PolyBio Seminar summaries.

By @dave_it_up on X (Twitter)
Names may be spelled wrong and some typos.

The key points from Christina Dell's presentation (standing in for David Price) are:

1. Research Focus:
   - The talk focused on infectious immune and microbiome signals in the lungs as clues to the pathogenesis of long COVID.

2. Blood Analysis Findings:
   - High-dimensional flow cytometric analysis of the circulating immune system showed no major differences in lineage composition or SARS-CoV-2 specific T cell frequencies between healthy, convalescent, and long COVID individuals.
   - There was upregulation of co-inhibitory receptors on non-spike specific CD8 T cells, indicating ongoing antigen exposure in long COVID patients.

3. Humoral Immunity:
   - No significant differences in total antibody titers against SARS-CoV-2 or antibody-dependent NK cell cytotoxicity between healthy individuals and people with long COVID.
   - A significant deficit in antibody-mediated neutralization of SARS-CoV-2 was found in long COVID patients.

4. Proteomic Analysis:
   - Proteomic analysis of blood plasma revealed upregulation of proteins associated with cardiometabolic and neurological diseases, cancer, and inflammatory responses.
   - The findings suggest systemic upregulation of apoptosis (programmed cell death) and proliferation pathways in long COVID patients.

5. Complement Activation:

- The alternative complement pathway was activated in long COVID patients, triggered by direct exposure to damaged cells or pathogens.
- This activation serves as a predictive feature of long COVID.

6. Summary of Blood Analyses:
- No major differences in circulating immune lineages and virus-specific T cell immunity.
- Evidence of ongoing antigen recognition and activation/inhibitory regulation of SARS-CoV-2 specific T cells in long COVID patients.
- Viral persistence possibly due to suboptimal antibody-mediated neutralization.

7. Hypothesis on Tissue Damage:
- Substantial perturbation of the plasma proteome suggests a pathological process driving systemic disease without widespread viral replication.
- Ongoing tissue damage associated with localized reservoirs of SARS-CoV-2 could be a key driver of long COVID.

8. Lung Tissue Analysis:
- The study aims to decode the tissue origins of long COVID by focusing on the lungs.
- Collection of bronchial alveolar lavage, blood, and lung biopsies from healthy, convalescent, and long COVID patients.
- Use of molecular virology, metagenomics, metatranscriptomics, and single nuclei RNA sequencing for comprehensive analysis.

9. Challenges and Optimization:
- Optimization of tissue biopsy processing methods was necessary due to the presence of RNAses in lung tissues.
- Integration of data into a lung cell atlas and ongoing work to identify mechanisms of impaired neutralization in long COVID patients.

10. Potential Future Directions:
- Linking experimental parameters with clinical metadata to define key pathological associates of long COVID.
- De novo assembly of antibody hypervariable regions from single nuclei RNA sequencing data to address mechanisms of impaired neutralization.
- Potential development of antibodies for future immunotherapy based on these findings.

11. Acknowledgments:
- Collaboration with groups at Karolinska Institute, JCVI La Jolla, and other institutions.
- Thanks to healthy volunteers, long COVID patients, and funding from PolyBio Research Foundation and other major funders.

The key points from Morgane Bomselt's presentation are:

1. Research Focus:
   - Morgane discussed the persistence of SARS-CoV-2 and its impact on long COVID, particularly focusing on megakaryocytes and platelets.

2. Background and Hypothesis:
   - Previous research in the lab showed that viruses like HIV can persist in megakaryocytes and platelets, contributing to chronic infection.
   - The hypothesis is that SARS-CoV-2 might similarly persist in megakaryocytes and platelets, forming replication-competent reservoirs that contribute to long COVID symptoms.

3. Megakaryocytes and Platelets in Acute COVID:
   - In acute COVID-19, **some individuals have detectable SARS-CoV-2 in their platelets and megakaryocytes**.
   - This presence is linked to worse outcomes in COVID-19.

4. Study Goals:
   - To determine if SARS-CoV-2 persists in megakaryocytes and platelets in long COVID patients.
   - To characterize the function and transcriptome of these cells in long COVID patients.
   - To search for spike protein in the plasma and correlate with the presence of microclots.
   - To evaluate tryptophan metabolism in relation to immune system modulation in long COVID.

5. Sample Collection and Analysis:
   - Over 100 samples from long COVID patients have been collected, including plasma, platelets, and megakaryocytes.
   - Comparisons are made with samples from COVID-recovered individuals and pre-COVID samples.

6. Initial Findings:
   - Megakaryocytes in long COVID patients contain SARS-CoV-2 RNA and spike protein, **indicative of viral replication.**
   - Platelets from long COVID patients also contain SARS-CoV-2 RNA and spike protein.

- Spike protein is detected in the plasma of a subset of long COVID patients, stratifying them into groups based on spike protein levels.

7. Implications:
- SARS-CoV-2 persistence in megakaryocytes and platelets suggests these cells may serve as viral reservoirs in long COVID patients.
- The presence of spike protein in plasma is associated with specific long COVID symptoms, particularly those related to cardiovascular and neurological issues.

8. Future Directions:
- Further analysis of the impact of SARS-CoV-2 persistence on megakaryocyte and platelet function.
- Exploration of the potential interaction between SARS-CoV-2 and other persistent viruses, such as herpesviruses.
- Investigating the broader implications of these findings for understanding long COVID pathogenesis and developing targeted treatments.

The key points from Peter Brodin's presentation are:

1. Research Focus:
- Peter Brodin discussed general aspects of immune responses in long COVID, including the involvement of various viruses and symptoms such as post-exertional malaise.

2. Viral Reactivation:
- There is an interest in investigating the role of viral reactivation in long COVID, particularly with viruses like Epstein-Barr Virus (EBV) and Cytomegalovirus (CMV).
- These viruses are common and can reactivate under certain conditions, potentially contributing to long COVID symptoms.

3. Exhausted T Cells:
- Discussion about whether there is evidence of exhausted T cells in long COVID patients.
- Exhausted T cells are characterized by upregulation of inhibitory receptors and reduced functionality.

4. Post-Exertional Malaise (PEM):
   - PEM is a common symptom in long COVID patients, characterized by worsening of symptoms following physical or mental exertion.
   - This symptom is similar to what is seen in conditions like ME/CFS (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome).

5. Clinical Observations:
   - Clinical colleagues have reported that PEM is frequently seen in long COVID patients.
   - Understanding PEM and its underlying mechanisms is important for managing long COVID.

6. Potential Therapies:
   - There was a question about whether there will be trials of T cell checkpoint inhibitors to help address immune exhaustion in long COVID patients.
   - Current evidence does not suggest a significant presence of exhausted T cells in long COVID, so this may not be the most immediate therapeutic target.

7. Current Trials:
   - Ongoing trials, such as those using Paxlovid (an antiviral), aim to reduce viral reservoirs and assess their impact on long COVID symptoms.
   - The focus is on eliminating persistent viral infections that may be driving long COVID symptoms.

8. Future Research:
   - Plans to look at other reactivating viruses, such as Varicella Zoster Virus (VZV), and their potential role in long COVID.
   - Continued exploration of immune responses and their regulation in long COVID to develop targeted therapies.

9. Collaboration and Acknowledgments:
   - Collaboration with various researchers and institutions to advance the understanding of long COVID.
   - Acknowledgment of funding sources and the contribution of clinical and research teams in conducting these studies.

The key points from Chiara Giannarellie of NYU Langone Health presentation are:

1. Research Focus:
   - Chiara Gianna Reale discussed the deep characterization of SARS-CoV-2 cardiovascular reservoirs and plaque formation.
   - The study focuses on understanding how SARS-CoV-2 affects the cardiovascular system and contributes to atherosclerosis.

2. Observation of Cardiovascular Manifestations:
   - Early observations indicated an increased risk of cardiovascular events such as stroke and myocardial infarction during acute COVID-19.
   - The hypothesis is that SARS-CoV-2 can directly infect human vessels, particularly diseased arteries.

3. Study on Coronary Arteries:
   - Analysis of coronary arteries from autopsy specimens of patients who died from COVID-19.
   - Patients showed varying degrees of atherosclerotic plaque formation and obstruction in coronary vessels.

4. Findings in Macrophages and Foam Cells:
   - SARS-CoV-2 RNA and spike protein were detected in macrophages (CD68 positive cells) within atherosclerotic lesions.
   - Foam cells, which are lipid-laden macrophages, were found to have higher levels of viral replication compared to regular macrophages.
   - Foam cells and macrophages infected with SARS-CoV-2 produce lower levels of interferon over time, indicating a compromised antiviral response.

5. Ex Vivo Infections and Cytokine Production:
   - Ex vivo infections of atherosclerotic tissue showed that SARS-CoV-2 infection leads to strong cytokine production, including IL-6 and TNF-α, which can exacerbate inflammation.
   - This cytokine production suggests that the virus can aggravate atherosclerosis by increasing local inflammation.

6. Mechanism of Viral Entry:

- The study identified the neuropilin-1 (NRP1) receptor as a potential mechanism for viral entry into macrophages and foam cells.
- Blocking or silencing NRP1 reduced the infection of these cells.

