Secrets revealed by myositis autoantibodies

Neil McHugh, University of Bath and Royal National Hospital for Rheumatic Diseases
Louisville September 2018
The origins of ‘rheumatic’ disease

Rheuma – Greek for flow;  Rheumatism – to suffer from a ‘flux’
The ‘flux’ of ‘rheumatic’ disease

- Scleroderma
- Dermatomyositis
- Systemic lupus erythematosus
- Psoriatic arthritis
Antibodies are part of the ‘flux’ of the immune system
B lymphocytes make antibodies
The immune system (innate and adaptive)
Autoantibodies are antibodies that recognise self-constituents (autoantigens) rather than foreign particles.

Autoantibodies are the hallmark of autoimmunity.
Autoimmunity

- 1903
  - Paul Ehrlich ‘horror autotoxicus’
- 1943-1946
  - Eric Waaler and Harry Rose described Rheumatoid factor
- 1948
  - Hargreaves. LE cell
- 1966
  - Tan & Kunkel described anti-Sm
- 1976
  - Reichlin described anti-Mi2
- 1980
  - Moroi et al described anti-centromere antibodies in scleroderma
Timeline of myositis specific autoantibody discovery

- Anti-Mi2
- Anti-PL7
- Anti-PL12
- Anti-OJ
- Anti-Ha
- Anti-Zo
- Anti-SAE
- Anti-NXP2
- Anti-HMGCR
- Anti-Jo1
- Anti-EJ
- Anti-KS
- Anti-TIF1
- Anti-MDA5
- Anti-cN1A
Since 2005 the majority of juvenile and adult myositis cases have an identifiable myositis autoantibody.
So our journey begins…

- Wellington Rheumatology trainee 1982-1984
- RACP Grant Melbourne 1985
- Dorothy Eden Fellowship RNHRD, Bath 1985-1986
- Senior Registrar RNHRD 1987-1990
The Australian experience

A HIGHLY CONSERVED 72,000 DALTON CENTROMERIC ANTIGEN REACTIVE WITH AUTOANTIBODIES FROM PATIENTS WITH PROGRESSIVE SYSTEMIC SCLEROSIS

L. JANE McNEILAGE,1 SENGA WHITTINGHAM,2 NEIL McHUGH,3 AND ALFRED J. BARNETT4

From The Clinical Research Unit of The Walter and Eliza Hall Institute of Medical Research and the Royal Melbourne Hospital, Post Office Royal Melbourne Hospital, Victoria 3050, Australia
The golden age of treatment at ‘The Min’
Perkins tractors

- Cure for gout, rheumatism, headaches and epilepsy
- Distributed in England by a Bath Physician with a thriving practice (also a superintendent of mental asylum)
- 1799 Dr Haygarth at the Min performed placebo study with fake wooden tractors on five patients

‘the wooden tractors were drawn over the skin such as to touch it in the lightest manner... distinctly proving to what a surprising degree mere fancy deceives the patient’
The spectrum of autoimmune connective tissue disease

- Scleroderma
  - Nucleolar RNP

- Dermatomyositis
  - Transcription factors
  - RNA synthetase

- Rheumatoid arthritis
  - ACPA

- Sjogren’s
  - Ro/La (SS-A/SS-B)

- SLE
  - snRNPS
  - Nucleosome
Autoantibodies in CTD

- SRP
- SAE
- TIF1
- Mi-2
- MDA5
- NXP2
- CN1A
- IBM (SLE / SS)
- DNA
- Rib P
- SLE
- U1 RNP
- CL
- La
- SJOGREN
- MCTD
- U3 RNP
- EIF2B
- Topo I
- RNA Pol III
- Th /To
- Centromere
- ACPC
- U11 / U12 RNP
- Limited SSc
- Diffuse SSc
- Myositis-SSc Overlap
- HMGCR
- Necrotising Myositis
- Dermatomyositis
- Anti-Synthetase Syndrome
- Jo-1
- PL12
- Zo
- KS
- PL7
- OJ
- EJ
- Ha
- KS
- Th /To
- Centromere
Scleroderma (systemic sclerosis)

- Abnormal accumulation of collagen and other matrix proteins in affected tissue
- Mainly affects
  - Skin
  - Blood vessels
  - Lungs, Kidneys, Gut
- Presence of disease specific autoantibodies
Autoantibodies in CTD

- SRP
- Mi-2
- SAE
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- MDA5
- NXP2
- CN1A
- IBM (SLE / SS)
- HMGCR
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Autoantibodies in scleroderma

