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ABSTRACT BOOK

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Table of contents

Oral Presentations 03

Poster Presentations 54

Young Investigators' Abstracts 136

Late Breaking Abstracts 149

Authors' Index 166



ORAL PRESENTATIONS



O001

Reconciling Functional and Evolutionary Descriptions of HCMV

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Abstract

The relationship between genome evolution and functional output remains poorly resolved for complex DNA viruses such as human cytomegalovirus (HCMV). Recent studies have independently highlighted two key features of the HCMV genome: extensive hidden coding capacity and structured genetic diversity. Ribosome profiling by Stern-Ginossar et al. (2012) uncovered hundreds of previously unannotated open reading frames and pervasive translational complexity, while population genomic analysis by Charles et al. (2023) revealed a mosaic genome architecture comprising hypervariable regions shaped by distinct evolutionary forces. However, these perspectives remain unlinked, limiting our ability to interpret how specific coding elements contribute to viral adaptation.

We have developed a novel computational approach to integrate functional and evolutionary annotations of the HCMV genome. We use a metric called the Group Diversity Ration to allow us to jointly analyze experimentally defined coding elements and patterns of genomic variability, mapping individual ORFs and isoforms to distinct evolutionary regimes. This integrative approach reveals that subsets of coding elements are preferentially associated with regions under balancing selection or population structure, suggesting differential functional constraints and roles in host interaction.

Together, our findings bridge a critical gap between genome annotation and evolution, providing new insight into the functional architecture of HCMV and enabling more biologically informed genome annotation.



O002

Human Cytomegalovirus co-opts FcRn-mediated IgG transport to cross the placental barrier

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Abstract

Congenital human cytomegalovirus (HCMV) infection remains a leading infectious cause of sensorineural hearing loss and neurodevelopmental impairment which occurs despite maternal antibodies. The syncytiotrophoblast forms the principal barrier between maternal and fetal compartments, but also mediates selective maternal IgG transfer through the neonatal Fc receptor (FcRn). We therefore asked whether HCMV co-opts this physiological antibody transport pathway to cross the placenta. Using primary human trophoblast organoids and polarized transcytosis models, we show that IgG promotes transfer of infectious HCMV virions across trophoblast barriers. Transcytosed infectious virions were quantified by fibroblast infection, while viral genome transfer was measured by qPCR. IgG enhanced both infectious virion and genome transcytosis. Mechanistically, transcytosis required host FcRn and the HCMV-encoded viral Fcγ receptors (vFcγRs) gp34 and gp68, which are incorporated into the virion envelope. Genetic deletion of gp34, gp68, or FcRn abrogated virion transcytosis. Neutralizing hyperimmune globulin prevented infectious virion transcytosis but did not prevent genome transcytosis, indicating that neutralized virions can still undergo FcRn-dependent transport and that neutralization is maintained during transcytosis. Monoclonal antibodies and antibody fragments targeting gp34 or gp68 blocked transcytosis, identifying vFcγRs as targetable mediators of this process. Analysis of sera from women with primary HCMV infection during pregnancy showed that transmitter sera promoted greater infectious virion transcytosis than non-transmitter sera, whereas genome transfer was comparable. Neutralization capacity did not correlate with inhibition of transcytosis, suggesting that incomplete neutralization allows infectious virions to traverse the trophoblast barrier. Finally, RhCMV also underwent IgG- and vFcγR-dependent transcytosis, supporting conservation among cytomegaloviruses. Together, these findings identify the gp34/gp68-IgG-FcRn axis as a mechanism by which HCMV exploits antibody transport to enable placental dissemination.



O003

Novel insights into the HCMV "effectome" from multiomic analysis of single gene expressing cells

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Abstract

Currently available therapies for HCMV suffer from significant side effects and/or the potential for drug resistance. A comprehensive understanding of the function of viral proteins is therefore critical for rationally-designed new treatments.

We have previously shown that HCMV can regulate the abundance of thousands of host proteins and transcripts, leading to degradation of antiviral restriction factors, components of cell death pathways and proteins involved in viral sensing. HCMV also upregulates pro-survival proteins and proteins required for viral transcription and translation. However, a systematic understanding of which viral proteins drive each of these host protein-level changes is lacking.

We have developed a large-scale multiomic screen to discover the whole HCMV 'effectome' for 171 canonical HCMV proteins and 16 novel ORFs. We used 18-plex tandem mass tags and RNAseq to multiplex lysates from 187 individual human fibroblast cell lines each stably expressing a single HCMV ORF, measuring ~8,000 human proteins and ~40,000 transcripts in each cell line. In addition to validating the up- or down-regulation of multiple positive controls, we characterised novel functions for ~90 viral ORFs, including >5 novel ORFs. This included a role for a novel ORF in the downregulation of several MAP4Ks, which we investigated using phosphoproteomics. We observed significant alterations in the cellular response to TNFα, including changes in both MAPK and NF-κB signalling. We further found that this novel ORF significantly reduces inflammatory cytokine production upon TNFa stimulation or HCMV infection, thereby identifying a novel viral antagonist of this important pathway.

In addition to presenting findings from this large screen, we will introduce insights into the overlap between this data and our previous proteomic analyses of HCMV, leading to a unified model of HCMV protein function.



O004

Control of gamma delta T cells by human cytomegalovirus

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Abstract

Human Cytomegalovirus (HCMV) encodes numerous mechanisms to modulate the immune response, with many described that target αβ T cells and NK cells. However, the γδ T cell repertoire of healthy HCMV seropositive individuals and whether HCMV expresses functions that modulate γδ T cells, is less well studied. γδ T cells are functionally similar to NK- and T cells, but express a T-cell receptor (TCR) composed of γδ chains rather than the αβ chains found in CD4/CD8 T cells. There are expansions of the $CD3^+$ $\alpha\beta TCR^-$ $V\delta1^+$ subset of γδ T cells described as adaptive-like and HCMV responsive, reported in HIV+ individuals, individuals experiencing HCMV reactivation following transplantation, and infants with congenital infection. However, these expansions have not been well studied in healthy individuals. We found that a subset of γδ T cells defined as $CD3^+$ $CD56^+$ $\gamma\delta TCR^{hi}$ (mAb B1 clone) $\alpha\beta TCR^-$ $V\delta1^+$ was expanded in healthy individuals seropositive for HCMV, potentially related to the γδ T cell subset previously reported to expand during active disease. To determine whether HCMV encodes proteins that modulate this response, we screened a range of virus mutants. This identified the US29-34A region as containing gene(s) which control the expansion of $\gamma\delta TCR(B1)^{hi}$ T cells, but not $\gamma\delta TCR(B1)^{lo}$ T cells. Proteomics analyses identified two proteins as most significantly differentially expressed in the ΔUS29-34A block deletion infected cells, PlexinA1 and PlexinB2. Individual gene knockouts showed US31 as responsible for the downregulation of PlexinB2, which has been previously described as a regulator of tissue-resident epithelial γδ T cells in mice. Expansion assays and CD107a assays showed increased expansions and degranulation of *ex vivo* γδ T cells in response to ΔUS31/ΔUS29-34A HCMV infected cells that did not alter other effector cells. Our findings reveal an immunomodulatory mechanism of HCMV which specifically targets γδ T cells.



O005

Soluble Immune Checkpoint Profiles in Congenital Cytomegalovirus (cCMV) Infection: A Balancing Act Between Activation, Exhaustion and Anergy?

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Abstract

Background/Aim: Soluble Immune Checkpoints (sICPs) are molecules reflecting a patient's immune response with applications mostly in tumor immunity. Chronic infections such as CMV may alter a patient's immune system and lead to activated, anergic or exhausted states, reflected by changes in sICPs, which could affect prognosis. The aim of this study was to quantify sICPs in a cohort of cCMV-infected neonates and healthy controls and investigate potential correlations with cCMV infection and clinical presentation at birth.

Materials/Methods: Neonates with documented cCMV infection born post first or unknown trimester of maternal infection and a QuantiFERON®-CMV (QF-CMV) sample were included. Controls consisted of healthy, CMV-negative, gestational age-matched neonates, born both to CMV IgG positive and negative mothers. 14 sICPs (sBTLA, sCD27, sCD28, sCD80, sCD137/s4-1BB, sCD152/sCTLA-4, sGITR, sHVEM, sIDO, sLAG-3, sPD-1, sPD-L1, sPD-L2, sTIM-3) were quantified using the Invitrogen™ ProcartaPlex™ Human Immuno-Oncology Checkpoint Panel 1 for the Luminex™ 200 analyzer. The CMV-specific sICP profile was calculated as the difference of the sICP value post CMV stimulation (CMV tube) minus the background sICP value (nil tube).

Results: 18 neonates were included; 12 cases (8 asymptomatic) and 6 CMV-negative controls. sCD152/sCTLA-4, sIDO and sPD-L1 were significantly upregulated in cases compared to controls (p=0.019, p=0.007 and p=0.039). Notably, sIDO upregulation significantly correlated with measured IFN-γ levels in cCMV-infected neonates (Spearman's rho=0.764, p=0.006). Symptomatic infants significantly upregulated sTIM-3 compared to asymptomatic (p=0.007).

Conclusion: In this exploratory study limited by sample size, specific patterns of sICPs discriminating cCMV-infected neonates from healthy controls, and symptomatic from asymptomatic neonates were revealed. We have previously shown that neonates with balancing Th1 and Th2 responses have a better outcome, while herein, sTIM-3, a driver of T cell suppression and exhaustion, is linked to symptomatic infection. Further studies exploring both the role as well as potential correlations of sICPs with long-term outcome are needed.



O006

Transcriptional profiling of T cells and NK cells in infants with congenital CMV infection

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Abstract

Introduction/Aim

Children with congenital cytomegalovirus (cCMV) infection frequently have prolonged viral replication, low CD4 T cell Th1 cell responses, and variable CD8 T cell Tc1 responses. The aim of this study was to characterize global T cell and NK cell responses to cCMV via transcriptional profiling.

Materials and Methods

Blood PBMCs from 26 cCMV infected and 11 uninfected (control) infants were processed for cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq) using Totalseq universal antibody cocktail (Biolegend) and single cell sequencing (10x Genomics). Single cell data for 10,000 cells per subject were analyzed using CellRanger multi v8.0.0, R (v.4.3.3) and the Seurat (v5) package using principal component analysis (PCA), and uniform manifold approximation and projection (UMAP). Differentially expressed genes and proteins were identified in T cell and NK cell clusters and were used for gene set enrichment analysis.

Results

Sex, race, ethnicity, and gestational age were similar between cCMV and control groups. Within the cCMV group, 5 were asymptomatic and 21 were symptomatic at birth. Both cCMV and control groups had large clusters of naïve CD4 and CD8 T cells. CD4 T cell subsets expressed genes and proteins consistent with Th2 cells (*GATA3*, CCR4), and Tregs (*FOXP3*, CD25), which differentially expressed interferon-α stimulated genes (*IRF7, IRF9, MX1, OAS1, OASL, IFIT3, ISG15, RSAD2*) as well as some IFN-γ stimulated genes such as *STAT1* and *IRF1* in the cCMV group compared to control. CD8 T cells and NK cells expressed transcripts and proteins associated with cytotoxicity (*PRF1, GZMB, GZMA, GZMK, GZMM;* CD107A). NK cells also expressed numerous type I interferon stimulated gene transcripts.

Conclusions

Congenital CMV infection induces differentiation of CD4 Th2/Treg cells, cytotoxic CD8 T cells/NK cells, and type I interferon stimulated gene signatures in CD4 T cells and NK cells.



O007

Evolution of HCMV non-primary infection and host immune response in HCMV-seropositive mothers of children attending day-care centers. An observational prospective study

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Abstract

Introduction: Human cytomegalovirus (HCMV) is the leading infectious agent causing congenital infections (cCMV). Epidemiological studies have documented that almost half of the burden associated with cCMV would be due to non-primary maternal infection. Whether cCMV is the consequence of a reactivation of the latent strain or a reinfection with a new strain remains undefined. This study focused on the natural history of non-primary HCMV infection in seropositive Italian women at high risk of reinfection because of exposure to young children attending day-care center.

Materials and Methods: Between June 2017 and September 2022, 204 HCMV-seropositive women and their infants were enrolled at University Hospital Fondazione IRCCS Policlinico San Matteo (Pavia, Italy). Maternal saliva, urine, vaginal swab, milk, and infant saliva were collected after delivery and 3-6 months later. HCMV-DNA was tested and a mother-child pair continued the study whenever viral DNA was detected. After day-care admission of the infant, the same samples were collected together with maternal blood every 3 months, up to a year. Genotypes of gB and gH were tested by type-specific real-time PCR, and the appearance of a new genotype was considered a marker of reinfection. HCMV-specific T-cell and humoral responses were compared in women who did or did not have a reinfection.

Results: Of 204 mother-child pairs screened, 47 were eligible and completed the study. The gB and gH genotype of 44 pairs was analyzed at baseline. After day-care admission, 14/47 women shed the virus, and 5 (11%) showed a different genotype from baseline. No statistically significant difference emerged in cellular and humoral responses, but a trend towards lower levels of HCMV-specific long-term memory T cells expressing IL-7R was observed in women with reinfection.

Conclusion: A reinfection rate of 11% was observed. The lower percentage of LTM cells could be associated with reinfection, but the small sample size suggests further investigation.



O008

The role of IFN-α and IFN-β in the immune defence against viral infections

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Abstract

Type I interferons (IFN-I) are key antiviral cytokines that signal through a common heterodimeric IFNAR receptor complex. The IFN-I family comprises multiple IFN-α subtypes, IFN-β, IFN-ε, and IFN-κ, with IFN-α and IFN-β serving as main mediators of systemic antiviral host defence. Previous studies using knockout models have already provided insights into the roles of IFN-β and IFN-κ during viral infection. However, the specific and potentially distinct functions of IFN-α and IFN-β during infection remain poorly understood, and direct comparative analyses of their antiviral activities are lacking. Here, we investigated the distinct contributions of IFN-α and IFN-β to antiviral defence against murine cytomegalovirus (MCMV).

In this study, we used gene-targeted mice lacking either the entire *Ifna* locus, the *Ifnb* gene, or both. MCMV replication in the spleen was assessed by qPCR, plaque assays, and immunohistochemistry. Immune cell composition at steady state and following infection was analyzed by flow cytometry. IFN-α and IFN-β expression was measured by RT-qPCR and RNAscope. Single-cell RNA-seq analyses to identify IFN-I producing and responding cells at steady state and during infection is ongoing. Furthermore, we used in vitro studies in primary mouse embryonic fibroblasts and bone marrow-derived macrophages to assess cell type-specific contributions of IFN-α and IFN-β to the antiviral response and uncover potential cross-regulatory circuits.

