MOMENTA

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

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VP Research

May 5, 2015

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

6.5 million PATIENTS

Psoriasis

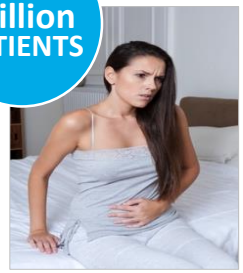
2 million PATIENTS

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

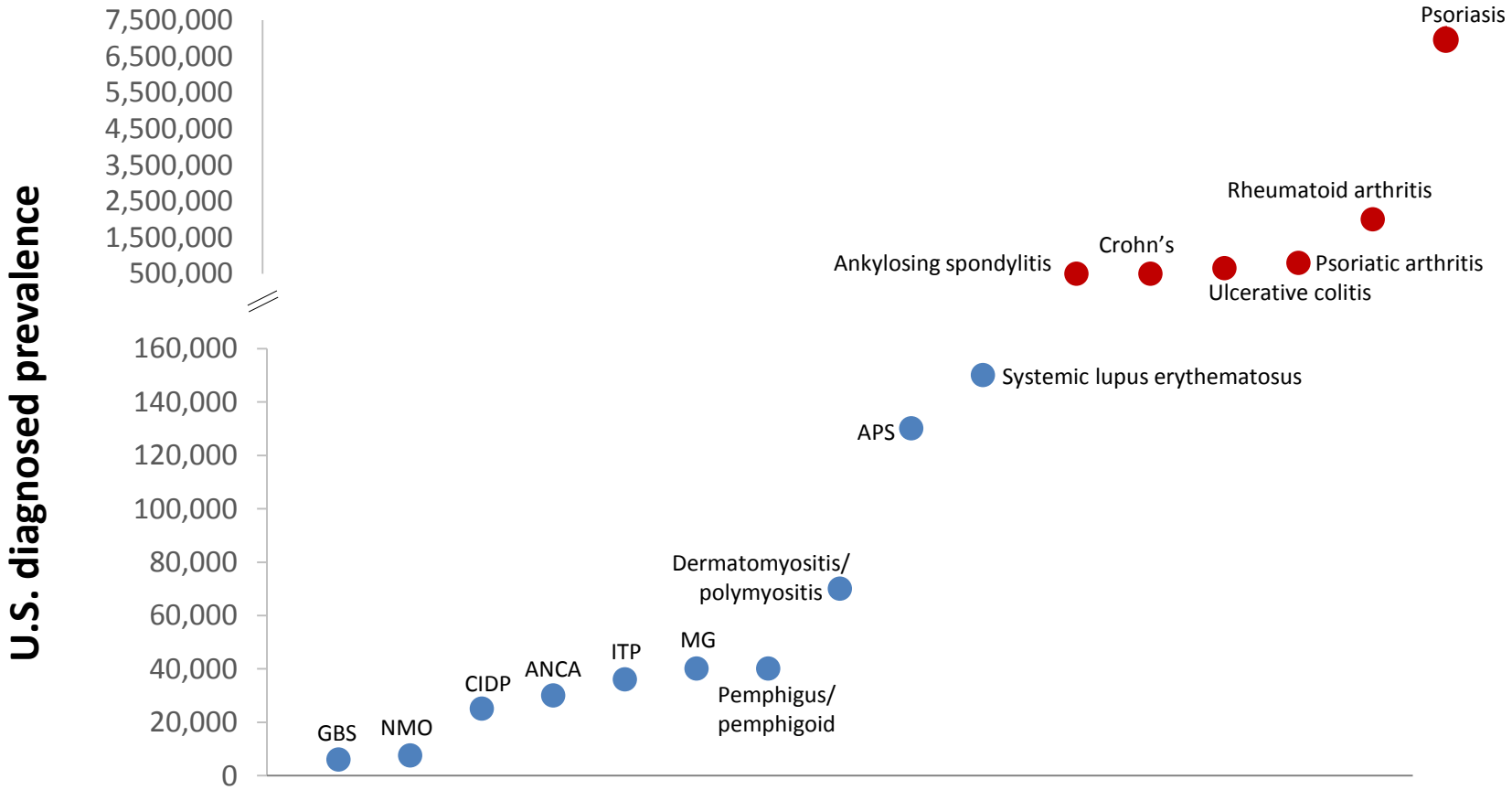
Mysthemia Gravis

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

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

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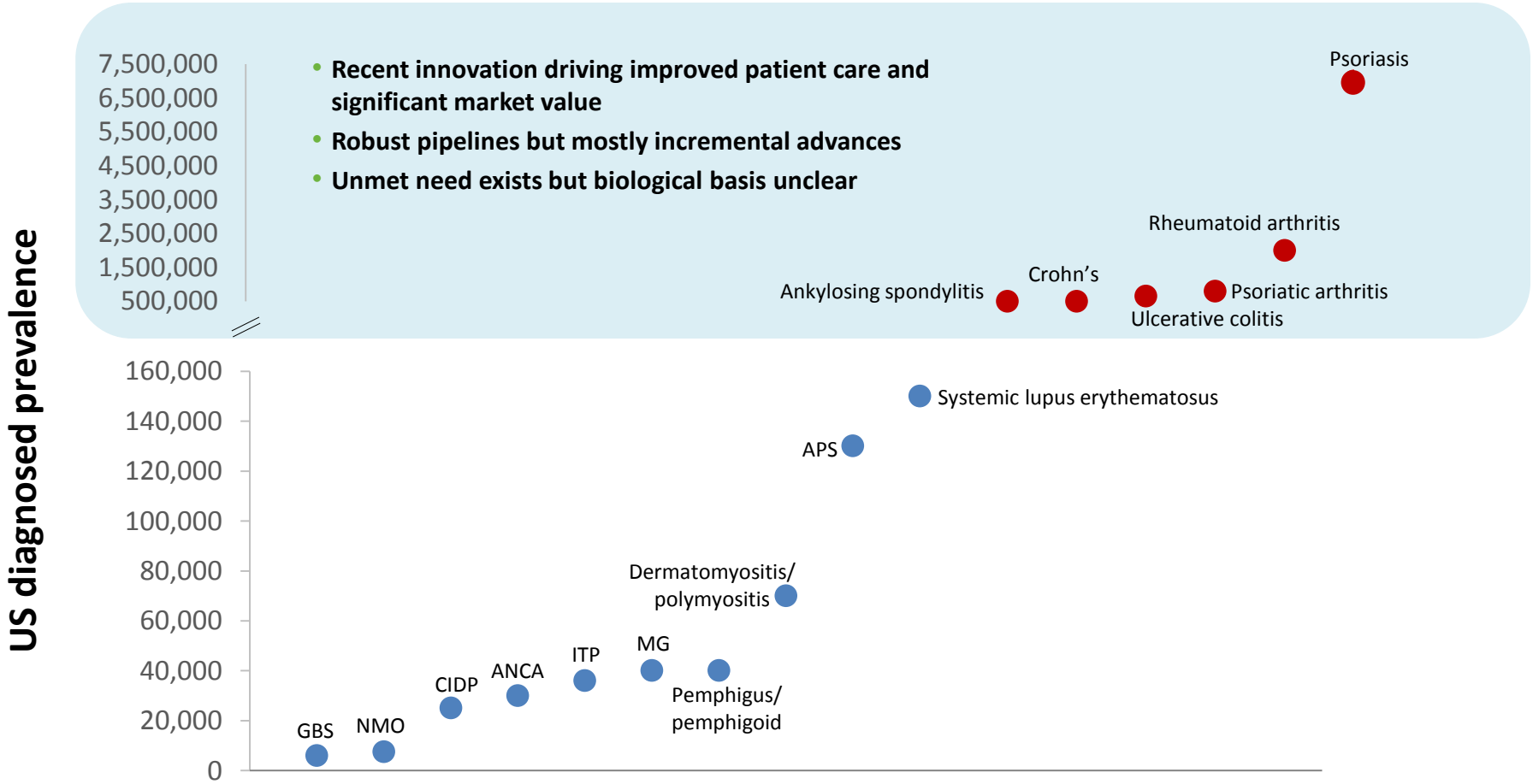

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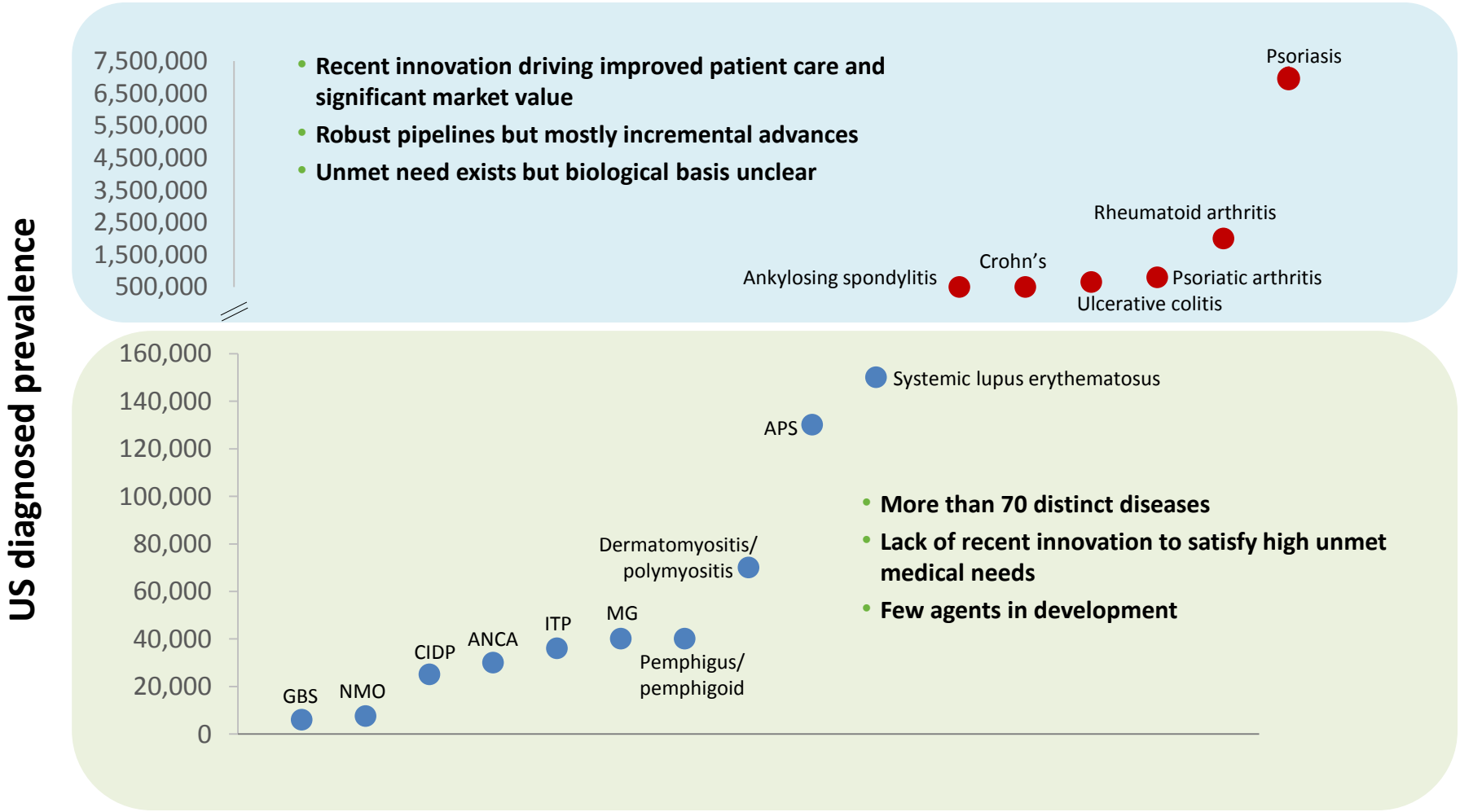

