Datasheet recombinant autoantigens:

Jo-1	**– histidyl-tRNA synthetase**	**(Cat. No. 12900) 05/03**
PL-7	**– threonyl-tRNA synthetase**	**(Cat. No. 15600) 05/03**
PL-12	**– alanyl-tRNA synthetase**	**(Cat. No. 15700) 05/03**

DIARECT-autoantigens for Polymyositis / Dermatomyositis.

Polymyositis (PM) and Dermatomyositis (DM) are autoimmune diseases which primarily affect the skin and/or the muscles, but may also afflict other organs such as the lungs or the heart. These illnesses severely reduce the quality of life and are, if untreated, prone to develop into a life-threatening state. Although therapy is rather unspecific, an early treatment can significantly slow the progression of these illnesses and can ease the symptoms in about 90% of all cases. PM/DM are connective tissue diseases which – like most autoimmune diseases – are of an uncertain etiology. PM and DM are different illnesses but they have common symptoms. Additionally they tend to overlap with e.g. SLE or scleroderma thereby complicating diagnosis, which is intrinsically difficult because it comprises a mosaic of different techniques. Serologic testing for autoantibodies against particular aminoacyl-tRNA synthetases substantially contributes to diagnosis.

The course of PM/DM may vary from mild forms to severe cases that sometimes imply a development with poor prognosis. In particular the development of DM may be associated with malignancy. Classical symptoms of PM/DM are, though rather unspecific, a skin irritation (skin rash, mostly but not exclusively in DM, or calcinosis in DM) often caused or increased by sunlight, and proximal symmetrical muscle weakness, which often coincides with muscle pain. Infiltration of lymphocytes in muscle tissue is also a common feature of PM. The early symptoms of PM/DM, such as myalgia, weakness or fatigue, can be easily mistaken for minor unpleasantness or illness but are (not only!) typical for PM/DM. Even the symptoms of cases with good prognosis can be severe enough to substantially reduce the quality of life. For example muscle weakness can affect virtually any rump muscle. In case of a swallowing weakness, patients must pay attention to sleeping with an elevated head position and abstaining from eating just before sleeping in order to minimize the risk of suffocation. The development of an interstitial pulmonary disease is the most frequent affection of vital organs in PM/DM, which often coincides with a poor prognosis. On a molecular level we can observe the occurrence of autoantibodies to several aminoacyl-tRNA synthetases; hence PM/DM are also called anti-synthetase syndromes. The etiology of these syndromes is uncertain and multiple factors may play a role. Hormonal status may be of relevance (women are more affected than men), and a genetic predisposition is also discussed, as well as external factors like drugs or exposure to strong radiation (sunlight).

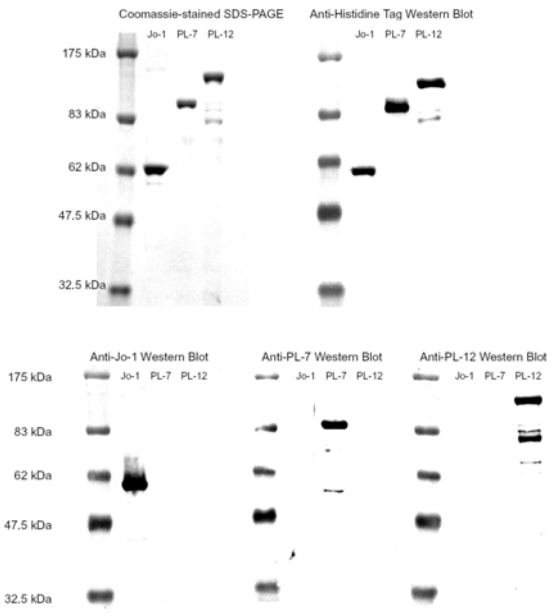
Standard therapy of PM/DM is immunosuppression – as it is the case for most autoimmune diseases. This therapy leads to a remission of the symptoms in 90% of the cases, in which however a residual weakness normally remains. Severe cases require the application of cytotoxic substances or even plasmapheresis. Skin irritations are easy to manage by topical application of corticoids. Immunosuppression (by steroid and non-steroid substances) is rather unspecific but currently the best practical therapy of PM/DM. But, especially in the long run, immunosuppressive substances may cause severe side effects. An early and reliable diagnosis helps keep the dosage of immunosuppressive substances low and helps minimize side effects. The development of more specific diagnostic tools may also accelerate the development of a more specific therapy.

