR gene and EML4–ALK chromosomal translocation in lung cancer, amplification of the ERBB2 gene and HER2 protein overexpression in breast cancer, and BRAF mutation in melanoma distinguish subsets of cancer amenable to unique treatment approaches. Biologically targeted agents are established therapies for these tumor subsets, and have important implications for brain metastases, including uncommon but impressive responses of EGFR-mutant lung tumours to agents such as erlotinib. Similar responses to crizotinib, and especially to second generation ALK inhibitors such as LDK378, have been observed in NSCLC with the EML4–ALK translocations. In addition, efficacy has been observed with the combination of trastuzumab and lapatinib in HER2-positive breast cancer, resulting in some control of brain metastases in these patients. Finally, successful control of (at least small) melanoma metastases by BRAF inhibitors and the immunomodulatory agent ipilimumab, has been encouraging.

1. Berghoff AS, Magerle M, Ilhan-Mutlu A, et al. Frequent overexpression of ErbB - receptor family members in brain metastases of non-small cell lung cancer patients. APMIS. 2013 Jun 12
2. Berghoff AS, Birner P, Streubel B, Kenner L, Preusser M. ALK gene aberrations and the JUN/JUNB/PDGFR axis in metastatic NSCLC. APMIS. 2014 Apr 3.
3. Peddi PF, Hurvitz SA. PI3K pathway inhibitors for the treatment of brain metastases with a focus on HER2+ breast cancer. J Neurooncol. 2014;117:7-13.
4. Hohensee I, Lamszus K, Riethdorf S, et al. Frequent genetic alterations in EGFR- and HER2-driven pathways in breast cancer brain metastases. Am J Pathol. 2013;183:83-95.
5. Azer MW, Menzies AM, Haydu LE, Kefford RF, Long GV. Patterns of response and progression in patients with BRAF-mutant melanoma metastatic to the brain who were treated with dabrafenib. Cancer. 2014;120:530-6.
6.Dummer R, Goldinger SM, Turtschi CP, et al. Vemurafenib in patients with BRAF(V600) mutation-positive melanoma with symptomatic brain metastases: final results of an open-label pilot study. Eur J Cancer. 2014;50:611-21.

Dr Hamilton is a graduate of the University of Nebraska Medical Center and was trained in Anatomic Pathology and Neuropathology at the University of California San Diego and at the University of Pittsburgh. He is an Associate Professor of Pathology at the University of Pittsburgh School of Medicine. His research interests include Lewy Body Dementia, Chronic Traumatic Encephalopathy and molecular oncology in pediatric and adult brain tumors, and molecular oncology of metastatic tumors to the brain.

Poster Session II

(Not Offered for CME Credit)

133. *Autopsy Neuropathology of a Case of Microcephaly-Thin Corpus Callosum Syndrome*

Malak Abedalthagafi, David Urion, Elizabeth Engle, Hannah Kinney, Rebecca Folkerth

134. *Rhombencephalosynapsis in a Patient with Goldenhar Syndrome*

Melissa Gener, Stephanie Slemp, Justin Richey, Dean Hawley, Jose Bonnin

135. *Characterization of Neuropathologic Findings in a 16 month-old Female with Pfeiffer Syndrome*

Bret Evers, Dennis Burns, Charles Timmons, Veena Rajaram

136. *Novel Nonsense Mutation of FLNA in a 26 year Old Female with Periventricular Nodular Heterotopias and Severe Emphysema*

Patricia Kirby, Erica Savage, Benjamin Darbro

137. *Cortical and Leptomeningeal Angiomatosis Associated Epilepsy in a 68 Year Old Female: A Case Report*

Nishant Tiwari, Daniel Grimmer, J Goodman, Meenakshi Bhattacharjee

138. *Neuropathology of a Case of Joubert Syndrome with an Unusual Genetic Background*

Douglas Miller, Eric Destrampe, Carl Stacy

139. *BRAFV600E Mutation is Not Associated with Focal Cortical Dysplasia*

Sonika Dahiya, Devon Haydon, Jeffrey Leonard, David Gutmann, Robert Schmidt

140. *Development of the Hippocampal Formation in Human: Part II- Dentate Gyrus*

Sara Cipriani, Catherine Verney, Jeannette Nardelli, Pierre Gressens, Homa Adle-Biassette

141. *Aprosencephaly-Atelencephaly in a Neonate with Severe Facial features of Holoprosencephaly*

Nitin Agarwal and Ada Baisre

142. *Shaken Baby – Review of Old Cases*

Roland Auer

143. *Toddler with Microcephaly and Basal Ganglia Calcifications: ? Aicardi-Goutieres Syndrome*

Veena Rajaram, Esther Bit-Ivan, Russell Fetzer, Jason Wang, Naseem Uddin

144. *Mesial Temporal Sclerosis with Dysplastic Dentate Fascia Neurons: A Case Report*

Matthew Wood and Arie Perry

145. *Glycogen Storage Disease Type III: Neuropathologic Phenotype Associated with Mutations in the AGL Gene*

Kathy Newell, Robert Reynders, Jill Murrell

146. *Inadvertent Intrathecal Vincristine Administration with Widespread Axonal Injury Demonstrated by APP Immunohistochemistry*

Jesse Kresak, Marie Rivera-Zengotita, Martha Burt, Anthony Yachnis

147. *Leptomeningeal Transthyretin Amyloidosis: A Case Study*

Jennifer Ziskin, Anna Okumu, Christopher Adams, Edward Plowey

148. *3R Predominant Tauopathy with Globular Glial Inclusions*

Stewart Neill, Jonathan Glass, Allan Levey, Monica Parker, Deborah Cooper, Marla Gearing

149. *Childhood Neurodegenerative Disease with Widespread Tauopathy*

Dibson Gondim, Jill Murrell, Adrian Oblak, Deborah Sokol, Laurence Walsh, Gregory Bosh, Ruben Vidal, Michel Goedert, Bernardino Ghetti, Jose Bonnin

Poster Session II

(Not Offered for CME Credit)

150. *Creutzfeldt-Jakob Disease: Review of the Past Twenty Three Year Experience*

Francine Epperson, Adrian Oblak, Jill Murrell, Rose Richardson, Brenda Dupree, Pedro Piccardo, Pierluigi Gambetti, Bernardino Ghetti

151. *Gerstmann-Sträussler-Scheinker Disease PRNP A117V: Prion Protein Deposition in Neurosensory Retina*

Kathy Newell, Francine Epperson, Masaki Takao, Martin Farlow, Frederick Unverzagt, Bernardino Ghetti

152. *Familial Creutzfeldt-Jakob Disease Associated with the PRNP E200K-129V Haplotype: Report of a New Kindred*

Adrian Oblak, Jill Murrell, Rose Richardson, Francine Epperson, Bernardino Ghetti, Wei Chen, Daniel Bonnin, Martin Farlow, Pierluigi Gambetti

153. *Gerstmann-Sträussler-Scheinker Disease Associated with the P102L-129M Haplotype: Clinical and Pathologic Heterogeneity*

Daniel Bonnin, Jill Murrell, Francine Epperson, Matthew Frosch, E Tessa Hedley-Whyte, Bernardino Ghetti

154. *Neuronal Tau and Parenchymal PrP in Gerstmann-Straussler-Scheinker Disease Associated with the PRNP Q217R Mutation*

Adrian Oblak, Jill Murrell, Rose Richardson, Francine Epperson, Bernardino Ghetti

155. *The Presence of Total Tau in Peripheral Tissues of Alzheimer's Disease*

Brittany Dugger, Charisse Whiteside, Chera Maarouf, Thomas Beach, Travis Dunckley, Bessie Meechoovet, Alex Roher

156. *Neuropathologic Assessment of Alzheimer's Disease Neuroimaging Initiative (ADNI) Participants*

Nigel Cairns, Richard Perrin, Erin Householder, Deborah Carter, Benjamin Vincent, John Morris

157. *The Dominantly Inherited Alzheimer Network (DIAN): The Essential Role of the Neuropathology Core*

Nigel Cairns, Richard Perrin, Erin Householder, Deborah Carter, Benjamin Vincent, John Morris

158. *Alzheimer Disease and Diffuse Lewy Body Disease Coexist in a PSEN1 N135S Mutation Carrier*

Bernardino Ghetti, Jill Murrell, Martin Farlow, Frederick Unverzagt, Adrian Oblak, Francine Epperson, Rose Richardson, Shannon Risacher, Andrew Saykin, John Morris, Nigel Cairns

159. *Familial Dementia Associated with the Novel PSEN1 F176V Mutation*

Bernardino Ghetti, Adrian Oblak, Rose Richardson, Francine Epperson, Jill Murrell

160. *Neuropathologic Phenotype of Dementia Associated with PSEN1 H163R Mutation*

Bernardino Ghetti, Jill Murrell, Adrian Oblak, Rose Richardson, Jordan Grafman, Alan Lerner

161. *Oxidative Damage is Correlated with Mitochondrial Abnormalities in Aging but not Alzheimer Disease*

George Perry, Rasha Shammas, Xiongwei Zhu, Xinglong Wang, Hyoung-gon Lee, Rudy Castellani, Akihiko Nunomura

162. *Screening for Pathology Consistent with Chronic Traumatic Encephalopathy in Neurodegenerative Diseases*

Kevin Bieniek, Ann McKee, Dennis Dickson

163. *"APP and AB-immunoreactive Plaques" in Traumatic Brain Injury: An Underappreciated Neuropathological Finding?*

Ross Reichard and Cristiane Ida

164. *Myopericytoma Involving The Orbit In A 78-year-old Female*

Jenny Smith and Jeremy Deisch

165. *An Unusual Presentation of Gliosarcoma: A Case of Primary Tumor Arising in the Optic Nerve*

Yevgeniy Sychev, Luis Gonzalez-Cuyar, Raghu Mudumbai, C. Dirk Keene

166. *The Prognostic Value of EGFR Amplification in MGMT Methylated Glioblastomas*