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Innovation in a Low-prevalence Autoimmune Disease Creates Substantial Value

IVIg

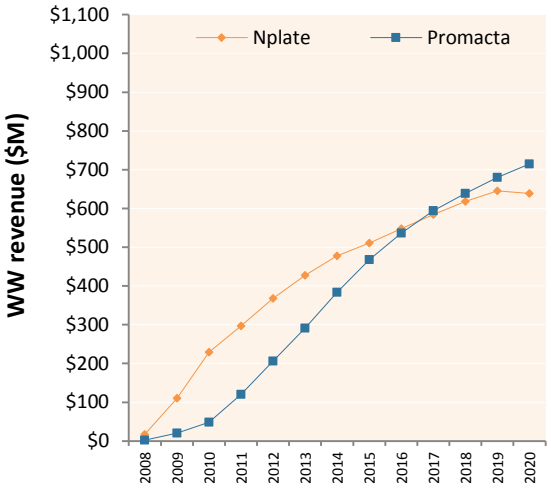
IgG fraction from pooled plasma of ~10K donors

Approved therapy for PID and 5 inflammatory diseases

Used in >50 other indications

2013 WW sales $6.2Bn

Nplate & Promacta



TPO agonists

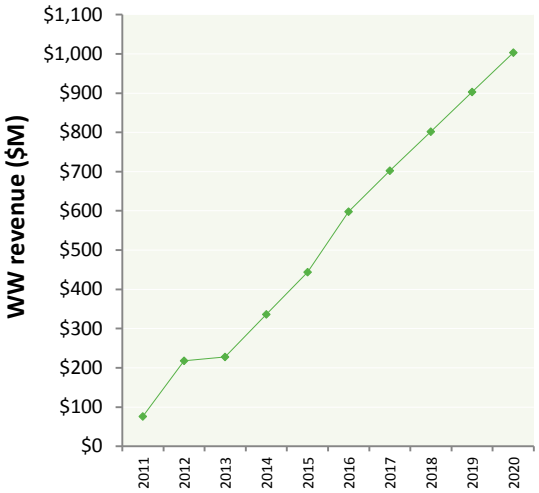
Third-line agents in ITP

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

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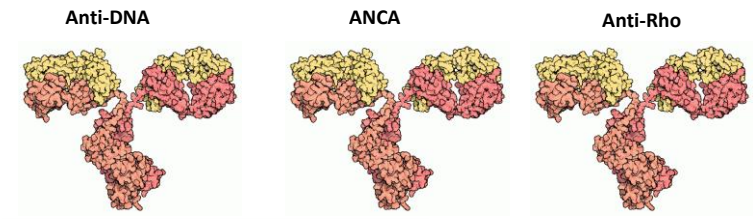
Auto-antibodies Mediate Disease and Are Not Targeted by Current Therapeutics

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



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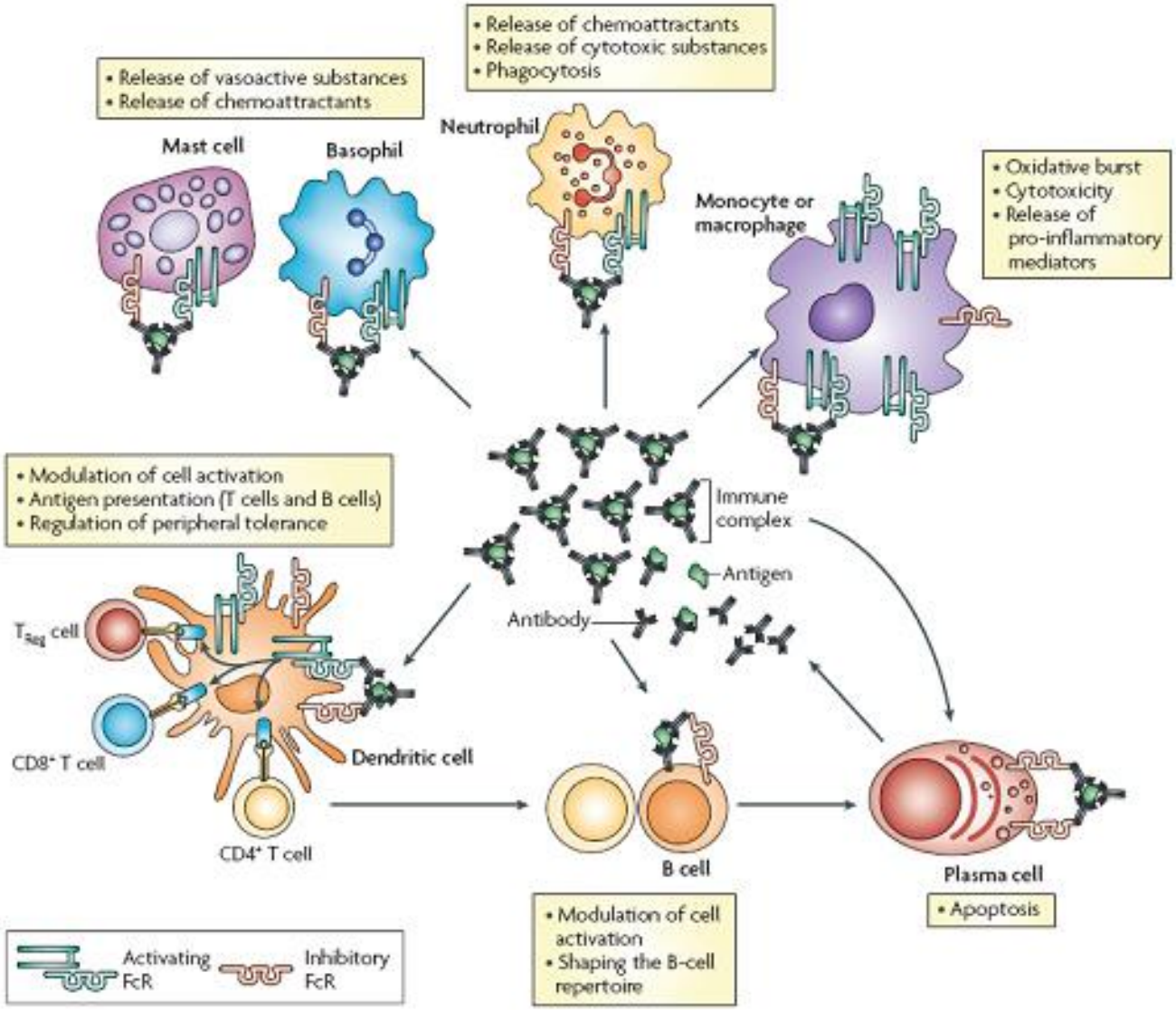
Central Role for Fcγ Receptors in Autoantibody-mediated Diseases



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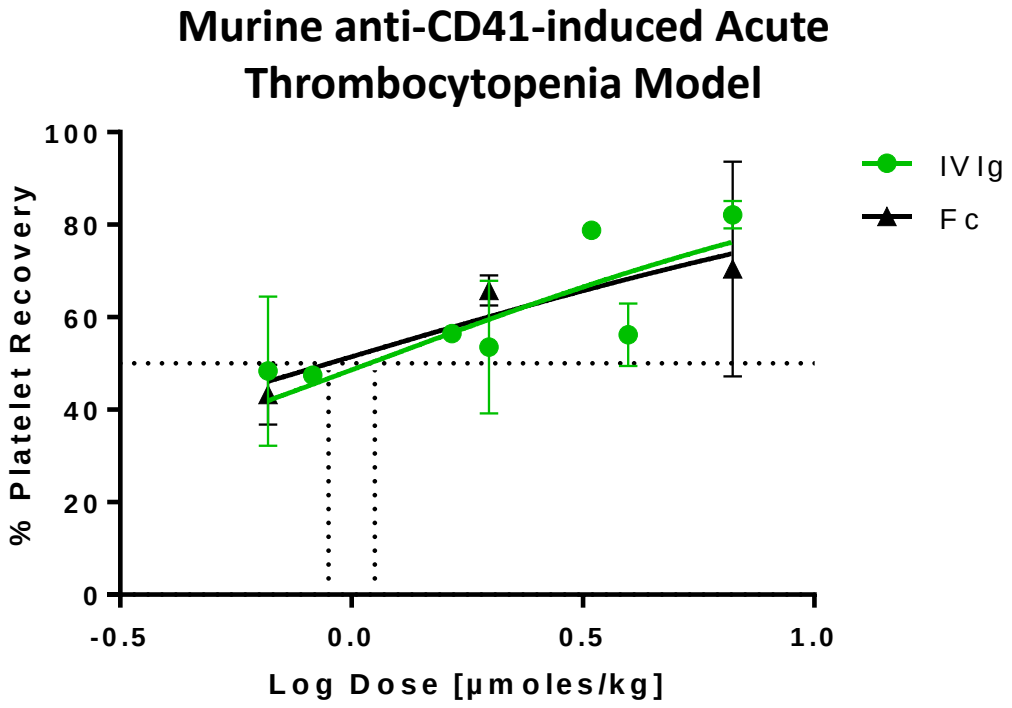
IVIG Activity is Replicated by the Fc Domain Alone

