protagen DIAGNOSTICS

The NavigAID concept: subgrouping of autoimmune diseases to assist clinical trials in rheumatic diseases

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BioM

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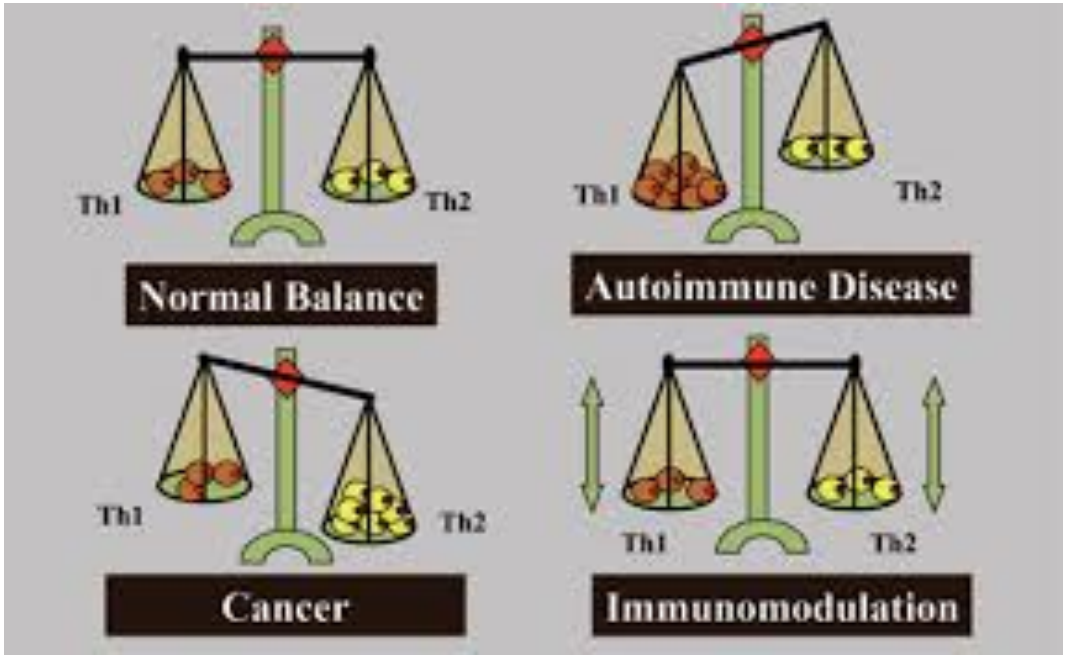
Today´s Situation in Autoimmune Therapy

- Established, 2nd most important drug development market with significant annual growth rate
- Novel autoimmune drugs will drive future pharma business
- Unmet medical and diagnostic need
- Clinical scores dominate guidelines and therapy decisions
- Limited number of diagnostic tests, only one CDx
- New markers required to define subgroups

- **Patient stratification is key to success**

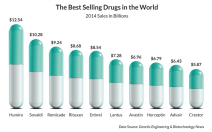
Autoimmune Diseases



Autoimmune Diseases and Cancer, in particular Immuno-Oncology, are inter-dependent….

Immune System profiling is a tool to measure that inter-dependence!

Autoimmune Diseases & Immuno-Oncology



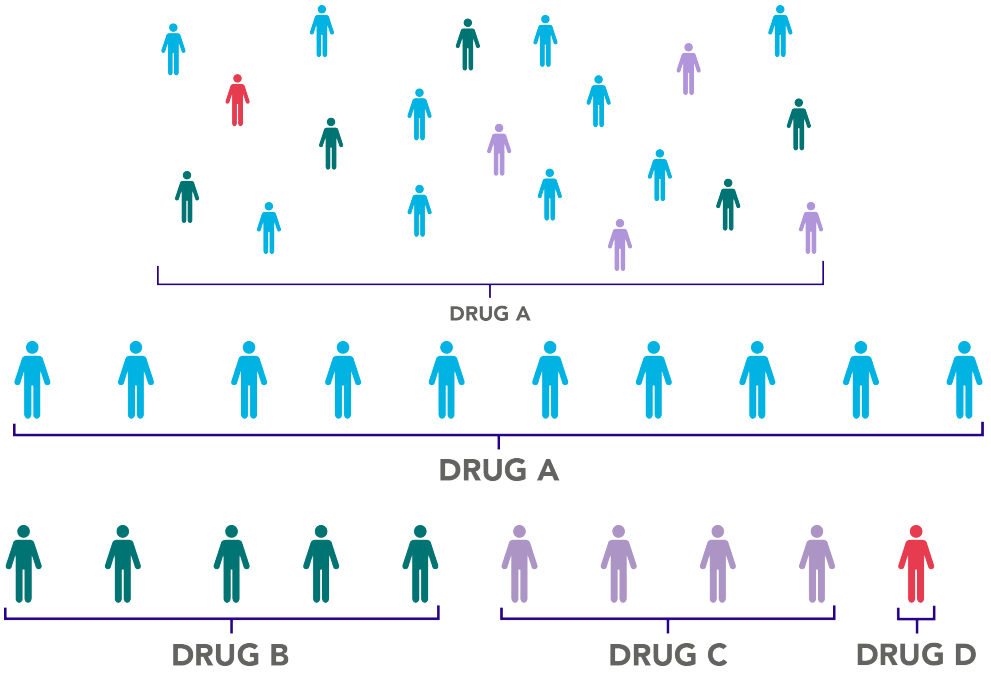
- The 2 most important pharma markets today
- Directly linked markets that are in need of novel biomarker strategies
- High prevalence (1 out of 3), low responder rates (20-50%) and spiraling health care costs (100 billion US$ annually for autoimmune only*)
- 4 of the TOP10 Best Selling Drugs in the World are used in autoimmune indications but no CDx in autoimmune today, limiting therapeutic options
- Precision Medicine by definition relies on biomarkers and by reality is hampered by the lack of it

