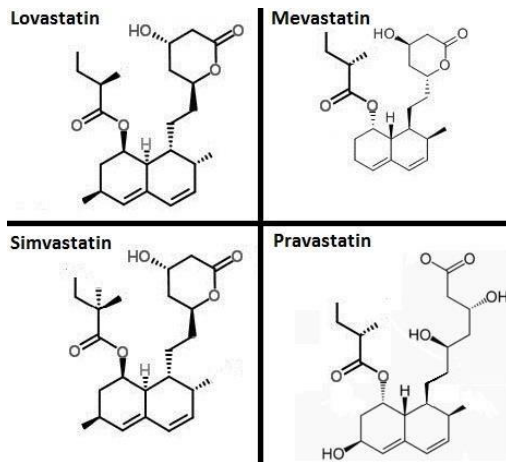


# The Statin-Associated Necrotizing Autoimmune Myopathy Story: Breaking all the Rules

## *Uncovering a Novel Paradigm for Statin Associated Myotoxicity*



**Lisa Christopher-Stine, MD, MPH**

**Associate Professor of Medicine and Neurology**

**Director, Johns Hopkins Myositis Center**

**Johns Hopkins University School of Medicine**

**Medicine Grand Rounds**

**Hofstra Northwell School of Medicine**

**March 1, 2018**



# CME ACCREDITED UPDATES IN MEDICINE ELEARNING SERIES

**COURSE NAME:**

Medicine RSS eLearning Modules

**CME eLEARNING ACTIVITY NAME:**

The Statin-Associated Necrotizing Autoimmune Myopathy Story: Breaking all the Rules Uncovering a Novel Paradigm for Statin Associated Myotoxicity

**PROGRAM DESCRIPTION, EDUCATIONAL GOAL AND RATIONALE:**

Evidence based guidelines are constantly changing and being updated for several core areas of Internal Medicine throughout the year. It is important for physicians to practice the most up-to-date standard of care in all specialties to promote patient health and well-being. Our series of lectures at the medicine regularly scheduled series promotes continuing education for the practicing internist and highlights important updates in medical practice in these core areas. Physicians in general practice often and do not have the time to keep themselves up-to-date with medical advances as they are busy seeing patients in the clinical setting. The Medicine Regularly Scheduled Series gives these physicians the opportunity to learn these advances in an academic setting.

# CME ACCREDITED UPDATES IN MEDICINE ELEARNING SERIES

## **TARGET AUDIENCE:**

Physician Partners and Premium Network community-based providers

## **LEARNING OBJECTIVES:**

Upon successful completion of this activity, participants should:

- Identify current knowledge about self –limited statin myopathy
- Recognize the discovery and subsequent laboratory and clinical features of statin-associated necrotizing autoimmune myopathy (SANAM)/ Statin-Associated Immune mediated necrotizing myopathy
- Identify when to suspect SANAM and to recognize how to distinguish it from the self-limited form

# CME ACCREDITED UPDATES IN MEDICINE ELEARNING SERIES

## FACULTY PRESENTER/AUTHOR:

### **Lisa Christopher-Stine, MD, MPH**

Professor of Medicine  
Associate professor of Medicine and Neurology  
Director, John Hopkins Myositis Center  
John Hopkins University School of Medicine

### **Thomas McGinn, MD**

Thomas McGinn MD MPH  
Professor and Chair of Medicine  
Donald and Barbara Zucker Hofstra /Northwell School of Medicine  
SVP and Deputy Physician in Chief, Northwell Health

### **Course Director:**

George Boutis, MD  
Attending Physician  
Department of Medicine  
Northwell Health

### **Planners:**

John Raimo, MD  
Division of Hospital Medicine  
Site Director, Internal Medicine Residency Program

### **Sean LaVine, MD**

Site Director, Division of Hospital Medicine  
Long Island Jewish Medical Center

# CME ACCREDITED UPDATES IN MEDICINE ELEARNING SERIES

## **ACCREDITATION:**

Northwell Health is accredited by the Accreditation Council for Continuing Medical Education to provide Continuing Medical Education for physicians.

## **CREDIT DESIGNATION:**

Northwell Health designates this Continuing Medical Education activity for a maximum of 1 AMA PRA Category I credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity

## **METHOD OF PHYSICIAN PARTICIPATION:**

### **To receive credit the participants must:**

Read/view the entire educational activity.

Input name and credentials to gain CME credit.

Answer at least 80% of the Post-Test questions correctly.

Complete and return Post-Test.

Complete and return Program Evaluation.

# CME ACCREDITED UPDATES IN MEDICINE ELEARNING SERIES

**COURSE HOST:**

Department of Medicine  
Northwell Health

**ESTIMATED TIME TO COMPLETE ACTIVITY:**

90 minutes

**ACKNOWLEDGEMENT OF COMMERCIAL SUPPORT:**

An announcement of program support will be made to all attendees at the beginning of each educational activity.

# CME ACCREDITED UPDATES IN MEDICINE ELEARNING SERIES

## **DISCLOSURE POLICY:**

Northwell Health adheres to the ACCME's Standards for Commercial Support. Any individuals in a position to control the content of a CME activity, including faculty, planners, reviewers or others are required to disclose all relevant financial relationships with commercial interests. All relevant conflicts of interest will be resolved prior to the commencement of the activity.

## **FACULTY DISCLOSURES:**

Drs. Thomas McGinn, George Boutis, John Raimo and Sean LaVine have nothing to disclose.

## **SPEAKER DISCLOSURES:**

Dr. Christopher-Stine has intellectual property interest in a novel autoantibody assay detection for anti- HMGCR (ELISA and IP). [Inova Diagnostics]. She references unlabeled or unapproved use of drugs in her presentation.

**RELEASE DATE:** 4/16/2018

**REVIEW DATE:** 4/16/2018

**PROGRAM EXPIRATION:** 7/30/2018

# Objectives

(1) To illuminate current knowledge about self-limited statin myopathy

(2) To illustrate the discovery and subsequent laboratory and clinical features of statin-associated necrotizing autoimmune myopathy (SANAM)/ Statin-Associated Immune mediated necrotizing myopathy

(3) To investigate when to suspect SANAM and to recognize how to distinguish it from the self-limited form



Let's start with three  
“mysterious” patients...



# Patient #1

58-year-old woman with a history of hyperlipidemia

5/29/04: **Atorvastatin 80 mg x 5 months**

ALT 21 ; AST 20 ; CK unknown

10/04: **Muscle pain occurs; atorvastatin d/c**

08/05: ALT 110 AST 81; CK unknown

06/06: ALT 24; AST 24; CK 116 IU/L

05/07: **Pravastatin 40 mg x 3 months**

08/07: **Muscle pain occurs; pravastatin d/c**

09/11/07: ALT 114; AST 102; CK 1897 IU/L

01/17/08: CK 2122 IU/L

02/08: **Muscle pain intensifies and weakness begins**

02/08- 9/09: Progressively weaker; muscle biopsy shows patchy necrosis without inflammation; EMG is inconclusive; CKs rise dramatically to 8728 IU/L

# Patient # 2

- 72 year-old male, in mid-2011 after incidentally discovered transaminase elevation while on longstanding atorvastatin, found on subsequent workup to have
  - CPK of 5325 IU/L
  - Hamstring edema on MRI
  - Active necrosis with atrophic muscle fibers on muscle biopsy
- While he has been limited in terms of thigh strength, interpretation was complicated by concurrent radicular back pain.

# Patient # 3

- 59-year-old female who has a history of longstanding diabetes (10 years) HTN, and hypercholesteremia, who was in her usual state of health until the fall of 2003. At that point she had been taking **Rosuvastatin** for approximately **one month**.
- She noted that when she attempted to get into her brother-in-law's vehicle, she had experienced what was said to be a groin pull and she was unable to sit. She was then, over time, not able to get off a chair or reach over her head.
- CPK was not checked until approximately 8 months later (CK>17,000 IU/L).
- Rosuvastatin was stopped and a muscle biopsy was pursued (May 2004): Consistent with a necrotizing myopathy with a chronic inflammatory infiltrate present as well.
- An electromyogram was performed in June, 2004 consistent with an irritable myopathy. At that point, it was noted that the patient had 4+/5 proximal strength in her hips and shoulder girdle was normal strength distally.

# Statin Myopathy: What we knew

# Statin Myopathy: What we knew

# Scope of Statin Use

- Statin use grew from 47% to 87% of all lipid lowering therapies (1992→2002).
- From 2000 to 2005, statin use nearly doubled.
- With approx 2.78 million people added per year, this places estimates between 43.2 and 47.5 million people in US currently taking a statin (2015).

# Statins

## **Statin**

Atorvastatin

Cerivastatin

Fluvastatin

Lovastatin

Mevastatin

Pitavastatin

Pravastatin

Rosuvastatin

## **Brand Name**

Lipitor, Torvast

Lipobay, Baycol

Lescol, Lescol XL

Mevacor, Altocor, Altoprev

Compactin

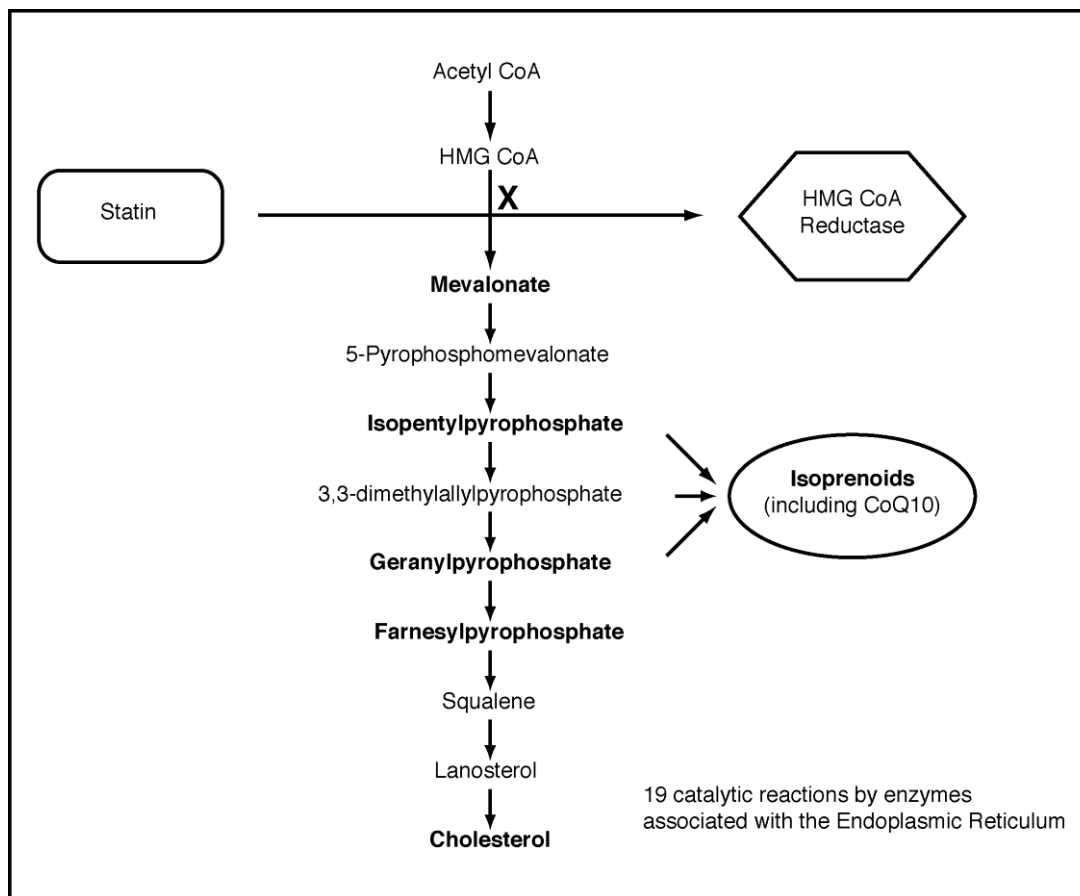
Livalo (**NOT Lovaza\***), Pitava

Pravachol, Selektine, Lipostat

Crestor



# Brief Biochemistry Review: Cholesterol Synthesis



Christopher-Stine L. Curr Opin Rheumatol. 2006 Nov;18(6):647-53.



# STATIN TOXICITY MECHANISMS

HMG-CoA

Statin  
HMG-CoA reductase

Mevalonate

Isopentenyl PP

Farnesyl PP

Heme A

Geranylgeranyl PP

Squalene

Cholesterol

*Altered myocyte membranes?*



Isoprenylated Proteins

*Depletion activates apoptotic pathway?*

Dolicho

Ubiquinone

*Reduced CoQ10 disrupts mitochondrial function?*

# Statins: Clinical Aspects

- Statin use has been thought to contribute to a 30% reduction in cardiovascular disease “with minimal ADRs and morbidity.”
- Previous guidelines recommended serum low-density lipoprotein-cholesterol (LDL-C) levels of below 100 mg/dl as the target for patients with stable coronary heart disease (CHD), and below 70 mg/dl for those at very high risk.
- Current guidelines do not focus specifically on LDL but rather predict risk using multiple demographic and clinical variables in a 10-year risk prediction model

Harper CR, Jacobsen TA.. *Curr Opin Lipidol* 2007; 18:401–408.