7. Proposed Model:
- SARS-CoV-2 can infect and persist in macrophages and foam cells within atherosclerotic plaques.
- This persistence can increase inflammation and contribute to the instability of plaques, leading to cardiovascular events.

8. Future Directions:
- Leveraging ongoing clinical cohorts to collect tissue and blood samples from patients undergoing vascular surgery and heart transplants.
- Using ex vivo models to study viral reservoirs in cardiovascular tissues and how they respond to secondary infections.
- Investigating the long-term impact of SARS-CoV-2 persistence on cardiovascular health.

9. Implications for Long COVID:
- The study aims to link the presence of SARS-CoV-2 in cardiovascular tissues with long COVID symptoms, particularly cardiovascular complications.
- Understanding these mechanisms could help develop targeted therapies to mitigate long COVID's impact on the cardiovascular system.

The key points from Nicolas Hout's presentation are:

1. Research Focus:
- Nicholas is working on HIV inflammation and viral persistence at the Institut Pasteur in France.
- His talk focused on SARS-CoV-2 persistence, particularly in natural killer cells and macrophages.

2. Study Design:
- The study involved cynomolgus macaques, with 15 macaques infected with SARS-CoV-2 and 7 used as controls.

- The macaques were followed for 18 months, with regular collection of blood, bone marrow, and bronchoalveolar lavage samples.

3. Findings on Viral Persistence:
- After 18 months, viral RNA was detected in macrophages from bronchoalveolar lavage samples.
- Macrophages containing high levels of spike protein also showed the highest levels of viral RNA.

4. Macrophage Activation:
- Staining for spike protein revealed that spike was present inside CD64-positive cells, which are macrophages.
- Macrophages from monkeys with high viral RNA levels showed higher levels of spike protein.

5. Interferon Gamma and Viral RNA:
- Interferon gamma treatment was found to decrease viral RNA levels in infected macrophages.
- There was a decrease in interferon gamma production in NK cells from infected macaques, potentially contributing to viral persistence.

6. NK Cell Dysfunction:
- NanoString analysis showed differential gene expression in NK cells from infected macaques compared to controls.
- There was an upregulation of genes involved in NK cell function, suggesting changes in NK cell phenotypes.

7. MHC Class I Expression:
- Interferon gamma treatment increased MHC Class I expression on macrophages, potentially regulating NK cell cytotoxic activity.
- Differences in MHC expression might influence the ability of NK cells to recognize and kill infected cells.

8. Implications for Viral Persistence and Immune Response:
- The study highlights the complexity of SARS-CoV-2 persistence and its impact on the immune system, particularly in macrophages and NK cells.
- Understanding these mechanisms is crucial for developing therapeutic strategies to clear persistent viral infections.

The key points from Lael Yonker, MD presentation are:

1. Focus on Pediatric Long COVID:
   - Leila is a pediatric pulmonologist and an associate assistant professor of pediatrics at Harvard Medical School.
   - Her talk focused on long COVID in children and the importance of pediatric-focused research.

2. Long COVID in Children:
   - Studies have shown variable long COVID symptoms in children, affecting a significant number of them.
   - Symptoms in children can last for three months or longer, impacting their daily activities, schooling, and social interactions.

3. Underrecognition and Stigma:
   - Long COVID is often underrecognized in children, partly due to the stigma associated with reporting symptoms.
   - Children may not report symptoms to avoid feeling different or because pediatricians may attribute symptoms to other causes.

4. Impact on Children's Development:
   - Long COVID can have a long-lasting impact on children’s development, education, and socialization.
   - There are significant economic and social costs associated with long COVID in children.

5. Overlap with MIS-C:
   - Leila highlighted the overlap between MIS-C (Multisystem Inflammatory Syndrome in Children) and long COVID.
   - Both conditions show evidence of SARS-CoV-2 persistence in the gut and increased Zonulin levels, leading to a leaky gut.

6. Zonulin and Gut Permeability:
   - Increased Zonulin levels, which regulate tight junctions in the gut, are associated with a higher risk of developing long COVID.

- Loosening of tight junctions allows SARS-CoV-2 spike protein to enter the bloodstream, contributing to inflammation and symptoms.

7. Clinical Trials with Larazotide:
- Clinical trials are being conducted to test Larazotide, a medication that binds to Zonulin receptors and prevents the loosening of tight junctions.
- Preliminary results in treating MIS-C with Larazotide showed a faster resolution of gastrointestinal symptoms and clearance of spike protein from the blood.

8. Ongoing Research and Collaboration:
- The study involves screening children for long COVID and enrolling them in clinical trials.
- Blood samples and other data are being collected to better understand the pathology of long COVID in children and to identify potential treatments.

9. Call for Participation:
- Leila encouraged sharing information about the clinical trial to enroll more participants and enhance the understanding of long COVID in children.
- The study aims to build a cohort for further research and collaboration with other researchers.

The key points from Dianna Griffin presentation are:

1. Research Focus:
- Dianna is studying germinal center responses in lymph nodes of long COVID patients.
- Her research aims to understand how germinal center reactions contribute to long COVID, focusing on the quality and dynamics of B cell responses.

2. Fine Needle Aspirate (FNA) Technique:
- The study uses fine needle aspirate (FNA) to collect samples from cervical lymph nodes, which are secondary lymphoid organs.
- This minimally invasive technique allows for the analysis of immune responses directly in lymphoid tissues.

3. Study Design:

- The study includes convalescent and long COVID patients, with samples collected at three different time points (T1: 3 weeks to 6 months, T2: 6 months to 1 year, T3: over 1 year post-infection).
- These samples are analyzed to compare immune responses over time between the two groups.

4. Germinal Center B Cells:
- Total germinal center B cell populations in lymph nodes did not show significant differences between long COVID and convalescent patients.
- However, SARS-CoV-2 specific germinal center B cells were found to be lower in long COVID patients at the early time point (T1) and more persistent at later time points (T2), suggesting ongoing immune activation.

5. Neutralizing Antibodies:
- Preliminary serological analysis indicated no major abnormalities in binding antibodies between long COVID and convalescent patients.
- However, neutralizing antibody levels were found to be lower in long COVID patients compared to convalescent individuals, indicating a potential impact on the quality of the antibody response.

6. Ongoing and Future Research:
- The study is conducting additional analyses, including binding antibody assessments, transcriptomic and proteomic analysis of lymph node samples, and single-cell RNA sequencing.
- The research aims to further understand the mechanisms underlying the altered germinal center responses and their impact on long COVID.

7. Potential Implications:
- The findings suggest that persistent SARS-CoV-2 specific germinal center responses in long COVID patients might contribute to the prolonged symptoms and altered immune responses.
- Further understanding of these mechanisms could lead to targeted therapies to improve immune function and resolve long COVID symptoms.

8. Collaborative Efforts:
- Mikayla highlighted the importance of collaboration with other researchers and institutions to advance the understanding of long COVID.
- The study is open to sharing data and samples to facilitate broader research efforts in this field.

The key points from Steve Deeks' presentation are:

1. Overview of LIINK Program:
   - Steve provided an overview of the LINK program at UCSF, which focuses on studying the long-term consequences of COVID-19.
   - The program leverages existing infrastructure from HIV research to study long COVID.

2. Cohort Details:
   - The LIINK cohort includes over 1,000 individuals with extensive biological specimen collection.
   - The cohort captures a diverse range of participants, including those from early in the pandemic when there were fewer confounding factors like reinfections or vaccinations.

3. Mechanistic Studies:
   - The program is conducting various mechanistic studies to understand immune responses, viral persistence, and inflammation in long COVID.
   - Research includes examining immune dysfunction, viral reservoirs, and chronic inflammation.

4. Tissue-Based Research:
   - Emphasis on the importance of tissue-based research for understanding long COVID.
   - LIINK has been conducting tissue biopsies, including gut biopsies, lymph node aspirations, lumbar punctures, and bone marrow biopsies.

5. Clinical Trials and Therapeutic Interventions:
   - The program is exploring clinical trials to test therapeutic interventions targeting persistent viral reservoirs and inflammation.
   - Trials include monoclonal antibodies, antiviral drugs, and immune-boosting therapies such as IL-15.

6. Monoclonal Antibody Trial:
   - A controlled study of a monoclonal antibody provided by Ariat has been conducted.
   - The study aims to determine if targeting SARS-CoV-2 with monoclonal antibodies can reduce viral persistence and alleviate long COVID symptoms.

7. Engagement and Collaboration:
   - The program emphasizes collaboration with external researchers and institutions.
   - LIINK is open to sharing data, blood samples, and tissue samples to support broader research efforts.

8. Future Directions:
   - Plans to expand the research model to other post-infectious conditions like ME/CFS and other chronic conditions.
   - The goal is to build a rigorous cohort, identify key pathways, and test targeted interventions across various chronic conditions.

9. Team and Support:
   - The LIINK program is supported by a diverse and dedicated team, with significant funding from PolyBio Research Foundation.
   - The program aims to continue leveraging its resources and expertise to advance the understanding and treatment of long COVID and related conditions.

The key points from Timothy Henrich's presentation are:

1. Research Focus:
   - Timothy Henrich discussed the use of molecular imaging and tissue-based research to study long COVID, emphasizing the importance of understanding tissue-specific immune responses and viral persistence.

