

Plasma cell targeting for durable remission in an antibody associated subgroup of Long COVID

A testable hypothesis and staged research framework

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Abstract

Passive transfer studies show that immunoglobulin G (IgG) from some people with Long COVID can induce neurological abnormalities in mice. These findings support pathogenic IgG activity in experimental systems, but do not establish the antibody source, its necessity for ongoing human illness, or the reversibility of established injury. I propose that, in a subgroup with neuropathic or autonomic manifestations and reproducible pathogenic IgG activity, long-lived plasma cells contribute to persistent disease and may represent a target for durable remission. This proposal contains three separable hypotheses: IgG contributes to disease; a persistent plasma-cell compartment maintains the relevant IgG; and reducing that compartment improves clinical outcomes. Negative trials of antibody-directed interventions constrain these hypotheses and cannot be dismissed solely as failures of patient selection or transient antibody removal. A staged program should first validate functional assays against experimental pathogenicity, then investigate antibody production and persistence, and only then undertake a biomarker-enriched randomized trial with adequate safety oversight. Clinical efficacy should be assessed by a prespecified between-group comparison, with longitudinal antibody activity and target engagement providing supporting mechanistic evidence. Durable clinical improvement would support further development but would not, by itself, prove a long-lived plasma-cell mechanism. This manuscript proposes research; it reports no new patient data and does not establish a treatment for Long COVID.

1 Background and scope

Long COVID encompasses overlapping clinical presentations, making it important to specify the population and biological process a treatment is intended to address. Passive transfer experiments provide a rationale for investigating an antibody-associated neurological subgroup. De Sá and colleagues reported that patient IgG induced pain and fatigue-like phenotypes, altered coordination, and small-fiber injury in mice [1]. Chen and colleagues independently reported pain-associated behavioral effects after patient IgG transfer, with effects varying across patient subgroups [2].

These experiments demonstrate that selected patient IgG preparations can produce disease-relevant effects under the conditions tested. They do not establish that all Long COVID is antibody-mediated, that all tissue-binding antibodies are pathogenic, or that the same antibodies are necessary to maintain illness in humans. Demonstrating pathogenic activity in a mouse also does not identify the human cells producing that activity. These distinctions define the research questions addressed here.

The proposed population has persistent Long COVID with prominent dysautonomia, neuropathic pain, or small-fiber abnormalities, together with reproducible IgG activity in a validated research assay. Clinical phenotype alone would not establish the proposed mechanism. The framework is intended to connect an experimentally supported signal to a test of disease modification without assuming the missing causal steps.

2 The hypothesis and its alternatives

The central hypothesis is that a long-lived plasma-cell compartment sustains pathogenic IgG activity in a subset of patients, and that reducing production sufficiently and for long enough allows clinically meaningful recovery. Durable remission is a proposed outcome, not an established consequence of plasma-cell depletion.

Three claims must be tested separately. First, the relevant IgG activity must contribute to disease rather than merely accompany it. Second, a persistent plasma-cell compartment must be an important source. Third, the ongoing effects must remain sufficiently reversible for treatment to improve symptoms and function. Support for one claim does not establish the others.

Alternatives include continuing generation of short-lived antibody-secreting cells, repeated activation of autoreactive memory B cells, persistent antigenic stimulation, and disease sustained by downstream injury after the initiating antibody response has subsided. Non-antibody mechanisms may coexist. Persistent antibodies or failure of a B-cell-directed treatment cannot, alone, distinguish these explanations.

The proposed sequence is infection-associated immune dysregulation, emergence of pathogenic IgG, persistence of its cellular source, and continuing neural or vascular dysfunction. Tissue injury could reinforce autoreactivity, but that feedback loop is an additional hypothesis. Long-lived plasma-cell survival and continued recruitment of new antibody-secreting cells should not be treated as interchangeable mechanisms.