Pasternak R, Smith S, Bairey-Merz C, et al.. *J Am Coll Cardiol* 2002; 40:567–572.

Four major groups of patients for whom statins have the greatest chance of preventing stroke /MI

- Patients who have cardiovascular disease
- Patients with an LDL level of 190 mg/dL or higher
- Patients with Type 2 diabetes who are between 40 and 75 years of age
- Patients with an estimated 10-year risk of cardiovascular disease of  $\geq 7.5\%$  between 40 and 75 y.o.

**Moderate or high-intensity statin recommended**

# Statin Intensity

## **HIGH INTENSITY**

Atorvastatin 80 mg

Rosuvastatin 20 mg (40 mg)

## **MODERATE INTENSITY**

Atorvastatin 10 mg (20 mg)

Rosuvastatin 10 mg

Simvastatin 20-40 mg

Pravastatin 40 mg

Fluvastatin 40 mg BID

## **LOW INTENSITY**

Pravastatin 10-20 mg

Lovastatin 20 mg

## Expanding Scope of Statin Use: The 2013 guidelines of the ACC–AHA

- The new guidelines would **increase the number of U.S. adults receiving or eligible for statin therapy** from **43.2 million (37.5%)** to **56.0 million (48.6%)**- a **net increase of 12.8 million**.
- Among adults between the ages of 60 and 75 years without cardiovascular disease who are not receiving statin therapy, the **percentage** who would be eligible for such therapy **would increase from 30.4% to 87.4% among men and from 21.2% to 53.6% among women**.

# Statin Myopathy in a Clinical Setting

- Nonspecific muscle pain and weakness are more common than frank rhabdomyolysis/ myopathy (20% vs 0.1-5%)
- Incidence of the most common complaint of nonspecific muscle or joint pains in the absence of elevated CPK is 5% (does not differ significantly from placebo)
- Prevalence of CK>1500 U/L is 1.6 cases per 1000 patients or 69,760 cases per all US patients estimated to be taking statins (2010)
- Muscle symptoms and high serum CK levels may persist even after statin withdrawal

# Statin Myopathy Clinical Aspects

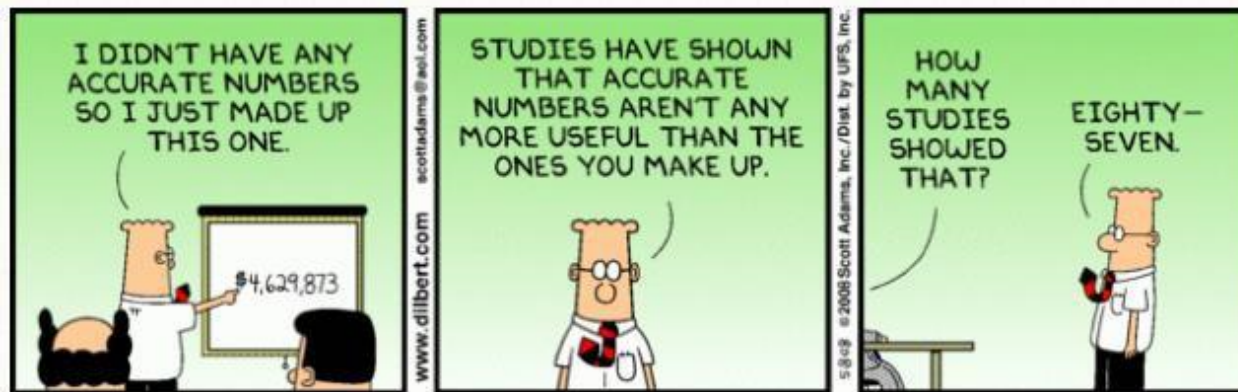
- Nonspecific muscle pain and weakness are more common than frank rhabdomyolysis/ myopathy (20% vs 0.1-5%)
- Incidence of the most common complaint of nonspecific muscle or joint pains in the absence of elevated CPK is 5% (does not differ significantly from placebo)
- Prevalence of CK>1500 U/L is 1.6 cases per 1000 patients or 69,760 cases per 43.6 million US patients estimated to be taking statins currently (2010)
- **Muscle symptoms and high serum CK levels may persist even after statin withdrawal**



## Definitions of statin-associated muscle symptoms proposed by the EAS Consensus Panel

Symptoms	Biomarker	Comment
Muscle symptoms	Normal CK	Often called 'myalgia'. May be related to statin therapy. Causality is uncertain in view of the lack of evidence of an excess of muscle symptoms in blinded randomized trials comparing statin with placebo.
Muscle symptoms	CK >ULN <4x ULN  CK >4 <10X ULM	Minor elevations of CK in the context of muscle symptoms are commonly due to increased exercise or physical activity, but also may be statin-related; this may indicate an increased risk for more severe, underlying muscle problems. <sup>19</sup>
Muscle symptoms	CK >10X ULN	Often called myositis or 'myopathy' by regulatory agencies and other groups (even in the absence of a muscle biopsy or clinically demonstrated muscle weakness). Blinded trials of statin vs. placebo show all excess with usual statin doses of about 11 per 1000 per year. <sup>4</sup> Pain is typically generalized and proximal and there may be muscle tenderness and weakness. May be associated with underlying muscle disease.
Muscle symptoms	CK >40x ULM	Also referred to as rhabdomyolysis when associated with renal impairment and/or myoglobinuria.
None	CK >ULN <4 XULN	Raised CK found incidentally, may be related to statin therapy. Consider checking thyroid function or may be exercise-related.
None	CK >4X ULM	Small excess of asymptomatic rises in CK have been observed in randomized blinded trials in which CK has been measured regularly. Needs repeating but if persistent, the clinical significance is unclear.

# How accurate are our current estimates for statin myopathy prevalence?



## Understanding Statin use in America and Gaps in Patient Education (USAGE)

- Internet based self-administered survey of >10,000 current or former statin users in U.S. conducted over one month in 2011
- Respondents predominantly Caucasian (92%), female (61%) with mean age of 61.
- Of the 1220 respondents who stopped taking a statin, 62% cited side effects compared with 17% who cited cost and 12% who cited lack of efficacy
- Of the 8918 survey respondents who were currently on a statin but had switched brands, **28% cited side effects**
- **Muscle pain or weakness was reported by 29% of all survey respondents** . Rate was higher among **former** users compared to **current** users (**60% vs. 25%**)

# Statin Myopathy :Clinical Practice Implications

- Nonspecific muscle pain and weakness are more common than frank rhabdomyolysis/ myopathy.
- Incidence of the most common complaint of nonspecific muscle or joint pains in the absence of elevated CPK is 5% in clinical trials (does not differ significantly from placebo)
- However, community-based studies suggest a higher prevalence of **up to 33%**
- Prevalence of CK>1500 U/L is approx 1.6 cases per 1000 patients or about 70,000 among U.S. statin takers
- Muscle symptoms and high serum CK levels may persist even after statin withdrawal

*Am J Cardiol 2006;97:89C–94C*

*Am J Cardiol 2006;97:6C–26C*

# Statin Myopathy :Clinical Practice Implications

- Nonspecific muscle pain and weakness are more common than frank rhabdomyolysis/ myopathy.
- Incidence of the most common complaint of nonspecific muscle or joint pains in the absence of elevated CPK is 5% in clinical trials (does not differ significantly from placebo)
- However, community-based studies suggest a higher prevalence of **up to 33%**
- Prevalence of CK>1500 U/L is approx 1.6 cases per 1000 patients or about 70,000 among U.S. statin takers
- Muscle symptoms and high serum CK levels may persist even after statin withdrawal

*Am J Cardiol 2006;97:89C–94C*

*Am J Cardiol 2006;97:6C–26C*

# Statins, Myopathy and the interplay of Autoimmunity



“Although statin-related myotoxicity is generally believed to be a noninflammatory, toxic myopathy, experimental evidence suggests that statin myopathy may be triggered by an autoimmune reaction or, conversely, statin use may trigger an autoimmune process. The precise mechanism of statin-related autoimmune reactions is uncertain.”

Christopher-Stine L. Curr Opin Rheumatol. 2006 Nov;18(6):647-53.



“IMNM”

“PM”

## EDITORIAL REVIEW

# **Neurologists are from Mars. Rheumatologists are from Venus: differences in approach to classifying the idiopathic inflammatory myopathies**

Lisa Christopher-Stine

Johns Hopkins University, Baltimore, Maryland, USA

Correspondence to Lisa Christopher-Stine, MD, MPH,  
Johns Hopkins Bayview Medical Center, Johns  
Hopkins Myositis Center, Mason F. Lord Building  
Center Tower, Suite 4100, Baltimore, MD 21224, USA  
Tel: +1 410 550 6962; fax: +1 410 550 3542;  
e-mail: [lcs@jhmi.edu](mailto:lcs@jhmi.edu)

### **Purpose of review**

Inflammatory myopathy (IM) classification criteria have been the source of considerable debate. In the three decades since Bohan and Peter published their criteria which have long stood as the gold standard for diagnosis in clinical practice as well as inclusion into clinical trials, more sophisticated understanding of immunopathogenesis, histology,

# Idiopathic Inflammatory Myopathies (IIM)

- Polymyositis
- Dermatomyositis
- Inclusion body myositis
- Giant cell myositis
- Eosinophilic myositis
- Granulomatous myositis
- Macrophagic myofasciitis
- Pipestem capillary disease
- Myositis related to other connective tissue diseases



# Idiopathic Inflammatory Myopathies (IIM)

- Polymyositis
- Dermatomyositis
- Inclusion body myositis
- Immune Mediated Necrotizing Myopathy (IMNM)
- Giant cell myositis
- Eosinophilic myositis
- Granulomatous myositis
- Macrophagic myofasciitis
- Pipestem capillary disease
- Myositis related to other connective tissue diseases

# Bohan and Peter Diagnostic Criteria for Polymyositis/Dermatomyositis

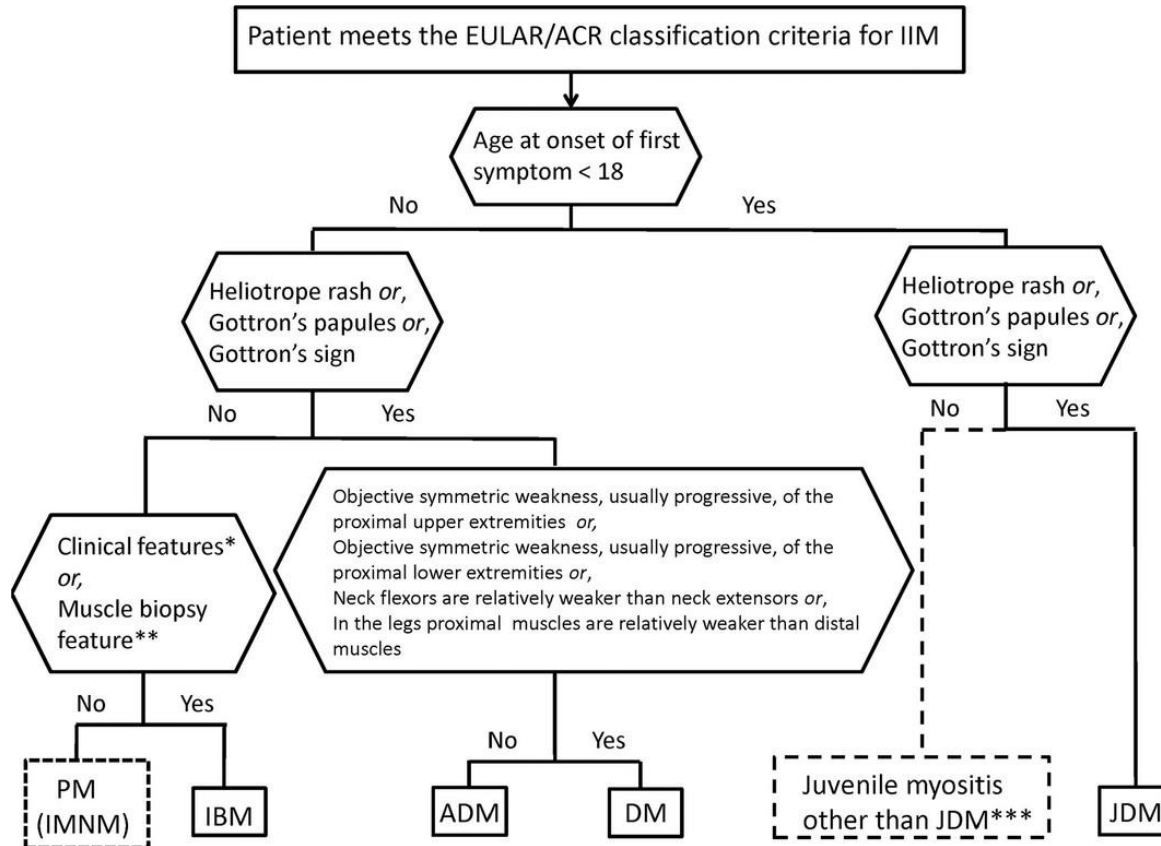
- Symmetric Proximal Muscle Weakness
- Elevated Muscle Enzymes (CK, Aldolase, Transaminases, LDH)
- Myopathic EMG Abnormalities
- Typical Changes on Muscle Biopsy
- Typical Rash of Dermatomyositis

\*PM diagnosed as Definite with 4/5 criteria; probable with 3/5 criteria

\*DM Diagnosed as Definite with Rash + 3/ 4 Criteria; probable with Rash + 2/4 criteria

Bohan A, Peter JB, Bowman BS, et al.. Medicine (Baltimore). 1977;65:255-286.