MYOSITIS-SSc OVERLAP

LIMITED SSc

DIFFUSE SSc

PmScI

U11/ U12 RNP

Centromere

Th /To

U3 RNP

Topo I

RNA Pol III

EIF2B
Serological subsets in scleroderma

- Lung
- Topo-I
- Centromere
- U3RNP
- U1RNP
- Pm-Scl
- Th RNP
- PHT
- EIF2b
- Diffuse skin disease
- Kidney
- Limited skin disease
- Overlap features
SEGREGATION OF AUTOANTIBODIES WITH DISEASE IN MONOZYGOTIC TWIN PAIRS DISCORDANT FOR SYSTEMIC SCLEROSIS

Three Further Cases

NEIL J. McHUGH, GEORGINA R. HARVEY, JEAN WHYTE, and J. KEVIN DORSEY
ANTI–TOPOISOMERASE I ANTIBODIES IN SILICA-ASSOCIATED SYSTEMIC SCLEROSIS

A Model for Autoimmunity

NEIL JOHN McHUGH, JEAN WHYTE, GEORGINA HARVEY, and UWE F. HAUSTEIN
.....the journey continues
The American dream
Antibodies to small nuclear RNAs complexed with proteins are produced by patients with systemic lupus erythematosus

(nuclear ribonucleoprotein/rheumatic disease/RNA processing)

MICHAEL RUSH LERNER AND JOAN ARGETSINGER STEITZ

Two Novel Classes of Small Ribonucleoproteins Detected by Antibodies Associated with Lupus Erythematosus

Abstract. The RNP and Sm antigens recognized by lupus erythematosus antibodies are located on discrete particles containing single small nuclear RNA's complexed with proteins. The antigens Ro and La are also on ribonucleoproteins. The small RNA's in ribonucleoproteins with Ro are discrete, like those associated with RNP and Sm; in contrast, ribonucleoproteins with La contain a striking highly banded spectrum of small RNA's from uninfected cells as well as virus-associated RNA from adenovirus-infected cells.

The spectrum of autoimmune connective tissue disease

- Scleroderma
  - Nucleolar RNP

- Dermatomyositis
  - Transcription factors
  - RNA synthetase

- Rheumatoid arthritis
  - ACPA

- Sjogren’s
  - Ro/La (SS-A/SS-B)

- SLE
  - snRNPS
  - Nucleosome
Methods for detecting autoantibodies

Autoantibody Screening by Indirect Immunofluorescence
- Hep-2
- Human neutrophil
- Hep-2
- Hep-2

Autoantibody identification by second technique
- Immunodiffusion
- ELISA
- Western blot
- Lineblot
- Immunoprecipitation

ENA anti-RNP
- anti-PR3
- anti-centromere

Anti-fibrillarin U3RNP
Indirect Immunofluorescence

- **Antigen source** - tissue section (mouse LKS, monkey oesophagus) whole cell (HEp-2, neutrophil, *crithidia luciliae*)

- **Autoantibody from patient serum** - Apply autoantibody that if present will bind to the antigen source

- **Secondary antibody** - anti-human IgG FITC

- **Visualization** - green fluorescence in a recognizable pattern corresponding to location of antigen read under a specialized immunofluorescence microscope
Indirect immunofluorescence test I
Indirect immunofluorescence test II

Serum from scleroderma patient with anti-centromere autoantibodies
Indirect Immunofluorescence test III
Indirect immunofluorescence

- If test positive the patient will be reported as having an antinuclear antibody (ANA)
- Sometimes the pattern will reveal the type of ANA (specificity) but usually another method will be necessary for exact identity
Systemic Lupus Erythematosus

**Systemic lupus erythematosus**

- **Skin**
  - butterfly rash
  - red patches

- **Heart**
  - endocarditis
  - atherosclerosis
  - inflammation of the fibrous sac

- **Lungs**
  - pleuritis
  - pneumonitis
  - pulmonary emboli
  - pulmonary hemorrhage

- **Kidneys**
  - blood in the urine

- **Muscle and Joints**
  - pain and arthritides
  - swollen joints

- **Blood**
  - anemia
  - high blood pressure

- **Severe abdominal pain**

- **Hair loss**
- High fever
- Abnormal headache
Autoantibodies in SLE
Autoantibodies in SLE

**Autoantibody**
- Anti-ds-DNA
- Anti-phospholipid
- Anti-Sm (U1RNP)
- Anti-Ro/La
- Anti-C1q
- Anti-ribosomal P

**Autoantigen**
- Nucleosomes
- Complex phospholipids
- snURPs
- RNA-binding proteins
- Early complement proteins
- Ribosomal proteins