Our results demonstrate that IFN-α is critical for controlling MCMV replication in the spleen, whereas IFN-β is dispensable for the antiviral defence and the induction of IFN-α during infection. Notably, deficiency of either IFN-α or IFN-β resulted in upregulation of the other. In vitro studies in fibroblasts and macrophages exhibited distinct, cell type-specific roles of IFN-α versus IFN-β in the antiviral defence. Together, these findings uncover non-redundant and context-dependent functions of IFN-α and IFN-β during MCMV infection and provide new insights into the complexity of IFN-I-mediated antiviral immunity.

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O009

Performance of serological and molecular markers to predict congenital CMV infection (cCMV) in offspring's of pre-immune pregnant women

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Abstract

Introduction/Aim: In Europe and the USA, cCMV infection occurs in 30 to 50% of cases in pregnant women with preconceptionnal immunity. We aimed to assess the performance of serological and molecular markers in this population.

Materials and Methods: Pregnant women with preconceptionnal immunity were enrolled between October 2022 and November 2024 during their first visit (11-14 weeks of gestation) at Necker Hospital (Paris, France). Serum samples (IgG, IgM, and IgG avidity) were collected during the first trimester (T1), also blood and urine samples at T1 and at delivery (T3). Neonatal saliva samples were collected within the first 15 days after birth. Quantitative CMV PCR was performed on blood, urine and saliva specimens.

Results: 1,297 pre-immune pregnant women were followed throughout pregnancy. Neonatal saliva PCR was positive in 2/1072 newborns, corresponding to a cCMV rate of 0.19%. Followed up to 12 and 17 months, neither developed sequelae. One pregnancy was terminated at 27 weeks' gestation due to severe cCMV infection. At T1, 5.2% of women shed virus in urine and 2.3% in blood, the majority of whom already had a child. The sensitivity to predict cCMV of IgM and CMV DNA in blood at T1 and T3 was 33.3%, whereas CMV DNA detection in urine at T1 reached 66.6%. The positive predictive value (PPV) of these assays did not exceed 6.2%. When combining positive urine and blood PCR at T1, the PPV reached 16.7% (sensitivity: 50.0%). The rate of vertical transmission in women with CMV replication was 2.6%.

Conclusion: In this population of women with pre-existing immunity, both vertical transmission rate and cCMV rate were low (2.6 and 0.2%). Virological markers showed low sensitivity and very limited PPV, highlighting their poor diagnostic value. Our findings underscore the need to develop news markers to identify pregnant women at risk of cCMV.



O010

A Roadmap for Congenital Cytomegalovirus (CMV) Research in Australia and New Zealand: a Modified Delphi Consensus Informed by Lived Experience

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Abstract

Introduction/Aims

Congenital cytomegalovirus (CMV) is the leading infectious cause of disabilities in newborns in high-income countries. Despite its impact, prevention and management research priorities have not previously been defined. This study, developed with people with lived experience (PWLE), aimed to identify and prioritise consensus-based research questions for the prevention and management of congenital CMV in Australia and New Zealand.

Methods

An online, modified Delphi process was conducted for a) PWLE of congenital CMV and b) professionals interested in congenital CMV in Australia and New Zealand. Participants submitted and rated the importance of research questions over three survey rounds, distributed between June and November 2025. PWLE also participated in online consultation meetings between round 1 and 2. Consensus was defined as ≥75% agreement on priority level (high, medium, or low) with an interquartile range ≤1. Questions that reached consensus were ranked by means. Data were analysed separately for PWLE and professionals to preserve lived experience perspectives.

Results

A total of 142 participants (28 PWLE and 114 professionals) contributed, generating 419 research questions in Round 1. Following Rounds 2 and 3, consensus was achieved on 65 high-priority research questions. Priority areas shared by PWLE and professionals included CMV awareness, antenatal CMV screening, maternal treatment following CMV infection, vaccine development, fetal prognosis and neonatal screening. PWLE ranked maternal treatments to prevent fetal infection as their highest priority, whereas professionals prioritised vaccine development. Research questions uniquely prioritised by PWLE focused on family support across the lifespan and the need for clear, compassionate CMV information about treatment options and outcomes.

Discussion

This study provides a clear roadmap to drive research, policy action, and advocacy for congenital CMV in Australia and New Zealand, as identified by PWLE and professionals. Aligning research investment with these lived experience informed priorities will improve research impact and outcomes for children and families.



O011

PEDIATRIC FOLLOW-UP AND OUTCOMES OF CONGENITAL CYTOMEGALOVIRUS INFECTION AFTER MATERNAL VALACICLOVIR TREATMENT: A MULTICENTER MEGAL-ITALI STUDY

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Abstract

Background

Congenital cytomegalovirus (cCMV) infection is a leading cause of sensorineural hearing loss in childhood. Maternal primary infection (MPI) treated with valaciclovir reduces vertical transmission at amniocentesis to 10-15%. Long-term outcomes of children with cCMV despite maternal therapy are limited.

Method

MEGAL-ITALI is a multicenter retro-prospective Italian observational study, conducted between January 2020 and October 2025, evaluating clinical, laboratory, instrumental findings and outcomes of children with cCMV born to mothers with MPI treated with valaciclovir.



Results

A total of 266 newborns from 13 Italian centers were enrolled; 132 (49.6%) had cCMV. Of these, 45/132 (34.1%) were diagnosed after a positive CMV PCR on amniocentesis; while late transmission after amniocentesis occurred in 37/132 (28%). In the remaining cases amniocentesis was not performed. Two children were excluded due to concomitant genetic diagnosis.

Overall, 21/130 (16.2%) infected newborns had moderate/severe symptoms at birth. Two symptomatic infants had negative amniocentesis results, presenting with thrombocytopenia and bilateral temporal white matter abnormalities on MRI, respectively.

Audiological follow-up was available for 53/130 (40.8%) children, with a median follow-up of 19.3 months (IQR 9.7–33.7). Among 34 asymptomatic children, one case (2.9%) of unilateral late-onset hearing loss was detected at 9.2 months. Neurodevelopmental follow up was available for 40/130 (30.8%) children (median 13 months, IQR 9-23.7). One asymptomatic child developed global neurodevelopmental delay at 12.2 months. Notably, no late-onset symptoms were observed in children born to mothers with negative amniocentesis. No major adverse effects attributable to valaciclovir were observed during a one-year follow-up of 134 uninfected newborns.

Conclusions/Learning Points

These findings confirm the safety of valaciclovir in pregnancy. The incidence of late-onset hearing loss among asymptomatic patients appears lower than reported rates, although longer follow-up is needed to draw definitive conclusions.



O012

Observed changes in the cohort of cCMV-infected children post implementation of effective antiviral secondary prophylaxis in pregnant women with CMV infection

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Abstract

Introduction

Secondary prevention of congenital CMV (cCMV) through diagnosis and treatment in women with primary CMV infection (PI) early in pregnancy has been increasingly implemented in countries with maternal screening in place.

Aim

We aimed to describe the changes observed in our cohort of cCMV infected children over the past 15 years during transition from hyperimmune globulin (HIG) to valacyclovir secondary prophylaxis in women with PI.

Methods

This is a single center retrospective cohort study including all cCMV infected children enrolled during: Period A (2011-2020) and B (2021-5.2026). Cohorts (Period A vs Period B) were compared in terms of maternal infection parameters (trimester of infection, maternal treatment), neonatal symptoms (clinically apparent/inapparent cCMV disease), and long-term outcomes (SNHL, neurodevelopmental impairment- NDI).

Results

Overall, 171 children were included; 98 (Period A) and 73 (Period B). Median age at last visit was 5 years and 21 months, respectively. Most children (92.4%) were born to mothers with PI. Among treated women, a transition from HIG (period A 98.3%) to valacyclovir (period B 83.9%) was noted. During period B, more cCMV infected babies were born to mothers with unknown status (p=0.005), while maternal treatment for known PI significantly decreased (64.9% versus 43.7%, p=0.007). Moreover, a significant increase of children born with clinically apparent disease (p=0.0064) and SNHL at birth (p=0.031) was noted. Neonatal MRI evaluation (p<0.001) and neurodevelopmental assessment (p<0.001) increased. Severe NDI was more prevalent in period A (26.9% versus 8.33%, p=0.019) while notably children in period B were significantly younger.

Conclusions

Post implementation of effective antiviral secondary prophylaxis in pregnant women with PI, a transition to a group of children born to untreated women of unknown CMV infection status, with more clinically apparent disease and SNHL at birth was noted. Prevention of vertical transmission and increased awareness among neonatologists possibly explain our results.



O013

Genomic diversity of congenital cytomegalovirus: first findings from the cCMV Sequencing Consortium

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Abstract

Introduction/Aim: Cytomegalovirus (CMV) is the most common congenital viral infection and a leading cause of sensorineural hearing loss and neurodevelopmental disability. CMV is the most genetically diverse herpesvirus, yet efforts to link viral genomics to disease severity have been hampered by small cohorts, sequencing limitations, and incomplete characterisation of CMV diversity. The Congenital CMV (cCMV) Sequencing Consortium is a multi-centre pilot study designed to close these gaps and identify viral genetic determinants of cCMV outcome. Our central aim is a genome-wide association study (GWAS) linking viral sequence variation to standardised clinical metadata, including symptoms at birth, hearing loss, and neurological sequelae.

Methods and Results: Samples (urine, saliva, blood, amniotic fluid) from foetuses and congenitally infected newborns across UK and European sites undergo CMV target-enrichment Illumina whole-genome sequencing at UCL, with clinical data captured through cCMVnet. We present a pilot cohort of ~50–60 isolates from the UK and France. As in host GWAS, association testing requires control for population structure. Two further considerations are specific to CMV: mixed infections and the comparability of genomes across sample types. Phylogenetic analysis shows diversity consistent with our cosmopolitan populations, clustering alongside European, African and Asian references. This geographic structure will be modelled in the association analysis. Within-host analysis identifies a single dominant strain per infant, with no evidence of mixed infection, permitting unambiguous genotype assignment. Sequences are concordant across urine, oral swab and plasma, so any sample type is informative and the full cohort is retained.

Conclusions: These findings establish proof-of-concept for the Consortium's framework and confirm the cohort is tractable for association testing. Continued recruitment across European and global sites will provide statistical power for a GWAS connecting viral determinants to clinical outcomes such as symptoms at birth, hearing loss, and neurological sequelae, with the goal of predicting cCMV severity.



O014

Prognostic performance of a neonatal risk stratification model and the role of brain MRI in congenital Cytomegalovirus infection

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Abstract

Background. Congenital cytomegalovirus (cCMV) infection affects 0.7% of live births and is a major cause of sensorineural hearing loss (SNHL) and neurodevelopmental impairment. Fourgeaud et al. (Pediatrics, 2024) proposed a neonatal prognostic score based on hearing status at birth, platelet count, and cranial ultrasound findings to identify infants at low risk of long-term sequelae. We assessed the performance of the Fourgeaud prognostic score in an Italian tertiary-care cohort of infants with cCMV and explored the additional prognostic value of neonatal brain MRI.

Methods. We retrospectively reviewed infants with confirmed cCMV followed at Meyer Children's Hospital IRCCS, Florence, Italy, between 2009 and 2026. The Fourgeaud score was applied to patients with complete neonatal data and ≥24 months of follow-up. Brain MRI was classified as normal or abnormal according to the original clinical report. Long-term sequelae were defined as SNHL and/or neurodevelopmental impairment at the last follow-up visit.

Results. Among 99 infants (65% symptomatic at birth, 61% treated with valganciclovir; median follow-up 55 months, IQR 24-72), 32 (33%) developed sequelae. The Fourgeaud score was assessable in 68 patients; 29 (43%) were classified as low risk. The score showed a sensitivity of 76%, specificity of 51%, negative predictive value (NPV) of 83%, and AUC of 0.64. High-risk classification showed a non-significant trend toward sequelae (OR 3.28, 95% CI 0.95-13.38; p=0.062). In the 37 patients with available MRI, abnormal MRI was associated with sequelae (OR 11.73, 95% CI 1.05-89.82; p=0.027), with sensitivity 86%, specificity 68%, NPV 94%, and AUC 0.77.

Conclusions. The prognostic performance reported in the original cohort was not reproduced in our tertiary-care population, possibly reflecting differences in disease severity and follow-up duration. Neonatal brain MRI showed the highest predictive accuracy for long-term sequelae and may improve risk stratification in infants with cCMV. Further evaluation using structured MRI-based scoring systems is warranted.



O015

Exploratory proteomics of amniotic fluid extracellular vesicles in congenital cytomegalovirus

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Abstract

Introduction: Congenital cytomegalovirus (cCMV) is the most common congenital viral infection and a leading non-genetic cause of neurodevelopmental impairment. Current diagnostic methods using fetal biofluids provide limited insight into fetal pathophysiology. Extracellular vesicles (EVs) in amniotic fluid (AF) are a source of intentionally-packaged, stable biomolecules that provide a unique window into real-time fetal physiology. This proof-of-concept study compared amniotic fluid EV (AF-EV) characteristics in fetuses with severe CMV infection with those of uninfected fetuses to develop hypotheses about fetal response to CMV.

Methods: AF samples were collected from pregnancies with symptomatic CMV infection and gestational-age-matched uninfected controls (4 pairs, n=8 total). EVs were isolated and characterised by Western blotting, cryo-electron microscopy, and nanoparticle tracking analysis. Label-free quantitative proteomics identified CMV-associated changes in the AF-EV proteome.

Results: CMV-infected AF showed higher vesicle levels (Hedges' g = 1.55), indicating inflammation and virus-induced changes in EV biogenesis. Proteomic analysis found 8.6% of proteins dysregulated. Upregulated proteins included haemoglobin subunits, immunoglobulin heavy chain mu, and myeloperoxidase (Hedges' g = 1.51 to 1.88), indicating haemolysis and immune activation. Eleven host proteins related to neurodevelopment, mitochondrial function, lipid metabolism, and Golgi trafficking were absent in infected cases, indicating viral disruption of host pathways. Protein enrichment analysis revealed differences in neurological, haematological, and immune pathways, aligning with severe cCMV pathology.