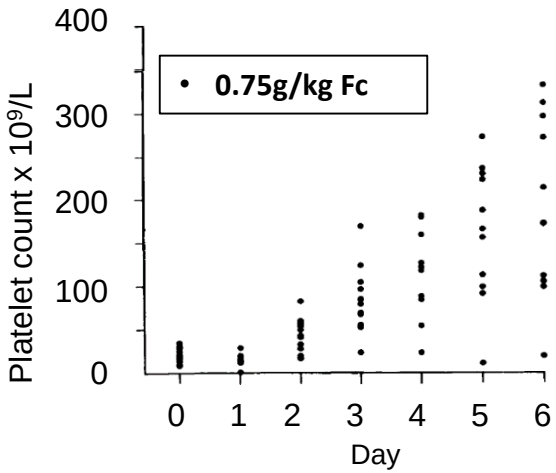


- **Fc domain provides equivalent efficacy to IVIG in the mouse ITP model**
- **Fc materials derived from IVIg or recombinant Fc are comparable**

Fc Fragment is Efficacious in Humans

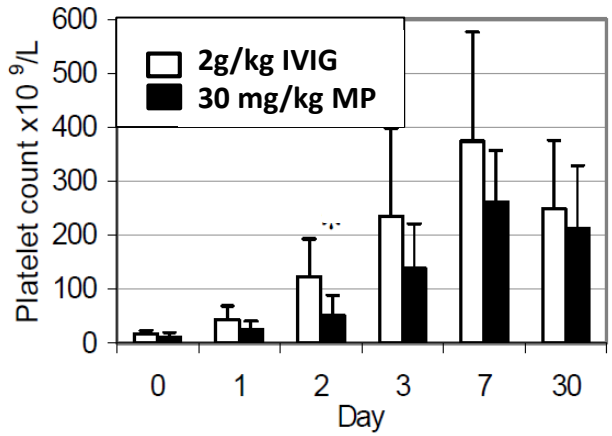
Fc fragment efficacy is comparable to IVIG or corticosteroids in ITP patients*

Platelet recovery after IVIG Fc Fragment



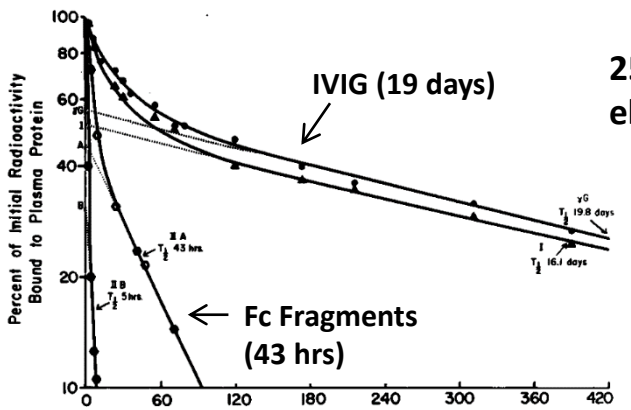
Pediatric ITP patients
Debre et al 1993

Platelet recovery after IVIG or methylprednisolone (MP)



Pediatric ITP patients
Balkan et al 2009

But Fc fragment halflife is short



25-50 kDa Fc fragments are rapidly eliminated via renal excretion

Adult patients or volunteers
Janeway et al 1968

***Efficacy was also shown with the Fc fragment in Kawasaki disease**
Hsu et al 1993

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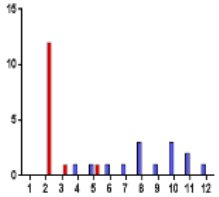
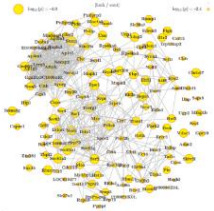
IVIg Treatment Suppresses FcR biology

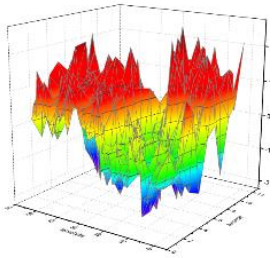
Application of Momenta Patient Bio-characterization Toolkit

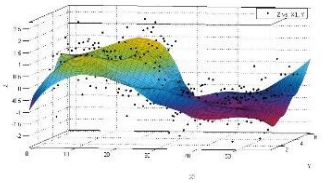
Momenta bio-characterization toolkit



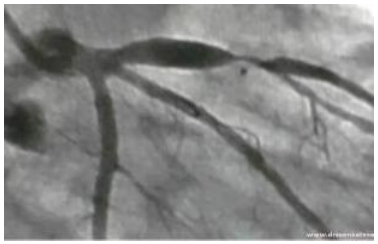


Proprietary IPDA algorithms

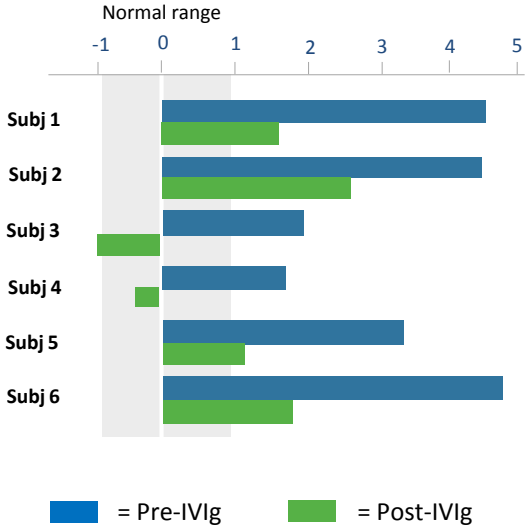




Kawasaki's disease study



FcR biology index



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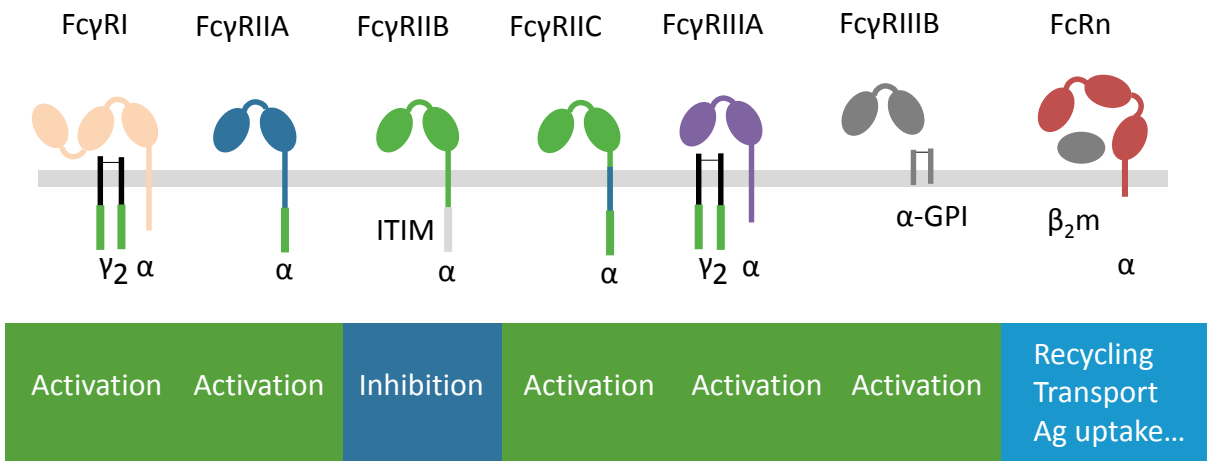
IgG Receptors Play a Key Role in Disease and Therapy

IgG Receptors



A family of receptors binding the Fc portion of IgGs

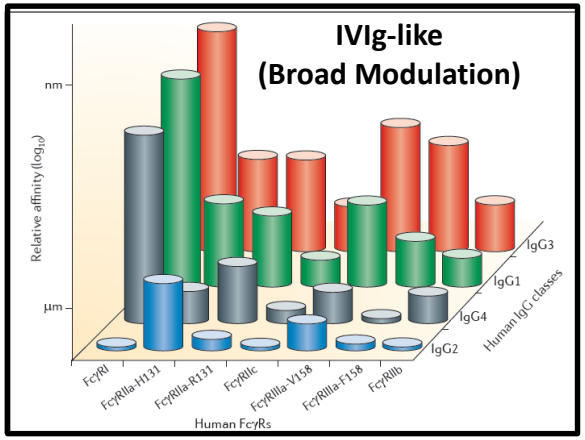
Key mediators of auto-antibody and immune complex functions

Genetic variants associated with autoimmune diseases

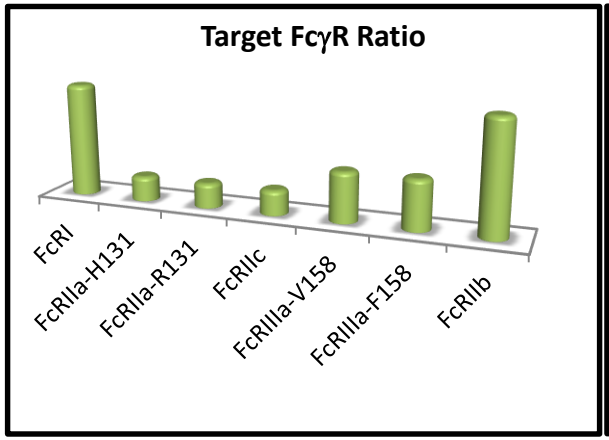
FcγR Modulation Profiles that Might Offer Benefit in Autoimmune Disease

