

2<sup>ND</sup> ANNUAL ALAN COOPER  
EPIDERM LECTURE



THE UNIVERSITY  
OF QUEENSLAND  
AUSTRALIA

# ***PARANEOPLASTIC SYNDROMES: PAST, PRESENT AND DIVINING THE FUTURE***



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Mayo Clinic College of Medicine  
Scottsdale, AZ***

# **DISCLOSURE**

**No financial or other relevant  
conflicts of interest**

**Off-label discussion of  
therapy**

# MAYO CLINIC



## Mayo Clinic Three Shields

- Patient Care
- Research
- Education

# **MAYO CLINIC**

*“The Enterprise”*

## **Overview-2015**

- **1.3 million people from all 50 states and 140 countries came to Mayo Clinic for care.**
- **Staff physicians and scientists: 4,500**
- **Residents, fellows and others: 2,400**
- **Allied health staff (clinic and hospital): 57,100**
- **Total: 64,000**



# **MAYO CLINIC**

## ***Patient care-***

- **Total clinic patients: 1,318,300**
- **Hospital admissions: 128,000**
- **Hospital days of patient care: 641,000**

## ***Research-***

- **Physicians and medical scientists: 575**
- **Allied health personnel: 3,392**

## ***Research activity-2015***

- **New human research studies approved by Institutional Review Board: 2,723**
- **Active human research studies: 11,028**
- **Research publications and review articles in peer-reviewed journals: 7,305**
- **Education and Research funding: \$946M**
- **Government, foundations and industry: \$440M**
- **Mayo Clinic funds and benefactor gifts: \$506M**

# ***MAYO CLINIC***

## ***Education-***

- **Mayo trains doctors in 273 residency and fellowship programs, representing virtually all medical specialties.**
- **Enrollment: 1,696**

# 2<sup>ND</sup> ANNUAL ALAN COOPER EPIDERM LECTURE



- *Distinguished Mayo alumnus*
- *Exceptional physician, dermatologist and clinician*
- *Cherished colleague, mentor and friend*
- *Husband, father (and grandfather!) extraordinaire*
- *Golf partner, raconteur, humorist*
- *And... so much more!*

# ***PARANEOPLASTIC SYNDROMES***

## **Introduction**

- **Among the most fascinating disease associations of the early era of clinical as well as 21<sup>st</sup> century medicine**
- **Presentations range from the obvious to obscure...some of the most challenging and elusive primary tumors and cutaneous pathologies**
- **Breadth of clinical presentations and associations present dilemmas in further investigating and uncovering the underlying tumor.**

# ***PARANEOPLASTIC SYNDROMES***

## **Definitions**

- **Hormonal, neurological, hematological, and other clinical and biochemical disturbances associated with malignant neoplasms but not directly related to invasion by the primary tumor or its metastases.**

# ***PARANEOPLASTIC SYNDROMES***

## **Definitions**

- ***Hormonal, neurological, hematological***, and other clinical and biochemical disturbances associated with malignant neoplasms but not directly related to invasion by the primary tumor or its metastases.
- Neoplasia (paraneoplasia)  $\neq$  malignancy. In selected cases, a non-malignant tumor growth is associated with the disorder
- ***What's missing here?***

# ***PARANEOPLASTIC SYNDROMES***

## **Definition**

- paraneoplastic syndrome (par"ah-ne"o-plas'tik) a collective term for disorders arising from metabolic effects of cancer on tissues remote from the tumor; such disorders may, for example, appear as **primary endocrine, hematologic, or neuromuscular disorders.** *Dorland's*
- ***NOTE! No mention of skin or cutaneous manifestations!***



# **PARANEOPLASTIC SYNDROMES**

## **A Brief History**

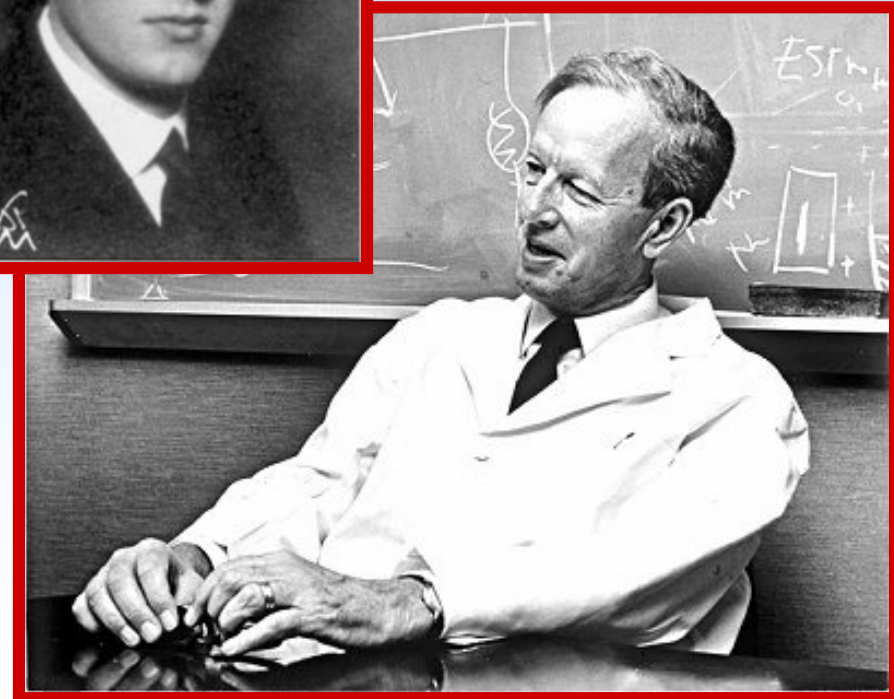
- **Armand Trousseau, M.D. (1801-1867)**  
**Birth: Tours and career in Paris**
- **Trousseau('s) syndrome or sign**
- **1865-- migratory thrombophlebitis ("phlegmasia alba dolens")**
- **Gastric and hepatobiliary malignancy (esp. mucin-secreting adenoCA) Uro-gynecologic, lymphoma, brain, etc**
- **Approximately 50% of cases are malignancy related. Hypercoaguable state-coag factors, platelets, vasculature**
- **Diagnosed his own (occult) gastric CA**  
**"I am lost, a phlegmasia that showed itself last night leaves no doubt about the nature of my affliction" 1-1-1867**



# ***PARANEOPLASTIC SYNDROMES***

## **A Brief History**

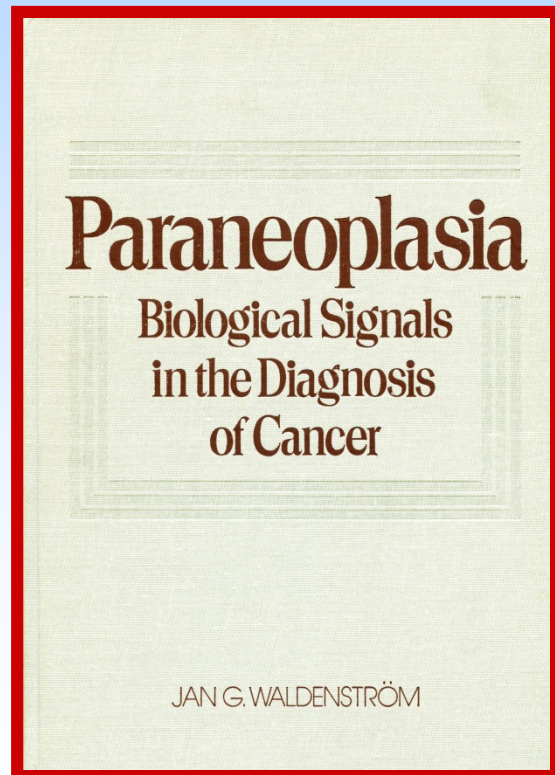
- **Prof. Jan Waldenström (1906-1996) Born: Stockholm, career Malmö**
- **Macroglobulinemia, paraproteins, porphyrias and carcinoid syndrome**
- **Monoclonal vs polyclonal gammopathies**
- **Later career interested in Paraneoplasia as “biological signals in the diagnosis of cancer”**



# PARANEOPLASTIC SYNDROMES

## A Brief History

“Experiences from a lifetime in clinical medicine and in biochemical research... to combine bench and bedside” JGW



| Contents   |     |
|--|-----|
| Introduction   | 1   |
| Part 1. Signals From Organ Systems Indicating the Presence of Neoplasia                                  | 9   |
| 1. Skin  | 11  |
| 2. Nervous System  | 28  |
| 3. Blood   | 41  |
| 4. Vascular System   | 54  |
| 5. Kidney  | 59  |
| 6. Skeleton and Ossification   | 67  |
| Part 2. General Signals and Specific Substances Indicating Neoplasia                                     | 71  |
| 7. General Symptoms and Immunological Markers  | 73  |
| 8. Specific Tumor-Produced Biochemical Disorders   | 78  |
| 9. Disorders of Derepressed Immunoglobulin Synthesis   | 85  |
| 10. Neoplasias Producing Specific Substances   | 98  |
| 11. Ectopic Production of Hormonally Active Polypeptides   | 113 |
| Appendix 1. The Most Convincing Results of Investigations on Hormone Production by Cancer Cells in Vitro | 141 |
| Appendix 2. Molecular Characteristics and Source of Hormones and Other Specific Substances               | 142 |
| References   | 145 |
| Index  | 167 |

# ***PARANEOPLASTIC SYNDROMES***

## **The Dermatologic Perspective!**

- Pollitzer and Janowsky, 1890. Darier, 1893. Acanthosis Nigricans
- Pollitzer, Unna et al 1891. Florid Cutaneous Papillomatosis (Named in 1978, Schwartz and Burgess)
- Gougerot and Rupp 1922 (Bazex, 1965) Acrokeratosis Paraneoplastica (Bazex syndrome)
- Becker, Rothman et al 1942. Necrolytic Migratory Erythema
- Sweet, 1964. Acute Febrile Neutrophilic Dermatositis
- Anhalt et al 1990. Paraneoplastic Pemphigus (PNP)-  
Grando et al, 2001. Paraneoplastic Autoimmune Multi-Organ Syndrome (PAMS)