Conclusion: This study acts as a proof-of-principle investigation of the AF-EV proteome in cCMV. These results have highlighted key protein signatures associated with severe fetal outcomes and generated hypotheses to inform larger prospective studies.



O016

Characterization and Immunologic Signatures of GMP Grade Related Donor Cytomegalovirus Virus (CMV) Cytotoxic T-Lymphocytes (CTLs) Manufactured by the CliniMACS Prodigy® CCS (IFN-gamma) System

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Abstract

Background

CMV, a ubiquitous herpes DNA virus, has a large genome that is designed to facilitate evasion, blocking, impairing and modulating host immune responses. CMV infections in immunocompromised host (Allogeneic Hematopoietic Stem Cell Transplant (AlloHSCT) recipients, solid organ transplantation (SOT) recipients or hosts with primary immunodeficiencies (PID) have a significantly increased risk of morbidity, mortality and/or allograft rejection. Importantly, restoring CMV viral specific (VS) T-cell immunity is the key driver of eradicating CMV refractory infections in immunocompromised hosts. Adoptive CMV specific T-cells may improve outcome in immunocompromised hosts.

Methods

We developed a method of GMP grade manufacturing of CMV-CTLs from related donors following non-mobilized MNC apheresis and utilizing a CMV Peptivators®, generously provided by Miltentyi Biotec, to manufacture and enrich related donor-derived CMV-CTLs using the CliniMACS Prodigy® CCS (IFN-gamma) System on the CliniMACS Prodigy® device. We subsequently characterized these enriched populations of CMV CTLs by Single Cell RNAseq (scRNAseq), Nanostring® Immunoprofiling, Mass Cytometry and Multidimensional Flow Cytometry (MDFC).

Results

Compared to the control population of PBMNC the CMV-CTLs enriched population having significantly decreased in T-cell Naïve subtype (CD45RA) ($P<0.05$), were significantly enriched for central memory (CM) and effector memory CD4 and CD8 T-cell ($P<0.01$) by MDFC, were significantly increased in CD4 TH1 and CD4 Follicular Cells and CD8 EM and CD8 EMRA cells ($P<0.05$) and INFγ and Granzyme B expression ($P<0.01$) by scRNAseq, had significantly increased distinct gene expression of cytokine expression INFγ, IL-21, TNF+, GM-CSF and had restrictedTCR variable region by Nanostring® immunoprofiling ($P<0.01$) and significantly increased T_{EM} and T_{EMRA} by Mass Cytometry

Conclusion

Related donor CMV-CTLs enriched by the CCS® on the CliniMACS® Prodigy® demonstrated a highly enriched population of both CD4 and CD8 effector memory and central memory T-cells, highly restricted TCR variable region and a predilection to expressing INFγ, IL-21, Granzyme B, GM-CSF and TNFγ.



O017

The Safety and Efficacy of Related Donor Derived CMV Cytotoxic T-Lymphocytes Manufactured and Enriched by the CliniMACS Prodigy® CCS (IFN-gamma) System in Immunocompromised Children and Adolescents with Medically Refractory CMV Infections

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Abstract

Background:

CMV infection in immunocompromised patients, including recipients of Allogenic Hematopoietic Stem Cell Transplantation (AlloHSCT), Solid Organ Transplantation (SOT) and patients with Primary Immunodeficiencies (PID), are at significantly increased risk of morbidity, mortality and/or allograft rejection. CMV anti-microbial therapy can be associated with drug resistance and/or significant dose-limiting toxicity such as bone marrow suppression and/or acute kidney injury, limiting their effectiveness. Here, we report the feasibility, safety and efficacy of a Phase II trial of related donor-derived CMV CTLs in immunocompromised children and adolescents with medically refractory CMV Infections (NCT03266640) (IND17449).

Methods:

Patients (1 - <30yrs) who were immunocompromised (AlloHSCT, SOT/PID) with a medically refractory CMV infection with a positive screened related donor (either HLA matched or haploidentical matched) were treated with CMV-CTLs (either $2.5x10^4$ CD3/kg/dose or $0.5 x10^4$ CD3/kg/dose, respectively) enriched utilizing the CMV Peptivators®, generously supplied by Miltenyi Biotec®, using the CliniMACS Prodigy® CCS (IFN-gamma) System on the CliniMACS Prodigy® device. A maximum of 5 doses q2wks until CR (undetectable levels of CMV by PCR) or dose-limiting toxicity was allowed.

Results:

20 patients (Median Age: 6.0 (1.0 – 19yrs); M/F: 14/6; HLA Matched: 30% and Haplo Matched: 70%; AlloHSCT: 90%, SOT: 5%, PID: 5%. CMV CTLs were well tolerated with no CRS, IRR, ICANS, graft failure or neurological toxicities. There were 2 transient skin GVHD treated with topical steroids. Eighty five (85%) achieved a CR with a median of 29 days and a median of 2 doses. Day +100 and Day +365 probability of OS was 84.4% and 79.2%, respectively. No patients died of CMV.

Conclusion:

Related donor-derived CMV-CTLs were well tolerated, associated with a 85% CR rate and probability of CMV associated mortality at 1yr of zero percent in children and adolescent immunocompromised hosts with medically refractory CMV infection.



O018

pp65-specific T cell response is a predictor of the risk for clinically significant HCMV infection after the stop of Letermovir prophylaxis

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Abstract

Introduction: Letermovir (LTV) prophylaxis has changed human cytomegalovirus (HCMV) management in hematopoietic stem cell transplant recipients (HSCTR). However, HCMV breakthrough infections and late HCMV reactivations remain crucial issues. We aimed to analyse the role of HCMV-specific T-cell response as a prognostic marker for predicting the risk of clinically significant HCMV infection after the stop of LTV prophylaxis.

Patients and Methods: We enrolled 173 adult HCMV-seropositive HSCTR receiving LTV prophylaxis for 100 days. HCMV DNAemia was prospectively monitored for one year. At day 100, 180 and 360, lymphocyte T-cell count was quantified and HCMV-specific T-cell response was measured by ELISpot (T-SPOT and T-Track, using pp65 and IE1 antigens) and QuantiFERON-CMV.

Results: The analysis focused on the 70/173 enrolled patients who completed a 180-day follow-up. After the stop of LTV prophylaxis, 16/70 (22,8%) patients showed clinically significant HCMV infection (i.e. infection requiring additional courses of antiviral therapy with ganciclovir/valganciclovir), whereas the remaining 54/70 patients (77,2%) controlled spontaneously HCMV infection. A significant increase in CD3+, CD3+CD4+ and CD3+CD8 T cells was observed between day 100 and 180. No difference was found between patients who developed clinically significant infection (Non-CTR) and who controlled spontaneously HCMV infection (CTR) in any of these lymphocyte populations. When using pp65 as stimulus, both T-SPOT and T-Track assays gave significantly higher results ($p=0.0005$ and $p=0.0031$, respectively) in CTR than in Non-CTR. Both tests showed a high positive predictive value for detecting HCMV infection after prophylaxis (>95%), but a lower negative predictive value (approximately 50%). The predictive values of IE-1-specific ELISpot and QuantiFERON-CMV assays were lower.

Conclusion: Our results show that pp65-specific T-cell response, measured by ELISpot, can identify patients at risk for clinically significant HCMV infection after prophylaxis. These interim results suggest that HCMV-specific T-cell measurement could be adopted to identify patients who would benefit from longer prophylaxis.



O019

Neonatal characteristics and outcomes of asymptomatic congenital cytomegalovirus infection: A Single-Center Experience

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Abstract

Introduction/Aim: While the majority of infants with congenital CMV (cCMV) are asymptomatic at birth, approximately 20% of all children with cCMV will develop sequelae (including sensorineural hearing loss, SNHL). Longitudinal follow-up data of asymptomatic neonates have been limited. The aim of this study was to describe the distribution of neonatal features and the long-term virological and clinical outcomes among children with asymptomatic cCMV.

Materials and Methods: A retrospective study of children diagnosed with asymptomatic cCMV (AcCMV) infection was conducted at a tertiary pediatric hospital between October 2019 and March 2026. Children with confirmed cCMV (a positive CMV PCR in urine and/or blood taken within the first 3 weeks of life) and no apparent abnormalities at birth to suggest cCMV were included. Prenatal findings, delivery data, and neonatal diagnostic evaluation data (including cranial ultrasound (cUS), audiology, laboratory findings, CMV viral load in blood and urine by PCR), and data from follow-up visits were collected.

Results: A total of 95 infants were included (median follow-up 7.2 months; range 0.7-72.6). Among 95 AcCMV cases, 26 (27.4%) had an incidental cUS finding (cystic lesion and/or lenticulostriate vasculopathy). Both viremia and viruria at baseline were significantly associated with the presence of incidental cUS findings (OR 1.69; 95% CI 1.10-2.88; p=0.030; and OR 1.72; 95% CI 1.16-2.76; p=0.013, respectively for blood and urine viral load). Neurological abnormalities (including developmental delays) were observed in 14 children (none had SNHL). There was no significant difference in baseline urine and blood viral load between patients stratified by neurodevelopmental outcome.

Conclusions: In our cohort, a higher baseline viral load in urine and blood was a significant predictor of early, subclinical structural CNS changes (incidental cUS findings) in asymptomatic cCMV. Despite this association, initial viral burden was not associated with neurodevelopmental outcomes. Longer follow-up is warranted to provide further details on neurological outcomes.



O020

Long-term neurodevelopmental impairment in children with clinically inapparent congenital CMV disease at birth: a prospective cohort study

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Abstract

Introduction/Aim

Congenital cytomegalovirus (cCMV) infection is associated with neurodevelopmental impairment (NDI). NDI awareness among asymptomatic children is increasing. We aimed to estimate NDI prevalence in children with clinically inapparent cCMV disease (CICMV) at birth, and reveal related risk factors.

Materials and Methods

Retrospective cohort study. Neonates with confirmed cCMV in our center since 1/1/2011 were eligible. CCMV neonates with CICMV were included, as well as neonates characterized as Clinically Apparent CMV disease (CACMV) solely based solely on neuroimaging data (Alarcon scale 2). Children were evaluated using Bayley III scale by a Developmental Specialist, beginning at 12 months of age. Primary outcome was NDI; demographic, somatometric, and clinical characteristics were also recorded.

Results

84 children were included, 74 CICMV and 10 CACMV, 37 males (44.0%). Median age (25th, 75th perc.) at the last NDI evaluation was 43 (28.5, 60.0) months. NDI was present in 36/84 (42.9%); in 12/84 (14.3%) severe, while 30/84 (35.7%) were under intervention and 4.8% of the children needed special schooling. Severe NDI was significantly more evident in children evaluated for NDI for the first time after 36 months of age (29.2% vs 8.6%, p=0.034). Amongst this group, NDI correlated with lower z-score for Head Circumference (HC, p=0.022); Z-score for HC remained an independent risk factor for NDI after multivariate analysis, including male gender. Amongst CICMV children alone, severe NDI significantly correlated with lower gestational age. Additionally, severe NDI was more frequent in 1st trimester (22.8%) versus 2nd/3rd trimester infections (7.7%), and also in cases where the mother was either not treated during pregnancy or treated with HIG (7/27 vs 0/13 in the valaciclovir group), but both not statistically significant.

Conclusions

Amongst children with CICMV disease, lower HC z-score, gestational age, and maternal first trimester infection are potentially associated with severe NDI. Early diagnosis and intervention are important.



O021

Quality of life among infants with congenital CMV and their caregivers

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Abstract

Introduction/Aim: Congenital cytomegalovirus (cCMV) diagnosis has major implications for infants and caregivers due to complex neonatal diagnostic evaluations, frequent follow-ups, and long-term outcome uncertainty. We sought to quantify quality of life (QoL) among infants with cCMV and their caregivers.

Methods: PROACTIVE NYS is a longitudinal study of children with cCMV identified through universal newborn dried blood spot screening or routine clinical care in New York State, US from 2023 – 2024 and enrolled with parental consent. One year after study initiation, we performed cross-sectional assessments of child and caregiver QoL with the PedsQL Infant Scales and Parental Stress Scale (PSS), respectively. We defined cCMV disease as having any cCMV-related abnormality within the first month of life and cCMV infection as having none. We performed descriptive analyses, Wilcoxon rank-sum tests for associations between cCMV disease and QoL, and univariable regression to assess child age as a predictor of QoL.

Results: Among 107 enrolled participants, PedsQL was completed for 39 (36%), including 22/39 (56%) with cCMV disease, at mean age 8.8 months (range 2.5-14.5 months). Mean PedsQL Physical Health score was 89.2 (range 67-100), Psychosocial Health score 84.6 (range 50-100), and Total Score 86.5 (range 58-100). PSS was completed by 34 (32%) caregivers, including 18/34 (53%) whose child had cCMV disease, at mean age 9.3 months (range 2.5-14.5 months). Mean PSS score was 39.2 (SD 13.8). No association was found between cCMV disease and PedsQL or PSS scores. Child age was not a predictor of PedsQL or PSS score.

Conclusions: Children with cCMV and their caregivers had overall good health-related QoL, similar to healthy infant norms. Scores did not vary by presence of cCMV disease or child age. Findings may be limited by participant attrition and small sample sizes. Future work should focus on QoL by cCMV disease severity and longer follow-up.



O022

Plasma biomarkers are predictors of severity of brain abnormalities in infants with congenital cytomegalovirus

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Abstract

Introduction/Aim: Congenital cytomegalovirus (cCMV) can cause brain abnormalities such as microcephaly and cortical malformations [2], resulting in neurodevelopmental problems including cerebral palsy and cognitive disability. There are limited prognostic tools for cCMV, however cranial magnetic resonance imaging (MRI), although expensive, is promising. A cCMV-specific validated score grades cranial MRI severity to predict neurodevelopmental outcomes (Alarcón score 0-3, 3=most severe) [3]. We investigated whether plasma inflammatory proteins in neonates correlate with the Alarcón score and could guide the need for cranial MRI in infants with cCMV.

Materials & Methods: Plasma samples from infants with cCMV and healthy controls, from a multi-centre observational cohort study in the United Kingdom (TINI-CC), were analysed using a panel measuring 45 inflammatory proteins and cytokines (Olink®). CMV quantification was measured by digital droplet PCR. Alarcón scores were assigned by a neuroradiologist from cranial MRI performed <3 months of age.

