Autoantibodies and prognosis

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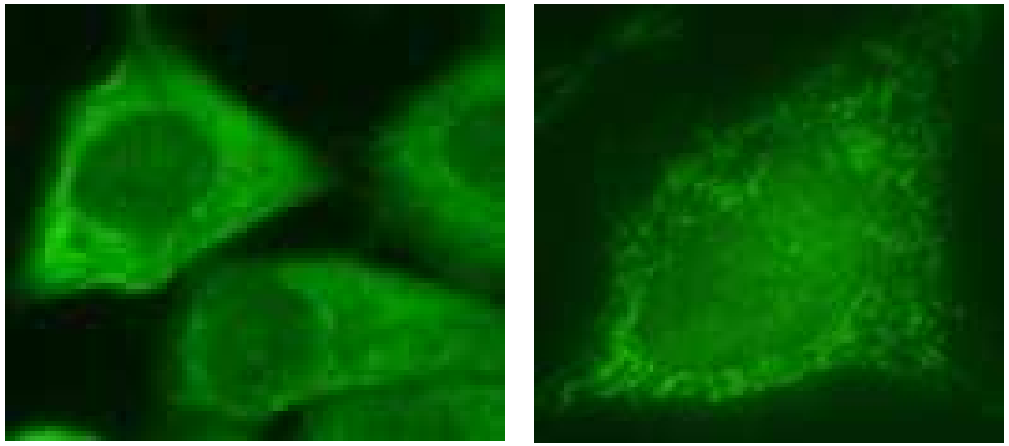
Heterogeneity of IIMs

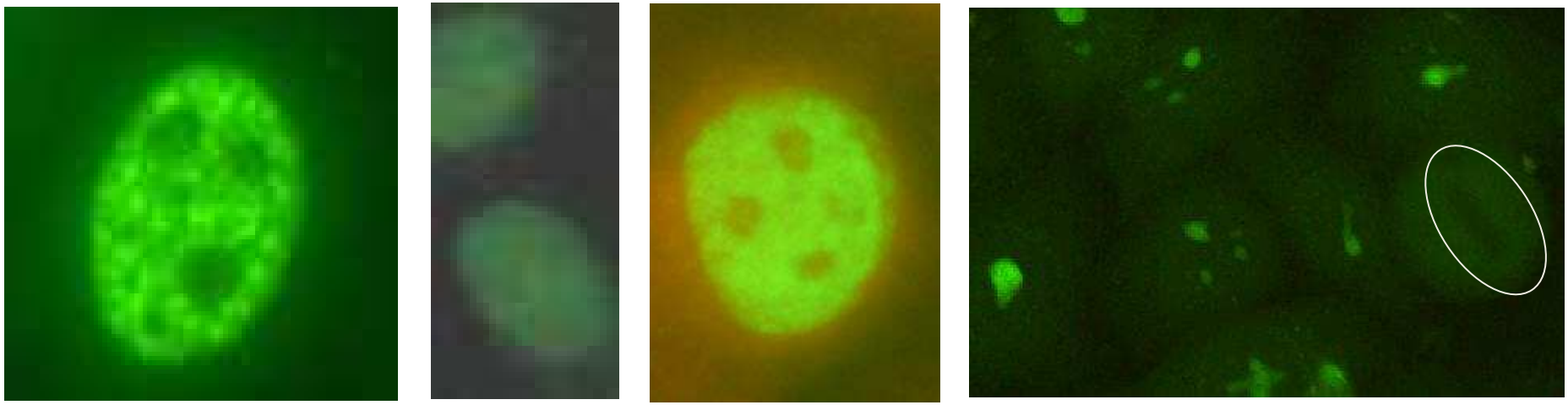
Diagnosis	Autoantibody	Organ involvement
Polymyositis	Negative	Lung
Dermatomyositis	Jo-1	Heart
IBM	Other ARS	Oesophagus
Necrotising myopathy	SRP	Calcinosis
Paraneoplastic	Mi-2	Joints
Amyopathic DM	PM-Scl	Other
Myositis in overlap	U1-RNP	
	p155/140	
	CADM-140	

Autoantibodies in myositis

Variable frequencies

30-90%





Autoantibodies in myositis

- Diagnostic tool
- Define clinically similar situations
- Correlation with disease activity
- Mediate disease pathogenesis?

Case 1

Diagnosis:

Immune mediated necrotizing myopathy

with anti-SRP positivity.

Treated with Rituximab

11/2009 muscle strength markedly improved

walks with a cane

normal muscle enzymes

Case 2

Diagnosis:

Cancer associated dermatomyositis

with p155/140 positivity.

Conclusions

In daily clinical practice, myositis specific autoantibodies may help to:

Establish diagnosis and estimate prognosis

Justification for aggressive therapy in Case 1

Early cancer detection in Case 2

Autoantibodies in IIMs

- Myositis specific autoantibodies (MSA)
- Myositis associated autoantibodies (MAA)
- New autoantibodies

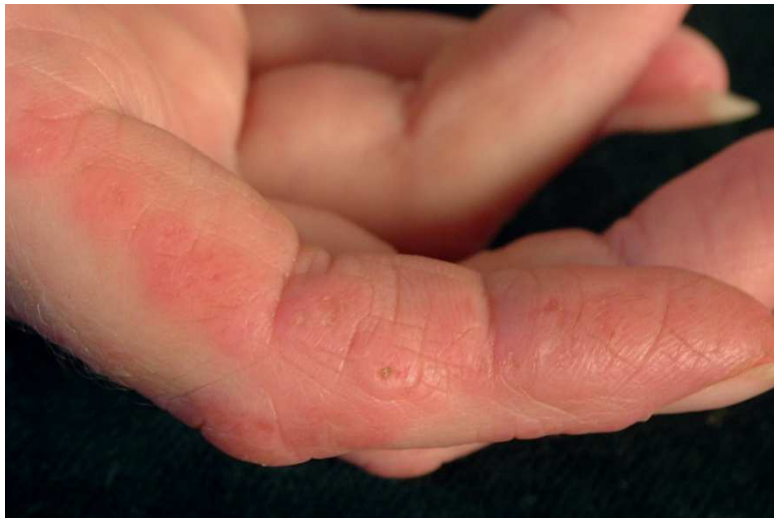
Myositis specific antibodies (MSA)

