Antigens in Idiopathic Inflammatory Myopathies

Idiopathic inflammatory myopathies (IIMs) are characterized by the presence of inflammatory infiltrates within skeletal muscle and are defined by a variety of syndromes. The most prevalent subtypes include adult polymyositis (PM) and dermatomyositis (DM), along with inclusion body myositis (IBM) and myositis in overlap with another autoimmune connective tissue disease (overlap syndrome) (Betteridge *et al.* 2011; Bohan *et al.* 1975a/b). DM and PM are diseases with different pathophysiological mechanisms. DM has been found to be humorally elicited while PM seems to be caused by a T-cell mediated mechanism (Gherardi 2011). The main difference from a clinical perspective is that the skin is involved in DM but not in PM while symptoms such as muscle inflammation are characteristic for both diseases (Mammen 2010).

To date, a variety of autoantibodies have been identified to be involved in the onset of IIMs and these can function as biomarkers for further demarcating the subtypes of the disease (Betteridge and McHugh 2016; Targoff *et al.* 1992). These autoantibodies can be further categorized into myositis specific autoantibodies (MSAs) and myositis associated autoantibodies (MAAs) with the earlier being a mainly exclusive PM/DM marker and the later also occurring in other connective tissue diseases (Betteridge and McHugh 2016; Love *et al.* 1991). Many MSAs are also associated with a unique clinical subset of PM/DM, making them useful in predicting and monitoring certain clinical manifestations (Satoh *et al.* 2017) (Figure 1).

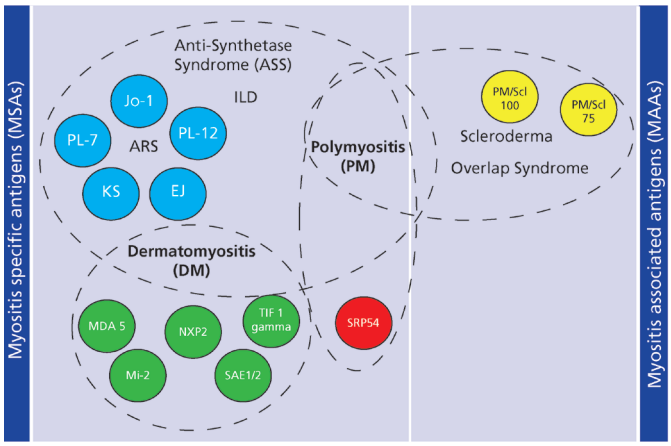


Figure 1: Categorization of DIARECT's antigens in idiopathic inflammatory myopathies (IIM).

Autoantibodies targeting eight of the 20 aminoacyl-tRNA synthetases (anti-ARS antibodies) have been identified so far, being found in up to 30% of sera from patients with myositis (Satoh *et al.* 2017). They are highly specific for this disorder and strongly associated with complicating lung disease (ILD) (Betteridge *et al.* 2011; Hirakata *et al.* 1999). The most prevalent one identified in 20 % of IIM patients is Jo-1; antibodies against other ARS can collectively be found in another 20% of patients (Gunawardena *et al.* 2009; Satoh *et al.* 2017). Although the anti-synthetase syndrome (ASS) comprises all eight synthetases, the symptoms associated with each autoantibody are slightly different. While patients with antibodies against Jo-1 show the classic PM symptoms, other patients with autoantibodies against OJ, KS or PL-12 can also exhibit DM-like skin lesions and they are very likely to develop ILD. Patients with autoantibodies against PL-7 show a milder muscle weakness compared to the one observed in patients with anti-Jo-1 antibodies (Betteridge *et al.* 2011).

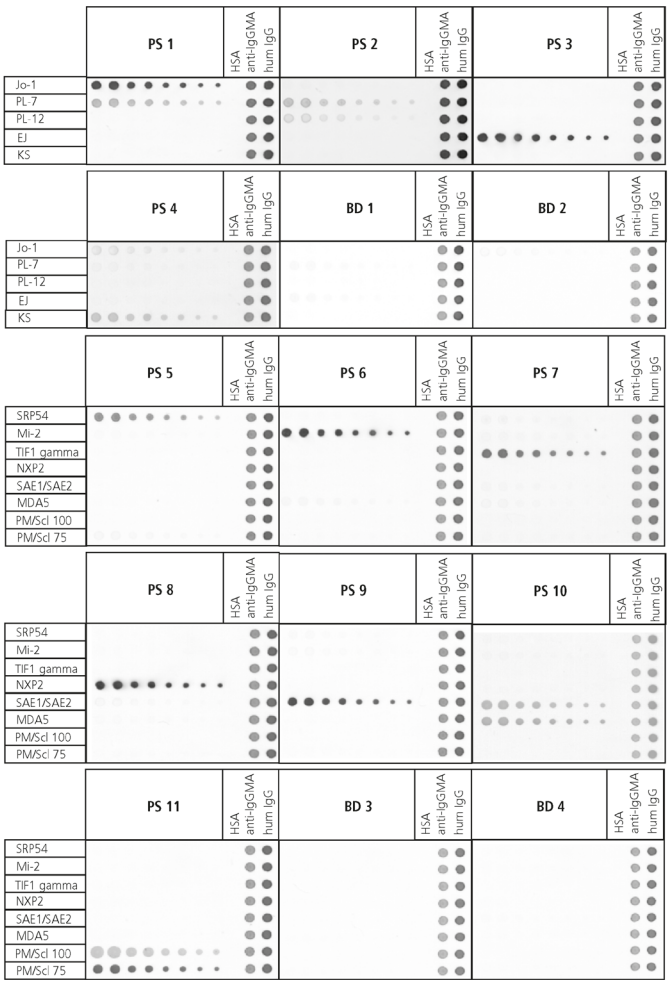
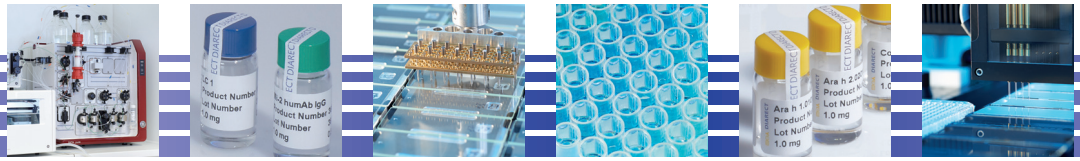