2017 European League Against Rheumatism/American College of Rheumatology  
 Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies and  
 Their Major Subgroups

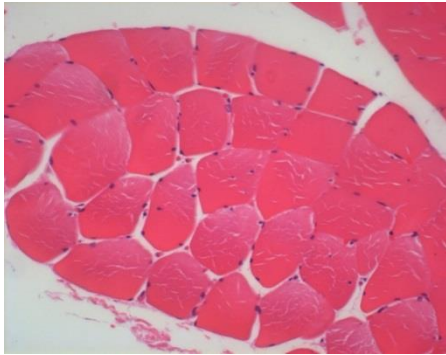


# Immune Mediated Necrotizing Myopathy Diagnostic Criteria (October 2003 at the 119th ENMC workshop)

Diagnostic Categories	Criteria
Clinical criteria	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> <li>• Age &gt; 18 years</li> <li>• Subacute or insidious onset</li> <li>• Symmetric proximal muscle and neck flexor weakness &gt; distal and neck extensor weakness</li> </ul> <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> <li>• Clinical features of IBM</li> <li>• Ocular weakness, isolated dysarthria, neck extensor&gt;flexor weakness</li> <li>• Toxic myopathy, active endocrinopathy, amyloidosis, family history of muscle dystrophy or proximal motor neuropathies (SMA)</li> </ul>
Elevated CK	
Laboratory Criteria (1 of 3)	<ul style="list-style-type: none"> <li>• Positive EMG: Fibrillation potentials, positive sharp waves, or complex repetitive discharges. Short-duration, small amplitude, polyphasic MUAPs</li> <li>• Muscle MRI: Increased signal (edema) within muscle on STIR images</li> <li>• Myositis-specific antibodies detected in serum</li> </ul>
Muscle biopsy	<ul style="list-style-type: none"> <li>• Prominent muscle fiber necrosis</li> <li>• Sparse inflammatory infiltrate, no perimysial infiltrate</li> <li>• MAC deposition on small vessels or perivascular capillaries</li> <li>• Rare tubuloreticular inclusions in endothelial cells</li> </ul>

# Muscle histology review: Distinct Histologic Patterns in PM and DM

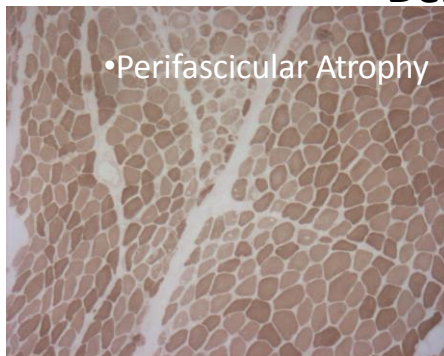
## Normal muscle



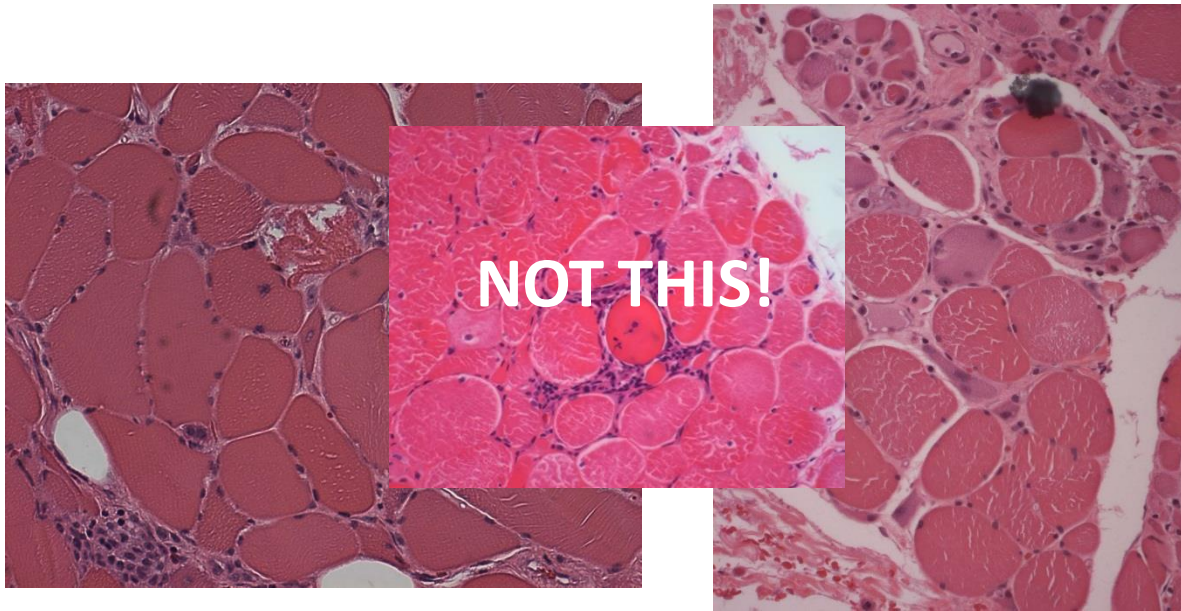
## Polymyositis



## Dermatomyositis



# Immune Mediated Necrotizing Myopathy



# Necrotizing Myopathy

- Nonspecific histopathologic finding

- Nevertheless, a substantial proportion of patients with necrotizing myopathies have none of these

Associated conditions:  
known associations

- Malignancy (GI, lung)
- Immune mediated myopathies (anti SRP, anti Jo-1)
- Toxic myopathies
- Other

# Fast facts about IMNM

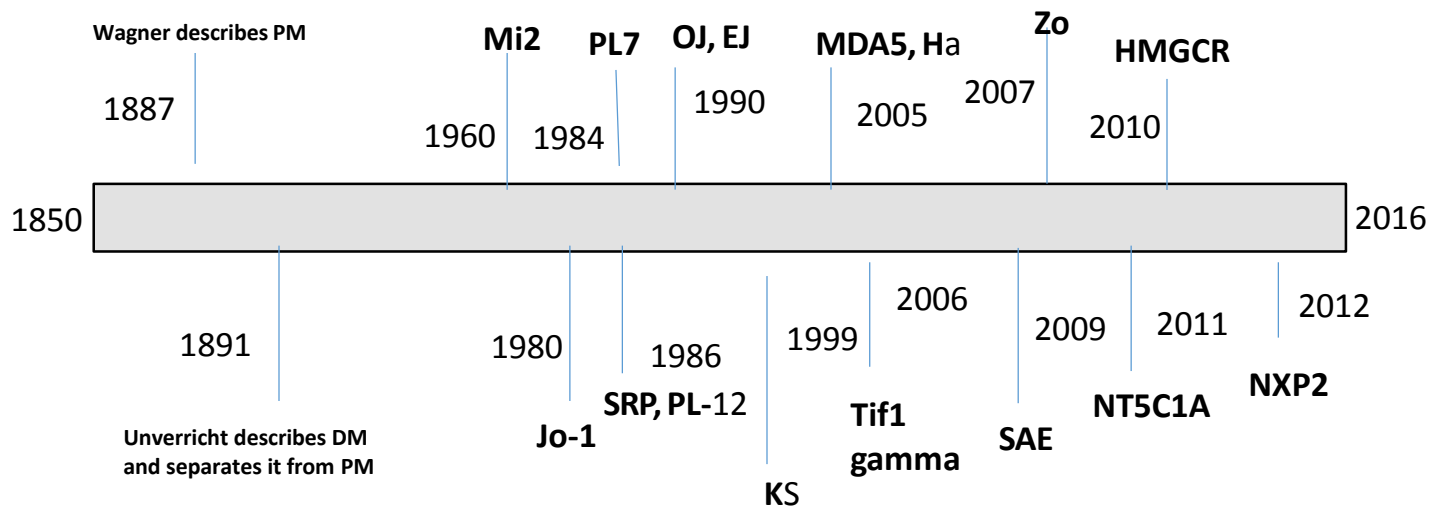
- Approximately 20% of idiopathic inflammatory myopathies can be subclassified as IMNM [also known as necrotizing autoimmune myopathy (NAM)]
- Like other idiopathic inflammatory myopathies, IMNM is thought to have:
  - an autoimmune etiology based on upregulation of MHC Class I on muscle fibers
  - presence of specific autoantibodies
  - clinical response to immunosuppression.
- Although IMNM was not previously differentiated from polymyositis in the 1975 Bohan and Peter criteria, there has been an increasing recognition that IMNM is a distinct clinical entity.



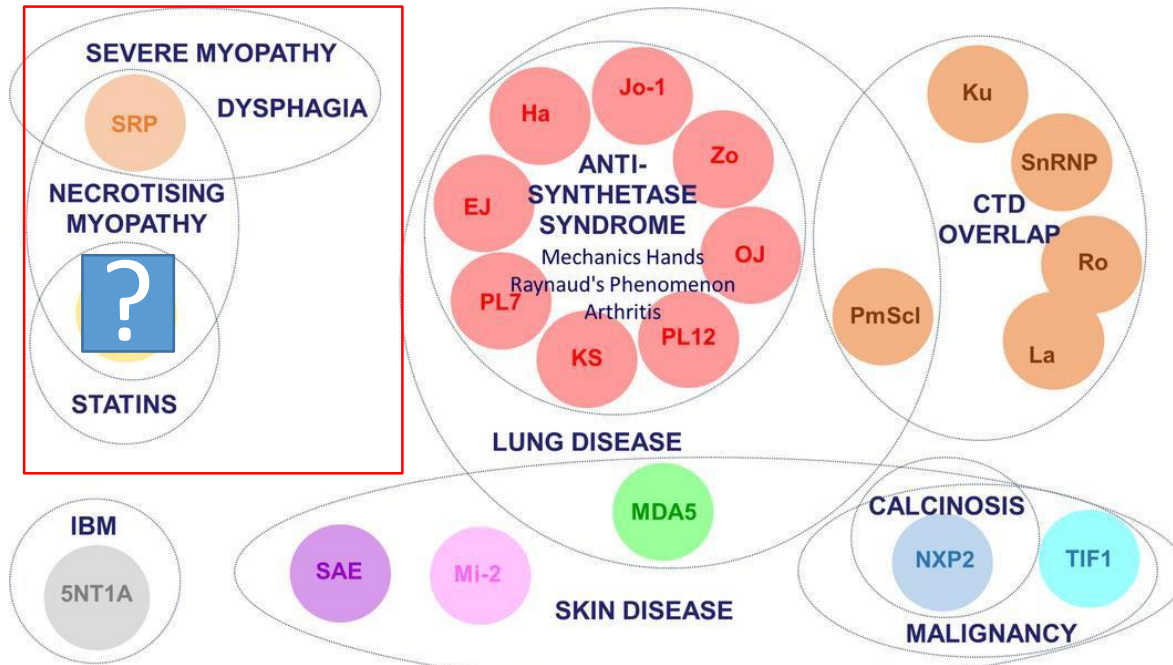
# Distinct profiles of autoantibodies in clinically distinct autoimmune syndromes

<b><u>SLE</u></b>	<u>Scleroderma</u>	<u>Myositis</u>	<u>Sjogren's</u>
Nucleosome	Topoisomerase I	Mi-2	Ro/La
U1-RNP	Fibrillarin	Anti-SRP	a,b-Fodrin
Sm	RNA polymerases	PM- Scl	NuMA
Ro/La	CENPs A, B, C	tRNA synthetases	DNA-PK
aPL	B23	U1-RNP	M3-R
SR proteins	NOR-90	Anti-MDA5	Golgins
			PARP

