Embracing Complexity: Understanding IVIg to Rationally Design Novel Therapeutics

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VP Research
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• The Momenta approach to product development

• Application to intravenous immunoglobulin (IVIg) and autoimmune diseases

• New products that may deliver enhanced benefit to IVIg
  • Sialylation of IVIg
  • Sialylation of recombinant IgG’s
  • Recombinant products
Momenta Embraces Complexity
Three Critical Components to Deliver Medicines

Thorough Structural Characterization
High resolution physicochemical analytics platform to fully characterize any product

Control of Manufacturing
Understanding the nonlinear chemical and biosynthetic reactions that drive production

Thorough Biological Characterization
High resolution biology analytics platform to fully characterize any product in non- and clinical settings

ANDA Generics
- Generic Lovenox®
- Generic Copaxone® (under FDA review)

Biosimilars & Potentially Interchangeable Biologics

Novel Drugs
- M402 oncology Phase 1

SANDOZ

Baxter
Momenta has Extended this Approach to IVIg and Autoimmune Diseases

**Complex Mixture Drugs**
Intravenous Immunoglobulins

- IgG fraction derived from pooled plasma of ~10K donors
- Approved therapy for PID and 5 inflammatory diseases; used in ~100 other indications
- Poorly characterized mixture and MOA debated

**Complex Diseases**
RA, Lupus, Psoriasis, etc

- Dysregulation of complex immune system underlies >100 distinct diseases
- ~50M Americans affected
- Significant unmet needs despite recent advances
IVIg Is An Important....but Poorly Understood Anti-inflammatory Therapeutic

Widely Used as an Anti-inflammatory

Poorly Understood MOA

Source: GBI Research, Review of Australia's PFA 2007
Thorough Physicochemical Characterization Defines IV Ig Composition
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Number of distinct data readouts in characterization of IVIg lots

Data Readouts

EU Pharmacopeia | Momenta
---|---
21 | >500

- IgG isotypes
- IgG1 Fc glycoforms
- IgG2 Fc glycoforms
- IgG3 Fc glycoforms
- IgG4 Fc glycoforms
- IgG2 disulfides
- IgG4 mixed antibodies
- IgG allotypes
- IgG Fc glycoform asymmetry
- Conformational aggregates
- Anti-idiotypic Ab complexes
- Glycation
- IgG1 Fab glycoforms
- IgG2 Fab glycoforms
- IgG3 Fab glycoforms
- IgG4 Fab glycoforms
- Deamidation
- Oxidation
- Glycation
- Distribution of antigen specificity
- Non-IgG proteins

........
Thorough Biocharacterization Defines IVIg Mechanism of Action

Combination of orthogonal analytics and informatics to deconstruct disease networks and complex mechanisms

Deep understanding of biological mechanisms of action of existing therapies & unmet medical needs

Model Systems

- CAIA
- KBxN
- EAE
- ITP

Glycan
Protein and Cellular
Metabolic
Genetic

New Drugs
Thorough Characterization Reveals New Products that May Deliver Improved Patient Benefits

• Sialylation of the Fc region of IVIg
  • Exploits natural mechanism of modulating IgG function
  • Potential for lower dose, higher potency Ig products (e.g. SC delivery)
  • Improved Ig products, targeted to existing or new inflammatory disorders

• Sialylation of the Fc region of biologic therapeutics
  • Enhanced anti-inflammatory activity of any recombinant biologic

• Novel Recombinant Products
  • Exploit major mechanisms of action of IVIg
  • Homogeneous recombinant products with improved patient safety
  • Potential to integrate anti-inflammatory properties of controlled sialylation
Alterations in the Sialylation of IgG are Associated with Autoimmune Disease and Disease Activity

RA and JIA Patients have less Sialylation (and its Precursor Galactosylation) in their IgG

Sialylation of the Fc region of IgG mediates enhanced anti-inflammatory activity

**THE LANCET, APRIL 30, 1988**

**SCIENCE VOL 320 18 APRIL 2008**

![Graph showing sialylation levels across different ages and disease conditions](image1.png)

*Parekh et al., 1988*

![Graph showing clinical scores for different treatments](image2.png)

*K/BxN arthritis model

**Anthony, R. & Ravetch, J et al., 2008**

US8470318

US7846744

US 20130273040

**sFc and Fc dose: 0.035 g/kg**

**IVIG dose: 1 g/kg**
We Optimized the Enzymatic Process for Site-Specific Sialylation

IVIg Drug Substance

> 80% Pure S1-IVIg

> 80% Pure S2-IVIg

IVIg

B4GalT1

ST6Gal1

S1-IVIg

S2-IVIg

Drug Substance

IVIg

S1-IVIg

S2-IVIg

> 80% Pure S1-IVIg

> 80% Pure S2-IVIg
Avoiding Undesirable Modifications Introduced in Original Process

ST6 enzyme produced from certain sources can introduce other chemical modifications into the product. These modifications could impact biological functions, which could confound results if not controlled.

