Thorough Bio-characterization of Autoimmune Disease Patients Yields Unique Insights into Unmet Medical Need

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Momenta - Creating Value Through Scientific Capabilities

Thorough Structural Characterization

High resolution physicochemical analytics platform to thoroughly characterize any product

Control of Manufacturing

Understanding the nonlinear chemical and biosynthetic reactions that drive production

Thorough Biological Characterization

High resolution biology applied pre-clinically and in clinical settings

Biosimilars to

- HUMIRA®
- ORENCIA®
- Five additional biosimilars in development

Novel Drugs

- Necuparanib - oncology in Phase 2
- 3 novel autoimmune drugs:
  - hsIVIg
  - SIF3
  - Anti-FcRn

ANADA Generics

- Generic LOVENOX®
- Glatopa® (Generic daily COPAXONE®)

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We Avoid Complexity Even Though We Know It Will Catch Up With Us

• **Very, very** few human diseases are driven by a single pathway
  • Success or failure of our drugs will depend on many aspects of biology
  • Most will become part of multi-drug regimens when actually used

• **Many drugs fail** for reasons we rarely understand before we get to late stage trials
  • Genotypic or phenotypic variations
  • Metabolic or disease state variations
  • Delivery limitations

We are applying precision medicine tools to develop the right drug for the right patient
Applying Patient Biocharacterization to Drug Discovery & Development

- Identify molecular signatures associated with unmet need using human samples

- Replicate and expand findings across indications to identify addressable patient population

- Identify drug targets based on molecular signatures associated with unmet need

- Identify drug candidate and companion biomarkers

- Use the signatures during development for patient selection & outcome measure
The Glatopa Story

~10^{29} theoretical chain structures spanning varied lengths; MOA unknown

- Physical Chemical: 47,000 tests. 15 elements of biology to be measured
- Bio Characterization
- Final Analytic Set: >60 methods
- Process Development
- ANDA Submission: ~10,000 pages

FDA Approval!
Momenta’s Approach to Deconvoluting Complexity

Momenta has developed a powerful engine—not unlike other companies, but differentiated by our core know-how of deconvoluting complexity—resulting in unique, actionable insights into new healthcare solutions.

- Identify / Access Dynamic Biological Systems *(drug, patient, etc.)*
- Measurement Science *(orthogonal and select targeted analytics)*
- Multi-Omics Data Points
- Analytical Insights *(Signatures)*
- Data Integration and Analysis
- Validation and Interpretation
High-Resolution Analytics for Understanding Complexity

Key principles:

1. **Application of orthogonal analytics (What to measure)**

2. **Finding the signal (Where to measure)**
   - Average properties, while important, do not capture the microheterogeneity of the complex system
   - Signatures can be buried by average properties
   - Fractionation / filtering / sub-setting is a key part of identifying signatures

3. **Data integration and analysis (How to interpret)**
Approaches to Patient Biocharacterization: 
*Single- versus Multi-Omic*

Today, most companies approach target and biomarker discovery through large-scale genomic research; Momenta has adopted a different approach.

**Large-Scale Genomics**
- Target Identification
- Lower quality/level of insight from single approach

**Small-Scale Multi-Omics**
- Target Identification
- Higher quality/level of insight from multiple/orthogonal approach
We have applied our knowledge/expertise and the same approach we took with complex generics and biosimilars to measure signatures in human biology.

- “Sub-populations” amplify key signatures
- Gets averaged out in heterogeneous sample

- SLE Blood Study
- Vaccination Study
- Kawasaki’s Disease Study
- Rheumatoid Arthritis Study
Study Design
Study of immune response during vaccination with Pandemrix, the H1N1 swine flu vaccine.

Goals
1. Understand the molecular and cellular evolution of response to vaccination
2. Examine the factors involved in non-response to vaccination.

Vaccination

Product Attributes + Host Attributes → Immunologic Consequences

Nature Immunology 17, 204-213 (2016).
H1N1 Vaccination Leads to Early and Reversible Changes
Multivariate analysis uncovered a pronounced age effect in Day 1 response to vaccination and more subtle differences at day 0 and 7.

No significant age effect
Non-responders did not show elevated levels of B-cells at Day 7

Individual Patient Data Analysis (IPDA) uncovered the fact that there are several routes to non response. There is no one “non-responder signature”.
Characterizing Human Immune Response Dynamics

Adjuvanted influenza-H1N1 vaccination reveals lymphoid signatures of age-dependent early responses and of clinical adverse events

Olga Sobolev1−3,10, Elisa Binda1−3,9,10, Sean O’Farrell1−3, Anna Lorenc3, Joel Pradines4, Yongqing Huang4, Jay Duffner4, Reiner Schulz3,5, John Cason6, Maria Zambon7, Michael H Malim3,6, Mark Peakman1−3, Andrew Cope3,5, Ishan Capila5, Ganesh V Kaundinya5 & Adrian C Hayday1−3

Adjuvanted vaccines afford invaluable protection against disease, and the molecular and cellular changes they induce offer direct insight into human immunobiology. Here we show that within 24 h of receiving adjuvanted swine flu vaccine, healthy individuals made expansive, complex molecular and cellular responses that included overt lymphoid as well as myeloid contributions. Unexpectedly, this early response was subtly but significantly different in people older than ~35 years. Wide-ranging adverse clinical events can seriously confound vaccine adoption, but whether there are immunological correlates of these is unknown. Here we identify a molecular signature of adverse events that was commonly associated with an existing B cell phenotype. Thus immunophenotypic variation among healthy humans may be manifest in complex pathophysiological responses.

* Nature Immunology 17, 204 -213 (2016).

