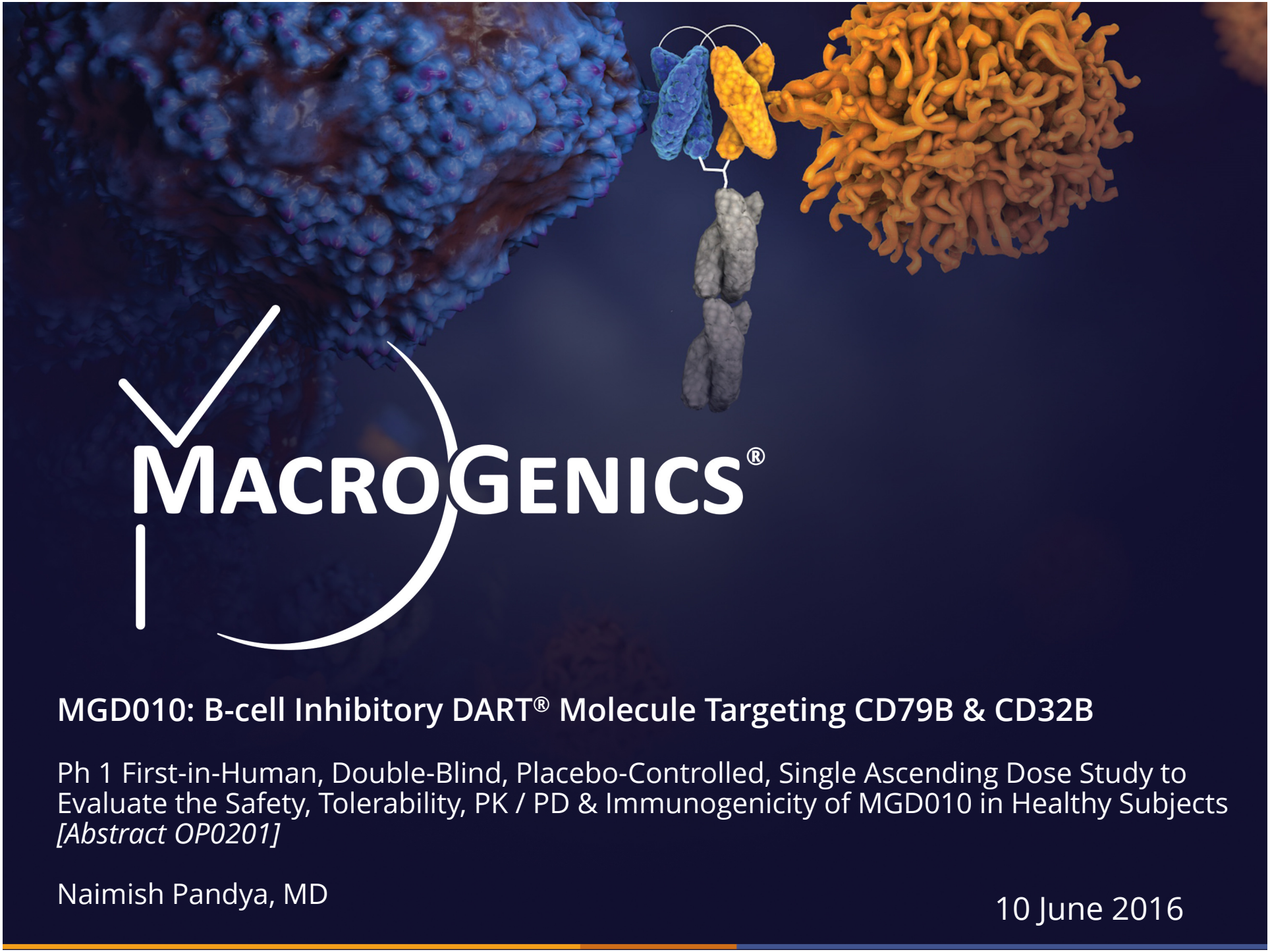


MACROGENICS®

MGD010: B-cell Inhibitory DART® Molecule Targeting CD79B & CD32B

Ph 1 First-in-Human, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, PK / PD & Immunogenicity of MGD010 in Healthy Subjects *[Abstract OP0201]*