# ***PARANEOPLASTIC SYNDROMES***

## **Dermatologic Pioneers**

- Helen(e) Ollendorf Curth (1899-1982) Born:Breslau. Died: NYC
- Benign and malignant forms of acanthosis nigricans and other cutaneous signs of cancer
- Many other genetic and epithelial syndromic disorders described and investigated (Buschke-Ollendorf syndrome)
- Defined the requirements for Paraneoplastic Syndromes (Koch's postulates for disease causality)



*Burgdorf, Scholz JAAD 51: 84, 2004*

# **PARANEOPLASTIC SYNDROMES**

## **Curth “Postulates”**

- **Malignancy and syndrome must appear at the same time, and their clinical courses should not significantly differ**
- **Remote cutaneous manifestations should be specific to the tumor causing them**
- **Paraneoplastic syndromes should be uncommon relative to the prevalence of the cancer**
- **The paraneoplastic syndromes and the cancer should be demonstrably associated.**
- **A genetic association exists between the malignancy and a specific cutaneous disease**

*Curth et al, Cancer 15:364, 1962   Curth, Int J Derm 15:592, 1976.  
Thiers et al CA Cancer J Clin 59:73,2009.*

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# ***PARANEOPLASTIC SYNDROMES***

## **The Literature**

- **Pubmed search: 08-16-2016**
- **Cumulative Citations:**
  - “Paraneoplastic” 11849**
  - “Paraneoplastic syndrome” 1910**
  - “Paraneoplastic” skin 1506**
  - “Paraneoplastic” neurologic 715**
  - “Paraneoplastic” brain 1479**
  - “Paraneoplastic” endocrine 1673**
  - “Paraneoplastic” kidney 699**
  - “Paraneoplastic” GI 381**
  - “Paraneoplastic” blood 2660**



# ***PARANEOPLASTIC SYNDROMES***

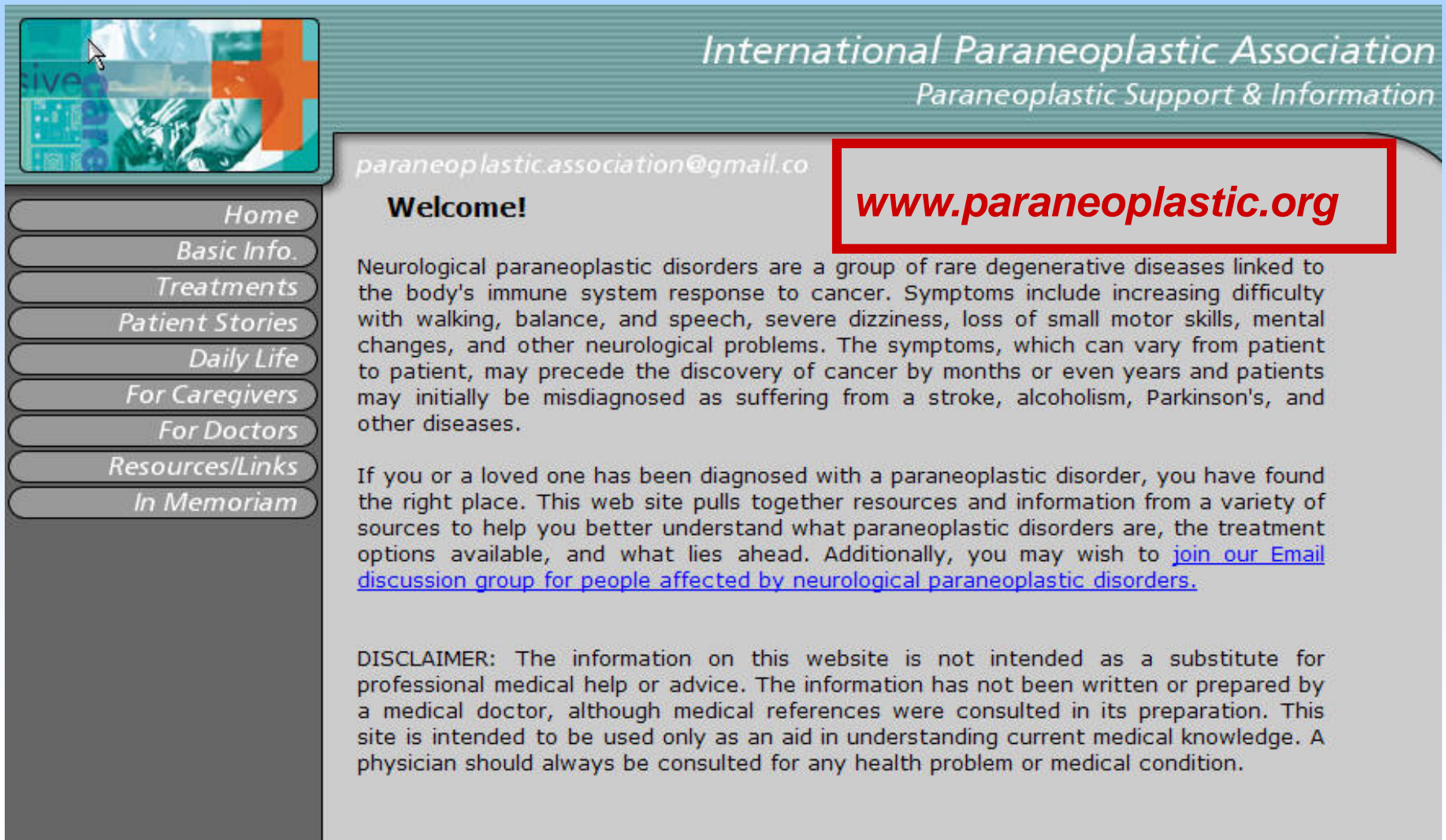
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# PARANEOPLASTIC SYNDROMES

## The Internet

Patient with Paraneoplastic Neurologic Disorder (PND) as site creator/webmaster



*International Paraneoplastic Association*  
*Paraneoplastic Support & Information*

*paraneoplastic.association@gmail.co*

**Welcome!**

**[www.paraneoplastic.org](http://www.paraneoplastic.org)**

Neurological paraneoplastic disorders are a group of rare degenerative diseases linked to the body's immune system response to cancer. Symptoms include increasing difficulty with walking, balance, and speech, severe dizziness, loss of small motor skills, mental changes, and other neurological problems. The symptoms, which can vary from patient to patient, may precede the discovery of cancer by months or even years and patients may initially be misdiagnosed as suffering from a stroke, alcoholism, Parkinson's, and other diseases.

If you or a loved one has been diagnosed with a paraneoplastic disorder, you have found the right place. This web site pulls together resources and information from a variety of sources to help you better understand what paraneoplastic disorders are, the treatment options available, and what lies ahead. Additionally, you may wish to [join our Email discussion group for people affected by neurological paraneoplastic disorders.](#)

**DISCLAIMER:** The information on this website is not intended as a substitute for professional medical help or advice. The information has not been written or prepared by a medical doctor, although medical references were consulted in its preparation. This site is intended to be used only as an aid in understanding current medical knowledge. A physician should always be consulted for any health problem or medical condition.

*Home*  
*Basic Info.*  
*Treatments*  
*Patient Stories*  
*Daily Life*  
*For Caregivers*  
*For Doctors*  
*Resources/Links*  
*In Memoriam*

# ***PARANEOPLASTIC SYNDROMES***

## **Classification Schemes**

- **By organ system: Cutaneous/mucosal, neurologic, hematologic, endocrine, etc.**
- **By mechanism or mediating factors**
- **Clinically—Cutaneous/mucosal**
  - **Papulo-squamous lesions**
  - **Erythematous lesions**
  - **Vascular lesions**
  - **Bullous lesions**
  - **Miscellaneous lesions**

# ***PARNEOPLASTIC SYNDROMES***

## **The Clinical Challenges**

- **Detecting** the subtle, early manifestations developing in skin and oral cavity
- **Recognizing** the potential link between the new skin signs/symptoms and underlying tumor or neoplasia
- **Selecting** diagnostic tools to identify the tumor/neoplasia
- **Managing** the cutaneous manifestations
- **Eliminating** the primary neoplastic cause

# ***PARANEOPLASTIC SYNDROMES***

## **Skin ...and Much, Much More!**

- **Muco-Cutaneous (Dermatologic)  $\approx$  Neurologic  
Hematologic > Endocrine> Musculoskeletal,  
Renal, GI, Lung, Cardiac, etc.**
- **Pathologic targeting of one or more organ  
systems**
- **Understanding mechanisms of paraneoplastic  
response.**
- **The challenge: to not only understand the  
disease, but also provide accurate diagnosis  
and effective treatment**

# **PARANEOPLASTIC SYNDROMES**

## **Papulosquamous Conditions**

- **Acanthosis nigricans**
- **Acquired ichthyosis**
- **Acrokeratosis neoplastica**  
**Bazex syndrome**
- **Florid cutaneous papillomatosis**
- **Palmoplanta keratoderma**
- **Pityriasis rotunda**
- **Sign of Leser-Trélat**
- **Tripe palms**  
**Acanthosis palmaris**
- **Extramammary Paget**

