Selected opportunities in Immunology

IVIG Composition and Method of Treatment of Antibody Deficient Patients

(BIO18376)

IVIG COMPOSITION AND METHOD OF TREATMENT OF ANTIBODY DEFICIENT PATIENTS (BIO 18376)

Product factsheet

Target

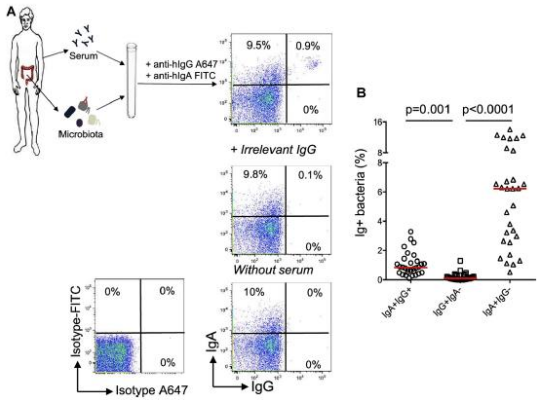
- **Target:**
  - Commensal Microbiota inducing gut dysbiosis and intestinal translocation in common variable immunodeficiency (CVID)
- **Product:**
  - Intravenous Immunoglobulins (IVIGs) composition – at least 1% of Ig from Selective IgA Deficiency (SIgAd)
- **Application:**
  - Antibody deficiency disorders such as immune diseases, inflammatory disorders and autoimmune disease
- **Rational / POC:**
  - Convergence of intestinal IgA and serum IgG toward the same bacterial cells + Interindividual variability and nonoverlapping anticommensal IgA and IgG molecular targets
  - Private antimicrobiota IgG specificities are induced in IgA-deficient patients
  - IgG specifically recognizes a broad spectrum of bacteria
  - High antimicrobiota IgG levels correlate with reduced systemic inflammation
  - Patients with SIgAd could benefit from oral IgA supplementation. Intravenous immunoglobulin preparations can be supplemented with IgG from IgA-deficient patient pools to offer better protection against gut bacterial translocations in patients with CVID
- **Patent and publication:**
  - *Synergistic convergence of microbiota-specific systemic IgG and secretory IgA. Translational and clinical Immunology. 2018*
  - PCT/EP2019/079369

IVIG COMPOSITION AND METHOD OF TREATMENT OF ANTIBODY DEFICIENT PATIENTS (BIO 18376)

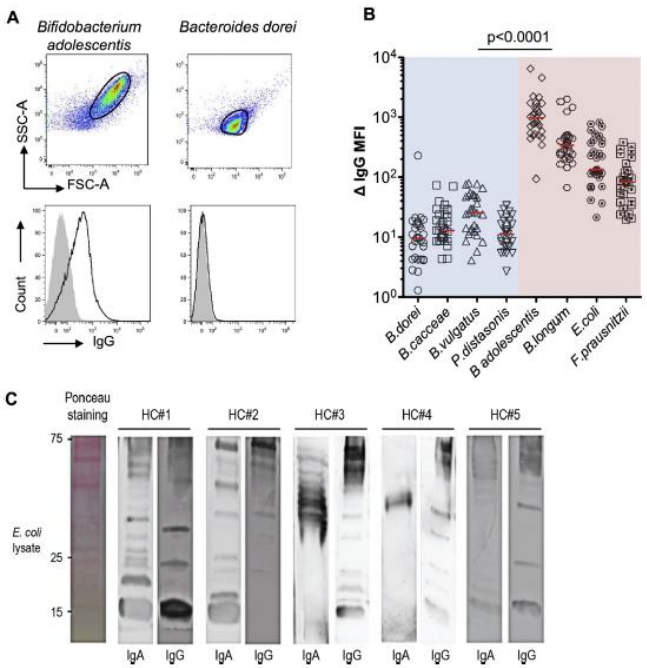
Rational

Convergence of Intestinal IgA and Serum IgG Toward the Same Bacterial Cells + Interindividual Variability and Nonoverlapping Anticommensal IgA and IgG Molecular Targets

- **Systemic IgG and secretory IgA recognize a common spectrum of commensals.**
  - (**A**) Representative flow cytometric dot plot showing (from bottom to top) isotype control, endogenous secretory IgA (without serum), human IgG anti-TNF (10 mg/mL, irrelevant IgG), and autologous systemic IgG (10 mg/mL) to fecal microbiota in a healthy donor.
  - (**B**) Flow cytometry analysis of the fraction of fecal microbiota bound by either secretory IgA, serum IgG, or both in healthy donors (n = 30). Median values are indicated, and subgroups are compared with a nonparametric Mann-Whitney test.



