BIOMARKER DISCOVERIES IN SYSTEMIC RHEUMATIC DISEASES (SRD)

Laurentian Rheumatology Conference
May 11Biomarker Discoveries in Systemic Rheumatic Diseases (SRD), 2018

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Check against delivery

UNIVERSITY OF CALGARY

Disclosure: Dr. M. Fritzler

Is or has been a consultant to Inova Diagnostics Inc., BioRad, Euroimmun GmbH, Mikrogen GmbH, Dr. Fooke Laboratorien GmbH, ImmunoConcepts, SKF Canada, Amgen and Pfizer.

Has received gifts in kind from ImmunoConcepts, Inova Diagnostics, Euroimmun GmbH, and Alexion Canada.

Does not own or trade shares in companies associated with medical diagnostics.

Is the Director of Mitogen Advanced Diagnostics Laboratory.

OUTLINE

- What are the key drivers of innovative biomarker technologies?
- What are some newer autoantibodies of interest?

Goals of Biomarker Discovery

- **Early and Accurate Diagnosis**
  - Intent to **PREVENT**
- **Establish/Confirm DIAGNOSIS**
  - Intent to **TREAT**
  - Guide to further investigations and referrals (biopsy, imaging, etc.)
  - Guide to treatment: **Precision Medicine**
    - CLINICAL CARE PATHWAYS
- **Follow clinical course**
  - **Confirm remission**
  - **Predict or confirm flares**
- **Understand PATHOGENIC processes**
- **Indicators of PROGNOSIS/OUTCOMES**
- **ECONOMICAL: key to adoption**

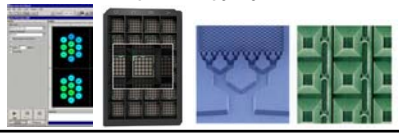
Biomarkers ' OMICS Patient Profiling

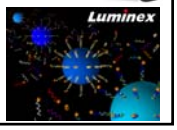
- Genomics
  - Epigenomics advancing rapidly
- Proteomics
  - Autoantibody subsets
  - Cytokine/Chemokine subsets
  - Complement
- T and B cell subset profiles
- Markers of cell death: necrosis, apoptosis, NETosis
- Ribonomics: miRNA, CIRCULAR RNA
- Liquid biopsies: Microbody"omics"
- Metabolomics, Metalomics
- Lipidomics, Glycomics
- Bioinformatics, Artificial Intelligence, Big Data!

INTERACTOME

Biomarker Diagnostic Technologies

- **Antigen Arrays on Planar Surfaces: Line Immunoassays (LIA)**
- **ELISA**
- **Addressable Laser Bead Assays (ALBIA, BioFlash, SNOW)**
- **Chemiluminescence (CIA): Bio Flash**
- **Cell Based Assays (CBA)**
- **Point of Care Diagnostics: *'Lab on a chip'***
- ***SOMAScan***
- **Electrochemiluminescence Arrays**
- **Nanotechnology — nanobarcodes**
- **Mass & NMR Spectroscopy: CyTOF**





Newer Autoantibodies

- Cancer-Associated Autoantibodies
  - RNP C3
  - PUF 60
  - ?MPP-1/KIF20B
- Bicaudal D2 (BICD2)
- Survival of Motor Neuron (SMN)/gemins
- Mup44

Age-old question: Biomarkers of cancer in autoimmune rheumatic diseases?

SPECIAL ARTICLE

Dr Eng. M Tan: a tribute to an enduring legacy in autoimmunity

MJ Fritzler[1] and EKL Chan[2]

[1]University of Calgary, Cumming School of Medicine, Calgary, Canada; and [2]Department of Oral Biology, University of Florida, Gainesville, USA

Age-old question: Biomarkers of cancer in autoimmune rheumatic diseases?

