Selective Modulation of Fc Receptors for Improved Therapy of Orphan Autoimmune Diseases: Lessons from IVIg

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Presentation Outline

• Unmet Needs in Autoimmune Disease

• Key Role for FcγR System in Pathogenesis & Learnings from IVIg

• Rational Design of SIFs

• Pre-clinical Profile of SIF3

• Next Steps in Development
There is an Immunologic Basis for Many Diseases

Over 80 distinct diseases, 50 million Americans affected, $100B+ annual economic burden

6.5 million
PATIENTS
Psoriasis

2 million
PATIENTS
Rheumatoid Arthritis

13 million
PATIENTS
Asthma

1 million
PATIENTS
IBD

370 thousand
PATIENTS
Multiple Sclerosis

600 thousand
PATIENTS
Ankylosing Spondylitis

150 thousand
PATIENTS
Lupus

130 thousand
PATIENTS
APS

70 thousand
PATIENTS
Dermatomyositis

40 thousand
PATIENTS
Mysthemia Gravis

NIH Autoimmune Diseases Coordinating Committee 2013; AARDA Report 2011
Autoimmune Indications ... A Tale of Two Cities

U.S. diagnosed prevalence of 16 autoimmune indications

- NMO: Neuromyelitis optica
- CIDP: Chronic inflammatory demyelinating polyneuropathy
- ANCA: ANCA associated vasculitis
- MG: Myasthenia gravis
- APS: Antiphospholipid syndrome
- GBS: Guillain-Barre Syndrome
- ITP: Idiopathic thrombocytopenic purpura

Sources: Orphanet, Medscape, Triangle Insights’ analysis, Health Advances’ analysis

NMO: Neuromyelitis optica; CIDP: Chronic inflammatory demyelinating polyneuropathy; ANCA: ANCA associated vasculitis; MG: Myasthenia gravis; APS: Antiphospholipid syndrome; GBS: Guillain-Barre Syndrome; ITP: Idiopathic thrombocytopenic purpura; Sources: Orphanet, Medscape, Triangle Insights’ analysis, Health Advances’ analysis
Recent innovation driving improved patient care and significant market value

Robust pipelines but mostly incremental advances

Unmet need exists but biological basis unclear

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Innovation in a Low-prevalence Autoimmune Disease Creates Substantial Value

**IVIg**

- IgG fraction from pooled plasma of ~10K donors
- Approved therapy for PID and 5 inflammatory diseases
- Used in >50 other indications
- 2013 WW sales $6.2Bn

**Nplate & Promacta**

- TPO agonists
- Third-line agents in ITP
- Not disease-modifying
- Approved 2008
- Combined 2013 WW sales $718M

**Benlysta**

- Anti-BAFF antibody
- Chronic maintenance of SLE
- Approved 2011
- Incremental improvement
- 2013 WW sales $228M
Auto-antibodies Mediate Disease and Are Not Targeted by Current Therapeutics

Auto-antibodies and immune complexes mediate tissue damage and dysfunction in autoimmune and inflammatory disease.

Therapeutic strategies that indirectly target auto-antibody production have been only partially successful.

Strategies that directly target auto-antibodies and immune complexes have proven valuable in challenging clinical settings, but have limited utility in chronic or maintenance settings.
Central Role for Fcγ Receptors in Autoantibody-mediated Diseases
IVIG Activity is Replicated by the Fc Domain Alone

- Fc domain provides equivalent efficacy to IVIG in the mouse ITP model
- Fc materials derived from IVIg or recombinant Fc are comparable
**Fc Fragment is Efficacious in Humans**

**Fc fragment efficacy is comparable to IVIG or corticosteroids in ITP patients**

Platelet recovery after IVIG Fc Fragment

- **0.75g/kg Fc**

Platelet recovery after IVIG or methylprednisolone (MP)

- **2g/kg IVIG**
- **30 mg/kg MP**

**But Fc fragment half-life is short**

- **IVIG (19 days)**
- **Fc Fragments (43 hrs)**
- 25-50 kDa Fc fragments are rapidly eliminated via renal excretion

*Efficacy was also shown with the Fc fragment in Kawasaki disease*

- Hsu et al 1993

**Pediatric ITP patients**

- Debre et al 1993

**Pediatric ITP patients**

- Balkan et al 2009

**Adult patients or volunteers**

- Janeway et al 1968
IVIg Treatment Suppresses FcR biology

Application of Momenta Patient Bio-characterization Toolkit

**Momenta bio-characterization toolkit**

**Kawasaki’s disease study**

**FcR biology index**

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- = Pre-IvIg
- = Post-IvIg

Proprietary IPDA algorithms
IgG Receptors Play a Key Role in Disease and Therapy

A family of receptors binding the Fc portion of IgGs
Key mediators of auto-antibody and immune complex functions
Genetic variants associated with autoimmune diseases
FcγR Modulation Profiles that Might Offer Benefit in Autoimmune Disease