How to identify a bad vaccine reaction before it happens

news.sciencemag.org

A new study uncovers immune "signatures" that predict side effects to a flu shot
In a recent RA study, unique value came from Momenta’s combined targeted and multi-omic measurement approach.

<table>
<thead>
<tr>
<th>Analytic</th>
<th>Method</th>
<th>Biological Aim</th>
<th>Measure Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>**Gene Expr/</td>
<td>NextGen Sequencing (RNA-Seq)</td>
<td>Pathways, Cell populations active in whole blood cells including IFN signature; FcR’s; NFkB, Stat signaling</td>
<td>&gt;4,600,000</td>
</tr>
<tr>
<td>Gene Variants</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Proteomics</strong></td>
<td>Shotgun method on abundant plasma protein-depleted fraction</td>
<td>Moderate abundance plasma proteins including those assoc. with inflammation, acute phase proteins, complement, IgA, IgM, coagulation, cell migration, ECM breakdown</td>
<td>&gt;110,000</td>
</tr>
<tr>
<td><strong>Glycomics</strong></td>
<td>Glycopeptide – IgG, abundant plasma proteins</td>
<td>Identify patterns of glycosylation vs other clinical and disease biomarker changes in disease. IgG Fc sialylation/galactosylation associated with disease in multiple autoimmune diseases.</td>
<td>&gt;6,000</td>
</tr>
<tr>
<td></td>
<td>Total glycan – abundant plasma protein-depleted</td>
<td>Glycosylation of moderate abundance plasma proteins including acute phase proteins, migration associated proteins</td>
<td>&gt;3,000</td>
</tr>
<tr>
<td></td>
<td>FcR glycans</td>
<td>Evaluate glycosylation profiles of Fc-receptors</td>
<td>&gt;3,000</td>
</tr>
<tr>
<td><strong>Drug Exposure</strong></td>
<td>Drug Level/ADA</td>
<td>Measure and control for this major determinant of nonresponder</td>
<td>&gt;200</td>
</tr>
<tr>
<td><strong>Immuno-assay</strong></td>
<td>RayBio Quantitative Array</td>
<td>Measure low abundance plasma cytokines, chemokines, soluble receptors, ECM components</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td></td>
<td>ST6 ELISA</td>
<td>Inflammation-, acute phase- and sialylation-associated plasma protein which may associate with sialylation of cells or proteins in distant tissue or in circulation</td>
<td>&gt;100</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>&gt;40K analytes per patient sample</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>&gt;4,800,000</td>
</tr>
</tbody>
</table>
RA Study Insights:
*Anti-TNF Treatment Signature*

Analysis of complex data sets led to an anti-TNF treatment signature.

- Several RA relevant genes are part of this signature
- Good correlation of Momenta’s anti-TNF response signature to published study
RA Study Outcomes: Multiple Approaches Generate Key Insights

The top two signatures Momenta identified from the recent RA study were detected by non-genomic measurements only.*

<table>
<thead>
<tr>
<th>Signatures in Non-Responders</th>
<th>Genomic (RNA-seq)</th>
<th>Proteomic (Shotgun &amp; Targeted)</th>
<th>SNP analysis</th>
<th>Glycan and Glyco-proteomic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature A</td>
<td></td>
<td></td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Signature B</td>
<td></td>
<td></td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Signature C</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Signature D</td>
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<td></td>
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</tr>
<tr>
<td>Signature E</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* Signal / signature detected  
† Signal / signature not detected
RA Study Insights: Response/Non-Response Signature

The combination of several haplotypes is indicative of a signature of response and non-response.

Initial finding from glycomics and supported by proteomics

Polymorphism in C increases segregation of non-responders

These haplotypes constitute 48% of the non-responders

These haplotypes captures 73% of all non-responders

Delta DAS28

A + B

Non-responders
Responders

p-value = 0.006004

Non-responders
Responders
Momenta’s insights from the recent RA study represent potential for a novel test to identify responders to anti-TNF therapy in rheumatoid arthritis.

- Currently there exist no diagnostics that enable effective identification of patients who will or will not respond to anti-TNF treatment.
- Combination of analytes from different platforms in the RA study provide an ability to identify non-responders to Anti-TNF treatment.
- Metrics are comparable to other tests (see Table 1) in this area, although not for the same purpose.
- We are working to add genetic polymorphisms to attempt to further improve this test set.

### Table 1. Sensitivity and Specificity of RF, CCP, and 14-3-3ζ Biomarkers for Detecting RA

<table>
<thead>
<tr>
<th>Markers</th>
<th>Early RA (n=99)</th>
<th>Established RA (n=135)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Only RF+</td>
<td>57</td>
<td>85</td>
</tr>
<tr>
<td>Only CCP+</td>
<td>59</td>
<td>99</td>
</tr>
<tr>
<td>Only 14-3-3ζ+</td>
<td>64</td>
<td>93</td>
</tr>
<tr>
<td>RF+ and/or CCP+</td>
<td>72</td>
<td>84^b</td>
</tr>
<tr>
<td>14-3-3ζ+ and/or RF+</td>
<td>78</td>
<td>78^b</td>
</tr>
</tbody>
</table>

^a Comparison with healthy controls.
^b For multi-marker tests in which a positive result in any of the markers leads to a positive result for the overall test, specificity declines relative to tests of the individual markers.
Conclusions

• High-resolution analytics can be applied to humans from diverse clinical settings to yield deep insights into disease biology and drug response

• This approach allows the classification of disease and drug response at the molecular and personalized level

• This technology has the potential to:
  • Enable the development of improved therapeutics to meet unmet medical needs
  • Enable personalized care for individual patients
  • Improve the drug discovery & development success rate