Seema Shroff, Katharine McNeill, Irina Mikolaenko, David Zagzag, Matija Snuderl

Poster Session II

(Not Offered for CME Credit)

167. *Improved Adenoviral Transduction of Glioblastoma Cells by Aptamer Modification*

Qinwen Mao, Hao Chen, Esther Bit-Ivan, Eileen Bigio, Haibin Xia

168. *Overexpression of Eg5 Correlates with High Grade Astrocytic Neoplasm*

Liqiong Liu, Xichun Liu, Marcus Mare, Aaron Dumont, Haitao Zhang, Dong Yang, Zhenggang Xiong

169. *Detection of CD133 Expression in U87 Glioblastoma Cell Line Using Novel Anti-CD133 Monoclonal Antibodies*

Esther Bit-Ivan, Haibin Xia, Eileen Bigio, Qinwen Mao

170. *Recurrent Glioblastoma Is Associated With Increased Expression of Mesenchymal Markers*

Matthew Wood, Gerald Reis, Joanna Phillips

171. *Genomic Sequencing Reveals PI3KCA Mutations in Two Cases of Glioblastoma with Sarcomatous Differentiation*

Lyndsey Emery, Elizabeth Azzato, Robert Daber, Maria Martinez-Lage

172. *Glioblastoma with Melanoma-like Histology and Widespread Extracranial Metastases. A Case Report with EM Analysis*

Michael Presta, Rami Al-Rohil, Walter Jacobson, Julie Pilitsis, Jiang Qian

173. *Prevalence, Pathology, Prognostic Factors, and Survival in Latino Americans with Glioblastoma*

Maryam Shabihkhani, Yalda Behbahanian, Kourosh Naeini, Diviya Gupta, Bowen Wei, Gregory Lucey, Lauren Hanna, Desiree Sanchez, Sergey Mareninov, Timothy Cloughesy, William Yong

174. *Glioblastoma Presenting As Lung Metastasis: A Unique Case Report And Review Of The Literature*

Denise Ng, Annie Wu, Yalda Behbahanian, William Yong, Neda Moatamed, Negar Khanlou, Phioanh Nghiemphu, Linda Liau, Harry Vinters

175. *VE1 Immunoreactivity Patterns in Epithelioid Glioblastomas Positive for BRAF V600E Mutation*

Bette Kleinschmidt-DeMasters, Nicholas Foreman, Seth Lummus

176. *"Gliomatosis encephali" as a Novel Category of Brain Tumors: The First Autopsy Case Report of Gliomatosis Cerebelli*

Asa Nakahara, Toshikazu Yoshida, Masanobu Yazawa, Takashi Ehara, Jun Nakayama, Akiyoshi Kakita, Ryosuke Ogura, Mika Asakawa, Emi Suzuki-Kouyama, Kiyomitsu Oyanagi

177. *Astrocytomas as Secondary Tumors in Patients Treated for Medulloblastoma: A Case Series*

Dilys Chen, Marco Hefti, Sandro Santagata, Rolf Pfannl

178. *ImmunoFISH is a Reliable Technique for the Assessment of 1p and 19q Status in Oligodendrogliomas*

Peter Gould, Céline Duval, Marie de Tayrac, François Sanschagrin, Karine Michaud, Stéphan Saikali

179. *A Case of Bone-Only Extraneural Metastatic WHO Grade II Oligodendroglioma*

Zachary Hoffer, Desiree Marshall, Luis Gonzalez-Cuyar, C. Dirk Keene, Theodore Burke, Marc Chamberlain, Donald Born, Margaret Flanagan

180. *Alpha-Internexin Immunoexpression in Oligodendrogliomas – Potential Diagnostic and Pathogenetic Relevance*

Suash Sharma and Dustin Gertsch

181. *Ki-67 and GFAP Dual Stain Employed in Surgical Neuropathology*

Paul Mckeever, Sandra Camelo-Piragua, Kristina Fields, Jonathan Mchugh

182. *Methylthioadenosine Phosphatase Expression in Pilocytic Astrocytomas and its Relationship with Oncogene-Induced Senescence*

Aline Becker, Cristovam Scapulatempo-Neto, Weder Menezes, Carlos Clara, Ricardo Oliveira, Helio Machado, Marileila Varella-Garcia, Luciano Neder, Rui Reis

183. *Immunohistochemical Characteristics of Centyrin & DARPin Targets in Brainstem Gliomas and Correlation with Molecular Markers*

Viktor Zherebitskiy, Sakir Gultekin, Cynthia Hawkins, Christopher Corless, Kellie Nazemi, Charles Keller

Poster Session II

(Not Offered for CME Credit)

184. *Adult Brainstem Gliomas: A Case Series With Radiological, Pathological, And Clinical Correlation*

Kimmo Hatanpaa, Gregory Martin, Jack Raisanen, Chan Foong, Bruce Mickey, Charles White, Robert Oberle

185. *Pediatric Brainstem Tumors with Features of Angiocentric Glioma: Report of Two Cases*

Marie Rivera-Zengotita, Jesse Kresak, David Pincus, Anthony Yachnis

186. *Composite Atypical Ganglioglioma (GG)-Pleomorphic Xanthoastrocytoma (PXA), Recurrent: A Case Report*

Areli Cuevas-Ocampo and Luis Moral

187. *Molecular Analysis of Pilomyxoid Astrocytoma and Variable Tendency Toward Maturation to Pilocytic Astrocytoma*

Bette Kleinschmidt-DeMasters, Andrew Donson, Nicholas Foreman

188. *BRAF Testing in Pleomorphic Xanthoastrocytoma: Insights from 3 Pediatric Cases*

David Pisapia and Ehud Lavi

189. *Cerebellar Pleomorphic Xanthoastrocytoma in a Patient with Neurofibromatosis Type 1: A Case Report*

Hidehiro Takei and Meenakshi Bhattacharjee

190. *Anaplastic Pleomorphic Xanthoastrocytoma: Report of Two Diverse Cases*

Suash Sharma and Ravi Raghavan

191. *Anaplastic Pilocytic Astrocytoma of the Cerebellum with a BRAF V600E Mutation*

Ada Baisre, Nitin Agarwal, Anjali Seth, James Liu

192. *Low Grade Glioneuronal Neoplasm of the Third Ventricle With PIK3CA Mutation. A Case Report and Review of the Literature*

Patrick Malafronte, Laurence Davidson, Brett Theeler

193. *Multinodular and Vacuolating Neuronal Lesions: An Evolving Classification of Low-Grade Neoplasms of the Cerebrum*

Lyndsey Emery, Donald O'Rourke, Maria Martinez-Lage

194. *Synaptophysin Positive Atypical Neuroepithelial Tumor With Diffuse GFAP Expression at Recurrence: A Case Report*

Areli Cuevas-Ocampo and Luis Moral

195. *An Intracranial Secondary Malignant Neoplasm after Wilms Tumor in a Four- Year -Old Girl*

Rong Li, Dava Sue Cleveland, Jeffrey Blount, Alyssa Reddy, James Post, David Kelly

196. *Malignant Evolution of Desmoplastic Glioma with Anaplastic Features, Including Postmortem Examination*

Catherine Stefaniuk, Mohamed El Hag, Duncan Stearns, Michael Coffey, Mark Cohen, Marta Couce

197. *Disseminated Choroid Plexus Papillomas in Adults. A Review of the Literature*

Marwah Abdulkader, Gregory Bosh, Edward Dropcho, Aaron Cohen-Gadol, Jose Bonnin

198. *Recurrent Subependymoma of Fourth Ventricle with Unusual Histological Features: A Case Report*

Nishant Tiwari, Suzanne Powell, Hidehiro Takei

199. *Ependymal Tumor of the Pituitary*

Derick Aranda, Joseph Parisi, John Atkinson, Mark Jentoft

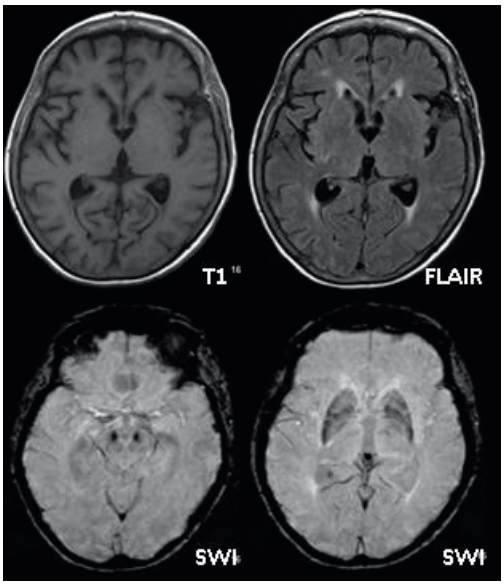
200. *Combining Whole Slide Imaging with Telepathology for Neuropathology Intraoperative Consultation*

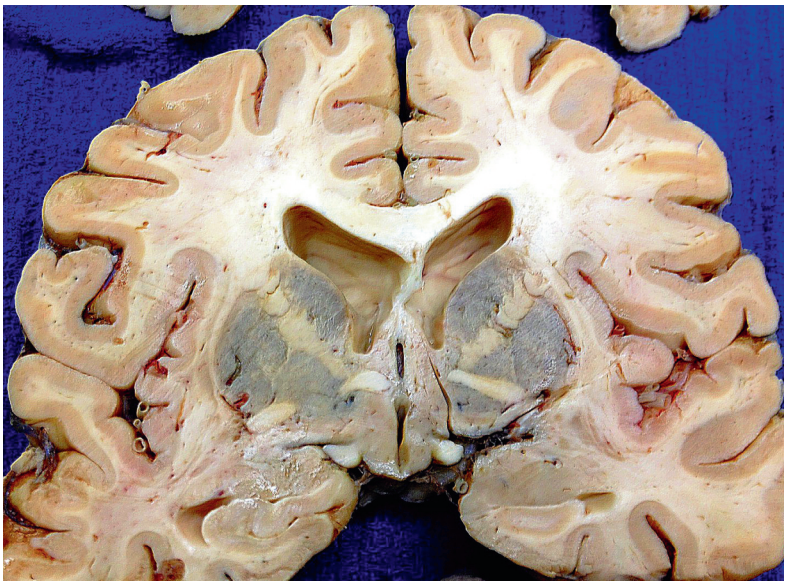
Jo Elle Peterson, Andreana Rivera, J Goodman, Michael Thrall, Suzanne Powell