Immune System profiling provides a solution outside Next Generation Sequencing

*http://www.aarda.org

Addressing the CDx Needs

Today‘s world

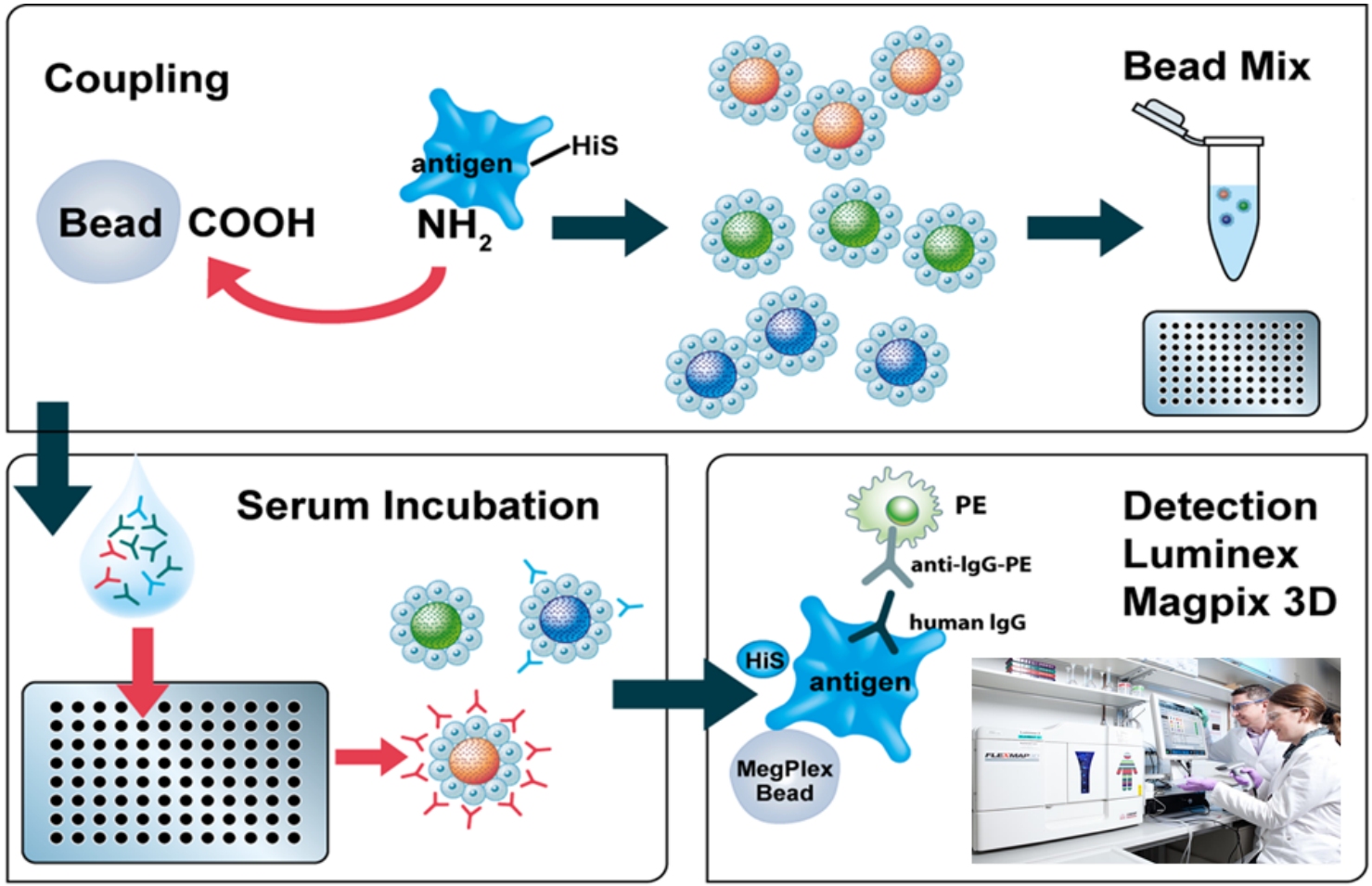


Disease stratification leads to targeted Tx development in autoimmune diseases & immuno-oncology

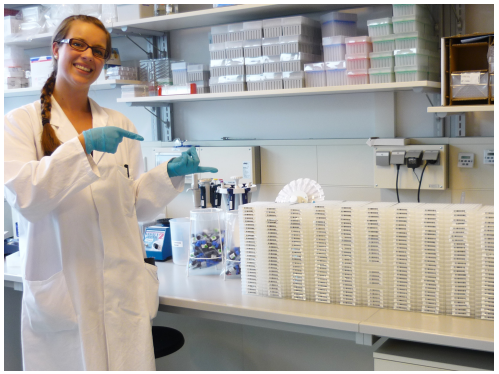
Game Plan

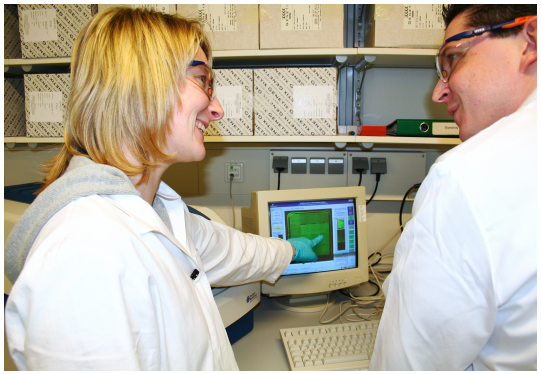
- High performance “omics” discovery of novel autoantibodies
- Partner with high class academia
- Harvest through many Autoimmune Diseases and stratification needs
- Establish Immune System Profiling in Immuno-Oncology
- Develop novel Diagnostics
- Support Pharma drug development