Anti-ARS

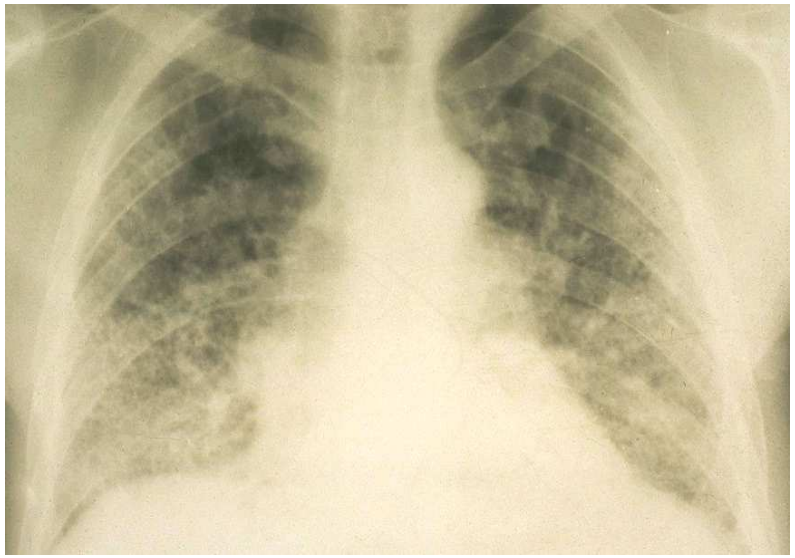
– Anti-Jo-1	Histidyl-tRNA synthetase	15-30%
– Anti-PL-7	Threonyl-tRNA synthetase	< 5%
– Anti-PL-12	Alanyl-tRNA synthetase	< 5%
– Anti-EJ	Glycyl-tRNA synthetase	< 5%
– Anti-OJ	Isoleucyl-tRNA synthetase	< 5%
– Anti-KS (AsnRS)	Asparaginyl-tRNA synthetase	Rare
– Anti-Zo	Phenylalanyl-tRNA synthetase	Rare
– Anti-YRS (Ha)	Tyrosyl-tRNA synthetase	Rare

Antisynthetase syndrome

- Myositis
- Interstitial lung disease (89%)
- Arthritis (94%)
- Raynaud‘s phenomenon (67%)
- Fevers (87%)
- Mechanic‘s hands (71%)

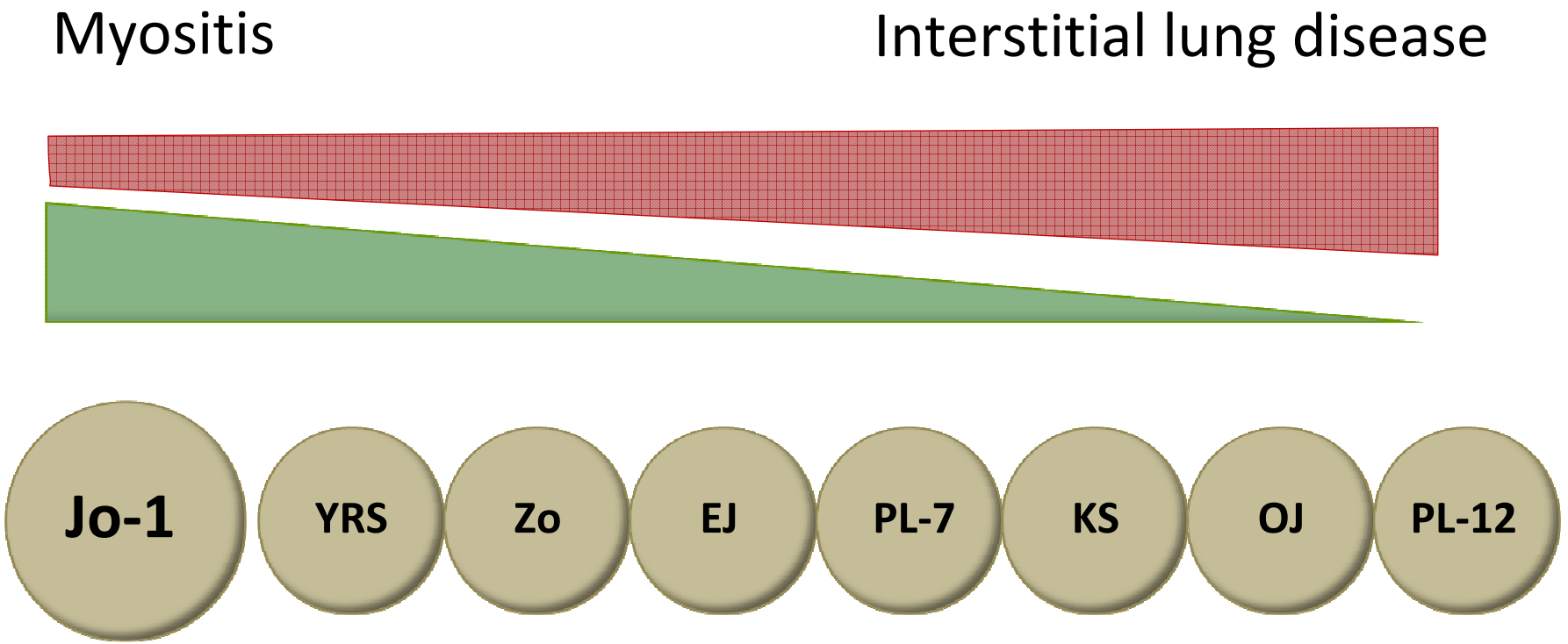


- Anti-Jo-1 – similar pathology
  - Perimysial fragmentation
  - Macrophage predominance
  - Perifascicular changes (atrophy, regeneration, some necrosis)
  - Normal capillary density



Marguerie, etal. Q J Med 1990, Love LA et al. Medicine 1991;70:360-74, Mozaffar T, Pestronk A. J Neurol Psychiatry 2000;68:472-8.