Results: Of 30 neonates with cCMV, median age 17 days [IQR 5.25-29.75]) with median plasma CMV viral load (VL) of 74 IU/ml IQR 0-149.25], 73% (n=22) were symptomatic at birth. Alarcón scores: 3 (n=8), 2 (n=5), 1 (n=4), and 0 (n=13). Nine infants without cCMV were controls, median age 40 days [IQR 12-70.5]. Independent of CMV VL, three proteins were significantly lower (CXCL11, EGF, IL-2; p=<0.05) in neonates with cCMV and Alarcón scores 2-3 versus 0-1. IL-2 was significantly higher (p=<0.05) in controls versus Alarcón Scores 2-3 versus 0-1.

Conclusions: Lower plasma levels of CXCL11, IL-2, and EGF are associated with more severe MRI-defined brain injury in cCMV, independent of CMV VL. This suggests a state of impaired immune activation coupled with reduced regenerative signalling. With further validation, these biomarkers could represent a novel, cost-effective approach to support risk stratification and guide decisions for cranial MRI in infants with cCMV.



O023

THROMBOCYTOPENIA AND SUBSEQUENT HEARING AND NEURODEVELOPMENT OUTCOMES IN CHILDREN WITH CONGENITAL CMV

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Abstract

Introduction/Aim

Thrombocytopenia at diagnosis in congenital CMV (cCMV) infection has been shown to be an important prognostic factor. The aim of this study is to determine the association of neonatal thrombocytopenia with long-term outcomes in a large international cohort.

Materials and Methods

Multicenter study including children enrolled in the cCMVnet database (2011-2026). Diagnosis of cCMV was confirmed by blood, saliva or urine PCR within 3 weeks of life. Thrombocytopenia was defined as platelets <100.000µL at diagnosis. Hearing assessment was performed via auditory brainstem response (ABR) whereas neuroimaging included cranial ultrasound (CRUSS) and/or brain MRI. Neurodevelopmental sequelae included the following outcomes: motor impairment (spasticity, paresis) and/or epilepsy (requiring treatment).

Results

Overall, thrombocytopenia was present in 186 (9.4%) out of 1,988 newborns; 95 were boys (51.1%) with a median gestational age at birth of 37 weeks (IQR: 35-39). Of the 81 children with known type of maternal infection, 43 (53%) were primary and occurred at a median gestational age of 20 weeks (IQR: 10-26). [AN1] Baseline neuroimaging abnormalities were more prevalent in the thrombocytopenic group (brain MRI p<0.0001, CRUSS p<0.0001). Hearing impairment (any severity, at least in one ear) was also more common in the thrombocytopenic group at diagnosis, at 6 and 24 months, and at last visit (p=0.0009, p=0.0005, p=0.0005 and p=0.058, respectively). During follow up, motor impairment was more frequent in the thrombocytopenic group at 6, 12, 24 months and at last recorded visit (p=0.0004, p=0.0025, p=0.0496 and p=0.01445, respectively). Epilepsy prevalence was higher at 4 years in the thrombocytopenic group (p=0.0188[AN2] [LS3]).

Conclusions

In this large cohort, thrombocytopenia in newborns with cCMV infection was associated with adverse hearing and neurodevelopmental outcomes both at diagnosis and during long-term follow-up.



O024

A NEONATAL PROGNOSTIC SCORE FOR INFANTS WITH CONGENITAL CYTOMEGALOVIRUS INFECTION (cCMVnet Score)

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Abstract

Introduction/aim: To identify risk factors for long-term sequelae in children with congenital cytomegalovirus (cCMV) infection and develop a prognostic scoring system (cCMVnet score) to support individualized patient management.

Material and methods: Retrospective study performed in the prospective cohort of the European Registry of Children with cCMV (cCMVnet registry) including children with confirmed cCMV born between 2011–2024 across 11 countries. Eligible participants underwent cranial ultrasound (cUS) and/or brain MRI within 90 days of life and had at least six months of follow-up. The primary outcome was the presence of moderate-severe cCMV related sequelae (sensorineural hearing loss [SNHL] or motor impairment (paresis/spasticity, epilepsy, or visual impairment). Predictors were assessed in a "train group" using multivariable logistic regression analysis with Elastic-Net selection. Prognostic risk scoring system was built and was evaluated in the "test group".

Results: Among 1,671 children within the cCMVnet Registry, 570 patients were included. 360/570 (63.2%) were symptomatic at birth. Sequelae were observed in 165/570 (28.9%) cases: SNHL (24.7%), motor impairment (8.2%), epilepsy (4.0%), and visual impairment (2.6%). Splenomegaly and the severity of hearing loss at birth were strongly associated with sequelae. Neuroimaging abnormalities (white matter abnormalities, intracranial calcifications, caudothalamic/subependymal cysts, germinolysis, ventriculomegaly, and migration abnormalities) and other findings in physical examination (microcephaly, hypotonia and petechias) were included in the Score. The final cCMVnet Score showed good predictive accuracy with an area under the ROC curve of 0.870 (95% CI: 0.787–0.952). Using a threshold of 2.99 points, sensitivity was 84.4% and specificity 81.0%, with a high negative predictive value (91.7%).

Conclusions The cCMVnet score reliably predicts long-term sequelae in children with cCMV by integrating clinical, hearing, and neuroimaging findings. It enables individualized risk stratification beyond the traditional symptomatic/asymptomatic classification, supporting tailored follow-up and management. External validation is required in other cohorts before widespread implementation.



O025

Autism Spectrum Disorders in congenital cytomegalovirus infection

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Abstract

OBJECTIVE: Several aspects of the clinical spectrum of congenital CMV (cCMV) infection remain poorly understood, including its potential role in neurodevelopmental conditions such as autism spectrum disorder (ASD). Current literature lacks conclusive evidence for this association. This study investigates ASD incidence in children with cCMV infection.

MATERIALS AND METHODS: With parental consent, the Modified Checklist for Autism in

Toddlers (M-CHAT) was administered to cCMV-affected children aged 12–36 months (mean: 21.3 months) at our regional referral Centre for perinatal infectious diseases. Controls were children congenitally exposed to Toxoplasma gondii and Treponema pallidum, including those with congenital toxoplasmosis (CT). Children scoring >4 were referred for neuropsychiatric evaluation. Data collection began May 2025.

RESULTS: Of 90 questionnaires administered (24 cCMV, 6 CT, 60 Toxoplasma/Treponema- exposed), 5 were excluded (4 Toxoplasma-exposed, 1 cCMV), leaving 85 evaluable. cCMV children had a mean M-CHAT score of 4.7±6.1 (0–20); 9 scored >4, of whom 3 received an ASD diagnosis. Infection-exposed-only children had a mean score of 2.3±2.1 (0–10), with 8 scoring >4 and recommended for reassessment. All CT patients scored 0. M-CHAT scores were significantly higher in cCMV patients (p=0.019), with more pathological scores than controls (8/21 vs 7/47; p=0.026). Among the 9 cCMV children scoring >4, 8 were asymptomatic at birth; 1 mother received antenatal therapy; seroconversion occurred in the first trimester (2 cases), second (3 cases), and third (3 cases). Sample size precluded further statistical analysis.

CONCLUSIONS: These findings suggest cCMV infection increases the risk of neurodevelopmental conditions, including ASD, compared with exposure to or congenital infection by other pathogens.

The study is ongoing and aims to validate these findings in a larger cohort, with further stratification by trimester of infection, maternal therapy, disease severity at onset, and neuroimaging findings.



O026

Developing a Prediction Model for congenital Cytomegalovirus (cCMV)-associated Sensorineural Hearing Loss (SNHL)

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Abstract

Introduction: CMV is the most common congenital viral infection and a leading cause of sensorineural hearing loss (SNHL) and neurodevelopmental delays. Despite major advances, the pathogenesis of cCMV-associated SNHL remains elusive with a lack of predictors to enable early identification of those at-risk to individualize anti-viral treatment and audiological monitoring.

Aim: To develop and validate a prediction model for cCMV-associated SNHL by analyzing demographic, clinical, virological and neuroradiological findings in the newborn period.

Materials and Methods: We analyzed a cohort of 1,202 children with confirmed cCMV from CMV natural history studies with well-defined clinical outcomes. Candidate predictors for SNHL included demographics (maternal age, gestational age and birth weight), newborn clinical findings (hepatomegaly, splenomegaly, petechiae, purpura, seizures, hypotonia, and microcephaly) with laboratory, virological and neuroimaging findings when available. Children were categorized into groups with 0, 1 or ≥ 2 newborn findings. The dataset was split into a stratified 70% training and 30% locked test set. The primary model was penalized logistic regression, and performance was assessed using the receiver operating characteristic curve (AUROC), area under the precision-recall curve (AUPRC), Brier score, calibration intercept, calibration slope, and threshold-based metrics. Robustness was assessed using stratified 5-fold cross-validation repeated 20 times.

Results: Of 1,202 infants with cCMV, 173 developed hearing loss (14.4%). The primary model demonstrated good discrimination in the locked test set, with an AUROC of 0.801 (95% CI: 0.738–0.863) and APRUC of 0.484 (95% CI: 0.355–0.625). Calibration was strong, with a Brier score of 0.099. Risk of SNHL increased stepwise with greater burden of newborn findings: 8.6% with 0 findings, 25.2% with 1 finding, 47.7% with ≥ 2 findings. The model is currently undergoing expansion and validation to incorporate laboratory, virological and neuroimaging predictors.

Conclusions: In children with cCMV, a leakage-protected penalized logistic regression model demonstrated good discrimination and calibration for predicting cCMV-associated SNHL.



O027

Nucleosomal Sequestration of Human Cytomegalovirus Proteins IE1 and pp65 Limits Their Proteasomal Degradation and Promotes Establishment of Latency

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Abstract

The double-stranded DNA genomes of human cytomegalovirus (HCMV) and other herpesviruses associate with host cell histones to form nucleosomes during latent and lytic infection. We have previously shown that HCMV immediate-early protein 1 (IE1) binds to core histones and targets the nucleosome surface by interacting with H2A-H2B dimers via its chromatin tethering domain. Using a chromatin proteomics approach, we identified several additional HCMV core histone binding proteins that were not previously known to bind to chromatin. One of these new histone binding proteins is phosphoprotein 65 (pp65), the major component of the HCMV tegument. Like IE1, pp65 binds to H2A-H2B in the acidic pocket of the nucleosome core particle, and the nucleosome binding motif was mapped to conserved residues in the linker domain of the viral protein. AlphaFold3 and NMR results indicate that the pp65 nucleosome binding domain is intrinsically disordered in the absence of histones. Wild-type IE1 and pp65 show nuclear retention and colocalise with mitotic chromatin, whereas nucleosome-binding deficient mutant proteins show a much more diffuse localisation pattern in the nucleus and cytoplasm of both MRC-5 fibroblasts and THP-1 monocytes. Nucleosome binding correlates with increased stability of IE1 and pp65, since mutant proteins unable to bind the nucleosome have a significantly reduced half-life as determined by cycloheximide chase assays. Treatment with the proteasome inhibitor MG132 improves the stability of mutant IE1 and pp65, suggesting that the proteins are more readily degraded by the proteasome when not complexed with nucleosomes. Surprisingly, nucleosome binding and increased stability were associated with reduced transcriptional activity of the viral proteins. Consistently, mutant viruses lacking the nucleosome binding motifs of IE1 or pp65 failed to efficiently establish latency, suggesting that nucleosomal sequestration impairs their 'lytic' functions. Our results identify new histone binding HCMV proteins and suggest novel mechanisms of chromatin control during latent infection.



O028

Human cytomegalovirus antagonizes SMC5/6 driven genome silencing via UL35 instituted proteasomal degradation of SLF2

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Abstract

Human cytomegalovirus (HCMV) is an important human pathogen which establishes a life-long persistent infection. Previous research revealed that host intrinsic defense mechanisms can silence HCMV gene expression and thereby foster latency. However, during lytic infection, viral effector proteins like the structural protein pp71 (UL82) and the viral immediate-early protein IE1 act as antagonists of this defense. Here, we report on the identification of a novel antagonist of host-mediated viral gene silencing which targets the SMC5/6 complex. SMC5/6 belongs to a highly conserved family of protein complexes that act as loop extrusion machines to facilitate the folding of chromatin. While SMC5/6 core factors were not attacked by HCMV, we found that the SMC5/6 associated protein SLF2 was degraded by the viral tegument protein UL35 which is imported into infected cells. This abrogates the accumulation of SMC5/6 at PML nuclear bodies which compromises the entrapment of viral genomes in these subnuclear structures. Since SLF2 is also important for genome stability and pathogenic variants of SLF2 cause the neurodevelopmental disease Atelis syndrome, we speculate that depletion of this factor via a viral tegument protein may also contribute to DNA damage induced during congenital HCMV infection.



O029

The Variable HCMV pUL9 shapes NK Cell Responses via Strain-Specific Activation of Killer Cell Immunoglobulin-like receptors

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Abstract

Human cytomegalovirus (HCMV) is a ubiquitous pathogen, and NK cells play a crucial role in its control. The genetic diversity of killer cell immunoglobulin-like receptors (KIRs) and their human leukocyte antigen (HLA) ligands influence the NK cell-mediated response to HCMV infection and reactivation. KIRs are a family of highly polymorphic paired receptors with inhibitory and activating members that fine-tune NK cell activity. Pathogens such as HCMV are thought to have driven the evolution of these paired receptors; in particular activating KIRs are proposed to have emerged as a countermeasure to viral immune evasion strategies targeting inhibitory receptors. Here, we show that HCMV modulates KIR-mediated NK cell degranulation through the RL11 protein pUL9. This phenotype requires direct, high-avidity interaction between pUL9 and KIRs. pUL9 interacts and induces signaling of both inhibitory and activating KIRs, inducing distinct functional outcomes. Expression of pUL9 on K562 target cells reduced degranulation of NK cells expressing the inhibitory receptor KIR2DL1, while increasing activity in cells expressing the activating KIR2DS1. Importantly, inhibition of KIR3DL1+ NK cell activity was significantly reduced during infection of fibroblasts with a Merlin pUL9 deletion virus compared to wild-type. Notably, pUL9 is among the most variable HCMV proteins. Analysis of pUL9 from seven laboratory and clinical strains revealed substantial variation in KIR binding profiles and functional modulation of NK cell activity. Remarkably, we identified variants capable of inhibiting KIR2DL1+ NK cells, while evading recognition by KIR2DS1+ NK cells, supporting an ongoing evolutionary arms race between HCMV and the immune system. We hypothesize that the pUL9-KIR interaction contributes to the individual disease outcomes after HCMV reactivation, providing a novel target for immunotherapeutic intervention.