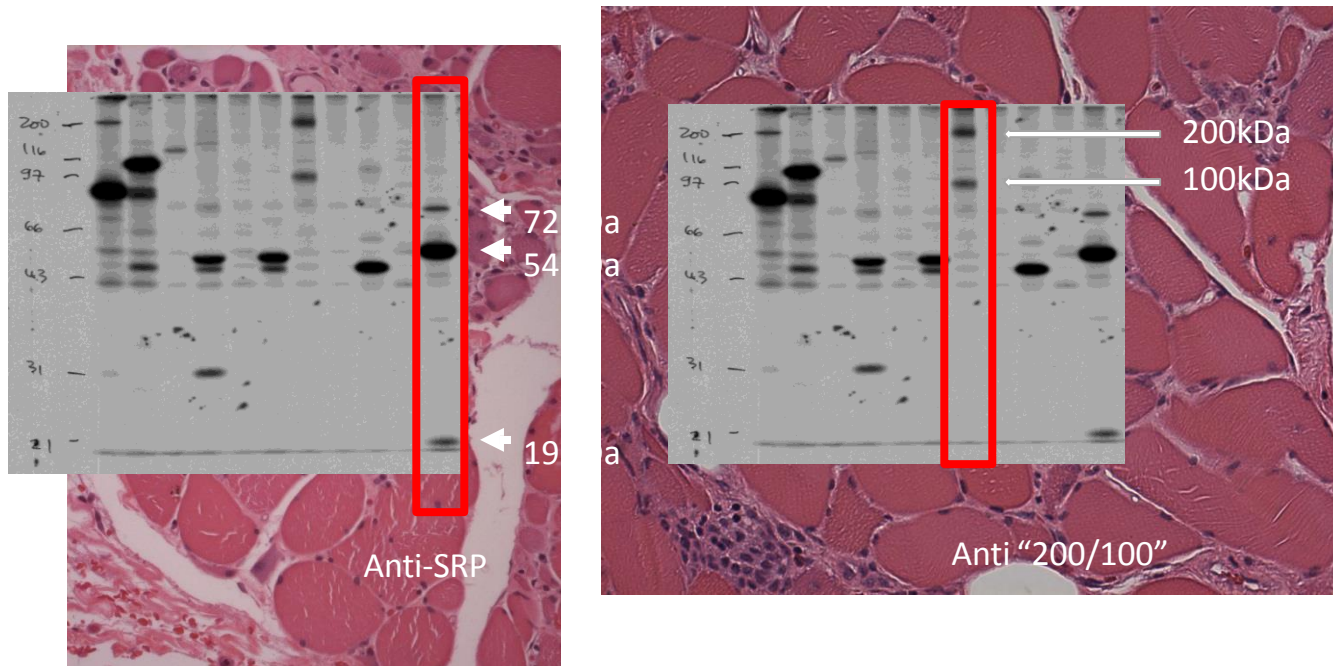
# A brief timeline of IIM and Autoantibody Discovery



# Myositis-specific autoantibodies: an important tool to support diagnosis of myositis



# Anti SRP vs. "Anti 200/100"



# Methods

- Study approved by the Johns Hopkins IRB
- 454 consecutive patients referred to Johns Hopkins Myositis Center for suspected/confirmed muscle disease
- 225 pts with both sera and muscle biopsy specimens available

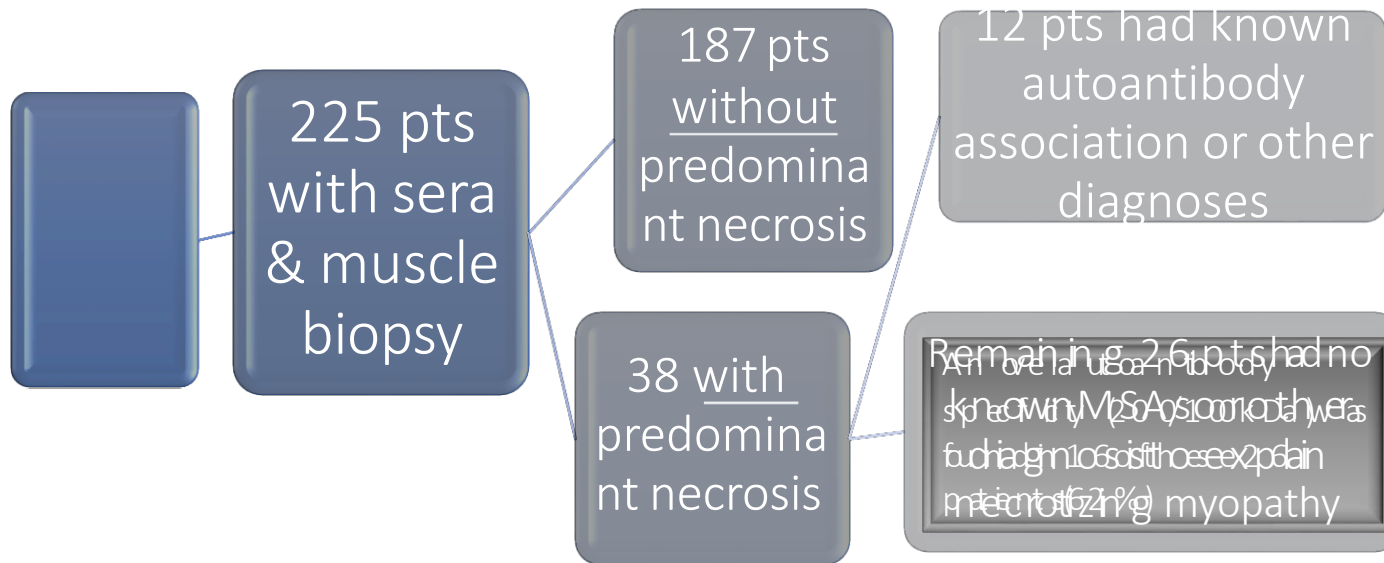
## Clinical information ascertained:

- History and Physical examination
- EMG/NCS
- MRI bilateral thighs
- PFTs
- Malignancy screening (CT scans of chest, abdomen and pelvis)
- Standard laboratory evaluation

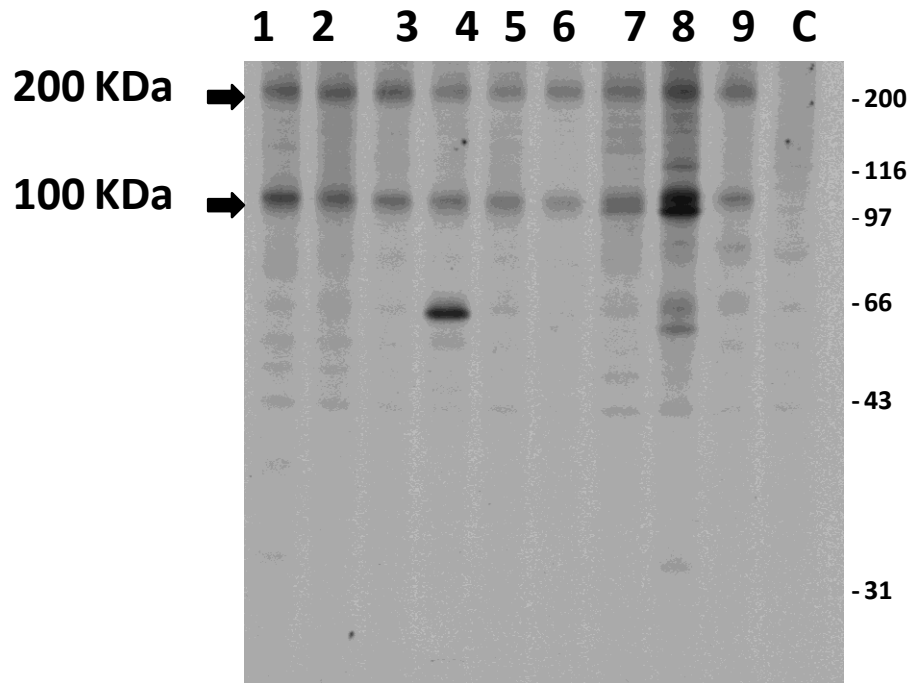
# Methods

- Antibody specificities assessed by immunoprecipitations from  $^{35}\text{S}$ -methionine labeled HeLa cell lysates.
- Muscle biopsies evaluated for :
  - Inflammation, Regeneration, Degeneration, Necrosis, Vacuolar change
- Biopsies stained for MAC, MHC I , Endothelial cells

# Results



# Sera from Patients with Necrotizing Myopathy Immunoprecipitate 200/100kDa Proteins



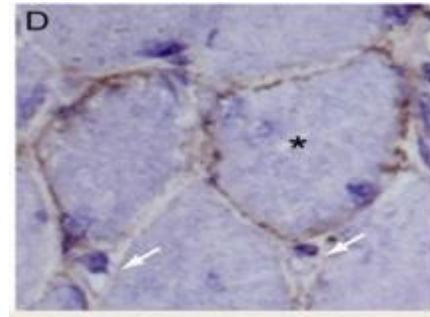
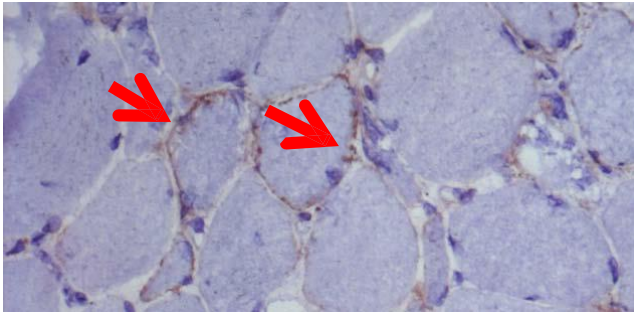
Nine of the sixteen patient sera recognizing the ~200/100kDa doublet are shown in lanes 1-9. Control sera did not immunoprecipitate this pair of proteins (lane C.)



## Muscle Biopsy Features of Patients With the Anti-200/100kDa Specificity

- Endomysial and/or perivascular collections of inflammatory cells in 5 (31%) of the 16 muscle biopsy specimens
  - MILD degree of inflammation c/w typical DM or PM muscle biopsies
- Mild or no denervation
- No biopsy positive for abnormal glycogen or amyloid

# MAC Deposition on Non-necrotic Myofibers



This muscle specimen from an anti 200/100 patient reveals MAC deposition on scattered non-necrotic fibers (red arrows). Note the absence of MAC staining on endomysial capillaries (white arrows.)

# Clinical Features

- Mean age of 54 years
- 10 females: 6 males (63% F)
- 50% Caucasian
- Proximal weakness in 100%
- High CK levels (mean 10,333 IU/L; range 3,052-24,714)
- MRI evidence of muscle edema (100%)
- Irritable myopathy on EMG (88%)
- Myalgias 12/16 (75%)
- Arthralgias 8/16 (50%)
- Dysphagia 10/16 (63%)
- Raynaud's phenomenon 2/16 (13%)

# Statin use in anti-200/100 patients

- Duration of use before onset of muscle symptoms: 31.3 +/- 27.4 months (range 0-84 months)
- Statin use (all ages): 10 /16 (63%)
- Statin use (age>50 ): 10/12 (83.3%)
- Statin used: variable
- Length of time between statin discontinuation and muscle biopsy: 5.2 +/- 4.6 months (range 1-14 months)

# Anti-200/100: Response to Immunosuppression

Complete or near-complete response	9/14 (64%)
Partial response	5/14 (36%)
Relapsed with taper	6/14 (43%)
Not relapsed to date	7/14 (50%)

Christopher-Stine et al., 2010

Increased statin use in anti-200/100 subjects vs. age-matched controls

Phenotype	Statin exposure rate	Mean age
HMGCR	10/12 (83.3%)	64.4 +/- 9.2
DM	4/16 (25%)*	61.0 +/- 8.3
PM	7/19 (36.8%)*	60.4 +/- 7.6
IBM	10/30 (33.3%)*	68.4 +/- 9.2

All subjects enrolled in 2003-2008 time period

\* Indicates proportions significantly different from the anti-200/100 group by use of chi<sup>2</sup>-test

## **A Novel Auto antibody Recognizing 200-kd and 100-kd Proteins Is Associated With an Immune-Mediated Necrotizing Myopathy**

**L**ia Christophe r-Stine, Livia A. Ca ciola-Ro en, Grace Hong, Tae Chun g,  
Andrea M. Cor e, and Andr ew L. Mammen

# Distinct profiles of autoantibodies in clinically distinct autoimmune syndromes

<b><u>SLE</u></b>	<u>Scleroderma</u>	<u>Myositis</u>	<u>Sjogren's</u>
Nucleosome	Topoisomerase I	Mi-2	Ro/La
U1-RNP	Fibrillarin	Anti-SRP	a,b-Fodrin
Sm	RNA polymerases	PM- Scl	NuMA
Ro/La	CENPs A, B, C	tRNA synthetases	DNA-PK
aPL	B23	U1-RNP	M3-R
SR proteins	NOR-90	Anti-MDA5	Golgins
		<b>"Anti-200/100"</b>	PARP



# Conclusions from our initial study

- Our findings show that patients with the anti-200/100 kDa specificity represent a distinct subgroup of necrotizing myopathy patients previously considered to be "autoantibody negative"
- Evidence to support an immune –mediated myopathy responsive to immunosuppression
- Statin exposure enhanced in this patient population
- 200/100 kDa may be subunits of a protein complex
- Next task at hand: identify the autoantigen(s) recognized by these autoantibodies

What about our three  
patients?