Naimish Pandya, MD

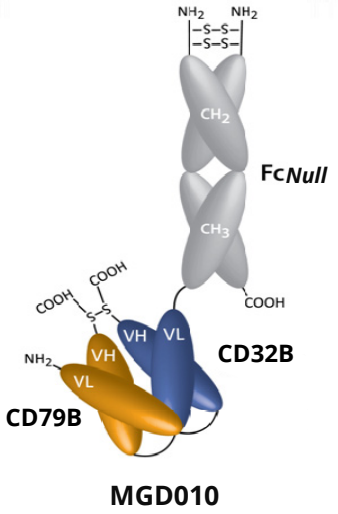
10 June 2016

DISCLOSURES

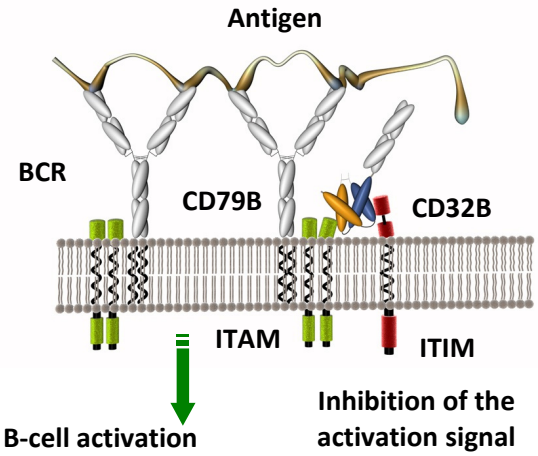
- Employee of MacroGenics

Introduction

- B cells play an important role in immune tolerance and autoimmunity
  - CD32B (FcγRIIb): a checkpoint molecule on B cells
  - CD79B: signal transducing component of B-cell receptor
- MGD010, a bi-specific Dual-Affinity Re-Targeting (DART®) molecule, inhibits B-cell activation
  - Co-ligation of CD32B with CD79B leverages a natural physiologic B-cell inhibitory loop, delivering a negative signal that limits B-cell activation
- **MGD010 provides a novel therapeutic approach to autoimmune disorders**
  - Non-depleting intervention (*vs* rituximab)
  - Rapid onset of activity (*vs* belimumab)



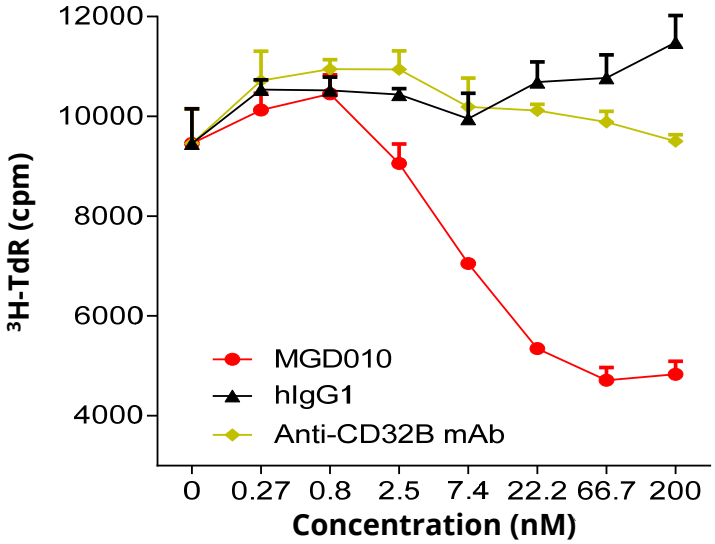
MGD010



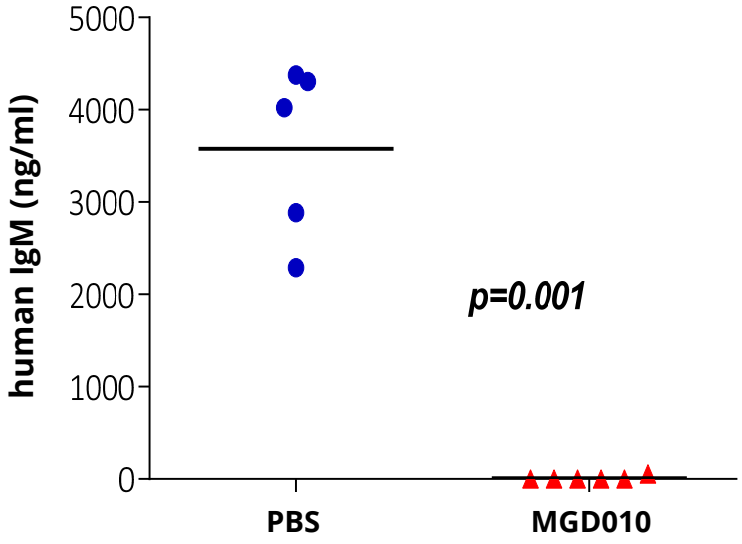
MGD010-mediated Inhibition of B-cell Function