- **Historically:**
  - **Anti-RNAP III increased risk in SSc**
  - **Anti-TIF1-γ and anti-NXP2 increased risk in IIM**
  - **Anti-dsDNA decreased risk (protective) in SLE**
    - **Threads of evidence:**

1. Bernatsky S, et al (SLICC). Breast cancer in systemic lupus. *Lupus. 26:311, 2017.*
When compared to the general population, there is a decreased breast cancer Risk in systemic lupus erythematosus (SLE)

2. Noble, M. R. Young, S. Bernatsky, R. H. Weisbart, and J. E. Hansen.
A nucleolytic lupus autoantibody is toxic to BRCA2-deficient cancer cells.
Sci.Rep. 4:5958, 2014.
Lupus derived antibody 5B6 kills BRCA2-deficient cancer cells

Other Autoantibodies Associated with Cancer

Yang et al. Arthritis Research & Therapy (2017) 19:259
DOI 10.1186/s13075-017-1469-8

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

Identification of multiple cancer-associated myositis-specific autoantibodies in idiopathic inflammatory myopathies: a large longitudinal cohort study

Hanbo Yang[1,2†], Qinglin Peng[1†], Liguo Yin[1], Shanshan Li[1], Jingli Shi[1], Yamei Zhang[1], Xin Lu[1], Xiaoming Shu[1], Sigong Zhang[1] and Guochun Wang[1,2*]

Study of 667 IIM patients

Anti-SAE1, **anti-TIF1-γ** and **anti-NXP2** all associated with a significantly increased risk of cancer in IIM.
In some cases, anti-HMGCR, anti-Jo-1 and anti-PL-12 antibodies might also be driven by malignancy.

Other Autoantibodies Associated with Cancer

Systematic autoantigen analysis identifies a distinct subtype of scleroderma with coincident cancer

George J. Xu[a,b,c,d,e,1], Ami A. Shah[f,1], Mamie Z. Li[c,d,e], Qikai Xu[c,d,e], Antony Rosen[f], Livia Casciola-Rosen[f,2,3], and Stephen J. Elledge[c,d,e,2,3]

Proc.Natl.Acad.Sci.U.S.A. 113:E7526, 2016

- Phage screening technologies (Phi-P Seq, PLATO) used to screen for target autoantigens
- RNPC3 identified as the major target in SSc-Cancer
  - Minor splicesome removes introns from pre-RNA
- Confirmed intra- and inter-molecular epitope spreading
  - POLR3A>POLR3F>POLR3H
  - 2 – 4 epitopes on RNPC3
  - U11/12 snRNP (SNRNP25, SNRNP35), Programmed Cell Death 7
- Limitations:
  - Sensitivity
  - Linear epitopes
  - Not all proteins in human proteome

ARTHRITIS & RHEUMATOLOGY
Vol. 69, No. 6, June 2017, pp 1306–1312
DOI 10.1002/art.40065

BRIEF REPORT

Anti–RNPC-3 Antibodies As a Marker of Cancer-Associated Scleroderma

Ami A. Shah,[1] George Xu,[2] Antony Rosen,[1] Laura K. Hummers,[1] Fredrick M. Wigley,[1] Stephen J. Elledge,[3] and Livia Casciola-Rosen[1]

- **318 SSc patients with cancer**
- anti-**C**ENP 30.2%; anti–**T**opo I 17.0%; anti–RNA**P** III 22.0% (**CTP group**)
- Anti-RNP-C3 seen in **3.8% of entire cohort**; **12.2% of CTP-negative**
  - Anti–RNPC-3 had a short cancer–scleroderma interval (median 0.9 years).
  - Relative to patients with anti-CENP, **patients with anti–RNPC-3 and those with anti–RNAP III had a >4-fold increased risk of cancer** within 2 years of scleroderma onset

Conclusion. Anti–RNPC-3 autoantibodies, like anti–RNAPIII, are associated with an increased risk of cancer at the onset of SSc.

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Anti-RNPC3 biomarker for cancer in SARD?

