Disclosure Information

I hereby declare that I have had business or personal interests in the following industrial enterprises since 1 September 2016:

Name of the enterprise / Nature of the interest

<table>
<thead>
<tr>
<th>Enterprise</th>
<th>Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nothing to declare</td>
</tr>
</tbody>
</table>
Autoantibody-Based Classification of Inflammatory Myopathies

Dr. Debora Pehl
Department of Neuropathology
Charité - Universitätsmedizin Berlin
Germany
Idiopathic Inflammatory Myopathy (IIM)  
definition of ‘myositis’

• clinical presentation with muscle weakness (muscle pain), elevated serum CK levels, and characteristic histopathological changes on muscle biopsy

• unknown origin (probably autoimmune process)

• various additional organs can be involved

• ! exclusion of other aetiologies !  
  (toxic, metabolic, genetic etc.)
Idiopathic Inflammatory Myopathy (IIM) spectrum of diseases

- Dermatomyositis – DM (spectrum)
- Necrotizing Myositis – NM (spectrum)
- Anti-Synthetase-Syndrome-associated myositis – ASS (spectrum)
- Sporadic Inclusion Body Myositis – sIBM
Myositis Spectrum Disease Antibodies & Clinical Associations in Adult Myositis

## Myositis Specific Autoantibodies - MSAs

<table>
<thead>
<tr>
<th>Name of antibody</th>
<th>Target of antibody</th>
<th>Acuteness and severity of proximal weakness</th>
<th>Myopathology</th>
<th>Type of skin lesion</th>
<th>Life-threatening complication</th>
<th>Frequency (% IIM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Jo-1</td>
<td>Histidyl-tRNA synthetase</td>
<td>++++/+++</td>
<td>ASS-associated myositis</td>
<td>MH</td>
<td>ILD+/cardiac+</td>
<td>juvenile 1-3% adult 30-40%</td>
</tr>
<tr>
<td>Anti-PL-7</td>
<td>Threanyl-tRNA synthetase</td>
<td>++/+</td>
<td>ASS-associated myositis</td>
<td>MH</td>
<td>ILD++</td>
<td>5%</td>
</tr>
<tr>
<td>Anti-PL-12</td>
<td>Alanin-tRNA synthetase</td>
<td>+/-</td>
<td>ASS-associated myositis</td>
<td>MH</td>
<td>ILD++</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Anti-OJ</td>
<td>Isoleucyl-tRNA synthetase</td>
<td>+/-</td>
<td>not characterized</td>
<td>MH</td>
<td>ILD++</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Anti-EJ</td>
<td>Glycyl-tRNA synthetase</td>
<td>+/-</td>
<td>not characterized</td>
<td>MH</td>
<td>ILD++</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Anti-Zo</td>
<td>Phenylalanyl-RNA synthetase</td>
<td>+/-</td>
<td>not characterized</td>
<td>MH</td>
<td>ILD++</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Anti-Ha</td>
<td>Anti-Tyrosyl-RNA synthetase</td>
<td>+/-</td>
<td>not characterized</td>
<td>MH</td>
<td>ILD++</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Anti-KS</td>
<td>Asparaginyl-tRNA synthetase</td>
<td>+/-</td>
<td>not characterized</td>
<td>MH</td>
<td>ILD+</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td>Nuclesome remodeling-deacetylase</td>
<td>++</td>
<td>DM</td>
<td>DM exanthema</td>
<td>none</td>
<td>juvenile 3-5% adult &lt;10%</td>
</tr>
<tr>
<td>Anti-TIF1γ</td>
<td>Transcriptional intermediary factor 1 gamma</td>
<td>++</td>
<td>DM</td>
<td>DM exanthema</td>
<td>malignancies, severe skin affection</td>
<td>juvenile 22-36% adult 13-21%</td>
</tr>
<tr>
<td>Anti-MDA5</td>
<td>Melanoma differentiation-associated protein 5</td>
<td>±</td>
<td>amyopathic</td>
<td>DM exanthema, ulcers finger tips, palmar papules</td>
<td>ILD++</td>
<td>Juvenile 7-38% adult 13-35%</td>
</tr>
<tr>
<td>Anti-SAE</td>
<td>Small ubiquitin-like modifier activating enzyme</td>
<td>+</td>
<td>not characterized</td>
<td>DM exanthema</td>
<td>none</td>
<td>juvenile &lt;5% adult 5%</td>
</tr>
<tr>
<td>Anti-NXP2</td>
<td>Nuclear matrix protein 2</td>
<td>++</td>
<td>not characterized</td>
<td>DM exanthema, calcinosis</td>
<td>neoplasms, calcinosis</td>
<td>juvenile 20-23% adult 1.6-17%</td>
</tr>
<tr>
<td>Anti-SRP</td>
<td>Signal recognition particle</td>
<td>++++/±</td>
<td>ANM</td>
<td>none</td>
<td>cardiac++</td>
<td>juvenile &lt;5% adult 5%</td>
</tr>
<tr>
<td>Anti-HMGCR</td>
<td>3-hydroxy-3-methylglutaryl-coenzyme A reductase</td>
<td>+++/±</td>
<td>ANM</td>
<td>none</td>
<td>malignancies</td>
<td>juvenile &lt;5% adult 6%</td>
</tr>
<tr>
<td>Anti-cN1A</td>
<td>Cytosolic 5'-nucleotidase 1A</td>
<td>-</td>
<td>sIBM</td>
<td>none</td>
<td>none</td>
<td>33% IBM ~4% DM/PM</td>
</tr>
</tbody>
</table>

