AXA1125 in Long COVID - A Bibliography

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AXA Platform and Design

1) Hamill MJ, Afeyan R, Chakravarthy MV, et al. Endogenous metabolic modulators: emerging therapeutic potential of amino acids. *iScience* 2020;23:101628. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7569218/
Key takeaway: There is an opportunity to develop EMM compositions, which are uniquely designed to enable a comprehensive approach to multifactorial diseases and have the potential to simultaneously and safely target pathways to regulate biological processes that promote overall health.

2) Comb W, Cokol M, Flaender M, et al. Development of an in vitro platform to predict and screen combinations of endogenous metabolic modulators capable of influencing muscle physiology. International Conference on Frailty and Sarcopenia Research (ICFSR). March 11–13, 2020. https://axcellatx.com/publications/development-of-an-in-vitro-platform-to-predict-and-screen-combinations-of-endogenous-metabolic-modulators-capable-of-influencing-muscle-physiology/
Key takeaway: EMMs have a fundamental role in biology and function. Axcella has identified three EMM compositions to be investigated in IND clinical trials for their ability to diagnose, cure, mitigate, treat, or prevent targeted diseases. Development is pending final data readouts from ongoing non-IND clinical studies and feedback from the US FDA.

3) Bai JPF, Earp JC, Florian J, et al. Quantitative systems pharmacology: landscape analysis of regulatory submissions to the US Food and Drug Administration. *CPT Pharmacometrics Syst Pharmacol* 2021;10:1479–1484. https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/psp4.12709
Key takeaway: Through multiscale spatial and temporal modeling, quantitative systems pharmacology mechanistically connects the pharmacological mechanism(s) of a proposed product to quantitative changes in pharmacodynamic biomarkers/clinical endpoints, and is increasingly applied to model/simulate the responses to and safety of proposed small molecular drugs and biological products in humans to optimize the dosing regimen, therapeutic window, and length of use.

4) Azer K, Kaddi CD, Barrett JS, et al. History and future perspectives on the discipline of quantitative systems pharmacology modeling and its application. *Front Physiol* 2021;12:637999. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8027332/
Key takeaway: With increasing use of system models for pharmacology application, there is an opportunity to enhance development and application of the systems pharmacology field, and this review summarizes the milestones in the evolution of systems pharmacology models, highlights some of the gaps and challenges in developing and applying those models, and provides a vision for an integrated strategy that leverages advances in adjacent fields to overcome the challenges.

Hypothesis for AXA1125 Activity in Long COVID

1) Wu J, Zhao M, Li C, et al. The SARS-CoV-2 induced targeted amino acid profiling in patients at hospitalized and convalescent stage. *Biosci Rep* 2021;41:BSR20204201. https://portlandpress.com/bioscirep/article/41/3/BSR20204201/227924/The-SARS-CoV-2-induced-targeted-amino-acid
Key takeaway: The study shows that, although patients with COVID-19 exhibit an amino acid imbalance that is mostly reversed in 1 month, incomplete fatty acid oxidation with increased levels of medium-chain acyl-carnitines suggests that it may take longer for these patients to completely recover from the disease.

2) Vishwanath VA. Fatty acid beta-oxidation disorders: a brief review. *Ann Neurosci* 2016;23:51–55. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4934411/
Key takeaway: Mitochondrial fatty acid β-oxidation disorders (FAODs) are a heterogeneous group of autosomal recessive defects that can affect long-chain fatty acid transport or binding, carnitine uptake or transport (across mitochondrial membranes), or acyl-coA metabolism, and have a wide range of potentially life-threatening clinical presentations but limited long-term treatment options.

3) Vockley J, Marsden D, McCracken E, et al. Long-term major clinical outcomes in patients with long chain fatty acid oxidation disorders before and after transition to triheptanoin treatment–a retrospective chart review. *Mol Gen Metab* 2015;116:53–60. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4561603/
Key takeaway: Management of long-chain fatty acid oxidation disorders (which lead to a deficiency in mitochondrial energy production at times of physiologic stress and fasting) relies heavily on dietary management, and this study showed that long-term (12.5 years) use of the triglyceride triheptanoin improved the course of disease by decreasing the incidence and duration of major clinical manifestations (eg, hospitalizations).

4) Newsholme EA, Blomstrand E. Branched-chain amino acids and central fatigue. *J Nutr* 2006;136:274S–276S. https://academic.oup.com/jn/article/136/1/274S/4664137?login=false
Key takeaway: Physical fatigue during endurance events can be peripheral or central in origin, and this study provides evidence that central fatigue could be due to changes in plasma amino acid concentrations and that use of the branched-chain amino acids (BCAAs) leucine, isoleucine, and valine can delay central fatigue, while highlighting the commercial potential of BCAAs in other therapeutic areas.