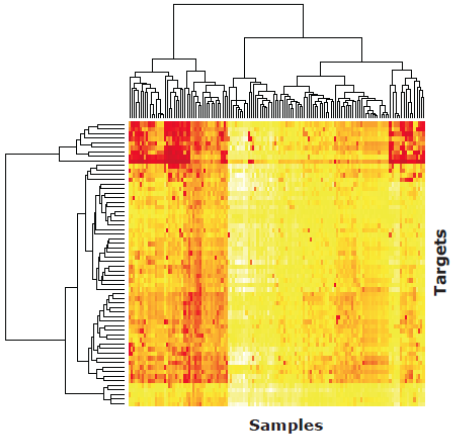
The Technology - SeroTag®



Screening of serum samples



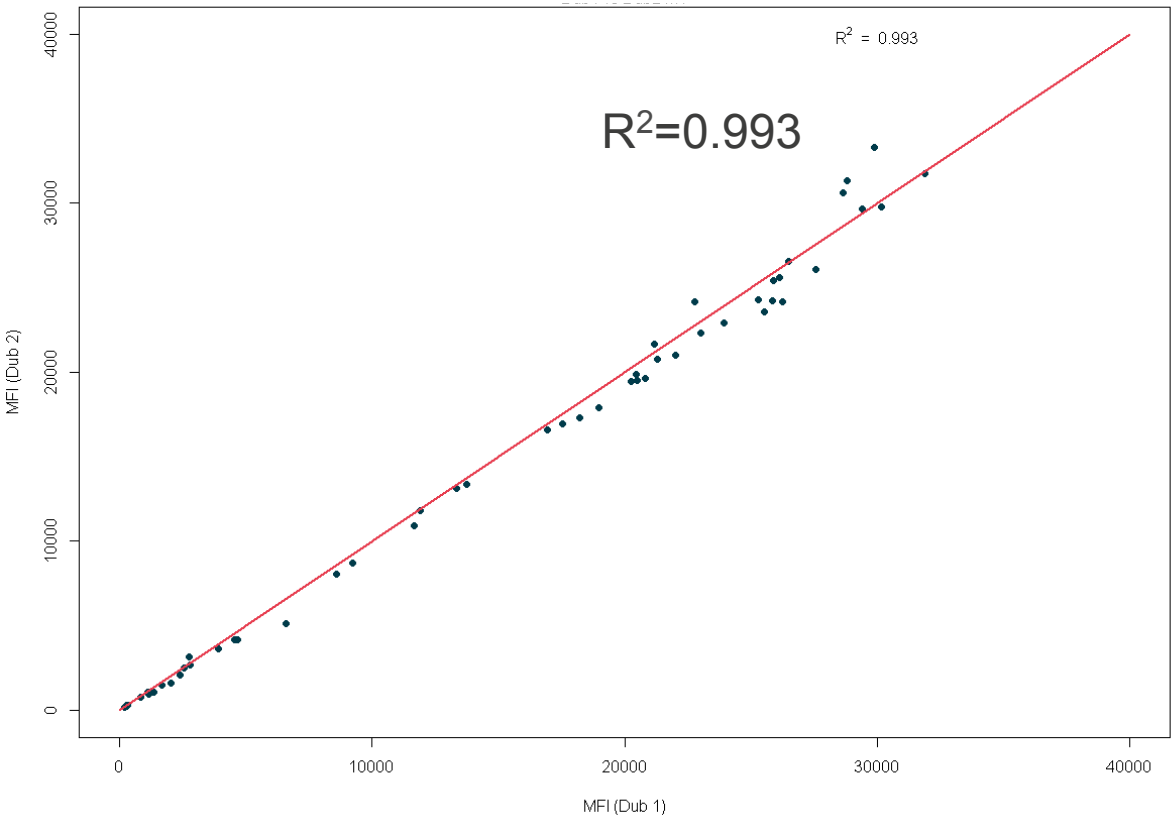


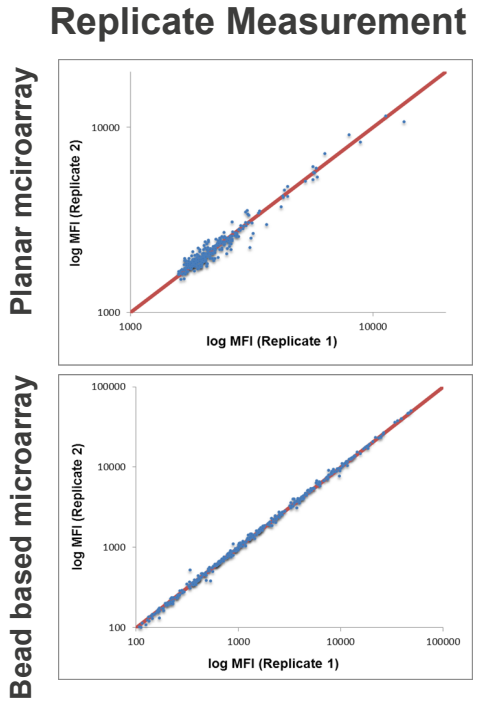


Raw data output

Sample capacity: 8 – 2,000 sera
Performance: ~ 5% repeatability
1 – 8,000 antigens (in sets)

Technical Quality: Sensitivity, Reproducibility, Dynamic Range

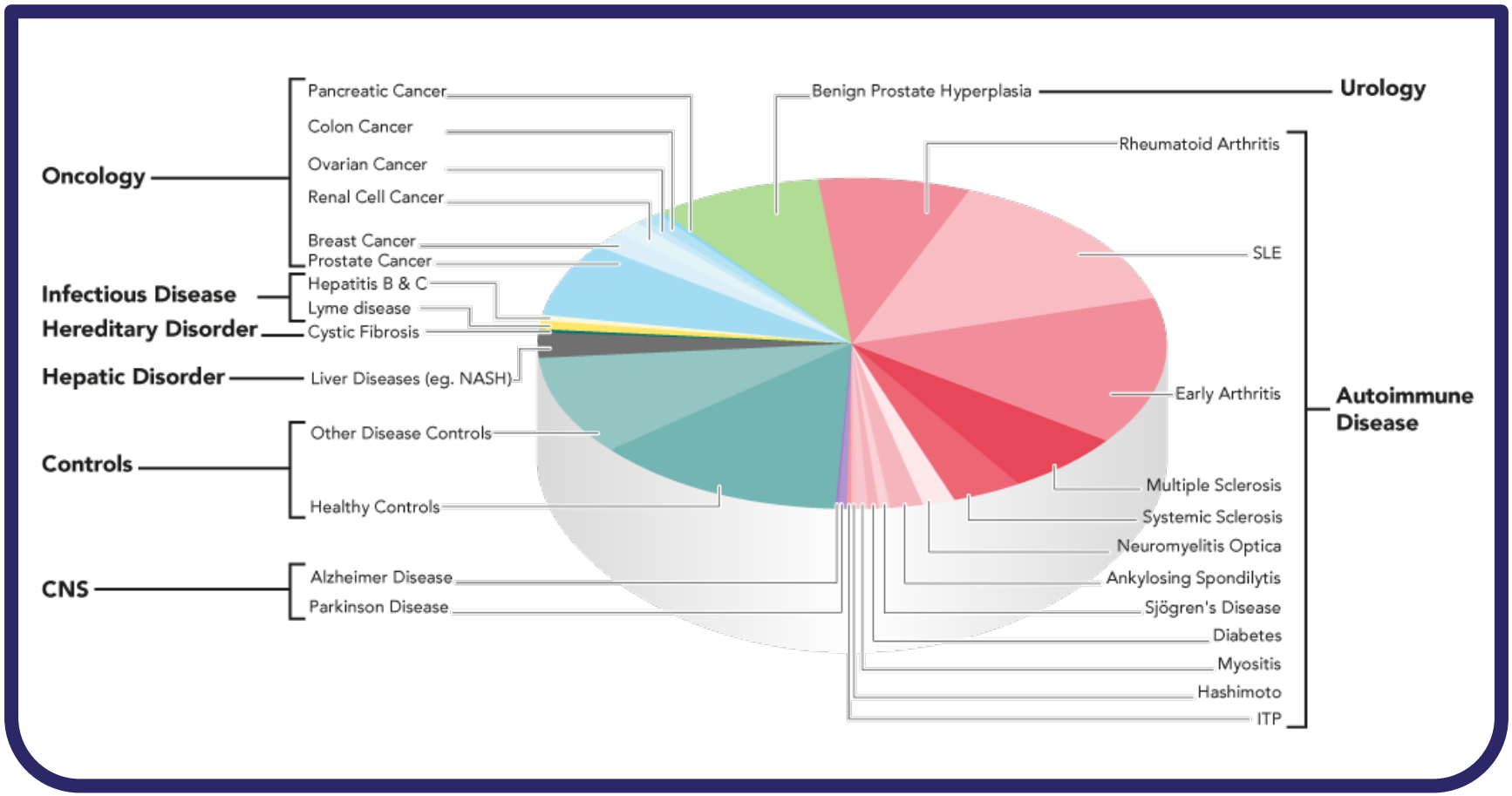




Left: Scatterplot of TROVE2 antigen obtained for duplicate 1 (x-axis) versus duplicate 2 (y-axis) for 50 rheumatic disease samples
Data were from routine study setup with 400 different antigens as multiplex
Right: comparison of a 400plex planar microarray (top) to Luminex bead based array (bottom) demonstrating technical superiority for bead based arrays