- **Systemic IgG binds a broad spectrum of commensals.**
  - (**A**) Flow cytometric analysis of serum IgG binding to cultivated bacterial strains. Gray histograms represent isotype controls, and dark lines represent anti-IgG staining.
  - (**B**) Flow cytometric analysis of serum IgG binding levels to 8 different bacterial strains in healthy donors (n=30). Blue strains (left) are typically poorly coated by secretory IgA from healthy subjects, and pink strains (right) are representative of typical IgA targets. Results are presented as delta median fluorescence intensity (MFI): IgG = MFI IgG serum - MFI IgG negative control. Red bars show medians.
  - (**C**) Representative immunoblotting of *E coli* lysates probed with 5 different healthy human serums, with normalized IgA and IgG levels. Ponceau staining indicates total amounts of bacteria lysates loaded. IgA and IgG binding were assessed by using a horseradish peroxidase–conjugated secondary antibody.



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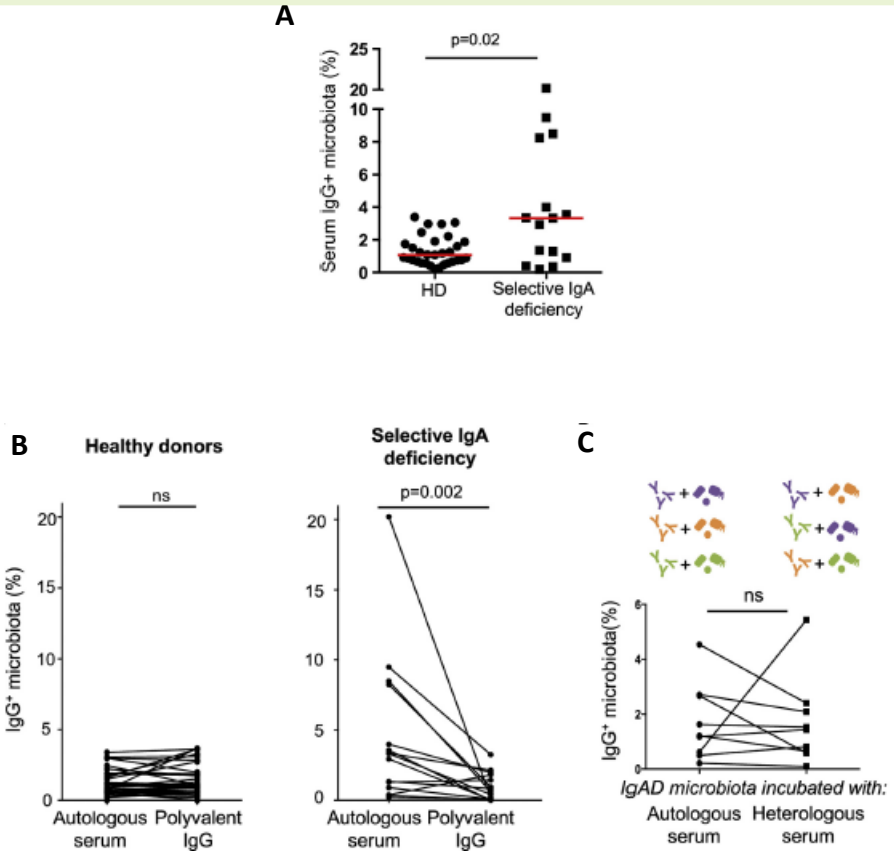
Rational

Private Antimicrobiota IgG Specificities are Induced in IgA-deficient Patients

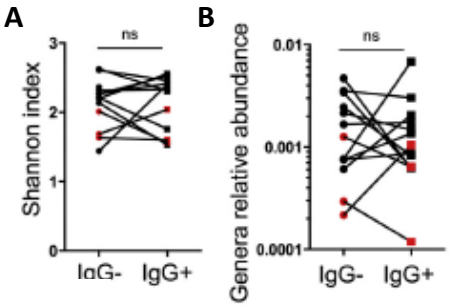
- **IgA-deficient patients harbor private anticommensal IgG responses.**
  - (**A**) Flow cytometric analysis of fecal microbiota bound by autologous serum IgG in healthy donors (n 5 30) and IgA-deficient patients (n 5 15). Red bars represent medians. P values were calculated by using the Mann-Whitney test.
  - (**B**) Flow cytometric analysis of the IgG-bound fecal microbiota with IgG from autologous serum or polyvalent IgG in healthy donors (n 5 30) and IgA-deficient patients (n 5 15). P values were calculated by using the Wilcoxon paired test.
  - (**C**) Flow cytometric detection of IgG on IgA-deficient microbiota (n59) after incubation with autologous serum or heterologous serum from another randomly chosen IgA-deficient subject. P values were calculated by using the Wilcoxon paired test. ns, Not significant.