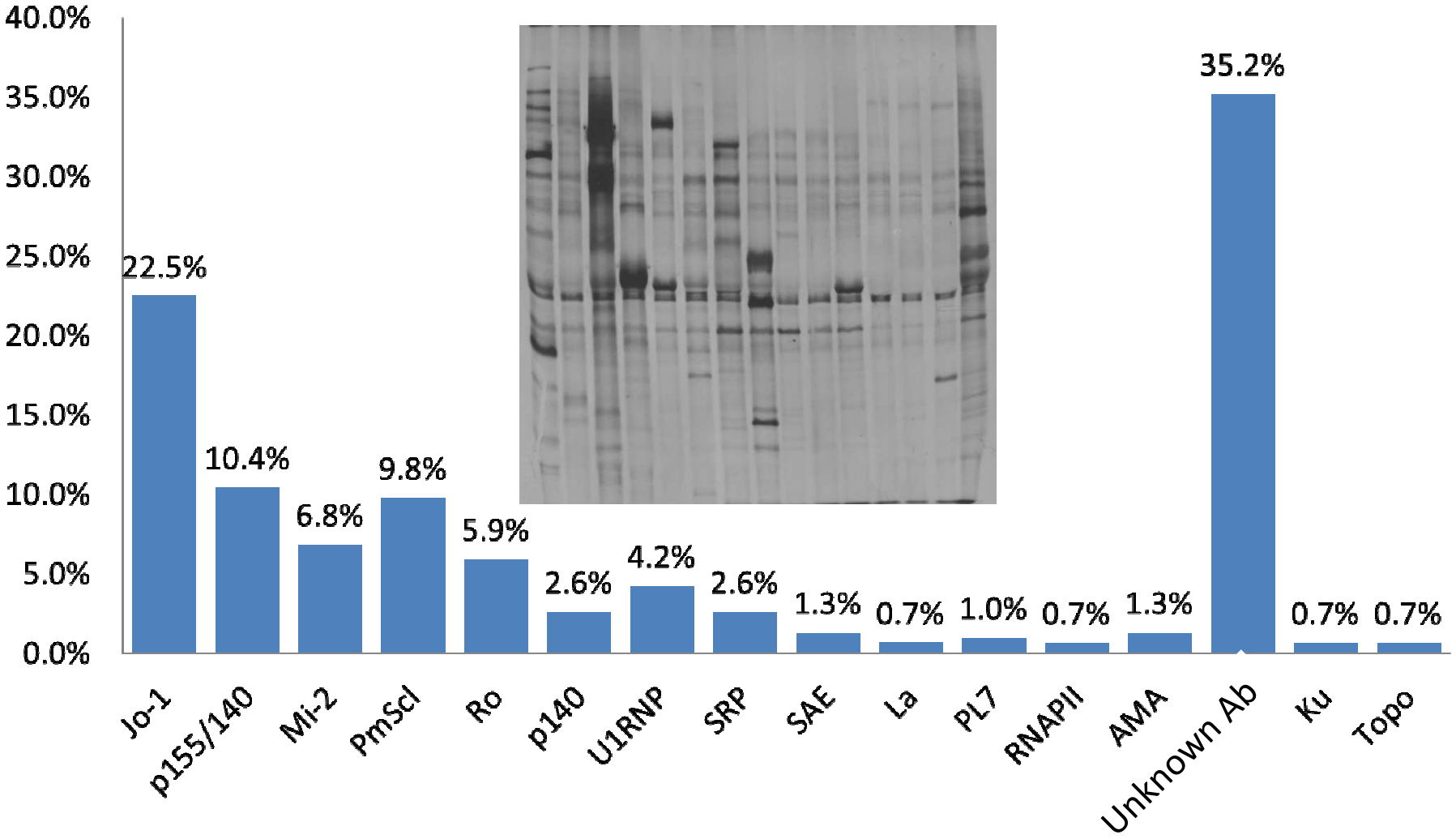
Antisynthetase syndrome and ARS antibodies



Myositis specific antibodies (MSA)

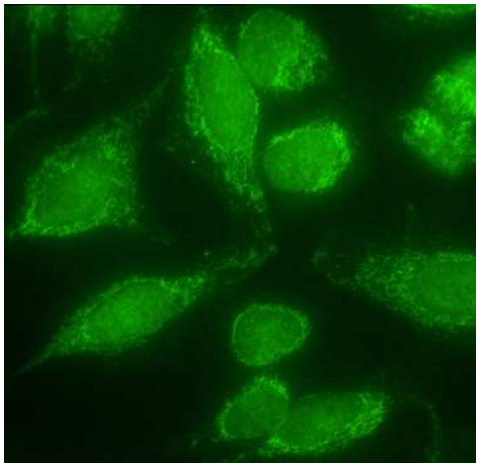
Anti-SRP	Signal recognition particle	4-6%
Anti-Mi-2	Nuclear helicase	4-18%
Anti-CADM-140	MDA5	19% of DM
Anti-p155/140	TIF-1	13-30%
Anti-NXP-2 (p140)	Nuclear matrix protein	<5%
Anti-SAE	SUMO-1 act. enz.	4% (8% DM)
Anti-200/100	HMGCR	6%
Anti-Mup44 (43kDa)	cN-IA	52-63% IBM

Immunoprecipitation in 308 patients with IIMs from a single centre

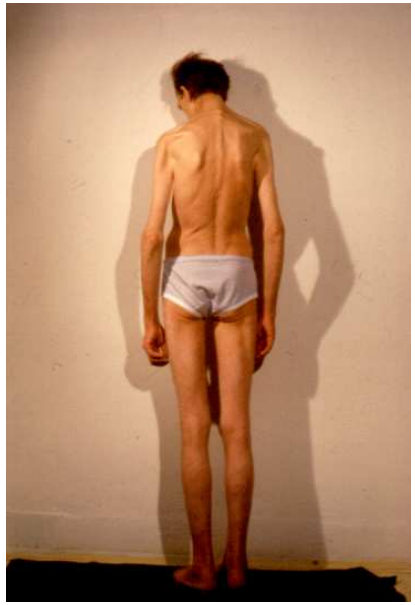


Lenka Pleštilová, in collaboration with Zoe Betteridge and Neil Mc Hugh, Bath, UK

Anti-SRP antibodies



- Older studies
  - severe disease
  - onset in the fall (anti-7SL RNA)
  - myalgia
  - bad response to treatment
  - short survival