55TH ANNUAL DIAGNOSTIC SLIDE SESSION 2014
CASE 2014-1

Submitted by
Vanessa D. Smith, Dianne Wilson, Janna Neltner, Peter Nelson and Craig Horbinski
Department of Pathology, University of Kentucky Chandler Medical Center,
Lexington KY 40536

Clinical History:
The patient was a 72-year-old woman hospitalized for management of pleural and pericardial effusions and shock complicating chronic rheumatoid arthritis. As the patient was encephalopathic on admission, neurologic evaluation was limited. Per her family and primary care provider, the patient had a history of depression and possible wide-based gait, but no other overt neurological symptoms. She was employed as a substitute teacher and living independently. MRI of the head without gadolinium contrast was obtained, showing generalized cerebral and cerebellar atrophy, in addition to susceptibility-weighted imaging signal loss involving the bilateral substantia nigra and striatum, suggesting increased iron (radiographic image provided). She expired ten days after admission following withdrawal of life support.





Autopsy Findings:
Gross CNS findings were significant for well-delineated prominent blue coloration of the bilateral caudate nucleus, putamen and globus pallidus. The gross exam was otherwise unremarkable.

Materials Submitted:
1 H&E stained slide of the basal ganglia, serial MRI imaging and post-mortem gross photograph

Points for Discussion:
1. Additional stains
2. Differential diagnosis
3. Disease characteristics

55th ANNUAL DIAGNOSTIC SLIDE SESSION 2014
CASE 2014-2

Submitted by:
Joseph M Fullmer MD, PhD
Upstate Medical University
Neuropathology and Surgical Pathology
750 East Adams Street, UH-6804B
Syracuse, NY 13210

Clinical History:
The patient is a 74 yo woman with a skull based tumor. She underwent resection of what was reported to be a pituitary adenoma, evaluated at an outside hospital 16 years ago in 1997, underwent radiation therapy and had reportedly done well in the interim while receiving intermittent follow up. However, several months before presentation (early 2013), she had mild bitemporal hemianopsia, slowly progressing right cheek numbness, chronic rhinosinusitis, and deviated nasal septum. Examination of CT scan revealed a 4.3 cm mass centered in the sphenoid sinus eroding right sphenoid bone, invading and extending beyond the sella, infiltrating muscle and the right carotid canal wall. Due to having a pacemaker, the patient was unable to undergo MRI which limited evaluation to some degree. The lesion was in the previous radiation field and beyond. Radiographically it was uncertain if the current lesion was a recurrence, related to any previous treatment (i.e. radiation induced), or something entirely new.

The mass was biopsied. H&E sections revealed the mass as shown. Many stains were performed and the lesion was positive for Vimentin, variably positive for S-100 and negative for HMB-45, MART-1, PAX-8, neurofilament, chromogranin, synaptophysin, and GFAP. Other stains were performed and will be reported at the DSS. She underwent a partial resection (tumor near the carotid could not be resected and tumor was adherent to some of the bones in the sinuses) where the majority of tumor was resected. The immunophenotype of the resected material was identical to that seen in the biopsy. The patient is receiving radiation therapy and follow up imaging. Slides from the 1997 lesion reported to be a pituitary adenoma were also obtained and will be discussed at the DSS.

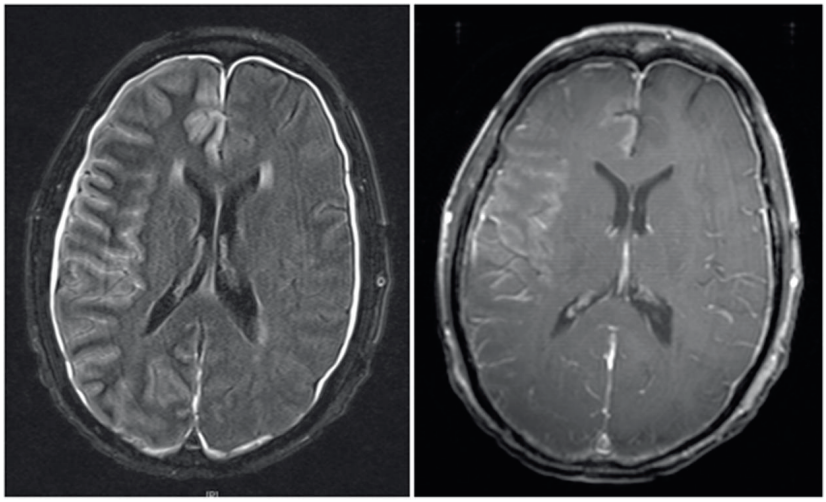
Material submitted:
H&E stained slide of resected lesion

Points for discussion:
1. Diagnosis
2. Obtaining previous material, when possible
3. Appropriate workup of pituitary adenomas

55TH ANNUAL DIAGNOSTIC SLIDE SESSION 2014
CASE 2014-3

Submitted by: Pallavi P. Gopal, MD, PhD and Edward B. Lee, MD, PhD
Division of Neuropathology, Department of Pathology and Laboratory Medicine
University of Pennsylvania, Philadelphia, PA 19104

Clinical History: The patient is a 57 year old male with history of non-small cell lung cancer status post pneumonectomy and whole brain radiation therapy for brain metastases eight years prior to presentation. He was in his usual state of health until two days prior to admission, when he complained of headache for which he took imitrex and excedrin, and went to sleep. However, he did not wake up the next day and apparently had an episode of bladder incontinence. The patient was taken to the ED by his family, where he had altered mental status and fever (102.4 deg). On neurologic exam, he was able to follow commands, but had a left facial droop, left hemiplegia, and left sided neglect with right gaze preference. A stroke evaluation was negative. A head CT showed an old lacunar infarct but no acute hemorrhage. An MRI showed cortical FLAIR signal in the right frontoparietal region. An EEG revealed right centrotemporal slowing and decreased background activity on the right. Cerebrospinal fluid analysis revealed elevated protein at 74 mg/dl, normal glucose at 50 mg/dl, 0 WBC/microliter, and 0 RBC/microliter. CSF cultures and PCR for VZV and JC virus were negative. A comprehensive workup for CSF and serum paraneoplastic autoantibodies was negative. A repeat MRI performed one week after initial presentation was notable for diffuse gyral thickening in the right hemisphere (increased from prior study) and progressive diffuse meningeal enhancement.



Brain MRI. Left: Axial T1 Post contrast, Right: Axial Flair T2

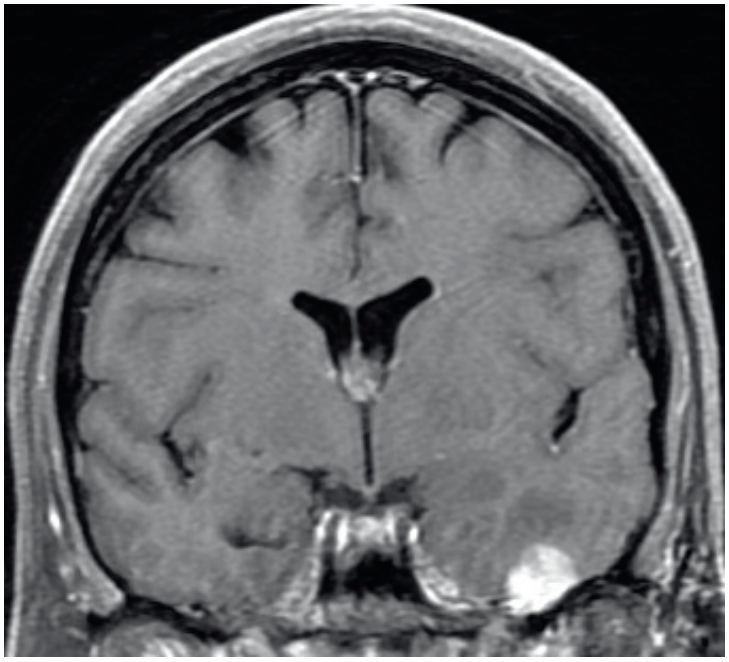
Material submitted:
1. Image of brain MRI: Axial T1 post contrast and axial Flair T2
2. H&E section of “Right frontal lesion" (Virtual Slide)

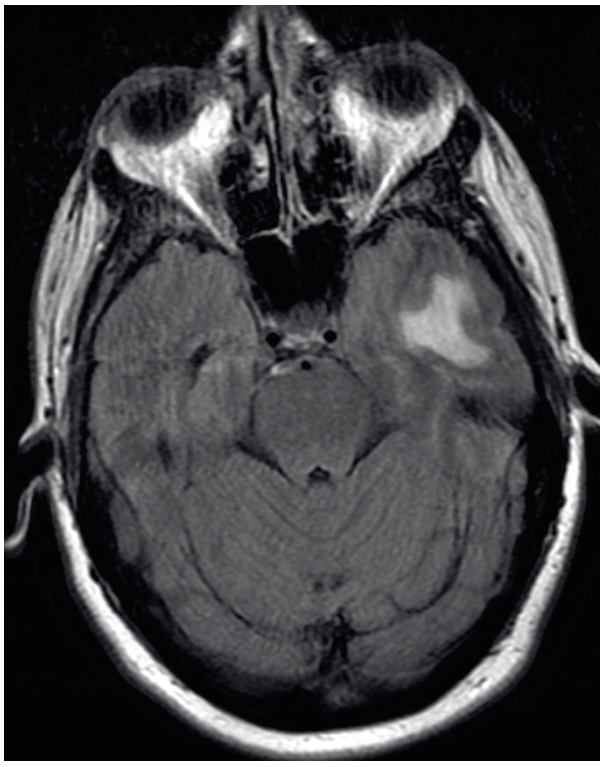
Points for discussion:
1. Additional stains?
2. Differential diagnosis
3. Pathogenesis

55th ANNUAL DIAGNOSTIC SLIDE SESSION 2014
CASE 2014-4

Submitted by:
Leonidas Arvanitis M.D. and Geoffrey Murdoch M.D.
Division of Neuropathology, Department of Pathology,
University of Pittsburgh Medical Center,
200 Lothrop Street, South Tower, Room M8715, Pittsburgh, PA 15213

Clinical History: The patient is a 39 year-old female who presented to UPMC after having a witnessed seizure while shopping. Her past medical history was significant only for a biopsy proven benign thyroid nodule. She's newly married and has a remote history of tobacco use. She was transferred to the emergency room where an MRI was performed and showed a 1.7 cm mass along the floor of the left middle cranial fossa with adjacent mild vasogenic edema in the elevated overlying left temporal lobe. The patient underwent a left temporal craniotomy with subsequent excision.