A further distinction concerns how pathogenic IgG acts, not only which cells produce it. Transferred IgG could disrupt function through antigen binding by its Fab region, or through its Fc region engaging Fcγ receptors on effector cells, producing antibody-dependent phagocytosis, cellular cytotoxicity, or immune-complex-driven neuroinflammation. These routes are not mutually exclusive, and the transfer evidence does not settle which predominates; de Sá and colleagues reported enhanced antibody-dependent phagocytosis for one target, an Fcγ-receptor-dependent effector function [1]. The distinction matters here because a largely Fab-mediated mechanism and a largely Fc- or Fcγ-receptor-mediated mechanism imply different functional assays and different additional therapeutic options, while

neither, by itself, changes the rationale for reducing antibody production at its source.

3 Evidence from plasma cell targeting

Fluge and colleagues studied daratumumab in an open-label pilot involving ten women with ME/CFS. Six showed clinical improvement, with five having major sustained improvement during the reported follow-up [3]. The study offers a rationale for further investigation, but its small size, lack of a control group, and different study population prevent inference of efficacy in Long COVID. The reported association between baseline natural-killer-cell counts and improvement remains exploratory rather than a validated selection rule.

Daratumumab also affects CD38-expressing cells beyond plasma cells; the pilot documented natural-killer-cell depletion [3]. A response to anti-CD38 treatment would therefore not uniquely identify plasma-cell depletion as the therapeutic mechanism. The proposed contribution here is a staged Long COVID program linking functional IgG activity, evidence about its cellular source, and controlled clinical outcomes. Plasma-cell targeting itself is an existing therapeutic hypothesis [3].

4 What previous trials constrain

Prior negative studies are evidence against benefit from the tested interventions in the enrolled populations. They may leave narrower hypotheses unresolved, but they do not provide affirmative evidence that a different intervention will work.

The randomized IAMPOCO crossover trial enrolled 40 patients and found no symptom benefit from immunoadsorption over sham despite antibody reduction [4]. A separate randomized trial assigned 50 participants to six sessions of therapeutic plasma exchange or sham and found no discernible clinical benefit over its 90-day follow-up [5]. These findings require examination of which IgG activities were reduced, by how much, and for how long. Rebound, tissue distribution, inadequate biological selection, and persistent injury are possible explanations to test, rather than established reasons for the null findings.

BC007 evidence must be separated by study. The small exploratory reCOVER trial reported favorable findings and used functional GPCR-autoantibody assessment [6]. Its publication described a sponsor-reported failure of the larger BLOC study to meet its primary endpoint; that report is a different evidentiary category from a full trial publication. BLOC is registered as NCT05911009 [7]. Functional GPCR assays differ from binding assays such as ELISA; however, functional receptor activity does not automatically establish the tissue-pathogenic mechanism proposed here.

The efgartigimod ALPHA program in post-COVID POTS assessed outcomes over a 24-week treatment period; the sponsor discontinued development in this indication following the results [8]. This repeated-treatment design cannot reasonably be grouped with a single antibody-removal procedure. Whether the relevant pathogenic IgG activity was suppressed adequately is a specific question for pharmacodynamic data and banked samples.

The negative RituxME trial tested rituximab in ME/CFS rather than an IgG-defined Long COVID subgroup [9]. Its result does not establish long-lived plasma cells as the remaining explanation. Any proposed advantage of plasma-cell targeting must be demonstrated directly rather than inferred from rituximab failure.

5 Stage one validating the selection assay

The first study should test whether a reproducible laboratory measure identifies IgG with disease-relevant activity. Tissue binding, altered cell function, and experimental pathogenicity should be evaluated separately. A positive result in one category must not be used as a substitute for the others. Because disease-relevant activity may act through antigen binding or through Fcγ-receptor-mediated effector function, the assay program should include effector-function readouts, for example antibody-dependent phagocytosis or cellular cytotoxicity and Fcγ-receptor engagement, and not binding alone.

An assay-development cohort should include patients with the proposed neuropathic or autonomic phenotype, patients with other Long COVID presentations, recovered individuals, and appropriate healthy or disease controls. Record illness duration, severity, infection history, vaccination timing, and relevant medications. Process samples in blinded batches and assess test-retest reliability, dilution effects, assay interference, and inter-laboratory reproducibility. Develop thresholds in one dataset and evaluate performance in an independent validation dataset.