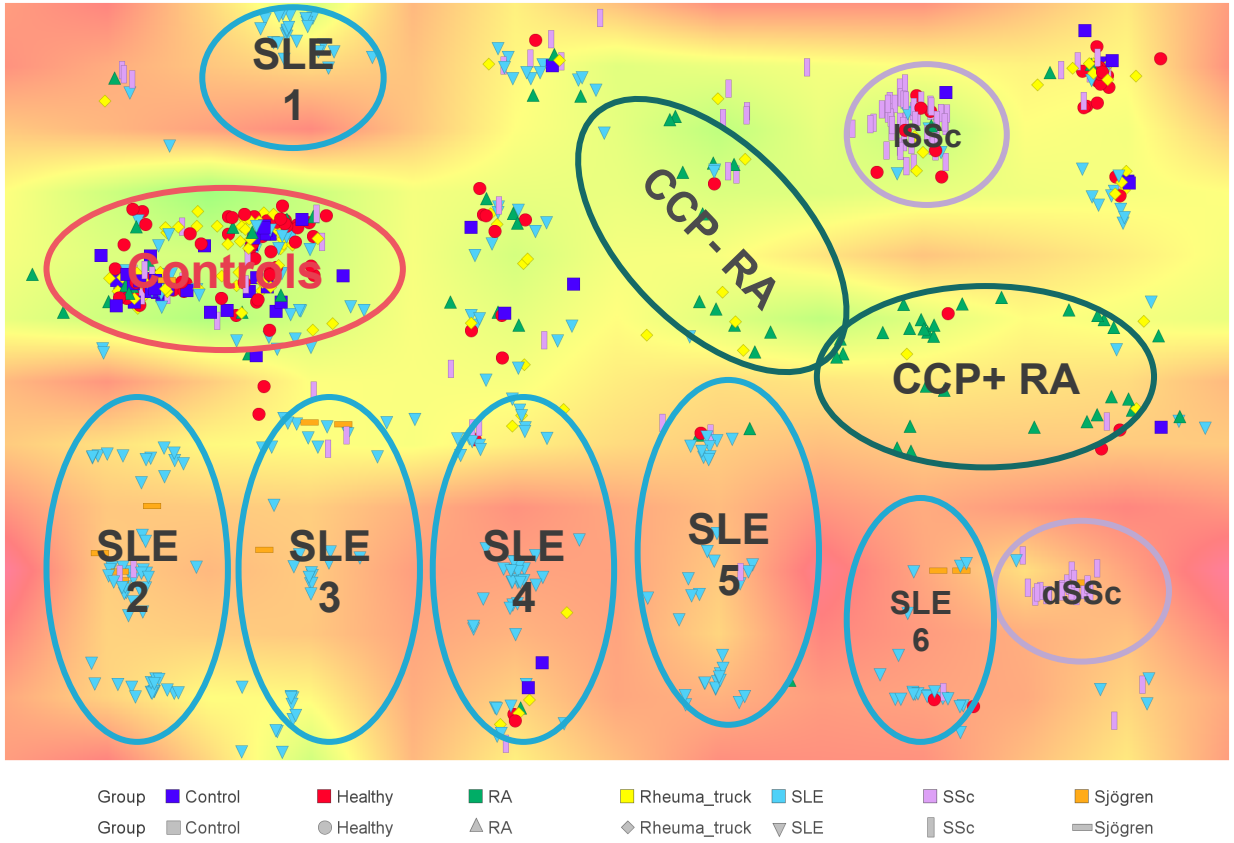
The Protagen Experience

Therapeutic Areas and Samples Tested



A total of more than 14,000 patient samples from numerous therapeutic areas and indications were tested to date.

Refining the Autoimmune Landscape



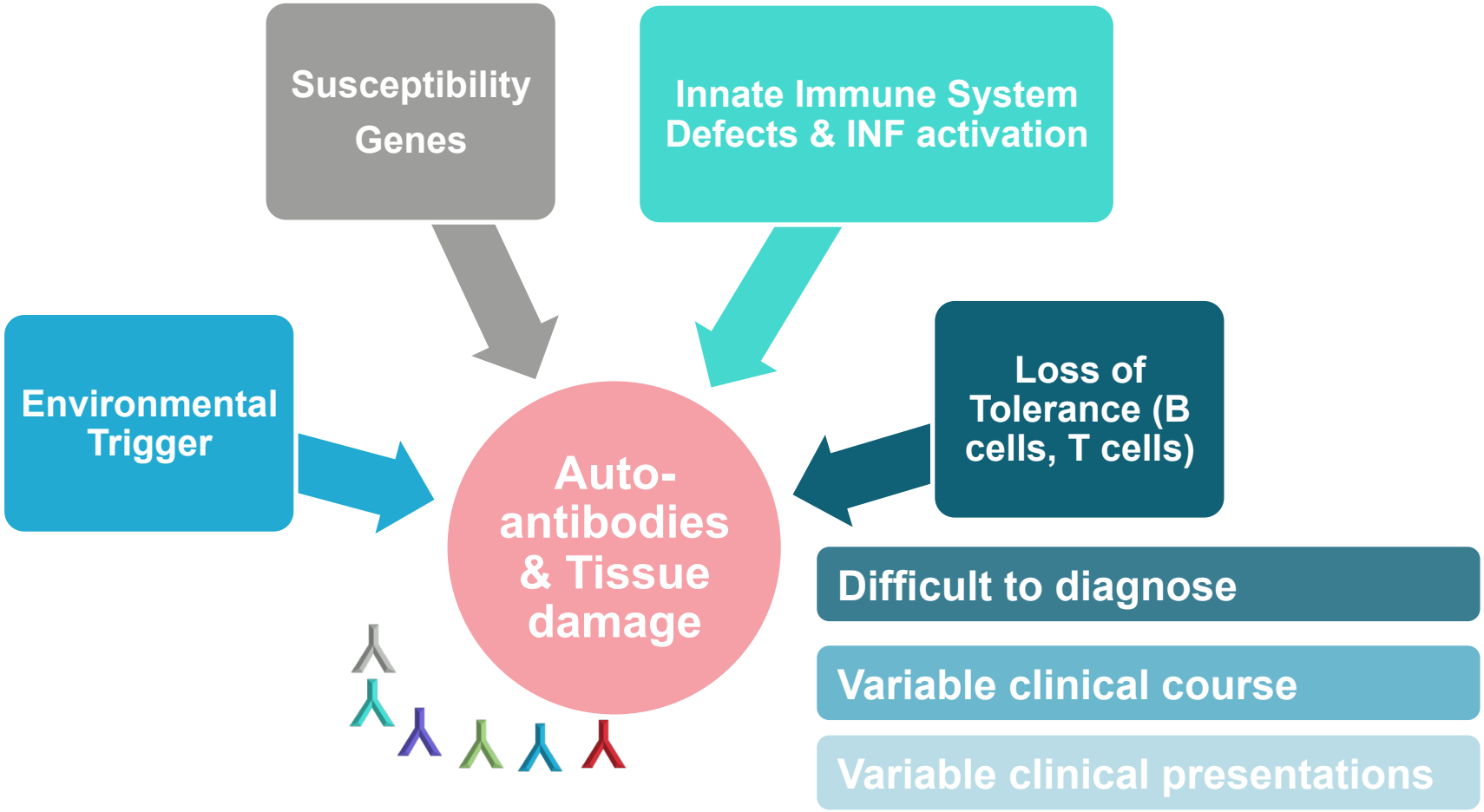
Kohonen maps (SOM) produce a low-dimensional representation of the input space of the training samples called a map. Similar samples are placed next to each other.