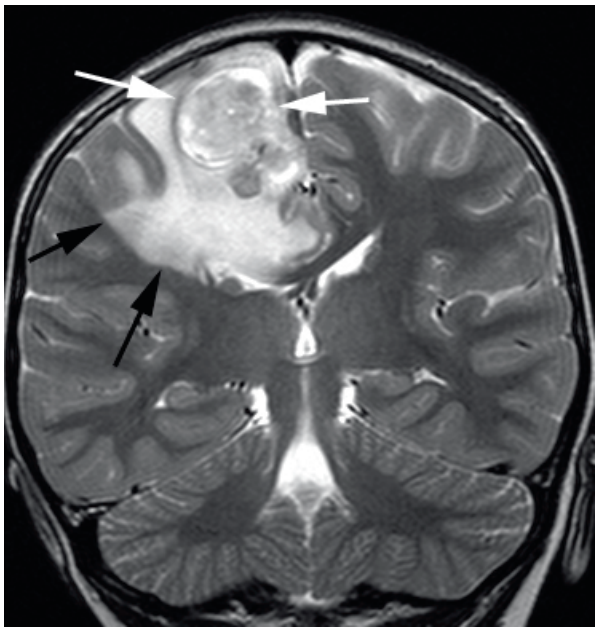
Material submitted: MRI images (T1+contrast and FLAIR), Scanned H&E section

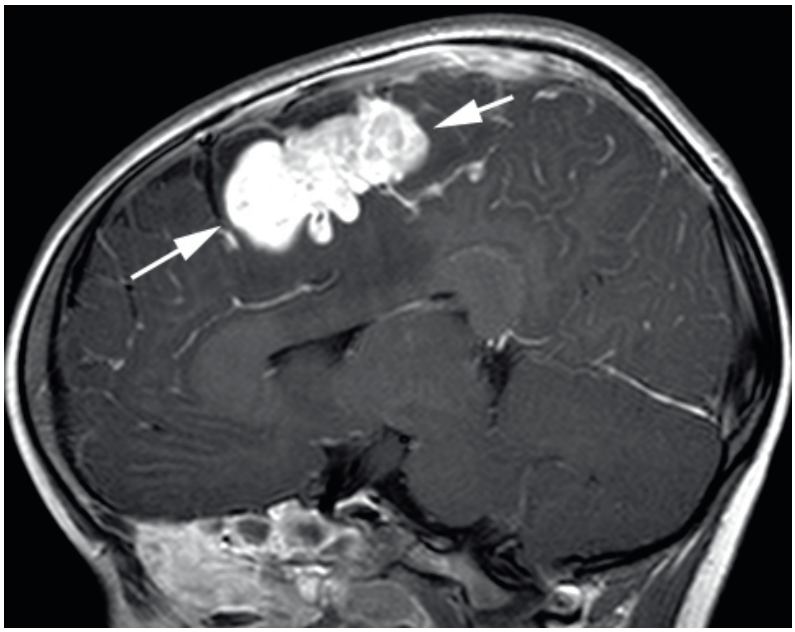
Points for discussion:
1. Diagnosis
2. Differential Diagnosis
3. Outcome

55th ANNUAL DIAGNOSTIC SLIDE SESSION 2014
CASE 2014-5

Submitted by:
Esther N. Bit-Ivan[1], Jason Wang[2], Jason Park[2],
Korgun Koral[2], Charles Timmons[2], and Veena Rajaram[2]
1.Northwestern University/Feinberg School of Medicine, Chicago, IL
2.Children's Medical Center, Dallas, TX

Clinical History:
The patient is a 5 year old female with a history of macrocephaly, developmental delay, seizure disorder, and cerebellar ectopia. She underwent neuroimaging in the form of CT or MRI periodically, the last of which was a head CT obtained 20 months prior to presentation and was normal. She presented to the emergency room with bilateral lower extremity weakness lasting about two hours with concomitant headache, and one episode of emesis. Two weeks prior to presentation, she had had a viral upper respiratory infection. There was no history of trauma. The emergent head CT and subsequent brain MRI showed an intensely enhancing mass (measuring 5.1 cm x 3.1 cm x 3.1 cm) in the right parasagittal frontal lobe. The mass was associated with extensive vasogenic edema of the right frontal lobe and leftward shift of the midline structures. Excision of the lesion was attempted where the tumor "seemed to blend into the brain".





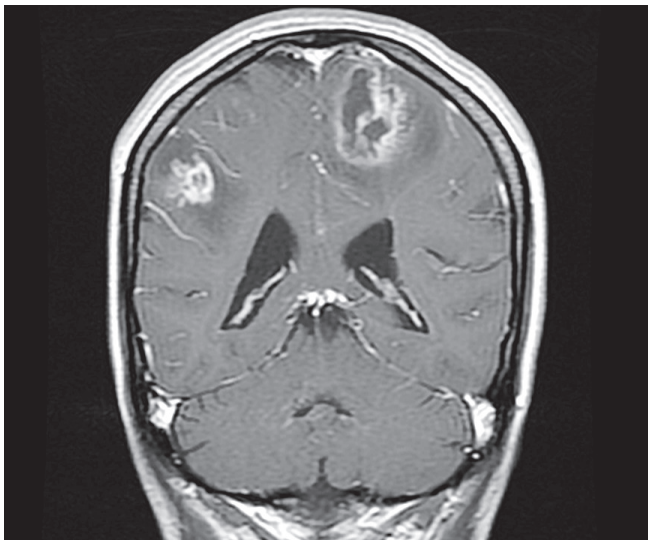
Material submitted: MRI images at initial presentation and H&E stained slide of the mass

Points for discussion:
1. Diagnosis and differential diagnosis
2. Immunohistochemical and genetic findings

55TH ANNUAL DIAGNOSTIC SLIDE SESSION 2014
CASE 2014-6

Submitted by:
Matthew D. Cykowski, MD, Suzanne Z. Powell, MD, and J. Clay Goodman, MD
Department of Pathology and Genomic Medicine, Houston Methodist Hospital, and
Department of Pathology and Immunology, Baylor College of Medicine
6565 Fannin Street, Suite M227, Houston, Texas 77030

Clinical History:
A 49-year-old right-handed woman originally from Honduras was admitted with a 3-week history of progressive altered mental status, headache, and right-sided weakness. On the day of symptom onset, she presented to an outside hospital and MRI of the brain revealed two ring-enhancing lesions associated with edema (Figure 1). She was also diagnosed with AIDS (CD4 count of 38 cells/uL and an HIV viral load of 375,000 copies/mL). The patient underwent an MRI-guided biopsy of the left parietal lesion at the outside hospital. The patient was hospitalized for two additional weeks and eventually was discharged on sulfadiazine and pyrimethamine based on the biopsy diagnosis. On admission to Ben Taub General hospital, she was afebrile and physical examination was notable for altered mental status and weakness of the right upper and lower extremities (Medical Research Council (MRC) grade of 3/5). There was no sensory deficit. MRI of the brain showed worsening ring-enhancing lesions within the right superior frontal gyrus (1.4 x 1.2 cm) and left parietal lobe (2.4 x 2.2 cm), moderate vasogenic edema and regional mass effect, and adjacent leptomeningeal enhancement. She was started on oral sulfadiazine, pyremethamine, and glucocorticosteroids. On hospital day 5, the patient had worsening mental status and a CT of the head showed enlargement of the right frontal lesion with increased edema.



The brain biopsy slides were obtained from the outside hospital. The patient was treated with the appropriate therapy and HAART and she survived but remains severely impaired.