# Patient #1

- She is believed to have the phenotype consistent with statin-associated IMNM and begins treatment with prednisone and azathioprine. She responds partially, undergoes a second muscle biopsy four months after her initial visit to JHH that shows widespread necrotizing myopathy in the absence of primary inflammation and IVIG is then added.
- Within four months of starting IVIG, her strength is normal both proximally and distally and her CK normalizes from its peak at 8728 IU/L to 43 IU/L.
- Presence of “anti-200/100” autoantibodies is confirmed in our research lab- and eventually verified commercially.

# Patient # 2

- “Anti-200/100” autoantibodies are found.
- He was treated with azathioprine for 7 months in early 2012 for persistently elevated CPK's, but as his weakness was not progressing and CPK levels did not change, this was stopped in 8/12.
- He has not been on immunosuppression since. EMG did not show evidence of a myopathy.

Finger flexors 5/5  
Finger extensors 5/5

	Delt	Bicep	Tricep	WE	WF	HE	HF	KE	KF	AE	AF
R	5 (16.1)	5	5	5	5	5	4+ (30.8)	5	5	5	5
L	5 (16.3)	5	5	5	5	5	4 (24.5)	5	5	5	5

Patient can rise from chair with arms crossed.

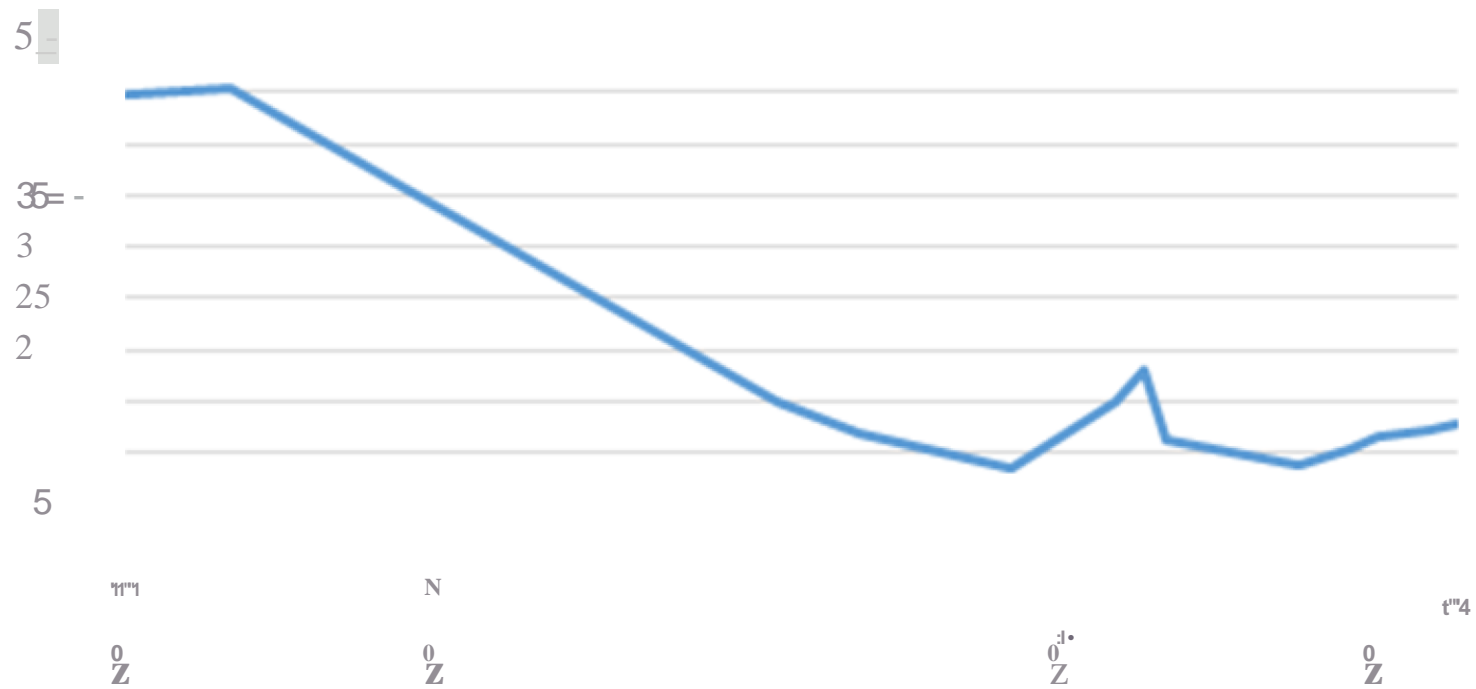
Patient cannot rise from 6 inch stool with arms crossed

Patient can walk on toes.

Patient can walk on heels.

Gait: His walking evaluation is within normal limits.

# CKo e t me



- His strength at this time is stable, and CK has been fluctuating in the range of about 1000-1200 IU/L. He has ongoing rather significant truncal weakness despite his good strength elsewhere. Given that his strength is stable, we favored not altering current therapy.
- In the setting of any worsening of his muscle strength, we would have a low threshold to start IVIG.

# Patient # 3

- IVIG was started by an outside provider--given only one time in addition to 80 mg of prednisone when she was admitted to rehabilitation facility for 2 months' time.
- She did well with a slow taper of prednisone over time. Referred to an outside rheumatologist who prescribes MTX (liver toxicity); Infliximab.
- CK rises to 8050 IU/L. Prednisone was started at 15 mg which increased to 60 mg x3 days, then back down to 40 mg and was held. MMF was added.
- She is referred to our Center for consultation and IVIG is added. Her CK falls to 2622 IU/L after one dose of IVIG and her strength returns to baseline. Within 3 months, her CK falls to 271 IU/L.
- "Anti 200/100" autoantibodies are noted.
- After 4 years, she is off all immunosuppressive agents including prednisone and no longer requires IVIG. She has full strength on exam, a CK of 236 IU/L, and she is tolerating ezetimibe.

## We were not the first to recognize a seemingly statin-associated autoimmune myopathy

8 cases : investigated muscle pathology of patients with persistent myopathy despite statin withdrawal.

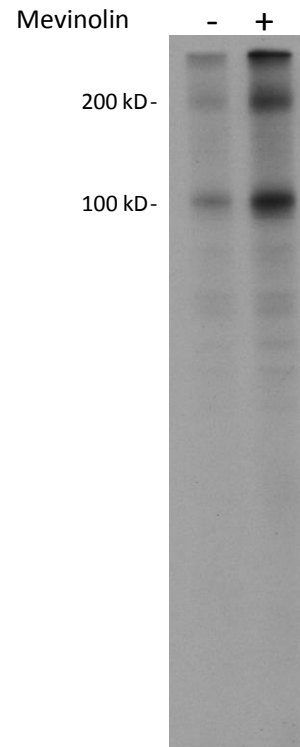
- All had myofiber necrosis
- only 3 had an inflammatory infiltrate.
- In all cases there was diffuse or multifocal up-regulation of MHC-I expression even in non-necrotic fibers.
- Progressive improvement occurred in 7 cases after commencement of prednisolone and methotrexate, and in one case spontaneously.



- 25 patients from two neuromuscular centers (2000 – 2008) and met the following criteria:
- (1) proximal muscle weakness occurring during or after treatment with statins
- (2) elevated CK
- (3) persistence of weakness and elevated CK despite discontinuation of the statin
- (4) improvement with immunosuppressive agents
- (5) muscle biopsy showing necrotizing myopathy without significant inflammation.

- It was reasoned that statin-associated autoimmune myopathy with anti-200/100 autoantibodies provides a model system for defining the mechanistic relationship between drug exposure and developing a specific autoimmune response.
- Identification of the autoantigen(s) targeted by the immune response is a critical first step.

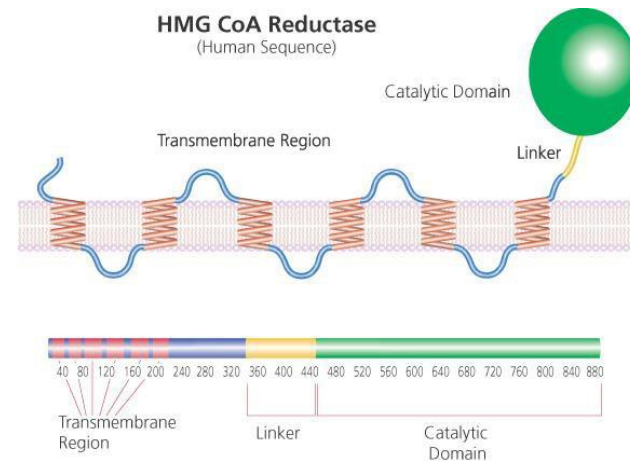
# An important clue: statin treatment up-regulates autoantigen expression



With and without 10 uM  
mevinolin for 24 hours  
prior to labeling

- It was demonstrated that statin exposure upregulates expression of ~100 and ~200 kDa autoantigens
- Given that statin exposure increases expression of HMGCR (97 kDa), it was investigated whether this enzyme may be the 100 kDa autoantigen.
- Identity of the 100 kD autoantigen was confirmed by precipitating in vitro-translated HMGCR protein.

- Serum from anti 200-100 positive patients specifically recognized the intracellular catalytic domain of HMGCR.
- Experimental evidence suggests that the ~200 kDa protein is either co-precipitated with HMGCR or is an HMCR dimer.
- All 16 of the anti-200/100 patient samples previously identified by IP were HMGCR positive in contrast to 0/33 DM patients and 0/31 IBM patients.



Slide courtesy of Andrew Mammen, MD, PhD

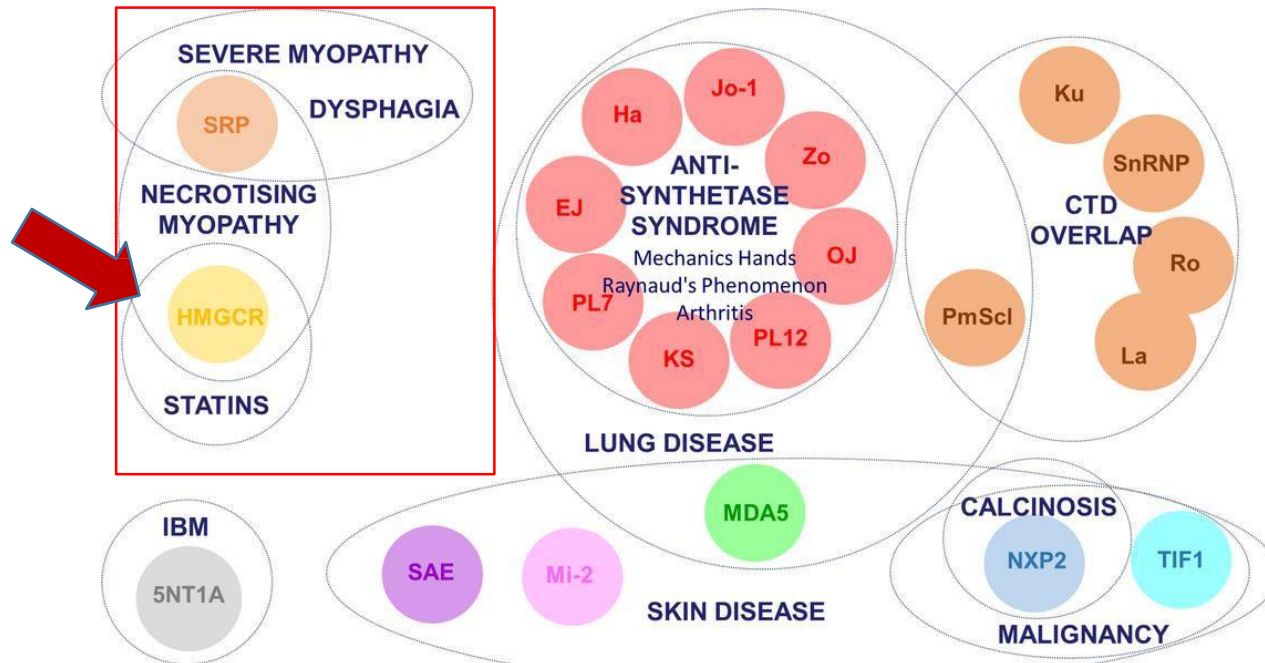
ARTHRITIS & RHEUMATISM  
Vol. 63, no. 3, March 2011, pp 713-721  
DOI10.1002/art.30156  
© 2011, American College of Rheumatology

---

## **Autoantibodies Against 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase in Patients With Statin-Associated Autoimmune Myopathy**

Andrew L. Mammen, Tae Chung, Lisa Christopher-Stine, Paul Rosen,  
Antony Rosen, Kimberly R. Doering, and Livia A. Casciola-Rosen

# Myositis-specific autoantibodies: an important tool to support diagnosis of myositis



# The composition of cellular infiltrates in anti-HMG-CoA reductase-associated myopathy

Initial description of muscle biopsies from anti-HMGCR positive subjects:

11% of statin exposed and ~39% of statin-naïve subjects had inflammatory cell infiltrates on routine histological staining, mostly perivascular

The cellular composition of these infiltrates had not been described previously and were therefore investigated.

As expected, CD68+ macrophages were the most prevalent inflammatory cells in biopsies from anti-HMGCR myopathy subjects; they were located in both endomysial and perivascular areas.