Inhibition of B-cell Proliferation in vitro and Immunoglobulin Secretion in vivo

Inhibition of BCR-induced B-cell Proliferation



Blockade of Ig Secretion in Humanized Mouse Model



- Co-ligation of both targets is essential for functional activity of MGD010
  - Monospecific engagement of CD32B does not result in B-cell inhibition
  - Preclinical models confirm inhibitory properties of MGD010 with a decrease in B-cell proliferation and suppression of immunoglobulin secretion

Study Objectives

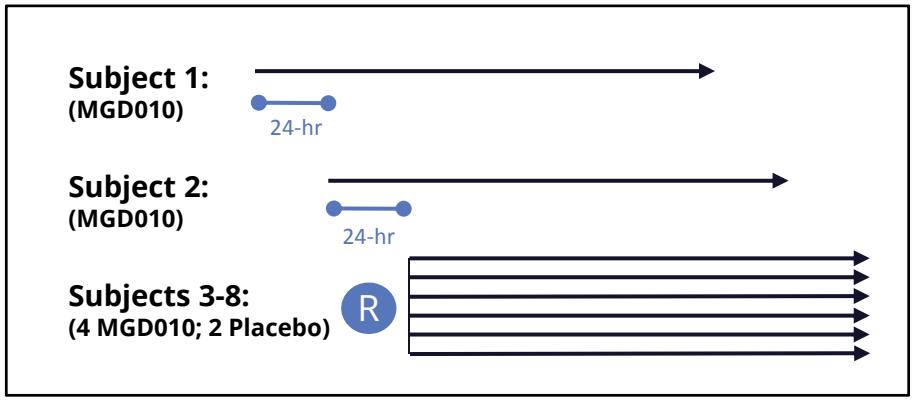
- **Primary Objective**
  - Assess safety and tolerability of single dose of MGD010 in healthy adult subjects
- **Secondary Objectives**
  - Evaluate single MGD010 dose pharmacokinetics
  - Assess pharmacodynamics effects of MGD010 on humoral immune responses
  - Evaluate potential anti-drug antibodies
- **Exploratory Objectives**
  - Evaluate MGD010 binding to CD32B and CD79B on peripheral B cells
  - Evaluate activation status of peripheral B cells and B-cell subsets
  - Assess immune phenotype, including modulation of B-cell subsets
  - Assess response of peripheral B cells to ex-vivo BCR stimulation

Eligibility

- **Key Inclusion criteria**
  - Age: 18 – 50 years
  - BMI: 18 – 30 kg/m^2
- **Key Exclusion criteria**
  - Women of child bearing potential or who are pregnant and/or breastfeeding
  - Medical history and concurrent diseases
    - Any significant acute or chronic medical illness (use of any prescription drugs within 4 wks of dosing or OTC drugs within 1 wk of dosing)
    - Major surgery within 4 wks of dosing
    - Smoking > 10 cigarettes per day
    - Infectious disease (TB, Hep B, Hep C, HIV)
    - Known history of autoimmune or vascular disorders
    - Physical and lab findings:
      - QTc > 450 msec, HR < 45 bpm or > 120 bpm, SBP > 140 mmHg, DBP > 90 mmHg
      - AST/ALT > 1.25 > ULN, Tbili > 1.25 x ULN, abnormal PT/PTT
      - Positive urine drug screen

Study Design

- **Enrolled healthy volunteers in six escalation cohorts**
  - Healthy volunteers represent homogeneous population to ascertain safety and pharmacodynamics effects of MGD010
- **Eight subjects to enroll at each dose cohort**
  - Six subjects were treated with MGD010 and two were treated with Placebo
- **Staggered dosing at each dose cohort to assess safety & tolerability**
  - Randomized 6 subjects in double-blind manner after treating two sentinel subjects with MGD010