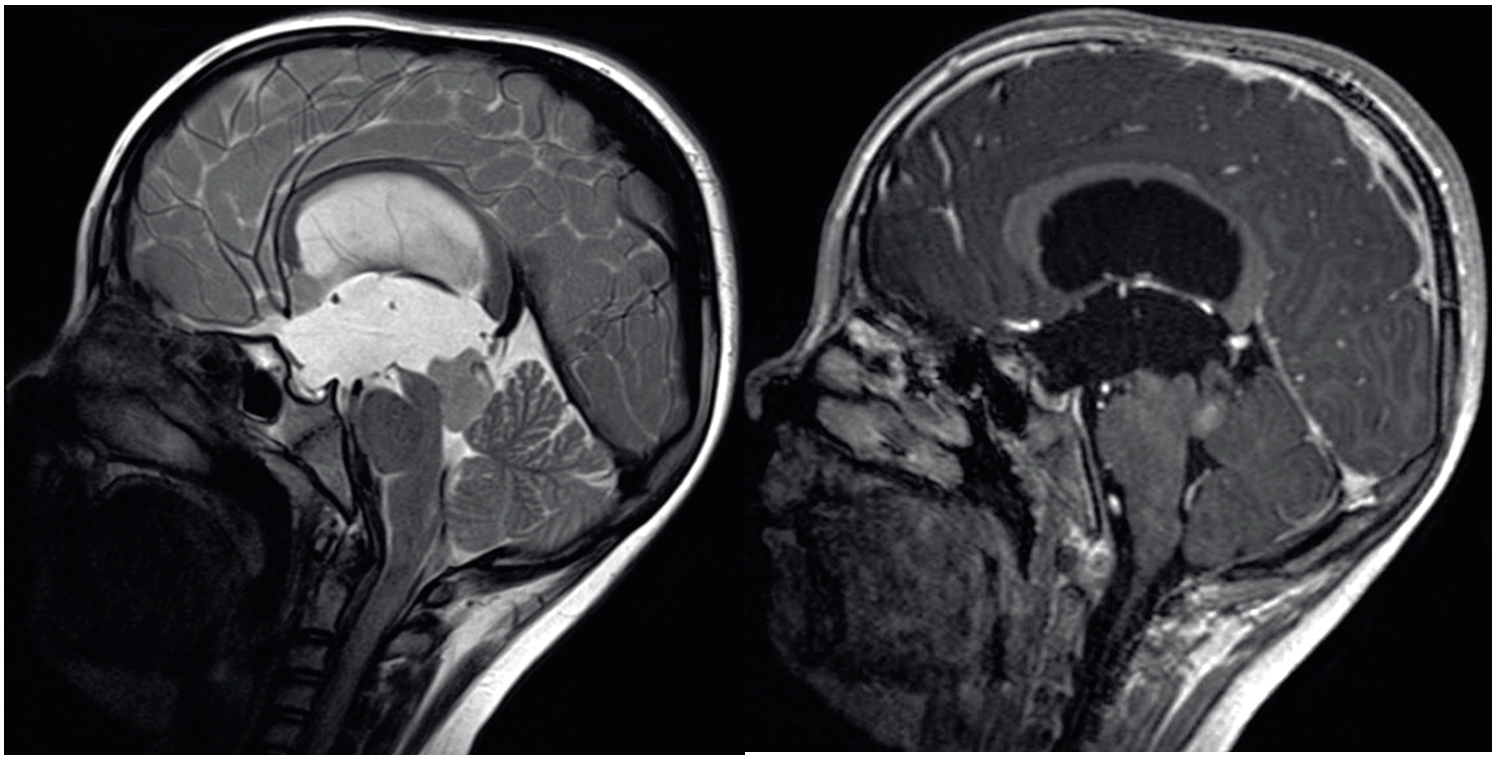
Material submitted:
1. Virtual H&E stained glass slide from a biopsy of left parietal mass.
2. Coronal MRI of the brain.

Points for discussion:
1. What are the important epidemiologic factors underlying this disease and how are these relevant to the practice of neuropathology in the United States?
2. What are the neurologic sequelae that may arise from this disease?

55th ANNUAL DIAGNOSTIC SLIDE SESSION
CASE 2014 – 7

Submitted by:
Sanda Alexandrescu, M.D.1, Clinton Turner M.D.2, and Arie Perry, M.D.1,
Department of Pathology, University of California San Francisco, San Francisco, CA 94143
Department of Anatomical Pathology, Auckland City Hospital, New Zealand2

Clinical history: 7-year-old girl with a medical history of headaches of two years duration. The past medical history was otherwise unremarkable. Magnetic resonance imaging (MRI) of the brain with and without contrast showed a relatively discrete mass in the tectal area, blocking the aqueduct of Sylvius and causing hydrocephalus (Fig.1). The mass demonstrated focal contrast-enhancement (Fig. 2). A biopsy was submitted for evaluation.



Material submitted:
1) Brain MR images (sagittal T2, sagittal T1+contrast)
2) One hematoxylin-eosin-stained virtual slide

Points for discussion:
1) Differential diagnosis
2) Ancillary studies
3) Prognostic implications

55th ANNUAL DIAGNOSTIC SLIDE SESSION 2014
CASE 2014-8

Submitted by: Julia Keith MD, FRCPC
Department of Anatomical Pathology
Sunnybrook Health Sciences Centre
University of Toronto
2075 Bayview Avenue, room E403
Toronto, Ontario, Canada
M4N 3M5
(416)480-6100 x 88055

Clinical History:
A previously well 18-year-old man presented with a 2 month history of headache, progressive clumsiness and difficulty walking. Neurological examination documented nystagmus, dysarthria, and ataxia. MRI of the brain revealed multiple T2 hyperintense lesions throughout both cerebellar hemispheres and the cerebellar folia enhanced following gadolinium administration with a leptomeningeal pattern. CSF analysis revealed cellular pleocytosis (69 WBC/hpf (lymphocytic predominance) with mild elevation of protein (0.468 g/L). CSF microbiological studies, flow cytometry and cytology were negative. CT chest, abdomen and pelvis, and testicular ultrasound were normal. Over the ensuing 3 days the patient's cognitive status deteriorated and repeat MRI showed worsening of the cerebellar lesions. Given the non-diagnostic investigations and worsening clinical condition, biopsy of the left cerebellum was undertaken to investigate for potentially treatable conditions including lymphoma.

Material submitted:
H&E section of left cerebellar biopsy

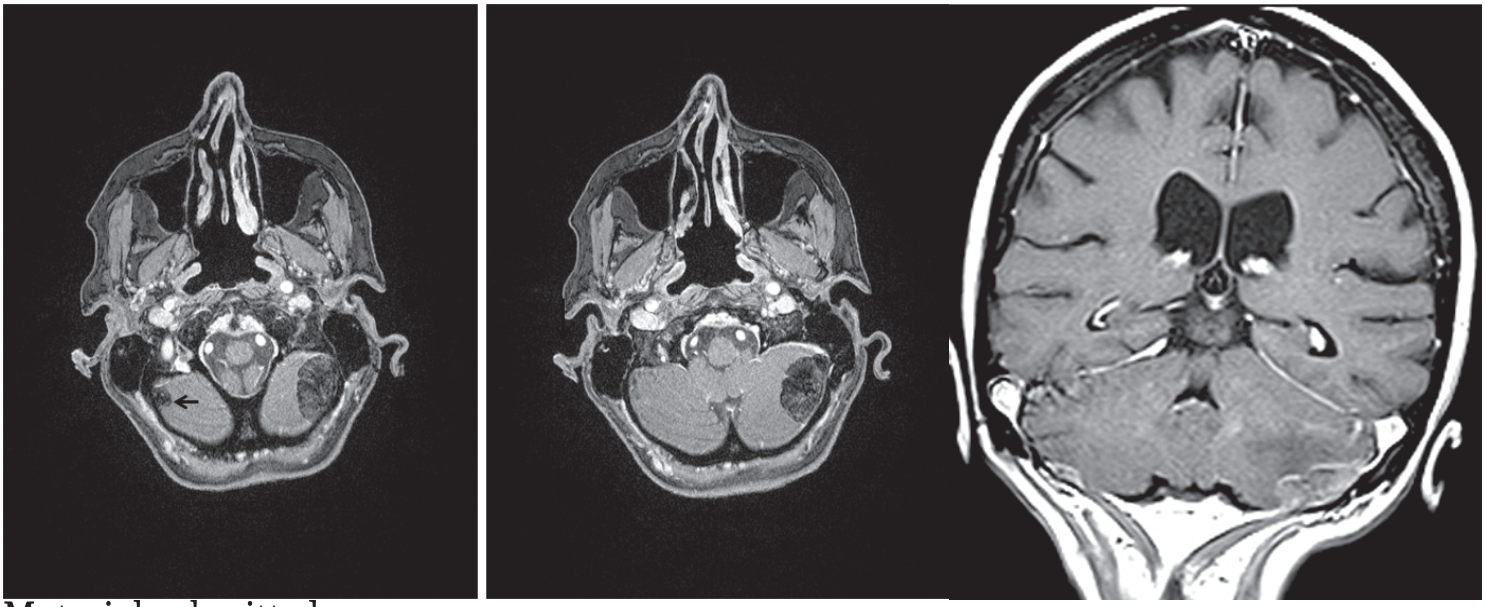
Points for discussion:
1. Diagnosis
2. Pathogenesis

55th ANNUAL DIAGNOSTIC SLIDE SESSION 2014
CASE 2014 – 9

Submitted by:
Jesse Lee Kresak, MD, Marie Rivera-Zengotita, MD, Ahmed Alkhasawneh, MD, Samer Al-Quran, MD, Anthony T. Yachnis, MD
University of Florida College of Medicine, 1600 SW Archer Rd
PO Box 100275, Gainesville, FL, 32610

Clinical History:
A 64-year-old female presented with constant right-sided frontal headache that radiated to her cheek and jaw for one month. The patient had a past medical history of cervical cancer, myelofibrosis secondary to polycythemia vera, splenomegaly, and GERD. She had been receiving blood transfusions approximately every 3 weeks and had been hospitalized 3 weeks prior for urosepsis secondary to nephrolithiasis.

An MRI study on admission revealed 2 extra-axial posterior fossa lesions along the inferior cerebellar surfaces that showed variable post-contrast enhancement (left and center image). The left lesion measured 2.5 x 1.2 cm and showed evidence of perilesional edema by T2 (right image) and FLAIR images. The right lesion measured 1.1 x .05 cm. Susceptibility weighted images suggested hemosiderin deposition. A surgical procedure was performed, which yielded the tissue submitted for study.