O030

Neuroimmune regulation of neuron-restricted cytomegalovirus latency in the central nervous system

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Abstract

Introduction: Neurons are common targets of neurotropic viral infections and have evolved survival strategies to limit damage from cytolytic immune responses. Therefore, viral control in neurons relies on non-cytolytic mechanisms, including IFN-γ. Certain herpesviruses, such as HSV-1 and VZV, are not eliminated from neurons but instead establish lifelong latency, with the potential for periodic reactivation. Human cytomegalovirus (HCMV), is a ubiquitous β-herpesvirus and the leading cause of congenital infection in the brain.

Materials and methods: To investigate the mechanisms underlying neuroimmune regulation of CMV persistence in the brain, we used a well-established mouse model of congenital murine CMV (MCMV) infection. Recombinant MCMV strains and transgenic mouse lines were employed to track viral spread and manipulate virus–immune cell interactions in vivo, while human fetal organotypic brain slice cultures (hfOBSCs) were used to validate findings in a human model. Immune responses were characterized by flow cytometry, whereas viral tropism and latency were assessed by immunohistochemical analyses. Bulk RNA sequencing was performed to determine the impact of latent MCMV infection on hippocampal gene expression.

Results: We show that MCMV persists in neurons and that $CD4^+$ T cells and IFN-γ are critical for restricting productive viral replication in this cell type. We further demonstrate that MCMV establishes latency in neurons and that $CD4^+$ T cells are essential to prevent viral reactivation. Furthermore, our data indicate that IFN-γ does not act directly on neurons, astrocytes, or microglia during MCMV infection, suggesting a novel mechanism of viral control in the brain.

Conclusion: This study provides novel insights into the virus-host interactions involved in controlling CMV infection in the brain. MCMV establishes latent infection in neurons, where $CD4^+$ T cells and IFN-γ are critical for suppressing productive viral replication and preventing viral reactivation; notably, IFN-γ-mediated control occurs independently of direct signaling in brain resident cells.



O031

Strategies for management of Human Cytomegalovirus (HCMV) reactivation in Hematopoietic stem cell transplant recipients (HSCTRs) during Letermovir prophylaxis

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Abstract

Introduction. Letermovir (LTV) has changed the landscape of HCMV prevention after HSCT. However, the clinical relevance of HCMV DNAemia during prophylaxis needs to be evaluated. Here, we evaluated the incidence and outcomes of breakthrough HCMV DNAemia in allogeneic HSCT recipients (allo-HSCTRs) receiving LTV.

Methods. Adult allo-HSCTRs were randomized (1:1) in two arms in case of positive HCMV DNAemia and followed two different diagnostic strategies to assess HCMV refractivity to LTV prophylaxis. Specifically, in the control arm, patients stopped LTV shifting to pre-emptive therapy in case of positive HCMV DNAemia confirmed in two consecutive samples. In the study arm, patients stopped LTV shifting to pre-emptive therapy in case of positive HCMV DNA and subsequent confirmation of productive infection by detection of DNAse-resistant HCMV plasma DNAemia and UL21.5 mRNA.

Results. 147 allo-HSCTRs (median age 60 range 19-75 years) which completed LTV prophylaxis were prospectively enrolled in five Italian centers. HCMV DNAemia was positive in 29/147 patients (19.7%) during prophylaxis (median HCMV DNAemia 1020, IQR 450-8809 copies/mL). Peak of HCMV DNAemia was detected at 25 days after transplant (range 13-57 days). Nine patients were randomized (median HCMV DNAemia 9360 copies/mL, range 2465-69301 copies/mL) in study group (n=5) and control group (n=4). The second level assays were negative in patients of the study arm. Patients included in the control arm stopped LTV and were treated with GCV and FOS. Additional tests retrospectively performed in patients included in the control arm tested positive in 3 patients and were associated with presence of C325W, C325C/W+ R369T and C325Y mutations.

Discussion. Breakthrough HCMV DNAemia may occur but rate of actual LTV failure (i.e. LTV resistance) is low (about 2%). A correct interpretation of HCMV DNAemia breakthrough events and identification of patients at risk for post-prophylaxis infection is feasible.



O032

Humoral and cellular immunity predict the risk of clinically significant CMV infection in kidney transplant recipients

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Abstract

Introduction/Aim. Cytomegalovirus (CMV) is a major infectious complication following organ transplantation. While current guidelines are increasingly incorporating cell-mediated immunity (CMI) assays, accurate risk identification for CMV events in seropositive recipients (R+) remains challenging. In this study, we aim to identify new biomarkers based on antibody features that could predict CMV viraemia and disease; characterize the dynamics of the antibody response in R+ patients; and integrate these findings with existing CMI data to create a comprehensive risk assessment tool.

Materials and Methods. We analysed a prospective cohort of 144 R+ kidney transplant recipients (KTR) classified according to one-year outcome: no CMV event (n=96), transient untreated viraemia (n=19), and clinically significant CMV infection (CMV-SI; n=29). Antibody responses to nine CMV antigens — including IgG subclasses, Fcγ-receptor binding, and antibody-dependent effector functions (ADCD, ADCP, ADNP) — were profiled before and after transplantation, alongside CMV-specific IE1 $CD8^+$ T-cell responses by ELISpot.

Results. Before transplantation, KTR who later developed CMV-SI showed significantly lower levels of CMV-specific antibody-mediated immunity than event-free recipients across almost all antigens, extending from IgG levels to functional assays. The difference was particularly pronounced for envelope glycoproteins (Pentamer and gB). Post-transplant CMV-specific humoral immunity increased in proportion to disease severity (CMV-SI > viraemia > no event), indicating preserved responsiveness of vulnerable patients. Finally, an elastic-net model integrating one humoral (anti-Pentamer IgG), one cellular (IE1 ELISpot) and one clinical (prophylaxis/preemptive) feature predicted CMV-SI with an AUC of 0.85 and stratified recipients into three risk groups (log-rank $p<0.001$).

Conclusions. Humoral and cellular immunity independently predict the risk of clinically significant CMV infection in KTR. Increased antibody responses following CMV reactivation suggest that vulnerable patients could be protected through vaccination.



O033

Increasing CMV Seroprevalence in Belgium: Results from a Nationwide Laboratory Survey

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Abstract

Introduction. Contemporary Belgian CMV seroprevalence data in women of childbearing age are lacking. Due to societal changes, such as changes in childcare attendance and migration, CMV epidemiology may have changed over the past decade. This study aimed to determine the current CMV seroprevalence and assess temporal changes since 2014.

Methods. A questionnaire was distributed to Belgian laboratories as part of an external quality control program. Participants reported the numbers of CMV IgG tests performed in women aged 15-45 years in 2014, 2019, and 2024 and the corresponding numbers of positive, negative, and borderline results. Information on assay manufacturer and laboratory location was also collected. Borderline results were excluded when calculating CMV seroprevalence.

Results. 77 laboratories responded, including 47 from Flanders, 26 from Wallonia, and 4 from Brussels. Laboratory-based CMV seroprevalence ranged from 10.6% to 76.8%. CMV seroprevalence increased from 35.3% (72,903/206,589) in 2014 to 42.0% (91,618/218,117) in 2019 and 46.0% (100,348/216,917) in 2024 ($p<0.001$). Participating laboratories used CMV IgG assays from seven manufacturers. No significant differences in seroprevalence were observed between assay manufacturers in any study year (2014: $p=0.396$; 2019: $p=0.664$; 2024: $p=0.420$). Seroprevalence increased significantly over time in both Flanders and Wallonia (both $p<0.001$). In all study years, median seroprevalence was significantly higher in Flanders than in Wallonia (2014: 37.5% vs 29.3%, $p=0.002$; 2019: 42.9% vs 37.9%, $p=0.003$; 2024: 47.3% vs 42.3%; $p=0.002$). Only three laboratories from Brussels reported seroprevalence data, precluding meaningful regional comparisons.

Conclusions. Laboratory-based CMV IgG positivity rates in women of childbearing age increased significantly in Belgium between 2014 and 2024. Positivity rates were consistently higher in Flanders than in Wallonia, whereas assay manufacturer had no significant impact. These findings provide updated epidemiological data that may inform future strategies for congenital CMV prevention and screening.



O034

Letermovir resistance in French stem cell and solid organ graft recipients, from the Navire cohort and the National Reference Center database

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Abstract

Introduction. Letermovir was first marketed in France as primary prophylaxis in stem cell recipients (SCT) in 2020, extended to solid organ transplant recipients (SOT) in 2024; but also used since 2018 as secondary prophylaxis, or curative treatment. All contexts deserving resistance survey.

Materials and Methods. We collected data associated with resistance genotyping in all French territory since 2018 up to end 2025, both from the NaVire Cohort (400 SCT, NCT) and the National Reference Center CMV-resistance database. This retrospective study included all the patients receiving letermovir with resistance-related mutation, proven by genotyping.

Results. We identified 96 patients (<10% overall) with at least one episode of letermovir resistance : mean age 58.3y.o for adults and 8.5y.o. for children; 71.6% were SCT and 28.4% SOT. By the time of resistance letermovir was administered as (77 patients documented) primary prophylaxis (37%, only SCT), secondary prophylaxis (44.8%: 26,9% SCT, 17.9% SOT), or curative treatment (16.9%: 6.4%SCT 11.5%SOT). In 73 documented patients, resistance was mainly associated with R+ CMV serostatus in SCT (47/51) and R-status in SOT (18/22). Treatment exposure before resistance was 58 days versus 88 and 103 days for secondary and primary proplylaxis (p=0,009) and 40% of resistance during primary prophylaxis occurred after 100 days of treatment. Mean viral load was 3.83logUI/mL, from 3.66 in primary prophylaxis up to 4.37 (p=0.008) during curative treatment. The UL56 Cystein 325 was mutated in 77,1% of cases conferring absolute resistance. Other UL56 mutations were V236M (n=6) V236L (n=3) R369G (n=3) R369S (n=2) L257I (n=2) and R369T, R369M, V231L+R369T, F261L, L254F, R396T (n=1) one new mutation L254I. Clinical issue was favorable in 66,7% of patients. Navire data will be detailed. .

Conclusion. Letermovir resistance remains less frequent than other drugs, but can occur in any patient's setting, even with low viral loads, mostly in high-risk patients, reflecting letermovir use, albeit with preserved outcome.



O035

LAVR-289: A Safer New Weapon Against HCMV

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Abstract

Introduction/Aim: LAVR-289 is a novel broad-spectrum nucleoside phosphonate prodrug containing an active group derived from the DNA polymerase inhibitor cidofovir (CDV), but with substantially reduced toxicity and demonstrated *in vitro* efficacy (*Marcheteau E, et al., 2025*). This study aims to further investigate the antiviral kinetics and mechanism of action of LAVR-289.

Materials and Methods: We first evaluated the *in vitro* antiviral activity of LAVR-289 and CDV at 5×IC_{50} (1.7µM and 2.8µM, respectively) against the reference HCMV AD169-GFP strain by monitoring viral kinetics and resilient activity after withdrawal of LAVR-289. Viral replication was assessed by focus counting and DNA qPCR in cells and supernatants at different time points (D1 to D8) with/without drug removal. The step of the viral cycle targeted by LAVR-289 was investigated by Western blot analysis of immediate-early (IE) and late protein (gB) expression up to D5. Viral mutations associated with CDV resistance were selected from *in silico* models available from CHARMD database. HCMV-Bacmids were produced to test LAVR-289-CDV cross-resistance.

Results: LAVR-289 consistently reduced HCMV focus formation and DNA synthesis by 68.2% and 18%, respectively, more effectively than CDV (41.7% and 17.6%, respectively). While CDV efficacy persisted, LAVR-289 efficacy decreased slightly after drug removal at D5. LAVR-289 did not affect immediate-early protein (IE1) expression but blocked late protein (gB) and late IE2 expression, as with CDV. Antiviral assay with HCMV-bacmids harboring CDV-resistant variants (N408S, D413del, Del524, and Y538C) showed no cross-resistance with LAVR-289. The enzymatic activity of wild-type and mutant polymerases produced in reticulocyte lysates with/without LAVR-289 or CDV is currently under investigation.

Conclusions: LAVR-289 inhibits HCMV DNA replication, late proteins synthesis, and infectious particle production. Its mechanisms resemble those of CDV, albeit with different kinetics. Importantly, LAVR-289 remains active against CDV-resistant strains, supporting its potential as a safer therapeutic option for HCMV infection.



O036

REACTR assay for rapid and user-friendly ganciclovir triphosphate monitoring in dried blood spots and peripheral blood mononuclear cells

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Abstract

Introduction: (Val)ganciclovir is the first-line antiviral agent for CMV treatment or prophylaxis. While effective, (val) ganciclovir has substantial interindividual variability and frequently leads to underexposure or hematological toxicity, necessitating therapeutic drug monitoring. (Val)ganciclovir's active metabolite, ganciclovir triphosphate (GCV-TP), is associated with concentration-dependent neutropenia and may better predict outcomes compared to plasma ganciclovir. However, GCV-TP monitoring is currently performed using liquid chromatography tandem mass spectrometry (LC-MS/MS), which is costly, labor-intensive, and requires specialized equipment. We recently demonstrated that our rapid and minimally instrumented REverse transcriptase ACTivity with CRISPR (REACTR) assay measures clinically relevant GCV-TP concentrations in dried blood spots (DBS) from infants with CMV and correlates with LC-MS/MS measurements ($r = -0.789$, $p < 0.0001$). Here, we improved REACTR sensitivity and speed and demonstrate that REACTR can measure GCV-TP in peripheral blood mononuclear cells (PBMCs) at concentrations relevant to transplant recipients.

Materials and methods: REACTR assays were performed by combining CRISPR-Cas12a, CRISPR RNA, DNA template, DNA primer, fluorescent DNA reporter, HIV reverse transcriptase, and lysed PBMC or DBS eluate spiked with GCV-TP. Water-eluted DBS samples underwent digestion with thermolabile proteinase K at 25°C for 15 minutes and heat denaturation at 97.5°C for 2 minutes before adding the supernatant to REACTR assays. Assays were incubated at 37°C in a thermal cycler for 60 minutes and fluorescence was measured every minute.