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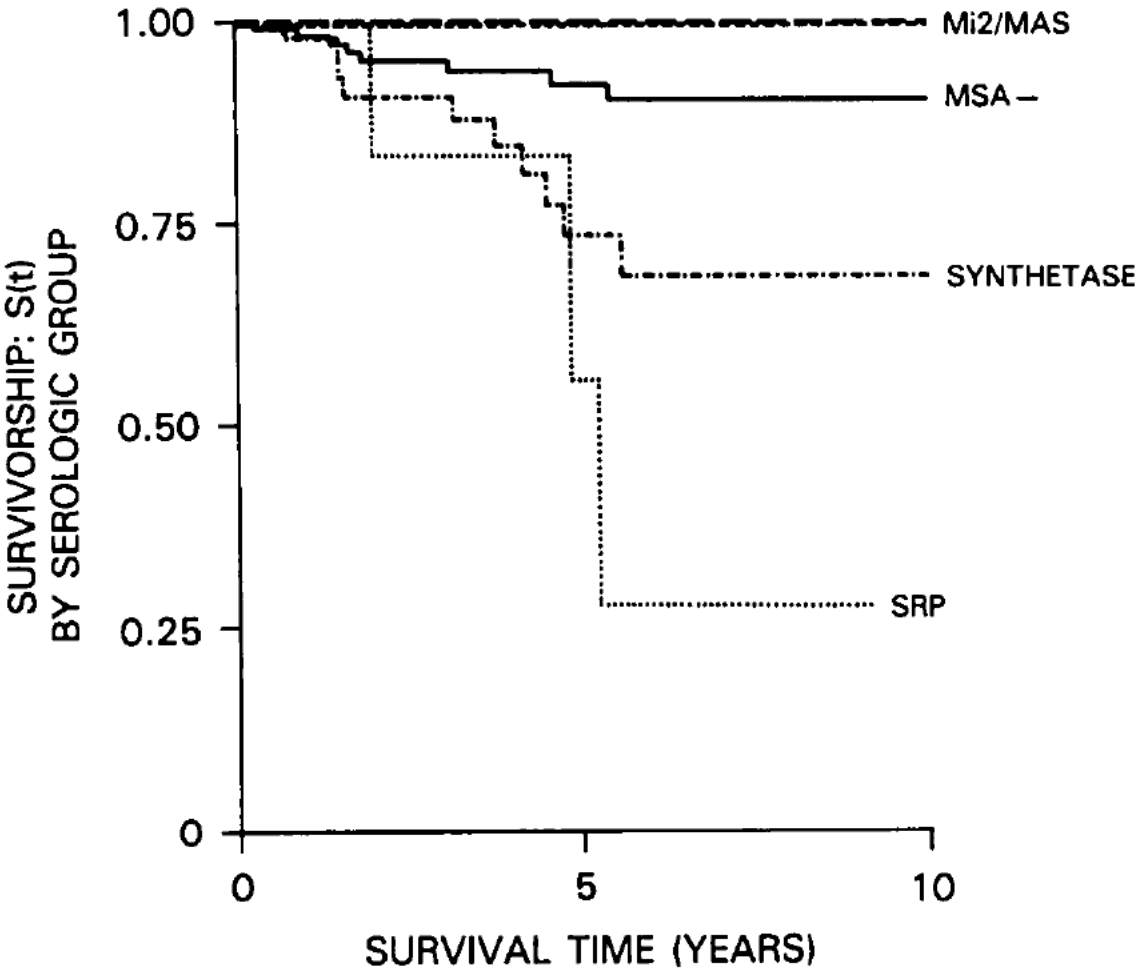
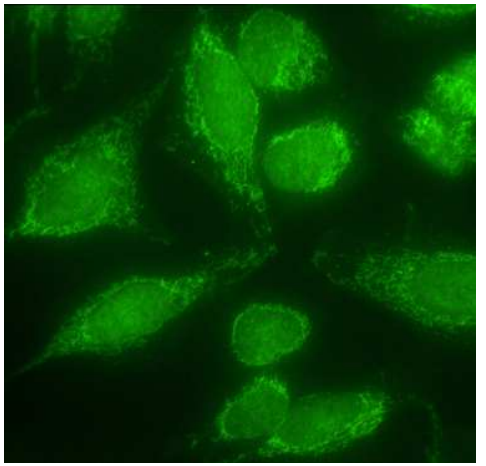
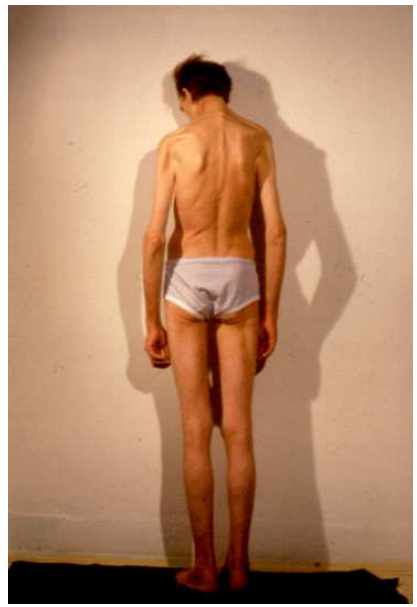
A New Approach to the Classification of Idiopathic Inflammatory Myopathy: Myositis-Specific Autoantibodies Define Useful Homogeneous Patient Groups

LORI A. LOVE, M.D., PH.D., RICHARD L. LEFF, M.D., DAVID D. FRASER, M.D., IRA N. TARGOFF, M.D., MARINOS DALAKAS, M.D., PAUL H. PLOTZ, M.D., AND FREDERICK W. MILLER, M.D., PH.D.







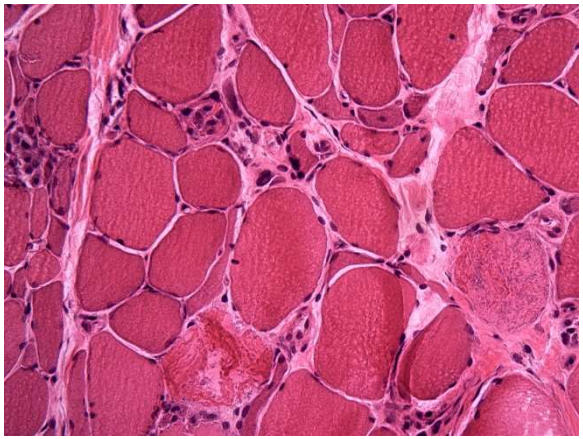
EXTENDED REPORT

Anti-signal recognition particle autoantibodies: marker of a necrotising myopathy

G J D Hengstman, H J ter Laak, W T M Vree Egberts, I E Lundberg, H M Moutsopoulos, J Vencovsky, A Doria, M Mosca, W J van Venrooij, B G M van Engelen

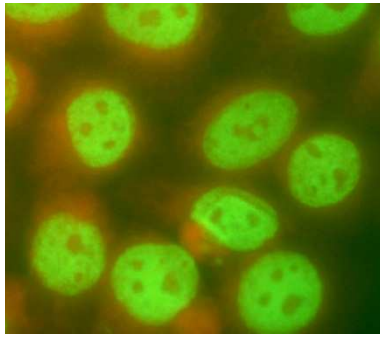
Ann Rheum Dis 2006;**65**:1635–1638. doi: 10.1136/ard.2006.052191

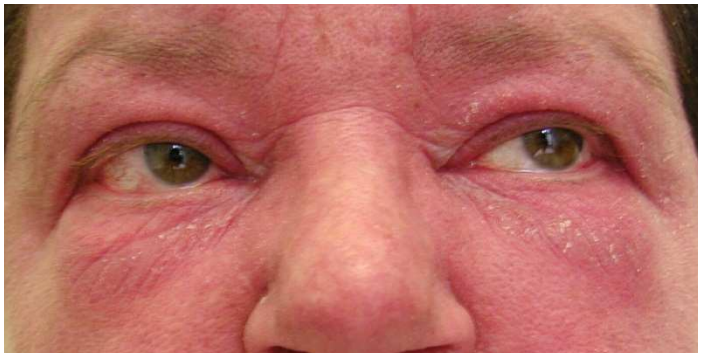
- 23 European anti-SRP patients
  - disease onset in the fall and winter, 3 DM
  - severe weakness, marked disability, dysphagia
  - highly elevated CK
  - ILD in 21%
  - no association with cardiac involvement
  - necrotizing myopathy with capillary abnormalities
  - reasonably favorable prognosis
  - (response to rituximab?)