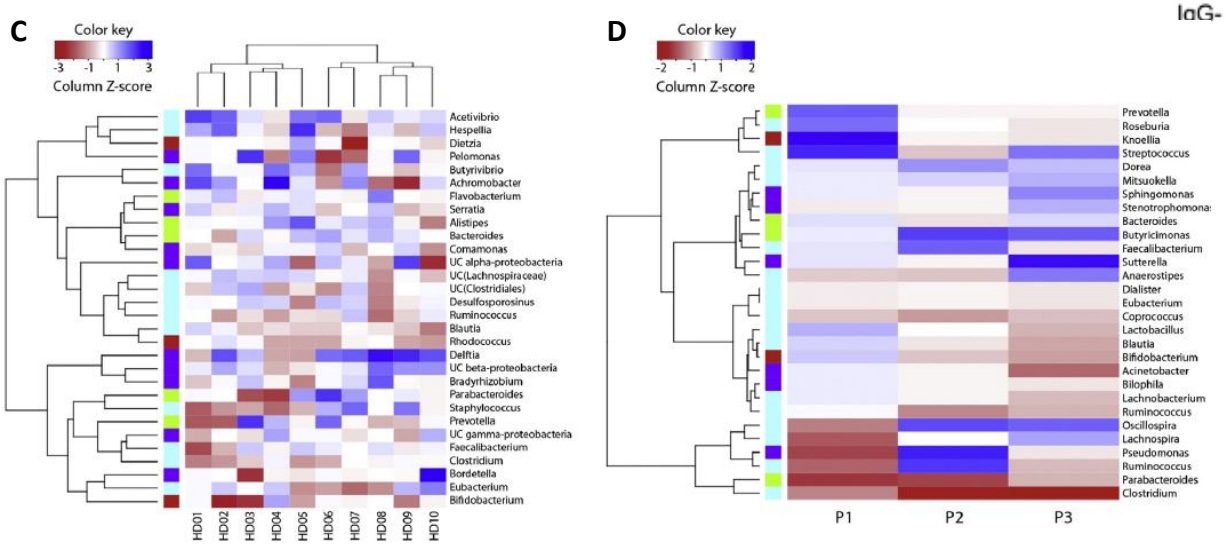


Rational

IgG Specifically Recognizes a Broad Spectrum of Bacteria

- **Private IgG antimicrobial signatures.**
  - (**A**) Genera diversity in IgG1 and IgG2 sorted fractions calculated by using the Shannon index. Dark symbols correspond to healthy donors, and red symbols correspond to IgA-deficient patients.
  - (**B**) Median relative abundance of genera in IgG1 and IgG2 sorted fractions. Dark symbols correspond to healthy donors, and red symbols correspond to IgA-deficient patients.
  - (**C**) IgG responses to the 30 most frequent genera in 10 healthy donors. IgG response to a given bacterium is expressed as a calculated IgG index (as defined in the box), outlining genera more likely serum IgG bound in red. Genera and subjects are grouped by using a hierarchical clustering algorithm.
  - (**D**) IgG responses (defined by IgG index) to the 30 most frequent genera in 3 IgA-deficient patients.