Disease	N	% +ve*	% High +ve*	Comments
SSc Incident Cancer	31	9.7	3.2**	CSRG Cancer **Colon cancer
Adult SSc	59	6.8	1.7	Unselected CSRG
Adult SSc	30	3.3	3.3	Calgary: MJF
Child SSc	83	3.6	0	Torok: U Pittsburgh
SLE Cancer	39	**23**	2.6	Johns Hopkins Cohort
SLE Random	64	**1.6**	0	STARLET
Inflammatory Myopathy	66	1.5	0	CIMS Cohort
IBM	24	**8.3**	**4.2**	McMaster University
NHS	40	2.5	0	Healthy Controls

* ALBIA using purified recombinant RNPC3:
– cutoff using normal serum += > 200 units
– high cutoff =>500 units

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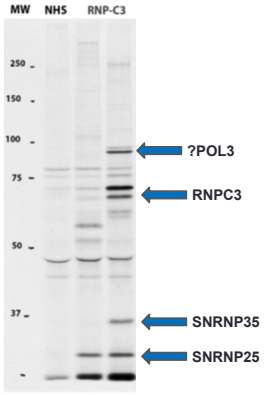
IP anti-RNPC3 sera (ALBIA)



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Anti-RNPC3 biomarker for cancer in SARD?

- **The jury is out**
- **To do**
  - All CSRG
    - Cancers (incident + prevalent)
    - Aab negative (serology gap)
  - SLE-cancer cohort (Sasha Bernatsky)
  - Larger IBM cohort
  - Epitope mapping revealed a single “hot” region of RNPC3
    - Assay developed and evaluation underway
  - Sjögren’s syndrome (40% in small cohort of 10): need larger cohort

Speaking of Sjögren's syndrome — What about PUF60?

- **PUF60:** **P**oly(**U**)-binding-splicing **F**actor = c-myc repressor

Ref 1:

- **25/84 (30%) SjS**; 6/71 (8.5%) SLE; 2/39 (5.0%) control subjects
- **48/267 (18.0%) DM**; 4/45 (8.9%) DM; 5/45 (11.1%) PM.
- Significantly associated with anti-Ro52/TRIM21 antibodies, rheumatoid factor, and hyperglobulinemia in the primary SjS patients. In DM patients, the antibody was associated with TIF-1γ and Caucasian race.

- Ref 2:
  - found in 32% of early stage (pre-op) colon cancer
  - Titres decreased after tumor resection

So far – unable to validate
Project on back burner

1. Fiorentino, et al. PUF60: a prominent new target of the autoimmune response in dermatomyositis and Sjögren's syndrome. *Ann.Rheum.Dis. 75:1145-1151, 2016.*
2. Kobayashi S, et al. Anti-FIRs (PUF60) auto-antibodies are detected in the sera of early-stage colon cancer patients. *Oncotarget. 7:82493-82503, 2016.*

QUESTIONS ??

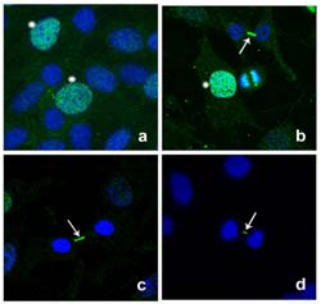
M-Phase Phosphoprotein 1 (MPP-1)

- Dr. P. Rao (MD Anderson Hospital, Houston) produced monoclonal antibodies to synchronized mitotic cells
- 2 monoclonals designated MPM-1 and MPM-2 of interest
  - IB: 55 – 220 kDa **M-phase** proteins
  - labelled with P^{32} / removed with phosphatase = **phosphoproteins**
  - 1994 Westendorf identified two cDNAs with unique sequences she named MPP1 and MPP2
  - 1996 MPP1 localized to midbody of dividing cells
  - 1999 immunoscreening an expression cDNA library identifies MPP1 as an autoantibody target in ~25% of idiopathic ataxia*
  - 2003 Abaza et al identify MPP1 as a kinesin related protein: 'molecular motor' named KIF20B

* Fritzler MJ *et al.* Autoantibodies from patients with idiopathic ataxia bind to M-phase phosphoprotein 1 (MPP-1). *J. Invest. Med.* **48**, 28-39 (2000).