Figure 2: Immunodot analyses of negative (BD 1 - 4) and positive samples (PS 1 - PS 11) for myositis. The presence of myositis autoantibodies was determined by spotting decreasing amounts of selected recombinant myositis antigens produced in the baculovirus / insect cell expression system. Proteins and controls (HSA, anti-IgGMA and hum IgG) were printed on nitrocellulose membrane as indicated.

Anti-signal recognition particle (SRP) antibodies are characteristic for PM and are mainly associated with a syndrome of a necrotizing myopathy with cardiac involvement, severe prognosis and poor response to therapy (Betteridge *et al.* 2011; Miller *et al.* 2002; Reeves *et al.* 1986).



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Until now, they have not been described in patients with DM involvement or overlap syndrome (Targoff *et al.* 1990).

Anti-Mi-2 autoantibodies are considered specific serological markers of DM. Detected in about 20% of myositis sera, they are proven markers for acute onset, good prognosis and good response to therapy (Ghirardello *et al.* 2014; Satoh *et al.* 2017; Targoff and Reichlin 1985).

More recent publications described a number of novel autoantibodies especially in DM patients (Satoh *et al.* 2017). Autoantibodies to anti-p155/140 (TIF1 gamma) are found in up to 20% of patients with DM. A strong link with cancer associated myositis was shown in anti-TIF1 gamma positive patient cohorts (Targoff *et al.* 2006; Fujimoto *et al.* 2012).

Autoantibodies to the cytoplasmic melanoma differentiation antigen 5 (MDA5) have been mainly reported in Asian patients suffering from DM. In addition, the occurrence of this novel autoantibody was shown to be associated with interstitial lung disease (Sato *et al.* 2005; Sato *et al.* 2013).

Autoantibodies directed against nuclear matrix protein 2 (NXP2), a 140kDa protein situated in the nuclear matrix, have been reported in about 25% of DM and very rarely in PM patients. NXP2 plays a role in the regulation of p53-induced apoptosis and autoantibodies against this protein had been associated with a higher risk for malignancies (Ceribelli *et al.* 2012; Ghirardello *et al.* 2014; Ichimura *et al.* 2012).

In 2009, Betteridge *et al.* were the first to associate antibodies that target the small ubiquitin-like modifier activating enzyme subunits 1 and 2 (SAE1/SAE2) with DM. Three years later, anti-SAE1/SAE2 antibodies had been confirmed as a marker for DM with mainly skin and muscle manifestations and the absence of other symptoms such as interstitial lung disease and arthritis. (Tarricone *et al.* 2012).

Autoantibodies against PM/Scl (mainly PM/Scl 100) occur in patients suffering from polymyositis, scleroderma or overlap syndrome. They are therefore classified as MAAs meaning that they cannot be specifically correlated with one specific clinical picture but two or more (Betteridge *et al.* 2011; Koenig *et al.* 2007). The presence of PM/Scl 100 antibodies had originally been reported to be a "good" prognostic sign in overlap syndrome, unlike the poor prognosis seen when other myositis- and systemic sclerosis-specific antibodies are present. However, this view was partially revised by Marie *et al.* in 2010 where 70% of patients positive for PM/Scl improved but 20% had a worsened clinical status after long-term observation.

DIARECT offers the most complete panel of antigens for IIM characterization. All our recombinant autoantigens are produced in the baculovirus / insect cell expression system.

Ordering Information

12900 12901	Histidyl-tRNA Synthetase (Jo-1)	0.1 mg 1.0 mg
15600 15601	Threonyl-tRNA Synthetase (PL-7)	0.1 mg 1.0 mg
15700 15701	Alanyl-tRNA Synthetase (PL-12)	0.1 mg 1.0 mg
11100 11101	Glycyl-tRNA Synthetase (EJ)	0.1 mg 1.0 mg
30100 30101	Asparaginyl-tRNA Synthetase (KS)	0.1 mg 1.0 mg
18400 18401	SRP54	0.1 mg 1.0 mg
18100 18101	Mi-2	0.1 mg 1.0 mg
11000 11001	TIF1 gamma	0.1 mg 1.0 mg
31600 31601	SAE1/SAE2	0.1 mg 1.0 mg
31700 31701	NXP2	0.1 mg 1.0 mg
30000 30001	MDA5	0.1 mg 1.0 mg
16000 16001	PM/Scl 100	0.1 mg 1.0 mg
17000 17001	PM/Scl 75	0.1 mg 1.0 mg

References:
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In some countries the use of certain antigens in diagnostic tests may be protected by patents. DIARECT is not responsible for the determination of these issues and suggests clarification prior to use.

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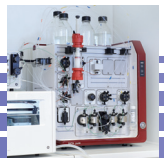

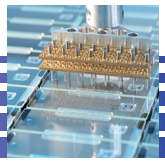
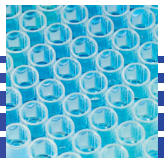

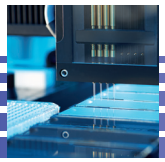

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