**Broad FcγR Modulation**

**FcγR Ratio Modulation**

**Specific FcγR Modulation**

**Spectra of Fcγ-Receptor Family Modulation**

**IVIg-like (Broad Modulation)**

*Supported primarily by IVIg MOA*

**Target FcγR Ratio**

*Theoretical based on a compilation of mouse data & human expression data*

**Specific FcγR**

*Supported primarily by mouse data & human cell assays & emerging competitor agents*

**Specific Abs**
SIF3: Powerful Anti-inflammatory Agent Fully Harnessing IVIg Mechanism of Action

- Homogeneous recombinant Fc-derived product
- IVIg-like specificity for FcγRs
- Unique molecular design enhances avidity and potency to modulate FcγR biology
- Potent antagonist of autoantibody-mediated diseases

> 100x increased affinity than IVIg
Establishing the SAR for Polymeric IgG Fc’s Large Polymers of Fc Activate FcγR’s

Calcium Release in Monocytes

Fc Multimer

FcγR Signaling in Monocytes

Establishing the SAR for Polymeric IgG Fc’s

Large Polymers of Fc Activate FcγR’s
Polymeric IgG Fc Results in Cellular Activation

Size Matters

SDS-PAGE of Fc Multimer Fractions

Monocyte Activation by Fc Multimer Fractions
A Library of Multimeric-Fc Structures

Diversity of Molecular Structures....

- Dimer
- Branched Trimer
- Inverted Trimer
- Linear Trimer
- Pentamer X
- Pentamer Y
- Uncontrolled Multimer CH-CL
- Uncontrolled Multimer 2

.....Assessed for Fc Receptor Modulation

Including unique mutations that regulate ordered subunit association
Structure-Activity Relationship of Polymeric Fc’s

Size Matters

**FcγRIIIA Receptor Binding Affinity**

Increased apparent affinity driven by increased avidity
Structure-Activity Relationship of Polymeric Fc’s

Size Matters

Ca Release in Primary Human Monocytes

FcγR Signaling in Primary Human Monocytes
Multimers Display Enhanced Avidity to Fcγ Receptors

**Notes:** Logarithmic y-axis for FcγRIIIa, IIa, and IIb. Lower IC50 = Higher relative affinity.

Multimerization increased low affinity FcγR binding through avidity
SIF3 is a Potent Antagonist of Immune-Complex-mediated FcγR Activation

Ca Release in Primary Human Monocytes

FcγR Signaling in Primary Human Monocytes

MOMENTA
SIF3 Inhibits Multiple Cellular Functions of Fcγ Receptors

Phagocytosis in Monocytes

Cytokine Production in Monocytes

Ca Release in Neutrophils

Cytokine Production in PBMCs
SIF3 Displays Enhanced Potency in an Acute ITP Mouse Model When Compared to IVIg

Murine anti-CD41-induced Acute Thrombocytopenia Model

*Fc-trimer displayed 100-fold higher potency than IVIg*

- IC50 IVIg = 338 mg/kg
- IC50 rFc dimer = 93 mg/kg
- IC50 rF trimer = 30 mg/kg
SIF3 Displays Enhanced Efficacy and Potency in K/BxN and ITP Mouse Models When Compared to IVIg

- Fc2 and Fc3 at 0.1 g/kg showed similar levels of protection to IVIg at 1 g/kg indicating that Fc2 and Fc3 were more potent than IVIg.
- Chronic ITP model suggest ~50 times potency increase for Fc3 over IVIg.
SIF3 Suppresses Collagen-Antibody-Induced Arthritis

Greater potency and efficacy than IVIg
28 Day Multi-Dose Safety Assessment in Mice

Study Design

Dosing with SIF3 @ 0.1g/kg and 0.01g/kg iv

Day 0
- Prebleed PK & ADA

Day 1
- Cytokines Day 3
- PK & ADA Day 6

Day 5
- PK & ADA Day 10

Day 7
- Cytokines

Day 13
- Collection of tissues PK & ADA Day 13

Day 14
- Cytokines

Day 21
- PK & ADA Day 20

Day 27
- PK, ADA & Tissue Parameters

Assessment parameters:
- PK assay: day -5, 6, 13, 20 & day 27
- ADA assays: day -5, 6, 13, 20 & day 27
- Cytokines: day -5, 3, 10, 13, 17 & 27
- Complement deposition in tissues-IHC Day 13 & 27
- Complement assay with Plasma
- PAF assay: day 13 & 27
- Blood cell count, Vet Scan: Day 13 & 27
- Toxicity/Clinical chemistry: Day 13 & 27
- Tissue assessment

SIF3 was well-tolerated and no remarkable findings were observed
SIF3 Has Appropriate Properties for Manufacturing

- Product is homogenous >98 % trimer by CE-SDS
- Titers greater than 3 g/l in early cell line development

Stability at 45C:
- SEC profiling of main species @ 45C

Stability at pH 3:
- SIF SEC profiling
- IgG1 SEC profiling
Next Steps in Development

• SIF3 is in pre-clinical development

• Anticipate initiation of clinical trials in 2H 2016

• Potential in multiple autoimmune diseases with autoantibody-mediated pathology and activated FcγR system

• Potential as a personalized therapy