Most of the macrophages in both anti-HMGCR myopathy and DM were of the M2 subclass



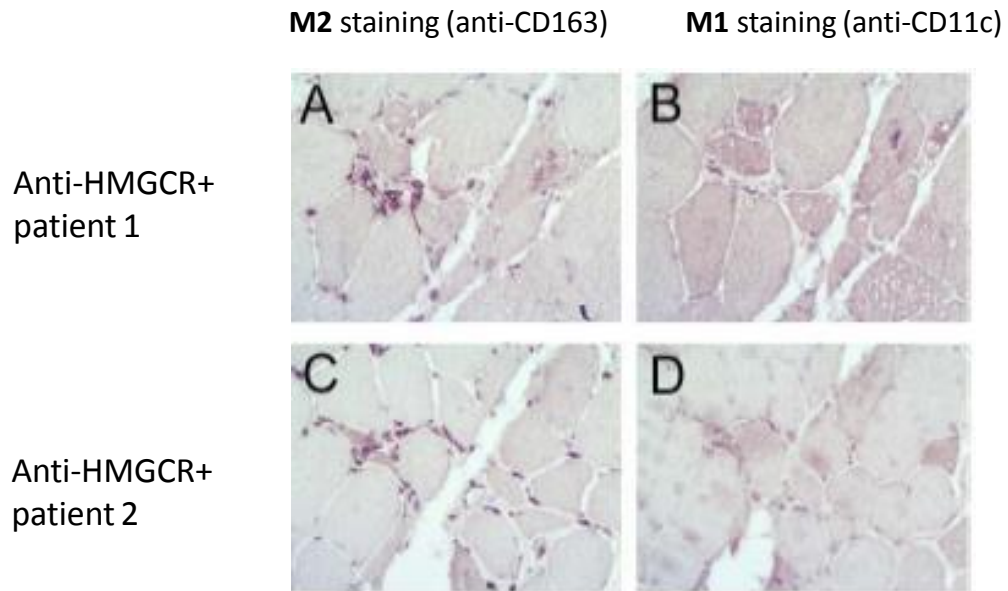
# The composition of cellular infiltrates in anti-HMG-CoA reductase-associated myopathy

Initial description of muscle biopsies from anti-HMGCR positive subjects:  
11% of statin exposed and ~39% of statin-naïve subjects had inflammatory cell infiltrates on routine histological staining, mostly perivascular

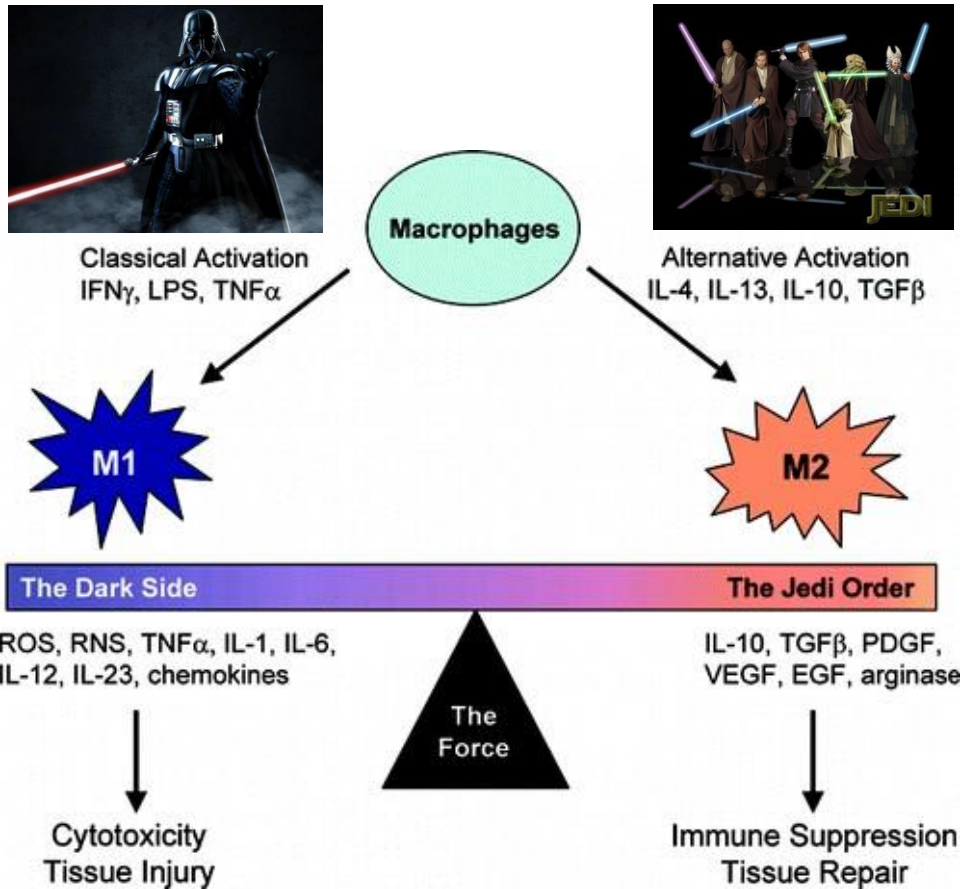
The cellular composition of these infiltrates had not been described previously and were therefore investigated.

As expected, CD68+ macrophages were the most prevalent inflammatory cells in biopsies from anti-HMGCR myopathy subjects; they were located in both endomysial and perivascular areas.

**Most of the macrophages in both anti-HMGCR myopathy and DM were of the M2 subclass**

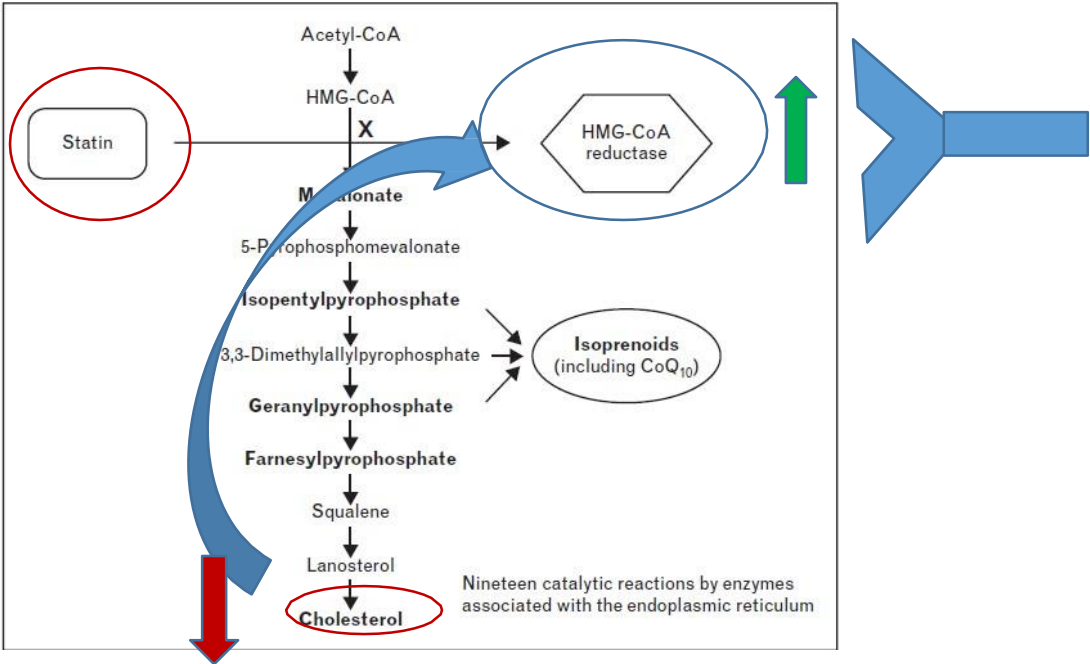


Representative serial sections from two typical anti-HMGCR myopathy patients (A,B and C,D) show significant staining for M2 macrophages with anti-CD163 (A,C) but no M1 macrophages staining positive for CD11c (B,D)



Statin Myopathy:  
What we think we  
now know

# Cholesterol Synthesis and Statins



# Why the myopathy persists even when the statin is withdrawn:

- Prior work from Casciola- Rosen and colleagues has shown that regenerating muscle cells express high levels of autoantigens (i.e., HMGCR) which may sustain the immune response even after statins are discontinued.
- Regenerating cells are abundant in IMNM and appear to be the repair mechanism for muscle injury in this instance, thus providing an endless supply of autoantigen.

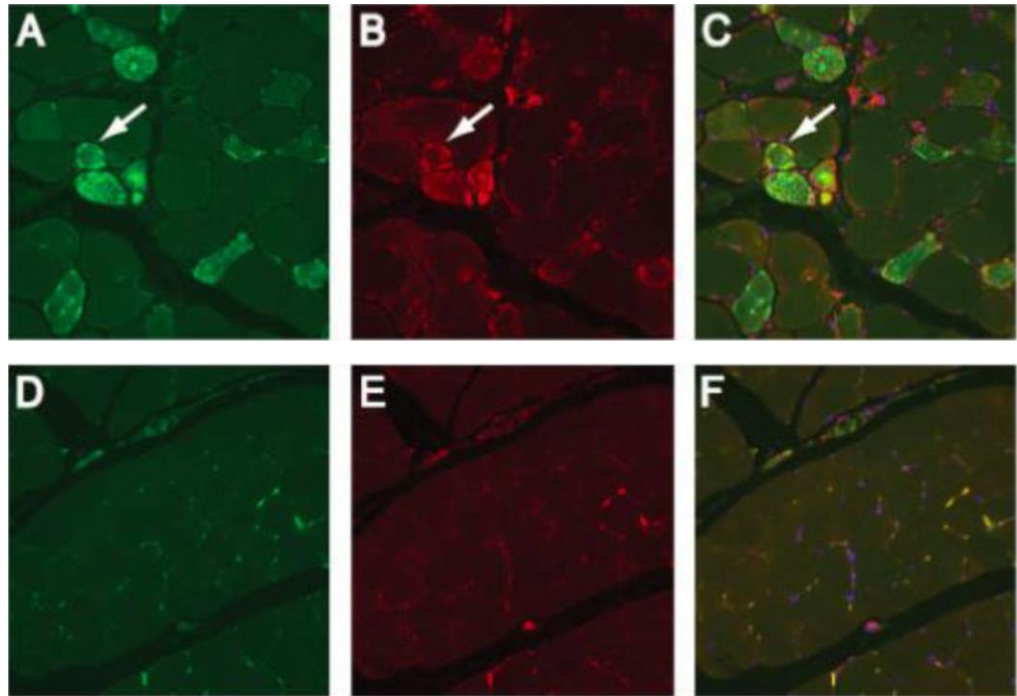


Figure 4. Up-regulation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) expression in regenerating myofibers expressing neural cell adhesion molecule (NCAM). Muscle biopsy samples from anti-HMGCR-positive patients (A-C) and control subjects (D-F) were costained with anti-NCAM antibodies (green) (A and D), anti-HMGCR antibodies (red) (B and E), and DAPI (blue) to stain nuclei. Overlay images (C and F) demonstrate that HMGCR and NCAM are frequently coexpressed at high levels in the same myofibers in anti-HMGCR-positive muscle biopsy tissues (arrows) but not control muscle biopsy tissues. To ensure comparability, images A-C and D-F were obtained using identical exposure settings for each channel. Results are representative of the staining seen in 6 anti-HMGCR-positive and 3 normal muscle biopsy samples. Original magnification X 20.

What is the prevalence of anti-HMGCR antibodies in statin-exposed and statin-unexposed patients?



# Atherosclerosis Risk in Communities (ARIC) Cohort

- Screened a sub-sample of ARIC cohort
  - 881 statin-naïve subjects
  - 763 current statin use
  - 322 prior statin exposure
- None of these were anti-HMGCR positive

Are anti-HMGCR antibodies found in patients with self-limited statin-intolerance?

## Anti-HMGCR screening in patients with statin intolerance

- 98 patients with familial hypercholesterolemia (FH) due to LDLR gene mutations
- 
- 51 with intolerance to statins requiring cessation of therapy
  - 33.3% with weakness
  - 60.9% with myalgias
  - 20% with elevated CK or myoglobinuria
- 47 on maximum dose statin therapy
- None of these 98 were anti-HMGCR positive

# Anti-HMGCR appears to be highly specific:

- Found only in patients with autoimmune myopathy
- Not found in those with self-limited statin-intolerance
- In patients with statin-associated muscle symptoms, a negative anti-HMGCR ELISA predicts self-limited disease

Are there immunogenetic risk factors for developing anti-HMGCR antibodies?