Broad FcγR Modulation | **FcγR Ratio Modulation** | **Specific FcγR Modulation**

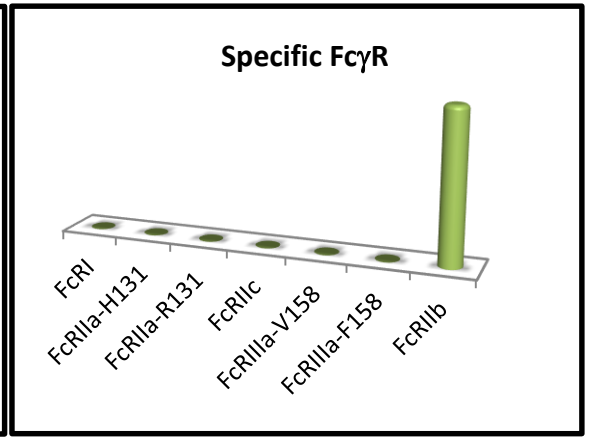
Spectra of Fcγ-Receptor Family Modulation



Supported primarily by IVIg MOA



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



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

IVIg | **Specific Abs**

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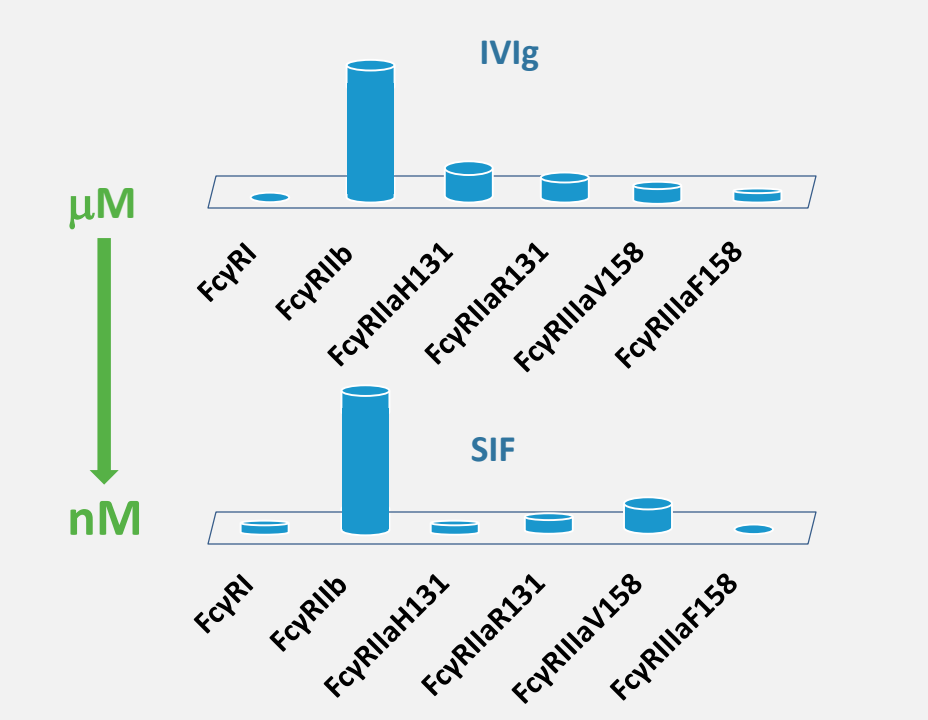
SIF3: Powerful Anti-inflammatory Agent Fully Harnessing IVIg Mechanism of Action

FcγR binding

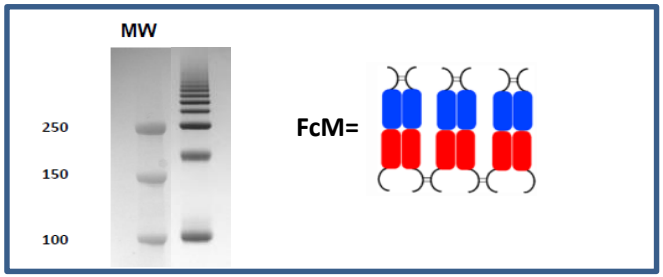


> 100x increased affinity than IVIg

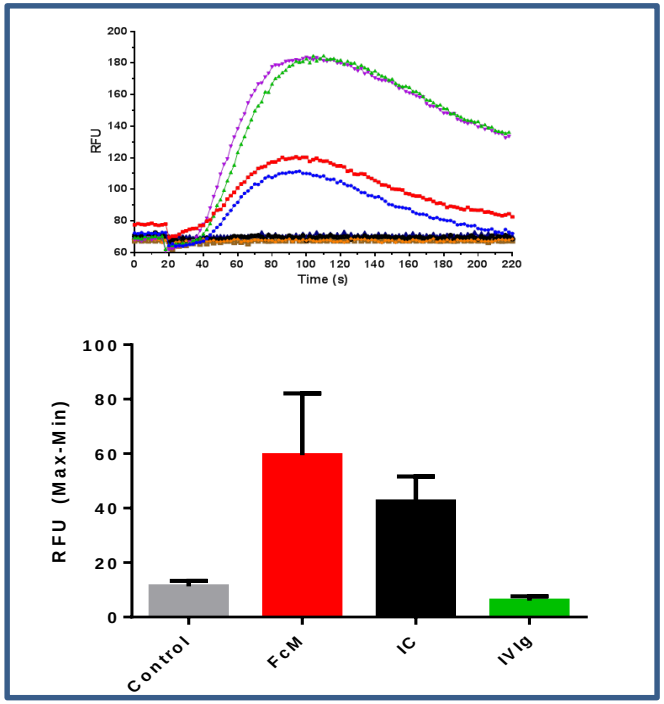
- Homogeneous recombinant Fc-derived product
- IVIg-like specificity for FcγRs
- Unique molecular design enhances avidity and potency to modulate FcγR biology
- Potent antagonist of autoantibody-mediated diseases