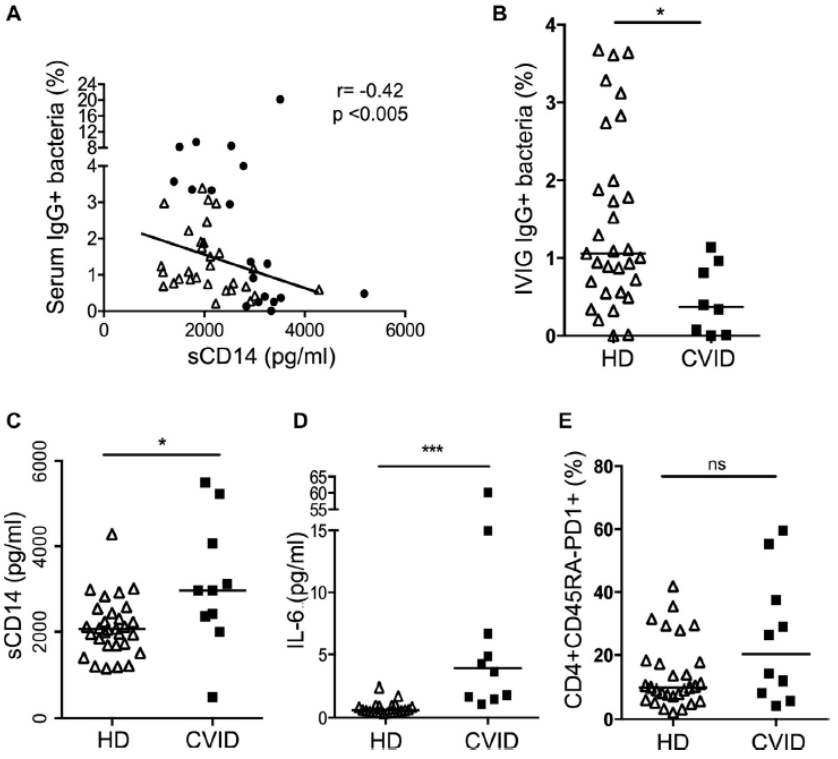


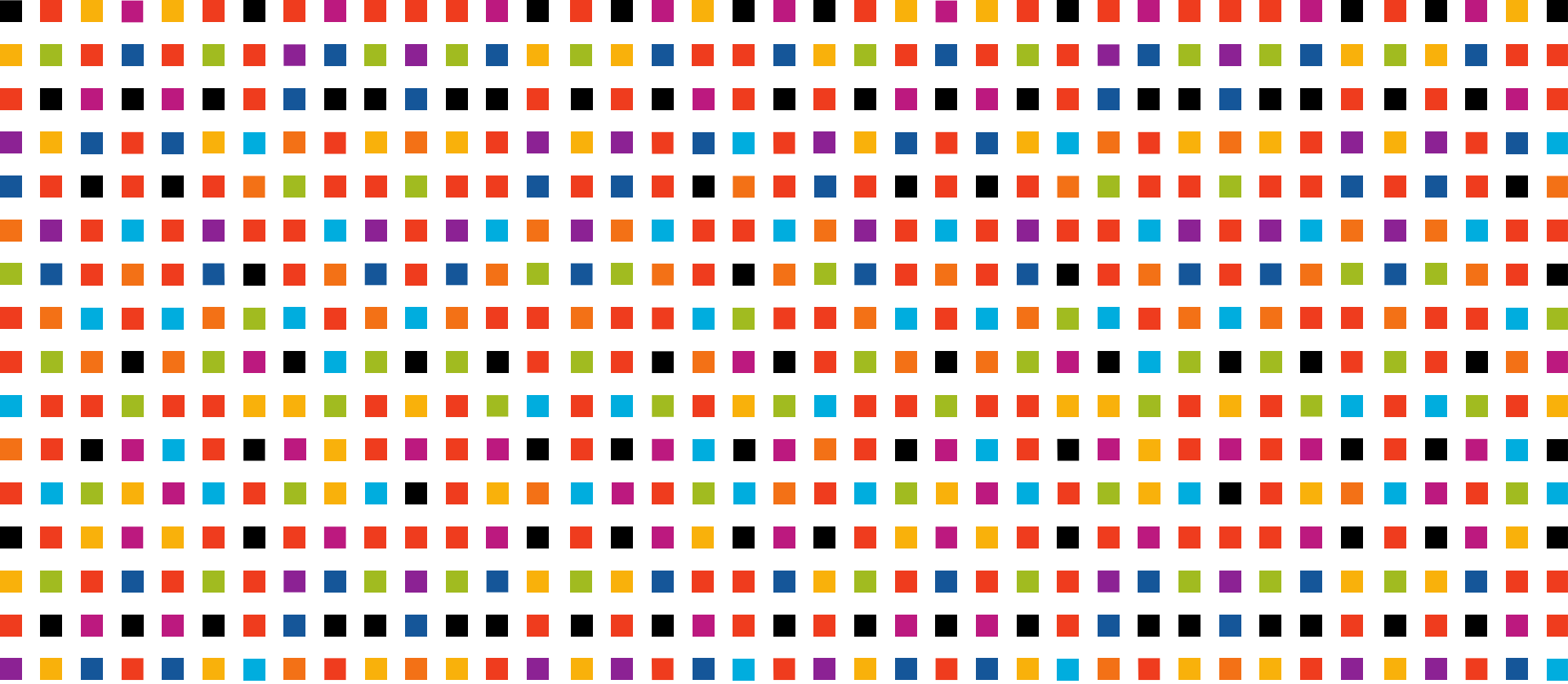


Rational

High Antimicrobiota IgG Levels Correlate with Reduced Systemic Inflammation

- **Microbiota-specific IgG and inflammation.**
  - (**A**) Percentage of serum IgG-bound microbiota correlated with sCD14 levels in autologous serum of healthy donors (triangles) and patients with SIgAd (dark points). Spearman coefficients (r) and P values are indicated.
  - (**B**) Flow cytometric analysis of IgG-bound microbiota after IVIG exposure in healthy donors and patients with CVID.
  - (**C**) sCD14 levels measured by means of ELISA in plasma of healthy donors and patients with CVID.
  - (**D**) IL-6 levels measured by using Simoa technology in plasma of healthy donors and patients with CVID.
  - (**E**) Flow cytometric analysis of CD4+CD45RA-PD-1+ lymphocytes in PBMCs of healthy donors and patients with CVID. Percentage among CD41 T cells is presented.





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