Results: REACTR measured clinically relevant GCV-TP concentrations (0.362nM – 16nM) within 30 minutes with a log-linear relationship in spiked DBS ($r = -0.973$, $p = 0.0011$) and spiked PBMCs ($r = -0.998$, $P < 0.0001$). The limits of detection in DBS and PBMCs were 0.492nM and 0.406nM, respectively, with coefficients of variation less than 5%.

Conclusions: This study demonstrates the potential of the REACTR assay as a rapid, accessible, and cost-effective alternative to LC-MS/MS for GCV-TP monitoring in DBS and PBMCs.



O037

Antigen-specific versus agnostic screening to develop broadly protective antibodies for immunotherapy against human cytomegalovirus

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Abstract

Introductions/aims: There remains an enormous unmet need for safe and effective therapies against HCMV. Studies on humoral immunity to HCMV found that human sera and human-derived monoclonal antibodies (mAbs) can neutralize HCMV in a strain-specific manner. Additionally, strain-specific antibody therapy prevents CMV reactivation in a murine model of hematopoietic stem cell transplantation. These results suggest that mAbs may present a viable alternative to current therapies, especially ones that broadly neutralize multiple strains of HCMV.

Materials and Methods: We are using high-throughput functional screening to identify potent neutralizing antibodies against HCMV in a both **antigen-specific** and **antigen-agnostic** manner. HCMV expresses as many as 25 glycoproteins on its surface to allow entry into diverse cells and tissues. Our antigen-specific screening workflow uses recombinant HCMV glycoproteins to sort B cells that are then screened for neutralization. In addition to antigen-specific sorting, we use **sequential sorting** to screen hundreds of thousands of memory B cells for virus neutralization without prior knowledge of antigenic targets.

Results: We have so far identified two antibodies (15-E5 and 62-2F4) using our two sorting methods. 62-2F4 was identified through antigen-specific sorting using a prefusion stabilized version of prefusion gB as the bait protein. 15-E5 was identified through antigen-agnostic sorting. Both antibodies bind both pre- and post-fusion gB with high affinity and neutralize infection by multiple strains of HCMV in both epithelial cells and fibroblasts.

Conclusions: The outcome of this work will result in production of several candidates for HCMV immunotherapy and an increased understanding of the HCMV antigenic landscape.



O038

Cytomegalovirus Promotes Colon Cancer Metastasis: Prevention by an M83-Directed Vaccine

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Abstract

Cytomegalovirus Promotes Colon Cancer Metastasis: Prevention by an M83-Directed Vaccine

1) Introduction/Aim: Cytomegalovirus (CMV) establishes a lifelong latent/persistent infection and has been detected in several cancer types, where it is suspected to promote tumor progression. This study aimed to investigate whether murine CMV (MCMV) influences colon cancer growth and metastasis and whether vaccination against MCMV could prevent these effects.

2) Materials and Methods: A combination of in vitro and in vivo approaches was used. CT26 colon cancer cells were infected with MCMV and assessed for changes in cell growth, migration, and invasiveness. In a murine colon cancer model, the effects of MCMV infection on tumor growth and metastatic potential were evaluated. Additionally, mice were vaccinated with an adenovirus-based MCMV vaccine expressing M83, the murine homolog of the human CMV pp65 antigen, to determine its protective effect against MCMV-associated metastasis.

3) Results: MCMV infection of CT26 cells reduced tumor cell growth but significantly enhanced cell migration and invasiveness in vitro by 82.9%–93%. In vivo, MCMV infection increased the metastatic potential of CT26 colon cancer cells. Vaccination with the M83-expressing adenovirus vaccine markedly reduced metastasis formation, resulting in a fivefold reduction (82% decrease) compared with unvaccinated controls.

4) Conclusions: MCMV promotes colon cancer metastasis by altering the biological characteristics of tumor cells, increasing their migratory and invasive capacities. Vaccination targeting M83 effectively prevented MCMV-driven metastasis, suggesting that improved immune control of CMV may represent a promising strategy to limit cancer progression and metastatic spread.



O039

Domain V of glycoprotein B serves as key regulator of HCMV fusion

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Abstract

Introduction/Aim

HCMV glycoprotein B (gB) mediates membrane fusion through a transition from a metastable prefusion to a stable postfusion conformation. Domain V (DomV) of gB undergoes major structural rearrangements during this process, yet the molecular determinants triggering fusion remain poorly understood. We previously identified two highly conserved DomV residues, Y667 and E671, which lie within the antigenic domain 6, and restored infectivity of a destabilized gB variant, indicating a prominent role in fusion regulation. We aim to determine how DomV point mutations Y667D and E671K affect gB fusion activity and viral infectivity, and to define their mechanistic roles in fusion regulation.

Methods

We performed comparative phenotypic analyses to assess viral growth kinetics, cell-free infectivity, and fusion efficiency of BAC-derived gB_DomV mutant virions in TB40 and FIX strains by using fibroblasts and epithelial cells.

Results

Although located in close proximity within DomV, Y667D and E671K displayed opposing phenotypes. Y667D caused severe replication defects and yielded non-infectious virions in TB40 in both cell types and was lethal in FIX, consistent with a predicted structural and possibly functional change of gB. In contrast, E671K enhanced viral growth and virion infectivity in both strains and cell types, suggesting increased fusogenicity.

Conclusion

Our results indicate that Y667 and E671 fulfil fundamentally distinct roles in gB-mediated fusion. Y667 is likely important for the prefusion-to-postfusion transition as its homolog in HSV-1 forms a hydrophobic cleft stabilizing fusion loop 2. Conversely, E671 seems to regulate gB fusion, as single amino acids are able to affect the fusion efficiency. These differential mechanisms identify DomV as a key regulator in CMV membrane fusion. Surprisingly, the point mutations additionally appear to act in a strain-specific manner, highlighting the need for further research on CMV strain-specificity.



O040

Controlling HCMV using engineered NK-mediated antibody dependent cellular cytotoxicity-inducing immunotherapies

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Abstract

Human cytomegalovirus (HCMV) causes substantial morbidity and mortality in immunocompromised individuals and after congenital infection. Yet despite many trials, no vaccines are licensed. Most vaccine strategies have focussed on the induction of neutralising antibodies, however, HCMV predominantly spreads via cell-to-cell transmission, reducing the effectiveness of this approach. Consequently, immunotherapies that directly target infected cells are required. We therefore investigated the capacity of monoclonal antibodies (mAbs) to bind HCMV-infected cells and activate natural killer (NK) cell–mediated antibody-dependent cellular cytotoxicity (ADCC). Proteomic and immunological profiling identified mAbs targeting the non-entry glycoprotein UL141 which could efficiently control virus through ADCC when used as a mix of 5. However, a mix of mAbs is difficult to translate into clinical use.

Comparisons of ADCC against HCMV and tumour antigens revealed that restricted cell-surface trafficking, and viral-induced changes to the infected cell, combine to limit ADCC efficacy. The former could be overcome through mAbs targeting UL141 and the latter through combining mAbs. To determine whether the requirement for multiple mAbs could be overcome, we engineered a range of antibody-like constructs, including BiKEs, TriKEs, ANKETs and Redirected Optimised Cell Killers (ROCKs), incorporating modifications to enhance NK cell binding, activation, and proliferation. Following systematic screening, ROCKs showed superior control of HCMV, mediating potent ADCC as single molecules and significantly enhancing virus control at concentrations 100-fold lower than polyclonal IgG from natural infection. ROCKs drove enhanced lytic granule convergence at the MTOC and polarisation towards ROCK-opsonised target cells, along with increased CD16 clustering at the NK immune synapse. Unlike conventional IgG, ROCKs engaged CD16 in a way that bypassed ADAM17-mediated CD16 shedding, enabling sustained NK cytotoxicity.

These findings establish a novel monoclonal immunotherapeutic strategy against HCMV and demonstrate how antibody-like molecules can be engineered to maximise NK antiviral activity against highly immune-evasive targets expressing low levels of antigen.



O041

Structural and immunological basis of cross-herpesvirus activity of a new humoral response induced by human cytomegalovirus vaccination

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Abstract

A human cytomegalovirus (HCMV) vaccine remains high priority status. Our ongoing studies of the humoral immune response to gB/MF59 vaccine have identified a novel antigenic domain (AD-6) in HCMV glycoprotein B (gB) which correlated with protection in a phase II study. Subsequently, we demonstrated that a rabbit pAb directed against AD-6 reduced HCMV cell-to-cell spread in fibroblasts as a potential mechanism of anti-viral activity and now we also demonstrate that the AD-6 antibody potently blocks HCMV reactivation – which is a likely source of viraemia in vivo further underpinning the importance of the AD-6 response.

Our overarching aim is to combine in silico and wet lab studies to comprehensively understand the clinical, immunological and functional importance of AD-6 within gB. First we utilised the high conservation of gB structure to identify analogues of AD-6 in other HHV gBs despite minimal sequence conservation. Intriguingly, molecular frustration analyses revealed that AD-6 within gB can exist in an energetically unfavourable state in the monomer driving trimerisation. In silico interrogation of HHV gB predicts overlapping immunogenicity within AD-6 suggesting that conformational epitopes could be important immunologically. Consistent with conformation-specific antibodies being important, the pAb raised against HCMV AD-6 was also anti-viral against HSV-1 whereas a mAb raised against a linear (thus sequence dependent) epitope in HCMV AD-6, and active against HCMV, is unable to prevent the cell-to-cell spread of HSV-1. Importantly, we demonstrated that human AD-6 antibodies generated in response to gB/MF59 vaccination also recognise conformational epitopes by demonstrating a correlation between binding HCMV/HSV-1 AD-6 peptides for individual vaccine recipients. We hypothesise AD-6 plays a key role in gB function which is inhibited, in part, by the binding of conformation-specific antibodies. Finally, it suggests the provocative concept that targeting cognate AD-6 could be a general strategy for HHV vaccination.



O042

Structural mapping of novel gH/gL antibody epitopes reveals epitope-specific synergistic HCMV neutralization

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Abstract

Introduction/Aim: Human cytomegalovirus (HCMV) causes severe disease in immunocompromised individuals and during congenital infection, yet no vaccine is available and therapeutic options remain limited. Antibody-based approaches are promising, but their rational development requires a deeper mechanistic understanding of HCMV neutralization. Building on our previous identification of gH/gL-targeting monoclonal antibodies (mAbs), we aimed to define novel vulnerable epitopes and determine how antibody combinations can enhance antiviral activity.

Materials and Methods: Representative mAbs from distinct gH/gL epitope groups were selected based on competition profiling and neutralization activity. We performed high-resolution cryo-EM analysis of 17 Fab–gH/gL complexes and functionally tested individual antibodies and non-competing antibody combinations across HCMV-susceptible cell types, multiple viral strains, and selected extended *in vitro* neutralization assays.

Results: Cryo-EM resolved diverse antibody binding modes, spatial orientations, and epitope locations across gH and gL, including simultaneous binding of up to nine non-overlapping antibodies to the same protein complex. Structural mapping revealed membrane-proximal and membrane-distal epitope classes and provided mechanistic insight into differences in neutralization capacity. Importantly, combinations of non-competing antibodies showed epitope-specific synergistic neutralization, frequently reducing residual infection beyond the activity of individual mAbs. These synergistic effects were conserved across different HCMV strains and susceptible host cell types and, in selected longer-term *in vitro* assays, supported sustained neutralization over extended observation periods.

Conclusions: This study structurally defines a broad landscape of vulnerable gH/gL epitopes and reveals that antibody synergy follows epitope-specific rules. Rationally selected non-competing combinations can convert incomplete single-antibody neutralization into more effective HCMV inhibition, including sustained neutralization over extended in vitro observation periods. These findings provide a mechanistic framework for next-generation HCMV vaccines and antibody-based therapies.



O043

Deciphering the Role of Checkpoint Pathways in Diminished Anti-HCMV T-Cell Functionality in the Elderly and Viraemic Solid Organ Transplant Patients

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Abstract

Human cytomegalovirus (HCMV) infection and reactivation are usually controlled by cellular immune responses in immunocompetent individuals. However, HCMV remains a major complication in immunocompromised populations, particularly following solid organ transplantation (SOT), where reactivation can cause significant morbidity. In older people, HCMV carriage is also associated with increased mortality risk and may act as an important co-morbidity factor. Using functional viral dissemination assays, we have shown reduced capacity of PBMCs, and specifically T cells, to control HCMV infection and spread in older donors and in viraemic patients from our SOT cohort.

We are now investigating mechanisms that underpin these defects, focusing on checkpoint inhibitory ligand (CIL) and checkpoint inhibitory receptor (CIR) pathways. Our earlier studies showed increased expression of several CILs on uninfected fibroblasts from older donors, including higher PD-L1 expression compared with young donor fibroblasts. We now show that HCMV infection further induces selected CILs and are extending this analysis to dendritic cells, macrophages and endothelial cells, which are central to HCMV pathogenesis. Analysis of ex vivo T cells from ageing and transplantation cohorts shows increased expression of several CIRs, including PD-1, TIGIT and KLRG-1, on T cells from older donors. Notably, PD-1 expression was also increased on T cells from viraemic transplant patients.

Importantly, HCMV-specific T cells upregulate PD-1 and TIM-3 following co-culture with autologous HCMV-infected fibroblasts. We also show that Galectin-9, a ligand for TIM-3, is upregulated on HCMV-infected fibroblasts. Together, these findings suggest that the PD-1:PD-L1 and TIM-3:Galectin-9 checkpoint axes may contribute to impaired T-cell control of HCMV. Supporting this, preliminary disruption of PD-1:PD-L1 signalling improves control of HCMV dissemination in vitro, indicating that targeting checkpoint ligand–receptor pathways may enhance antiviral immunity to HCMV, and provide a mechanistic explanation for functional immune defects observed in ageing and transplant-associated HCMV reactivation.



O044

A novel pp65-IGRA for monitoring cytomegalovirus-specific T-cell response in solid organ transplant recipients

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Abstract

Aim: This study aimed to assess the performance of a novel interferon-γ (IFN-γ) release assay (IGRA) based on direct whole-blood stimulation and for measuring HCMV-specific T-cell responses in solid organ transplant recipients (SOTRs).

Methods: Blood was stimulated with a pp65 peptide pool or recombinant protein, and an Immediate Early-1 (IE-1) peptide pool. An IFN-γ concentration ≥0.2 IU/mL was considered a positive response. The expression of the activation markers CD137 and CD69 on $CD4^+$ and $CD8^+$ T cells was also analyzed.