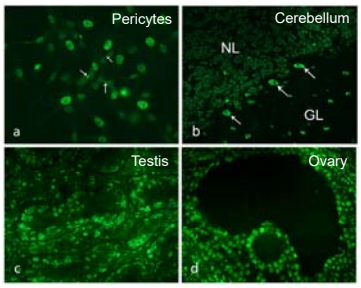
Anti-MPP1/KIF20B IIF staining

- 20% of nuclei (star)
- bright staining of mid-body/intracellular bridge (arrow) of anaphase cells
- Weak cytoplasmic staining
- Nuclei stained blue with DAPI

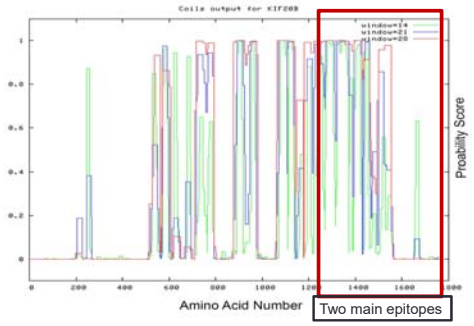


Anti-MPP1/KIF20B tissue staining

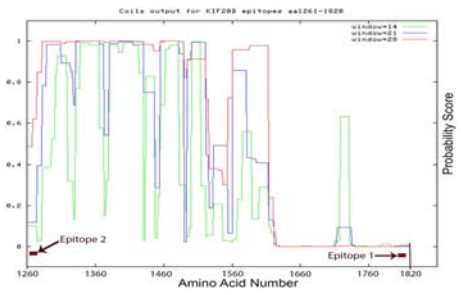
- 20% of pericyte nuclei (arrows)
- Bright staining of Purkinje cell and nuclear layer cell cytoplasm
- bright staining of nuclei of granular layer cells, testis and ovary



MPP1/KIF20B is a coiled-coil protein



Eptiopes of MPP1/KIF20B are not in coiled-coil regions

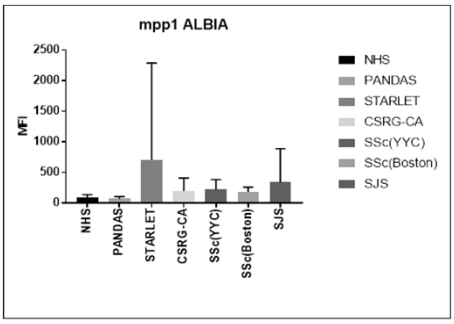


Anti-MPP1/KIF20B measured by ALBIA

Patient Group	N	% Positive	Cohort
SLE	140	26.0	STARLET
SLE (high titer*)	140	15.0	STARLET
SSc	77	10.9	Calgary
SSc – cancer	31	9.7	CSRG
SjS	18	11.1	Calgary
Paraneoplastic	54	13.7	Calgary
PANDAS	46	0	Missouri & Calgary
Normal	50	0	

* ALBIA using full length recombinant protein (conformational epitopes preserved)
Cutoff >499 median fluorescence units
High titer >1000 MFI)

ALBIA Titers anti-MPP1/KIF20B



Clinical Correlates High Titer anti-MPP1 in SLE*

- Higher total SLEDAI-2K score (OR 1.1, [95% CI 1.0, 1.3])
  - serositis (OR 3.0, [95% CI 1.4, 6.6])
  - immunological subscales (OR 2.0, [95% CI 1.4, 2.9])
  - anti-dsDNA (OR 5.5 [95% CI 1.8, 16.6])
  - anti-SSA/Ro60 (OR 3.1 [95% CI 1.0, 8.9])
  - anti-PS/PT complex-IgG (OR 3.6 [95% CI 1.1, 11.5]).