Tansley, Betteridge 2011, 2013; Allenbach & Benveniste 2015; Pehl & Stenzel 2016
Dermatomyositis spectrum

Anti-MDA5+ DM patients

contrast between severe clinical disease but mild affection of muscle
Anti-MDA5+ DM

MDA5+ DM
MHC class I

classical DM
Anti-MDA5\(^+\) DM

MDA5\(^+\) DM

CD56/NCAM → regeneration

classical DM
Dermatomyositis spectrum

Anti-Mi-2+ DM patients

- typical skin lesions (Gottrons’ papules, heliotrope erythema)
- typical severe proximal quadriplegia
- no other organ involvement
- very high CK levels
- good response to treatment
- very ‘severe’ morphology

Aggarwal 2014
Petri 2013
Taricone 2012
Anti-Mi-2⁺ DM

H&E
Anti-Mi-2+ DM

MHC class I

C5b-9

CD45
Anti-Mi-2+ DM

neonatal myosin → regeneration

CD56

Utrophin
Dermatomyositis spectrum

**Anti-TIF1γ + and anti-NXP2+ DM patients**

- typical clinical signs (muscle and skin affection)

- **IMPORTANT:**
  
  - association of anti-TIF1γ with **malignancy** in **adult patients** 27 times higher (neg. predictive value 95%)

  - association of anti-NXP2 with **malignancy** in **adult patients**

  - association of anti-NXP2 with **calcifications** and severe skin pathology (oedema and ulcerations) in **juvenile patients** - unfavourable prognosis
Anti-TIF1γ⁺ DM

Gömöri trichrome
conspicuous edema

H&E
Anti-TIF1γ⁺ DM

MHC class I

C5b-9 (MAC) on capillaries
Anti-TIF1γ+ DM

CD68

CD8
Anti-NXP2+ DM

courtesy of Ulrike Schara, Essen

severe oedema, dysphagia, dyspnoea, and subsequent renal failure
Anti-NXP2⁺ DM

H&E
Anti-NXP2⁺ DM

MHC class I

C5b-9
Anti-NXP2$^+$ DM
calcifications: juvenile $>>$ adult DM patients

courtesy of Yves Allenbach, Baptiste Hervier and Aude Rigolet
Immune Mediated Necrotizing Myopathy (IMNM) (first defined at the 119th ENMC workshop, 2003)

- inflammatory myopathy with myofibre necrosis, absence of significant inflammatory infiltrates, poor MHC class I expression, and variable complement deposition on capillaries

- “sarcolemmal deposition of complement should be considered as a criterium of exclusion ... evocative of dystrophic processes...”
# Necrotizing Myopathy Spectrum

- SRP-associated NM
- HMGCR-associated NM
- NM with pipestem capillaries
- Paraneoplastic NM
- NM associated with some systemic diseases
- Toxic / Drug induced NM
- Viral NM
- NM as part of an inherited disease (Muscular Dystrophies, Metabolic Myopathies, Mitochondriopathies, Congenital Myopathies esp. RYR-1 etc.)

