Immunotherapy with B cell activating antibody CPI-006 in patients with mild to moderate COVID-19 stimulates anti-SARS-CoV-2 antibody response, memory B cells, and memory/effector T cells.

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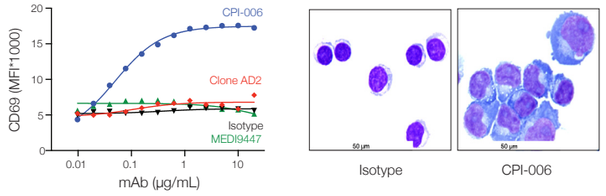
CPI-006 ACTIVATES B CELLS & INDUCES DIFFERENTIATION

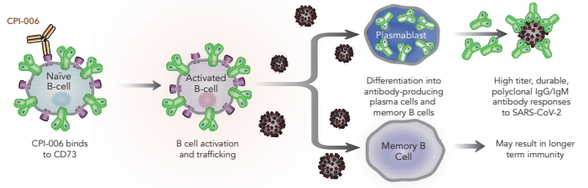
CPI-006 INDUCES CD69 EXPRESSION & PLASMABLAST DIFFERENTIATION



Left panel: B cell activation is unique to CPI-006 as other anti-CD73 antibodies do not induce CD69 expression. Expression of CD69 (MFI) was measured by flow cytometry. Right panel: Representative images of purified B cells cultured with isotype control or CPI-006 for 2 days.

IMMUNOTHERAPY OF COVID-19 WITH CPI-006

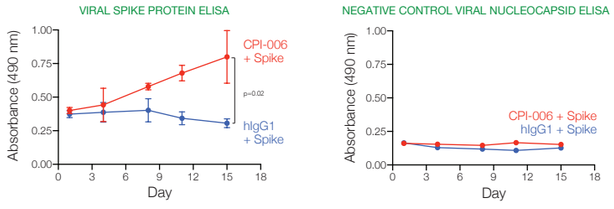
CPI-006 may increase anti-SARS-CoV-2 antibody responses to accelerate viral clearance, improve clinical outcomes, and impart long term immunity and protection from re-infection.



CPI-006 may be a foundational therapy for treatment or prevention of other infectious diseases or as an adjuvant to enhance the efficacy of vaccines.

VACCINATION OF HUMANIZED MICE WITH CPI-006 AND SPIKE PROTEIN ELICITS ANTIGEN SPECIFIC IMMUNITY

NSG-SGM3 MICE VACCINATED WITH SPIKE + CPI-006 MAKE ANTIGEN SPECIFIC HUMAN ANTI-SPIKE ANTIBODIES. MICE RECEIVING SPIKE + ISOTYPE DO NOT MOUNT A RESPONSE.



Mice (n=4/group) were immunized with the recombinant SARS-CoV-2 spike protein in incomplete adjuvant on Day 1 and treated with CPI-006 or human IgG1 control. Serum antibodies targeting the spike protein or viral nucleocapsid (negative control) were evaluated by ELISA.

PHASE 1 COVID-19 TRIAL & PATIENT CHARACTERISTICS

SINGLE DOSE (IV) ESCALATION STUDY IN HOSPITALIZED PATIENTS WITH MILD TO MODERATE COVID-19

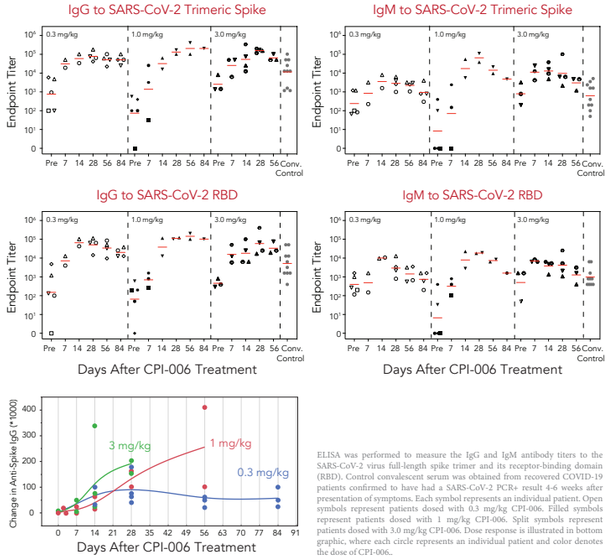
- ClinicalTrials.gov #NCT04464395. Enrollment has completed.
- No patient received convalescent plasma or other antibody therapy
- No drug related adverse events or changes in quantitative serum immunoglobulins
- 95% of patients were from high-risk racial groups