* Univariable analysis

Further studies

- SLE cancer cohort: Sasha Bernatsky
- Larger SLE cohort (SLICC: Ann Clarke, John Hanly)
- NPSLE: Dr. Zahi Touma, U of Toronto
- Epitope mapping

QUESTIONS?

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Bicaudal D2 (BICD2)

Contents lists available at ScienceDirect
Autoimmunity Reviews
EPub ahead of print, 2018
journal homepage: www.elsevier.com/locate/autrev

Bicaudal D2 is a novel autoantibody target in systemic sclerosis that shares a key epitope with CENP-A but has a distinct clinical phenotype

Marvin J. Fritzler [a,*], Marie Hudson [b,c,d], May Y. Choi [a], Michael Mahler [e], Mianbo Wang [d], Chelsea Bentow [e], Jay Milo [e], Murray Baron [b,c], Canadian Scleroderma Research Group:

J. Pope [1], M. Baron [2], J. Markland [3,1], D. Robinson [4], N. Jones [5], N. Khalidi [6], P. Docherty [7], E. Kaminska [8], A. Masetto [9], E. Sutton [10], J.-P. Mathieu [11], M. Hudson [2], S. Ligier [12], T. Grodzicky [13], S. LeClercq [8], C. Thorne [14], G. Gyger [2], D. Smith [15], P.R. Fortin [16], M. Larché [6], M. Abu-Hakima [8], T.S. Rodriguez-Reyna [17], A.R. Cabral [17], M.J. Fritzler [8]

A study of 451 unselected Canadian Scleroderma Research Group patients

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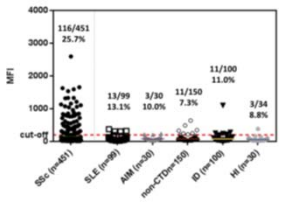
Anti-BICD2 Serology

- Anti-BICD2: Addressable Laser Bead Immunoassay
- 25.7% of SSc were anti-BICD2 positive
  - = second most common autoantibody in this cohort
  - 19.0% had single specificity anti-BICD2 (ANA negative SSc)
  - 81.0% had other autoantibodies, notably anti-CENP (83/94; 88.3%)



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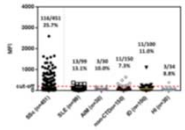
Anti-BICD2: Clinical Associations

- 25.7% of SSc were anti-BICD2 positive
  - = second most common autoantibody in this cohort
  - 19.0% had single specificity anti-BICD2 (ANA negative SSc)
  - 81.0% had other autoantibodies, notably anti-CENP (83/94; 88.3%)
- Compared to anti-BICD2 negative subjects, single specificity anti-BICD2 subjects had:
  - **interstitial lung disease** (ILD; 52.4% vs. 29.0%, p = .024)
  - **inflammatory myopathy** (IM; 31.8% vs. 9.6%, p = .004)
    - **40% BICD2+ had anti-Ro52/TRIM21** vs 25% ABN



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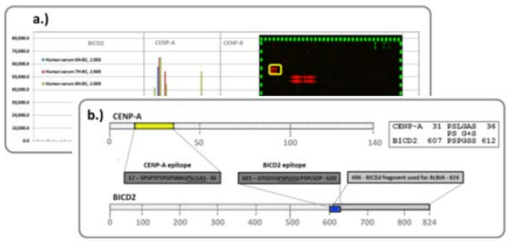
Anti-BICD2: Epitope Map

- Epitope mapping revealed a serine and proline-rich nonapeptide SPSPGSSLP comprising amino acids 606–614 of BICD2, shared with CENP-A but not CENP-B.