Where a candidate target or antibody fraction can be identified, a useful causal experiment would compare intact patient IgG, selectively depleted IgG, and depleted IgG with the candidate fraction restored. Loss of the effect after selective depletion, followed by restoration after add-back at matched exposure, would strengthen attribution. To separate Fab-mediated from Fc-mediated activity, a parallel experiment would compare intact IgG with F(ab')₂ or Fab fragments that lack Fc, test activity in Fcγ-receptor-deficient systems, and test enzymatically deglycosylated IgG that cannot engage Fcγ receptors; loss of activity when Fc engagement is removed would localize the mechanism. Total IgG concentration, handling, and nonspecific depletion effects need appropriate controls. Where antigen specificity is unresolved, the uncertainty should remain explicit.

Passive transfer can support validation in a limited research subset; it is not proposed as routine clinical screening. Banked samples from completed trials may help determine whether the proposed activity was present and whether treatment altered it. Such analyses would be retrospective and hypothesis-generating unless independently confirmed. Feasibility depends on sample availability, volume, quality, timing, and consent permissions.

6 Stage two identifying the antibody source

A second study should distinguish persistent production by long-lived plasma cells from continuing replenishment by other B-cell compartments. Serial functional activity, antigen-specific antibody measurements where available, B-cell and plasmablast phenotyping, and antibody or B-cell receptor sequence tracking could contribute. These are complementary observations; none should be assumed to identify the source on its own.

Direct investigation of tissue or marrow plasma cells would require a strong scientific and ethical justification. An important objective would be to connect an antibody secreted by a candidate cell population to the activity measured in stage one. Stable circulating antibody levels, total IgG reduction, or peripheral blood cell counts alone would not demonstrate depletion of the relevant long-lived tissue compartment.

The program should assess whether persistent antigenic stimulation or another immune process could regenerate the pathogenic response after treatment. Durable remission may require addressing that process as well as reducing antibody production. Antigen measurements can be exploratory stratifiers, but an unvalidated negative blood assay should not be interpreted as excluding a tissue reservoir.

7 Stage three a randomized proof of mechanism trial

This is a conceptual framework, not a complete trial protocol. Progression should depend on reproducible assay performance, a credible pharmacodynamic strategy, and an acceptable benefit-risk assessment. Agent selection, dosing, eligibility, stopping rules, and sample size require a multidisciplinary trial team, regulatory review, and patient partnership.

Population and allocation. A focused initial study could enroll adults with persistent Long COVID, a clinically documented autonomic presentation, and the validated IgG activity. Small-fiber abnormalities could define a nested subgroup. Record and stratify illness duration rather than assuming that an 18-month threshold excludes spontaneous improvement. Use concealed randomization to plasma-cell-directed therapy or an appropriate matched placebo, with blinded outcome assessment and laboratory analysis. Prespecify how premedication, background care, rescue therapy, and potential unblinding will be handled.

Clinical efficacy. For an autonomic cohort, a candidate primary endpoint is between-group change in COMPASS-31 at week 24, with the final choice determined by measurement suitability and a justified clinically meaningful effect. Standardized active-stand or tilt responses, daily function, and longitudinal symptom burden should provide complementary outcomes. Repeat skin biopsy could be a secondary endpoint in a prespecified small-fiber subgroup, with centralized blinded reading. These measures assess different aspects of illness; a prespecified endpoint hierarchy should separate the primary clinical question from secondary physiological and histological questions.

Target engagement. Measure the specific functional IgG activity serially, alongside total immunoglobulins and relevant immune-cell phenotyping. Distinguish reduced antibody concentration from reduced biological activity. Establish assay methods that account for therapeutic antibody interference and other treatment-related changes. General immunoglobulin reduction is insufficient evidence that the pathogenic activity was reduced or that its source was eliminated.

Mechanistic analysis. Prespecify longitudinal models testing whether treatment changes IgG activity and whether earlier changes predict subsequent clinical outcomes. Analyze all randomized participants rather than selecting responders after treatment. Such associations support a mechanistic explanation but do not establish mediation without additional assumptions. A biomarker-positive-only trial can test benefit in that population; it cannot show that the biomarker predicts differential benefit. That claim would require an ethically justified randomized biomarker-negative stratum and a treatment-by-biomarker interaction analysis.