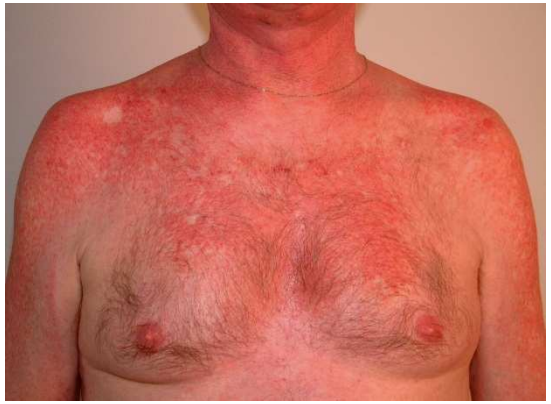


Josef Zámečník, 2nd Medical Faculty, Prague

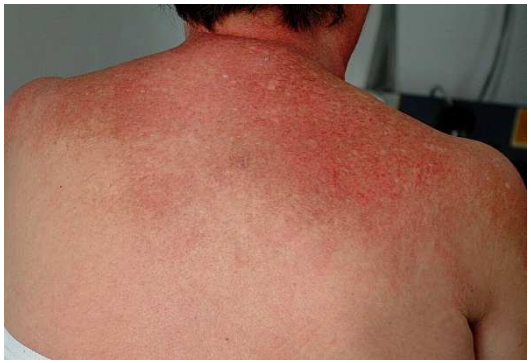
Anti-Mi-2 antibodies







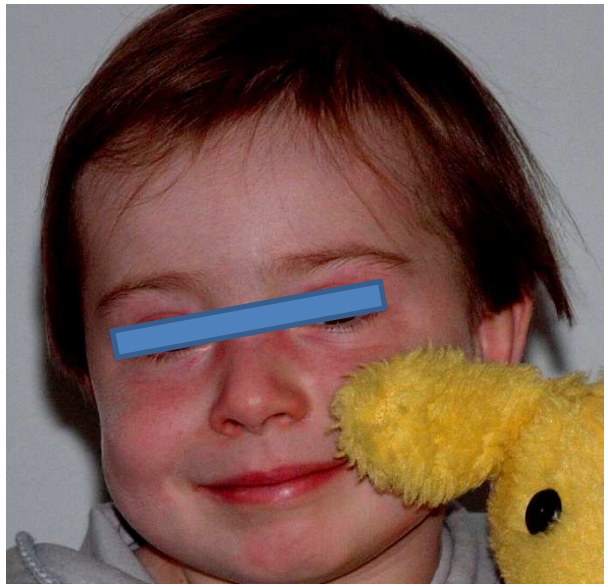
- Skin manifestations
- relatively mild disease
- treatment response - fair
- latitudinal gradient (UV intensity)
- tendency for antibodies to NT-fragment of the Mi-2β antigen to have a higher risk for malignancy

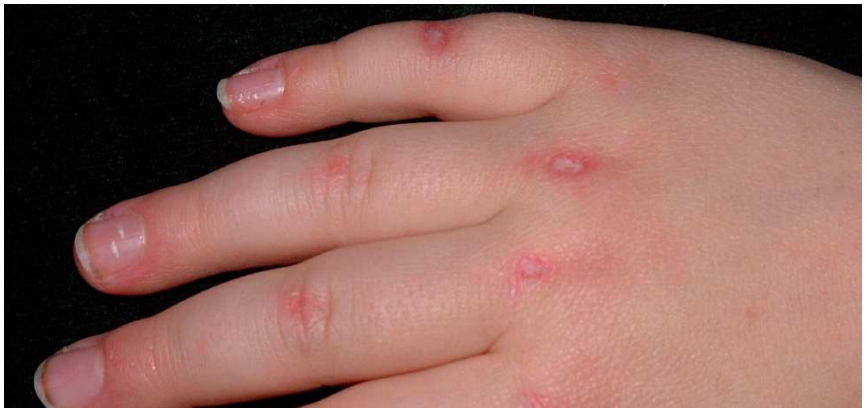


Hengstman GJD et al. Ann Rheum Dis 2006;65:242-5. Love LA et al. Arthritis Rheum 2009;60:2499-504.

Anti-p155/140 antibody

- 155 kD, 140 kD (K562). Nuclear speckled.
- 13, 21, 30% of myositis patients
  - Heliotrope rash, Gottron's papules, ulceration (in JDM), flagellate erythema
  - In 23, 29% JDM
  - In 75%, (71% vs. 11%), (50% vs. 4%) of cancer associated DM
- No ILD
- DQA1*0301 association
- Transcriptional intermediary factor 1γ