SOM: 27 selected markers from SLE, SSC, RA portfolio

6 x 6 Topology: Mexican hat, „Rifts“ in red

Autoantobodies create a landscape of autoimmune diseases with specific disease clusters

Challenges in the Development of SLE Drugs



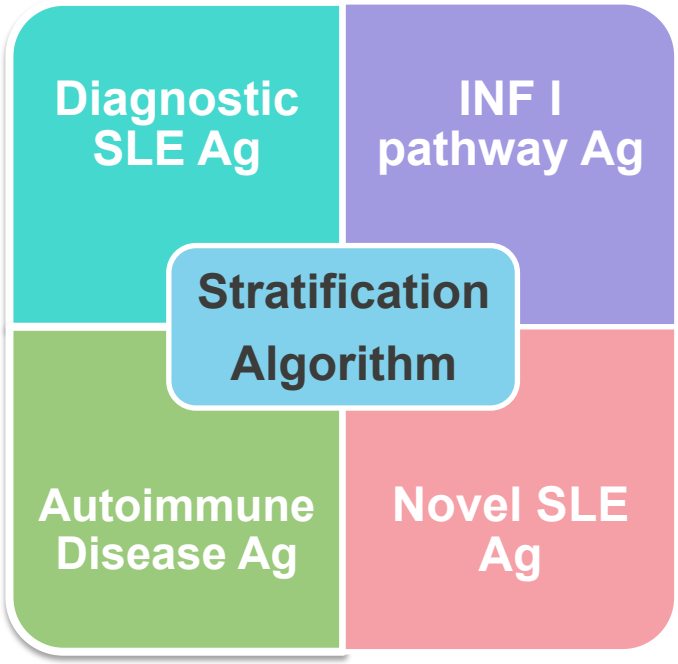
Can we define more homogeneous SLE patient populations?

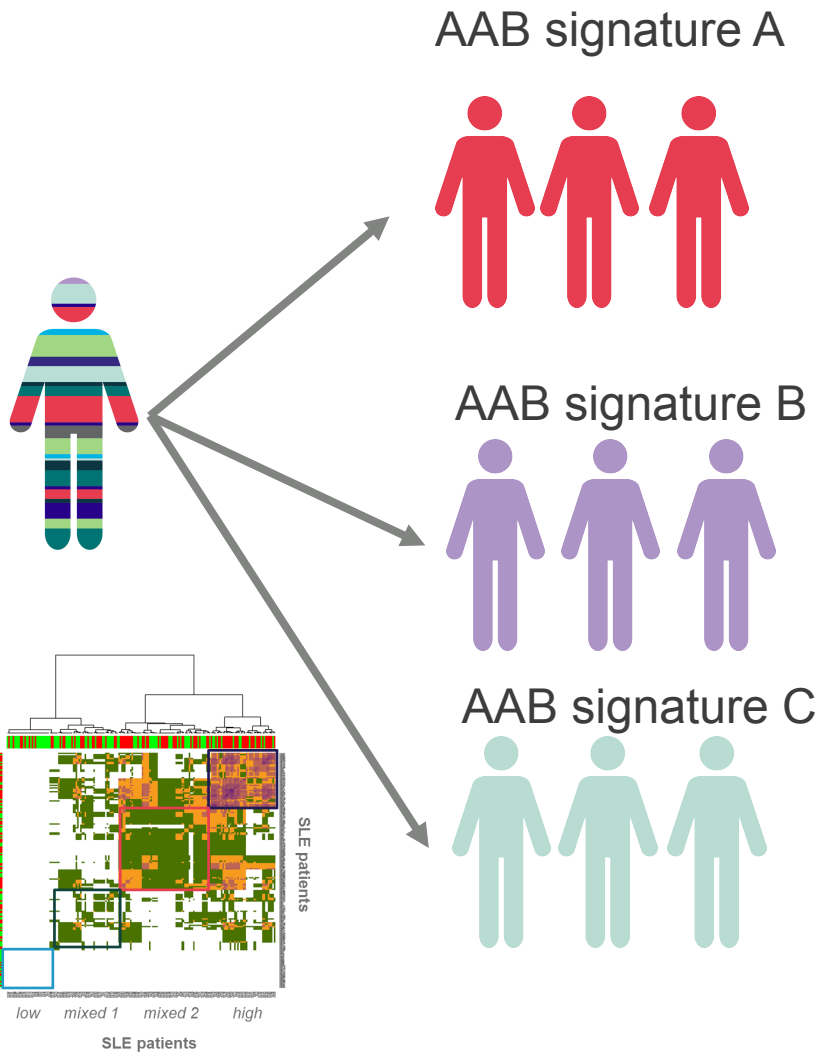
Protagen NavigAID SLE

Questions and Tasks (Pharma, Biotech, KOL)

- Can we ensure enrollment of an appropriate SLE patient population?
- Can we identify patients with high disease activity and/or an SLE specific IFN-1- inducible signature?
- Can we diagnose/predict SLE associated organ damage?
- Is it possible to stratify SLE into different subgroups?

