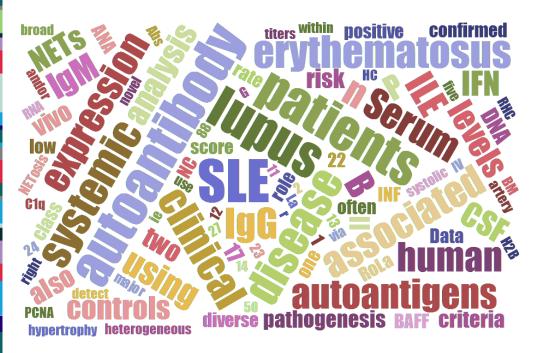


Discovery and initial validation of autoantibodies against the major vault protein (MVP) in systemic lupus erythematosus

Petra Budde, Stefan Vordenbäumen, Hans-Dieter Zucht, Heike Göhler, Peter Schulz-Knappe and Matthias Schneider

High-Content Autoantibody Profiling in SLE



- Pathogenic AABs are an essential part in the diagnosis of SLE
- In the clinical development, antidsDNA is used to enrich patients with active disease

AAB	Freq. (%)	Diagn.
ANA	95	yes
dsDNA	60–90	yes
Sm	20–40	yes
snRNP	20–30	no
SSA/Ro	30–40	no
SSB/La	10–15	no
PL	30–40	yes
ß2GP1	10–35	no
C1q	20–50	no
Rib P	10-40	no
NMDAR	30	no

Novel SLE antigens with diagnostic and patients stratification utility



Multiplex NavigAID SLE 86 Antigen Array

SLE-specific Ag

- dsDNA
- ribosomal P
- Sm
- Complement
- b2GBPI

INF I pathway Ag

- MVP
- INF, Mx1
- Ro52, SSB, Histone
- HNRNPA1, SP100, RPLP

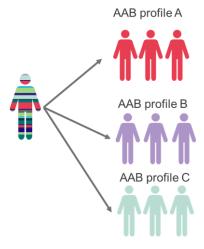
SLE subgroups based on autoantibody reactivity

AID Ag

- SSc: CENPB, Topo1
- RA: CCP
- SjS: Ro/SSA, SSB
- DM: Mi2-antigen
- Myositis: t-RNA synthetases
- U1-snRNP, ANCA, Ku

Novel SLE Ag

•MVP, TMPO, NONO, hnRNP, BCAP31, NCF2, IL6, BTBD7, PLVAP, FAF1, NRBF2

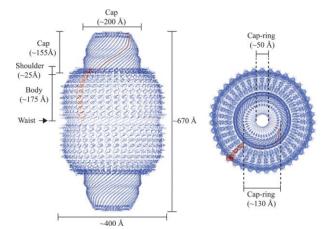


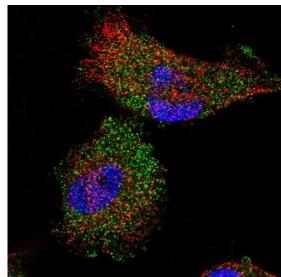
- Novel antigens associated with innate immune response pathways
- Antigens were discovered and validated in >700 SLE patients and used to develop an SLE stratification array



Major Vault Protein

- MVP is the major component of the 13
 MDa vault complex, which are
- large cellular ribonucleoparticles
- Plays a role in host proinflammatory response
- Highly expressed in macrophages
- Induced by viral infections and dsRNA (DOI:10.4049/jimmunol.1501481)
- IFN-gamma-responsive gene (DOI:10.1242/jcs.02773)
- MVP expression up-regulates INF type I production, leading to cellular antiviral responses (DOI:10.1002/hep.25642)