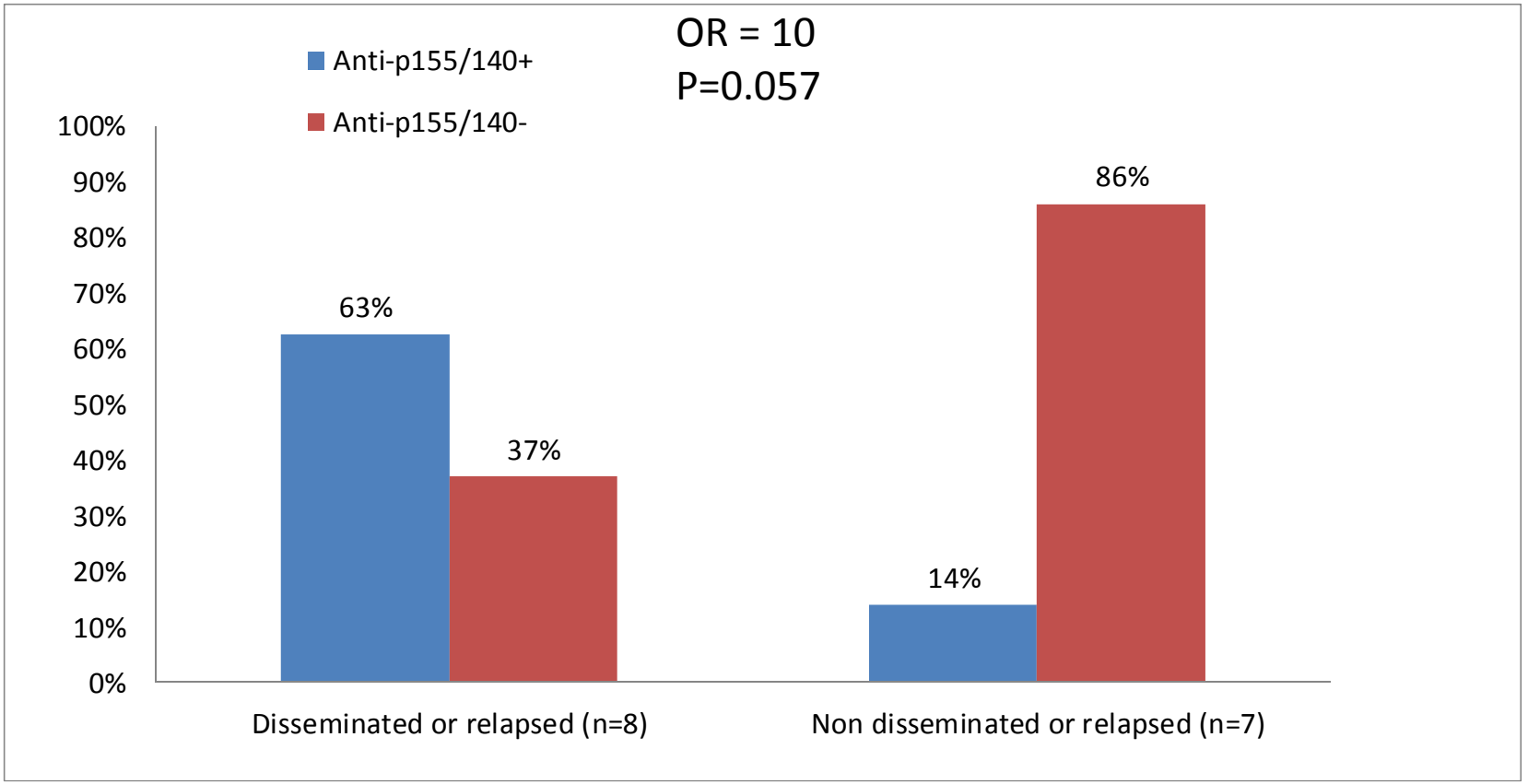
Targoff IN et al . Arthritis Rheum 2006;54:3682-9. Kaji K et al. Rheumatology 2007;46:25-8. Gunawardena H et al. Rheumatology (Oxford). 2008 ;47:324-8. Chinoy H et al. Ann Rheum Dis 2007;66:1345-9.

Anti-p155/140 antibodies in IIM patients

Author	All IIM	JDM	DM	PM	CAM	Anti-p155/140+ no CAM
Targoff	21%	29%	21%	0	75%	n=2
Kaji			13%		71%	
Gunawardena		23%	30%	0	100%	
Chinoy			18.4%		50%	n=11
Trallero-Araguás	19%		23%	5%	62.5%	n=6
Vencovský (152 pts)	10.5%		19%	1.6%	41%	n=9 (6.6%)

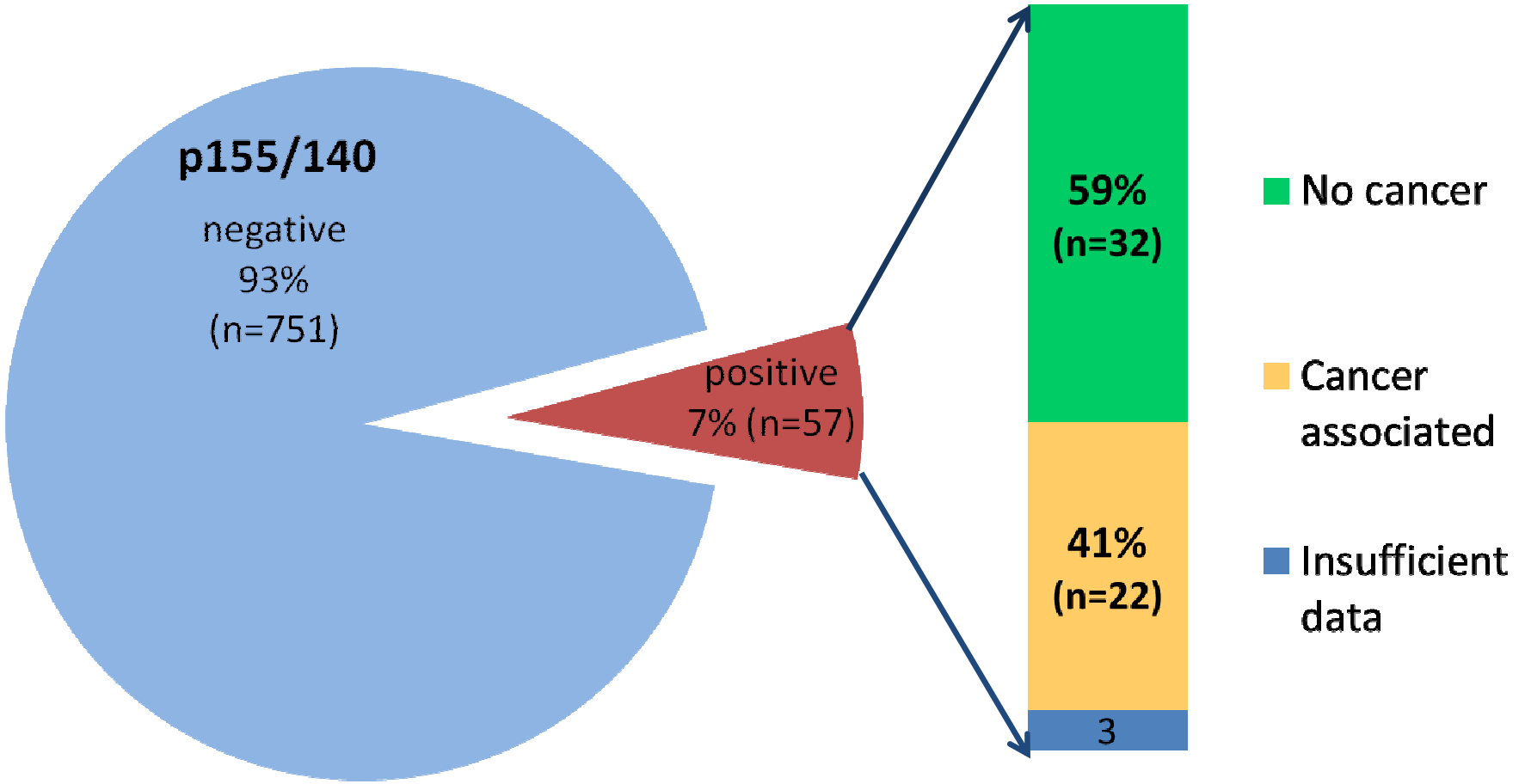
Targoff IN et al . Arthritis Rheum 2006;54:3682-9. Kaji K et al. Rheumatology 2007;46:25-8. Gunawardena H et al. Rheumatology (Oxford). 2008 ;47:324-8. Chinoy H et al. Ann Rheum Dis 2007;66:1345-9. Trallero-Araguás E. et al. Medicine (Baltimore). 2010 ;89(1):47-52. Vencovsky J. et al. ACR Meeting 2009.