5) Piotrowicz K, Gąsowski J, Michel JP, et al. Post-COVID-19 acute sarcopenia: physiopathology and management. *Aging Clin Exp Res* 2021;33:2887–2898. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8323089/
Key takeaway: COVID-19 is a multi-organ disease characterized by a severe inflammatory and highly catabolic status. This study discusses how the hyperinflammatory involvement exacerbates immunosenescence, enhances endothelial damage, and induces myofibrillar breakdown/muscle degradation (due to mitochondrial dysfunction and autophagy), concluding

that all of these mechanisms require an early, swift, holistic, multidisciplinary approach to minimize the disastrous functional outcomes of the disease and prevent Long COVID-19 syndrome.

6) Jin Y, Ji W, Yang H, et al. Endothelial activation and dysfunction in COVID-19: from basic mechanisms to potential therapeutic approaches. *Signal Transduct Target Ther* 2020;5:293. https://doi.org/10.1038/s41392-020-00454-7
Key takeaway: There is accumulating evidence suggesting that endothelial activation and dysfunction contribute to COVID-19 pathogenesis by altering the integrity of the blood vessel barrier, promoting a pro-coagulative state, inducing endothelial inflammation, and even mediating leukocyte infiltration. This review describes those proposed cellular and molecular mechanisms of endothelial activation and dysfunction, emphasizing the principal mediators and therapeutic implications.

7) Cash A, Kaufman DL. Oxaloacetate treatment for mental and physical fatigue in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and Long COVID fatigue patients: a non-randomized controlled clinical trial. *J Transl Med* 2022;20:295. https://pubmed.ncbi.nlm.nih.gov/35764955/
Key takeaway: This open-label study in 76 patients with Long COVID fatigue demonstrated that 6 weeks of anhydrous enol-oxaloacetate, a nutritional supplement, was associated with significant reductions in physical and mental fatigue on the Chalder Fatigue Questionnaire.

8) Maksoud R, Balinas C, Holden S, et al. A systematic review of nutraceutical interventions for mitochondrial dysfunctions in myalgic encephalomyelitis/chronic fatigue syndrome. *J Transl Med* 2021;19:81. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7890871/
Key takeaway: This review concludes that there is insufficient evidence on the effectiveness of mitochondria-targeting nutraceuticals in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Better designed studies are required to elucidate both the involvement of mitochondria in the pathomechanism or ME/CFS and the effect of mitochondrial modifying agents on illness severity.

9) Rathi A, Jadhav SB, Shah N. A randomized controlled trial of the efficacy of systemic enzymes and probiotics in the resolution of post-COVID fatigue. *Medicines* 2021;8:47. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8472462/
Key takeaway: This randomized, placebo-controlled trial in 200 patients with post-COVID fatigue demonstrates that 14 days' oral supplementation with a systemic enzyme and probiotic composition (ImmunoSEB + ProbioSEB CSC3) resolves post-COVID-19 fatigue and improves patients' functional status and quality of life.

10) Azer K. Treating fatigue in COVID long-haulers. 2022. https://www.flagshippioneering.com/stories/treating-fatigue-in-covid-long-haulers
Key takeaway: Current evidence suggests that Long COVID can affect individuals regardless of their vaccination status, COVID-19 variant, severity of initial symptoms, or overall initial health, but the cause of Long COVID remains unclear, and this article briefly summarizes emerging data implicating mitochondrial dysfunction and inflammation, as well as the key feature supporting

use of AXA1125 to treat the mitochondrial dysfunction and reverse the effects of SARS-CoV-2 in affected patients.

Mitochondria and Long COVID

1) Spinelli JB, Haigis MC. The multifaceted contributions of mitochondria to cellular metabolism. *Nat Cell Biol* 2018;20:745–754.
https://www.nature.com/articles/s41556-018-0124-1
Key takeaway: Mitochondria have long been appreciated for their role as powerhouse of the cell, but their metabolic functions reach far beyond bioenergetics This review discusses how mitochondria catabolize nutrients for energy, generate biosynthetic precursors for macromolecules, compartmentalize metabolites for the maintenance of redox homeostasis, and function as hubs for metabolic waste management in both normal physiology and disease.