Diagnosis of PM/DM is a mosaic comprised of medical history, physical examination, electromyography, biopsy and laboratory tests. PM/DM-patients have an increase in muscle enzymes, an electromyogram with short polyphasic motor potentials and unusual repetitive discharges of high frequency. Electromyography may direct muscle biopsies to potentially affected tissue. As mentioned before, a striking feature of PM/DM is the development antibodies to different but functionally related enzymes – aminoacyl-tRNA synthetases. At least five aminoacyl-tRNA synthetases (histidyl, threonyl, alanyl, glycyl and isoleucyl) have been associated with PM/DM, in which **all patients develop antibodies to only one type of synthetase**.

The most important antigen for serological PM/DM diagnosis is **Jo-1,** which has always been a part of DIARECT´s repertoire of recombinant autoantigens, known for their comparatively high specificity and high lot-to-lot consistency. **Now DIARECT offers two new recombinant antigens, PL-7 and PL-12,** to extend the set of PM/DM-specific markers.

Selectivity and specificity of Jo-1, PL-7, PL-12

(data from DIARECT R&D)



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Jo-1 – histidyl-tRNA synthetase – is the major target of autoantibodies in PM/DM, with a prevalence of about 33%. Anti-Jo-1 is specific for PM/DM, the antibodies being more frequent in PM than in DM. Despite the relatively low prevalence, a serological anti-Jo-1 diagnosis is of utmost importance: anti-Jo-1 antibody-positive patients have an increased risk for the development of interstitial pulmonary disease. With a positive test based on anti-Jo-1, the diagnosis is reliable, and hence therapy can start instantly, which is mandatory in light of the possible complications of untreated disease.

There are a small number of **non-anti-Jo-1** PM/DM cases in which other synthetases are targeted by the autoimmune system. **PL-7 and PL-12 together have a prevalence of about 25%** in this subgroup.

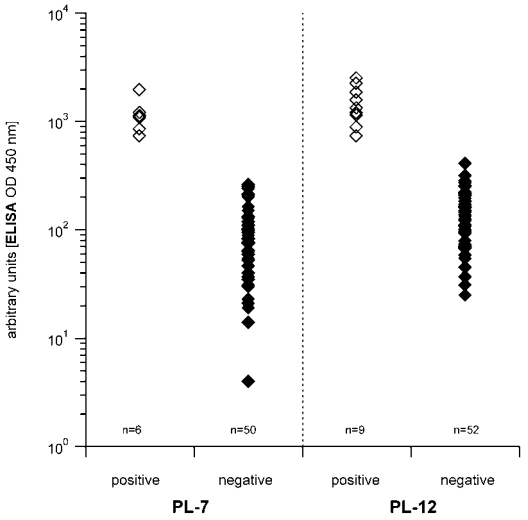
PL-7 – threonyl-tRNA synthetase – autoimmunity is specific for PM and DM and occurs with approximately equal frequency in these 2 diseases. There is some evidence that anti-PL-7-positive patients also have a higher risk of developing an interstitial lung disease (75% of the cases), although the number of patients with anti- PL-7 evaluated in this regard needs to be increased.

PL-12 – alanyl-tRNA synthetase – is a protein with a molecular weight of 108 kD. A specific feature of this anti-synthetase syndrome is the development of further antibodies to this functional unit (epitope spreading). Thus PL-12 antibodies are heterogeneous and can include antibodies to an isolated tRNA ^{ala} molecule (particularly the tRNA with an inosine-guanine-cytosine anticodon).

All autoantibodies yield a typical IIF pattern on HEp-2 cells, but only distinct recombinant antigens allows a clear differentiation. With DIARECT´s recombinant PL-7 and PL-12 the relatively difficult diagnosis of PM and DM will be significantly improved. Recombinant PL-7 and PL-12 are new and unique.

Significance of the diagnosis with recombinant PL-7 and PL-12 in ELISA with positive and negative sera

(with kind permission of Prof. R.L. Humbel and P. Schmit, CHL, Luxembourg)



PL-7 and PL-12 dilution plot

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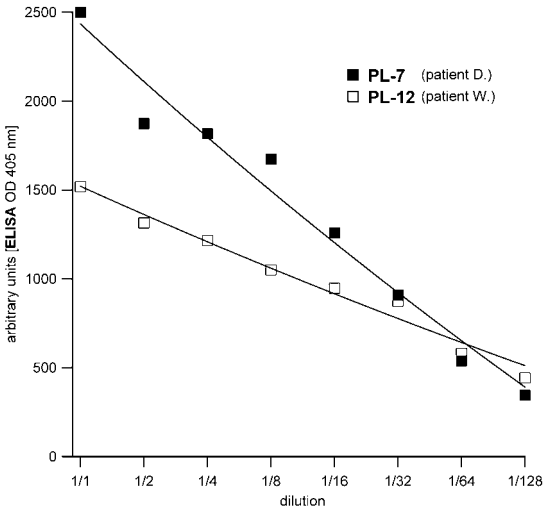

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