Durability. Continue follow-up for at least 12 months after the final dose as a proposed design target, adjusted to pharmacology and observed recovery kinetics. Prespecify a sustained clinical response and record relapse, reinfection, rescue treatment, and background medication changes. Improvement after dosing ends may still reflect ongoing pharmacological effects. A claim of remission beyond those effects requires corresponding exposure and biological recovery data.

Statistical design. Base sample size on a defensible effect size, variability, missingness, attrition, and the chosen primary endpoint. Enrichment does not guarantee that a cohort of a few dozen will be adequate. Report intention-to-treat results, confidence intervals, and prespecified handling of intercurrent events and multiplicity. A small feasibility study can estimate these parameters but should not be framed as a definitive efficacy trial.

8 Interpreting possible outcomes

A clinically meaningful randomized benefit accompanied by loss of pathogenic IgG activity would support an antibody-associated treatment mechanism. Evidence linking the relevant activity to a persistent plasma-cell population, and showing its reduction, would strengthen the more specific source hypothesis. Clinical benefit after anti-CD38 alone would remain compatible with other CD38-mediated effects.

Sustained reduction of validated pathogenic activity without clinical benefit would weaken the claim that suppressing that activity is sufficient for recovery at the tested disease stage. Interpretation would depend on magnitude, duration, tissue relevance, precision, and the time needed for repair. Persistent injury could explain continued disability without making the initiating antibodies harmless.

Clinical benefit without a measurable fall in the validated activity would weaken the proposed mediation pathway and prompt examination of assay limitations or alternative treatment effects. Failure to reduce the activity would primarily indicate failure to test the biological intervention as intended. Failure to link the activity to long-lived plasma cells would specifically weaken the source hypothesis even if IgG pathogenicity remained supported.

Comparable benefit across biomarker strata would challenge predictive selection only if both strata were randomized and the interaction estimate were sufficiently precise. A small null or subgroup comparison should not be presented as decisive refutation or confirmation.

9 Safety and patient participation

Anti-CD38 treatment is not established therapy for Long COVID. Daratumumab labeling identifies serious risks and practical requirements, including infections, administration reactions, cytopenias, hepatitis B reactivation, and interference with blood compatibility testing [10]. Immunoglobulin loss and changes in protective immunity also require monitoring. Safety observations from

ten participants cannot exclude uncommon or delayed harms [3].

Any trial would require specialist oversight, infection screening, immunoglobulin and blood-count monitoring, appropriate prophylaxis, and independent safety review. Reinfection prevention and access to clinical care should be integrated with patient partners. Persistent antigen and immunosuppression may interact; this possibility should be investigated without treating an unvalidated reservoir test as a reliable safety screen.

Patient partners should help design visits, remote measurements, and stopping criteria for post-exertional symptom exacerbation. Repeated maximal exercise testing is not proposed as a routine endpoint. Activity monitoring should measure ordinary behavior without prescribing an increase in activity. Patient-reported symptoms and function remain essential even when physiological or histological endpoints are included.

10 Contribution and limitations

This framework joins experimental IgG pathogenicity in Long COVID to a staged test of a plasma-cell-source hypothesis. It does not claim that plasma-cell targeting is a new concept, that a validated clinical selection assay already exists, or that an anti-CD38 response would establish a cure. No new experiments, patient observations, or quantitative evidence synthesis are reported.

The major uncertainties are the identity and reproducibility of the pathogenic activity, its source in humans, the reversibility of established injury, and treatment safety. The immediate priority is a blinded assay-validation study with independent replication and, where possible, selective depletion and add-back. A clinical trial becomes more informative when these uncertainties have been narrowed rather than embedded in its enrollment assumptions.

Disclosure of AI assistance

The original hypothesis and draft were developed with substantial assistance from LongCOVIDbot integrated with Claude by Anthropic. This revision was prepared with assistance from ChatGPT by OpenAI for source checking, scientific editing, and research-design clarification, and a subsequent revision added the Fab versus Fc / Fcγ-receptor distinction with assistance from Claude. AI-generated synthesis is not independent evidence. Michael Moran is the named author; the manuscript remains an author-review draft and requires final author verification before submission or public posting. No clinical study was conducted for this manuscript.

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