2. PET Imaging:
   - PET imaging with a tracer specific for activated T cells was used to visualize immune activation in tissues of long COVID patients.
   - Imaging showed increased T cell activation in tissues like the nasopharyngeal lymphoid space, gut wall, bone marrow, and brainstem, even up to two years post-infection.
   - This persistent activation suggests ongoing immune responses in these tissues.

3. Tissue Biopsies:
   - Tissue biopsies revealed the presence of SARS-CoV-2 RNA and double-stranded RNA, indicating viral persistence and potential replication.

- Double-stranded RNA was often found in clusters, suggesting localized immune evasion and inflammation.

4. EBV and SARS-CoV-2 Co-localization:
- Preliminary data indicated a possible interaction between Epstein-Barr Virus (EBV) reactivation and SARS-CoV-2 persistence in tissues.
- This co-localization could contribute to ongoing immune activation and viral persistence.

5. Digital Spatial Profiling:
- Digital spatial profiling using the Xenium Connect system allowed for detailed transcriptomic analysis of tissue samples.
- This technology identified unique gene expression patterns in macrophages and other immune cells, indicating immune evasion mechanisms by SARS-CoV-2.

6. Granzyme B Deficiency:
- The analysis showed a lack of granzyme B production in infected tissues, which is crucial for T cell and NK cell-mediated killing of infected cells.
- This deficiency suggests that SARS-CoV-2 may be evading immune responses by inhibiting cytotoxic activity.

7. Clinical Trial with IL-15 Superagonist:
- A clinical trial using an IL-15 superagonist, a cytokine that stimulates T cells and NK cells, is being conducted.
- The trial aims to boost tissue-based immune responses to clear persistent viral reservoirs and improve long COVID symptoms.
- Participants will receive two doses of the IL-15 superagonist, and the trial will measure viral reservoir reduction and symptom improvement.

8. Collaboration and Impact:
- Timothy emphasized the importance of collaboration with other researchers and institutions.
- The findings from this research could have significant implications for understanding long COVID and developing targeted therapies to treat it.

The key points from Resia Pretorius' presentation are:

1. Research Focus:
   - Resia Pretorius discussed the role of microclots and platelet pathologies in long COVID and ME/CFS.
   - Her research aims to understand the biochemical characteristics of these microclots and their implications for disease pathology.

2. Microclots in Various Diseases:
   - Microclots are not only found in long COVID but also in other diseases such as ME/CFS, sepsis, and others.
   - These microclots contain inflammatory molecules and are associated with endothelial damage and platelet hyperactivation.

3. Imaging and Flow Cytometry:
   - Advanced imaging techniques, including scanning electron microscopy and imaging flow cytometry, are used to study the structure and composition of microclots.
   - These techniques help identify significant differences in clot formation between healthy individuals and those with long COVID or ME/CFS.

4. Automated Detection Methods:
   - Resia's team developed an automated method to detect and analyze platelets using flow cytometry and specific markers.
   - This method groups platelets by size and counts them, showing distinct differences between control and long COVID samples.

5. Proteomic Analysis:
   - Proteomic studies revealed various proteins trapped inside microclots, providing insights into their composition and potential mechanisms.
   - Markers of endothelial damage, such as vascular endothelial growth factor (VEGF), were found within and around microclots.

6. Nattokinase as a Potential Treatment:
   - Preliminary studies suggest that nattokinase, an enzyme, can break down microclots and reduce their inflammatory markers.
   - This enzyme could be a potential therapeutic agent for conditions associated with microclots, including long COVID.

7. Future Directions and Collaborations:
   - Ongoing research aims to further validate the methods and findings, including collaborations with other researchers and institutions.
   - Upcoming studies will focus on additional diseases, such as POTS, and expand proteomic analyses to identify novel markers.

8. Commercial and Clinical Applications:

- The research team is working on commercializing the flow cytometry method for wider clinical use.
- The goal is to establish reference ranges for microclots and use this technology in pathology labs to diagnose and monitor diseases associated with clot formation.

9. Significance for Clinical Utility:
- The ability to detect and quantify microclots could have significant clinical utility in diagnosing and managing diseases characterized by clot-related pathology.
- This research contributes to understanding the underlying mechanisms of long COVID and ME/CFS and developing targeted therapies.

The key points from Gene Tan's presentation are:

1. Research Focus:
- Gene Tan is studying the characterization of antiviral immune responses in long COVID pathogenesis.
- His research aims to understand how the immune system responds to persistent viral antigens and inflammation in long COVID patients.

2. Immune Response Characterization:
- The study focuses on identifying specific immune responses that are altered in long COVID patients compared to those who have fully recovered from COVID-19.
- It involves analyzing various immune cell types and their functions to determine how they contribute to ongoing symptoms and viral persistence.

3. Viral Persistence:
- Persistent viral antigens may play a role in maintaining chronic inflammation and immune dysregulation in long COVID.
- The research explores how these persistent viral components interact with the immune system, leading to prolonged symptoms.

4. T Cell and NK Cell Dysfunction:
- The study examines the role of T cells and natural killer (NK) cells in long COVID.

- These immune cells are critical for clearing viral infections, and their dysfunction may contribute to the inability to fully eliminate the virus, leading to persistent symptoms.

5. Cytokine and Chemokine Profiles:
- Gene's research includes profiling cytokines and chemokines, which are signaling molecules that mediate and regulate immunity, inflammation, and hematopoiesis.
- Altered levels of these molecules in long COVID patients can provide insights into the inflammatory processes and immune responses that are dysregulated.

6. Autoimmunity and Inflammation:
- The potential role of autoimmunity in long COVID is being investigated, considering that chronic viral infections can sometimes trigger autoimmune responses.
- Understanding the balance between antiviral immune responses and autoimmunity is crucial for developing effective treatments.

7. Clinical Implications:
- The findings from this research can help identify biomarkers for diagnosing long COVID and monitoring disease progression.
- Insights gained can also inform the development of targeted therapies to modulate immune responses and reduce chronic inflammation in long COVID patients.

8. Collaboration and Integration:
- Gene emphasized the importance of collaboration with other researchers and integrating data from various studies to build a comprehensive understanding of long COVID pathogenesis.
- His work contributes to a broader effort to uncover the mechanisms behind long COVID and develop effective treatment strategies.

This research is crucial in identifying how long COVID affects the immune system and finding ways to mitigate its impact on patients' health.

The key points from the first speaker's presentation (introduction and study overview) are:

1. Study Collaboration:
   - The study was conducted through a collaboration with Dr. David Price and Helen Davis from Cardiff University in the UK.
   - The case-control study involves participants who were previously exposed to SARS-CoV-2.

2. Participant Groups:
   - The study consists of two groups: long COVID patients and convalescent controls.
   - Both groups have around 50% females and 50% males, with most participants being applications (likely implying healthcare or high-risk workers).

3. Health Measures:
   - Participants with long COVID reported significantly lower measures of health post-SARS-CoV-2 exposure compared to their pre-exposure health and to the convalescent control group.
   - Long COVID patients reported a lower quality of life and higher severity of health issues after exposure.

4. Body Mass Index (BMI):
   - Long COVID participants had a higher BMI compared to the convalescent controls.
   - Stratification by gender showed that females with long COVID had a higher BMI than female convalescent controls, while there was no significant difference in BMI between males in the two groups.

5. Antibody Responses:
   - The study characterized antibody responses to SARS-CoV-2, specifically targeting the receptor-binding domain (RBD) of the spike protein and nucleocapsid protein (NP).
   - Both long COVID and convalescent controls had comparable antibody responses to the RBD.
   - Long COVID patients had significantly higher antibodies against NP, suggesting higher viral replication during the acute phase of infection.

6. Neutralizing Antibodies:
   - Long COVID patients had significantly lower neutralizing antibody titers against both the ancestral strain (Wuhan) and the Omicron variant of SARS-CoV-2.
   - This decrease in neutralizing antibodies was more pronounced in females with long COVID compared to females in the convalescent control group.

7. Gender Differences:
   - The study suggested that risk factors influencing the progression to long COVID might differ between males and females.
   - Females with long COVID showed higher antibody responses to NP and lower neutralizing antibody titers compared to males.

8. Future Research:

- The study plans to explore the functional aspects of antibodies and other biomarkers to further understand the mechanisms driving long COVID.
- There is an interest in correlating these findings with other factors such as gut permeability and metabolic markers.

9. Acknowledgments:
- The speaker acknowledged the contributions of various collaborators, including team members, clinical partners, and funding sources like PolyBio.
- Special thanks were given to Dr. David Price and Helen Davis for their role in providing the cohort for the study.

The key points from Nadia Roan's presentation are:

1. Research Focus:
- Nadia Rowan discussed immune dysregulation during long COVID.
- The study aimed to compare immunological differences between individuals with long COVID and those who have recovered from SARS-CoV-2 infection without lingering symptoms.

2. Cohort and Methodology:
- The study utilized the LINK cohort from UCSF, involving 27 individuals with long COVID and 16 convalescent controls.
- Blood specimens were collected at the eight-month mark, ensuring none of the participants had been vaccinated or reinfected at that time to avoid confounding effects on immunological measurements.
- The study employed various omics assays, focusing on serological analyses and in-depth T cell analyses using cytometry by time-of-flight (CyTOF) technology.