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Autoantigens Targeted in Systemic Lupus Erythematosus Are Clustered in Two Populations of Surface Structures on Apoptotic Keratinocytes

By Livia A. Casciola-Rosen,* Grant Anhalt,* and Antony Rosen†

From the Departments of †Dermatology, and †Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

![Autoantigens in surface blebs of UV irradiated keratinocytes](image)
The spectrum of autoimmune connective tissue disease

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- Sjogren’s
  - Ro/La (SS-A/SS-B)
- SLE
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  - Nucleosome
Dermatomyositis

Muscle inflammation

Skin disorder

Interstitial lung disease
Timeline of myositis specific autoantibody discovery

- Anti-Mi2
- Anti-PL7
- Anti-PL12
- Anti-SRP
- Anti-OJ
- Anti-Ha
- Anti-Zo
- Anti-SAE
- Anti-NXP2
- Anti-HMGCR
- Anti-Jo
- Anti-EJ
- Anti-KS
- Anti-TIF1
- Anti-MDA5
- Anti-cN1A
Autoantibodies in Myositis

• MSA (myositis specific autoantibodies)
  • Anti-tRNA synthetases (e.g. anti-Jo-1)
  • Anti-Mi-2
  • Anti-signal recognition particle
  • Anti-SAE
  • Anti-TIF1-γ
  • Anti-NXP2
  • Anti-MDA5
  • Anti-HMGCR
  • Anti-cN-1A

• MAA (myositis associated autoantibodies)
  • Anti-PM-Scl
  • Anti-U1RNP
  • Anti-Ku
  • Anti-U3RNP
  • Anti-Ro (SSA)
## MSAs and target autoantigens

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>Target autoantigen</th>
<th>Autoantigen function</th>
<th>Clinical phenotype</th>
</tr>
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<tbody>
<tr>
<td>Anti-ARS</td>
<td>tRNA synthetase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Jo-1</td>
<td>Histidyl</td>
<td>Intracytoplasmic protein synthesis</td>
<td>ASS</td>
</tr>
<tr>
<td>Anti-PL-7</td>
<td>Threonyl</td>
<td>Binding between an amino acid and its cognate tRNA</td>
<td>Myositis</td>
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<tr>
<td>Anti-PL-12</td>
<td>Alanyl</td>
<td></td>
<td>Interstitial pneumonia</td>
</tr>
<tr>
<td>Anti-EJ</td>
<td>Glycyl</td>
<td></td>
<td>Mechanics hands</td>
</tr>
<tr>
<td>Anti-OJ</td>
<td>Isoleucyl</td>
<td></td>
<td>Arthritis</td>
</tr>
<tr>
<td>Anti-KS</td>
<td>Asparaginyl</td>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td>Anti-Zo</td>
<td>Phenylalanin</td>
<td></td>
<td>Raynauds</td>
</tr>
<tr>
<td>Anti-YRS</td>
<td>Tyrosyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td>Helicase protein part of the NuRD complex</td>
<td>Nuclear transcription</td>
<td>Adult and juvenile DM</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Hallmark cutaneous disease</td>
</tr>
<tr>
<td>Anti-SRP</td>
<td>SRP 6 polypeptides and ribonucleoprotein 7SLRNA</td>
<td>Intracytoplasmic protein translocation (endoplasmic reticulum)</td>
<td>Severe necrotizing myopathy</td>
</tr>
<tr>
<td>Anti-HMGCR</td>
<td>3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase</td>
<td>Biosynthesis of cholesterol</td>
<td>Necrotising myopathy associated with statin use</td>
</tr>
</tbody>
</table>

MSAs and target autoantigens
### MSAs and target autoantigens II

<table>
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<tr>
<td>Anti-p155/140</td>
<td>TIF1-γ</td>
<td>Nuclear transcription</td>
<td>Severe cutaneous disease in juvenile DM and cancer in adults</td>
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<tr>
<td></td>
<td></td>
<td>Cellular differentiation</td>
<td></td>
</tr>
<tr>
<td>Anti-p140 (MJ)</td>
<td>NXP-2</td>
<td>Nuclear transcription (tumour suppressor gene p53)</td>
<td>Juvenile DM</td>
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<tr>
<td>Anti-SAE</td>
<td>SAE</td>
<td>Post-translational modification – targets include nuclear transcription factors</td>
<td>Adult DM May present with CADM first</td>
</tr>
<tr>
<td>Anti-CADM-140</td>
<td>MDA5</td>
<td>Viral RNA recognition</td>
<td>CADM Interstitial pneumonia</td>
</tr>
<tr>
<td>Anti-Mup44</td>
<td>Cytosolic 5’nucleotidase 1A (cN-1A)</td>
<td>Hydrolysis of AMP</td>
<td>Inclusion body myositis (Sjogren’s)</td>
</tr>
</tbody>
</table>
Myositis antibodies identify patterns of disease
Case A female born 1957