*Nguyen et al Paraneoplastic Diseases  
eMedicine 9-18-2012 (updated)*

# ***PARANEOPLASTIC SYNDROMES***

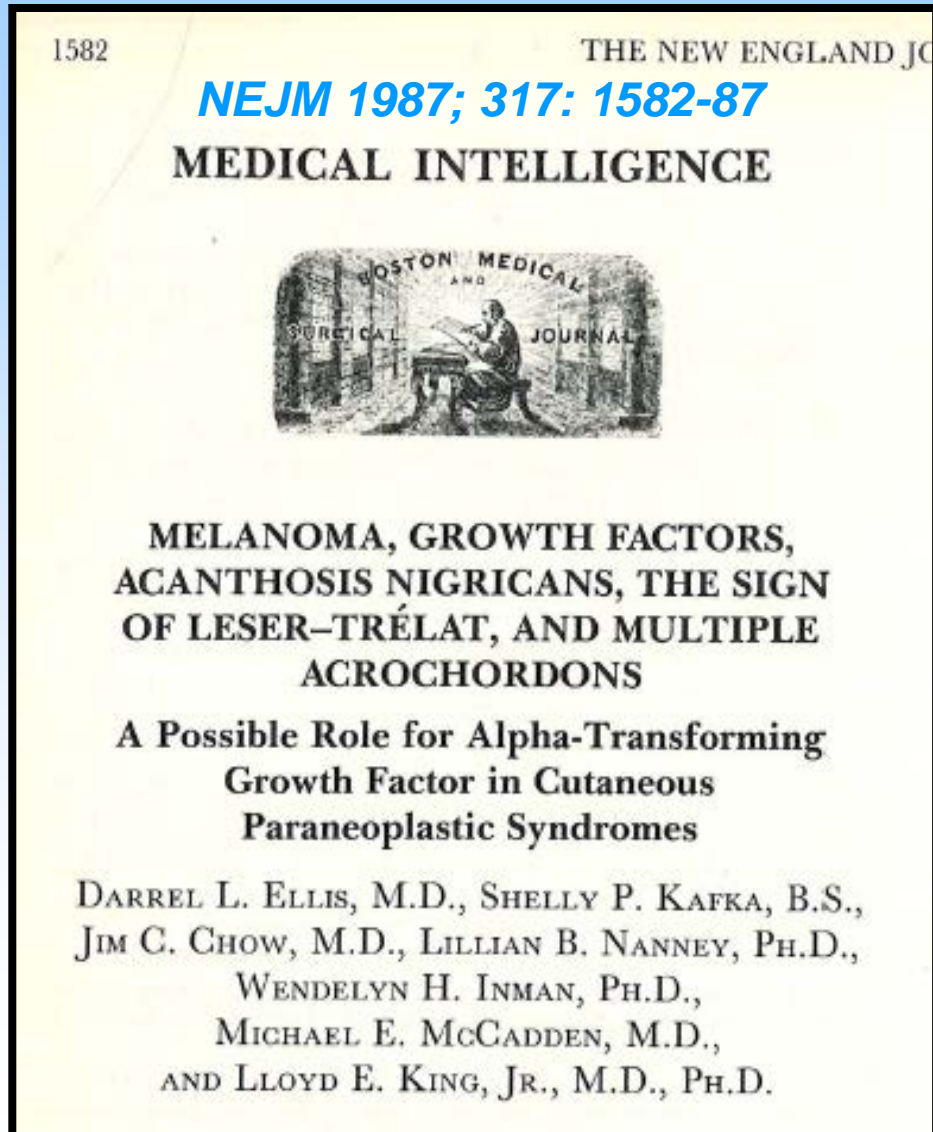
- **Skin...that which is before you and your eye can see! (Goethe anglicized)**
- **The power of careful, critical and astute observation**
- **Apply your talents and curiosity to drive you, your practice and your career in dermatology!**
- **Patience and reflective follow-up often provides you wisdom when the present (vis à vis the future) leaves you with unanswered questions**



# PARANEOPLASTIC SYNDROMES

## An Index Case Study

- 54 y/o M. Sudden, 3 mo. onset of multiple seborrheic keratoses
- Exam: acanthosis nigricans and mult. acrochordons
- Irregular dark brown (10x17mm) lesion left lower back..bx: SSM
- GI tract-endoscopy and contrast studies...benign polyps, no malignancy
- Immunochemistry exam of skin specimens and several urine collections
- WLE melanoma...clinical exam 5 mo later. Marked improvement of AN and improved seb kers and skin tags





# PARANEOPLASTIC SYNDROMES

## AN, SK and Skin Tag Index Case

- Detected marked increase in urinary excretion of transforming growth factor- $\alpha$  (TGF $\alpha$ ) by Western blot that decreased dramatically within 2 wks and remained undetectable at 5 mo following removal of the melanoma of the back

***Chance (and opportunity) favors the prepared mind!***

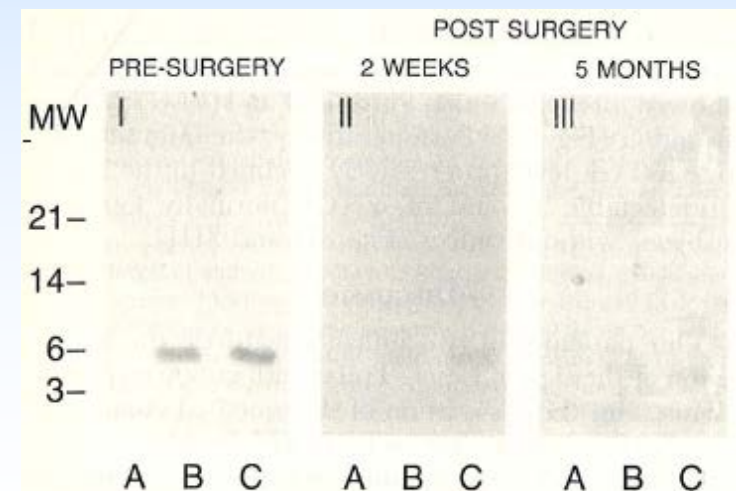


Figure 3. Western Blots of Patient's Urine Specimens Stained for Immunoreactive  $\alpha$ -TGF.

# ***PARANEOPLASTIC SYNDROMES***

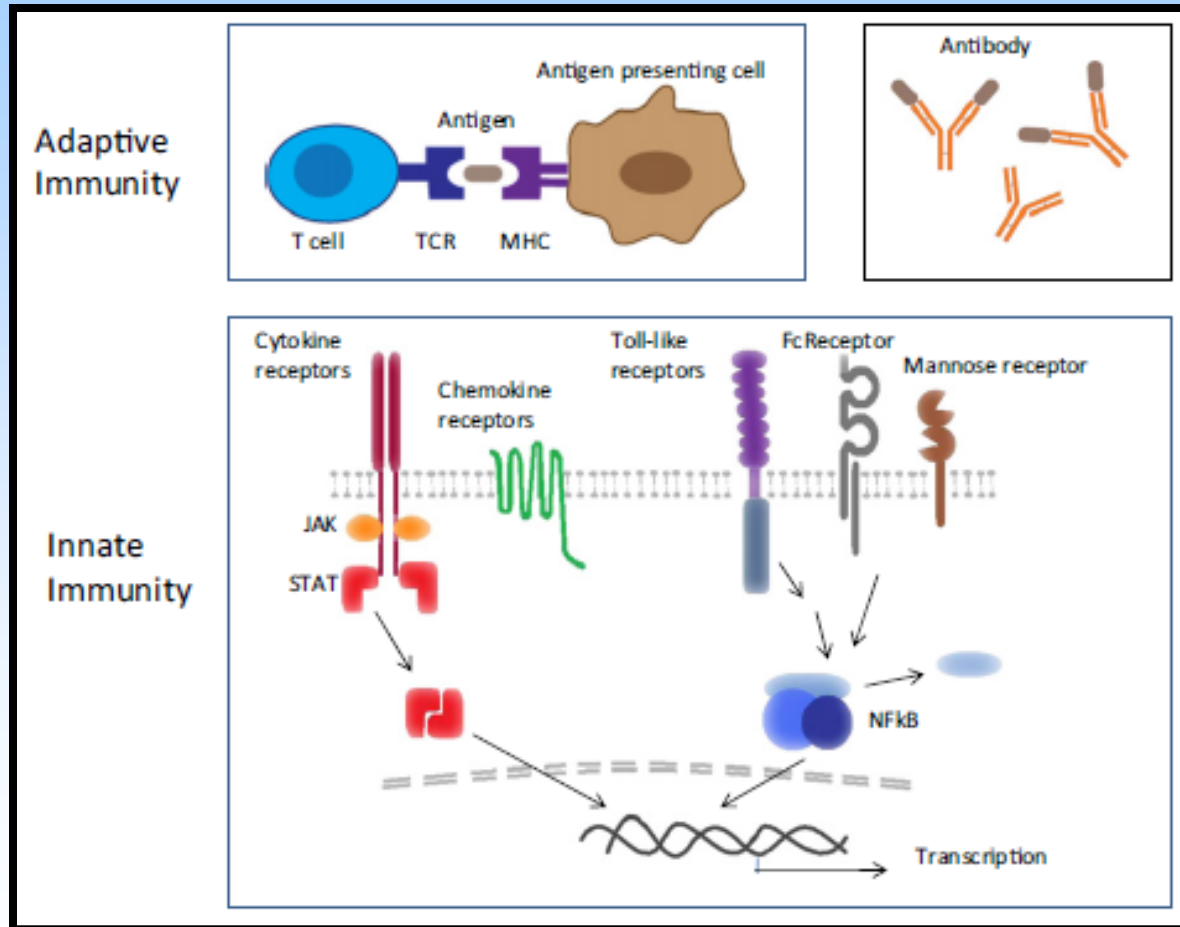
## **What's New?**

- **New (re-discovered) associations, particularly granulomatous- and pigmentation- associated conditions**
- **New approaches and diagnostic algorithms to identify underlying neoplasia/tumor**
- **New mechanisms being characterized to understand disease causes and possibly harnessing pathobiology of disease for therapy.**

# PARANEOPLASTIC SYNDROMES

## Disease Mechanisms

- Trophic--Growth factors, cytokines or small molecules
- Toxic -- Cell destructive mediators, uncontrolled necrosis or apoptosis
- Immunologic--Humoral or cell-mediated, innate or adaptive immunity



*Bhat and Steinman Neuron 64:123, 2009*

# ***PARANEOPLASTIC SYNDROMES***

## ***Neurological Associations***

- From 1960's onwards, immune mediated peripheral and brain disorders associated with tumors as well as autoimmune neural diseases
- Classics: Myasthenia gravis (thymoma) and Lambert-Eaton Myasthenic Syndrome (LEMS) (SCLC >50%)
- Targeting cerebral cortex, diencephalon, basal ganglia, cerebellum, brainstem, spinal cord, peripheral nerve and ganglia, neuromuscular junction and muscle

# ***PARANEOPLASTIC SYNDROMES***

## ***Neurological Associations***

- **Dr Edward Lambert-neurophysiologist and EMG pioneer at Mayo Clinic.**
- **Syndrome recognized and reported at the Mayo Clinic by Drs. Lambert, Eaton and Rooke in 1956**
- **By 1972, the association with autoimmunity and malignancy established**
- **1990's research demonstrated the link with antibodies against P/Q-type voltage-gated calcium channels (pre-synaptic membrane)**