3. T Cell Responses:
- No significant differences in the overall quantity of SARS-CoV-2 specific CD4+ and CD8+ T cells between long COVID individuals and convalescent controls.
- Significant differences were found in the coordination between T cell responses and antibody responses in long COVID individuals.

4. Antibody and T Cell Coordination:

- In convalescent controls, there was a positive association between T cell responses and antibody responses, indicating coordinated immunity.
- In long COVID individuals, this coordination was disrupted, with some individuals showing high T cell responses but low antibody responses, and vice versa.

5. Phenotypic Differences in T Cells:
- Long COVID individuals showed phenotypic differences in their T cells, particularly in the expression of chemokine receptors like CXCR4, CXCR5, and CCR6.
- These receptors are involved in directing immune cells to tissues, including inflamed tissues.
- CXCR4, in particular, was previously associated with severe and fatal COVID-19 and was also found to be upregulated in long COVID.

6. Mouse Model of Long COVID:
- The study also involved a mouse model using the Omicron BA.1 sub-strain to investigate post-acute phase immunological perturbations.
- Even with mild infections, there were lingering immune disturbances in the lungs of mice during the post-acute phase.
- Increased expression of CXCR4 was observed in various immune cell subsets in these mice.

7. Behavioral Analysis of Mice:
- Using machine learning-based approaches to analyze mouse behavior, the study found deficits in habituation and changes in behavioral motifs in mice that had recovered from SARS-CoV-2 infection.
- These findings suggest behavioral changes and potential cognitive impacts similar to long COVID symptoms in humans.

8. Summary and Implications:
- Long COVID individuals show a disjointed immune response, with disrupted coordination between T cell and antibody responses.
- Upregulation of CXCR4 and other chemokine receptors might be a key feature of immune dysregulation in long COVID.
- Machine learning approaches to quantify behavior in mouse models can help characterize long COVID and understand its mechanisms.

9. Acknowledgments:
- Nadia thanked the members of her lab, collaborators, and funding sources, including PolyBio.
- Special mention of collaborative efforts with the LINK cohort and other contributing researchers.

The key points from Mark Painter's presentation are:

1. Research Focus:
   - Mark Painter discussed using T cells as biosensors to study viral persistence in long COVID.
   - The research aims to explore two hypotheses: persistent SARS-CoV-2 infection and reactivation of other persistent viral infections like Epstein-Barr Virus (EBV) and Varicella Zoster Virus (VZV).

2. T Cells as Antigen Biosensors:
   - The approach leverages virus-specific T cells, which act as biosensors for detecting viral antigens in the body.
   - T cells circulate through the blood and tissues, encountering viral antigens and becoming activated, which can be detected through changes in gene expression, protein expression, and chromatin accessibility.

3. MHC Class I Tetramers:
   - The study uses MHC class I tetramers to identify and quantify virus-specific T cells.
   - These tetramers are loaded with viral peptides and conjugated with fluorescent markers, allowing the identification of T cells that recognize specific viral epitopes.

4. Proof of Concept:
   - In individuals with breakthrough infections after three doses of mRNA vaccines, the study detected SARS-CoV-2 spike-specific T cells that became activated during acute infection.
   - Activation of these T cells returned to baseline levels by day 45 post-infection in those who fully recovered.

5. Antigen Panel:
   - The research employs a panel of 70 viral epitopes, including those from SARS-CoV-2, EBV, VZV, cytomegalovirus (CMV), and influenza.
   - This panel helps screen for specific T cell responses to these viruses and assess their activation status.

6. Findings in Long COVID:
   - The study did not find significant differences in the overall activation or exhaustion of total T cells between long COVID patients and convalescent controls.

- However, virus-specific T cells showed different patterns of activation.

7. SARS-CoV-2 Specific T Cells:
- About 25% of long COVID patients had elevated activation of SARS-CoV-2 spike-specific T cells, compared to 5% in convalescent controls.
- Paired samples from the LINK cohort showed sustained activation of these T cells at both four and twelve months post-infection in a subset of long COVID patients.

8. Herpes Virus-Specific T Cells:
- EBV-specific T cells showed elevated activation during acute infection, which persisted in a subset of long COVID patients but returned to baseline in most convalescent controls.
- Similar patterns were observed for VZV-specific T cells.
- No significant activation changes were seen for CMV and influenza-specific T cells, suggesting the specificity of the observed immune dysregulation to certain viruses.

9. Conclusions:
- There is evidence supporting the hypothesis that persistent SARS-CoV-2 and dysregulation of EBV and VZV may contribute to long COVID in different subgroups of patients.
- At least one virus-specific T cell response showed elevated activation in about 40% of long COVID patients, compared to 15% of convalescent controls.

10. Acknowledgments:
- Mark thanked John Wherry and his lab at the University of Pennsylvania, clinical teams at Penn, UCSF, and Yale, and collaborators for their contributions.
- Special thanks to PolyBio and other funding sources for their support.

This research highlights the potential role of persistent viral infections and immune dysregulation in long COVID and emphasizes the importance of targeted therapies to address these underlying mechanisms.

The key points from Esen Sefik's presentation are:

1. Research Focus:

- Esen Sefik, discussed the use of humanized mouse models to study SARS-CoV-2 RNA persistence and the role of macrophages in long COVID pathology.

2. Humanized Mice:
- The study uses humanized mice, which are mice transplanted with human hematopoietic stem and progenitor cells, resulting in a comprehensive human-like immune system.
- These mice express human cytokines and support the development of human immune cells, including monocytes and macrophages.

3. Infection Model:
- The researchers used an adeno-associated virus system to express human ACE2 in the mice, enabling SARS-CoV-2 infection.
- Infected mice showed high levels of viral replication and a macrophage response similar to that seen in human COVID-19 patients.

4. Macrophage Infection:
- The study found that macrophages in the humanized mice were infected with SARS-CoV-2, evidenced by the presence of viral RNA and spike protein.
- This infection led to inflammasome activation and pyroptosis (a form of programmed cell death).

5. Subgenomic RNA Detection:
- Subgenomic RNA, indicative of active viral replication, was detected in macrophages both in vitro and in vivo.
- In vitro experiments showed that macrophages infected with SARS-CoV-2 had detectable subgenomic RNA at 24 and 48 hours post-infection.

6. CSF1R-Deficient Mice:
- To investigate the role of macrophages in viral persistence, the researchers created CSF1R-deficient mice, which lack macrophages.
- These mice showed significantly reduced levels of viral RNA and subgenomic RNA in the lungs compared to control mice, indicating that macrophages are a key reservoir for SARS-CoV-2.

7. Lung Pathology:
- In control mice, long-term infection led to significant lung pathology, including macrophage infiltration and fibrosis.
- CSF1R-deficient mice, which lack macrophages, showed reduced lung pathology and did not develop fibrosis, suggesting that macrophages contribute to chronic lung damage in long COVID.

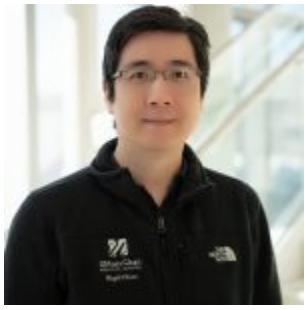
8. Implications for Long COVID:
- The findings suggest that human macrophages play a significant role in SARS-CoV-2 persistence and the development of long-term lung pathology.

- Targeting macrophages or their infection pathways could be a potential therapeutic strategy to mitigate long COVID symptoms.

9. Future Directions:
- Further studies are needed to understand the specific mechanisms by which macrophages contribute to viral persistence and lung pathology.
- The research aims to explore the potential of genetically targeting macrophage subsets to reduce viral reservoirs and improve outcomes in long COVID patients.

This research highlights the crucial role of macrophages in SARS-CoV-2 persistence and long COVID pathology, providing insights into potential therapeutic targets for managing long COVID.

The key points from Rigel Chan's presentation are:



1. Research Focus:
- Baijal Chan discussed the impact of SARS-CoV-2 infection on Alzheimer's and neurodegenerative diseases.
- The project investigates whether SARS-CoV-2 infection can increase the risk of Alzheimer's disease.

2. Herpes Virus and Alzheimer's:
- There is evidence that herpes virus infections, like HSV-1, can increase the risk of Alzheimer's disease.
- HSV-1 can enter the brain and usually remains asymptomatic, but in some individuals with dysregulated immune function, it can lead to the accumulation of amyloid-beta and tau proteins, which are associated with Alzheimer's pathology.

3. Alzheimer's Pathology:
- Amyloid-beta accumulation is thought to be a defense mechanism against viral infection, but it can become dysregulated, leading to Alzheimer's disease.
- This pathology eventually results in neurofibrillary tangles of hyperphosphorylated tau protein and cognitive decline characteristic of Alzheimer's.

4. Cerebral Organoids as a Model:
- The study uses cerebral organoids, 3D cell culture models derived from induced pluripotent stem cells (iPSCs), to study infection and its effects on brain cells.
- These organoids contain various brain cell types and can be used to simulate viral infections and study their impact on Alzheimer's disease biomarkers.