Establishing the SAR for Polymeric IgG Fc's
Large Polymers of Fc Activate FcγR's

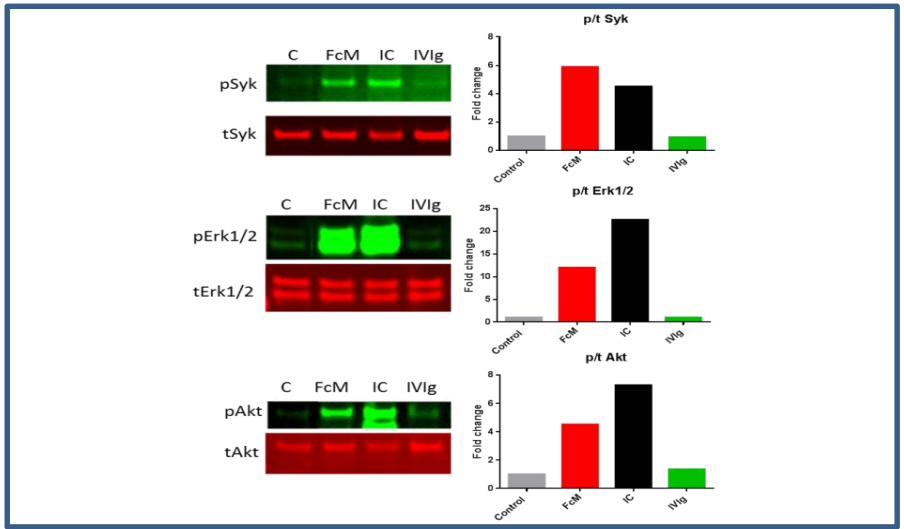
Fc Multimer

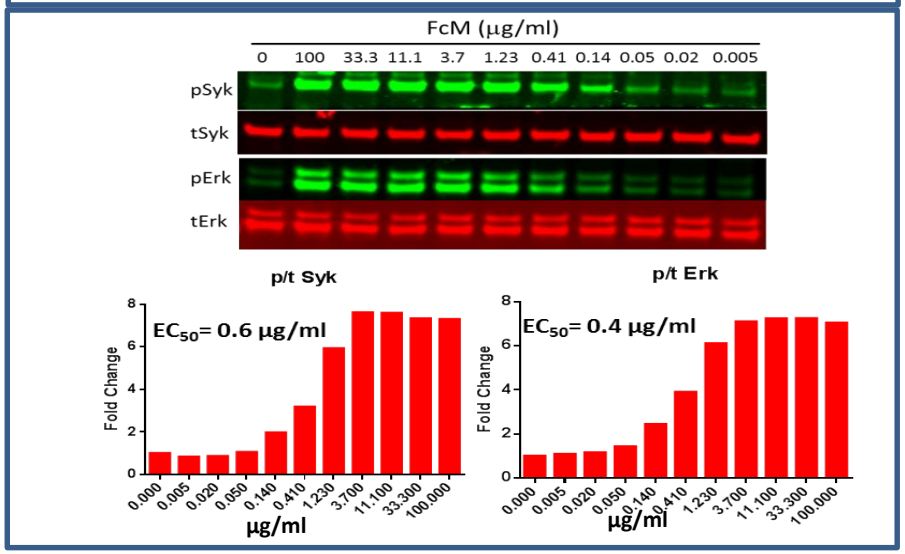


Calcium Release in Monocytes



FcγR Signaling in Monocytes

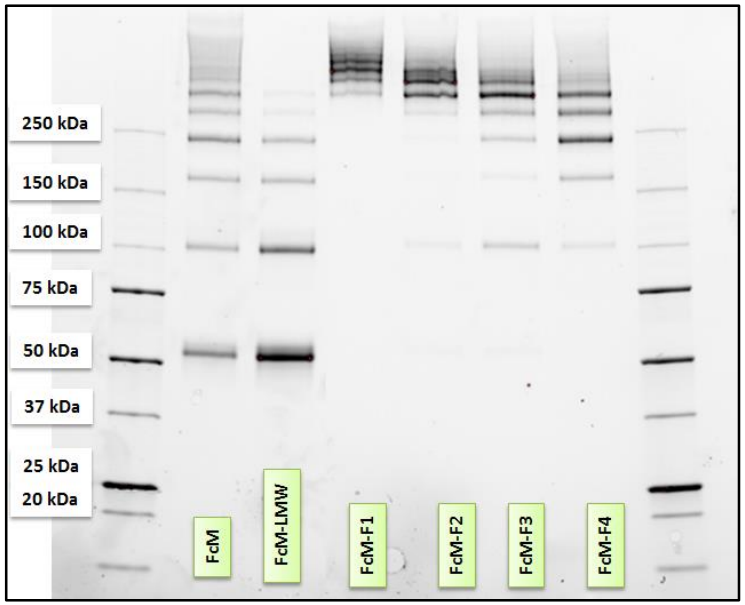




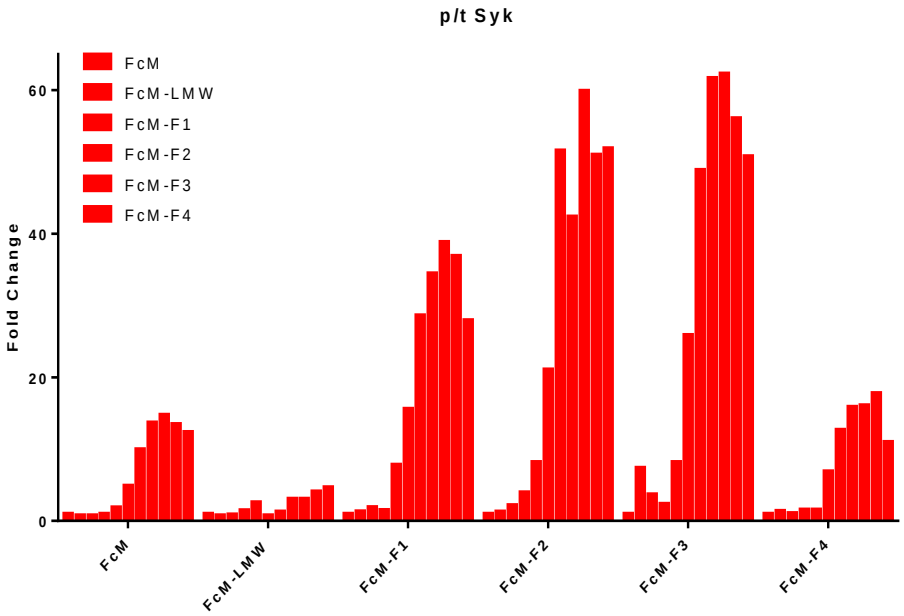
Polymeric IgG Fc Results in Cellular Activation

Size Matters

SDS-PAGE of Fc Multimer Fractions

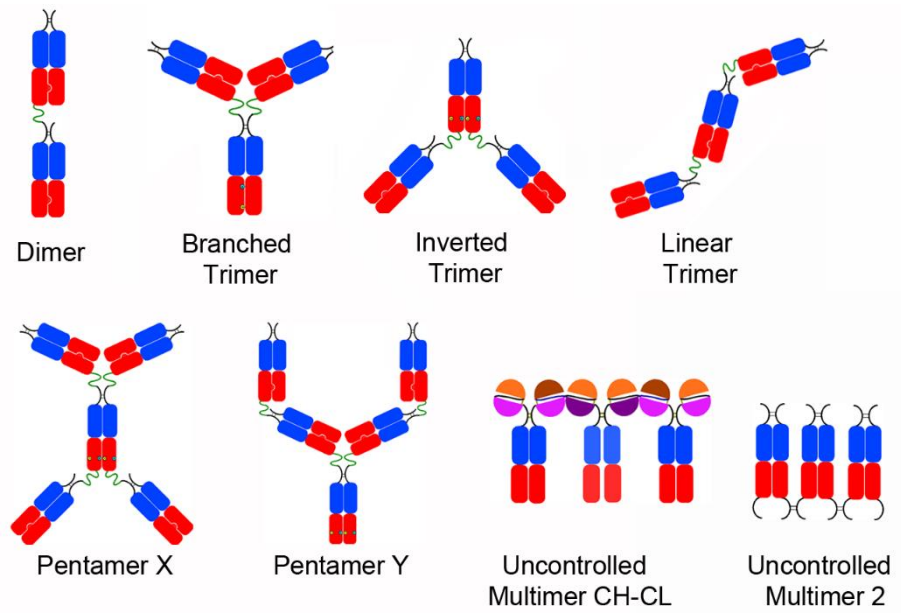


Monocyte Activation by Fc Multimer Fractions

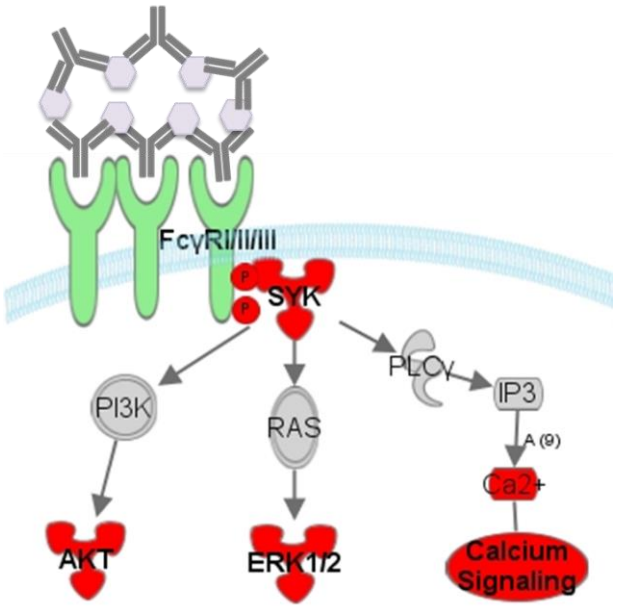


A Library of Multimeric-Fc Structures

Diversity of Molecular Structures….



…..Assessed for Fc Receptor Modulation

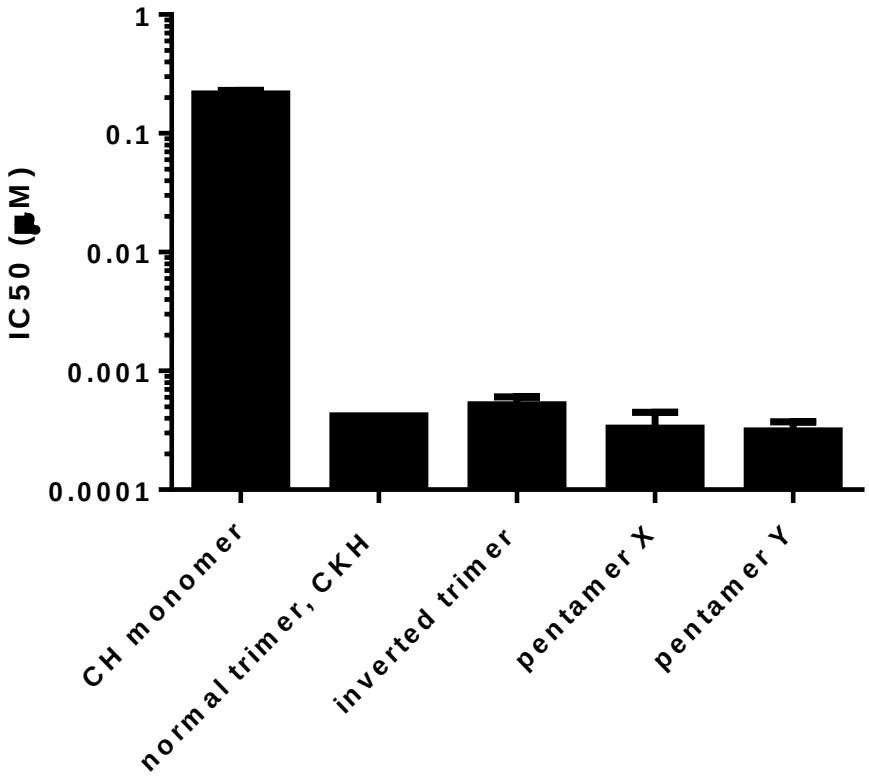


Including unique mutations that regulate ordered subunit association

Structure-Activity Relationship of Polymeric Fc's

Size Matters

FcγRIIIA Receptor Binding Affinity

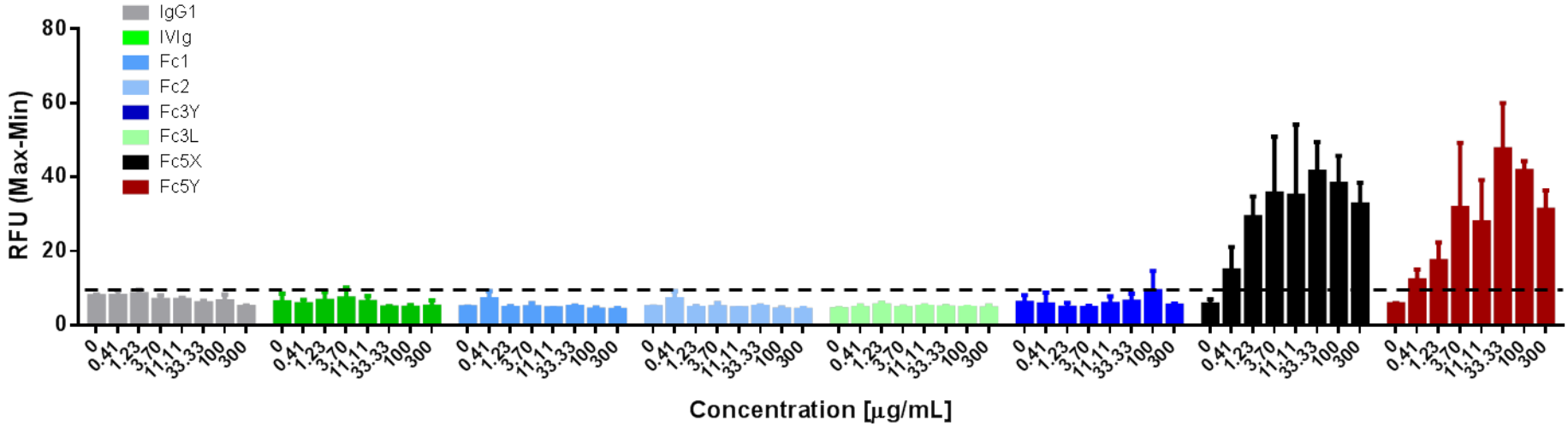


Increased apparent affinity driven by increased avidity

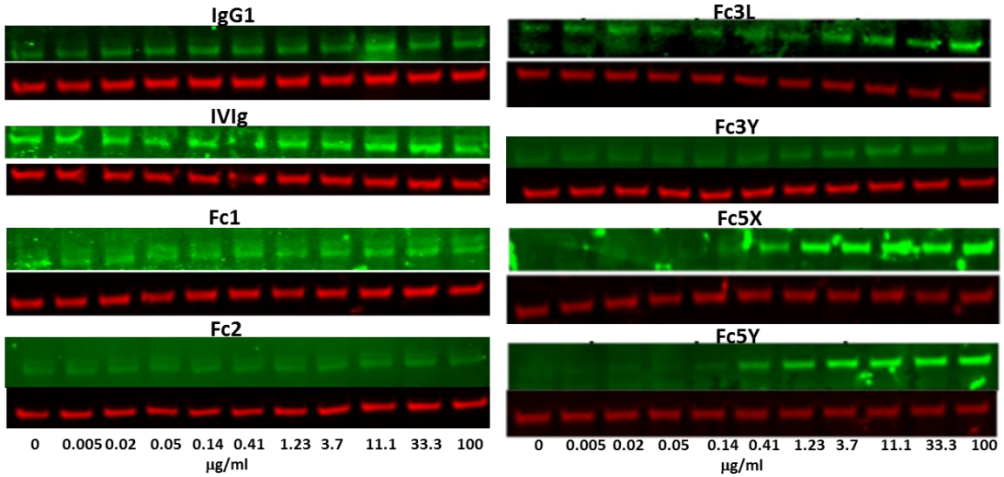
Structure-Activity Relationship of Polymeric Fc's