- 2006
- Breathlessness
- 6 months later
  - Proximal muscle weakness
  - Raynaud’s
  - Arthralgia
  - Puffy fingers with some fissuring
- Invs
  - ANA weak positive
  - CK 9533 IU/L
  - HRCT non-specific interstitial pneumonia

Strong Cytoplasmic Speckle on Indirect Immunofluorescence

Protein Immunoprecipitation of bands at approximately 60 kDa and 70 kDa – phenylalanyl tRNA synthetase

1. Normal Serum
2. Anti-Jo-1
3. Anti-PL-7
4. Anti-PL-12
5. Case 1 (anti-Zo)
Anti-synthetase syndrome

Clinical Features
- Myositis
- Interstitial pneumonia (50-80%)
- Arthritis (50-90%)
- Raynaud’s (60%)
- Mechanics Hands (70%)
- Fever (80%)

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<th>tRNA synthetase target</th>
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<td>Jo-1</td>
<td>Histidine</td>
<td>25-30%</td>
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<tr>
<td>EJ</td>
<td>Glycerine</td>
<td>&lt;2%</td>
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Key points regarding anti-synthetase syndrome

• Interstitial lung disease may be the predominant or even sole manifestation of myositis (anti-synthetase syndrome)

• Autoantibodies can be missed as they do not give a strong ANA on routine screening

• The additional presence of anti-Ro52 is associated with more severe ILD

• Uncommon in juvenile dermatomyositis (may relate to an association with smoking in adults)
Case B Chinese Female born 1960

- Admitted with fatigue, weight loss and ulcerative rash
- Rapidly progressive breathlessness
- No muscle weakness
- Invs
  - High Ferritin
  - Normal CK
  - Low O2 sats
  - PET normal
  - Anti-MDA5
- Diagnosis
  - CADM with RPILD
Anti-MDA5 Autoantibodies

• More common in Asian myositis population (48%) than Caucasian (13%)

• In adults
  • Rapidly progressing ILD
  • Skin manifestations
    • Especially ulcerations (skin and mouth) and palmar papules
    • Other DM type rashes

• In children (7-38%)
  • Skin and oral ulcers
  • Milder muscle disease
  • ?ILD

Fiorentino et al J Am Acad Dermatol 2011;65:25-34
Nakashima et al Rheumatol 2010;49:433-40
Kobayashi et al J Pediatr 2011;158:675-7
Tansley et al Arthritis Res Ther 2014;16:R138
Moghadam et al Arthritis Care Res 2015
Autoantibodies in Juvenile MSD

• MSDAs
  • Anti-TIF1g
  • Anti-NXP2
  • Anti-MDA5
  • Anti-Mi-2
  • Low frequency of anti-synthetase and anti-SRP

• MAAs
  • Overlap syndromes with scleroderma/lupus
    • Anti-PmScl
    • Anti-U1RNP

UK JDM Cohort and Biomarker study n = 347
MDSAs in Juvenile MSD

• **TIF1-γ**
  • 17-33% of cases
    • More severe skin disease, ulceration, generalised lipodystrophy

• **NXP2**
  • 18-36% of cases
    • Calcinosis, contractures, muscle atrophy

• **MDA5**
  • 7-38% of cases
    • Skin and Oral Ulcers, Arthritis, Milder Muscle Disease, ILD

• **Mi-2**
  • 2-5% of cases
    • Milder disease course

Bingham Medicine Baltimore 2008;87(2):70-86
Gunawardena Rheumatology 2008;47(3):324-8
Espada J Rheumatol 2009;36:2547-51
Rider Medicine Baltimore 2013 92(4) 223-43
Kobayashi et al J Pediatr 2011;158:675-7
Tansley Rheumatology 2014;53(12):2204-8
Tansley Arthritis Res Ther 2014;16:R138
Patterns of Juvenile versus Adult MSD

- Juvenile myositis
  - JDM more common
  - Calcinosis
  - Lipodystrophy
  - Interstitial lung disease rare
  - Malignancy rare
  - Polymyositis uncommon
  - Inclusion body myositis rare
  - Overlap e.g. with scleroderma

- Adult myositis
  - Dermatomyositis
    - Association with malignancy
  - Polymyositis
    - Antisynthetase syndrome
  - Inclusion body myositis
  - Overlap