5. HSV-1 Infection Studies:
- The team infected cerebral organoids with HSV-1 and observed increased amyloid-beta and phosphorylated tau, indicating a potential link between HSV-1 infection and Alzheimer's pathology.
- Gene set enrichment analysis and flow cytometry confirmed the association between HSV-1 infection and Alzheimer's disease biomarkers.

6. SARS-CoV-2 Infection Studies:
- Initial studies with SARS-CoV-2 showed that while the virus could enter the cells and produce viral RNA, it did not progress to produce viral proteins or cause significant infection in the cerebral organoids.
- Transfection of organoids with the SARS-CoV-2 spike protein led to an increase in microglial markers but did not increase amyloid-beta levels.

7. Future Directions:
- Further research is needed to understand the long-term effects of SARS-CoV-2 infection on different brain cell types.
- The team plans to conduct RNA sequencing to capture transcriptomic changes post-infection.
- They will also explore whether SARS-CoV-2 exposure affects the risk of subsequent HSV-1 infection and Alzheimer's pathology.

8. Implications:
- The findings suggest that while SARS-CoV-2 may not directly cause Alzheimer's disease, its impact on the brain's immune environment could have downstream effects on neurodegenerative diseases.
- Understanding these mechanisms is crucial for developing targeted interventions to mitigate the risk of neurodegenerative diseases following SARS-CoV-2 infection.

The key points from Christopher Dupont's presentation are:

1. Research Focus:
   - Christopher Dupont discussed developing a tissue analysis pipeline and microbiome single-cell analysis platforms to study various tissue samples, particularly for understanding bacterial and viral persistence.

2. Multi-Omics Approach:
   - The pipeline aims to use a multi-omics approach to study tissue types such as lung, intestinal lining, endometrial tissue, skin, and nerve and ligament tissues.
   - This approach involves both host cell gene expression profiling and microbiome profiling.

3. Challenges with Host Material:
   - These tissue types often contain high amounts of host material, making it challenging to capture the microbiome.
   - To address this, the team uses methods like digital droplet PCR and CRISPR-Cas to degrade host DNA and enrich microbial DNA.

4. Microbiome Analysis:
   - The team uses shotgun metagenomics and metatranscriptomics to reconstruct the microbiome from tissue samples.
   - They emphasize the importance of accurate microbial abundance measurements, using digital droplet PCR to establish absolute microbial abundance.

5. Data and Method Optimization:
   - Recent data shows the absolute abundance of bacteria in different tissue types, highlighting high bacterial loadings in samples from ligaments, endometrial tissue, lung fluid, and skin.
   - The team has optimized methods for various tissue types, such as transbronchial biopsies, endometrial tissue, and skin, to ensure accurate single nuclei RNA sequencing.

6. Single Nuclei RNA Sequencing:
   - They are developing single nuclei RNA sequencing to create cell atlases and identify gene expression in a cell type-specific manner.
   - This involves identifying marker genes for specific cell types and comparing data across different experiments and tissue types.

7. Tissue-Specific Findings:
   - The team has recovered genomes from low biomass samples, showing distinct strains in various tissues.
   - In some samples, they found strains of pathogens like Pseudomonas in ligament samples, indicating potential clinical relevance.

8. Single-Cell Analysis in Endometriosis:
   - Preliminary single nuclei RNA sequencing data from endometrial tissues revealed different cell types and marker genes.
   - They are starting to explore changes in cell type-specific gene expression, which may help understand diseases like endometriosis.

9. Future Directions:
   - The team plans to continue optimizing methods for different tissue types and integrating data to understand microbial and host interactions better.
   - Ongoing work includes creating a comprehensive tissue analysis pipeline that can be applied to various clinical and research contexts.

The key points from Victoria Cortes Bastos' presentation are:

1. Research Focus:
   - Victoria Cortez Bustos presented findings from an ME/CFS project under the supervision of Akiko Iwasaki, focusing on blood and cerebrospinal fluid (CSF) analysis in ME/CFS patients.

2. Study Design:
   - The study involved 39 plasma samples from ME/CFS patients and 40 demographically matched controls.
   - Additionally, 34 CSF samples were collected from the ME/CFS group.
   - The project included clinical data, multiplex analysis for cytokines, hormones, and matrix metalloproteinases (MMPs), and antibody profiling for pathogen reactivity and autoantibodies.

3. Clinical Data:

- ME/CFS patients scored higher in pain and fatigue, took longer to walk 10 meters, and scored lower in quality of life measurements compared to controls.

4. Cytokine Correlation Analysis:
- No significant differences were found in individual cytokine values between ME/CFS patients and controls.
- However, correlation analysis showed differences in how cytokines correlated with each other.
- A group of strong positive correlations present in controls was absent in ME/CFS patients, particularly involving the chemokine fractalkine.

5. Fractalkine and MMPs:
- Fractalkine can be cleaved into soluble fractalkine by MMPs like MMP-2.
- ME/CFS patients showed disrupted correlations between soluble fractalkine and MMP-2 levels compared to controls.

6. CSF Analysis and Patient Clustering:
- Unsupervised hierarchical clustering of CSF samples based on MMP levels identified two distinct clusters of ME/CFS patients.
- Cluster 1 had higher MMP signatures and cytokine levels, indicating higher tissue remodeling and inflammation.
- Cluster 2 showed a good correlation between soluble fractalkine and MMP-2, suggesting different underlying mechanisms.

7. Pathogen Reactivity:
- Cluster 1 patients had higher seropositivity for cytomegalovirus (CMV).
- Cluster 2 patients had higher seropositivity for SARS-CoV-2 and parvovirus B19, indicating different exposure patterns leading to varied underlying pathophysiological mechanisms.

8. Important Findings:
- Despite being equally sick, ME/CFS patients showed distinct immunological profiles, indicating different underlying mechanisms.
- Identifying these profiles is crucial for understanding ME/CFS and developing targeted therapies.

9. Summary:
- ME/CFS patients are divided into clusters based on MMP and cytokine signatures, reflecting different pathophysiological mechanisms.
- These findings highlight the need for sub-grouping ME/CFS patients in studies to uncover specific disease mechanisms.

The key points from Michael Peluso's presentation are:

1. Research Focus:
   - Michael Peluso discussed recent experiences with launching clinical trials for long COVID at UCSF, focusing on trials targeting viral persistence.

2. Current Trials:
   - Outsmart Lc: A study of SARS-CoV-2 monoclonal antibody involving about 30 participants, with results expected by the end of the year.
   - Prevail Lc: A study of ensitrelvir, an antiviral medication, which recently dosed its first participant.
   - Interrupt Lc: Planned to start in the summer, this trial will use an IL-15 agonist in collaboration with ImmunityBio.
   - Baricitinib Trial: Sponsored by the NIH, focusing on long COVID treatment.

3. Clinical Trial Phases:
   - Phase 1: Focuses on safety and dosage.
   - Phase 2: Focuses on tolerability and proof of concept, often exploratory and smaller in scale.
   - Phase 3: Proves efficacy and may lead to FDA approval.
   - Phase 4: Post-market surveillance.

4. Phase 2 Trials:
   - Most trials at UCSF are Phase 2, aiming to identify and validate important biological mechanisms in long COVID.
   - These trials are smaller, faster, and intended to inform larger Phase 3 studies.

5. Challenges and Observations:
   - High interest from long COVID patients in participating, highlighting the unmet clinical need and altruism among patients.
   - Eligibility criteria are complex due to factors like timing of infection, vaccination status, and other treatments patients may be using.
   - The intensity and demands of the trials often exclude homebound patients, which is a limitation.
   - The heterogeneity of long COVID symptoms complicates participant selection and outcome interpretation.

6. Adverse Event Reporting:
   - Challenges in attributing adverse events to treatments due to the fluctuating nature of long COVID symptoms.
   - Reinfections during the study period add complexity to interpreting trial results.

7. Endpoints and Measurements:
   - The optimal endpoints and timing for measuring outcomes in long COVID trials are still uncertain.
   - The team uses a combination of subjective patient-reported outcomes and objective measures to capture comprehensive data.

8. Importance of Patient-Reported Outcomes:
   - Emphasized that long COVID is primarily a disease of how people feel, making patient-reported outcomes crucial.
   - Biomarkers are important but should not delay the progress of clinical trials.

9. Learning from Trials:
   - Each trial contributes valuable data, even if it doesn't lead to a "slam dunk" result.
   - Incremental progress (singles and doubles) is still valuable for advancing understanding and treatment of long COVID.

10. Future Directions:
    - Ongoing trials will inform the design of future studies, not only for long COVID but also for other infection-associated chronic conditions.
    - Collaboration and scientific support from organizations like PolyBio are crucial for the success of these trials.

The key points from Marcelo Freire's presentation are:

1. Research Focus:
   - Marcelo Freire discussed defining long COVID oral systemic markers and insights from a new study on COVID.

- His laboratory aims to find specific markers for chronic conditions and understand their molecular basis using oral tissues and saliva as non-invasive measures of health.

2. Oral Tissues and Saliva:
- Oral tissues and saliva contain immune cells and are indicative of the body's overall health.
- Lesions in the oral cavity can reflect systemic health issues, and saliva can be used to study immune responses and microbial interactions.

