Dual IgA/IgG family autoantibodies from individuals at-risk for rheumatoid arthritis identify an arthritogenic strain of *Subdoligranulum*

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**Graphical Abstract**

**Conclusions**

*Subdoligranulum* isolate 7 is able to stimulate arthritis development characterized by C3, IgG, and IgA deposition

There is significant mature ILF development in the colon of isolate 7 gavaged mice

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**Hypothesis/Background**

A growing body of evidence supports the mucosal origins hypothesis of Rheumatoid arthritis (RA), indicating that the nidus for RA pathogenesis may begin at mucosal tissues. Herein we utilize human plasmablast-associated antibodies to identify and isolate an arthritogenic strain of *Subdoligranulum* and demonstrate high level mechanisms by which it immunomodulates its host. We hypothesize that our *Subdoligranulum isolate 7* is targeted by antibodies polyreactive against synovial targets, and is capable of inducing intestinal immune responses that become systemic responses cumulating in antibody-dependent joint inflammation.

**Methods**

Plasmablast-associated monoclonal antibodies (mAbs) were utilized as probes to determine binding against a diverse pool of commensal organisms. CD4+ T cells from individuals with RA were matched against *Subdoligranulum* strains 1 and 7, and CD154 and CD69 upregulation were determined.

Germ free DBA/1 mice were monocolonized with *Subdoligranulum* isolates 1, 7, and *Prevotella copri*. The mice were monitored for arthritis development weekly, and for microscopic joint damage after day 35. Joint slides from monocolonized mice were stained for endogenous complement C3, IgG, and IgA deposition, and were scored in a blinded fashion.

Colon from monocolonized mice were fixed and sectioned. ILF counts were performed. Total serum IgA was determined in monocolonized mice 14 days after bacterial gavage. Titers of autoantibodies against a variety of RA-relevant autoantigens was determined.

Serum from monocolonized mice was transferred intraperitoneally into healthy mice, and then mice were monitored weekly for arthritis development.

**Figure 1:** *IgA/IgG family plasmablast-derived mAbs cross-react with RA-relevant antigens and bind families Lymphoepithelioma and Lymphoepithelioma.

**Figure 2:** Monoclonized *Subdoligranulum* strains targeted by plasmablast mAbs and stimulate CD4+ T cells from RA patients.

**Figure 3:** *Subdoligranulum* strain stimulates joint swelling and inflammation in mice.

**Figure 4:** *Subdoligranulum* monocolonized mice exhibit increased IgG, IgA, and complement C3 deposition in joints.

**Figure 5:** *Subdoligranulum* isolate 7 causes development of increased serum IgA and systemic RA-related autoantibodies that are able to recapitulate phenotype through serum transfer.

**Figure 6:** *Subdoligranulum* isolate 7 causes development of intestinal isolated lymphoid follicles at colonic epithelum.