---

<table>
<thead>
<tr>
<th>Dysimmune</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allenbach, Benveniste et al. Drouot, Boyer et al. Christopher Stine, Mammen et al. Preusse, Stenzel et al.</td>
<td>Emslie Smith &amp; Engel Authier &amp; Gherardi Stenzel &amp; Goebel</td>
</tr>
</tbody>
</table>

Allenbach, Benveniste Brain 2016
clinical features of dysimmune NMs

• acute or **subacute** muscle weakness - proximal tetrasyndrome, BUT slowly progressive manifestation possible

• +/- myalgia

• **high CK**

• weight loss

• **systemic symptoms**
  pulmonary symptoms in anti-SRP$^+$ patients, anti-HMGCR$^+$ patients associated with malignancies

• frequent **cancer association** in patients without (known) ABs

• **complicated course and treatment**!
IMNM

H&E
necrosis and myophagocytoses

Gömöri trichrome
non specific esterase

acid phosphatase
IMNM

CD4

CD8
IMNM with pipestems capillaries

H&E
thickened capillary walls & reduced capillary density, myofibre atrophy and necrosis

PAS

laminin α5
IMNM with pipestem capillaries

MHC class I  C5b-9  HIF1α

Schroeder et al. NMD 2013
Anti Synthetase Syndrome (ASS) spectrum

- weakness of proximal muscles and myalgia
- **interstitial lung disease** (ILD)
- **mechanics hands**, hyperkeratotic fissures
- **skin symptoms** w/o heliotrope erythema etc.
- Raynaud phenomenon
- seronegative arthritis of distal joints
- fever (var.)
... associated with one (!) aminoacyl tRNA synthetase antibody (anti-ARS antibody)

- histidyl (Jo-1)
- alanyl (PL-12)
- isoleucyl (OJ)
- phenylalanyl (Zo)
- threonyl (PL-7)
- glycyl (EJ)
- tyrosinyl (YRS)
- asparaginyl (KS)
**ASS**

H&E
perifascicular pathology
necrosis

non specific esterase

CD68
asso

Alkaline phosphatase
Perimysial connective tissue fragmentation,

C5b-9
Perifascicular complement deposition

MHC class II

Mozaffar & Pestronk 2000
Pestronk 2011
Stenzel et al. 2015
Mescam-Mancini et al. 2015
nuclear actin filaments

found in 81% of Jo-1+ ASS patients,
not found in cDM, IMNM, sIBM

Stenzel et al. 2015
**sporadic inclusion body myositis (sIBM)**

**Anti-cN1A**

**TABLE: Prevalence of Anti-Mup44 Autoantibodies in Myositis and Other Neuromuscular Disorders**

<table>
<thead>
<tr>
<th>Sera</th>
<th>No.</th>
<th>High Anti-Mup44&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Total Anti-Mup44&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>sIBM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sIBM-N</td>
<td>30</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>sIBM-L</td>
<td>32</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>sIBM-S</td>
<td>32</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Total sIBM</td>
<td>94</td>
<td>31</td>
<td>56</td>
</tr>
<tr>
<td>DM</td>
<td>24</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>PM</td>
<td>22</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Neuromuscular disorders</td>
<td>94</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>NHS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>32</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Efficiency of immunoprecipitation >5% of input cN1A.

<sup>b</sup>Efficiency of immunoprecipitation >1% of input cN1A.

<sup>c</sup>Sera from healthy individuals.

cN1A = cytosolic 5'-nucleotidase 1A; DM = dermatomyositis; NHS = normal healthy serum; PM = polymyositis; sIBM = sporadic inclusion body myositis; sIBM-L = patients from the Leiden University Medical Center; sIBM-N = patients from the Radboud University Nijmegen Medical Center; sIBM-S = patients from the Karolinska University Hospital, Stockholm.

Salajegheh et al. 2011
Pluk et al. 2013
sIBM

H&E inflammation

CD8

MHC class I
sIBM

Gömöri trichrome
vacuoles and ‘degeneration’

p62 gold standard
Brady et al. 2014

pFTAA
Klingstedt et al. 2013
sIBM

**COX/SDH**
mitochondrial pathology

**electron microscopy**
sIBM

H&E
severe myopathic/dystrophic picture

collagen
• **muscle biopsy** with molecular & morphological analysis is a key element for correct diagnosis of myositis and has direct prognostic relevance

• ...and direct impact on therapeutic decisions

• **auto-antibody testing** has prognostic and therapeutic relevance

• identical myositis-specific autoantibodies in children and adults, no studies comparing clinical spectrum, antibody profiles and morphology in juvenile and adult IIMs

• **clinicopathological** and **autoantibody profiles** will probably be the basis for an ‘integrated’ myositis classification in the future