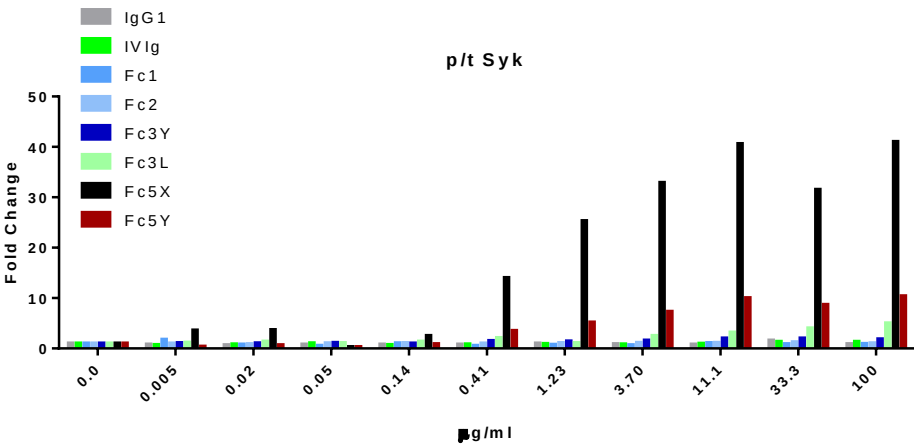
Size Matters

Ca Release in Primary Human Monocytes

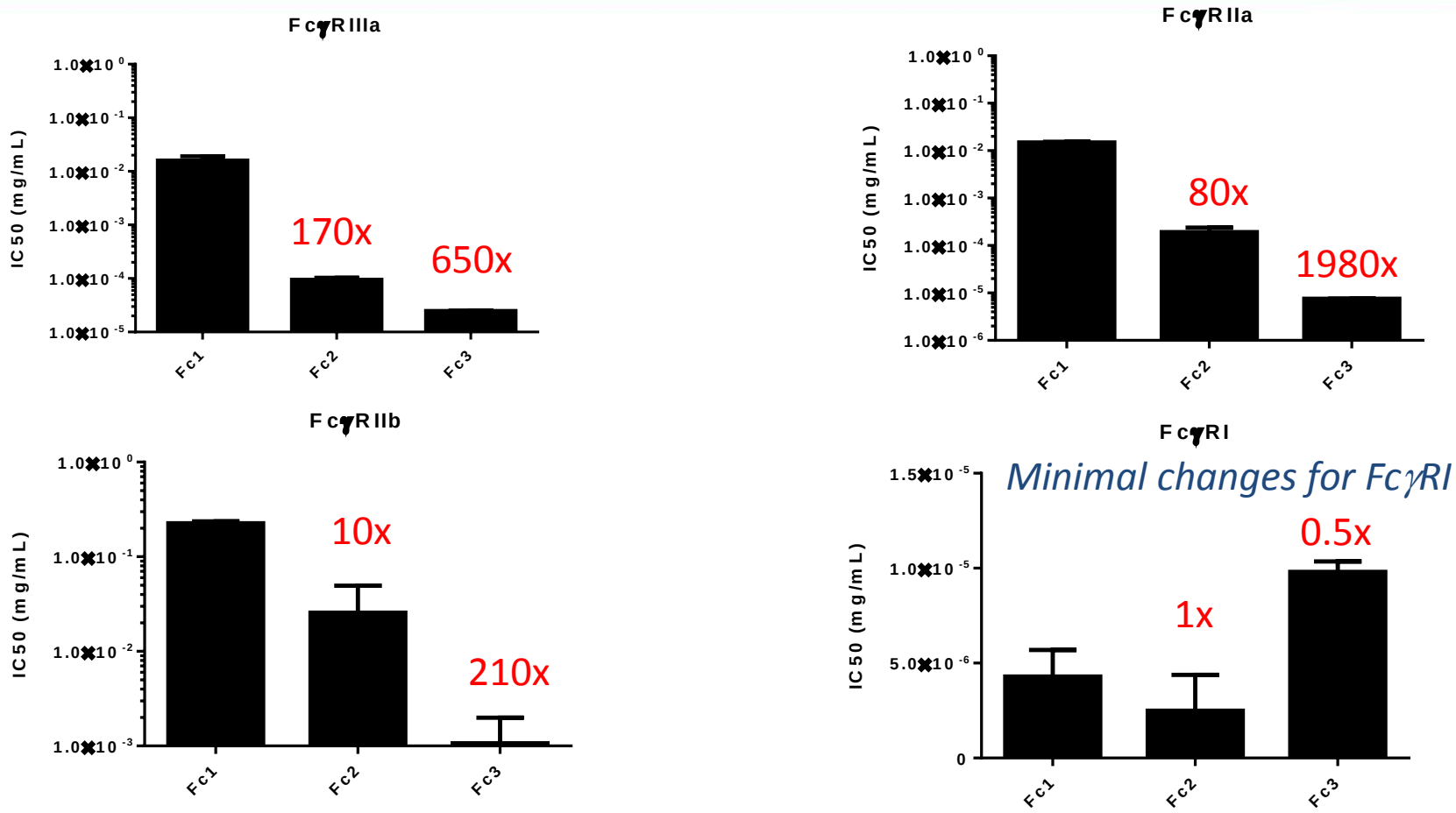


FcγR Signaling in Primary Human Monocytes





Multimers Display Enhanced Avidity to Fcγ Receptors

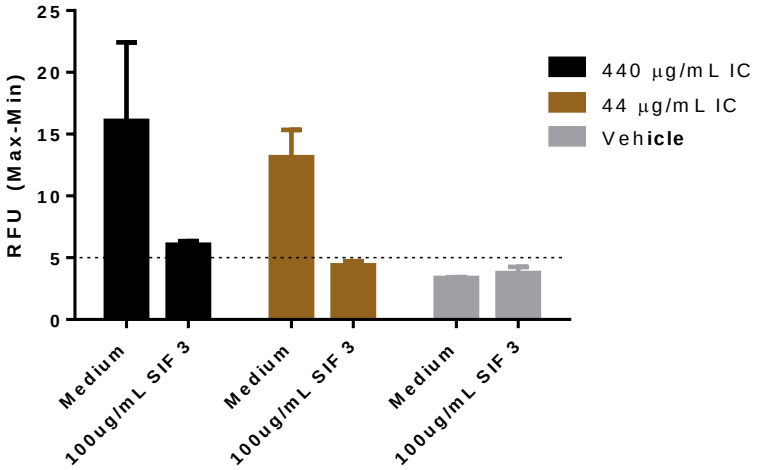


Notes: Logarithmic y-axis for FcγRIIIa, IIa, and IIb. Lower IC50 = Higher relative affinity.

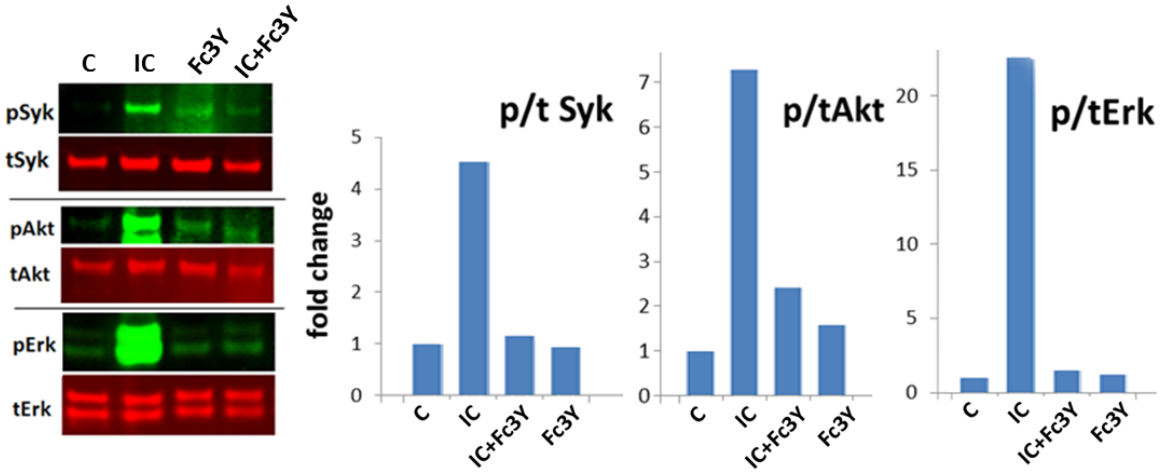
Multimerization increased low affinity FcγR binding through avidity

SIF3 is a Potent Antagonist of Immune-Complex-mediated FcγR Activation

Ca Release in Primary Human Monocytes

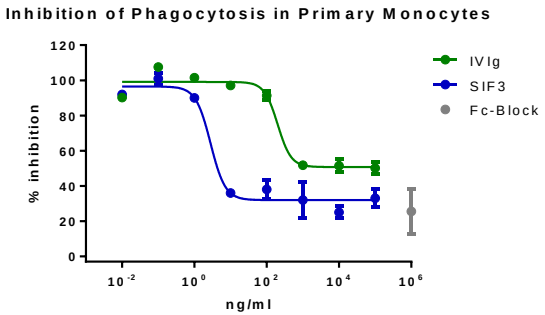


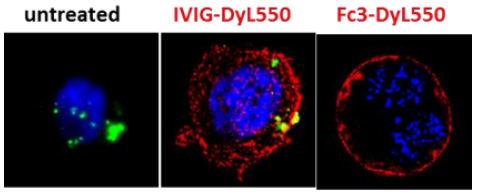
FcγR Signaling in Primary Human Monocytes