Dose Cohort	MGD010 Dose (mg/kg)
1	0.01
2	0.1
3	0.3
4	1.0
5	3.0
6	10.0

Study Enrollment

Baseline Demographics	
N	49[a]
Age (yrs)	33.4 ± 7.4
Gender (M:F)	48:1
Race:	
White	12
Black	35
Other	2
Mean Weight (kg)	78.0 ± 12.1
Mean Height (cm)	177.5 ± 7.8

[a]Forty-nine subjects were treated in Dose Escalation: 0.01, 0.1, 0.3, 1, 3 or 10 mg/kg MGD010

Adverse Events

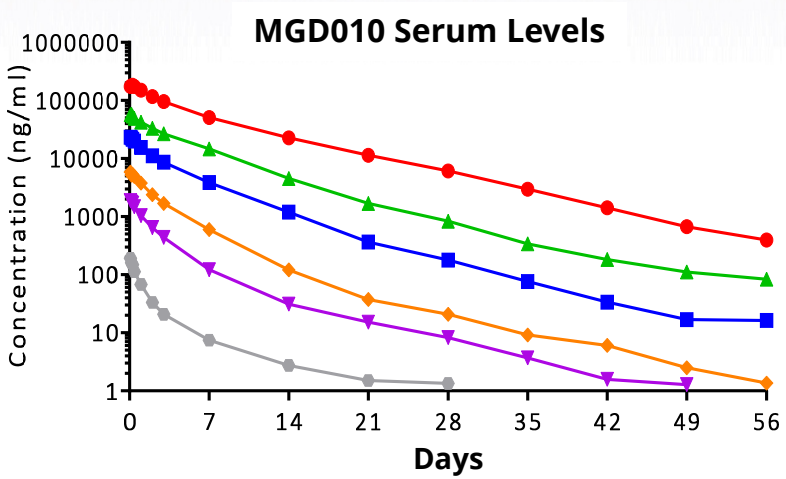
Adverse Event*	All Events		Related		Adverse Event*	All Events		Related	
	All	≥ Gr 3	All	≥ Gr 3		All	≥ Gr 3	All	≥ Gr 3
Conjunctival Haemorrhage	1	-	-	-	Periorbital contusion	1	-	-	-
Ocular Hyperemia	1	-	-	-	Muscle twitching	1	-	-	-
Pupils Unequal	1	-	-	-	Headache	3		3	-
Nausea	1	-	1	-	Somnolence	1	-	1	-
Chills	1	-	-	-	Terminal insomnia	1	-	-	-
Vessel puncture site bruise	1	-	-	-	Nasal congestions	1	-	-	-
Folliculitis	1	-	1	-	Rhinorrhea	1	-	1	-
Upper respiratory tract infection	2	-	2	-	Dry skin	1	-	-	-
Viral upper respiratory tract infection	2	-	-	-	Night sweats	1	-	1	-
Contusion	1	-	-	-	Pruritus	1	-	-	-
Ligament sprain	1	-	-	-	Rash	1		1	
Limb injury	1	-	-	-	Hypertension	1	1	-	-
Muscle strain	1	-	-	-					