# ***PARANEOPLASTIC SYNDROMES***

## ***Neurological “Associations”***

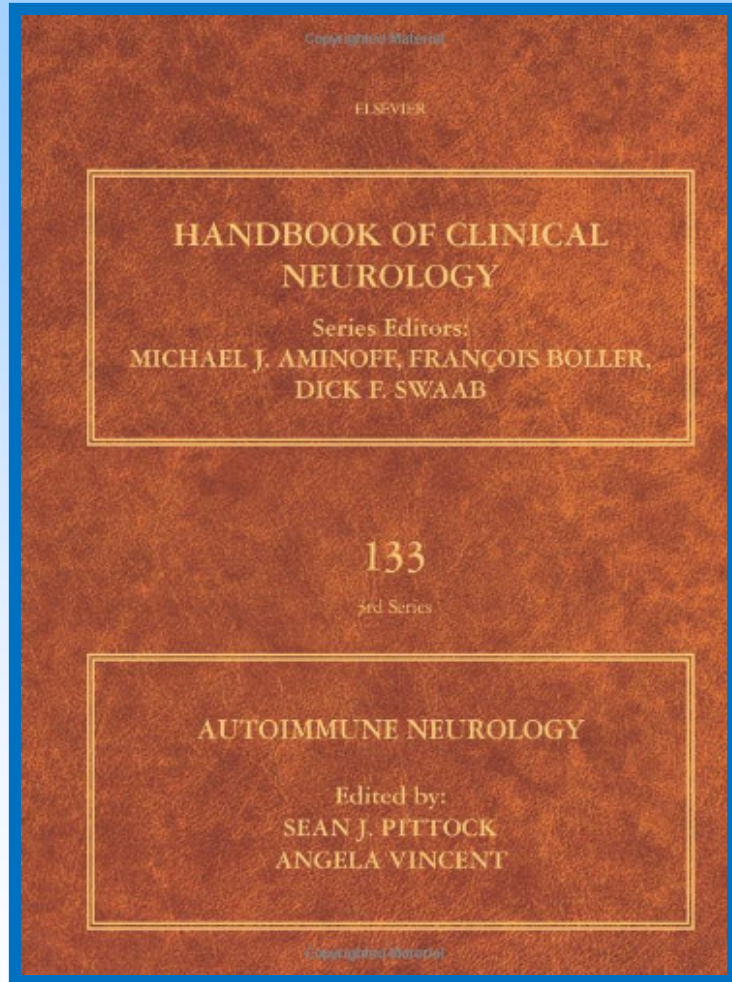
- Dr Ed Lambert, “father of EMG” (1915-2003)
- Dr Vanda Lennon, Professor of Neurology and Immunology, Mayo Clinic. Australian native, Sydney University Medical School, PhD-University of Melbourne and pioneering neuro-immunologist
- Described and characterized many autoimmune and paraneoplastic neurological syndromes and laboratory screening panels.
- Partners in marriage and research for many years





# ***PARANEOPLASTIC SYNDROMES***

## ***Neurological Associations***



**Ed. Mayo Clinic, 2016**

- Neuroimmunology section- Mayo Clinic
- Significant advances in better diagnostic and screening tests, biomarkers and therapeutic advances for Neurologic PNS
- Advancing understanding of mechanisms targeting brain, peripheral nerve and muscle
- Model to understand mechanisms and targeting of skin in paraneoplasia

# ***PARANEOPLASTIC SYNDROMES***

## ***Mayo-Arizona State University***



The Biodesign Institute





# ***PARANEOPLASTIC SYNDROMES***

## ***Mayo-Arizona State University***



# PARANEOPLASTIC SYNDROMES

## Mayo-Arizona State University



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## Welcome to the Center for Personalized Diagnostics

The mission of the Virginia G. Piper Center for Personalized Diagnostics is to drive the discovery and development of biomarkers for the early detection of diseases. With better disease detection and earlier treatment, we strive to have a profound impact on decreasing mortality caused by various **diseases** including cancer and autoimmune diseases. Towards this end, our center and its **10 research faculty** are driven by **innovation and technology development**, creating new tools that foster biomarker discovery. In particular, we have developed and continue to improve the NAPPA protein arrays and to couple the NAPPA technology with other technologies to better understand disease. Besides creating tools and technology for use within the center, we also make these **tools available** to facilitate research projects in the wider research community. Through the **plasmid repository**, **sequencing services** and our most recent effort with the **NAPPA protein array core**, we have provided the tools to accelerate research in hundreds of laboratories around the world.

# PARANEOPLASTIC SYNDROMES

## Mayo-Arizona State University

Home

Welcome

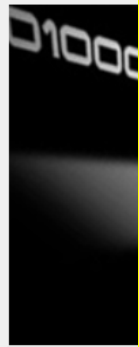
The mission of the Mayo Clinic is to advance the understanding of the most complex diseases, cancer and other conditions, and to develop new tools that, in combination with other therapies, will facilitate the treatment of these diseases and the prevention of protein and genetic diseases.

|             |                                  | Joshua LaBaer | Karen Anderson | Ji Qiu | Mitch Magee | Garrick Walstrom | Marco Mangone | Douglas Lake | Valentin Dinu | Wade Van Horn | Chad Borges | John Chaput |
|-------------|----------------------------------|---------------|----------------|--------|-------------|------------------|---------------|--------------|---------------|---------------|-------------|-------------|
| NAPPA       | NAPPA Technology Overview        |               |                |        |             |                  |               |              |               |               |             |             |
|             | Epitope Mapping                  |               |                |        |             |                  |               |              |               |               |             |             |
|             | High Density Arrays              |               |                |        |             |                  |               |              |               |               |             |             |
|             | High Sensitivity Arrays          |               |                |        |             |                  |               |              |               |               |             |             |
|             | SPRI                             |               |                |        |             |                  |               |              |               |               |             |             |
|             | Protein Protein Interactions     |               |                |        |             |                  |               |              |               |               |             |             |
|             | Post-translational Modifications |               |                |        |             |                  |               |              |               |               |             |             |
| Automation  | DNA Factory                      |               |                |        |             |                  |               |              |               |               |             |             |
|             | High throughput cell assays      |               |                |        |             |                  |               |              |               |               |             |             |
|             | High throughput cloning          |               |                |        |             |                  |               |              |               |               |             |             |
| Informatics | Sequence Analysis - ACE          |               |                |        |             |                  |               |              |               |               |             |             |
|             | Sample tracking - FLEX           |               |                |        |             |                  |               |              |               |               |             |             |
|             | Advanced Literature Mining       |               |                |        |             |                  |               |              |               |               |             |             |
|             | Next Generation Sequencing       |               |                |        |             |                  |               |              |               |               |             |             |
|             | NAPPA Tracking                   |               |                |        |             |                  |               |              |               |               |             |             |
| Other       | Mass Spec                        |               |                |        |             |                  |               |              |               |               |             |             |
|             | Affinity Reagents                |               |                |        |             |                  |               |              |               |               |             |             |
|             | NMR                              |               |                |        |             |                  |               |              |               |               |             |             |
|             | Protein Purification             |               |                |        |             |                  |               |              |               |               |             |             |
|             | X-ray crystallography            |               |                |        |             |                  |               |              |               |               |             |             |

# PARANEOPLASTIC SYNDROMES

## Mayo-Arizona State University

ASU



Home

Welcome

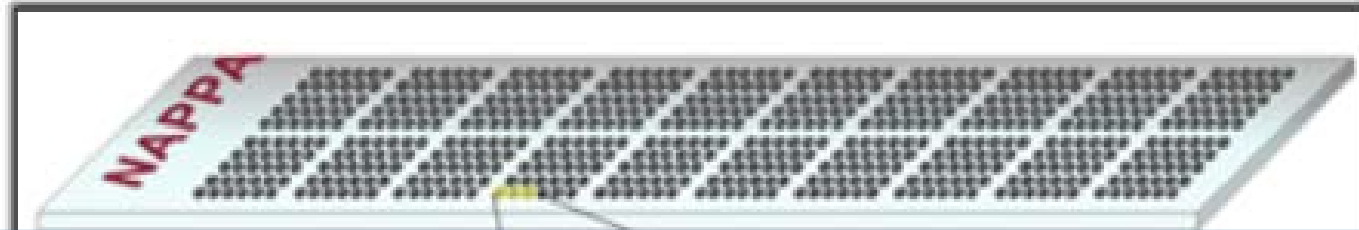
The mission of the Mayo Clinic is to advance the understanding of disease, to develop new treatments, and to provide the best possible care for our patients. We are committed to research, education, and patient care, and we are proud to be part of the Mayo Clinic family.

|                |                                     | Joshua LaBaer | Karen Anderson | Chad Borges | Valentin Dinu | Douglas Lake | Mitch Magee | Marco Mangone | Ji Qiu | Wade Van Horn | Garrick Wallstrom |
|----------------|-------------------------------------|---------------|----------------|-------------|---------------|--------------|-------------|---------------|--------|---------------|-------------------|
| Cancer         | Bladder                             |               |                |             |               |              |             |               |        |               |                   |
|                | Breast                              |               |                |             |               |              |             |               |        |               |                   |
|                | Burkitt's Lymphoma                  |               |                |             |               |              |             |               |        |               |                   |
|                | Chronic Myeloid Leukemia            |               |                |             |               |              |             |               |        |               |                   |
|                | Colorectal                          |               |                |             |               |              |             |               |        |               |                   |
|                | Desmoplastic small round cell tumor |               |                |             |               |              |             |               |        |               |                   |
|                | High Risk Neuroblastoma             |               |                |             |               |              |             |               |        |               |                   |
|                | HPV-associated                      |               |                |             |               |              |             |               |        |               |                   |
|                | Lung                                |               |                |             |               |              |             |               |        |               |                   |
|                | Melanoma                            |               |                |             |               |              |             |               |        |               |                   |
|                | Multiple Myeloma                    |               |                |             |               |              |             |               |        |               |                   |
|                | Ovarian                             |               |                |             |               |              |             |               |        |               |                   |
|                | p53-mutant                          |               |                |             |               |              |             |               |        |               |                   |
|                | Pancreatic                          |               |                |             |               |              |             |               |        |               |                   |
| Other Diseases | Alzheimer's                         |               |                |             |               |              |             |               |        |               |                   |
|                | Anthrax                             |               |                |             |               |              |             |               |        |               |                   |
|                | Arthritis                           |               |                |             |               |              |             |               |        |               |                   |
|                | Autism                              |               |                |             |               |              |             |               |        |               |                   |
|                | Cystic Fibrosis                     |               |                |             |               |              |             |               |        |               |                   |
|                | Diabetes                            |               |                |             |               |              |             |               |        |               |                   |
|                | Epilepsy                            |               |                |             |               |              |             |               |        |               |                   |
|                | Heart Disease                       |               |                |             |               |              |             |               |        |               |                   |
|                | Idiopathic subglottic stenosis      |               |                |             |               |              |             |               |        |               |                   |
|                | Infectious Disease                  |               |                |             |               |              |             |               |        |               |                   |
|                | Inflammatory Bowel Disease          |               |                |             |               |              |             |               |        |               |                   |
|                | POEMS syndrome                      |               |                |             |               |              |             |               |        |               |                   |
|                | Radiation Exposure                  |               |                |             |               |              |             |               |        |               |                   |
|                | Tuberculosis                        |               |                |             |               |              |             |               |        |               |                   |
|                | Valley Fever                        |               |                |             |               |              |             |               |        |               |                   |
|                | Vibrio Cholera                      |               |                |             |               |              |             |               |        |               |                   |