3. Previous Studies:
- His lab has shown that saliva is rich in immune cells like neutrophils, monocytes, and lymphocytes.
- They have also found that saliva can reflect immune responses and inflammatory processes in conditions like COVID-19.

4. COVID-19 Findings:
- During the acute and convalescent phases of COVID-19, patients showed persistent immune dysfunctions despite the presence of antibodies.
- Proteomic analysis revealed persistent inflammatory markers and mitochondrial dysfunction in saliva and plasma of COVID-19 patients.

5. Saliva vs. Plasma:
- The team found distinct cytokine profiles in saliva and plasma, indicating that saliva can provide unique insights into immune responses.
- Correlations between cytokine levels in saliva and plasma differed between healthy controls and COVID-19 patients, particularly in severe cases.

6. Predictive Power of Saliva:
- Salivary microbiome analysis showed high predictive power for distinguishing between health and disease and for stratifying disease severity.
- A multimodal model combining saliva and plasma data was also robust in predicting disease outcomes.

7. Long COVID Study:
- In collaboration with David Price, the team is studying long COVID patients using saliva and plasma samples.
- Preliminary data show that long COVID patients have lower antiviral antibody responses in plasma but higher responses in saliva, particularly in IGA levels.

8. Future Directions:
- The team plans to conduct proteomic analyses of long COVID samples to compare with acute and convalescent COVID-19 samples.
- They aim to identify specific immune pathways and markers unique to saliva and plasma in long COVID patients.

9. Viral Persistence:
   - The study will also investigate viral persistence in tissues and its impact on immune responses.
   - By stratifying samples, they hope to uncover distinct profiles that can inform targeted interventions for long COVID and other chronic conditions.

The key points from Sarah Cherry's presentation are:

1. Research Focus:
   - Sarah Cherry discussed efforts to define a viral reservoir in the gastrointestinal (GI) tract and its potential role in driving persistent long COVID symptoms.

2. Viral Reservoir Hypothesis:
   - The hypothesis is that a viral reservoir in the GI tract could be contributing to long COVID in a subset of patients.
   - This reservoir might persist despite the resolution of acute infection and could be a target for specific therapies.

3. Antiviral Treatments:
   - Discussion on various classes of antivirals, including direct-acting antivirals (e.g., molnupiravir) and immunomodulators, which have shown effectiveness in blocking acute SARS-CoV-2 infection.
   - The effectiveness of these treatments in the context of a potential GI viral reservoir is being explored.

4. Evidence from Autopsy Studies:
   - Autopsy studies revealed high levels of viral RNA in the GI tract of patients long after the acute phase of infection.
   - Stool samples from long COVID patients showed the presence of viral RNA, supporting the existence of a viral reservoir.

5. Non-Human Primate Studies:
   - Studies in non-human primates infected with SARS-CoV-2 showed persistent viral RNA in stool samples over extended periods.

- Ongoing work includes sequencing viral RNA to understand the persistence mechanisms and potential viral variants involved.

6. Air-Liquid Interface Models:
- The team uses air-liquid interface cultures to model respiratory and GI tract infections.
- These models help in studying the differential replication of SARS-CoV-2 and the effectiveness of antiviral treatments in these compartments.

7. GI Tract Infection Dynamics:
- Findings indicate that SARS-CoV-2 infection dynamics in the GI tract differ from the respiratory tract, with prolonged viral replication in the GI models.
- Treatment with antivirals like molnupiravir shows varying levels of effectiveness in these models, highlighting the need for targeted therapeutic strategies.

8. Combination Therapies:
- Exploration of combination therapies to identify the most effective treatments for clearing viral reservoirs in the GI tract.
- The use of different modalities, such as interferon beta and novel small molecules, is being investigated.

9. Therapeutic and Prophylactic Approaches:
- The research aims to differentiate between prophylactic and therapeutic approaches, assessing the timing and dosing of treatments to achieve optimal results.
- The goal is to find combinations that effectively reduce viral load and protect tissue integrity.

10. Future Directions:
- Further studies are planned to identify biomarkers for viral persistence in the GI tract and understand the implications for long COVID.
- The research will continue to explore the role of viral polymorphisms and immune responses in maintaining viral reservoirs.

The key points from Zian Tseng’spresentation are:

1. Research Focus:

- Zian Tseng discussed the post-mortem systematic investigation of sudden cardiac death (SCD) in the context of COVID-19, focusing on understanding the underlying causes and mechanisms.

2. Sudden Cardiac Death Overview:
- Sudden cardiac death is a leading cause of mortality in the United States, often determined based on presumptions without thorough autopsy.
- The study aims to systematically investigate the actual causes of SCD, challenging the assumptions made on death certificates.

3. Study Design:
- The study collaborates with the medical examiner in San Francisco to capture all sudden deaths in the county and apply systematic, research-grade autopsies and tissue sampling.
- This approach ensures comprehensive and unbiased capture of SCD cases, regardless of hospital admission status.

4. Findings from Autopsies:
- Initial findings showed that nearly half of the presumed sudden cardiac deaths were non-cardiac in nature, including neurological causes, infections, overdoses, and embolisms.
- This highlights the importance of autopsy in accurately determining the cause of death.

5. Insights into HIV and SCD:
- Previous research from the study indicated significant findings related to HIV's impact on SCD, providing a model for investigating COVID-19’s impact.

6. COVID-19 and Sudden Death:
- The COVID-19 study leverages existing data and new cases to examine the presence of SARS-CoV-2 in tissues and its potential role in SCD.
- The aim is to identify viral persistence, immune dysregulation, endothelial dysfunction, and other pathological mechanisms.

7. Temporal Analysis:
- By examining cases before and after the COVID-19 pandemic, the study can compare tissue samples to understand the long-term effects of SARS-CoV-2.
- The high prevalence of past COVID-19 infections allows for broad insights into post-COVID conditions.

8. Tissue Analysis:
- Tissues from various organs, including the brain, heart, lungs, liver, and kidneys, are analyzed to detect viral RNA and proteins, immune responses, and other pathological changes.
- This includes looking at cell-cell interactions and immune cell infiltration.

9. Findings and Preliminary Data:

- Preliminary data showed the presence of SARS-CoV-2 spike RNA in neuron tissues of individuals who had recovered from COVID-19, suggesting viral persistence.
- This finding supports the hypothesis of a viral reservoir contributing to post-acute sequelae of COVID-19.

10. Future Directions:
- The study will continue to collect and analyze tissues from more cases to understand the full impact of COVID-19 on sudden cardiac death.
- This includes exploring the interactions between SARS-CoV-2 and other conditions that may exacerbate the risk of SCD.

This research highlights the importance of systematic autopsy studies in understanding the true impact of COVID-19 on sudden cardiac death and potentially uncovering hidden mechanisms of post-acute sequelae.

The key points from David Petrino's presentation are:

1. Research Focus:
- David Petrino discussed clinical trial strategies for long COVID and ME/CFS, emphasizing the need for tailored approaches given the complexity of these conditions.

2. Complexity of Chronic Illnesses:
- Long COVID and ME/CFS are complex chronic illnesses with over 200 symptoms affecting multiple organ systems.
- The complexity requires nuanced clinical trial strategies rather than large-scale, mono-therapeutic trials.

3. Challenges with Mono-Therapeutic Trials:
- Mono-therapeutic trials are unlikely to work due to the diverse nature of long COVID symptoms and responses to treatments.
- Such trials may fail to identify effective therapies and could negatively impact future therapeutic strategies.

4. Personalized Treatment Approach:

- Effective treatment requires identifying responders and non-responders to specific therapies and understanding the underlying physiological basis.
- Personalized treatment approaches are essential for effective management of long COVID and ME/CFS.

5. Clinical Trial Phases:
- Phase 1: Small, rapid interventional trials with deep phenotyping to identify biomarkers associated with treatment response.
- Phase 2: Larger trials using identified biomarkers to recruit likely responders, validating the effectiveness of treatments.
- Phase 3: Adaptive platform trials testing multiple combinations of interventions to find effective treatment combinations for different patient phenotypes.

6. Deep Phenotyping:
- Deep phenotyping involves detailed immune profiling, pathogen persistence analysis, and biomarker identification.
- This approach helps to understand who responds to treatment and why, guiding more effective trial designs.

7. Adaptive Platform Trials:
- These trials test multiple interventions in combination, allowing for the identification of effective treatment regimens for specific patient subgroups.
- They are methodologically sound and can adapt based on ongoing results, optimizing the chances of finding successful therapies.

8. Examples of Trials:
- Trials at the Cohen Center for Recovery from Complex Chronic Illness include broad-spectrum antivirals, immune modulators, and other therapies.
- These trials focus on small patient groups with deep phenotyping to identify responsive biomarkers and optimize treatment strategies.

9. Collaboration and Data Sharing:
- Collaboration with other researchers and institutions is crucial for advancing understanding and treatment of long COVID and ME/CFS.
- Sharing data and findings will help build a comprehensive approach to managing these conditions.

This presentation underscores the importance of personalized, adaptive approaches in clinical trials for complex chronic illnesses, highlighting the need for deep phenotyping and collaborative efforts to find effective treatments.