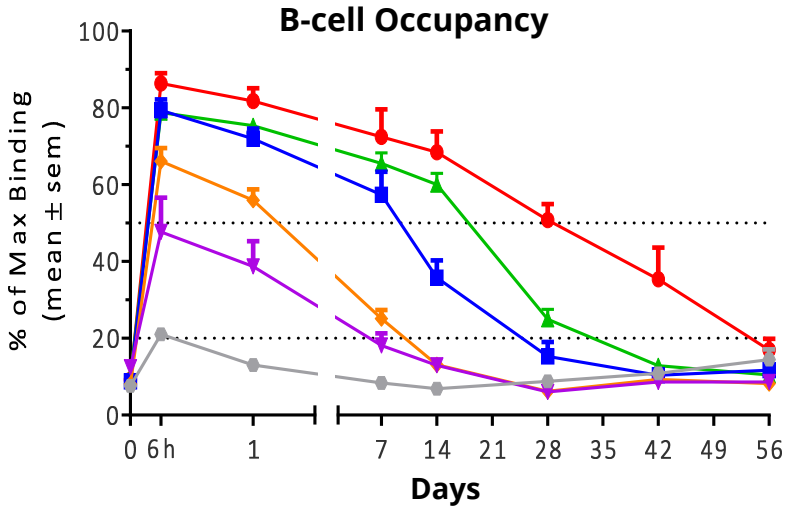
*MedDRA Preferred Term

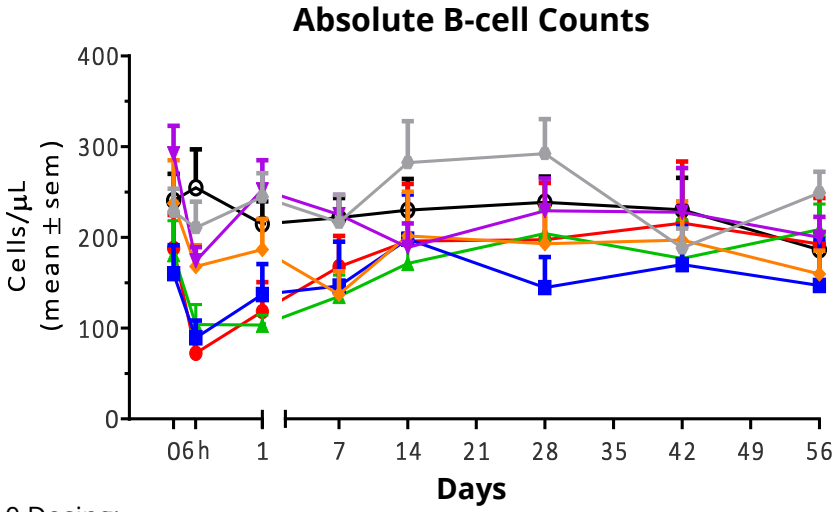
AEs assessed by 2007 FDA Guidance of Toxicity Grading Scale for healthy adult & adolescent volunteers enrolled in preventive vaccine clinical trials

Pharmacokinetics and Circulating B-cell Occupancy

- MGD010 serum concentrations increase linearly with dose
  - Half-life: ~8 days at ≥1mg/kg
- Maximum B-cell occupancy at doses ≥1 mg/kg
  - Sustained receptor occupancy beyond one week at doses ≥ 1 mg/kg
- No B-cell depletion or cytokine release (data not shown) at any dose levels