John Chaput

# PARANEOPLASTIC SYNDROMES

## Mayo-ASU Biodesign



Proc Natl Acad Sci U S A. 2014 Jul 29;111(30):E3072-80

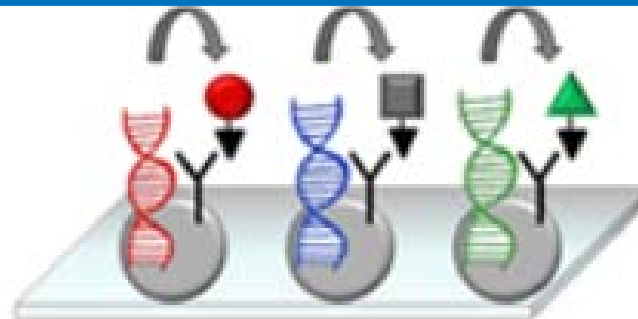
## Immunosignature system for diagnosis of cancer

Phillip Stafford<sup>1</sup>, Zbigniew Cichacz, Neal W. Woodbury, and Stephen Albert Johnston

Center for Innovations in Medicine, The Biodesign Institute, Arizona State University, Tempe, AZ 85287-5901

Edited by Philippa Marrack, Howard Hughes Medical Institute, National Jewish Health, Denver, CO, and approved June 23, 2014 (received for review June 19, 2014)

2. Express *in situ* & capture proteins



# PARANEOPLASTIC SYNDROMES

## Mayo-ASU Biodesign



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[contact](#)

DNA Array



Protein Array



Patient Response



Add expression mix



Add patient serum



### NAPPA Protein Array Core

The NAPPA Protein Array Core uses a novel protein array technology, called Nucleic Acid Programmable Protein Array (NAPPA), which replaces the complex process of spotting purified proteins with the simple process of spotting plasmid DNA. Our facility offers [high throughput DNA preparation](#), [pre-set and custom protein array production](#), and [array screening and analysis](#) services. For more information, please contact the [Core Manager](#).

#### NEWS AND ANNOUNCEMENTS

**January 2014:** We will be presenting a poster at the 2014 [SLAS Conference](#) about our High Throughput DNA preparation services. Visit our poster 258 on Monday January 20th.

**September 2013:** The NAPPA Protein Array Core formed a new collaboration with Emory University.

**July 2013:** Presented at the HighRes Biosolutions user group meeting in Boston, MA.

**April 2013:** Proteins are expressed using a new system extracted from human HeLa cells ([1-Step Human Coupled in vitro translation](#)) from Thermo Scientific. Take a look at our [publication](#) describing our use of this lysate to display protein on the NAPPA arrays.

**March 2013:** In collaboration with HighRes Biosolutions, we have installed a robotic DNA preparation system called the DNA Factory. This unique system allows us to prep 4,800 plasmids in 72 hours with limited technician intervention. Within the next few months, high throughput DNA preparation services will be available to the research community.

[more>>](#)

#### CPD LINKS



Center For Personalized Diagnostics



Plasmid Repository



Next Generation Sequencing



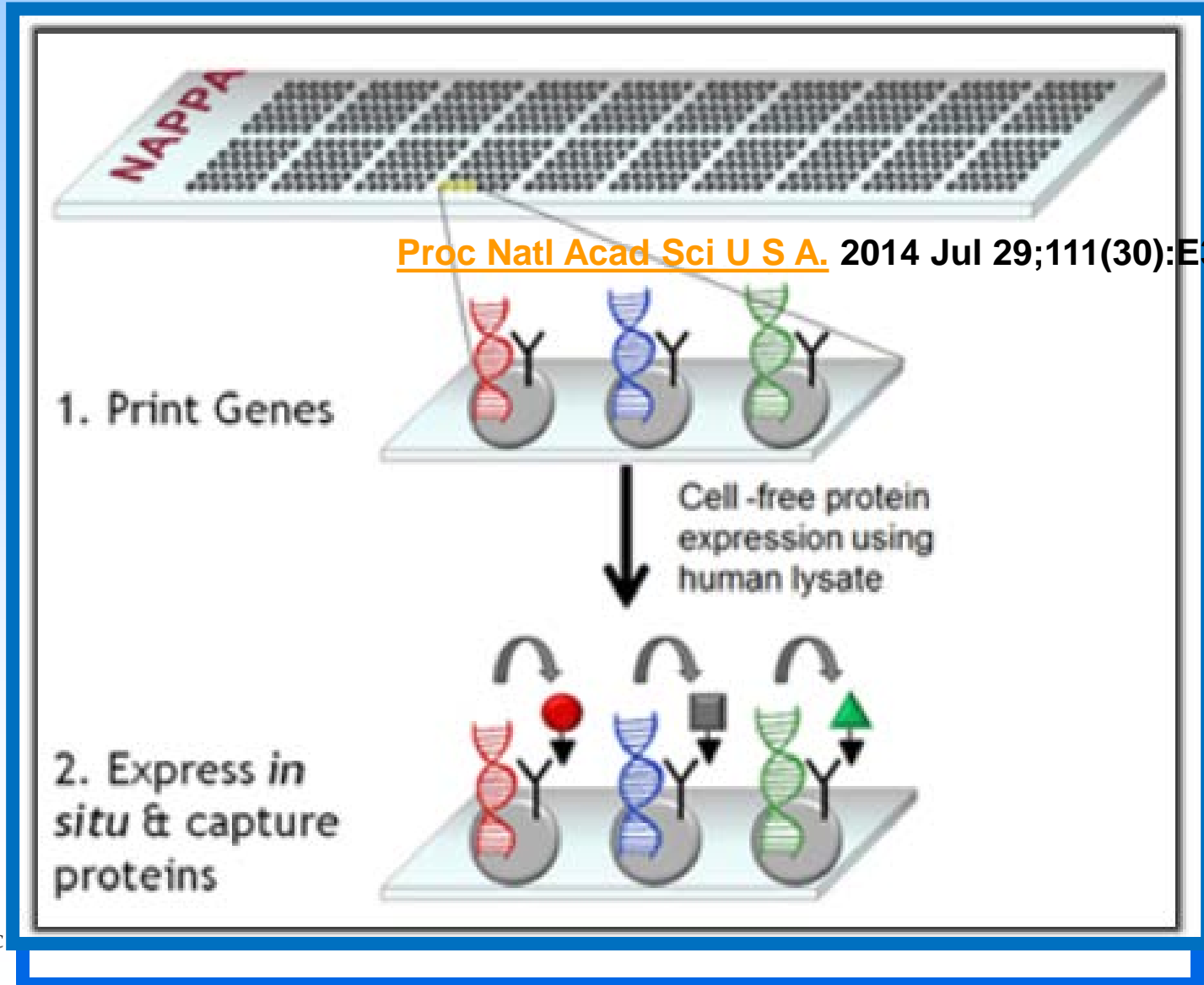
DNA Sequencing

Proc Natl Acad Sci U S A. 2014 Jul 29;111(30):E3072-80



# PARANEOPLASTIC SYNDROMES

## Mayo-ASU Biodesign



[Proc Natl Acad Sci U S A. 2014 Jul 29;111\(30\):E3072-80](#)



# ***PARANEOPLASTIC SYNDROMES***

## ***Blistering Skin Disease***

- **Paraneoplastic pemphigus (PNP)-  
Paraneoplastic Autoimmune multi-organ  
syndrome (PAMS)**
- **Described by Anhalt et al, 1990. A more broad,  
encompassing term for non-acantholytic cases,  
PAMS (Grando et al, 2001)**
- **Disease spectrum ranging from acantholytic to  
BP-like, EM-like and lichenoid pathologies**
- **Strong association (>90%) with malignancy,  
esp. Castleman disease, lymphoma, CLL and  
thymoma**