2) Nunn AVW, Guy GW, Brysch W, et al. SARS-CoV-2 and mitochondrial health: implications of lifestyle and ageing. *Immun Ageing* 2020;17:33.
https://immunityageing.biomedcentral.com/articles/10.1186/s12979-020-00204-x
Key takeaway: SARS-COV-2-related fatalities increase with age and underlying comorbidity (especially markers of the metabolic syndrome and diabetes). This review discusses data suggesting that immunosenescence could be a key contributory factor to the disease, ie, that mitochondrial health (induced by a healthy lifestyle) could be a key factor in resisting the virus, and that treatments that support mitochondrial function might be pivotal to the long-term recovery of people who are perhaps not in optimal health.

3) Salah J, Peyssonnaux C, Singh KK, et al. Mitochondria and microbiota dysfunction in COVID-19 pathogenesis. *Mitochondrion* 2020;54:1–7.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7837003/
Key takeaway: Mounting evidence links the accelerated progression of COVID-19 disease to a hyperinflammatory state, or "cytokine storm," that involves major systemic perturbations in affected patients. This review discusses several cellular and systemic incidents caused by the virus and how they may critically affect mitochondrial function and thus contribute to disease progression and severity.

4) Singh KK, Chaubey G, Chen JY, et al. Decoding SARS-CoV-2 hijacking of host mitochondria in COVID-19 pathogenesis. *Am J Physiol Cell Physiol* 2020;319:C258–C267.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7381712/
Key takeaway: Based on available data for the SARS-CoV-1 virus, the authors discuss how SARS-CoV-2 localization of RNA transcripts in mitochondria hijacks the host cell's mitochondrial function to the advantage of the virus by activating the inflammasome and suppressing innate and adaptive immunity, and further suggests that age-related declines in ACE2 and mitochondrial functions resulting in chronic metabolic disorders like diabetes or cancer may make the host more vulnerable to infection, complications, and mortality.

5) Ajaz S, McPhail MJ, Singh KK, et al. Mitochondrial metabolic manipulation by SARS-CoV-2 in peripheral blood mononuclear cells of patients with COVID-19. *Am J Physiol Cell Physiol* 2021;320:C57–C65.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7816428/
Key takeaway: This study shows that peripheral blood mononuclear cells from patients with COVID-19 exhibit mitochondrial dysfunction, metabolic alterations with increased glycolysis, and high levels of mitokine, and that fibroblast growth factor 21 levels correlate with disease severity and mortality, suggesting that patients with COVID-19 have compromised mitochondrial function and an energy deficit that is compensated by a metabolic switch to glycolysis. This in turn triggers an enhanced inflammatory response and contributes to the severity of symptoms.

6) Ramakrishnan RK, Kashour T, Hamid Q, et al. Unraveling the mystery surrounding post-acute sequelae of COVID-19. *Front Immunol* 2021;12:686029.
https://pubmed.ncbi.nlm.nih.gov/34276671/
Key takeaway: The authors review the literature to date on the pathological underpinnings of the persistent atypical chronic symptoms of Long COVID including ongoing abnormalities of the host immunoregulatory systems and mitochondrial dysfunction due to the viral insult.

7) Gibellini L, De Biasi S, Paolini A, et al. Altered bioenergetics and mitochondrial dysfunction of monocytes in patients with COVID-19 pneumonia. *EMBO Mol Med* 2020;12:e13001.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7645870/
Key takeaway: When peripheral blood monocytes from patients with COVID-19 pneumonia were analyzed, they showed signs of altered bioenergetics and mitochondrial dysfunction; a significantly high number of monocytes had depolarized mitochondria and abnormal mitochondrial ultrastructure.

8) Paul BD, Lemle MD, Komaroff AL, et al. Redox imbalance links COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome. *PNAS USA* 2021;118:e2024358118.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8403932/
Key takeaway: After a review of the symptoms of COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome, the authors speculate that the symptoms may stem from redox imbalance, which in turn is linked to inflammation and energy metabolic defects.

9) Thompson E, Cascino K, Ordonez AA, et al. Metabolic programs define dysfunctional immune responses in severe COVID-19 patients. *Cell Rep* 2021;34:108863.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7908880/
Key takeaway: The authors identified a unique population of T cells in patients with Long COVID that express increased voltage-dependent anion channel 1 accompanied by gene programs and functional characteristics linked to mitochondrial dysfunction and apoptosis.