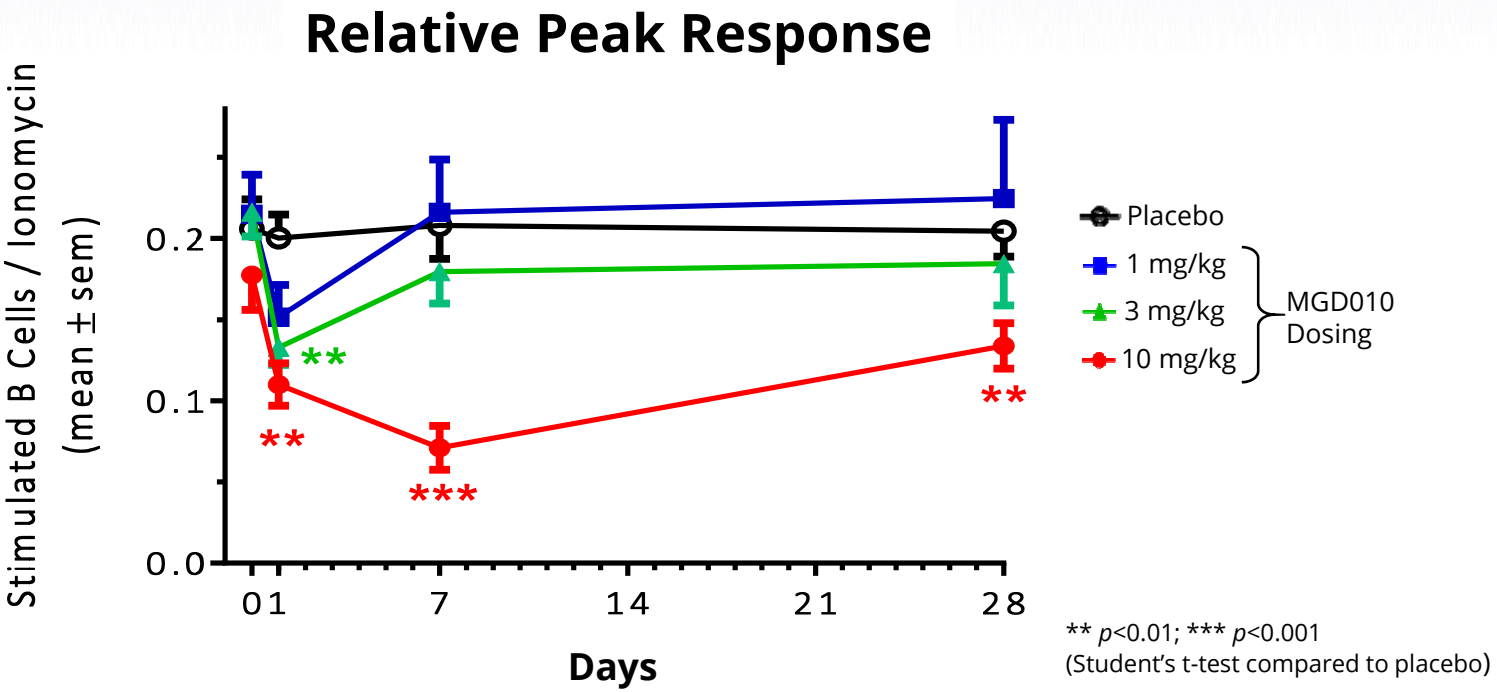




MGD010 Dosing:

Placebo | 0.01mg/kg | 0.1mg/kg | 0.3mg/kg | 1 mg/kg | 3 mg/kg | 10 mg/kg

Treatment with MGD010 Inhibited B-Cell Activation



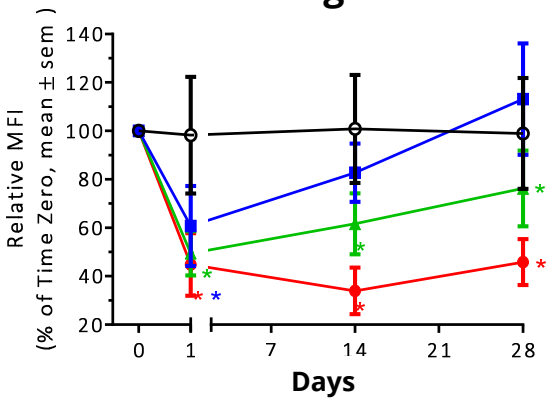
- PBMCs from enrolled subjects collected longitudinally after MGD010 treatment
  - Ca^{2+} flux (hallmark of B-cell activation) induced *ex vivo* by B-cell receptor ligation using anti-IgM
    - Data normalized to maximum Ca^{2+} permeability (maximum induction) via ionomycin
- Dose dependent B-cell inhibition demonstrated with increasing doses of MGD010
  - Inhibition sustained for several weeks at highest dose levels