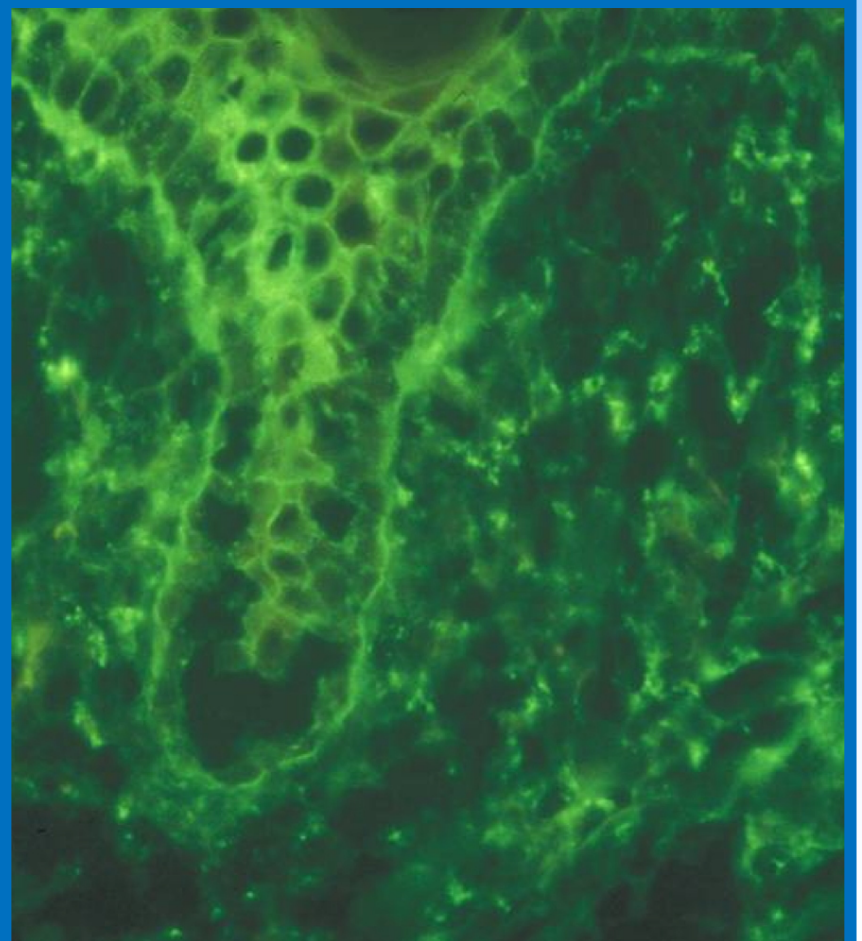
# ***PARANEOPLASTIC SYNDROMES***

## ***PNP-PAMS***

- **Can be challenging both diagnostically and therapeutically.**
- **Range of treatment options, targeting malignancy along with immunosuppressive and/or immunodepletion**
- **Improved imaging strategies and diagnostic biomarkers**

# ***PARANEOPLASTIC SYNDROMES***

## ***PNP-PAMS***



# ***PARANEOPLASTIC SYNDROMES***

## ***PNP-PAMS***

Diagnostic imaging in paraneoplastic autoimmune multiorgan syndrome: retrospective single site study and literature review of 225 patients

*Int J Dermatol, 2014*

Vance T. Lehman<sup>1</sup>, MD, Benjamin J. Barrick<sup>2</sup>, DO, Mark R. Pittelkow<sup>3</sup>, MD, Patrick J. Peller<sup>1</sup>, MD, Michael J. Camilleri<sup>4</sup>, MD, and Julia S. Lehman<sup>4</sup>, MD

- **CT and 18F-FDG PET/CT (~90 and 10% cases, resp)**
- **Both identified all solid tumors, but PET/CT facilitated staging and guided biopsies.**
- **Value of IIF, rat bladder, ELISA and improved biomarker screening**

# ***PARANEOPLASTIC SYNDROMES***

## **Disease Associations**

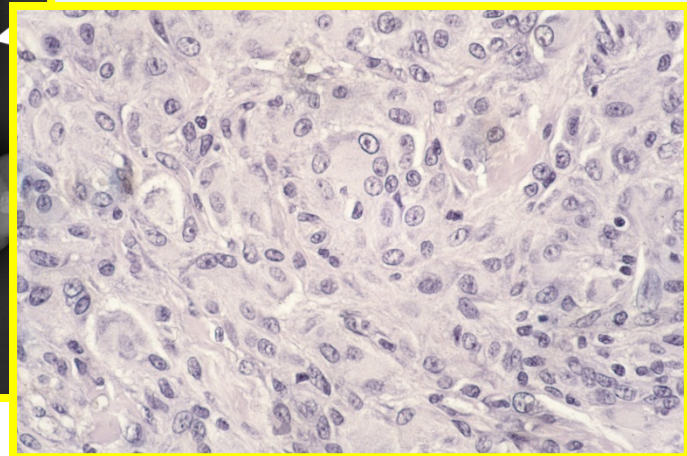
- **Granulomatous paraneoplastic syndromes**
  - **Multicentric reticulohistiocytosis**
  - **Granuloma annulare-like, interstitial granulomatous dermatitis, necrotizing-caseous granulomas**
  - **Miscellaneous histiocytic-granulomatous disorders**



# ***PARANEOPLASTIC SYNDROMES***

## **Granulomatous PNS**

- Multicentric reticulo-histiocytosis
- Progressive cutaneous and erosive joint and arthritis findings
- Malignancy associated, approx. one-third of cases
- Lymphoma, adenocarcinomas, SCC lung
- MTX, TNF alpha antagonists



# **PARANEOPLASTIC SYNDROMES**

## **Granulomatous PNS**

- 71y/o male, weakness and 60# wgt loss.
- 2 year history of progressive erythematous papules, coalescing to plaques over trunk and extremities
- Hgb11gm/dl, monocytosis 42%
- Biopsy: interstitial granulomatous dermatitis
- Bone marrow:  
Myelodysplastic Syndrome  
Within 2 months, developed AML, pneumonia and died.

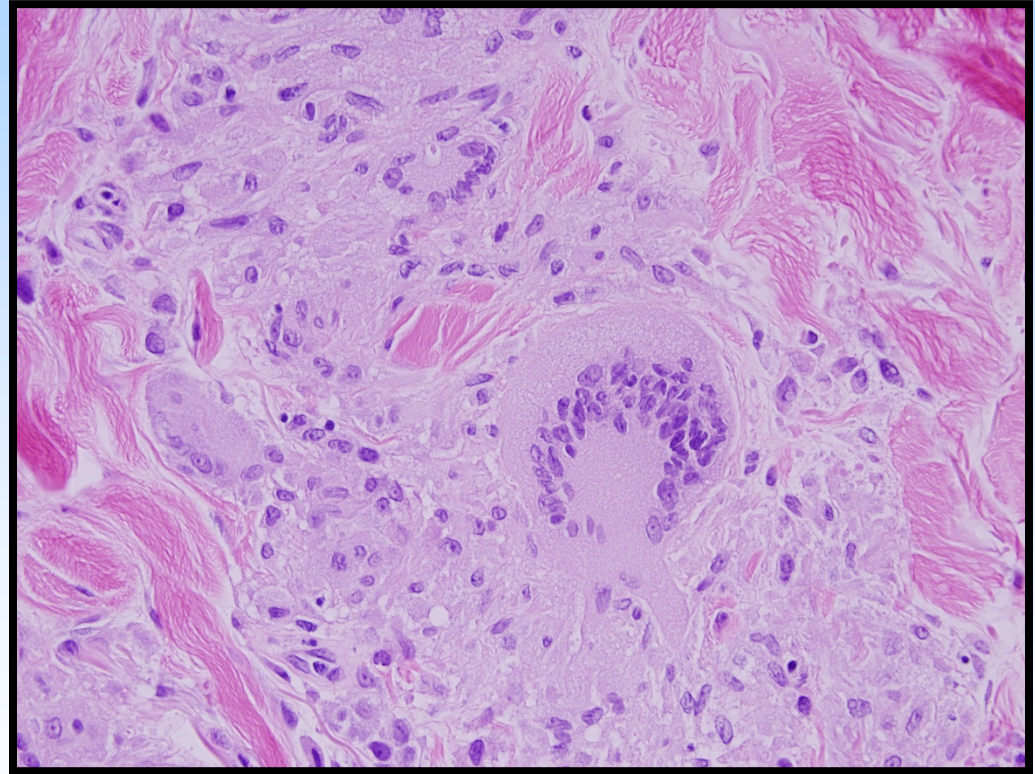
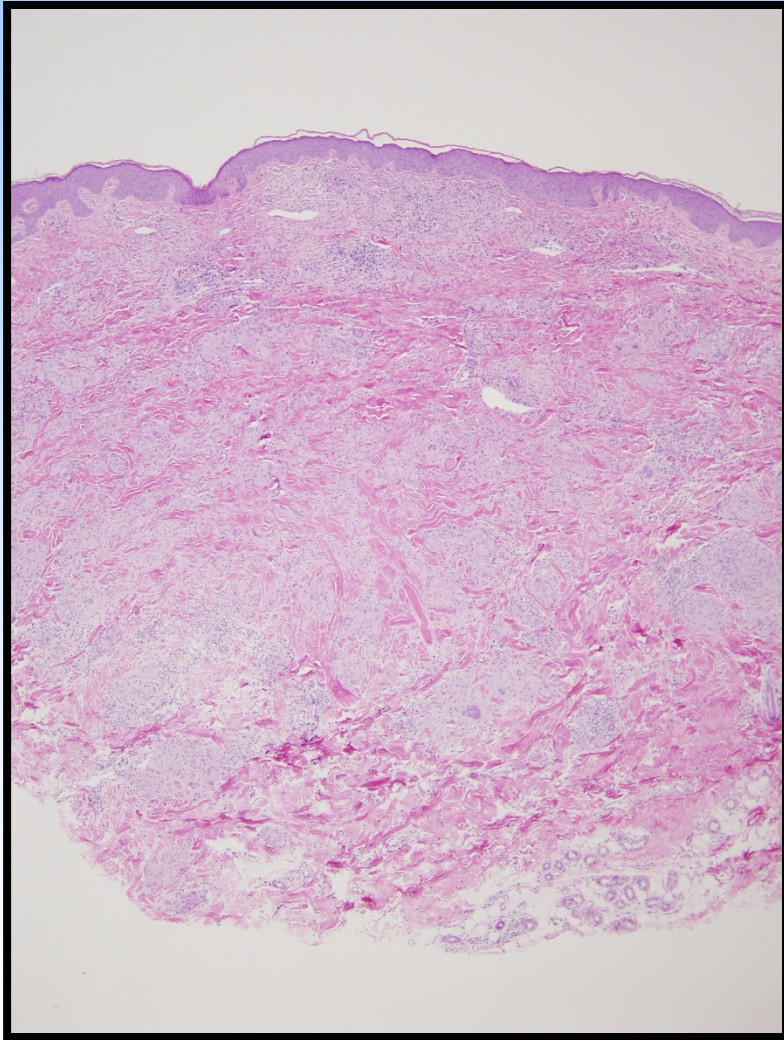