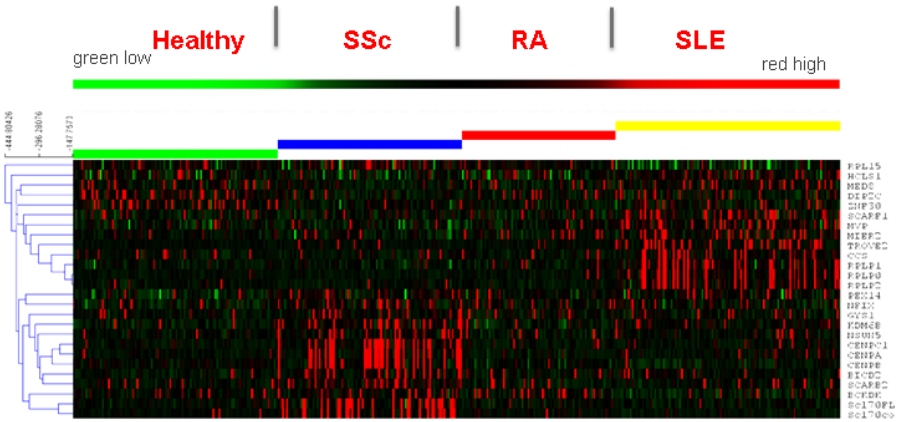
The new SLE Stratification Array



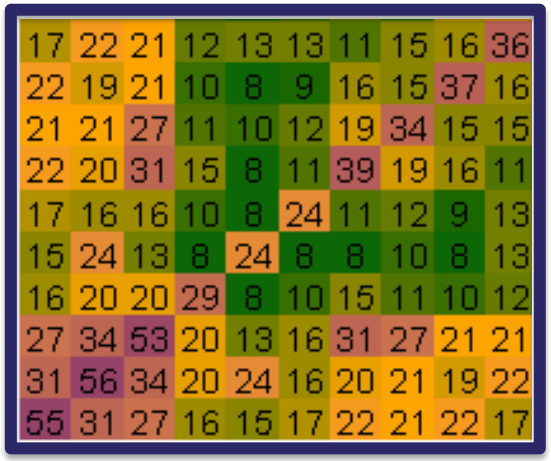


From Single Marker to Patient Subgroups

Classical Approach:
Heatmap of single marker

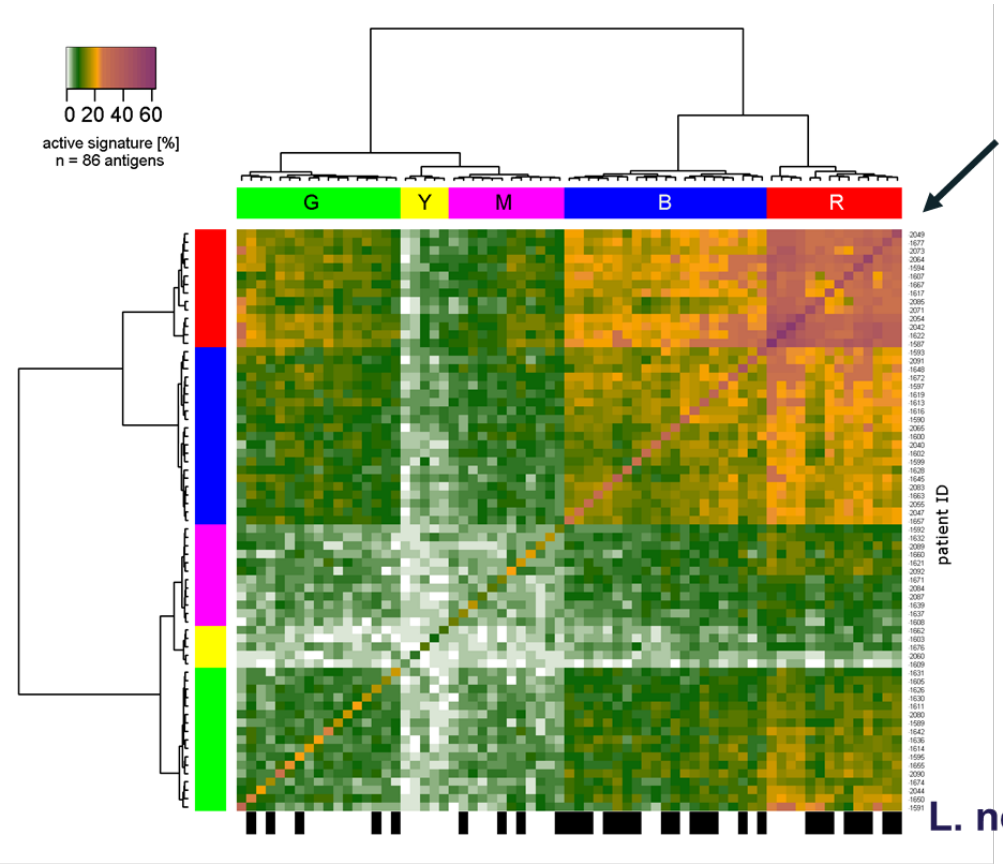


Heatmap of autoantibody prevalence



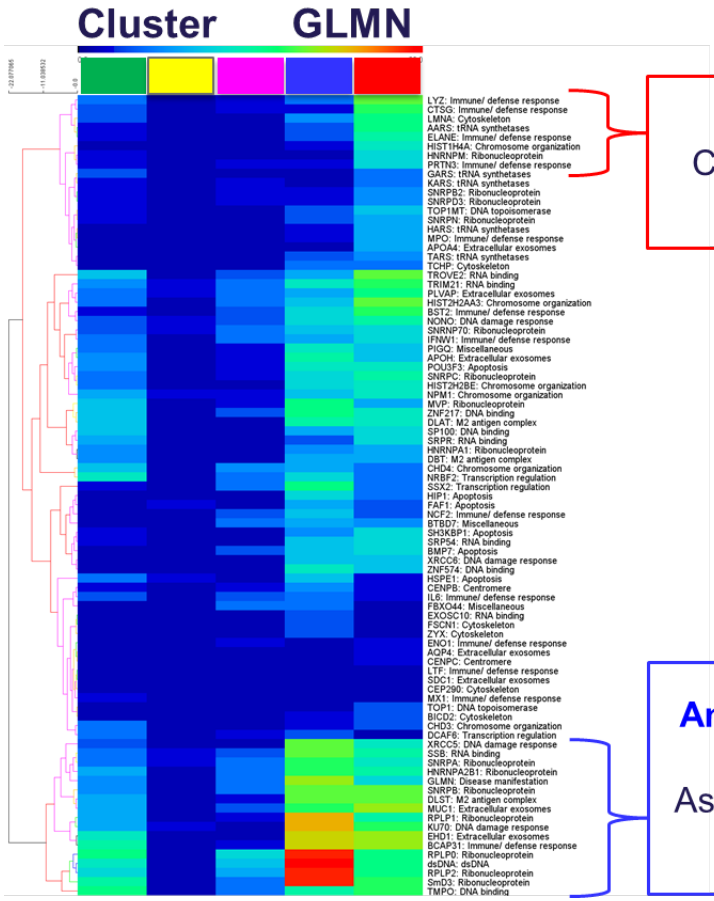
1. Quantitative autoantibody analysis
2. Overlap of autoantibody reactivities for co-prevalence assessment
3. Autoantibody signature per patient is calculated
4. Patient clustering by autoantibody reactivity

Shared Autoantibody Reactivity in SLE



- 5 distinct SLE subgroups with diverse reactivity profiles
- 70% of patients with Kidney damage have a similar autoantibody portfolio