MGD010 Modulated Cell Surface BCR and Serum Ig Levels

MGD010 Down-Regulation of Cell Surface Ig Expression

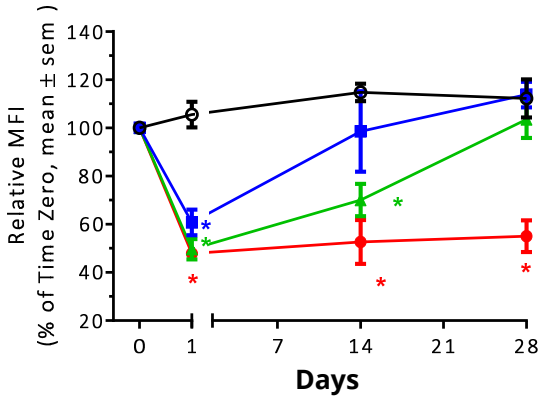
CD27 - Naïve B Cells

mIgD



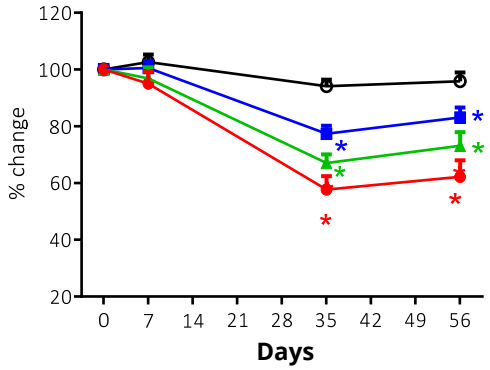
CD27 + Memory B Cells

mIgG

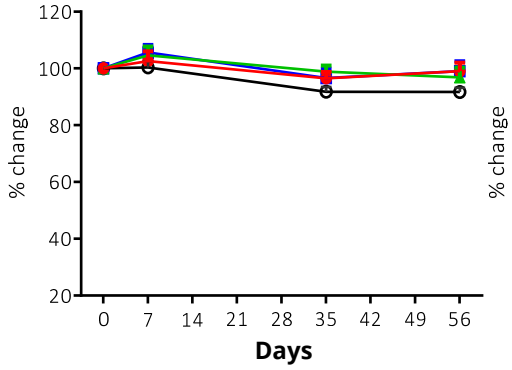


MGD010 Modulation of Circulating Serum Ig Levels

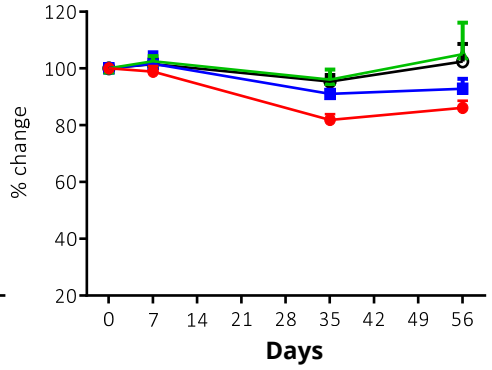
Serum IgM



Serum IgG



Serum IgA

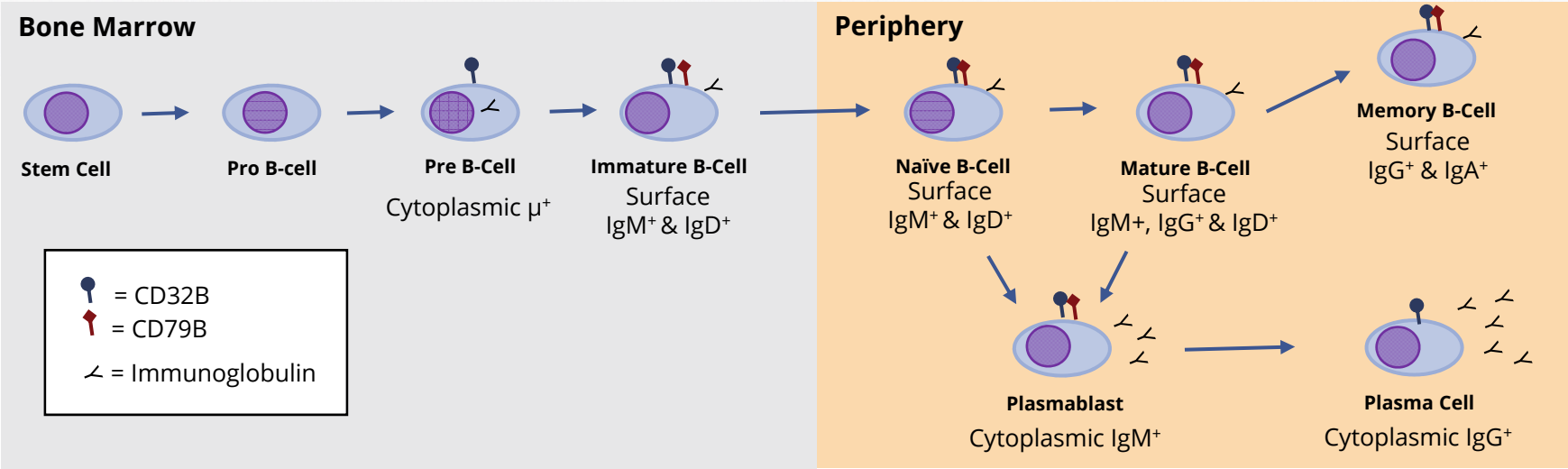


- Dose-dependent down modulation of cell surface BCR expression on both naïve and memory B cells

* $p<0.05$ (Paired t-test compared to baseline)