SIF3 Inhibits Multiple Cellular Functions of Fcγ Receptors

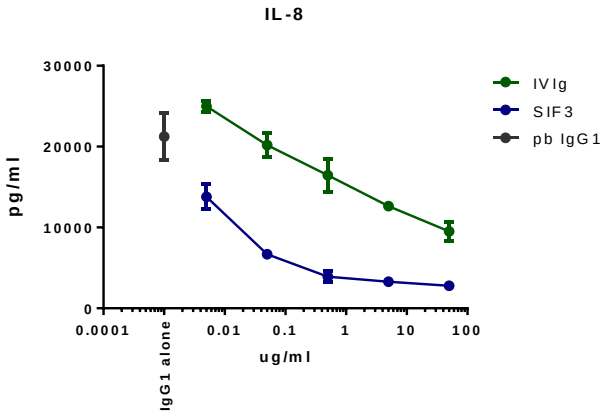
Phagocytosis in Monocytes



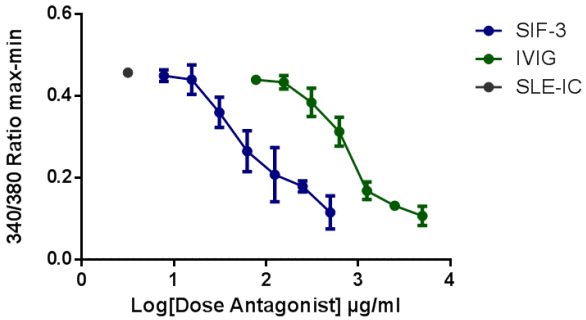


IgG-FITC beads internalization

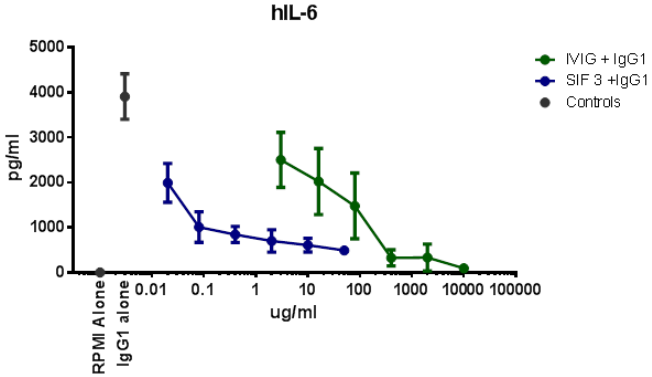
Cytokine Production in Monocytes



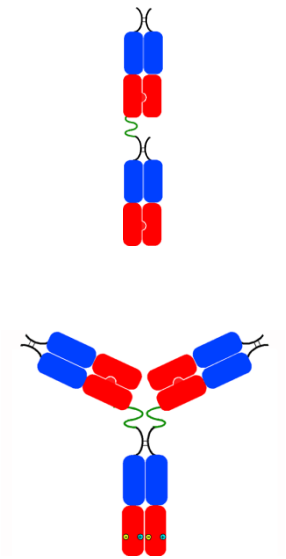
Ca Release in Neutrophils



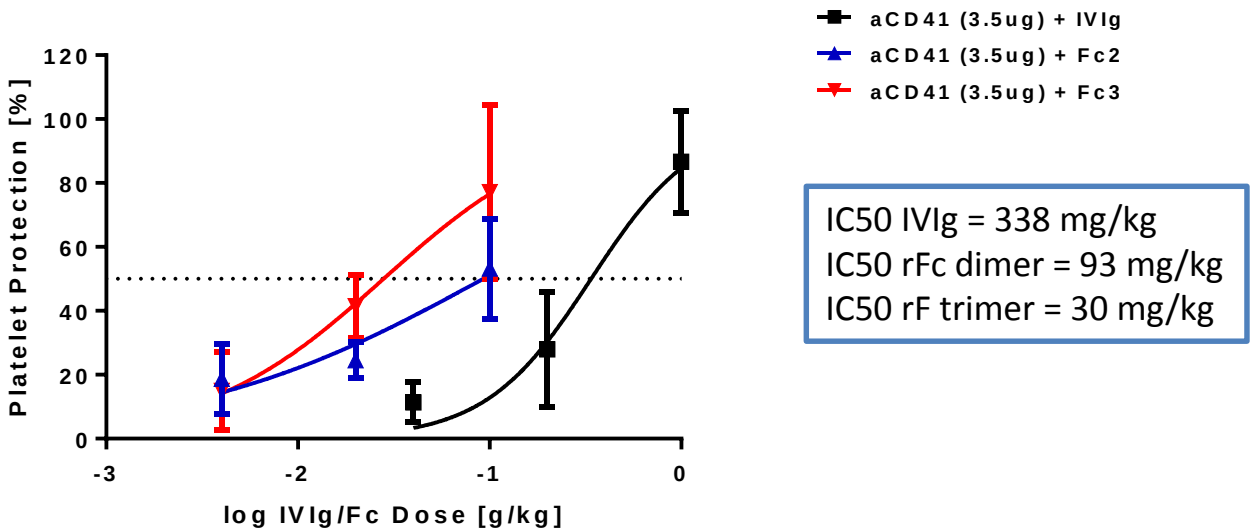
Cytokine Production in PBMCs



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



Murine anti-CD41-induced Acute Thrombocytopenia Model

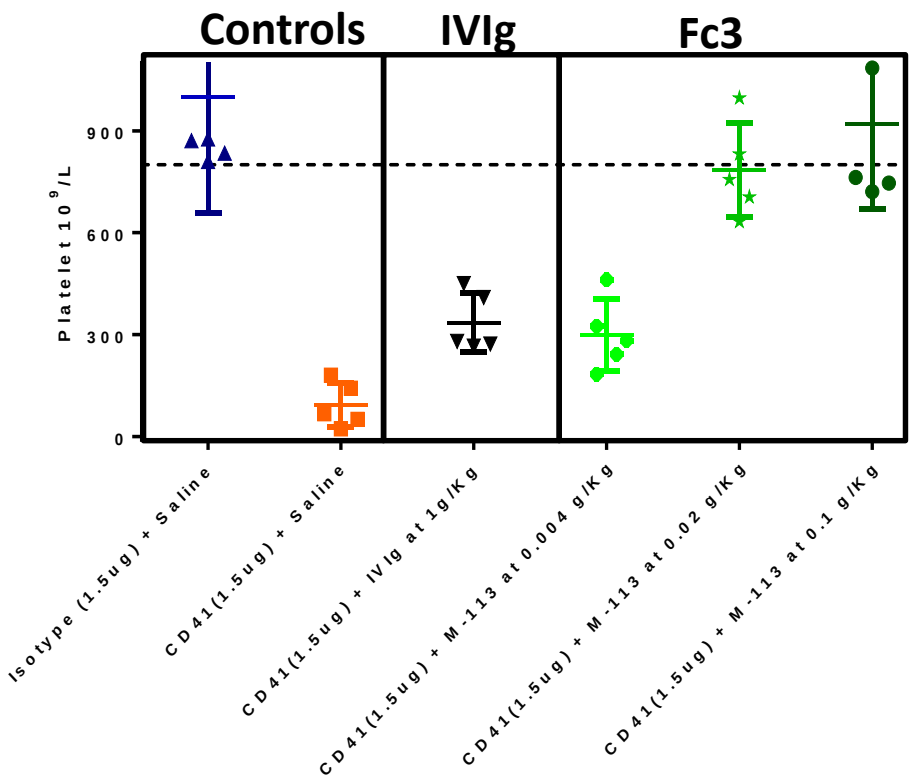


IC50 IVIg = 338 mg/kg
IC50 rFc dimer = 93 mg/kg
IC50 rF trimer = 30 mg/kg

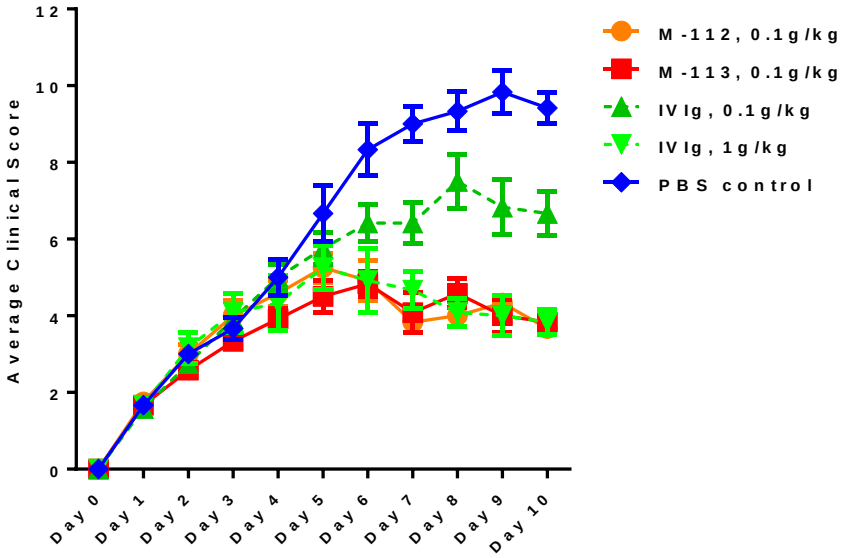
- **Fc-trimer displayed 100-fold higher potency than IVIg**

SIF3 Displays Enhanced Efficacy and Potency in K/BxN and ITP Mouse Models When Compared to IVIg