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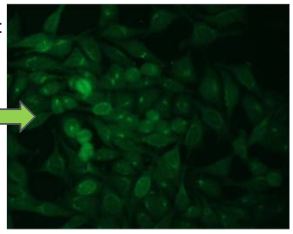
Anti-BICD2 Summary

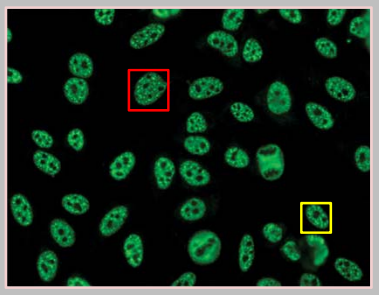
- Affinity purified anti-BICD2: no identifiable IIF pattern
- Monoclonal anti-BICD2



- **Autoantibodies to BICD2 represent a new biomarker as they were detected in patients without other SSc-specific autoantibodies**

Moving on…. An interesting patient…

- 27-year-old female admitted to hospital with 5 month history of polyarthritis, Raynaud's, dry eyes, photosensitivity
- Initial laboratory analysis:
  - **ANA was positive IIF on HEp-2 cells**
    - **Titre 1:5120**
    - **Coarse nuclear speckled and nuclear dots staining pattern**
  - ENA: anti-Sm and high titre anti-U1RNP
  - Rheumatoid factor (22 kU/l)



Nuclear dots

Coarse nuclear speckled

An interesting patient…P/E + Lab

- Complained of myalgias
- Mild proximal muscle weakness 4/5 strength in hip flexors bilaterally
  - CK was 1700 U/L
  - No statin exposure
  - EMG was normal except for area of a single positive sharp wave was noted in the iliopsoas muscle

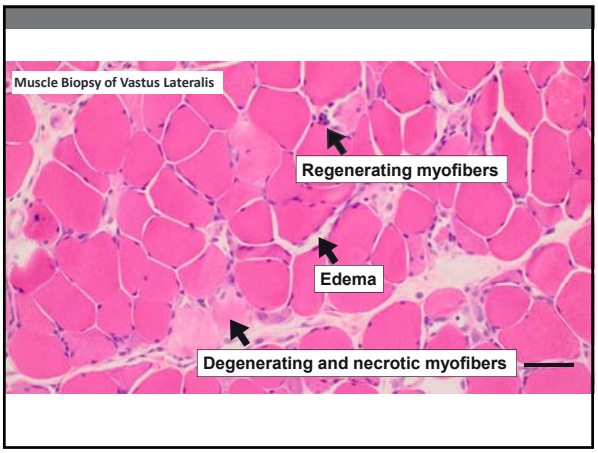
"Very confident that this *may be* lupus"?

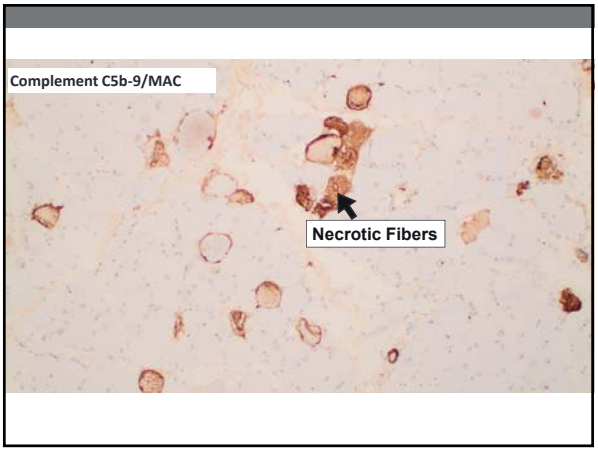
- SLE vs. undifferentiated or mixed connective tissue disease
  - Hydroxychloroquine and prednisone 15mg PO BID
  - Arthritis and weakness resolved within 4 days so she was discharged
- 30 days later, she returned with worsening symmetrical proximal muscle weakness and shortness of breath
- Creatine kinase increased to 7805 U/L