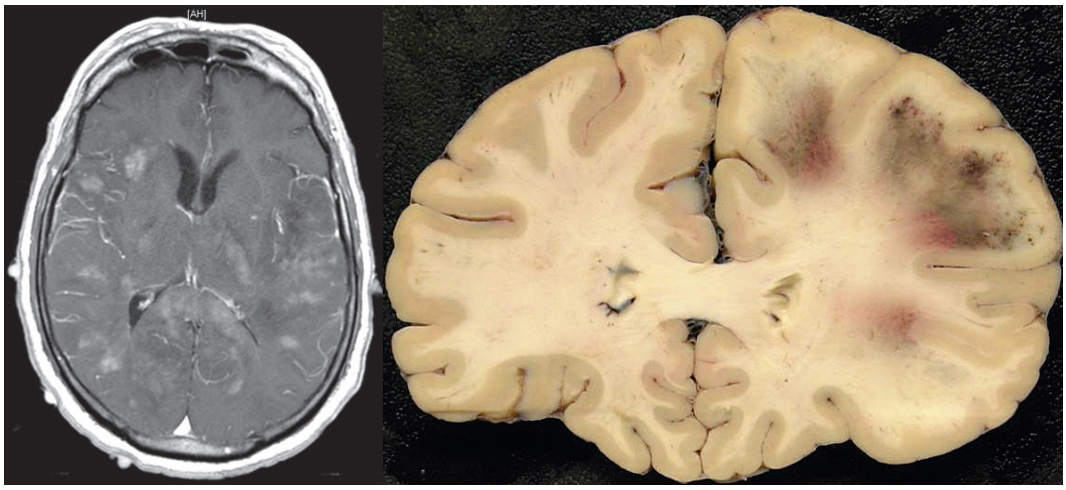
Material submitted:
MRI of brain and H&E stained section of left cerebellar lesion

Points for discussion:
1. Diagnosis
2. Etiology

55TH ANNUAL DIAGNOSTIC SLIDE SESSION 2014
CASE 2014-10

Submitted by:
Jane Cryan MD, Rebecca Gillani MD PhD, Rebecca Folkerth MD.
Brigham and Women's Hospital, Harvard Medical School, Boston MA

Clinical History:
A 76 year old man with hypertension and hyperlipidemia presented with 1 week of painful right T7 dermatomal rash and paresthesia in the bilateral lower extremities. Physical exam noted right T7 vesicular/erythematous rash, full strength throughout with the exception of mild hip flexor weakness. Reflexes were absent at the knee and trace at the ankles. He walked with an ataxic gait, had diminished pain, light touch and proprioception to the knees. He was treated with Solumedrol and Acyclovir IV. Thoracic spine MRI was limited by patient discomfort. Within several hours, he had speech difficulty, and right arm and bilateral leg weakness. Exam revealed intact cranial nerves, upper limb strength but 0/5 hip flexor strength bilaterally. The following day, he developed dysphagia and had increased work of breathing. He now had 0/5 strength throughout the upper and lower extremities with the exception of 4/5 strength in the hands and ankles. Reflexes were absent. CSF glucose 62, total protein 191.5, RBC 11857, WBC 130 (80% Neut, 16% Lymph); Serum varicella zoster virus PCR was positive; CSF positive IgG to VZV. He was intubated after which he was awake following commands. Eyes were open with full extraocular movements. He had profound proximal greater than distal weakness in all extremities. His exam deteriorated and by day 6 he was ophthalmoplegic and quadriparetic. His blood pressure was labile on pressors. Spine MRI showed questionable cauda equina enhancement. Brain MRI revealed enhancement of cranial nerves III and the right VI/VIII nerves. EMG/NCS revealed severe motor and sensory axonal polyneuropathy with demyelinating features. On day 17, repeat brain MRI was abnormal. After family discussion, he was made comfortable and extubated. An autopsy was performed.



Autopsy findings:
Zoster-like skin ulcers, no evidence of ongoing/active VZV skin infection (no viral cytopathic changes; negative VZV immunostain)
Hepatosplenomegaly
Pulmonary edema

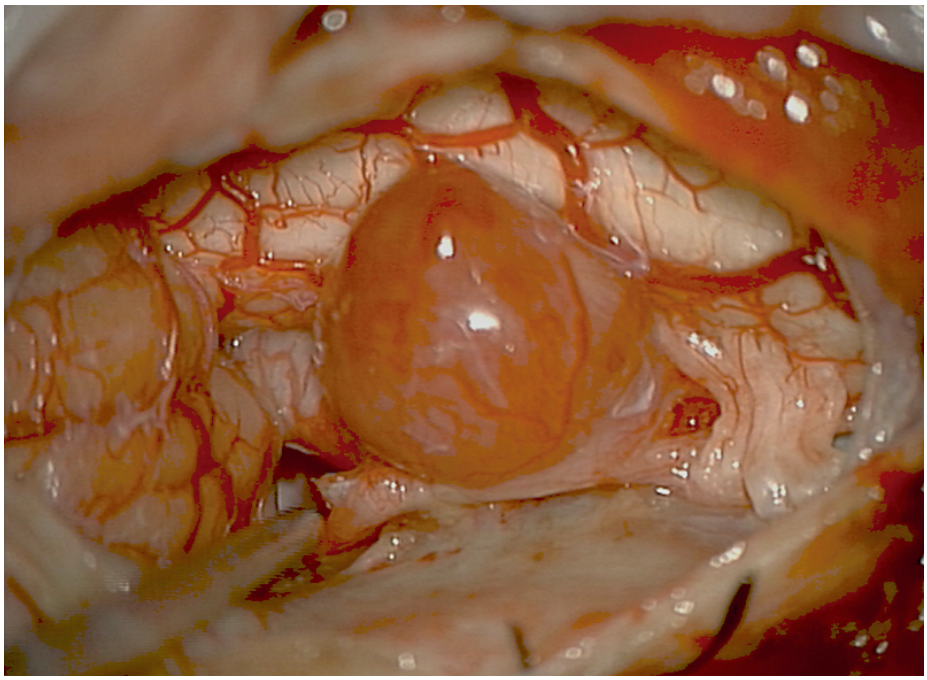
Material submitted:
H&E section(2) right frontal lobe and cauda equine;
MRI brain T1W post contrast, Coronal section at genu of CC.

Points for discussion:
Is there a unifying diagnosis?

55TH ANNUAL DIAGNOSTIC SLIDE SESSION 2014
CASE 2014-11

Submitted by:
Inma Cobos, M.D, PhD. and E Tessa Hedley-Whyte, M.D.
C S Kubik Laboratory of Neuropathology
Department of Pathology, Harvard Medical School
Massachusetts General Hospital, WRN 325
55 Fruit Street,
Boston, MA 02114

Clinical History:
A 64 year-old woman with past medical history of metastatic melanoma presented with progressively worsening headaches primarily in the left portion of her neck, extending into the suboccipital area and the area behind her left ear, developing over several months. An MRI of the brain performed to evaluate for metastatic disease showed a 7 x 3 mm homogeneously enhancing mass on the left side of the spinal cord at the C1-C2 area along the intradural course of the vertebral artery. A repeat MRI performed 5 weeks later showed that the mass was now 1 x 1 cm. An angiogram was negative for vascular malformation. A gross total resection of an intradural, extramedullary vascular-appearing tumor on the left side of the spinal cord at the level of the C1 root was performed.



Gross findings:
1 x 1 x 0.6 cm, well-circumscribed, shiny, firm mass with a fleshy, red, rubbery cut surface.

Material submitted:
Gross photograph and H & E (virtual) cross-section of the mass.

Points for discussion:
1. Diagnosis
2. Prognosis

Notes

SUNDAY, JUNE 15, 2014

PRESIDENTIAL SYMPOSIUM
State of the Art: Brain Tumor Diagnosis

8:00 – 8:05 am — Welcome and CME Pre-test
Anthony T. Yachnis, MD
University of Florida College of Medicine, Gainesville, FL

8:05 - 9:00 am — **Matthew T. Moore Lecture**
WHO's Next?
Suggested Guidelines for the Next WHO Classification of Brain Tumors
David N. Louis, MD
Massachusetts General Hospital, Boston, MA

9:00–9:45am — *Comprehensive and Integrative Genomic Characterization of Diffuse Lower Grade Gliomas*
Daniel Brat, MD, PhD
Emory University, Atlanta, GA

9:45 – 10:30 am — AWARD PRESENTATIONS AND REFRESHMENT BREAK

10:30 – 11:15 am — *Glioblastoma: The TCGA Findings*
Kenneth Aldape, MD, PhD
MD Anderson Cancer Center, Houston, TX

11:15 – 12:00 pm — *Meningioma Grading and Potential Biomarkers*
Arie Perry, MD
UCSF, San Francisco, CA

12:00 pm — INSTALLATION OF NEW OFFICERS AND ADJOURNMENT

PRESIDENTIAL SYMPOSIUM
State of the Art: Brain Tumor Diagnosis

Presidential Symposium Objectives

Anthony T. Yachnis, MD
University of Florida College of Medicine
Gainesville, FL

1. Describe how future diagnostic approaches to brain tumors will become more integrated with advanced imaging and molecular information.

2. Identify new insights provided by the Cancer Genome Atlas (TCGA) studies that use multiple advanced molecular platforms for glioma characterization.

3. Discuss advantages and limitations of current meningioma grading.

4. Review potentially useful immunohistochemical and genetic biomarkers for meningioma diagnosis and prognosis.

The Matthew T. Moore Distinguished Lectureship

In 1970, Dr. Matthew T. Moore made a contribution to the AANP to establish the Moore Award, which is given annually to recognize the "Best Paper on Clinico-Pathological Correlation Presented at the Annual Meeting." In 1987, Rechelle Fishman, a former patient of Dr. Moore, bequeathed $75,000 to the Moore Award Fund. Dr. Moore requested that this bequest be used to establish a "Rachelle Fishman-Matthew Moore Distinguished Lectureship" (later shortened to just the "Moore Lectureship"), which is "to be given by a distinguished lecturer, on a subject which represents the leading edge of advanced research in neuropathological subjects of contemporary interest. The lecture is to take place on the day of the Presidential Address." In 1988, it was decided that this Lectureship would replace the "Distinguished Lectureship" that had been sponsored each year by the Association. The Moore Lecturer is selected annually by the President in conjunction with the Nominating Committee and the Chair of the Program Committee.