Murine anti-CD41 Antibody-induced Chronic Thrombocytopenia Model



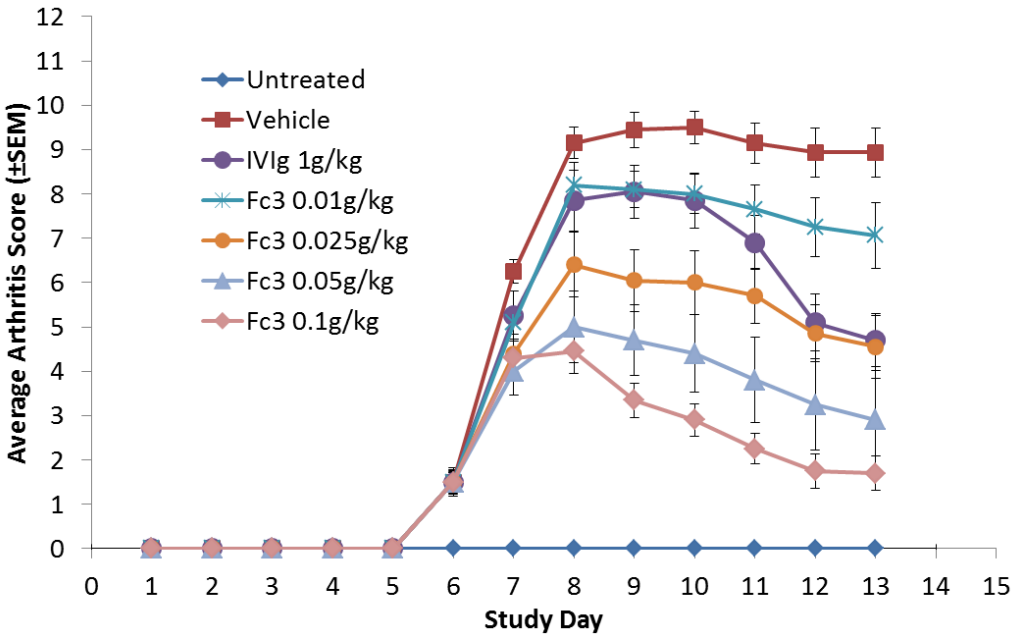
K/BxN Serum Transfer Arthritis Model

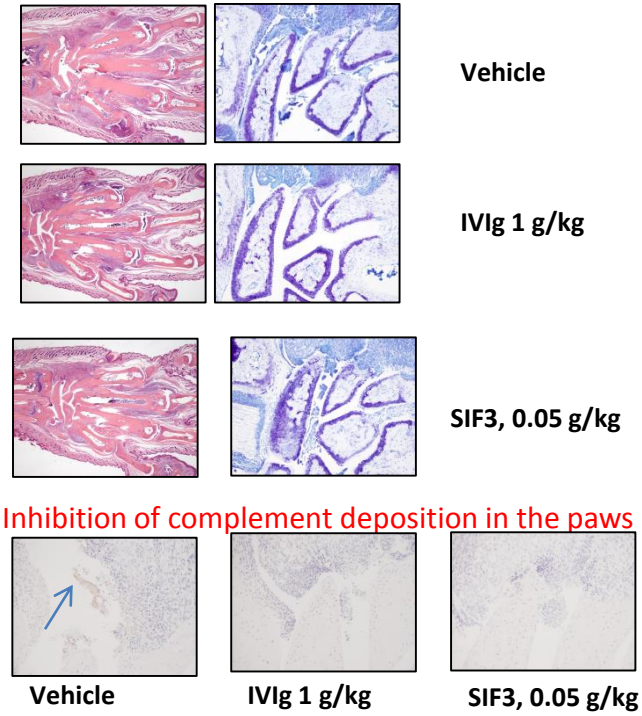


M112= Fc2
M113= Fc3

- 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

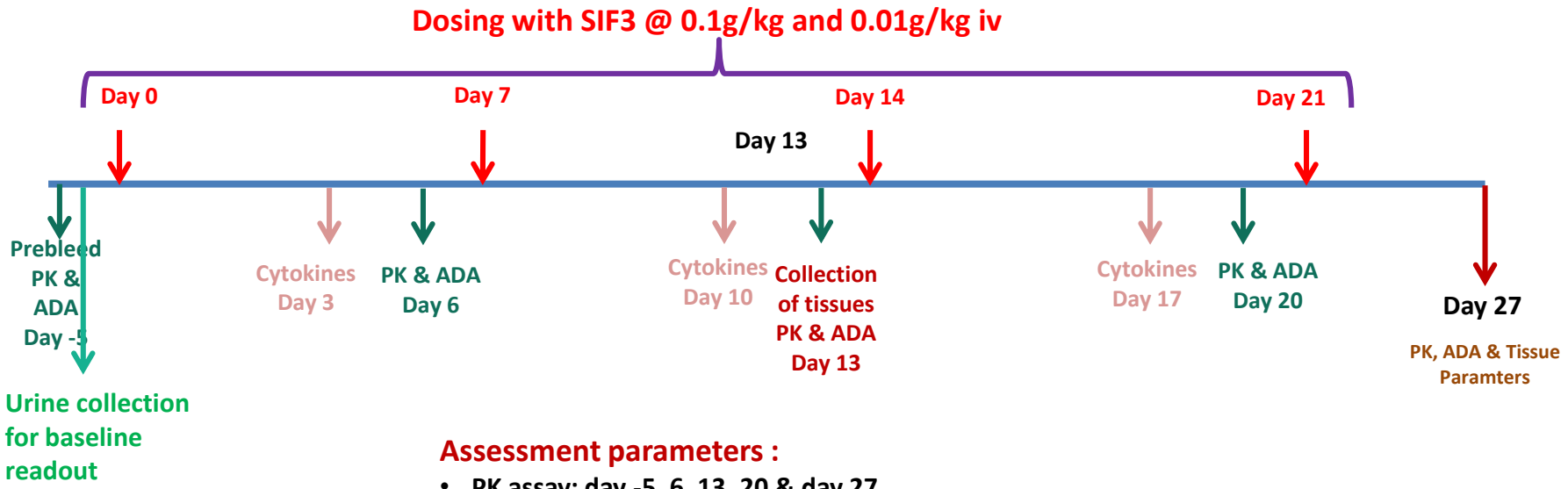




Greater potency and efficacy than IVIg

28 Day Multi-Dose Safety Assessment in Mice

Study Design

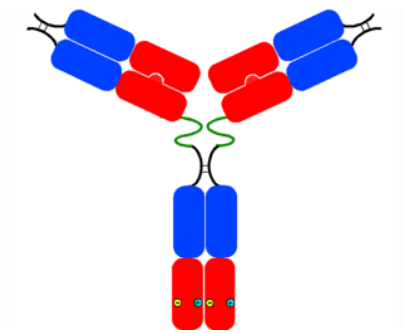


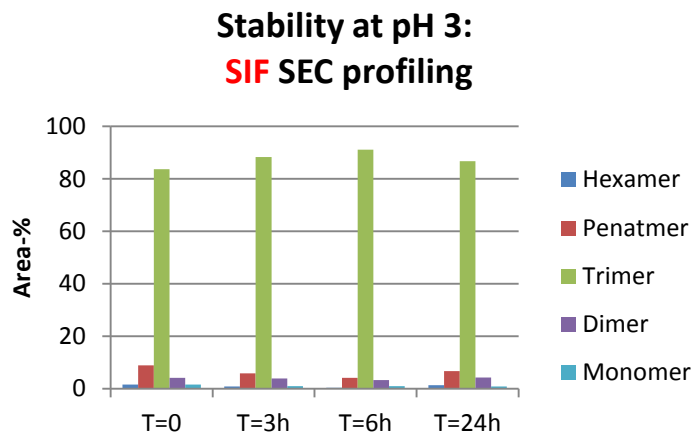
Assessment parameters :

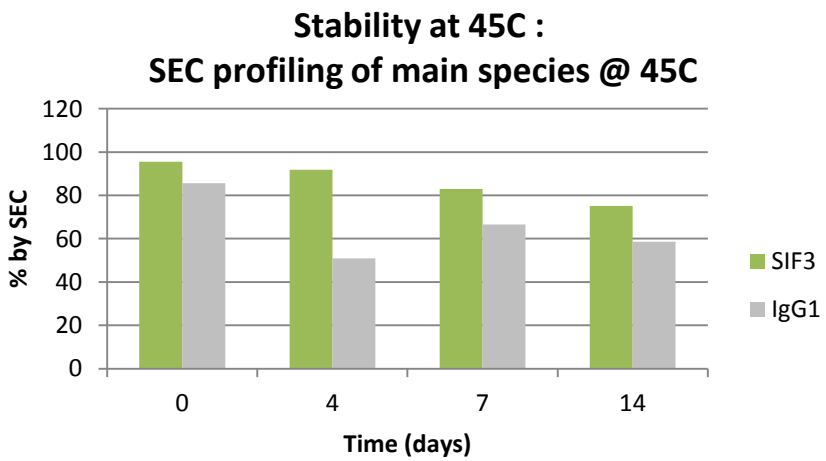
- PK assay: day -5, 6, 13, 20 & day 27
- ADA assays: day -5, 6, 13, 20 & day 27
- Cytokines: day -5, 3, 10, 13, 17 & 27
- Complement deposition in tissues-IHC Day 13 & 27
- Complement assay with Plasma
- PAF assay: day 13 & 27
- Blood cell count, Vet Scan: Day 13 & 27
- Toxicity/Clinical chemistry: Day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

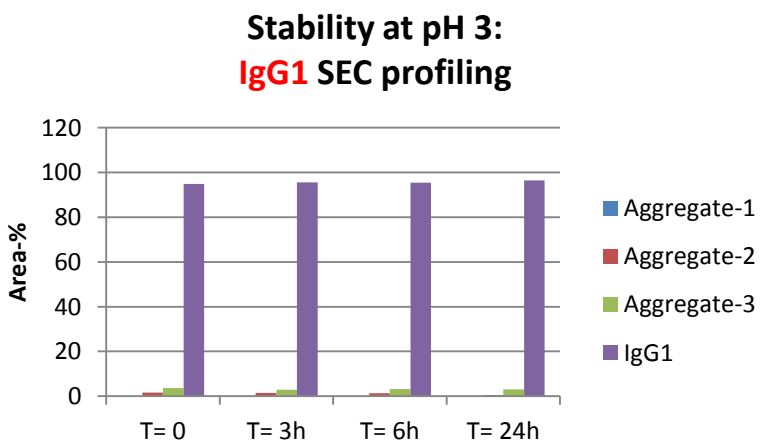
SIF3 was well-tolerated and no remarkable findings were observed

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**

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-mediate pathology and activated FcγR system
- Potential as a personalized therapy