Results: HCMV-specific T-cell responses were evaluated in 37 SOTRs at 3 months post-transplant. Seventeen patients experienced self-resolving HCMV infection (Controllers), whereas 20 required antiviral therapy (Non-Controllers). Controllers exhibited higher IFN-γ responses following stimulation with either the pp65 peptide pool or recombinant protein than Non-Controllers, whereas no difference was observed with the IE-1 peptide pool. By contrast, pre-transplant IFN-γ levels did not differ between Controllers and Non-Controllers. Subsequently, they declined significantly in Non-Controllers but remained stable in Controllers. A similar pattern was observed for both $CD4^+$ and $CD8^+$ T-cell activation; however, these markers showed lower efficacy in discriminating between Controllers and Non-Controllers. None of the 22 patients with a positive peptide pool pp65-IGRA at 3 months developed late-onset HCMV infection, whereas 4 of 15 (27%) patients with a negative response did. Similarly, none of the 15 patients with a positive recombinant pp65-IGRA at 3 months developed late-onset HCMV infection, whereas 4 of 22 (18%) patients with a negative response did.

Conclusion: Overall, these findings suggest that pre-transplant T-cell responses do not predict the risk of post-transplant HCMV infection. Conversely, impaired antiviral immunity at 3 months post-transplant was associated with the need for antiviral treatment. Notably, early post-transplant immune dysfunction detected by pp65-IGRA identified patients at increased risk of late-onset HCMV infection, whereas a positive pp65-specific response was associated with protection against subsequent viral reactivation.



O045

Differentiation-induced reduction in functional diversity restricts the ability of cytomegalovirus-specific CD8 T cells to eliminate virus-infected cells

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Abstract

Introduction

Human cytomegalovirus (HCMV) is one of the most influential pathogens that affects the functional diversity of CD8 T cell subsets and the expansion of virus-specific CD8 T cells. Nevertheless, it remains unclear why individuals with expanded CD8 T cells recognizing the pp65-HLA-A*02:01–restricted viral epitope NLVPMVATV (NLV-T cells) exhibit weakened immune control of HCMV reactivation.

Methods and Materials

To address individualized evolution of HCMV-specific CD8 T cell responses, we phenotypically and functionally characterized NLV-T cells in 116 healthy HCMV-positive donors, dividing them into two groups: those with low and those with high NLV-T cell frequencies (LF and HF, respectively). We phenotyped the cells using multi-color spectral flow cytometry and single-cell RNA sequencing coupled with TCR profiling and examined their killing properties against peptide-loaded and virus-infected target cells.

Results

Our comprehensive multimodal analysis revealed that NLV-T cells from HF donors exhibited a phenotype of advanced differentiation, marked by high levels of granzyme B and perforin expression, and efficiently eliminated peptide-loaded targets and HCMV-infected cells as long as cell surface HLA expression was unaffected. However, NLV-T cells from LF donors, possessing a less differentiated granzyme K-intermediate phenotype, demonstrated enhanced cytokine secretion and the ability to eliminate HCMV-infected cells, even in the presence of virus- induced HLA class-I downregulation.

Discussion and **Outlook**

Overall, these findings suggest that HCMV exploits CD8 T cell differentiation to evade immune protection. Hence, our data reveal individualized trajectories of HCMV-specific CD8 T cell differentiation that pave the way for personalized assessment of "immune aging" and the associated increased risk of coronary disease, frailty, and mortality in CMV-seropositive individuals. Furthermore, they underscore the need for personalized strategies in monitoring and managing HCMV reactivation, particularly in vulnerable populations such as transplant recipients.



O046

Inhibition of Inflammasome Signaling by Human Cytomegalovirus UL84

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Abstract

Multiple innate immune sensors detect infections by dsDNA viruses such as the cytomegaloviruses. One of these sensors is AIM2, which interacts with the adaptor ASC and the effector protease caspase-1 to form a multiprotein complex called the AIM2 inflammasome. This complex plays a critical role in host defense by promoting the maturation and secretion of the proinflammatory cytokines IL-1β and IL-18. It also cleaves gasdermin D (GSDMD), resulting in pyroptosis, an inflammatory form of programmed cell death. We previously demonstrated that the murine cytomegalovirus (MCMV) protein M84 inhibits inflammasome activation through interactions with AIM2 and ASC. Whether human cytomegalovirus (HCMV) disrupts inflammasome signaling in a similar way has remained unknown. Therefore, we investigated the role of the HCMV genes UL84 and UL83, two sequence homologs of MCMV M84, as modulators of inflammasome assembly, proinflammatory cytokine production, and pyroptosis. Expression of UL83 and UL84 in HEK-293A cells showed that both proteins bind to AIM2 and ASC proteins and that the release of an IL-1β reporter (iGLuc) was reduced, as measured by a luciferase assay. In HCMV-infected THP-1 macrophages, UL83 and UL84 proteins both localized to the nucleus, but only UL84 also co-localize with ASC-Specks in the cytoplasm. A recombinant HCMV lacking UL84 expression induced IL-1β release and GSDMD cleavage in THP-1 cells. Moreover, cell viability assays show that the UL84-deficient HCMV induced more cell death compared to the HCMV WT, a phenotype that could be rescued with VX-765, an inhibitor of caspase-1. These results suggest that UL84 interferes with inflammasome activation and signaling.



O047

Systematic Screening for Postnatal Cytomegalovirus Infection in Preterm Infants: Preliminary Results from an Ongoing Multicenter Prospective Study in Greece

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Abstract

Background: Postnatal cytomegalovirus (pCMV) infection has been associated with morbidity in very preterm infants. Recently published European guidelines proposed systematic screening in high-risk preterm populations to differentiate between congenital (cCMV) and pCMV infection and improve epidemiological surveillance. We aim to estimate the incidence of postnatal infection in a prospective multicenter cohort.

Materials & Methods: This ongoing prospective multicenter study includes infants born at <32 weeks' gestational age (GA) and/or with birth weight <1500 g admitted to participating Greek NICUs. Urine samples are collected within the first 21 days of life and before discharge. CMV DNA is detected by polymerase chain reaction (PCR). Postnatal CMV infection is defined as a positive urine PCR after 21 days of life following a negative early sample.

Results: At the time of interim analysis, 168 preterm infants have been enrolled in the 9 NICUs participating in the study. To date, 97 infants (53% girls) born to 79 mothers have completed the study protocol with paired urine samples available. Mean GA at birth was 30.1 (std± 2.0 weeks), mean BW was 1309 (std± 304 g), and median length of hospital stay was 53 days (IQR: 38–69 days). Overall, 38/66 (57.6%) mothers with available serology were CMV-seropositive, thus 48/97 infants were born to known CMV-seropositive mothers. Among these infants, 29/48 (60.4%) were exposed to maternal milk beyond colostrum, while 8/48 (16.7%) received pasteurized human milk. One infant acquired asymptomatic pCMV infection, corresponding to 1/48 (2.1%) of infants born to known CMV-seropositive mothers and 1/29 (3.4%) of those exposed to maternal milk. No cCMV infections have been identified among analyzed samples to date.

Conclusions: Based on currently available data, the rate of postnatal CMV infection was infrequent among screened very preterm infants. Ongoing screening enrollment will further characterize pCMV epidemiology and its relationship with feeding practices across Greek NICUs.



O048

The Screen cCMV study: congenital CMV prevalence and infant hearing loss in an Australian population

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Abstract

Introduction: Congenital cytomegalovirus infection (cCMV) is a leading infectious cause of hearing loss and neurodevelopmental disability. The Screen cCMV study aims to determine the 1) prevalence and 2) infant hearing outcomes of cCMV in an Australian population.

Methods: Screen cCMV partnered with GenV, a whole-of-state birth cohort recruited from Victoria, Australia between October 2021-October 2023. Screen cCMV tested saliva samples from newborns aged <3 weeks using viral nucleic acid extraction and real-time CMV polymerase chain reaction (PCR) in two steps: 1) eight-sample pooled CMV PCR testing, 2) individual CMV PCR retesting of samples from positive pools. Beta actin testing was completed on 192 samples to confirm genomic DNA in samples. cCMV results were linked with GenV-collected demographic data and state-wide hearing screening data in May 2026. Descriptive statistics describe cCMV and hearing loss prevalence. Adjusted cCMV prevalence accounts for the proportion of samples with no genomic DNA.

Results: GenV collected saliva from 33,309 infants aged <3 weeks (51.3% male, mean socioeconomic disadvantage score 1009 (SD: 59) similar to population norms, 76.2% living in a major city). PCR testing confirmed cCMV in 94 of 33,309 GenV newborns (prevalence: 0.28%, 95%CI: 0.23%, 0.35%). Beta actin was detected in 191/192 (99.5%) samples, resulting in an adjusted prevalence of 0.28% (95%CI: 0.23%, 0.35%). Hearing loss was audiologically confirmed in 6 of the 94 cCMV positive infants (6.4%). All hearing loss was unilateral with varying severities reported.

Conclusions: This is the first large scale study to determine Australian birth prevalence of cCMV. Approximately 3 out of every 1000 babies in the GenV cohort had cCMV, with unilateral sensorineural hearing loss detected shortly after birth in 6.4%. Future studies will explore longer term developmental outcomes of this cohort as they age.



O049

Addressing the gaps in CMV prevention in pregnancy: the burden of maternal cytomegalovirus infection across England

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Abstract

Introduction. Congenital cytomegalovirus (CMV) is the most common congenital infection and a leading non-genetic cause of childhood sensorineural hearing loss and neurodisability. Primary maternal infection in the first trimester carries the greatest risk of adverse foetal outcomes, yet UK seroprevalence data are limited. We aimed to estimate contemporary CMV seroprevalence and first-trimester primary maternal infection among women attending antenatal care across England.

Methods. We conducted a multi-site retrospective seroprevalence study using stored antenatal booking samples from six NHS sites selected to reflect the geographical, socio-economic and ethnic diversity of England. Samples were collected between April 2019 and April 2020. CMV testing followed a predefined laboratory algorithm. The primary analysis was restricted to samples collected before 91 days' gestation.

Results. 4,055 first-trimester samples were included in the primary analysis. Mean maternal age was 30.6 years and mean gestation at sampling was 9.7 weeks. Overall CMV seroprevalence was 54.6% (95% CI 53.1–56.2). Seroprevalence varied by ethnicity, ranging from 42.7% in White women to 91.7% in Black, African, Caribbean or Black British women. After adjustment, ethnicity remained the strongest independent predictor of seropositivity, with the highest adjusted odds observed in Black women (aOR 14.17, 95% CI 8.90–22.56) and Asian women (aOR 8.71, 95% CI 6.49–11.71), compared with White women. Evidence of first-trimester primary CMV infection was identified in 6 of 4,055 women (0.15%, 95% CI 0.07–0.32).

Conclusions. This study provides contemporary estimates of CMV seroprevalence and first-trimester primary infection in pregnancy across England. Nearly half of women entering antenatal care were CMV seronegative, representing a population susceptible to primary infection and potentially able to benefit from preventive strategies. Ethnic variation in seroprevalence highlights the need for prevention, screening and future vaccine studies to be appropriately designed, powered and delivered equitably across diverse antenatal populations.

POSTER PRESENTATIONS



P001

cCMV infection in an extremely preterm infant

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Abstract

Congenital cytomegalovirus infection remains the most common congenital viral infection worldwide and is an important cause of neonatal morbidity and long-term neurodevelopmental impairment. Slovenia currently lacks a national screening program for CMV infection during pregnancy; however, available Slovenian epidemiological data suggest a relatively low prevalence of congenital CMV infection, approximately 0.14% (1).

We present the case of a preterm infant born at 29 5/7 weeks of gestation due to chorioamnionitis and PPROM. The infant was admitted to the NICU, where non-invasive ventilatory support was required due to frequent desaturation episodes and mild respiratory distress. The neonate underwent extensive diagnostic evaluation for suspected congenital infection. Congenital CMV infection was confirmed by virological testing shortly after birth. Clinical management required a multidisciplinary approach because of extreme prematurity and the potential complications associated with congenital CMV infection. Laboratory testing showed mild thrombocytopenia and transient hyperbilirubinemia. Congenital CMV infection was confirmed following maternal primary CMV infection acquired during the second trimester of pregnancy. Analysis of maternal blood samples collected at 24 6/7 weeks of pregnancy confirmed acute primary CMV infection with positive CMV IgM and negative CMV IgG antibodies, consistent with recent seroconversion and a high risk for vertical transmission.

This case highlights important clinical and public health issues. First, it demonstrates that severe congenital cytomegalovirus infection may occur even in countries with low reported prevalence. Second, it emphasizes the importance of systematic screening for congenital and postnatal CMV infection, especially in preterm infants (2). Notably, in the major Slovene tertiary perinatal centre in Ljubljana, covering more than 80% of extremely preterm deliveries in Slovenia, between 2022 and 2025, the screening program included all infants born before 29 weeks of gestation (3), while since 15 September 2025, it has been expanded to include all infants born before 30 weeks of gestation.



P002

Modeling human cytomegalovirus (HCMV) infection and protective immunity at the nasal mucosal entry site

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Abstract

Introduction: HCMV entry into the human host is believed to occur via the nasal route. We recently developed a novel *ex vivo* model of viral infection in native human nasal-mucosal tissues, maintained in organ culture. Here, we investigated the protective effect of local innate immune responses and antiviral antibodies at the viral mucosal entry site.

Materials and methods: Inferior nasal turbinate tissues were maintained as integral 3D multi-cell-type organ cultures. Tissue levels of viral mRNA were determined by qRT-PCR. Viral cellular tropism was determined by confocal microscopy and by flow cytometry analysis of single cells dissociated from infected tissues. The neutralizing activity of anti-HCMV antibodies was determined employing quantitative viral mRNA measurements at 24h post infection.

Results: We have demonstrated active HCMV replication in the nasal mucosal tissues showing that HCMV preferentially infects nasal ciliated epithelial cells, with some infection of deeper stromal cells, macrophages, and vascular endothelial cells. We characterized distinct innate immune response patterns to HCMV infection in the nasal mucosa, with upregulation of antiviral and pro-chemotactic pathways. Notably, blocking the innate immune signaling did not affect HCMV replication in the nasal tissues. Analysis of the neutralizing activity of anti-HCMV IgG preparations on HCMV infection in the nasal tissues identified highly neutralizing antibodies, and further revealed both common and divergent effects of specific HCMV antibodies at the nasal entry site *vs* the vertical maternal-fetal transmission site.

