



Long-COVID

Prevention, Treatment,
& Mitigation

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BACKGROUND

NATURE OF LONG-COVID

- › Mysterious illness that follows COVID-19
 - › Can occur even in asymptomatic subjects, but more common with severe disease
 - › Not unique to COVID-19 as it also follows other viral infections (more cases now)
 - › Heterogenous symptoms which may occur in clusters
 - › Exact incidence is unknown (clinical vs. subclinical disease)
 - › Also termed post-acute sequelae of Covid (PASC) for direct viral effects (vs. indirect)
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SYMPTOMS OF LONG-COVID

- Consists of some 200 signs and symptoms and 50 conditions
- In one main study, four symptom clusters were described:
 - Cardio-respiratory;
 - Neurological;
 - Systemic-inflammatory;
 - Abdominal
- Most common reported symptoms are:
 - Fatigue
 - Brain fog
 - Cough, shortness of breath, breathing difficulties

DIAGNOSIS

- Symptoms appear or worsen >30 days to >90 days after COVID-19 diagnosis
 - Symptoms are not due to some other underlying condition or disease
 - Symptoms continue for months or even potentially years; new ones may appear
 - Most patients don't test positive for virus after initial acute phase (vs. chronic COVID-19 among immunosuppressed subjects)
 - Some subjects may test positive for spike protein in blood (new finding)
 - Symptoms may reflect the localization of the infection or its lingering effects
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PATHOPHYSIOLOGY

- Direct viral effects may lead to cellular damage and inflammation
 - Viral RNA or proteins may become incorporated into host genome or cells (vesicles)
 - Immune system dysfunction
 - Cytokine storm may be local or systemic
 - Continued exposure to viral proteins (e.g., spike protein) may exacerbate immune response
 - Abnormal blot clotting (Micro-clots) can lead to ischemia and stroke
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POTENTIAL TREATMENTS

PHARMACOTHERAPY

- Prevent infection (vaccination appears to lessen risk of Long-COVID)
 - Treat the infection (repertoire of agents diminished with Omicron subvariants)
 - Treat the symptoms (so far, nothing is effective)
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POTENTIAL FOR ENSEREPTIDE

- Ensereptide is a 25-amino acid subpeptide from lactoferrin
 - Ensereptide has several actions which contribute to wound healing:
 - Antimicrobial activity
 - Anti-fibrin activity
 - Modulation of immune response
 - Action of this peptide is limited by endogenous peptidases
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DESIGN A VECTOR

- › AAV6.2FF is a modified-capsid Adeno-Associated Virus with beneficial properties
 - › For our purposes, the vector was constructed using a triple plasmid method
 - › The vector carries the sequence for ensereptide and required regulatory elements
 - › Following IM administration of vector to mice, the peptide was expressed long term
 - › Potential for administration by inhalation to transfect lung cells for local expression
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POTENTIAL IN LONG-COVID

- Long-term expression of “*healing peptide*” in lungs or other sites
 - Mechanism of action includes:
 - Antimicrobial action - mostly against bacteria and fungi, potentially also viruses
 - Immunomodulation to slow immune cell recruitment and cytokine release
 - Antifibrin effects to stop formation of blood clots (common in lungs in Covid-19) as well as fibrin deposition in damaged lung (other) tissue
 - Healing of damaged tissues is promoted
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DEVELOPMENT PROGRAM

NON-CLINICAL STUDIES

- Proof of concept studies in vitro (cell culture, lung models, etc.)
 - Proof of concept and pharmacokinetics studies in vivo
 - Acute toxicity studies, including immunotoxicology
 - Special immunotoxicology (longer term) studies to support IND
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CLINICAL STUDIES

- › Phase 1, Phase 2 study in humans including PK component
 - › Phase 3 study in humans
 - › Early after testing positive for SARS-CoV-2
 - › Subjects at high risk for Long-COVID
 - › Endpoints of acute phase include hospitalization, death, severe disease
 - › Endpoint of chronic phase is number of subjects with Long-COVID
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