UK JDM Cohort and Biomarker Study n= 347

EUMYONET n = 1616
Myositis and cancer

• Association between cancer and myositis known for many years
• Risk of cancer 3 to 7 times higher in dermatomyositis
• Most common types of cancer
  • Ovary, lung, pancreas, stomach, colorectal, breast, lymphoma, nasopharynx (southeast Asians)
• The risk of malignancy development is highest within one year of myositis diagnosis
• Cancer-associated myositis (CAM) defined as concurrence of myositis and malignancy within 3 years
• Several studies have now shown that anti-transcriptional intermediary factor 1 is a myositis autoantibody and a risk factor for an associated cancer
Case C male born 1953

- **Acute admission March 2014**
  - PUO
  - 4/12 fatigue, muscle aching and weakness, weight loss
  - Worsening anaemia Hb 85
  - CRP 90, PV 2.71, normal myeloma screen, CK, CEA, CA19.9
  - Normal CT scans, colonoscopy and temporal artery biopsy
  - MR thighs – muscle atrophy
  - PET scan revealed recurrence of renal cell carcinoma
  - Anti-TIF1g positive
Transcriptional intermediary factor I
Clinical Associations of anti-TIF1 in EuMyoNet
(first 1616 cases – unpublished)

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>TIF1 Negative</th>
<th>TIF1 Positive</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial lung disease</td>
<td>31.2%</td>
<td>16.0%</td>
<td>=0.0038</td>
</tr>
<tr>
<td>Cancer (ever)</td>
<td>8.0%</td>
<td>32.2%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cancer-associated myositis</td>
<td>2.3%</td>
<td>20.5%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Learning points from Case C

• A thorough screen for cancer is needed in dermatomyositis, especially with the presence of anti-TIF1γ (also anti-NXP2)

• The risk of cancer is also higher with age and in the presence of clinically amyopathic DM (CADM)
Cancerous cells may initiate an autoimmune reaction against muscle cells

TIF1g is found in high levels within the nuclei of regenerating muscle fibres
Mohassel et al Arthritis Rheum 2015

TIF1g a tumour suppressing protein is over-expressed in tumour cells from a CAM patient
Pinal-Fernandex et al Rheumatology 2018

Mutated or abnormally expressed protein becomes a target for an autoimmune reaction. In certain circumstances (e.g. regenerating muscle cells over-express myositis autoantigens) the anti-tumour response is directed towards skeletal muscle cells
Case E male born 1964

- 2006
  - Fatigue, weight loss, dysphagia, severe weakness, sclerodactyly
  - CK 14,000, EMG positive, Muscle biopsy necrotising myositis, serology anti-SRP
  - Slow response to Prednisolone and IVIG
  - MMDS 5
  - Anti-SRP positive

- 2007
  - Partial response to IV cyclophosphamide
  - Myocarditis, CK 1700, MMDS 17
  - Good response to rituximab and MMF

- 2008
  - Returned to work as self-employed builder, MMDS 30, CK 207

- 2009
  - Died of acute coronary event
Anti-SRP and Anti-HMGCR autoantibodies

Anti-SRP

Necrotizing Myopathy

- Fatigue / Arthralgia
- Severe Weakness (Rapid Onset)
- High CK at Presentation
- Carditis
- Maybe refractory to standard treatments
- Titres may correlate with disease activity

Anti-HMGCR

Necrotizing Myopathy

- Statin-Induced
- Not seen in patients on statins without myositis
- Raised CK
- Mild to severe weakness
- Anti-HMGCR levels correlate with indicators of disease activity
- Responsive to immunomodulatory treatment

References:

Targoff et al. Arthritis Rheum 1990;33:1361-70
Wang et al. NMD 2014;24:335-41
Rider et al. 2013, Medicine Baltimore 92(4) 223-43
Acknowledgements

Musculoskeletal Medicine Research Group

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- Millie Green
- Richard Holland
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- Amel Badoume

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  - Amanda McKenzie
  - Mark Lindsay
  - Steve Ward

University of Exeter
  - Gavin Shaddick (statistics)

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  - Hector Chinoy, Janine Lamb (myositis)

University of Liverpool
  - Bob Cooper (myositis)

University of Leeds
  - Philip Helliwell (psoriatic arthritis)
  - Laura Coates (now Oxford) (psoriatic arthritis)
  - Leeds CTU

UCL
  - Lucy Wedderburn (Juvenile myositis)

University College Dublin
  - Oliver FitzGerald (psoriatic arthritis)

Consortia

- British Isles Lupus Assessment Group
- UK Myonet
- EuMyonet
- Psoriatic Arthritis European Genetic Consortium (PAGE)
- Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)
- PROMPT Study Group