10) Soares MN, Eggelbusch M, Naddaf E, et al. Skeletal muscle alterations in patients with acute Covid-19 and post-acute sequelae of Covid-19. *J Cachex Sarcopen Muscle* 2022;13:11–22. https://onlinelibrary.wiley.com/doi/10.1002/jcsm.12896
Key takeaway: Skeletal muscle-related symptoms such as muscle weakness/atrophy and exercise intolerance are common in both acute COVID-19 and Long COVID. This review discusses factors that contribute to this weakness and fatigue (eg, systemic inflammation, disuse, hypoxemia, and malnutrition), as well as cellular and molecular pathways that are affected in COVID-19 and Long COVID versus other conditions (eg, acute respiratory distress syndrome, critical illness myopathy, and post-viral fatigue syndrome).

11) Schneider JG, Tozzo E, Chakravarthy MV. Editorial: mitochondrial biology and its role in metabolic diseases. *Front Endocrinol* 2022;13:944728. https://www.frontiersin.org/articles/10.3389/fendo.2022.944728/full
Key takeaway: This editorial reviews the crucial, multiple roles of the mitochondria in cell differentiation, cancer, neurodegeneration, and metabolic diseases, and in energy homeostasis influencing nearly every tissue and organ in the body.

12) Stephens C. MEA Summary of review: the role of mitochondria in ME/CFS. https://meassociation.org.uk/wp-content/uploads/MEA-Summary-Review-The-Role-of-Mitochondria-in-MECFS-12.07.19.pdf
Key takeaway: L-carnitine, highly important in oxygen metabolism, is deficient in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and preliminary findings suggest a hypothetical role of mitochondrial hypometabolism in the pathogenesis of primary ME/CFS and a possible benefit of a nutraceutical treatment (eg, amino acids), but the conflicting evidence on the role of mitochondrial function in ME/CFS warrants more research.

13) De Boer E, Petrache I, Goldstein NM, et al. Decreased fatty acid oxidation and altered lactate production during exercise in patients with post-acute COVID-19 syndrome. *Am J Respir Crit Care Med* 2022;205:126–129. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8865580/
Key takeaway: Authors claim that this study provides the first evidence for the role of mitochondrial dysfunction in the pathogenesis of PACS in patients who have preserved pulmonary and cardiac function; this category covers patients with unexplained chronic fatigue.

14) Filler K, Lyon D, Bennett J, et al. Association of mitochondrial dysfunction and fatigue: a review of the literature. *BBA Clinical* 2014;1:12–23. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4136529/
Key takeaway: This review examines the potential contribution of dysfunctions in mitochondrial structure, function (mitochondrial enzymes and oxidative/nitrosative stress), and energy metabolism (ATP production and fatty acid metabolism) to fatigue. It reports that low levels of the mitochondrial enzyme coenzyme Q10 are consistently associated with fatigue.

Patient-Reported Outcome Measures

1) Weinfurt KP, Reeve BB. Patient-reported outcome measures in clinical research. *JAMA* 2022;328:472–473.
https://jamanetwork.com/journals/jama/fullarticle/2794492
Key takeaway: The concept, application, interpretation, and importance of patient-reported outcome measures are described.

2) Havervall S, Rosell A, Phillipson M, et al. Symptoms and functional impairment assessed 8 months after mild COVID-19 among health care workers. *JAMA* 2021;325:2015–2016.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8027932/
Key takeaway: In a cohort of 323 patients seropositive for COVID-19, 8 months after mild infection, 26% (vs 9% seronegative) reported at least one moderate to severe symptom lasting for at least 2 months and 15% (vs 6% seronegative) reported a moderate to severe symptom lasting for at least 8 months as measured by the Sheehan Disability Scale.

3) Han JH, Womack KN, Tenforde MW, et al. Associations between persistent symptoms after mild COVID-19 and long-term health status, quality of life, and psychological distress. *Influenza Other Respir Viruses* 2022;16:680–689.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9111447/
Key takeaway: Approximately 44% of 376 patients with mild COVID 19, had persistent symptoms after 6–11 months that were significantly associated with poorer long-term health status, quality of life, and psychological distress as measured by validated patient-reported outcome questionnaires, the EuroQol visual analogue scale, EQ-5D-5L, and Patient Health Questionnaire-4, respectively.

4) Hjollund NH, Andersen JH, Bech P. Assessment of fatigue in chronic disease: a bibliographic study of fatigue measurement scales. *Health Qual Life Outcomes* 2007;5:12.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1808447/
Key takeaway: A large number of fatigue scales exist, but there is no consensus on which ones are most appropriate for use in assessment of fatigue in different diseases. This review concludes that since fatigue is an unspecific symptom there is no need for developing disease-specific fatigue scales.