<table>
<thead>
<tr>
<th>Modifications Introduced During Sialylation Process</th>
<th>ST6 Enzyme Source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Original</td>
</tr>
<tr>
<td>Carboxymethyl lysine</td>
<td>5%</td>
</tr>
<tr>
<td>Carboxymethyl arginine</td>
<td>10%</td>
</tr>
<tr>
<td>Methylglyoxal arginine</td>
<td>20%</td>
</tr>
<tr>
<td>Imidazolidine</td>
<td>8%</td>
</tr>
<tr>
<td>Pentosidine</td>
<td>Yes</td>
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</tbody>
</table>
Sialylated IVIg (S-IVIg) reveals better efficacy than IVIg. IVIg loses activity at 0.3 g/Kg whilst sialylated IVIg shows good activity at 0.3 g/Kg.

In collaboration F. Nimmerjahn et al.
Sialylation Is Required for Efficacy of IVIg in a Mouse Model of Immune Thrombocytopenia

Murine anti-CD41 Antibody-induced Thrombocytopenia Model

- **IVIg**
- **Desialylated IVIG**

**Total Platelet Levels**

**Relative abundance (%)**

- IgG1
- IgG2/3
- IgG4

**Platelet Counts [10^9/L]**

- 0.3
- 0.6
- 1

- 0
- 1000
- 800
- 600
- 400
- 200
- 0

**g/kg**

- G0F
- G1F
- G2F
- G0
- G1
- G2

- G0F + BGlcNAc
- G1F + BGlcNAc
- G2F + BGlcNAc

- A1F1,3
- A1F1,6
- A2F

- G1F + NeuAc
- A1 1,3
- A1 1,6
- A2

- A1F + BGlcNAc 1,3
- A1F + BGlcNAc 1,6

- A2F + BGlcNAc

- G1F + NeuAc + BGlc…

**Desialylated IVIG**

**IVIg**

**Normal range**
Increased Sialylation of IVIg Accelerates Platelet Recovery in a Murine Model of ITP
Sialylated IVIg Suppresses Skin Blistering in a Murine Model of Pemphigus

In collaboration F. Nimmerjahn et al
Sialylated IVIg Suppresses Skin Blistering in a Murine Model of Pemphigus

In collaboration with F. Nimmerjahn et al

* p > 0.05
*** p > 0.01
Thorough Characterization Reveals New Products that May Deliver Improved Patient Benefits

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- **Sialylation of the Fc region of biologic therapeutics**
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- **Novel Recombinant Products**
  - Exploit major mechanisms of action of IVIg
  - Homogeneous recombinant products with improved patient safety
  - Potential to integrate anti-inflammatory properties of controlled sialylation
Sialylation of Recombinant Fc or an Anti-Cytokine mAb Enhances Suppression of Murine Arthritis

Murine K/BxN Serum Transfer Arthritis

- IVlg, 1.2gm/kg
- Fc, 0.1 g/kg
- PBS
- IL-4, ic
- sFc, 0.1 g/kg

Murine Anti-Collagen Antibody-Induced Arthritis

- Normal mice
- Vehicle/Disease
- Prednisone
- IgG1 at 7.5 mg/Kg
- Sialylated IgG1 at 7.5 mg/Kg

- Anti-inflammatory effect of Fc sialylation can be transferred to recombinant products
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Thorough Characterization of Kawasaki Disease (KD) Patients Reveals IVIg Treatment Signature

Kawasaki’s Disease
Inflammation of the coronary arteries pre-disposing to aneurysms (ballooning) and stenosis (narrowing) of the arteries.

In collaboration with J.C. Burns et al
Advanced Data Analytics Reveals IVIg Treatment Signatures

Cluster 1: Active disease + developing aneurysms

Cluster 2: Resolved disease + IVIG response

- Acute Phase
- FC-gamma Receptor Signaling
- Granulocyte Chemotaxis
- Defense Response to Bacterium
- Positive Regulation of NF-kappaB Activity
- .........

Identified analytes and their associated pathways which are major differentiators of cluster1 vs 2
Novel Recombinant Products Leverage IVIg MOA Resulting in Significantly Enhanced Potency

- >1,000-fold enhancement of molecular mechanism
- >50-fold enhancement of in vivo efficacy versus IVIg
Acknowledgements

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