Small Autoantibody Sets define Clusters linked to clinical Phenotypes

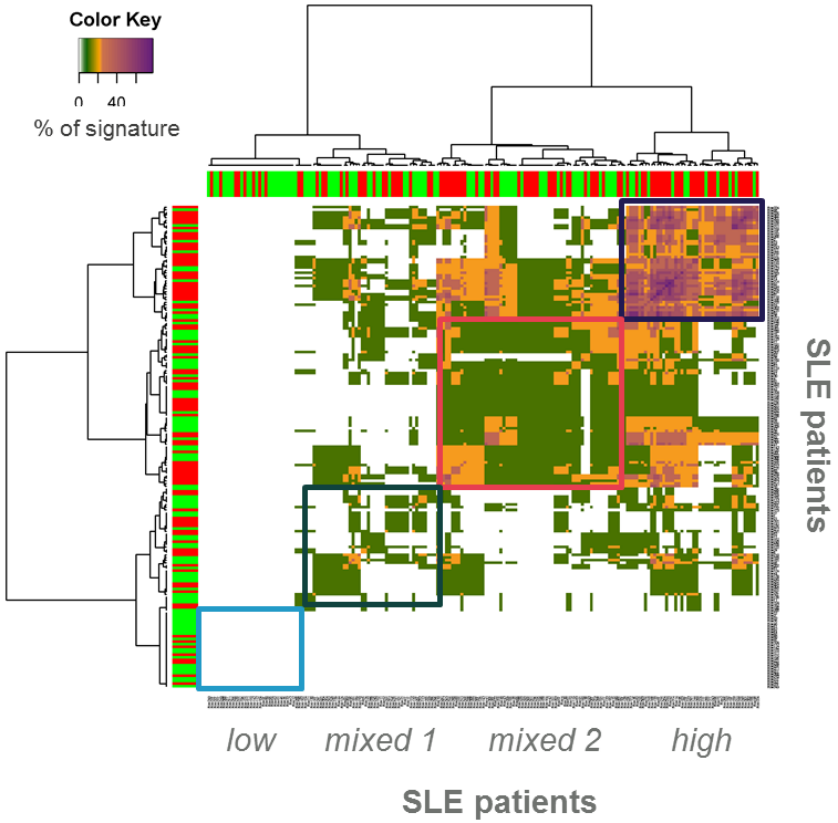


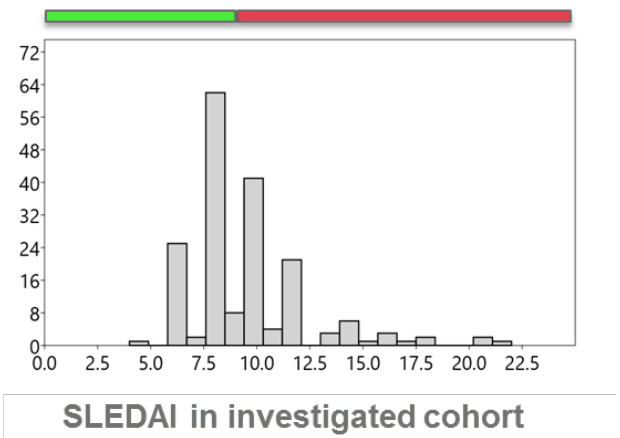
ANCA-associated glomerulonephritis
Cluster "red", shows unique reactivity to ANCA antigens (LYZ, CTSG, ELANE, PRTN3)

GLMN splits into 2 cluster with different autoantibody reactivity profile

Anti-dsDNA and immune-complex associated glomerulonephritis
Associated with dsDNA, ribosomal P, SmD, MVP, but ANCA negative

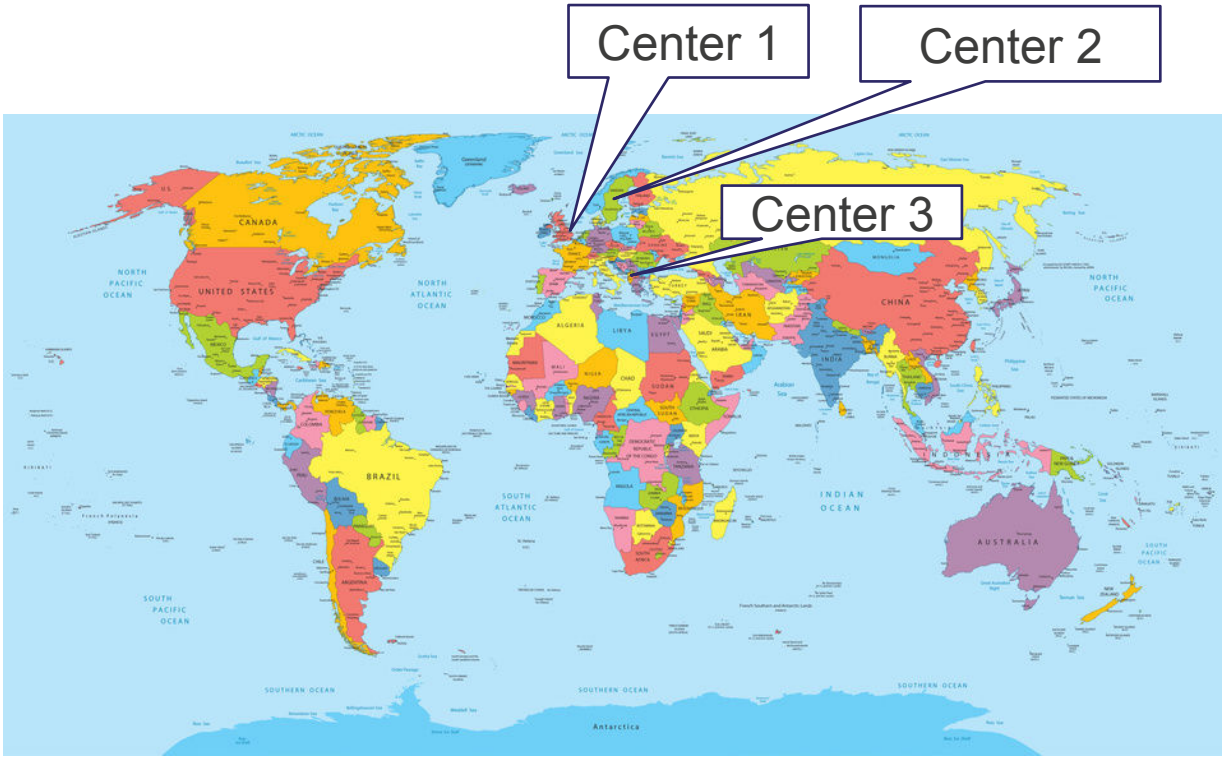
Autoantibodies to Interferon-Pathway Antigens: increased Disease Activity