5) Gnanasakthy A, Mordin M, Evans E, et al. A review of patient-reported outcome labeling in the United States (2011–2015). *Value Health* 2017;20:420–429.
https://pubmed.ncbi.nlm.nih.gov/28292487/
Key takeaway: In the period 2011–2015, 16.5% of the 182 NDAs had PRO labeling. Three-quarters of the PRO labeling was based on primary endpoints, and almost all PRO labeling was for concepts proximal to the disease.

6) Gnanasakthy A, Norcross L, Romano C, et al. A review of patient-reported outcome labeling of FDA-approved new drugs (2016–2020): counts, categories and comprehensibility. *Value Health* 2022;25:647–655.
https://pubmed.ncbi.nlm.nih.gov/34243825/
Key takeaway: During 2016–2020, 26% of the identified 228 NDAs identified had labeling based

on PRO endpoints. From 2016 to 2020, PRO labeling statements were included in 50.0% (47 of 94) of NDAs for PRO-dependent new molecular entities.

7) Bremelanotide package insert. Highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210557s000lbl.pdf
Key takeaway: The efficacy of VYLEESI for the treatment of hypoactive sexual desire disorder in premenopausal women was evaluated in two identical, Phase 3, randomized, double-blind, placebo-controlled trials (NCT02333071 and NCT02338960), both of which used PRO outcomes as their primary endpoints.

8) Milnacipran package insert. Highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022256s025lbl.pdf
Key takeaway: The efficacy of Savella for the management of fibromyalgia was established in two double-blind, placebo-controlled, multicenter studies. A larger proportion of patients treated with Savella than with placebo (i) experienced a simultaneous reduction in pain from baseline of ≥30% (VAS), (ii) rated themselves as much/very much improved on the patient global assessment (PGIC), and (iii) met the criteria for treatment response (composite endpoint of improvement in pain (VAS), physical function (SF-36 PCS), and PGIC).

Biomarkers

1) Klein J, Wood J, Jaycox J, et al. Distinguishing features of Long COVID identified through immune profiling. Preprint medRxiv and bioRxiv. 2022. https://www.medrxiv.org/content/10.1101/2022.08.09.22278592v1.full-text
Key takeaway: In this exploratory, cross-sectional study of 215 individuals with Long COVID, key significant immunological differences and putative biomarkers relative to matched controls were found at >400 days post infection, decreased levels of cortisol being one of the most significant distinguishing features.

2) Novak P, Mukerji SS, Alabsi HS, et al. Multisystem involvement in post-acute sequelae of coronavirus disease 19. *Ann Neurol* 2022;19:367–379. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9011495/
Key takeaway: In this retrospective study, individuals with Long COVID were found to have widespread multisystem dysregulation affecting cerebrovascular, peripheral neural/autonomic, respiratory system, and evidence of low-grade inflammation as evidenced by elevated inflammatory markers. The authors concluded that Long COVID resembles myalgic encephalomyelitis/chronic fatigue syndrome in many respects.

3) Su Y, Yuan D, Chen DG, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell* 2022;185:881–895. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8786632/
Key takeaway: Long COVID represent an emerging global crisis with poorly understood risk factors, and this study identified 4 risk factors that can predict Long COVID at the time of initial COVID-19 diagnosis, emphasizing the importance of early assessments in understanding and managing this disease.

4) Charfeddine S, Amor HIH, Jdidi J, et al. Long COVID 19 syndrome: is it related to microcirculation and endothelial dysfunction? Insights from TUN-EndCOV study. *Front Cardiovasc Med* 2021;8:745758.
https://www.frontiersin.org/articles/10.3389/fcvm.2021.745758/full
Key takeaway: Long COVID could be due to persistent endothelial dysfunction, and this study shows that, in a multivariate analysis, endothelial dysfunction (ie, endothelial quality index <2) was indeed an independent risk factor of Long COVID, along with female gender and severe clinical status at acute COVID-19 infection with a need for oxygen supplementation.

AXA1125 Safety and Effect on Inflammation

1. Harrison SA, Baum SJ, Gunn NT, et al. Safety, tolerability, and biologic activity of AXA1125 and AXA1957 in subjects with nonalcoholic fatty liver disease. *Am J Gastroenterol* 2021;116:2399–2409.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8631161/
Key takeaway: AXA1125 administered orally for 16 weeks in subjects with nonalcoholic fatty liver disease was safe and well tolerated; most frequently reported were mild and transient gastrointestinal adverse events. Positive trends in biomarkers related to liver inflammation were also demonstrated.