Further Investigation

- Cardiac **MRI - no myocarditis**, no edema
- **CT chest/abdomen/pelvis** - heterogeneous enhancement throughout the paraspinal, abdominal wall/pelvic musculature and psoas muscles
- **MRI hips/pelvis** - extensive and symmetric edema in pelvis and thigh musculature
- **Muscle biopsy** of vastus lateralis

"necrosis with minimal inflammation"





Myositis-Related Autoantibodies

- Myositis Panel: **Negative**
  - Jo-1, Mi2, Mi2-α, Mi2β, MDA5, NXP2, TIF1γ PL7, PL12, PM/Scl75, PM/Scl100, Ku, SRP, EJ, OJ, Ro52
- Immune Mediated Necrotizing Myopathy/Statin-Related Myopathy Serology: SRP, HMGCR
  - **Negative**

CK Continued to Rise…

- Pulse steroids and IVIG initially
- 1 week later, she developed respiratory failure → intubated

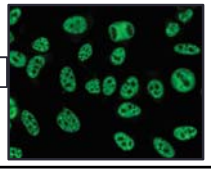
Transferred to ICU

- Multifactorial shock with severe biventricular dysfunction with rising lactate, WBC, and creatinine
  - Dialysis, vasopressors, empiric broad spectrum antibiotics
  - IV cyclophosphamide and PLEX x 5 days
- Disseminated intravascular coagulation, pulseless electrical activity cardiac arrest x 3 → Passed away on day 14

Challenges in Autoantibody Testing in Autoimmune Myopathies

- Autoantibodies known to be associated with a necrotizing autoimmune myopathy
  - HMG CoA reductase (anti-HMGCR)
  - Signal Recognition Particle (anti-SRP)
- In her case, both were negative, so what else could it be?

The ANA IIF pattern was a clue!



BRIEF REPORT

Autoantibodies to Survival of Motor Neuron Complex in Patients With Polymyositis: Immunoprecipitation of D, E, F, and G Proteins Without Other Components of Small Nuclear Ribonucleoproteins

ARTHRITIS & RHEUMATISM
Vol. 63, No. 7, July 2011, pp 1972–1978
DOI 10.1002/art.30349

Minoru Satoh,[1] Jason Y. F. Chan,[1] Steven J. Ross,[1] Angela Ceribelli,[1] Ilaria Cavazzana,[2] Franco Franceschini,[2] Yi Li,[1] Westley H. Reeves,[1] Eric S. Sobel,[1] and Edward K. L. Chan[1]

WHAT IN THE WORLD IS SMN

- SMN = Survival of Motor Neuron + gemins: 5-8 proteins
- Involved in mRNA splicing
- Nuclear proteins localized to Cajal bodies
- ICAP IIF staining pattern 'few nuclear dots = AC-7

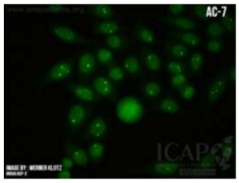


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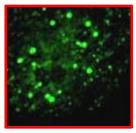
Table 1. Clinical features of the patients with anti-survival of motor neuron complex autoantibodies*

	Patient 1	Patient 2	Patient 3
Demographic features			
Age, years			
At diagnosis	30	26 (SSc) 36 (PM)	35
At last visit	36	45	35
Race	White	White	White
Sex	Female	Female	Female
Country	US	US	Italy
Diagnosis	PM	PM–SSc†	PM–SSc

ANA was the clue!

- Coarse nuclear speckled and nuclear dots IIF pattern:

Anti-Survival of Motor Neuron (SMN)/ Gemins Antibodies



- SMN gene deletion/mutation causes **spinal muscular atrophy**
- The SMN complex (SMN and gemin 3/4 proteins) play a critical role in the assembly of small nuclear ribonucleoproteins (snRNP): **Sm and U1RNP**

Are anti-SMN/Gemins associated with necrotizing autoimmune myopathy?