Presence of anti-p155/140 in patients with disseminated and/or relapsed tumor (DR) or single episode and non-disseminated (NDNR) malignancy



Vencovsky J et al. ACR 2010.

Anti-TIF-1γ in European patients with IIMs.



Mann H et al. ACR 2011.

Anti-SAE autoantibody

4% myositis (8% of DM)

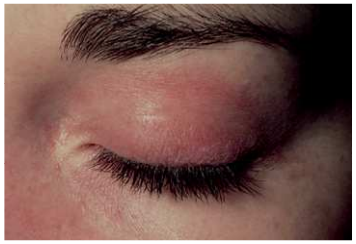
Severe classical skin

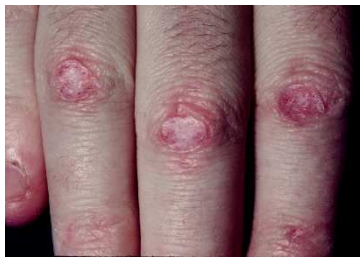
Mild myositis

Dermatomyositis

Periunugual changes

HLA-DRB1*04-DQA1*03-DQB1*03

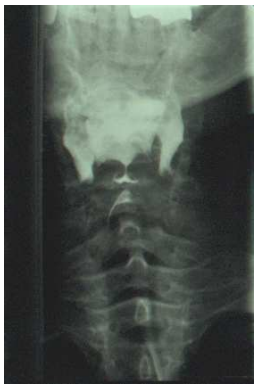


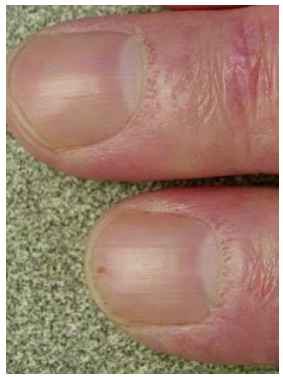


Systemic features – dysphagia

No or mild ILD

Rare cancer

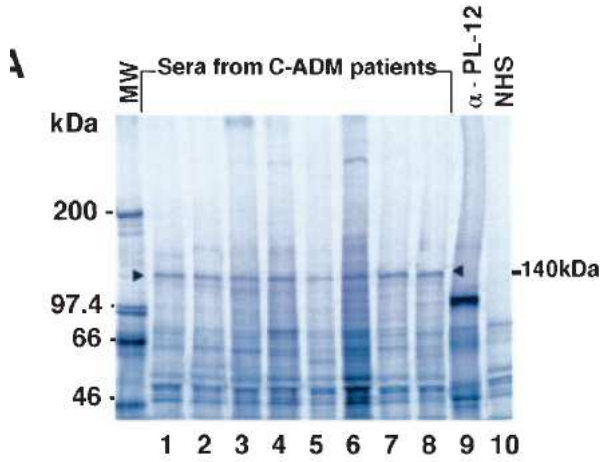


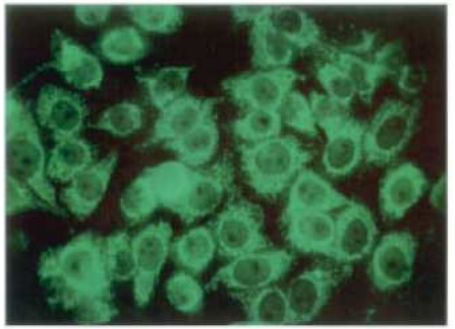


Betteridge ZE et al. Arthritis Rheum 2007, Betteridge ZE et al. Ann Rheum Dis 2009

Anti-CADM-140 (MDA5) autoantibody

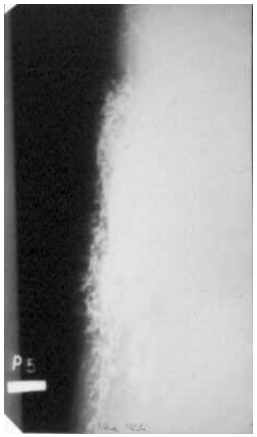
- First described in Japan (19 - 35% DM and 53 - 73% CADM), recently US 10 patients with DM (13%)
- Strongly associated with CADM and interstitial lung disease
- Poor prognosis (46% died within 6 months)
- Ulcerations, palmar papules, vasculopathy
- Drop in anti-MDA5 antibody <500 U/ml after treatment - improvement, whereas anti-MDA5 antibody >500 U/ml are resistant to treatment and die of respiratory failure in a short period.





Satoh S. et al. Arthritis Rheum 2005;52: 1571–1576

Anti-p140 (anti-MJ), anti-NXP-2

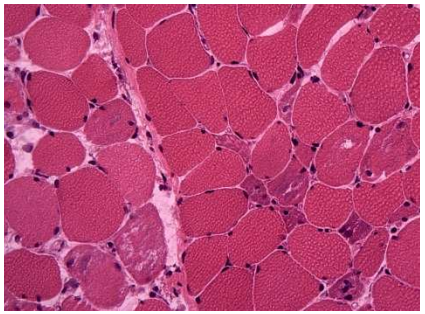


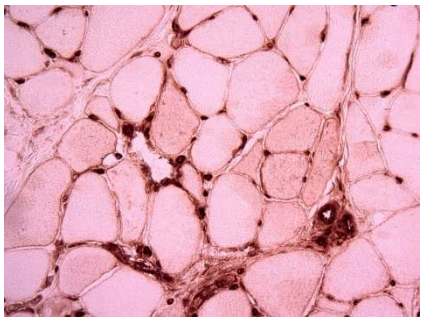
- 140 kDa protein (nuclear matrix protein NXP-2)
- Weak or no immunofluorescence, sometimes dots in ANA test
- 23% JDM
- Association with calcinosis in JDM
- HLA–DRB1*08
- Recently - most frequent antibody in Italian cohort (17%)
- Younger age at onset, no ILD, no malignancy, good response

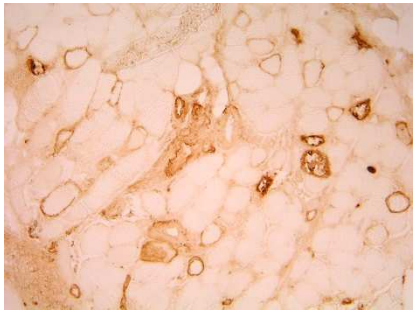
Gunawardena H. et al. Arthritis Rheum 2009; 60:1807-14. Ceribelli A. et al. Arthritis Res Ther 2012+14:R97.

