



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**
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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 blood 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**



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 enereptide 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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