We are pleased to have **David N. Louis, MD**
join our list of distinguished speakers as part of this year's Presidential Symposium.

1990 Robert H. Horvitz
The Genetic Control of GABAergic and Serotonergic Neuronal Differentiation and of Programmed and Pathological Cell Death in a Nematode Nervous System

1991 Charles Janeway
Induction, Mediation and Continuation of Immune Responses

1991 Ramzi S. Contran
Cytokine-Endothelial Interactions in inflammation, Immunity and Vascular Injury

1992 D. Carleton Gajdusek
The genetic Control of Spontaneous Generation of Infectious Amyloids: Kuru-CJD-GSS-Scrapie-BSE

1995 Leroy Hood
Deciphering the Human Genome: Implciations for Medicine of the 21st Century

1996 Martin Raff
Programmed Cell Death--Mechanisms and Social Controls

1998 James Eberwine
Single Cell Molecular Neuropathology

1999 Richard T. Johnson
Viral Pathogenesis, an Overview

2001 Dennis Choi
Ischemia-Induced Perturbations in Neuronal Ionic Homeostasis

2002 J. William Langston
MPTP: Its impact on Parkinson's Disease Research

2003 Carolyn C. Meltzer
Future of PET in the Study of Neurological Disease

2004 Henry L. Paulson
Toward Understanding the Pathogenesis of Repeat Expansion Diseases

2005 Peter St. George Hyslop
Molecular Genetics and Biology of Alzheimer Disease Generate Clues for Therapeutics

2006 Keith L. Ligon
Stem and Progenitor Cell Insights into Gliomas: Novel Origins, Markers and Targets

2008 William Mobley
Trafficking Trophic Signals to Prevent Neurodegeneration

2009 Donald W. Cleveland
From Charcot to Lou Gehrig: Mechanisms and Treatment of ALS

2011 Mark Gilbert
RTOG: Clinical Trials and the Increasing Role of Neuropathology

2012 Kevin P. Campbell
Mechanistic and Molecular Insights into the Pathogenesis of Glycosylation – Deficient Muscular Dystrophy

2013 Bradley Hyman
How does Alzheimer Disease Know Neuroanatomy?

2014 David N. Louis
WHO's Next? Suggested Guidelines for the Next WHO Classification of Brain Tumors

Matthew T. Moore Lecture

WHO's next? Suggested guidelines for the next WHO classification of brain tumors

David N. Louis, MD
Massachusetts General Hospital, Boston, MA

Learning objectives:
1. To identify the reasons that tumor classification and grading systems are used for both patient and population management.
2. To review proposed guideline differences between current and future WHO brain tumor classifications

The accurate classification of human neoplasms not only has implications for the care of individual patients (in estimating prognosis and guiding therapy) and for the conduct and interpretation of clinical trials of new therapeutic approaches, but also for the analysis and understanding of basic scientific experimental studies, for the elucidation of population-based disease trends that may implicate environmental or other etiologies, and for the allocation of resources by governments and health insurers to support health care. Periodic revisions of tumor classifications therefore have diverse and important effects on many aspects of individual and population health. In recognition of this level of importance, over the past approximately half century, the World Health Organization (WHO) has sponsored tumor classifications by international experts. The last classification of brain tumors (WHO 2007) emerged from a consensus meeting in 2006. Over the past decade, insights into the molecular basis of human tumors have radically changed both our biological understanding of neoplasms as well as our abilities to diagnose tumors and estimate their prognosis and likelihood of response to specific therapies. Brain tumors have shared in this molecular revolution, and in some areas have been at the forefront. As such, a critical scientific question has arisen with major practical consequences: how should molecular information change brain tumor classification? The lecture will present the background behind the current status of brain tumor classification and report on the results of a recent meeting that addressed this question and has begun to generate guidelines for greater incorporation of molecular pathology in the next WHO classification scheme.

David N. Louis, MD, is the Benjamin Castleman Professor of Pathology at Harvard Medical School and pathologist-in-chief at Massachusetts General Hospital. Pathology at MGH has nearly 100 faculty members, over 100 trainees and over 700 employees, and performs about 10 million laboratory tests as well as 80,000 surgical pathology evaluations, 400,000 microbiology analyses, and 50,000 cytologies each year. Dr. Louis' own clinical neuropathology practice and research focuses on brain tumors, with an emphasis on the molecular basis of malignant gliomas and the application of molecular diagnostics to glioma classification. He has published more than 250 original articles, as well as numerous reviews, chapters and books. His laboratory was the first to demonstrate that molecular approaches could be used to subdivide malignant gliomas in a biologically relevant manner, and that molecular approaches could be used to predict the response of particular malignant gliomas to specific therapies. This work has contributed to worldwide adoption of molecular testing for the management of patients with these tumors. Dr. Louis has received a number of prestigious awards for his work in brain tumors and was lead editor of the 2007 World Health Organization classification of central nervous system tumors. Dr. Louis served as President of the American Association of Neuropathologists in 2009-10, gave the Saul Korey Lecture at the 2008 meeting and has participated in many committees.

Comprehensive and Integrative Genomic Characterization of Diffuse Lower Grade Gliomas

Daniel Brat, MD, PhD
Emory University, Atlanta, GA

1) Explain the Cancer Genome Atlas (TCGA) approach to characterize lower grade gliomas by multiple advanced molecular platforms.
2) Describe the 3 molecular classes of lower grade gliomas that were identified in the TCGA analysis.
3) Review how IDH wild type lower grade gliomas have molecular alterations similar to glioblastoma.
4) Discuss how IDH mutant lower grade gliomas are characterized by either TP53 mutations or 1/19q co-deletion.

Diffuse lower grade gliomas (LGGs) are infiltrative neoplasms of the central nervous system that include astrocytoma, oligodendroglioma and oligo-astrocytoma histologies of grades II and III. We present a comprehensive analysis of 293 LGGs using multiple advanced genomic, transcriptomic and proteomic platforms from The Cancer Genome Atlas to provide a deeper understanding of the molecular features of this group of neoplasms, to classify them in a clinically-relevant manner, and to provide a public resource that identifies potential targets for emerging therapies. Clustering of gene expression, miRNA expression, protein expression, DNA methylation and DNA copy number profiles identified four, four, four, five and three clusters, respectively. When combined, the clustering results overwhelmingly pointed towards a natural grouping of LGG into three superclusters, which can be explained as follows: 1. IDH1/IDH2 wildtype 2; IDH1/IDH2 mutant and chromosome arms 1p/19q intact; and 3. IDH1/IDH2 mutant and co-deletion of chromosome arms 1p/19q. The three groups all included samples from grade II and III astro-, oligo- and oligo-astrocytoma histologies. Based on this result we evaluated genomic alterations according to these three LGG categories. The IDH wildtype subtype was characterized by genomic alterations that resembled GBM, including gains of EGFR, CDK4 and MDM4, mutations in NF1, EGFR and PTEN. Approximately 55% of these cases were anaplastic astrocytomas, WHO grade III, while the remainder were from a mixed grade and histology. The IDH mutant/1p-19q intact group showed focal amplification of PDGFRA, MYC and CCND2, 95% mutated TP53 and 84% with inactivation of ATRX. This group was not dominated by a single grade or histology, but represented all types. Finally, the IDH mutant and 1p/19q co-deleted subtype harbored frequent mutations in CIC, FUBP1, NOTCH1, TERT, relatively few copy number alterations and was populated mostly by oligodendrogliomas (84%). IDH mutant groups associated had a favorable prognosis, while IDHwt LGGs had clinical behaviors resembling GBM. Based on integrated analysis of genome, transcriptome, methylome and proteome we showed that LGG naturally separates into three distinct groups that traversed grades and histologies. Importantly, we identified a subtype with an LGG-like histology but a molecular GBM profile and clinical behavior resembling GBM. Classification of LGG can be greatly enhanced using IDH1/IDH2 mutation and 1p/19q deletion status.

Huse JT, Wallace M, Aldape KD,et al. (2014) Where are we now? And where are we going? A report from the Accelerate Brain Cancer Cure (ABC2) Low-grade Glioma Research Workshop. Neuro Oncol 16:173-8.
Appin CL, Brat DJ. (2014) Molecular Genetics of Gliomas. Cancer J 20:66-72.
Brennan CW et al. TCGA Research Network (2013). The somatic genomic landscape of glioblastoma. Cell 155:462-477.
The Cancer Genome Atlas Research Network. (2008) Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature 455:1061-1068.

Dr. Brat received his MD and PhD from the Mayo Medical and Graduate Schools and then completed Residency in Anatomic Pathology and a Fellowship in Neuropathology at Johns Hopkins Hospital. He joined the Department of Pathology and Laboratory Medicine at Emory University in 1999 and is now a Professor and Vice Chair of Translational Programs as well as the Director of the Neuropathology Division and Fellowship. He is a member of the Cancer Cell Biology Program of the Winship Cancer Institute and directs a basic and translational research lab that investigates mechanisms of glioma progression, including the contributions of hypoxia, genetics, tumor microenvironment and stem cells. His laboratory has been continuously funded by the NIH and the Georgia Research Alliance as a Distinguished Cancer Scholar. He also leads the scientific efforts of the In Silico Center for Brain Tumor Research at Emory, which uses large scale clinical and molecular databases, such as The Cancer Genome Atlas (TCGA), to address fundamental questions in human glioma behavior. He has over 15 years of experience in brain tumor research and has written more than 180 peer-reviewed manuscripts and reviews. He has also co-authored two textbooks in Neuropathology: Practical Surgical Neuropathology: A Diagnostic Approach and Biopsy Interpretation of Central Nervous System. Dr. Brat is the Director of the Cancer Tissue and Pathology Shared Resource at Winship, which includes a full service histology laboratory and a tissue procurement service. He is Board certified in Anatomic and Neuropathology and understands the critical issues in current neuro-oncology practice and research. He sits on five Editorial Boards and serves on numerous committees that oversee translational investigation in Oncology and Pathology, including the TCGA Glioblastoma and Lower Grade Gliomas (Co-Chair) Working Groups; the College of American Pathologists (CAP) Neuropathology Committee (Chair) and Council on Scientific Affairs; the Executive Council of the American Association of Neuropathologists; the Board of Directors for the Society of Neuro-oncology, and the WHO Committee for Classification of Brain Tumors. He was recently elected to the American Society for Clinical Investigation.