	Median Age Years (Range)	Median Days From POS to CPI-006 (Range)	Comorbidities	Median BMI in kg/m² (Range)	Median ALC k/mm³ (Range)	Median Time to Discharge (Range)
Cohort 4 (N=5) 5.0 mg/kg	56 (23-68)	5 (4-8)	DM, HTN, CKD, cancer	33.3 (23.3-47.5)	1.3 (0.7-2)	4.5* (3-8)
Cohort 3 (N=5) 3.0 mg/kg	53 (26-76)	5 (1-9)	DM, HTN, asthma, cancer	30.7 (26.5-33.9)	1.2 (1-2.2)	4 (2-23)
Cohort 2 (N=7) 1 mg/kg	63 (37-76)	7 (3->21)	DM,CAD, HTN, COPD	33.2 (16.5-35.1)	0.9 (0.6-2.3)	4 (2-12)
Cohort 1 (N=5) 0.3 mg/kg	48 (28-72)	4 (1-8)	DM, CAD, HTN asthma, cancer	30.3 (24.6-33.7)	1.3 (0.8-1.5)	3 (3-4)
OVERALL (N=22)	58.5 (23-76)	5 (1->21)		32.2 (16.5-47.5)	1.1 (0.6-2.3)	4* (2-23)

* One patient is still hospitalized
SoC=Standard of Care, DM=diabetes, CAD=coronary artery disease, COPD=chronic lung disease, CKD=chronic kidney disease, HTN=hypertension

MAGNITUDE AND DURATION OF ANTIBODY RESPONSES IN COVID-19 PATIENTS

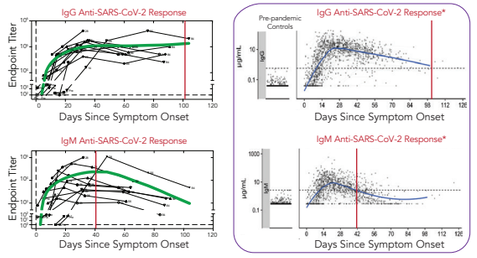
DOSE-DEPENDENT BOOSTING OF HUMORAL IMMUNITY



ELISA was performed to measure the IgG and IgM antibody titers to the SARS-CoV-2 virus full-length spike trimer and its receptor-binding domain (RBD). Control convalescent serum was obtained from recovered COVID-19 patients confirmed to have had a SARS-CoV-2 PCR+ result 4-6 weeks after presentation of symptoms. Each symbol represents an individual patient. Open symbols represent patients dosed with 0.3 mg/kg CPI-006. Filled symbols represent patients dosed with 1 mg/kg CPI-006. Split symbols represent patients dosed with 3.0 mg/kg CPI-006. Dose response is illustrated in bottom graphic, where each circle represents an individual patient and color denotes the dose of CPI-006..

ANTIBODY TITERS REMAIN ELEVATED 84+ DAYS AFTER PRESENTATION OF SYMPTOMS

CPI-006 TREATED PATIENTS COMPARED TO HOSPITALIZED PATIENTS IN LITERATURE*



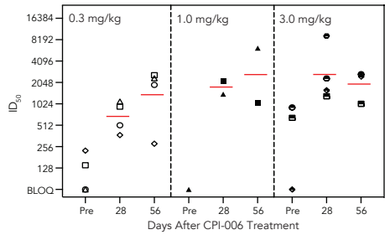
Left panels: IgG (top) and IgM (bottom) titers to SARS-CoV-2 in patients that were treated with CPI-006. Right panels: Concentrations of IgG (top) and IgM (bottom) in 343 North American hospitalized COVID-19 patients that did not receive CPI-006.

The red vertical line indicates the timepoint of seroreversion in Iyer et al study compared to hospitalized patients treated with CPI-006.

*Adapted from Iyer et al, Science Translational Med, 2020

NEUTRALIZING ANTIBODY ACTIVITY IN PSEUDOVIRUS ASSAY

INCREASED NEUTRALIZING ANTIBODY ACTIVITY IN COVID-19 PTS TREATED WITH CPI-006

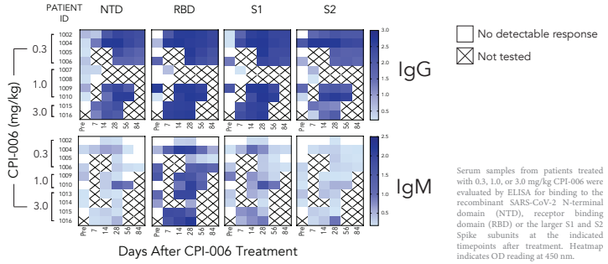


High and durable neutralization titers were observed in subjects following CPI-006 treatment. ID50 values up to 9000 that persist beyond 56 days following onset of symptoms compare favorably with those reported for other hospitalized COVID-19 patients, (Iyer et al., Sci. Immunol, Seow et al., Nat Microbiol)