**Balin et al, Arch Derm, 2011**



# ***PARANEOPLASTIC SYNDROMES***

## **Granulomatous PNS**



# ***PARANEOPLASTIC SYNDROMES***

## **Granulomatous PNS**

- 62 y/o male, B-CLL 5 years
- Fludaribine treatment. Remission, developed hypogammaglobulinemia
- IVIg x several yrs
- Generalize, widespread non-infectious, caseating granulomas
- Infliximab therapy with clearance. Development of leukemia cutis that cleared w/ PUVA

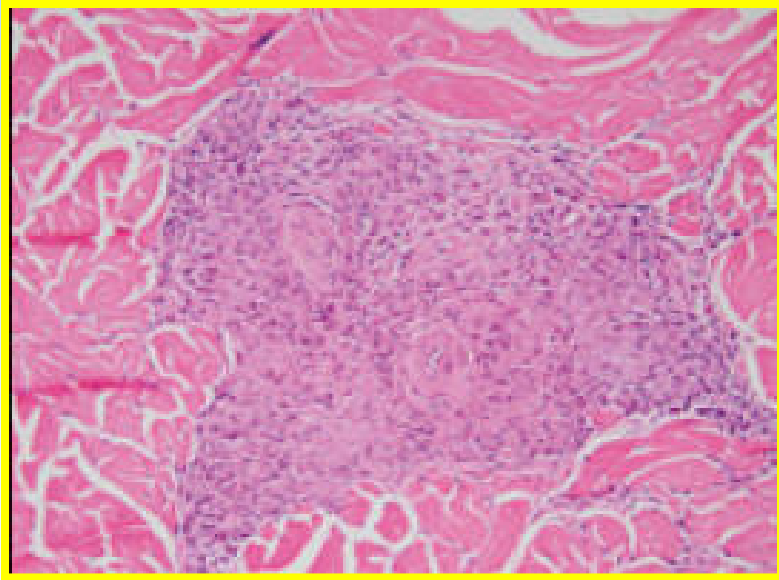


**Podjacek, Pittelkow. Med Derm Soc, Miami  
3-2010**



# ***PARANEOPLASTIC SYNDROMES***

## **Granulomatous PNS**

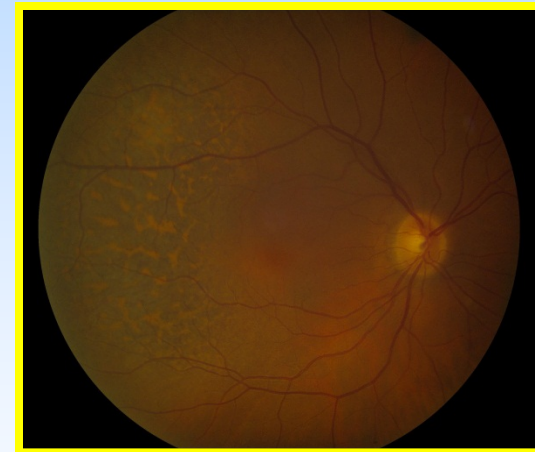
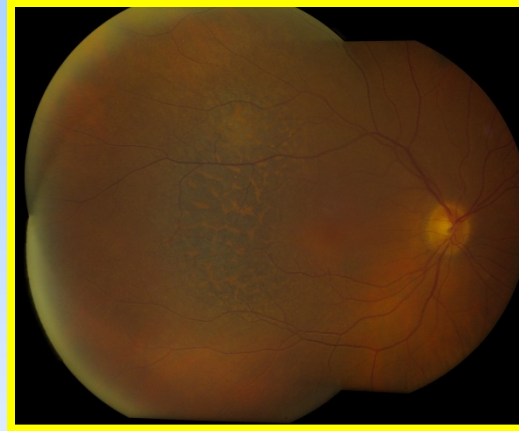


**Post-  
infliximab**

# ***PARANEOPLASTIC SYNDROMES***

## **Melanocytic PNS-BDUMP**

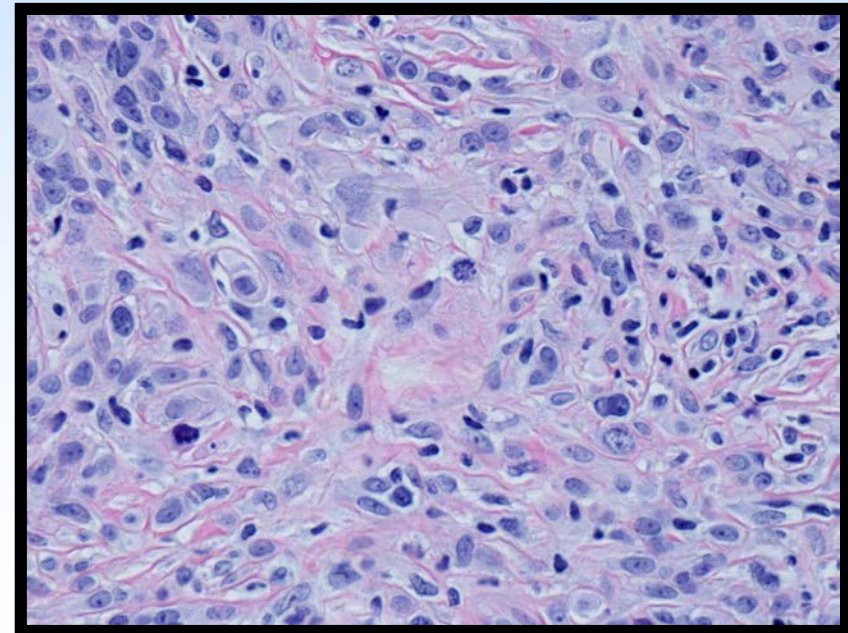
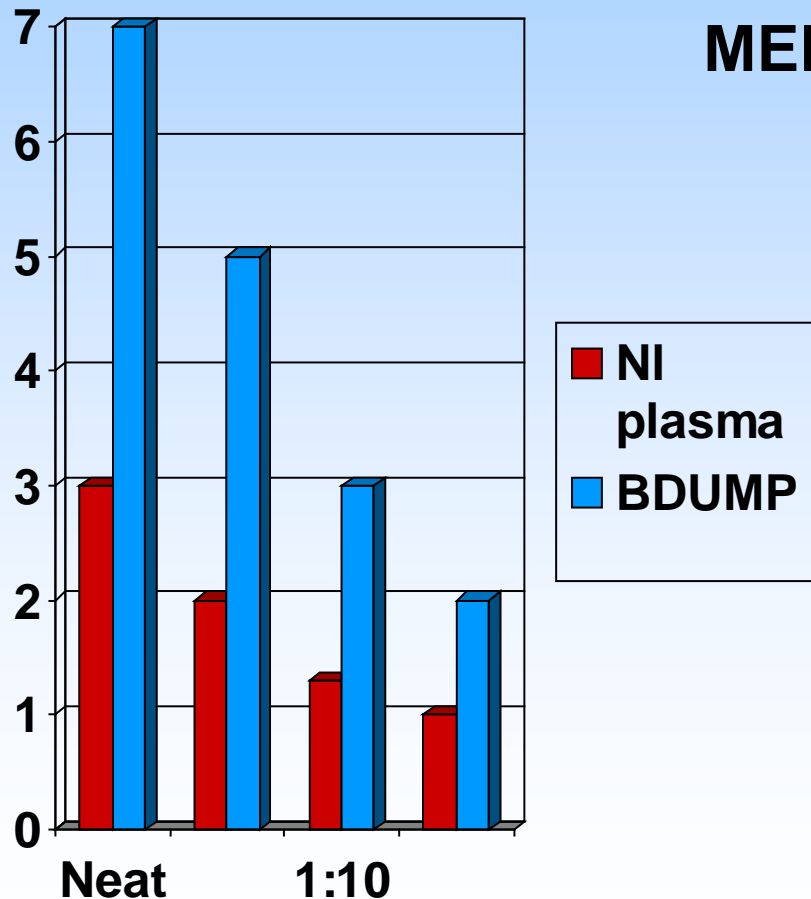
- **Bilateral diffuse uveal melanocytosis (BDUMP)**
- **Uniformly malignancy related**
- **64 y/o woman, uterine carcinoma and decreased vision over several mo.**
- **Plasmapheresis. Biologic analysis of plasma factors**