The key points from Michael VanElzakker's presentation are:

1. Research Focus:
   - Michael VanElzakker discussed neuroinflammation and neutrophil function in long COVID and ME/CFS (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome).
   - The study aims to understand the underlying mechanisms of neuroinflammation using advanced neuroimaging techniques.

2. Neuroinflammation and Glial Activation:
   - The research focuses on glial cells, which are resident immune cells in the brain that become activated in response to pathogens or immune signals.
   - Activated glial cells release neuroinflammatory mediators, contributing to symptoms like fatigue and cognitive dysfunction.

3. Dual MRI-PET Scanning:
   - The study uses dual MRI-PET scanning to measure glial activation in the brain, focusing on the translocator protein, which is upregulated during neuroinflammation.
   - This technique allows for the visualization of neuroinflammatory processes in living patients.

4. Study Design:
   - The study recruited 12 long COVID patients who were sick before August 2021 (pre-Omicron) and 43 matched healthy controls.
   - Long COVID patients reported ongoing fatigue and met criteria for ME/CFS.

5. Findings from PET Scans:
   - The PET scans showed increased glial activation across various brain regions in long COVID patients compared to controls.
   - The activation was widespread, involving both cortical and subcortical regions.

6. Hypothalamus and Blood-Brain Barrier:
   - Significant activation was observed in the hypothalamus, a region with leaky blood-brain barriers, suggesting a possible entry point for circulating immune signals.
   - The hypothalamus regulates critical functions like sleep, appetite, and body temperature, which could be disrupted in long COVID.

7. Blood and Vascular Health Markers:
   - The study correlated neuroinflammation with markers of vascular health, such as fibrinogen and alpha-2-macroglobulin, which are involved in clotting and immune responses.
   - Elevated levels of these markers were found in long COVID patients, suggesting a link between vascular health and neuroinflammation.

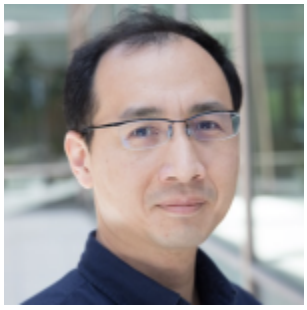
8. Microclots and Neutrophil Activity:
   - Collaborations with Resia Pretorius revealed the presence of fibrin amyloid microclots in long COVID patients' blood.
   - Activated neutrophils and neutrophil extracellular traps (NETs) were also observed, indicating ongoing immune activation.

9. Future Directions:
   - The study will continue to explore the relationship between microclots, neutrophil activity, and neuroinflammation.
   - Ongoing research includes measuring activated neutrophils and their motility, as well as investigating neuroinflammation in pre-COVID ME/CFS patients.

10. Implications for Treatment:
    - Understanding the mechanisms of neuroinflammation and its link to vascular health could inform targeted therapies for long COVID and ME/CFS.
    - Future research aims to identify biomarkers that can predict treatment response and improve patient outcomes.

This research highlights the role of neuroinflammation in long COVID and ME/CFS, suggesting that targeting glial activation and vascular health could be key to developing effective treatments.

The key points from Max Qian's presentation are:



1. Research Focus:
   - Max Quain discussed the use of machine learning to identify endotypes (subtypes) of long COVID based on patient symptoms and data from the LINK study.

2. Data Set:
   - The study utilized data from the LINK study at UCSF, which includes longitudinal data from approximately 600 patients with over 150 features, including demographics, symptoms, preconditions, and clinical visits.

3. Machine Learning Approach:
   - The team applied a topic modeling approach, commonly used in natural language processing, to identify patterns in the symptom data.
   - This method helped to group similar symptoms and identify patient clusters (endotypes) based on these patterns.

4. Identifying Topics:
   - The machine learning model identified 22 topics that best represented the entire cohort of long COVID patients.
   - These topics corresponded to groups of symptoms that tended to occur together.

5. Clustering Patients:
   - Patients were clustered into 15 distinct endotypes based on their symptom profiles and the identified topics.
   - Each endotype had a unique signature of symptom topics, allowing for better understanding and categorization of long COVID experiences.

6. Symptom Patterns:
   - The identified topics included clusters of symptoms related to neurological issues, respiratory problems, gastrointestinal symptoms, and others.
   - For example, one endotype might be characterized by symptoms like fatigue, brain fog, and headaches, while another might have cough, runny nose, and shortness of breath.

7. Demographic Correlations:
   - The study found interesting demographic patterns, such as a higher prevalence of certain endotypes in females compared to males.
   - Temporal analysis showed that females often reported symptoms for longer periods than males.

8. Validation of Results:
   - The endotypes were validated by mapping them to health-related quality of life measures and comparing temporal patterns of symptom persistence.
   - The machine learning model's ability to group similar patient profiles and identify key symptoms was confirmed through these analyses.

9. Temporal Analysis:
   - Temporal analysis of symptom data showed how symptoms evolved over time for different endotypes, providing insights into the progression of long COVID.

- This analysis helped to identify patterns such as initial improvement followed by a relapse of symptoms.

10. Future Directions:
- The team aims to further validate the identified endotypes using additional data sets and explore their clinical implications.
- This approach could help in developing personalized treatment plans and improving the management of long COVID.

This research demonstrates the potential of machine learning to uncover hidden patterns in symptom data, leading to a better understanding of long COVID and the development of targeted treatments.

The key points from Matthew Frank's presentation are:

1. Research Focus:
- Matthew Frank discussed a multi-inflammatory hit model of long COVID, focusing on how initial SARS-CoV-2 infection sensitizes the brain to subsequent inflammatory challenges, potentially exacerbating neurological symptoms.

2. Neuroinflammation and Its Mediators:
- Neuroinflammatory mediators are produced by various cell types, including astrocytes, macrophages, and microglia.
- These mediators can trigger symptoms such as fatigue and brain fog, which are common in long COVID.

3. SARS-CoV-2 Antigens and Neuroinflammation:
- SARS-CoV-2 antigens, particularly the spike protein (S1 subunit), are neuroinflammatory and can persist in serum and tissues for months.
- These antigens can cross the blood-brain barrier and enter the brain, where they may contribute to neuroinflammation.

4. Experimental Design:

- The study used a two-hit model to investigate the effects of prior S1 exposure on neuroinflammation.
- Mice were injected with the S1 subunit directly into the central nervous system, followed by a second hit with lipopolysaccharide (LPS), a bacterial endotoxin, after seven days.

5. Findings on Hypothalamic Inflammation:
- S1 exposure potentiated the neuroinflammatory response to LPS, particularly in the hypothalamus.
- Increased levels of interleukin-1 beta (IL-1β), a key pro-inflammatory cytokine, were observed in the hypothalamus following the second hit.

6. Role of the Hypothalamus:
- The hypothalamus is crucial for regulating many physiological functions, including sleep, appetite, body temperature, energy balance, and the autonomic nervous system.
- Neuroinflammation in the hypothalamus can disrupt these functions, contributing to the symptoms seen in long COVID.

7. IL-1β and Neuroinflammation:
- IL-1β is a gatekeeper of neuroinflammation and can cause various behavioral and physiological changes, such as disrupted cognition, fatigue, and anxiety.
- These changes overlap with many symptoms reported by long COVID patients.

8. Implications for Long COVID:
- The study suggests that prior exposure to SARS-CoV-2 antigens primes the brain for exaggerated neuroinflammatory responses to subsequent infections or stressors.
- This priming effect could explain the persistence and exacerbation of neurological symptoms in long COVID.

9. Future Directions:
- Further research is needed to understand the long-term impact of SARS-CoV-2 antigens on brain function and neuroinflammation.
- The study aims to explore potential therapeutic strategies to mitigate neuroinflammation and improve outcomes for long COVID patients.

10. Acknowledgments:
- Matthew thanked his colleagues, collaborators, and funding sources for their support in conducting this research.
- Special mention of the contributions from team members in data collection and analysis.

This research highlights the potential role of neuroinflammation in long COVID and suggests that targeting neuroinflammatory pathways could be key to developing effective treatments for neurological symptoms.

The key points from Matt's (last name not provided) presentation are:

1. Study Focus:
   - Matt discussed a study on the hypothalamus and its role in immune response priming, particularly in the context of infections and long COVID.

2. Hypothalamus and Immune Response:
   - The hypothalamus plays a critical role in regulating various physiological functions, including sleep, appetite, body temperature, energy balance, and the autonomic nervous system.
   - Neuroinflammation in the hypothalamus can disrupt these functions and contribute to the symptoms seen in long COVID.

3. Two-Hit Hypothesis:
   - The study explores the "two-hit" hypothesis, where an initial infection (such as COVID-19) sensitizes the immune system, making it more reactive to subsequent infections or stressors.
   - This priming effect could lead to exaggerated immune responses and prolonged symptoms in long COVID patients.

4. Experimental Design:
   - Mice were injected with the SARS-CoV-2 spike protein (S1 subunit) directly into the central nervous system.
   - Seven days later, the mice received a second injection with lipopolysaccharide (LPS), a bacterial endotoxin, to simulate a secondary infection or inflammatory challenge.