Anti-200/100 kDa

- Patients who take statins can develop immune mediated necrotising myopathy, which persists after statins discontinuation (some PM or DM)
- These patients only improve with immunosuppressive treatment
- 16 of 26 patients (62%) with necrotising myopathy had anti-200/100 kDa antibodies (63% exposed to statins)
- Worsened upon discontinuation of immunosuppression
- MAC deposition, capillary abnormalities, MHC-I expression (50-75%)







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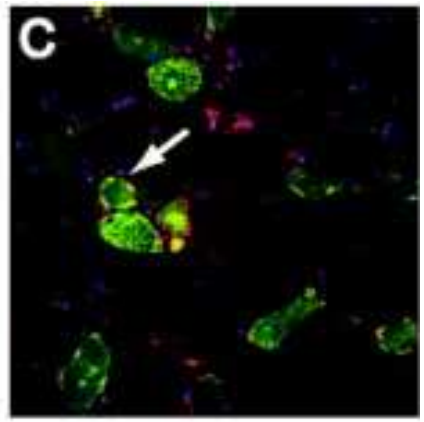
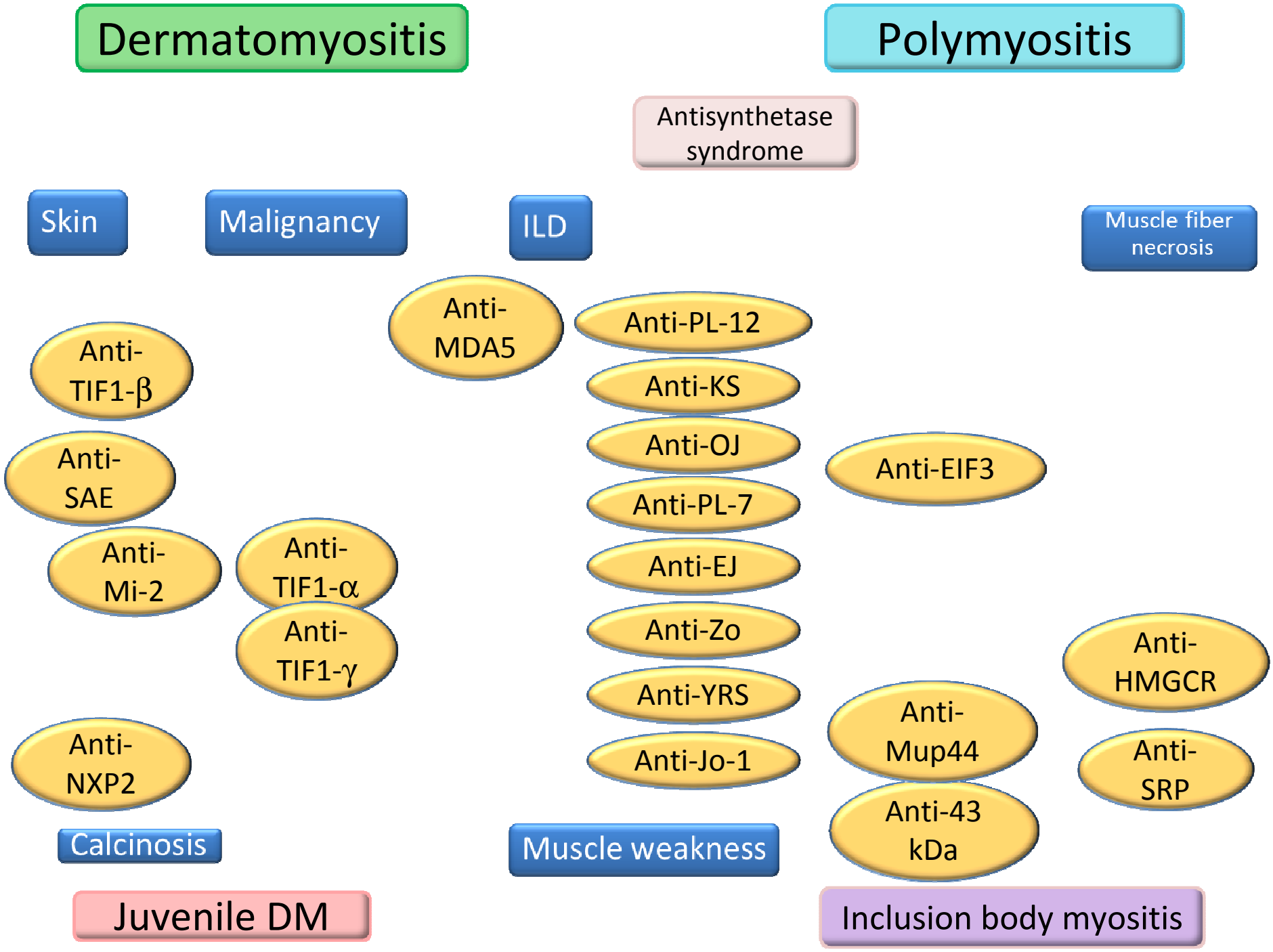
Christopher-Stine L, et al. Arthritis Rheum 2010;62(9):2757-66.

Anti-200/100 (anti-HMGCR)

- Autoantigen for anti-200/100 is 3-hydroxy -3-methylglutaryl-coenzyme A reductase (HMGCR)
- HMGCR is a target of statins
- Statins upregulate HMGCR protein levels
- Regenerating muscle fibres express high levels HMGCR



Mammen AL, et al. Arthritis Rheum 2011;63(3):713-21.


Dermatomyositis
Polymyositis
Antisynthetase syndrome
Skin
Malignancy
ILD
Muscle fiber necrosis
Anti-MDA5
Anti-PL-12
Anti-KS
Anti-OJ
Anti-EIF3
Anti-PL-7
Anti-EJ
Anti-Zo
Anti-YRS
Anti-Jo-1
Anti-TIF1-β
Anti-SAE
Anti-Mi-2
Anti-TIF1-α
Anti-TIF1-γ
Anti-NXP2
Anti-HMGCR
Anti-Mup44
Anti-SRP
Anti-43 kDa
Calcinosis
Muscle weakness
Juvenile DM
Inclusion body myositis

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Lenka Pleštilová
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