MGD010 Dosing:
Placebo
1 mg/kg
3 mg/kg
10 mg/kg

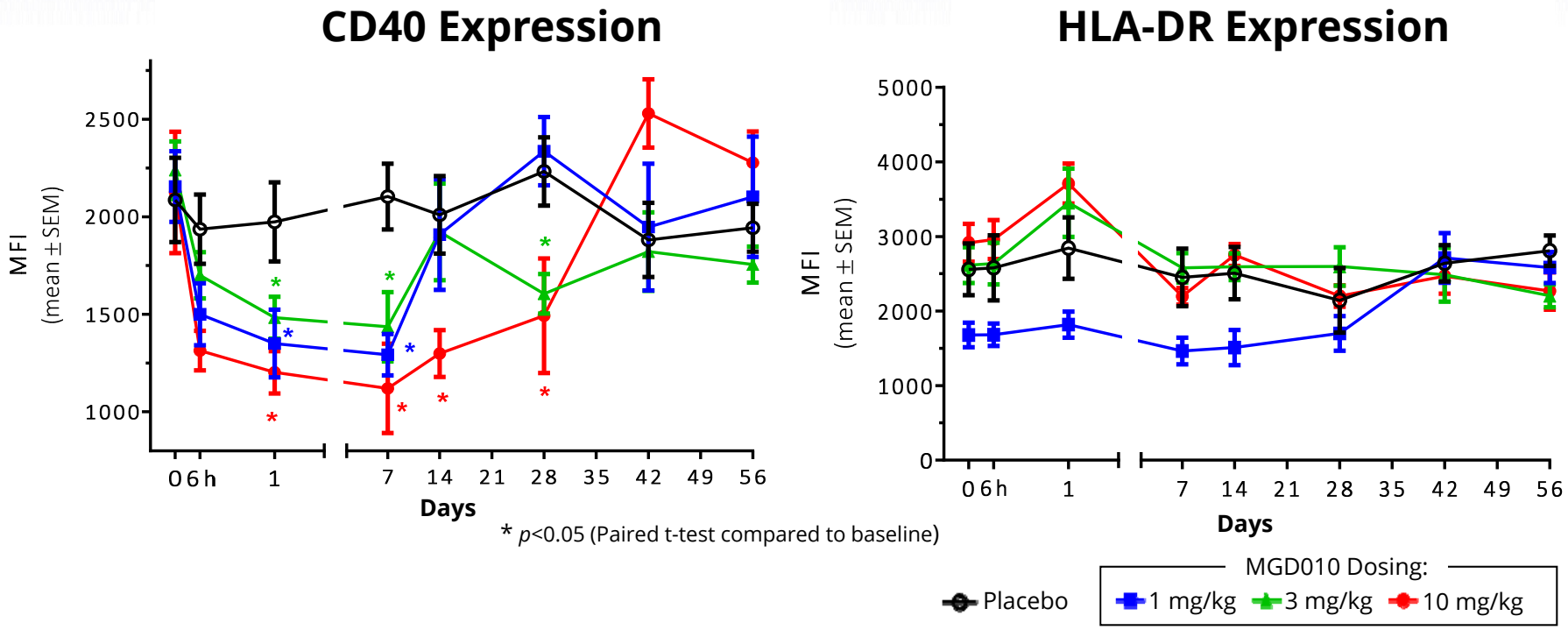
MGD010 Impacts Naïve & Mature B-cells



A single MGD010 dose in healthy volunteers:

- Modulated naïve and mature B-cell signal transduction via signaling blockade and/or down-regulation of surface Ig
- Decreased serum IgM levels, suggesting an impact on plasmablasts
  - Lack of CD79B expression on plasma cells is consistent with no effect on other serum Ig

MGD010 Reduced B-cell CD40 Expression



- MGD010 has potential impact on B-cell : T-cell interactions
  - Decreased cell surface expression of CD40, a B cell co-stimulatory molecule
  - No effect on other cell surface markers observed
    - HLA-DR (as shown), CD80/86, CD69, CD25

Summary

MGD010 is well tolerated as single dose up to 10 mg/kg in healthy subjects

1. No B-cell activation or cytokine release
2. No depletion of peripheral B cells
3. BCR saturated at ≥ 1mg/kg dose levels with sustained receptor occupancy with increasing doses

MGD010 down-modulated B-cell function at multiple levels

1. Reduction in BCR-induced Ca^{2+} mobilization
2. Decrease surface Ig expression
3. Decrease serum IgM levels

Data supports continued development of MGD010 in patients with autoimmune disorders

Acknowledgements

- In sincere appreciation to all volunteer subjects enrolled in this study for their contributions

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