SARS-CoV-2 spike pseudotyped lentivirus were produced with the Wuhan-Hu-1 isolate spike as the envelope glycoprotein and the firefly luciferase gene as a reporter. Neutralization activity was determined using heat inactivated serum mixed with pseudovirus before addition to HEK293T-hACE2 cells. Luciferase activity was measured seventy-two hours after transduction and SARS-CoV-2 neutralization titers were defined as the reciprocal dilution yielding a 50% reduction in signal relative to the average of uninhibited control wells.

ANTI-VIRAL ANTIBODY RESPONSES ARE POLYCLONAL AND POLYSPECIFIC

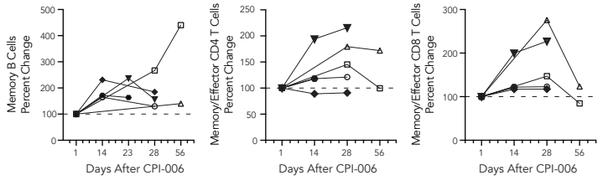
BROAD IgG ACTIVITY TO ALL SUBDOMAINS, IgM PREFERENTIALLY REACTS WITH THE RBD



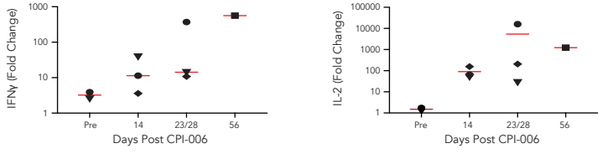
Serum samples from patients treated with 0.3, 1.0, or 3.0 mg/kg CPI-006 were evaluated by ELISA for binding to the recombinant SARS-CoV-2 N-terminal domain (NTD), receptor binding domain (RBD) or the larger S1 and S2 Spike subunits at the indicated timepoints after treatment. Heatmap indicates OD reading at 450 nm.

INCREASED MEMORY & ANTIGEN SPECIFIC CELL RESPONSES

FREQUENCY OF PERIPHERAL MEMORY B CELLS AND MEMORY/EFFECTOR T CELLS



INCREASE IN ANTIGEN SPECIFIC T CELL RESPONSES SUPPORTS Th1 BIASING



Top row: Flow cytometry used to measure the frequency of memory B cells ($CD19^{POS}IgD^{NEG}CD27^{POS}$) within $CD19^{POS}$ gate (left) or memory/effector $CD4^{POS}$ (mid) and $CD8^{POS}$ (right) T cells at baseline and after treatment in patients treated with 0.3-3.0 mg/kg CPI-006. Memory/effector T population was defined as $CD3^{POS}CD45RA^{NEG}$. Bottom row: Serial evaluation of PBMCs from patients treated with CPI-006 for ability to secrete IL-2 and IFNγ in response to SARS-CoV-2 membrane, nucleocapsid, and spike proteins.

CONCLUSIONS

- CPI-006 activates B cells, leading to lymphocyte trafficking, plasmablast differentiation, and antigen specific antibody secretion.
- In control experiments using humanized NSG-SGM3 mice, vaccination with CPI-006 and SARS-CoV-2 spike protein leads to an antigen specific humoral immune response. Mice receiving spike protein alone do not mount a response.
- Single doses of 0.3 mg/kg - 5 mg/kg CPI-006 are well tolerated in hospitalized COVID-19 patients with no drug related adverse events.
- Dose dependent increases in the titers of IgG and IgM to SARS-CoV-2 spike and RBD were significantly above convalescent controls.
- IgG and IgM titers to SARS-CoV-2 are sustained over 84+ days beyond presentation of symptoms.
- Mapping studies show polyclonal anti-viral responses targeting multiple epitopes within the N terminus, RBD, S1, S2 of SARS-CoV-2.
  - IgM antibodies preferentially targeted the RBD
- Increased frequencies of peripheral memory B cell and memory/effector T cell populations were observed following CPI-006 treatment
  - T cells release IFNγ and IL-2 consistent with antigen specific Th1 response
- B cell activation with CPI-006 may represent a novel immunotherapy for infectious diseases. A phase 3 randomized control trial in COVID-19 is planned.

Scan code for copy of medRxiv paper describing preclinical, translational, and clinical results in more detail

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