Glioblastoma:The TCGA Findings

Kenneth Aldape, MD, PhD
MD Anderson Cancer Center, Houston, TX

Objectives:
1) Summarize findings of glioblastoma molecular genetic analysis using gene expression profiling platforms of the Cancer Genome Atlas (TCGA).
2) Discuss advantages of studies comparing multiple gene expression datasets in the identification of new prognostic/predictive GBM biomarkers.
3) Compare the precision of determining patient outcomes as predicted by multi-gene expression panels vs. traditional diagnostic methods.

Rapidly evolving techniques for analysis of the genome provide new opportunities for cancer therapy. For diffuse gliomas this has resulted in molecular markers with potential for personalized therapy. In melanoma, lung-, breast-, gastric- and colorectal carcinoma several molecular markers are already being clinically implemented for diagnosis and treatment. These insights can serve as a background for the promise and limitations that pharmacogenomics has for diffuse gliomas. Glioblastoma is the most common and most aggressive diffuse glioma, associated with short survival and uniformly fatal outcome, irrespective of treatment. It is characterized by morphological, genetic and gene-expression heterogeneity. The current standard of treatment is maximal surgical resection, followed by radiation, with concurrent and adjuvant chemotherapy. Due to the heterogeneity, most tumours develop resistance to treatment and shortly recur. Following recurrence, glioblastoma is quickly fatal in the majority of cases. Recent genetic molecular advances have contributed to a better understanding of glioblastoma pathophysiology and disease stratification. Using a variety of data sets, both publicly available and from our own laboratory, we find that a multi-marker panel composed of specific prognostic genes is a more measure of patient outcome as compared to any single gene, perhaps due to heterogeneity of single gene measurements which is balanced out when averaging multiple expression measurements. Patients whose tumors show in unfavorable genetic signature may be given more aggressive therapy as compared to patients whose tumors show a more favorable molecular signature.

1. Kim YW, Koul D, Kim SH,et al. Identification of prognostic gene signatures of glioblastoma: a study based on TCGA data analysis. Neuro Oncol. 2013;15:829-39.
2. Olar A, Aldape KD. Using the molecular classification of glioblastoma to inform personalized treatment. J Pathol. 2014;232:165-77.
3. Beiko J, Suki D, Hess KR, et al. IDH1 mutant malignant astrocytomas are more amenable to surgical resection and have a survival benefit associated with maximal surgical resection. Neuro Oncol. 2014;16:81-91.
4. Sturm D, Bender S, Jones DT, et al. Paediatric and adult glioblastoma: multiform (epi)genomic culprits emerge. Nat Rev Cancer. 2014;14:92-107.
5. Vartanian A, Singh SK, Agnihotri S,et al. GBM's multifaceted landscape: highlighting regional and microenvironmental heterogeneity. Neuro Oncol. 2014 Mar 18.

Kenneth D. Aldape, MD, is Professor of Pathology, Division of Pathology and Laboratory Medicine at UTMD Anderson Cancer Center in Houston, Texas. He recieved his doctoral degree from the University of California, School of Medicine, San Francisco, completed a residency at the University of California, San Francisco, and a fellowship in Surgical Pathology. His research is focused on the characterization of molecular genetic aberrations in human brain tumors using genome-wide views of DNA, RNA and protein changes relevant to the clinical behavior of these neoplasms. In bedside-to-bench-to-bedside fashion, he uses surgically obtained tumor tissue to identify aberrations, model systems (including tissue culture and gene transfection) to characterize functional consequences of these aberrations, and bioinformatic systems to generate new hypotheses for investigation and treatment of these unfortunate patients.

Meningioma Grading and Potential Biomarkers

Arie Perry, MD
Professor of Pathology and Neurological Surgery, University of California San Francisco (UCSF), USA.

Learning Objectives
1. To describe how the current meningioma grading scheme was derived and appreciate its advantages and limitations
2. To review potentially useful immunohistochemical and genetic biomarkers that aid meningioma diagnosis and prognosis
3. To name the main driver mutations in meningioma tumorigenesis

Accounting for up to 35% of all primary CNS neoplasms, meningioma is one of the most common diagnoses encountered in neurosurgical practice. It has long been appreciated that the two most important prognostic variables for meningioma patients are extent of surgical resection and histopathologic grade. Grading criteria have varied greatly over time, although the current 2007 WHO scheme is largely derived from data reported in two large Mayo Clinic series published in the late 1990s. Since that time, the clinicopathologic associations have been independently validated, despite some concerns that the grade II category has become too commonplace. Of interest, a recent RTOG clinical trial revealed home pathology/central pathology concordance rates of 86.7%, 81.7%, and 94.0% for WHO grades I, II, and III respectively, suggesting substantial agreement for overall grade and moderate to substantial agreement over individual grading criteria. The derivation of the current grading scheme and remaining controversies will be discussed, along with the prominent role played by Dr. Bernd Scheithauer in both the grading of meningiomas in general and the identification of rare but biologically distinct variants, such as clear cell, chordoid, papillary, and rhabdoid meningiomas. There remains a great need to develop better diagnostic, prognostic, and predictive biomarkers for routine clinical practice. Two potentially sensitive and specific markers that have been recently reported include somatostatin receptor 2A (SSTR2A) and STAT6 immunostains for diagnoses of meningioma and hemangiopericytoma/solitary fibrous tumor respectively. Additionally, genetic advances beyond the role of NF2 will be highlighted and discussed. The latter includes the recently identified driver mutations involving the TRAF7, KLF4, AKT, and SMO genes, along with studies of progression associated alterations such as deletions of the CDKN2A gene on chromosome 9 and other commonly implicated chromosomal losses.

1. Brastianos PK, Horowitz PM, Santagata S, et al. (2013) Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. Nature Genet 45:285-9.
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Arie Perry is a Professor of Pathology and Neurosurgery at the University of California in San Francisco, where he also serves as Director of the Neuropathology Division and the Neuropathology Fellowship training program. He received his medical degree and residency training at the University of Texas Southwestern Medical Center in Dallas, Texas, followed by fellowships in surgical pathology, neuropathology, and molecular cytogenetics research at the Mayo Clinic in Rochester, MN, where he worked closely with his mentor, the late Dr. Bernd Scheithauer. His interests have focused mostly on classification, grading, and molecular characterization of adult and pediatric brain tumors, with some of his most notable contributions relating to meningiomas, oligodendroglial neoplasms, glioblastoma variants, and embryonal tumors. He currently serves as the chief editor for Brain Pathology and has over 320 publications. Dr. Perry maintains an active surgical neuropathology consult service and is a frequently invited lecturer. He has also been featured in several media stories for his innovative use of "neuropathology songs" as an educational tool.

Author/Abstract Index

Listed below are Self-Assessment Module (SAM) offerings made available by the AANP. In addition to the Prion Disease online activity, the Special Course, Diagnostic Slide Session and Presidential Symposium are listed as upcoming 2014 SAMs. This will be the fourth year we have offered SAM credit for these particular sessions. In addition, the AANP plans on adding three additional live activity SAMs based on the three special lectures that also take place as part of our Annual Meeting. Finally, we just launched a new JNEN journal-based SAM titled, Serrano-Pozo, A. et al. Examination of the Clinicopathologic Continuum of Alzheimer Disease in the Autopsy Cohort of the National Alzheimer Coordinating Center. JNEN (2013) 72:1182-1192. This Journal-based SAM/CME activity will offer a maximum of *1 AMA PRA Category 1 Credit™*.
In sum, we aim to offer approximately 18.0 hours of SAM credit in 2014.

Jack Lee
Chairman, Education Committee

AANP Self-Assessment Modules

Activity Title	Delivery Method	ACGME Competencies Addressed	Credits
Human Prion Diseases	Online Enduring	Medical Knowledge, Practice-Based Learning & Improvement	**1.00**
2014 Diagnostic Slide Session	Live Activity	Medical Knowledge, Patient Care	**3.00**
2014 Presidential Symposium	Live Activity	Medical Knowledge, Patient Care	**3.25**
2014 Special Course	Live Activity	Medical Knowledge, Patient Care	**7.25**
2014 Journal Review	Online Enduring	Medical Knowledge, Patient Care	**1.00**
2014 Korey Lecture	Live Activity	Medical Knowledge, Practice-Based Learning & Improvement	**1.00**
2014 Parisi Lecture	Live Activity	Medical Knowledge, Patient Care	**1.00**
2014 DeArmond Lecture	Live Activity	Medical Knowledge	**1.00**

Hot Topics

- Update in genetics, epigenetics and bioinformatics in gliomas
- The TCGA project
- Morphologic and molecular classification of pediatric brain tumors
- Stem cells in neurosciences
- Classification of cortical dysplasias and temporal lobe epilepsy.
- Prion diseases in Latin America
- Prion-like mechanisms in neurodegeneration
- Neuropathology of C9 ORF mutations
- Microvascular neuropathology
- New entities in neuroinflammation
- Update in myopathology
- Chronic traumatic encephalopathy related to sports
- Genetics, neurobiology and neuropathology of autism spectrum disorder.

DEADLINE TO REGISTRATIONS WITH REDUCED FEE AND ABSTRACT SUBMISSION, EXTENDED TO JUNE 16.

Preliminary Program on the website check at www.icn2014.com

Venue and Dates

The XVIII International Congress of Neuropathology will be held from Sunday 14h to Thursday 18th September 2014, at **Sheraton Rio Hotel Convention Center**, Rio de Janeiro, Brazil.

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