# HLA Typing of anti-HMGCR subjects vs. controls

- HLA-DR11 in Caucasians
  - 14/20 (70%) anti-HMGCR subjects
  - 89/487 (18%) controls
  - $P=1.2 \times 10^{-6}$
- HLA-DR11 in African Americans
  - 7/8 (88%) anti-HMGCR subjects
  - 35/167 (21%) controls
  - $p=0.0002$

# DRB1\*11:01 is strongly associated with anti-HMGCR

- Fine mapping: 95% DRB1\*11:01
- Odds ratios for DRB1\*11:01 in subjects vs. controls
  - Caucasians: 24.5 ( $p = 3.2 \times 10^{-10}$ )
  - African Americans: 56.5 ( $p = 3.1 \times 10^{-6}$ )
- One of the strongest links between an HLA allele and an autoimmune disease

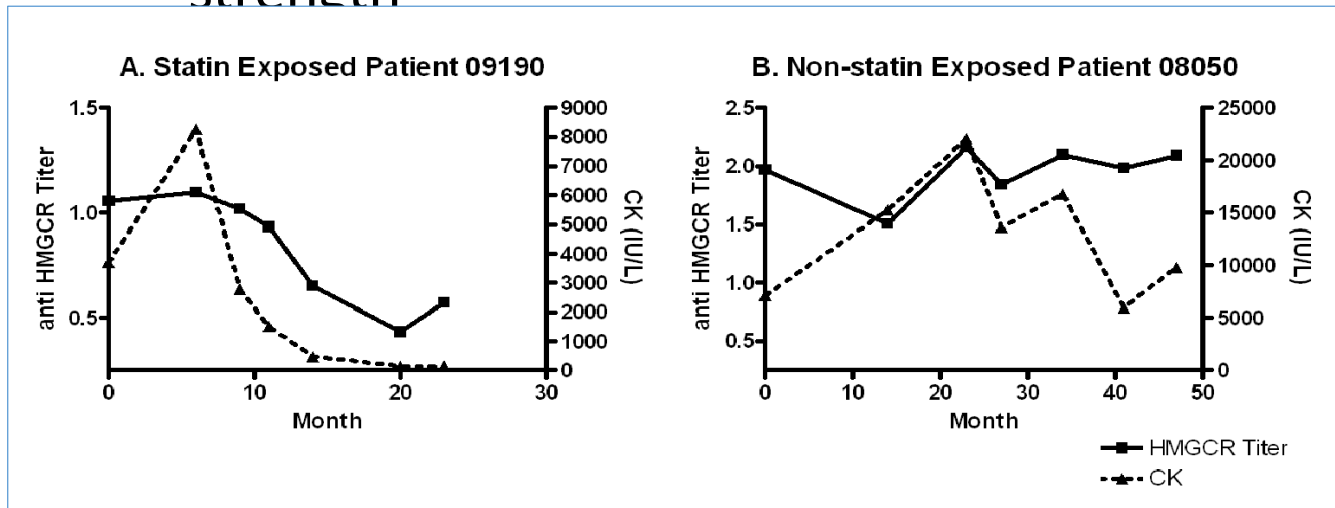
# Do Anti-HMGCR Titers Correlate with CK and Strength?

- Identified 55 anti-HMGCR subjects with at least one visit
  - 40 statin-exposed and 15 statin unexposed
  - Measured antibody levels, CK, and strength

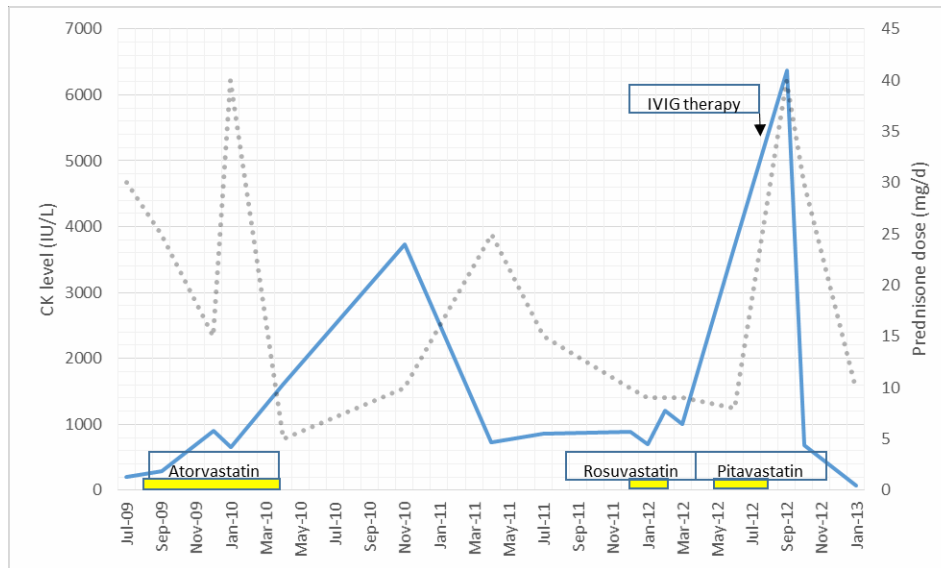


# Following Titers, CK, and Strength

- Followed 17 subjects longitudinally for 5+ visits over 26 months
  - 12 statin-exposed and 5 statin-unexposed
  - Measured antibody levels, CK, and strength



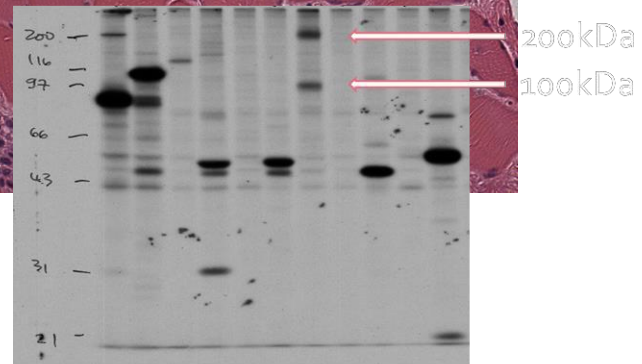
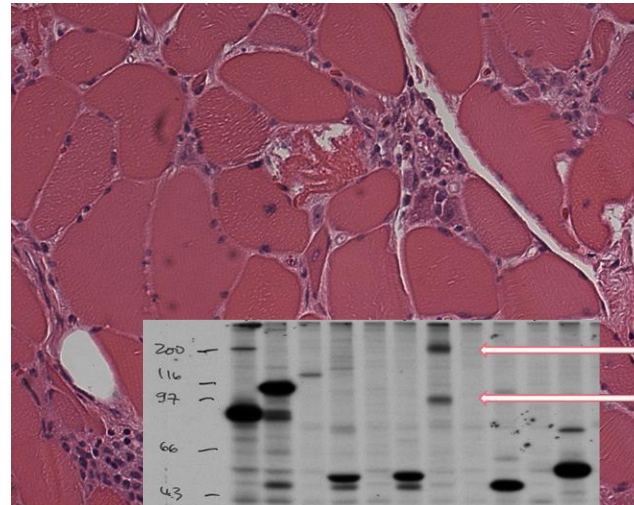
# Statin re-challenge leads to symptomatic myopathy with increased muscle enzymes



CK level (blue line) and prednisone dose (dotted line) in a 61-year-old Caucasian woman with statin-induced anti-HMGCR-associated myopathy

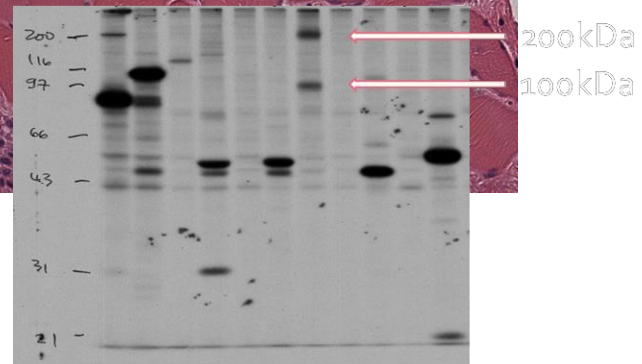
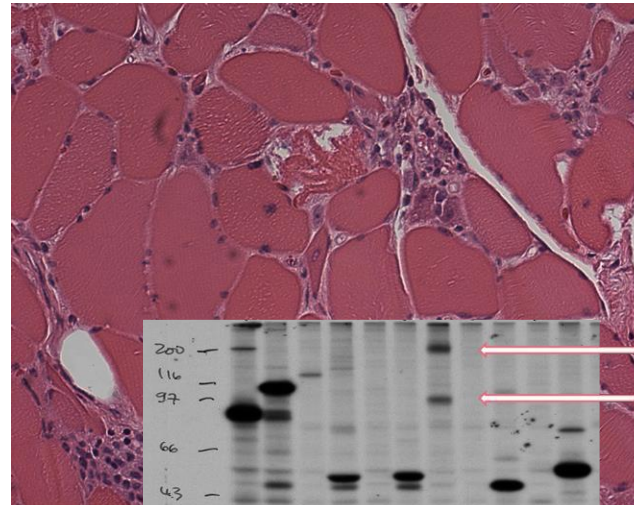
# Conclusions

- HMGCR is the major target of autoantibodies in statin associated IMNM.
- Regenerating muscle cells express high levels of HMGCR which may sustain the immune response even after statins are discontinued.
- Anti-HMGCR antibodies are found in those with IMNM but not in those with self-limited statin intolerance.
- Statins may trigger this autoimmune process by increasing expression of HMGCR.
- HLA-DRB1\*11:01 is a risk factor for developing anti-HMGCR antibodies.
- Statin-exposed subjects may\* be more responsive to treatment.
- May be seen in statin naïve patients as well (1/3 to 1/4 in US are statin naïve)



# Conclusions

- HMGCR is the major target of autoantibodies in statin associated IMNM.
- Regenerating muscle cells express high levels of HMGCR which may sustain the immune response even after statins are discontinued.
- Anti-HMGCR antibodies are found in those with IMNM but not in those with self-limited statin intolerance.
- Statins may trigger this autoimmune process by increasing expression of HMGCR.
- HLA-DRB1\*11:01 is a risk factor for developing anti-HMGCR antibodies.
- Statin-exposed subjects may\* be more responsive to treatment.
- May be seen in statin naïve patients as well (1/3 to 1/4 in US are statin naïve)



# Statin Naïve Anti-HMGCR Myopathy

- Increasing evidence that patients may develop this disease in the absence of statin exposure,
  - younger patients
  - Higher CKs
  - More racially diverse
  - Do not respond well to immunosuppression
- There are also reports of children with anti-HMGCR Ab+ myopathy
  - sometimes mistaken for congenital muscular dystrophy
  - highlights importance of checking autoantibody status/obtaining a muscle biopsy even in cases where statin use is not suspected.
- Many cases of this potentially treatable myopathy are missed
  - poor disease awareness
  - anchoring on the incorrect assumption that this disease can only occur in patients who are taking statins.

- The prevalence of statin exposure in anti-HMGCR-associated myopathy varies geographically
  - Johns Hopkins = 30/45 (67%)
  - European cohort = 20/45 (44%)
  - Australian cohort = 16/17 (94%)
  - Chinese cohort = 3/20 (15%)

# Comorbidities and detailed statin information

- 95 statin exposed myositis patients from our longitudinal cohort were studied.
- 58 HMGCR +
- 37 anti-HMGCR –
- Average duration of follow-up 29 months (0-100 months)

Basharat, et al. JACC

- In comparison to Statin exposed Anti-HMGCR negative myositis patients, Statin-exposed Anti-HMGCR positive myositis patients had:
  - Higher mean CKs (6800 vs 1900)
  - Greater mean hip flexor weakness at presentation (14.5 vs 18)
  - No difference in arm abduction
  - Dysphagia (60% vs 40%)
  - 38 months - mean duration of statin therapy before muscle symptom onset