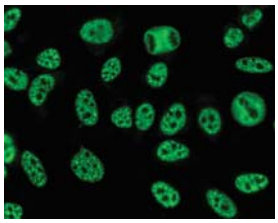
- Tested positive for anti-SMN1 / Gemin3 antibodies at Mitogen Advanced Diagnostics Laboratory
- Sera sent to Dr. Minoru Satoh (Japan) for immunoprecipitation

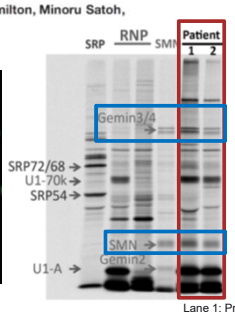
Letter to the Editor (Case report)

Autoantibodies to the survival of motor neuron complex in a patient with necrotizing autoimmune myopathy

Adam Amlani, Glen S. Hazlewood, Leslie Hamilton, Minoru Satoh, Marvin J. Fritzler

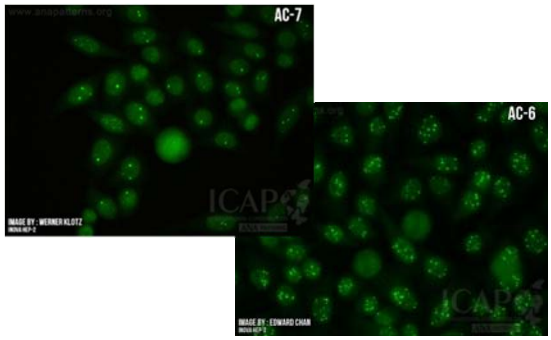
Rheumatology (Oxford) 57:199, 2018





Lane 1: Pre-Plex
Lane 2: Post-Plex

SMN: Is it AC-7 or AC-6 or both?



Anti-SMN pilot data

Serum Group	N	% Positive
Normal	50	0
AC-6/AC-7 Pattern Sera	80	6.3
SLE	150	1.3
SSc (CSRG)	58	17.3
Myositis (CIMS)	66	9.1

Is there a consistent clinical phenotype associated with anti-SMN? Overlap SSc/AIM; SLE/AIM?

50

NT5C1/MUP44

- Several decades searching for a biomarker for sporadic inclusion body myositis (sIBM)

* Pluk H, B. J. van Hoeve, S. H. van Dooren, J. Autoantibodies to cytosolic 5'-nucleotidase 1A in inclusion body myositis. *Ann. Neurol. 73:397-407, 2013.*

Biomarker for Inclusion Body Myositis?

- ***Antibodies to Mup44/NT5C1**
- Adam Amlani, Mark Tarnopolsky, Lauren Brady, Marvin Fritzler
  University of Calgary, McMaster University Medical Center
  - Study of 250 patients:
    - 19 sporadic IBM
    - Controls: healthy (n=28); autoimmune myopathies (n=40), statin-related myopathies (n=4); other SARD (n=97).
  - **Anti-Mup44 in sIBM: 11/19 (57.9%).**
    Anti-Mup44 12% in disease controls and 10.7% in healthy controls.
    - **Sensitivity 58%; Specificity ~88%**
  - sIBM: 1/19 (5%) positive for anti-HMGCR, but negative for all other myositis-related antibodies (Jo-1, OJ, TIF1y, PL-12, SAE, EJ, MDA5, PL7, SRP, NXP2, MI-2).
  - No consistent IIF pattern on HEp-2 seen in anti-Mup44 +ve

* See Poster # 165 this meeting

Biomarker for Inclusion Body Myositis?

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  - Study of 250 patients:19 had sIBM. Healthy controls (n=28); other autoimmune conditions (n=97); autoimmune myopathies (n=40), statin-related myopathies (n=4); osteoarthritis (n=47), other neuromuscular or metabolic disorders (n=13).
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CSRG Members	
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