# PARANEOPLASTIC SYNDROMES

## Melanocytic PNS-BDUMP

Melanocyte proliferation:  
Fold-stimulation

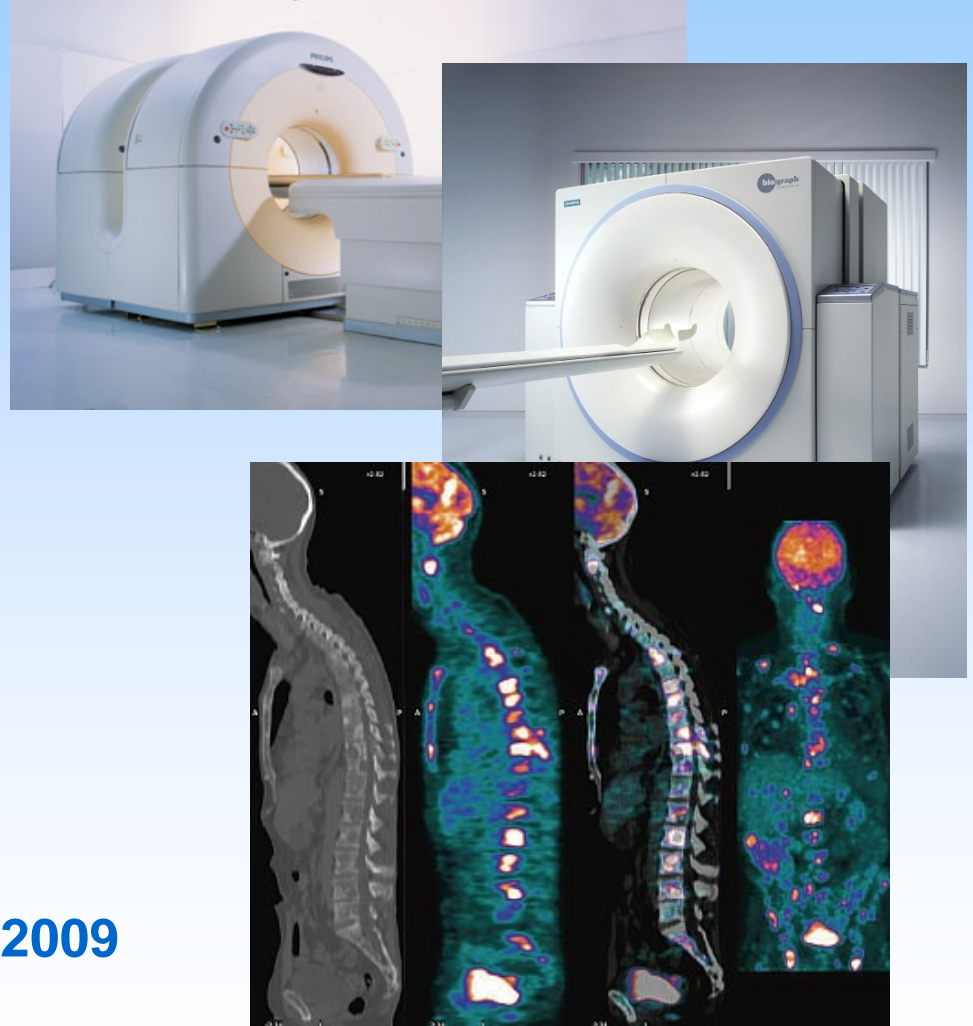




# ***PARANEOPLASTIC SYNDROMES***

## **Imaging Advances**

- **CT, MRI, PET, PET/CT, PET/MRI**
- **Indications and yields for dx of unknown primary malignancies**



**Podoloff et al JNCCN 7: Suppl 2, 2009**



# ***PARANEOPLASTIC SYNDROMES***

- 84y/o male. 2 yr hx of pruritus and urticarial eruption
- Extensive previous evals at regional VA hospital.
- w/u neg except eosinophilia and eosinophilic dermatitis.
- ANA >12, +anti-dsDNA. Periph. blood eosinophilia. DIF and IIF neg. Bxs: Eosinophilic dermatitis and LCV (ankle)



# PARANEOPLASTIC SYNDROMES

Prior PET scans for comparison: None.

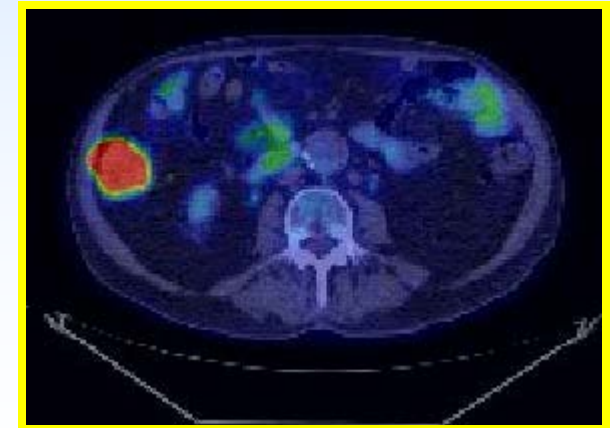
INDICATION: Evaluation of paraneoplastic syndrome. Possible vasculitis.

FINDINGS: FDG PET scan images with fused CT images show mild increased FDG uptake within hilar nodes bilaterally with the nodes on the left being calcified. Calcified anteromediastinal node also has mild increased FDG uptake. Mild increased uptake is seen in the subclavian, external iliac and femoral vessels bilaterally. No increased FDG uptake however seen within the aorta. Diffuse increased FDG uptake throughout the enlarged prostate. This is more likely inflammatory but evaluation to exclude prostate carcinoma is recommended. **There is prominent focal increased FDG uptake in the colon in the region of the hepatic flexure. This is likely normal physiologic uptake but a tumor mass cannot be complete excluded. Colonoscopy or CT colography may be helpful. The remainder of the images are normal.**

Additional CT findings from the non-diagnostic, non-contrast CT: Extensive vascular calcifications including coronary. Tortuous aorta. Dilated thoracic aorta measuring 4.4 cm. Cholecystectomy.

IMPRESSION: No definite findings for malignancy. **Diffuse FDG uptake in the prostate and focal tracer within the colon at the hepatic flexure can be seen with nonmalignant causes but malignancy cannot be completely excluded.** FDG uptake within the subclavian, external iliac and femoral vessels is mild but suggests vascular inflammation.

- 14.77 mCi F-18 FDG
- Finger-stick blood glucose level at time of PET scan injection was 104 mg/dL.
- Electronically signed by:



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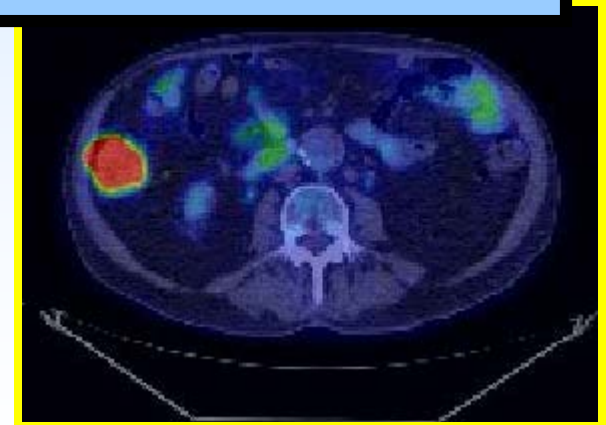


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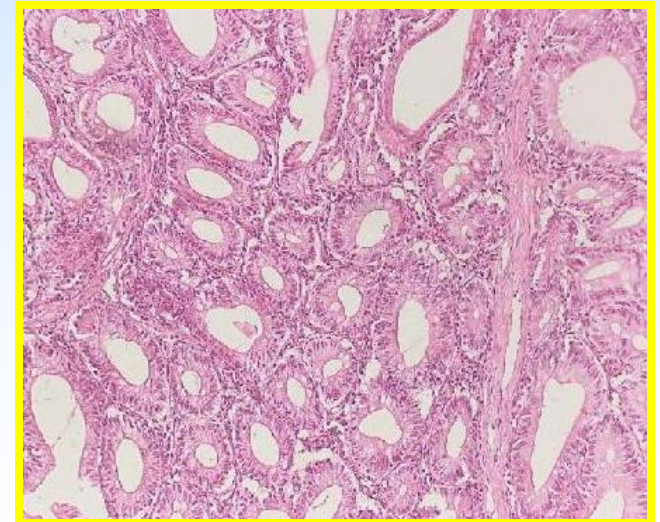
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# PARANEOPLASTIC SYNDROMES

**DIAGNOSIS:** Colon, right, hemicolectomy:  
**Tubulovillous adenoma with low grade dysplasia and focal high grade dysplasia,** forming a mass (8.4 x 4.1 x 2.4 cm) in the ascending colon. All surgical resection margins are negative for tumor. Multiple (26) regional lymph nodes are negative for malignancy. The appendix is grossly unremarkable





# ***PARANEOPLASTIC SYNDROMES***

## **Imaging in Paraneoplasia (PNS)**

- **Despite many clinical indications in dermatology, no studies have been performed on the rates of detection for muco-cutaneous PNS**
- **In neurologic PNS, presence of anti-neuronal antibodies and clinical suspicion of malignancy identified patients for PET/CT. Of 56 pts, PET/CT +ive in 22 (39%) and bx performed and positive in 10 pts (18%).**

***McKeon et al: PET/CT in Paraneoplastic Neurologic Disorders: Systematic Analysis and Review. Arch Neuro 67(3), 322-29, 2010.***

# ***PARANEOPLASTIC SYNDROMES***

## **Current PET Indications**

- **NCCN Task Force Report: Clinical Utility of PET in a Variety of Tumor Types**
- **National Oncologic PET registry (NOPR) (5-06)**
- **“Initial treatment strategy” and “Subsequent treatment strategy”**
- **~41,000 scans (~34,000 pts)**
  - **35% Initial staging**
  - **36% restaging after treatment**
  - **29% recurrence after treatment**

*Podoloff et al JNCCN 7:suppl. 2, 2009*



# PARANEOSPLASTIC SYNDROMES

## Current PET Indications

- Change in intended management in 38% of cases.
- Non-treatment to treatment -- 30%
- Treatment to non-treatment -- 8%
- “Imaging-adjusted impact” accounts for add. MRI or CT use

**Table 2** Impact of PET on Intended Management of the Top 10 Cancers in the National Oncologic PET Registry

| Cancer            | No. of Scans | % Change in Intended Treatment | % Imaging-Adjusted Impact |
|-------------------|--------------|--------------------------------|---------------------------|
| Prostate          | 5309         | 35.1                           | 15.0                      |
| Ovary             | 4509         | 41.4                           | 16.2                      |
| Bladder           | 3578         | 37.9                           | 15.4                      |
| Pancreas          | 3314         | 39.0                           | 14.8                      |
| Stomach           | 3025         | 36.9                           | 14.5                      |
| Small cell lung   | 2983         | 41.2                           | 13.1                      |
| Kidney            | 2877         | 35.8                           | 16.0                      |
| Uterus            | 2869         | 36.5                           | 15.1                      |
| Myeloma           | 1784         | 48.7                           | 11.5                      |
| Connective tissue | 1350         | 36.4                           | 13.6                      |

# ***PARANEOPLASTIC SYNDROMES***

## ***Past, Present and Divining the Future***

### ***Closing Quotable Quotes***

- **“People like us, who believe in physics, know that the distinction between past, present, and future is only a stubbornly persistent illusion.”** *Albert Einstein*
- **“All life is an experiment. The more experiments (observations) you make, the better”** *Ralph Waldo Emerson*

# ***PARANEOPLASTIC SYNDROMES***

## **Summary**

- **A wide-variety of muco-cutaneous PNS have been recognized over the past 150 years**
- **Dermatologic PNS represent a significant percent of all PNS, similar to neurologic PNS**
- **Skin biopsy and further imaging studies (PET, CT or PET/CT) should be part of the current work-up for suspected dermatologic PNS**
- **With newer, more sensitive imaging modalities and biomarkers earlier treatment may avert more advanced, complicated and worse prognosis cases of PNS**

# HONORING PROFESSOR ALAN COOPER