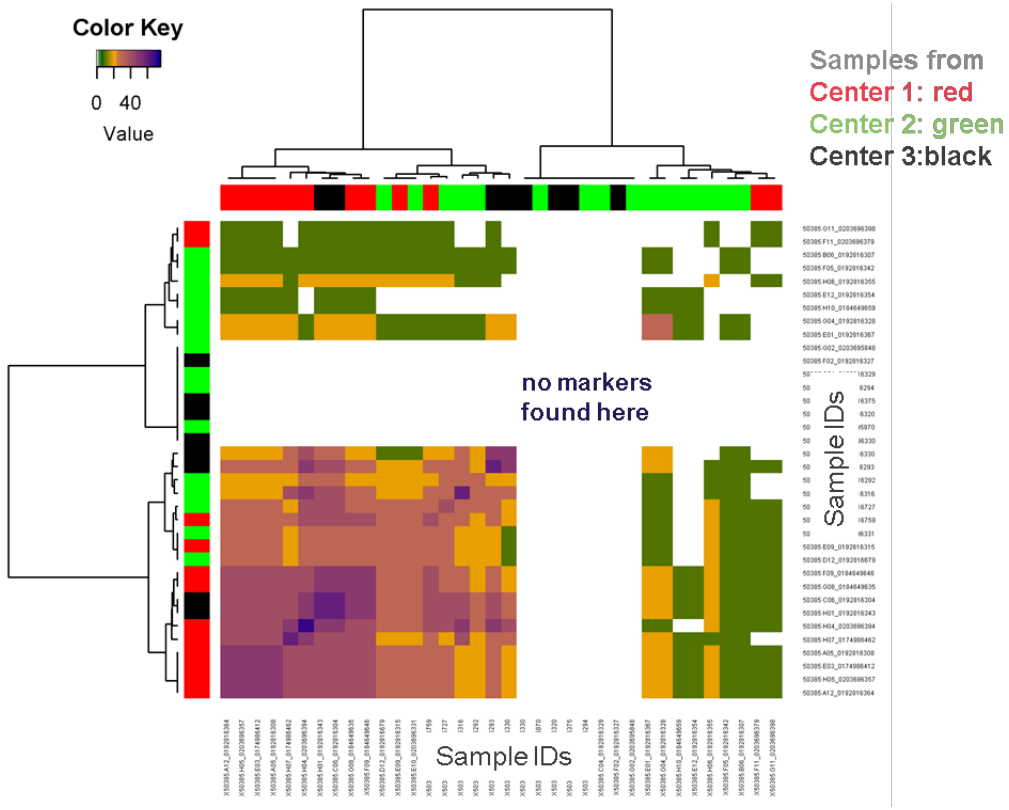
Subgroups of patients show distinctly different AAB reactivities to Interferon pathway antigens

Outlier Detection: Phase I Case Study



- 18 patients treated with investigational compound or placebo
- Samples enrolled by three study centers

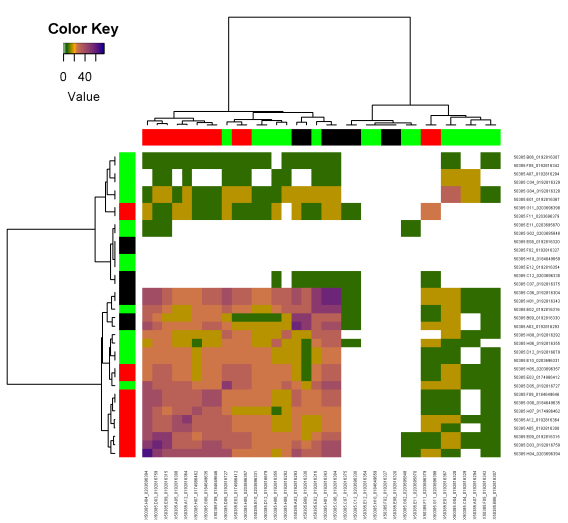
Diagnostic Signature: Is this SLE?



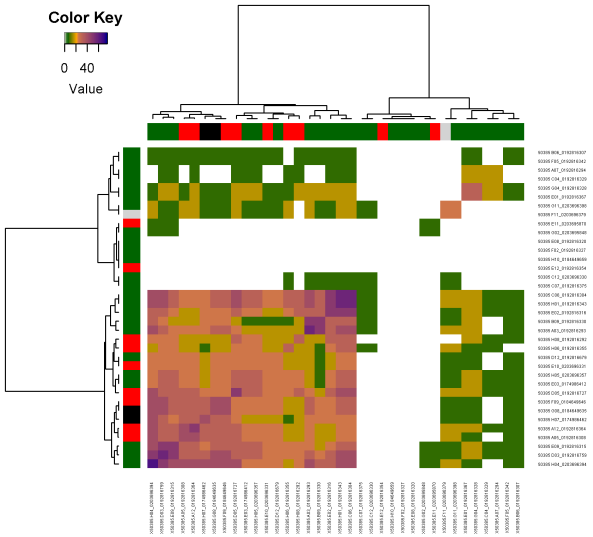
- A subset of samples has no reactivity against specific SLE antigens
- Patients form clusters according to centers, illustrating reactivity bias

IFN Signature Antigens and Disease Activity

Samples from
Center 1: red
Center 2: green
Center 3:black



Samples with
SLEDAI no activity: gray
SLEDAI mild: black
SLEDAI moderate: green
SLEDAI high+: red



- Center 1 provided more patients with high Interferon antigen reactivity typical for moderate /severe SLE samples
- Center 3 provided low reactive SLE samples

Protagen NavigAID SLE

Questions and Tasks (Pharma, Biotech, KOL)

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- ✓ Can we identify patients with high disease activity and/or an SLE specific IFN-1- inducible signature?
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Summary

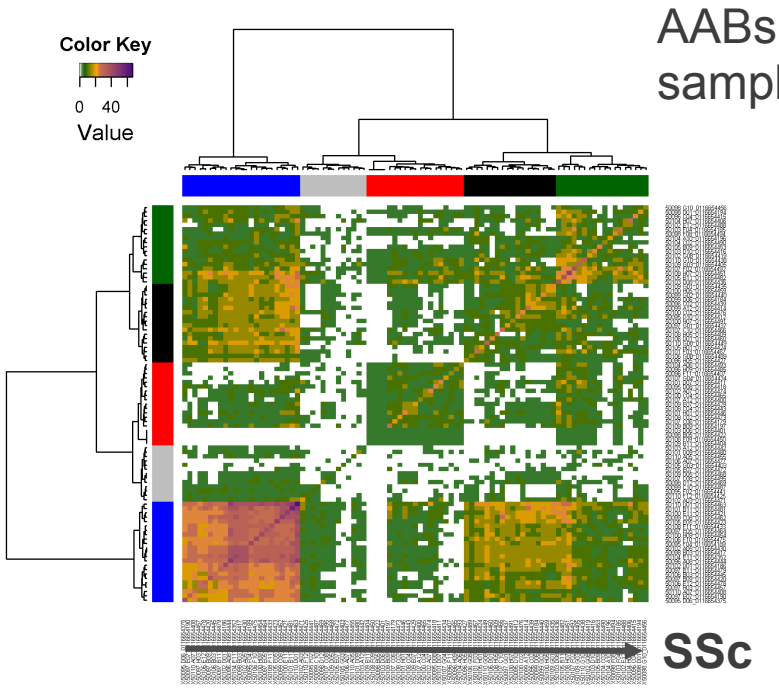
High content autoantibody analysis in SLE leads to

- **Improved differential diagnosis and outlier detection**
- **Subgrouping of patients based on**
  - **Response to Treatment**
  - **Adverse Events**
  - **Association with organ damage**
  - **Association with IFN I biology**
  - **Disease activity**
  - **Patient reported outcomes**

4 of TOP10 Pharma already use our approach

Further NavigAID panels to come

- NavigAID SSc
- NavigAID RA
- NavigAID SjS



What if the FDA decides tomorrow that all new approvals in autoimmune diseases & immuno-oncology require a CDx?

Thanks to our collaborators

- CAPEA (M. Schneider, HHU, Düsseldorf, D)
- HIT HARD (G. Burmester, Charitè, Berlin, D)
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- RA-MAP (J. Isaacs, Newcastle, UK)
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