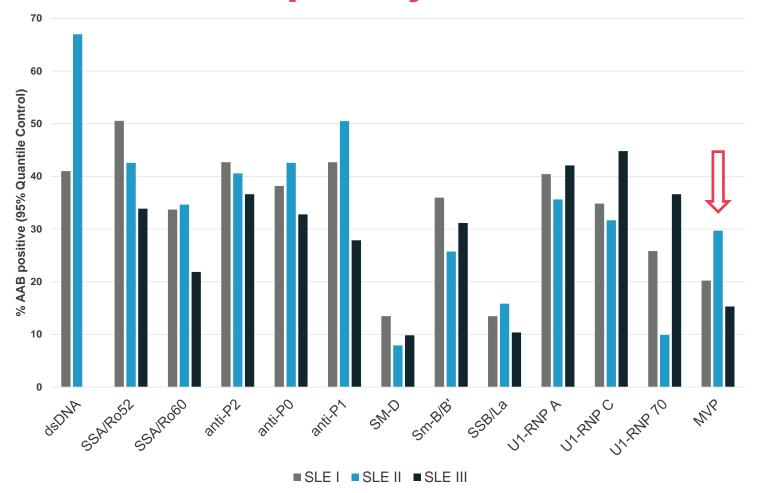


mouse mAb anti-MVP (green), Source: Protein Atlas

www.proteinatlas.org



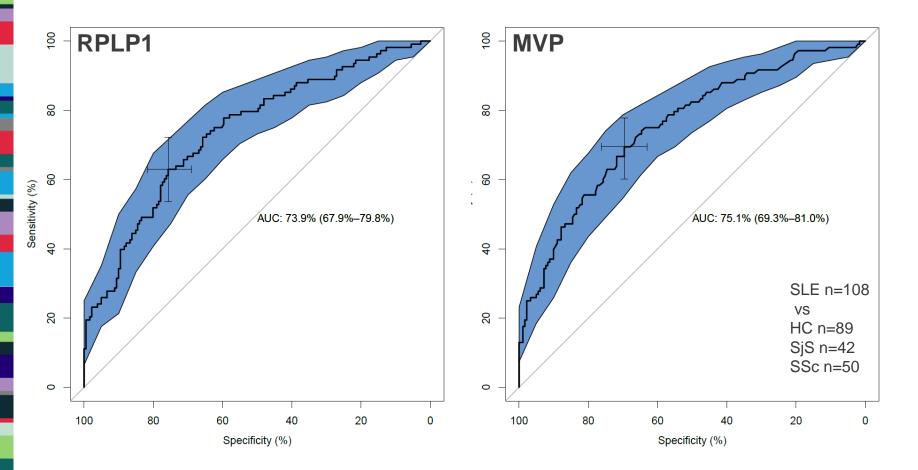
Anti-MVP Frequency in 3 SLE Studies



The frequency of anti-MVP antibodies among 3 SLE cohorts (400 samples) ranges from 15-30%



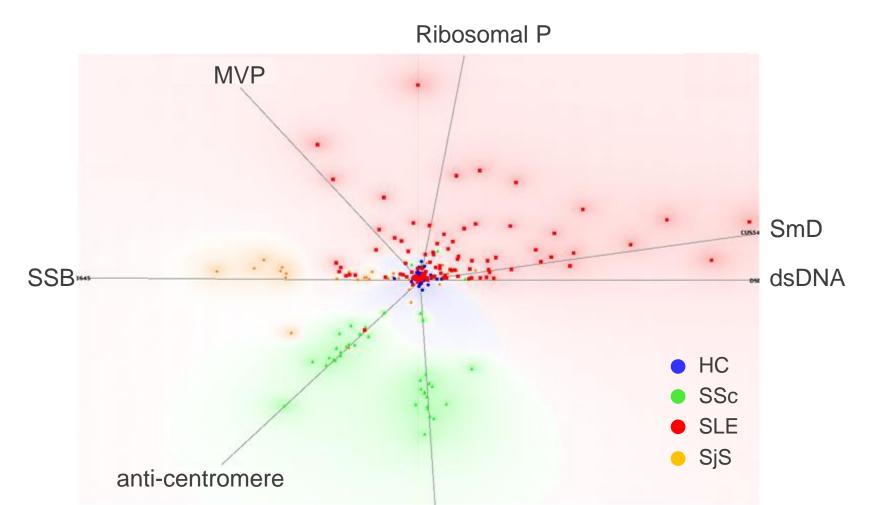
Anti-MVP has high Specificity for SLE



Anti-Rib P and anti-MVP have comparable sensitivity (23% vs 25%) and specificity (97%)



Anti-MVP defines a distinct SLE Subgroup

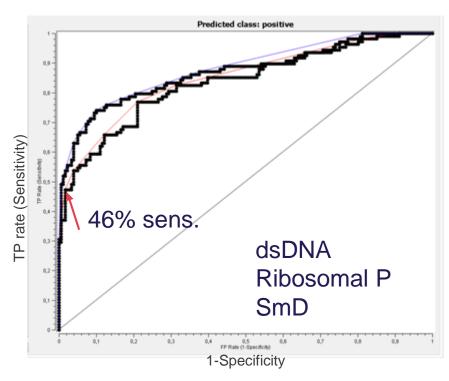


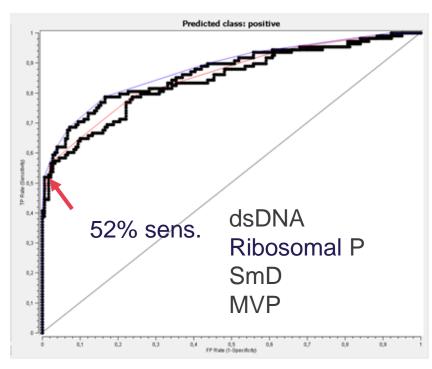
Scl70

VisRank plot of antigens and samples



Anti-MVP improves Sensitivity and Specificity of Marker Panels





Naive bayesLogistic regression

At 98% specificity 6% increase in sensitivity by adding MVP without loss of specificity



Summary

- High content autoantibody screening reveals multiple novel antigens
- MVP is a specific SLE antigen with prevalences of 17-30%
- MVP biology links this novel autoantibody to IFN-I biology and viral infections
- Anti-MVP defines a subgroup of SLE Patients with little overlap to other specific SLE autoantibodies (dsDNA, anti-ribosomal P, SmD)
- More studies are underway to investigate the disease characteristics of this SLE subgroup

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