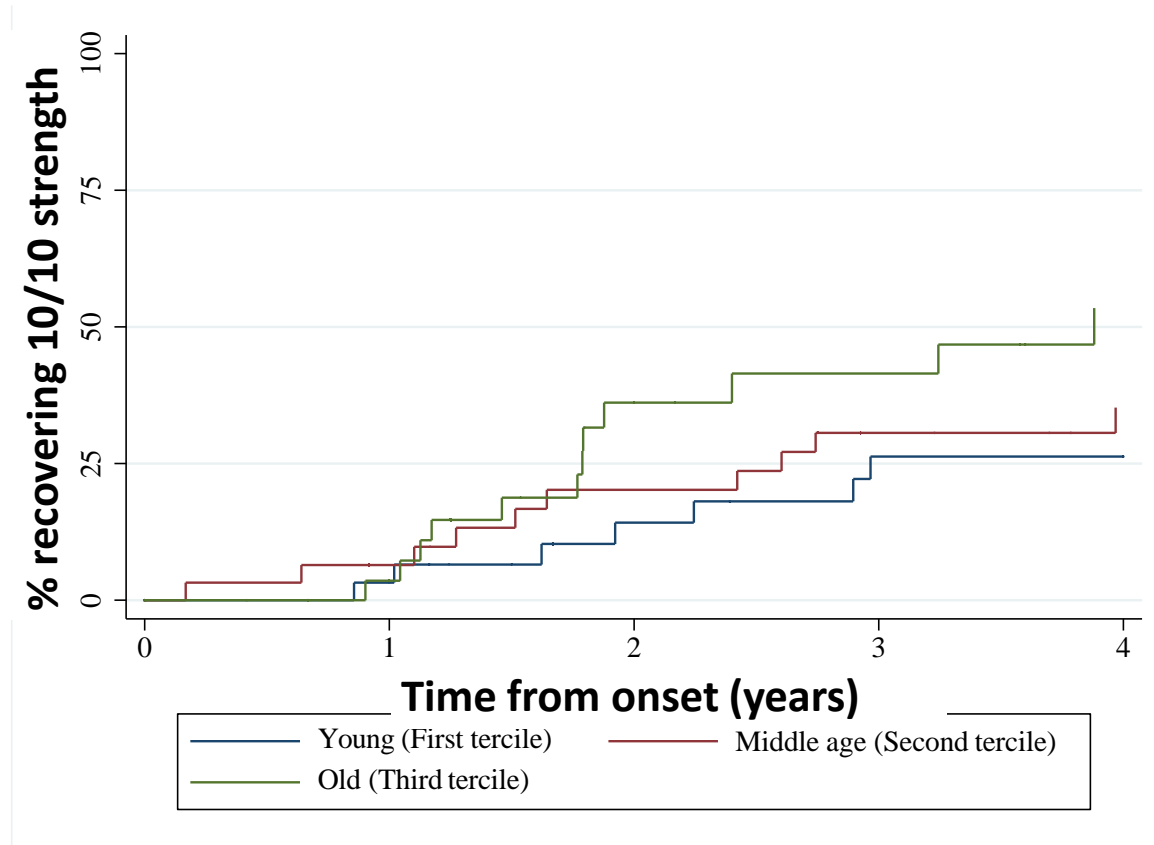
Multivariate logistic regression of factors correlated with statin-induced anti-HMGCR-associated myopathy (n=69)		
Risk factor	Odds ratio (95%CI)	P value
Type 2 diabetes mellitus	14.3 (2.2-90.6)	0.005
Statins		
Atorvastatin vs. Rosuvastatin	15.6 (2.2-110.5)	0.006
Simvastatin vs. Rosuvastatin	2.0 (0.2-21.8)	0.58
Atorvastatin vs. simvastatin	7.9 (1.3-49.5)	0.027
Age	1.04 (0.98-1.11)	0.32
Female vs male	1.4 (0.4-4-8)	0.63



# What about treatment choices?

- No systematic reviews of treatment choices nor response rate
- Anecdotally, most statin + Anti-HMGCR + patients required IVIG in order to see a robust treatment response
- Rituximab may play a role in statin naïve Anti-HMGCR + patient therapy
- IVIG Monotherapy effective in those who are statin-exposed and refused corticosteroids

Older anti-HMGCR patients have better outcomes than younger patients



# A quick note about children and anti-HMGCR associated Myopathy

- Five of 440 patients (1.1%) screened were anti-HMGCR-positive
  - *Three patients had rashes characteristic of juvenile dermatomyositis and 2 patients had immune-mediated necrotizing myopathies.*
  - *The median highest creatine kinase (CK) level of anti-HMGCR-positive subjects was 17,000 IU/liter.*
  - *All patients had severe proximal muscle weakness, distal weakness, muscle atrophy, joint contractures, and arthralgias, which were all more prevalent in HMGCR-positive subjects compared to MSA-negative patients or those with other MSAs.*
- Autoantibodies to (HMGCR) are present in a rare but distinct subgroup of patients with juvenile myositis, and, as in adult myositis, they are associated with severe weakness and high CK levels.
- Children with anti-HMGCR autoantibodies have an associated allele, DRB1\*07:01, which differs from the HLA-DRB1\*11:01 allele associated with adult patients with anti-HMGCR autoantibodies.
- Unlike adults, children do not have a documented prior exposure to statin medications.
- This was mistaken for muscular dystrophy in some children and may be treatable.

# Implications for Clinical Practice

- In addition to a self-limited toxic myopathy, statins are associated with an autoimmune myopathy which is progressive despite statin cessation.
- Most cases of statin-associated IMNM appear to respond to immunosuppression but combination therapy is often necessary.
- HMGCR+ myopathy can begin at any time during statin use (months to years after the onset of statin use)

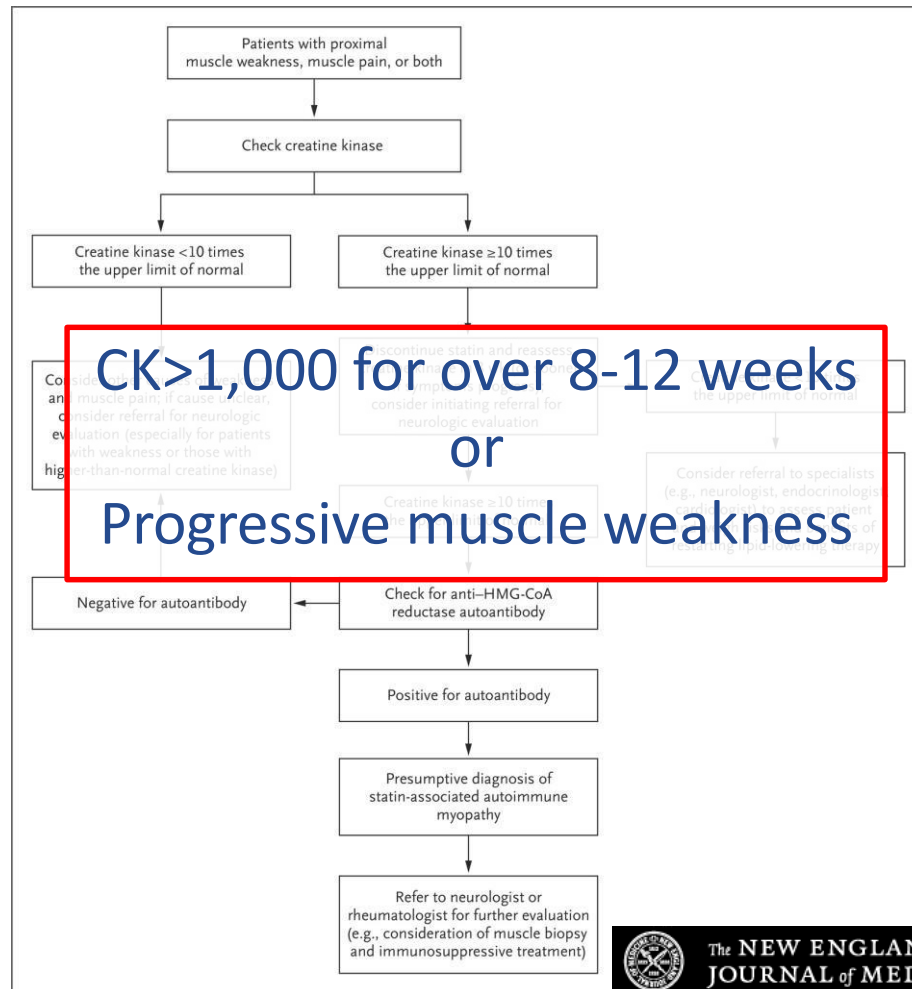
Anti-HMGCR+



STATIN ISLAND

	<b>Self-Limited Statin Myopathy</b>	<b>Statin-Induced IMNM</b>
<b>Occurrence</b>	Frequent	Rare
<b>Proximal Muscle Weakness</b>	Uncommon	Common
<b>Maximum CK value (IUL)</b>	Normal or slight elevation; >100,000 in rhabdomyolysis	1000-50,000
<b>Genetics</b>	SNP in SLC01B1	HLA-DRB1*11:01
<b>Statin Time Course</b>	Resolution after discontinuation	Variable presentation (may be after many years of use); persists after statin discontinuation
<b>IHNC/R autoantibody</b>	Absent	Present
<b>IEMG</b>	May be normal	Irritable myopathy
<b>MRI</b>	May be normal	Muscle edema
<b>Muscle biopsy</b>	Non-specific	Necrosis and mild to no inflammation
<b>Treatment</b>	Withdraw statin or reduce dose	Withdraw statin and start immunosuppressive therapy

# Algorithm for the Evaluation of Potential Cases of Statin-Associated Autoimmune Myopathy.

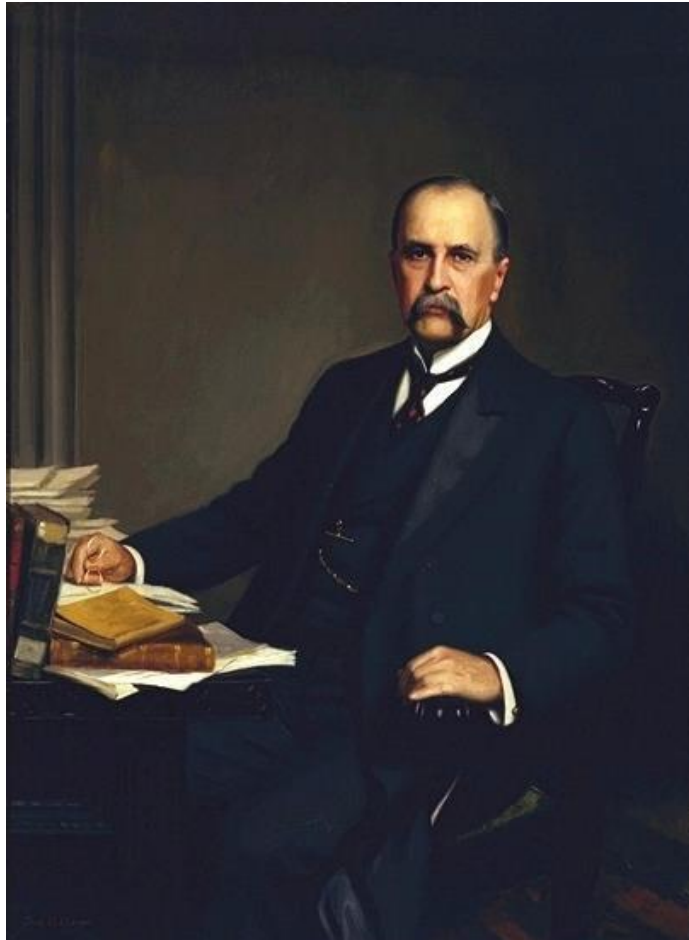


# Why is this entity a “rule breaker”?

- Disease onset is, on average, 3 years after drug exposure
- Disease does not improve or worsens despite statin withdrawal
- Disease occurs with and without drug exposure
- Older patients seem to do better than younger patients with treatment



“Listen to your patient; he is telling you the diagnosis.”

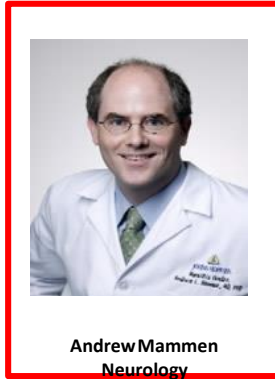


# The Johns Hopkins Myositis Center Team

[www.hopkinsmyositis.org](http://www.hopkinsmyositis.org)



Lisa Christopher-Stine  
Rheumatology



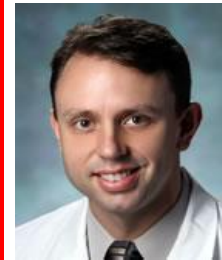
Andrew Mammen  
Neurology



Sonye Danoff  
Pulmonary



Livia Casciola-Rosen  
Rheumatology/Bench research



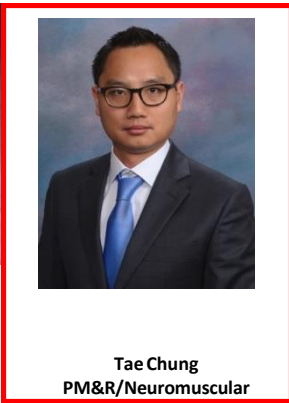
Tom Lloyd  
Neurology



Jemima Albayda  
Rheumatology



Cheilonda Johnson  
Pulmonary



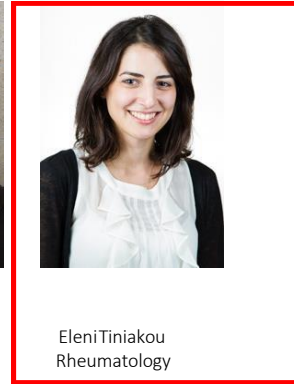
Tae Chung  
PM&R/Neuromuscular



Julie Paik  
Rheumatology



Doris Leung  
Neurology



Eleni Tiniakou  
Rheumatology



Christopher Mecoli  
Rheumatology



# Acknowledgments

- o Andrew Mammen
- o Livia Casciola-Rosen
- o Tae Chung



*Lahouti Pari*

## *Basharat*

- o Paul Rosen
- o Kimberly Doehring
- o Rosen lab members
  
- o Myma Albayda
  
- o Allan Gelber
  
- o Paul Plotz
- o Antony Rosen
- o Richard O'Brien
  
- o Andrea Corse

Supported by a Grant from



## All of our myositis patients

Also supported by:

The Ira Fine Discovery Fund  
The Stabler Foundation  
The Suiling and Huayi Zhang  
Discovery Fund