5. Findings on Neuroinflammation:
   - The initial S1 exposure potentiated the neuroinflammatory response to the subsequent LPS challenge, particularly in the hypothalamus.
   - Increased levels of interleukin-1 beta (IL-1β), a key pro-inflammatory cytokine, were observed in the hypothalamus following the second hit.

6. Implications for Long COVID:
   - These findings suggest that prior exposure to SARS-CoV-2 antigens primes the brain for exaggerated neuroinflammatory responses to future infections or stressors.
   - This priming effect could explain the persistence and exacerbation of neurological symptoms in long COVID patients.

7. IL-1β and Neuroinflammation:
   - IL-1β is a crucial mediator of neuroinflammation and can cause various behavioral and physiological changes, such as disrupted cognition, fatigue, and anxiety.
   - These changes overlap with many symptoms reported by long COVID patients.

8. Future Research:

- Further studies are needed to understand the long-term impact of SARS-CoV-2 antigens on brain function and neuroinflammation.
- The research aims to explore potential therapeutic strategies to mitigate neuroinflammation and improve outcomes for long COVID patients.

9. Acknowledgments:
- Matt thanked his colleagues and collaborators for their support in conducting this research.
- Emphasis on the importance of understanding the role of neuroinflammation in long COVID and the need for targeted treatments.

This research highlights the potential role of neuroinflammation in long COVID and suggests that targeting neuroinflammatory pathways could be key to developing effective treatments for neurological symptoms.

The key points from Ed Breitschwerdt presentation are:

1. Research Focus:
- Discussed the impact of tick-borne and vector-borne illnesses on post-COVID symptoms, with a particular focus on Bartonella and other vector-borne infections.
- His research explores the role of these infections in exacerbating or mimicking long COVID symptoms.

2. Tick-Borne Diseases:
- Schwartz's laboratory has focused on tick-transmitted infectious diseases for many years, particularly those that can affect both animals and humans.
- The primary focus is on the genera Bartonella, Borrelia (responsible for Lyme disease), Anaplasma, and Ehrlichia.

3. Multi-Microbial Infections:
- Many animals and humans are exposed to multiple vectors, leading to co-infections with various pathogens.
- Co-infections with vector-borne organisms are not uncommon and can complicate clinical presentations and diagnosis.

4. Sample Enrichment and Digital PCR:
- The lab has developed an enrichment culture technique combined with droplet digital PCR (ddPCR) to increase the sensitivity of detecting low-abundance pathogens in clinical samples.
- This method enhances the ability to detect and identify multiple co-infecting pathogens, even at low levels.

5. Validation of Digital PCR:
- Digital PCR has been validated for detecting Bartonella, Borrelia, and Babesia species, showing higher sensitivity than traditional quantitative PCR (qPCR).
- The method has been used to test samples from various animals and humans, providing more accurate diagnostics.

6. Veterinary and Human Health Implications:
- Research has shown that veterinary workers, particularly veterinarians and veterinary technicians, are at higher risk of Bartonella infections due to their exposure to animals and vectors.
- Studies have documented Bartonella DNA in the blood of veterinary workers, with common symptoms including headache, insomnia, and short-term memory loss.

7. Neuropsychiatric Illnesses:
- The research has extended to individuals with neuropsychiatric illnesses, finding a higher prevalence of Bartonella DNA in these patients compared to controls.
- Studies with collaborators have shown a statistical association between Bartonella infection and neuropsychiatric symptoms such as schizophrenia.

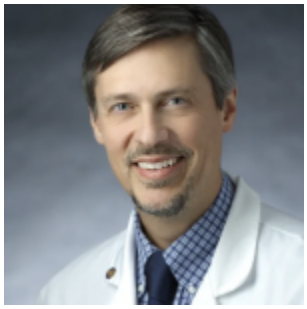
8. Reactivation of Infections Post-COVID:
- There have been case reports of Bartonella infection reactivating after exposure to SARS-CoV-2.
- This reactivation can lead to a complex interplay of symptoms, complicating the diagnosis and management of long COVID.

9. Future Directions:
- The lab will collaborate with the PolyBio study to test samples from long COVID patients for Bartonella and other vector-borne pathogens.
- The goal is to determine if these pathogens contribute to the symptomatology of long COVID and to understand the potential for reactivation of latent infections.

10. Acknowledgments:
- Bob acknowledged the contributions of his research team, particularly Dr. Ricardo Maggi, and the support from the Cohen Foundation and PolyBio Research Foundation.
- Emphasis on the importance of understanding the role of vector-borne infections in chronic illnesses and the need for sensitive diagnostic methods.

This research highlights the potential impact of co-infections with vector-borne pathogens on long COVID and the importance of accurate diagnostics in managing complex chronic illnesses.

The key points from Brent Harris's presentation are:



1. Research Focus:
   - Brent Harris discussed the development of a long COVID biobank and tissue bank with pathological and molecular analysis.
   - The project aims to systematically collect and analyze tissues from individuals with long COVID to understand the persistence of the virus and its pathological effects.

2. Project Overview:
   - The project is funded by PolyBio and will start on July 1, running for one year initially as a pilot study.
   - The primary focus is to work with long COVID clinical programs at MedStar Health and Johns Hopkins University to recruit participants and collect tissues post-mortem.

3. Awareness and Recruitment:
   - The project involves creating brochures and informational materials to inform patients and families about the biobank and tissue donation process.
   - The goal is to make patients and families aware of the opportunity to contribute to research, even in the event of death, to further scientific understanding of long COVID.

4. Rapid Autopsy Program:
   - The program aims to perform rapid autopsies to collect tissues, including the brain, GI tract, lungs, liver, kidneys, and lymphoid system.
   - Rapid freezing and fixation of tissues are essential to preserve the integrity of protein elements and allow for detailed pathological and molecular analysis.

5. Pathological Analysis:
   - Pathological analysis of the brain will be conducted at Georgetown, led by Brent Harris, while other tissues will be analyzed by the pathology team at NIH, led by Dr. Steven Hewitt.
   - The analysis will include detection and quantification of viral RNA, protein, and replication-competent virus using advanced methods like RNA scope and ddPCR.

6. Experience Leveraging:
   - The project leverages experience from other biobanking programs at Georgetown, including the ALS brain bank and the PANS/PANDAS brain bank.
   - These programs have established protocols for rapid tissue collection and distribution to researchers, ensuring high-quality samples for scientific study.

7. Molecular Analysis:
   - The molecular analysis will focus on identifying viral persistence, senescence, and neurodegeneration in the collected tissues.
   - The goal is to understand the long-term impact of SARS-CoV-2 on various organs and systems, particularly the brain.

8. Future Plans:
   - After the initial year, the project will assess the success of the logistics and consider expanding to other metropolitan areas.
   - The aim is to make the collected samples available to researchers with minimal administrative barriers, fostering collaboration and accelerating research.

9. Importance of Clinical Data:
   - Collaboration with long COVID clinics ensures that tissues collected have comprehensive clinical data, enabling detailed clinical-pathological correlations.
   - This approach will help link clinical symptoms and outcomes with underlying pathological changes.

10. Acknowledgments:
    - Brent thanked his team at Georgetown, collaborators at NIH, MedStar, and Johns Hopkins, and the PolyBio Research Foundation for their support.
    - Special recognition was given to the families of long COVID patients for their willingness to contribute to research, highlighting the importance of their participation.

This research initiative aims to create a valuable resource for understanding long COVID and its pathological effects, potentially leading to new insights and therapeutic strategies.

The key points from Amy Proal's (likely the organizer) closing remarks are:

1. Gratitude to Speakers:
   - Amy Proal expressed gratitude to all the speakers for their informative and passionate presentations.
   - Acknowledged the hard work and dedication of the research teams and the progress made in understanding long COVID and related conditions.

2. Importance of Diverse Research:
   - Highlighted the diversity of research presented, covering various aspects of long COVID, including viral persistence, neuroinflammation, immune responses, and co-infections.
   - Emphasized the importance of different research angles and methodologies in building a comprehensive understanding of long COVID.

3. Role of Patients:
   - Thanked the patients who have participated in the studies, donated samples, and provided data.
   - Stressed that patient contributions are crucial for advancing research and finding solutions to long COVID.

4. Support from Donors:
   - Expressed appreciation for the donors who have supported the research efforts, including major contributors like Vitalik Buterin, the Solving Foundation, the Wallace Research Foundation, and others.
   - Acknowledged the importance of financial support in enabling cutting-edge research and innovative projects.

5. Ongoing and Future Projects:
   - Mentioned that new projects and studies are continuously starting, reflecting the dynamic nature of the research field.
   - Encouraged continued collaboration and innovation to address the challenges of long COVID and related chronic conditions.

6. Call to Action:

- Encouraged patients with long COVID to consider registering their brain or body for research, similar to other serious illnesses.
- Highlighted the significance of brain and body donation programs in advancing scientific knowledge and developing effective treatments.

7. Wrapping Up:
- Concluded the symposium by reiterating the commitment to ongoing research and collaboration.
- Looked forward to future symposia and continued progress in the field.

Amy's remarks emphasized the collective effort required to tackle long COVID, the vital role of patients and donors, and the importance of sustained research and collaboration.