Conclusions: The study manifests the ability of the *ex vivo* human nasal-mucosal infection model to address correlates of immune protection at the viral entry site, and highlights the local protective role of HCMV adaptive immunity. Further studies in this clinically-relevant model could help evaluate new interventions against the horizontal transmission of HCMV and will inform the development of prevention strategies.



P003

Epidemiology, impact of early treatment and predictors of adverse outcomes in congenital CMV infection: a Swiss nationwide prospective study

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Abstract

Introduction/Aim: Congenital cytomegalovirus (cCMV) is the most common congenital infection (0.48% to 1.42 % of live births), with approximately 17-20% of infected neonates developing permanent sequelae. Early risk stratification remains challenging but critical for therapeutic decision-making. This study aimed to define epidemiology, identify early predictors of adverse neurological outcomes, and evaluate how early antiviral treatment impacts outcomes in a nationwide cohort.

Materials and Methods: We conducted a prospective multicenter observational study between 2017 and 2024, analyzing birth and one-year follow-up data of 209 neonates with confirmed cCMV in Switzerland.

Results: cCMV was confirmed within three weeks of life in 87% of cases, primarily by urinary PCR (79%); diagnosis was delayed after the neonatal period in 13%. Annual incidence ranged from 0.4 to 0.9 per 1000 live births, with a transient decline during the first wave of the SARS-CoV-2 pandemic (–0.51 per 1,000; p=.002). The most common findings at birth included intrauterine growth restriction (34%), and neuroimaging abnormalities (36%). Antiviral treatment was administered in 36% of patients. Hepatosplenomegaly and hypotonia at birth were independent predictors of late-onset sensorineural hearing loss (OR 13.2, 95%CI 2.3–75.2 and OR 6.6, 95%CI 1.1–41.1, respectively), and early antiviral treatment was associated with lower rates of neurodevelopmental disorders at one year, compared with delayed initiation (23% vs 50%, p=.004).

Conclusions: This first Swiss nationwide study shows a cCMV incidence lower than in other high-income countries, transiently reduced during the pandemic, and highlights the limitations of targeted screening. Hepatosplenomegaly and hypotonia at birth emerged as early predictors of late-onset hearing loss, supporting broader screening criteria and prompt antiviral treatment when indicated.



P004

Clinical Distribution of CMV DNA PCR Test Requests and Positivity Rates in Adult and Pediatric Patients: A Retrospective Evaluation

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Abstract

Aim: This study aimed to evaluate CMV DNA PCR positivity rates in adult and pediatric patients and to investigate their distribution according to age, gender, and referring clinic.

Materials and Methods: Blood samples from 219 pediatric patients aged 0–18 years and 490 adult patients older than 18 years were retrospectively evaluated. CMV DNA PCR testing was performed between September 2025 and June 2026. Only one sample per patient was included in the analysis. CMV DNA testing was performed using the ANATOLIA Bosphore CMV Quantification Kit and the CMV ELITe MGB® Kit.

Results: CMV DNA positivity was detected in 297 of 709 patients (41.8%). Among the positive patients, 76 (25.6%) were pediatric patients and 221 (74.4%) were adults. In the pediatric group, 51 (67.2%) patients were male and 25 (32.8%) were female, whereas in the adult group, 140 (63.4%) were male and 81 (36.6%) were female.In the pediatric group, CMV DNA positivity was most frequently detected in patients from the bone marrow transplantation unit (27.6%), followed by the hematology (25.0%), immunology (14.4%), and gastroenterology (10.5%) clinics.In the adult group, positivity was most commonly observed in the bone marrow transplantation unit (32.5%), followed by the hematology clinic (21.7%), internal medicine intensive care unit (13.1%), and nephrology clinic (11.3%).

Conclusion: In our study,CMV positivity was most frequently detected among patients followed in bone marrow transplantation units, hematology clinics, and intensive care units in both adult and pediatric populations.These findings suggest that patients receiving immunosuppressive therapy are at increased risk for CMV reactivation. CMV reactivation may present with a wide range of clinical manifestations in immunocompromised patients and is an important factor associated with allograft injury and organ rejection, particularly in transplant recipients.Therefore, monitoring CMV viral load for the detection of latent CMV reactivation remains important for disease prognosis and treatment planning.



P005

Sex differences in congenital CMV infection - an international cCMVnet study

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Abstract

Introduction/Aim The role of biological sex in congenital Cytomegalovirus-infection (cCMV) related neurodevelopmental impairment and hearing-loss is unknown. This study investigated sex-specific differences in clinical presentation, hearing-loss, neuroimaging, and long-term sequelae in children with cCMV.

Materials and Methods This longitudinal cohort study used data from the multicentre cCMVnet registry (2011–2026). Outcomes were assessed at birth, first postnatal evaluation, 6, and 24 months. Chi-square, Fisher's exact, and Wilcoxon rank-sum tests were used for cross-sectional comparisons. Risk ratios (RR) were estimated via Poisson regression; time-to-event analyses applied Kaplan–Meier curves and Cox proportional hazards models.

Results The cohort comprised 1,814 patients (905 male, 909 female). Birth characteristics and symptomatic cCMV rates were comparable between sexes (45.2% vs. 46.1%; p=0.732), as were sensorineural hearing loss (SNHL) (26.4% vs. 28.9%; p=0.313). Cranial ultrasound abnormality rates were similar (41.4% each; p=0.969). On brain MRI, females showed higher rates of any abnormality (57.5% vs. 50.9%; p=0.030) and periventricular cysts (8.6% vs. 5.5%; p=0.014). No sex differences in sequelae were observed at 6 months. By 24 months, females had higher SNHL prevalence (32.7% vs. 24.1%; RR 1.36, 95% CI 1.10–1.67; p=0.005) and borderline-excess epilepsy (4.8% vs. 2.2%; p=0.050). After multivariable adjustment, the sex-SNHL association attenuated to non-significance (adjusted RR 1.19, 95% CI 0.99–1.42; p=0.065), and time-to-event analyses showed no increased hazard in females (adjusted HR 0.89, 95% CI 0.58–1.35; p=0.569). Symptomatic cCMV at birth was the strongest predictor of SNHL (adjusted RR 2.01, 95% CI 1.42–2.87; p<0.001) and composite sequelae (adjusted HR 2.83, 95% CI 1.93–4.15; p<0.001) at 24 month.

Conclusions Female sex was associated with greater MRI abnormalities and tendentially higher cumulative SNHL prevalence at 24 months, yet neither conferred increased risk of composite neurological sequelae. Symptomatic cCMV at birth was the dominant predictor of adverse outcomes. Sex-differentiated surveillance is not warranted.



P006

Valganciclovir dosing in preterm infants for the treatment of cytomegalovirus using population pharmacokinetic modelling

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Abstract

Introduction/Aim Ganciclovir (GCV) and its prodrug valganciclovir (VGCV) are used as first-line treatment for cytomegalovirus (CMV). However, dosing is unavailable for preterm infants less than 32 weeks of gestational age (GA), at risk of GCV overexposure and toxicity, given glomerular filtration rate (GFR)-driven clearance. We developed a population-pharmacokinetic (PK) model to evaluate current and alternative optimized dosing schedules for GCV target attainment in preterm infants with CMV.

Methods Modelling was performed in NONMEM (v7.5), and simulation using rxode2 (v4.0.2). Volume was re-estimated from a published volume-weight function, and a GFR maturation function was used to predict drug clearance. PK profiles stratified by postnatal age (PNA: 0-4, 4-8, 8-12 weeks) and GA (<28, 28-32 weeks) were simulated for different dosing regimens. Doses were evaluated based on target of AUC_{12h} (20-55 mg*h/L).

Results Ganciclovir plasma concentrations from 15 preterm infants (65 samples) were analyzed. Median (range) GA was 25.9 (23.4-29.4) weeks, birth weight 0.64 (0.43-1.12) kg, and PNA at treatment initiation 18 (2-57) days. The final one-compartmental model with first-order absorption and covariate functions described the entire population well. Model-based simulations showed standard 16 mg/kg VGCV twice daily would cause overexposure (AUC_{12h} > 55 mg*h/L) in >80% of infants with GA <28 weeks (PNA < 8 weeks) and GA 28–32 weeks (PNA < 4 weeks). A stepwise mg/kg dose-escalation regimen reduces overexposure by 25-30%, while maintaining a 100% target AUC_{12h} > 20 mg*h/L. Starting doses are lowest in the most premature infants and escalate with postnatal age; re-evaluate at the 4- and 8-week PNA transitions.

Conclusions Standard “term-infant” VGCV dosing may lead to above target AUC in some of the very preterm infants. A stepwise dose-escalating regimen (i.e., starting with a lower dose, increasing to full dose) may reduce toxicity while preserving efficacy, but this requires prospective clinical evaluation.



P007

Evaluation of pUL56-derived peptides targeting the human cytomegalovirus terminase complex

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Abstract

Introduction/Aim: Antiviral treatments against human cytomegalovirus (HCMV) remain limited by toxicity and emergence of resistance. The HCMV terminase complex (TC) is an attractive target because of its essential role in viral DNA packaging. Based on the identification of the pUL56 $_{514}$EVNVRKRAY$_{522}$ (EY9) motif as a key region involved in TC assembly (Gourin *et al*., 2025) and initial evidence of a peptide-based therapeutic strategy (Mafi *et al*., 2025), this study aimed to assess the antiviral activity and cytotoxicity of two EY9-derived peptides coupled to cell-penetrating peptides (CPPs): penetratin (PT-EY9) and HIV-1 transactivator of transcription (TAT-EY9).

Materials and Methods: Antiviral assays were performed using confluent MRC-5 cells infected with the AD169-GFP HCMV strain and treated with PT-EY9 or TAT-EY9 at concentrations ranging from 1.25 to 80 µM. The inhibitory effect on viral replication was assessed at day 5 post-infection by counting fluorescent cytopathic foci. Cytotoxicity after 5 days of peptide exposure was evaluated in confluent MRC-5 cells using the CytoTox 96® Non-Radioactive Cytotoxicity Assay kit (Promega), based on lactate dehydrogenase (LDH) release.

Results: Antiviral assays showed a weak efficacy following treatment with TAT-EY9. However, the use of PT as CPP allowed to obtain a significant decrease of the number of cytopathic foci (IC_{50} = 15 µM). Cytotoxicity assays did not reveal significant toxicity for TAT-EY9, with slightly higher LDH release values at 80 µM compared with untreated cells (20.31% vs 15.30%). PT-EY9 showed a trend toward increased LDH release at higher concentrations (20.09% at 80 µM vs 9.82% in untreated cells), with no statistically significant cytotoxic effect observed.

Conclusions: These preliminary results suggest that peptides derived from the pUL56 EY9 motif, when combined with an effective CPP, may interfere with TC assembly without significant cytotoxicity. These findings support further investigations of EY9-derived peptides as potential antiviral candidates against HCMV.



P008

Comprehensive Herpesviruses Antiviral drug Resistance Mutation Database (CHARMD) and quality control of its integrated genotyping tool

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Abstract

Introduction: Human cytomegalovirus (CMV) antiviral resistance remains a major challenge affecting 5–30% of immunocompromised patients receiving long-term therapy. International guidelines recommend resistance genotyping in cases of treatment failure to detect resistance. Resistances may arise due to a diverse range of mutations. Appropriate genotyping tools should be able to detect all types of single or combined mutations. A comprehensive and accessible Herpesvirus drug resistance database was designed to serve as an international reference for diagnosis and clinical studies, including HSA (Herpesvirus Sequence Analysis) genotyping tool. (https://www.unilim.fr/cnr-herpesvirus/outils/codexmv/). Considering the need for homogenization of genotyping results worldwide, we aimed to compare sequence analysis results from different softwares used among the participating laboratories.

Material and Methods: The database content is revised by the CHARMD academic working group. The quality control consisted of a pool of 15 fasta sequences, mixing *in silico* and fully anonymized patient sequences. The mutations to detect included SNPs (both resistance-related and polymorphisms), ambiguous, silent, in frame insertions or deletions, frameshift giving indels, premature stop codons and start or ending truncations.

Results: Eleven laboratories (USA, Europe) responded. The used genotyping tools were MRA (ULM), CHARMD/HSA (CNR), HerpesDRG (UCL), Deepchek (ABL) and SmartGene. All the tools achieved 100% detection of all the mutations and combination of mutations tested, with differences only in the display of the results.

Conclusions: The CHARMD database serve as a reference comparator for new CMV genotyping tools, for both resistance-related mutations and natural polymorphisms. The tools tested showed good performance, allowing the community to decide the use of one or another, based on the display or the mode of use. A wider array of sequences may be constructed to ensure the maintenance of the genotyping quality.



P009

Comparison of Sanger Sequencing and the DeepChek® CMV Genotyping NGS Assay for Cytomegalovirus Antiviral Resistance Genotyping

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Abstract

Introduction/Aim

Accurate detection of HCMV resistance-associated mutations is critical for antiviral resistance management. This study assessed the performance of the DeepChek® CMV Genotyping NGS Assay compared with Sanger sequencing for detection of resistance-associated mutations.

Materials and Methods

Nine clinical samples from three patients (viral loads: 3.0–5.18 $\log_{10}$ IU/mL) were analysed by Sanger sequencing and DeepChek® NGS Assay. Comparisons were performed for UL97 and UL54 in all samples, and for UL56, UL27, UL89, and UL51 when available. For five samples, Sanger PCR amplicons were also sequenced on the Ion S5™ System and analysed using the DeepChek®-CMV software and an in-house pipeline ASPICmv.

Results

Insufficient sequencing depth was observed for some DeepChek® assay targets, particularly within UL54. Among interpretable results and considering variants with an allele frequency >10%, four discordant mutations were observed in four samples. UL97 L595S (96.78%), UL97 A594V (32.14%), and UL54 K513E (64.71%) were identified only by NGS, whereas UL97 A594V was identified only by Sanger sequencing in another sample. Additional low-frequency NGS-only variants included UL97 V356G (3.03%), M460I (10.37%), A594V (7.83%), H411Y (6.91%), C480F (5.48%), and UL56 C325F (9.79%).

Five samples from two patients were reanalysed on the Ion S5™ System. All mutations detected by Sanger sequencing were also detected by NGS. Most additional variants identified by the DeepChek® assay, including UL97 M460I, A594V and UL56 C325F, were also detected after Ion S5™ sequencing. Allele frequency estimates were highly concordant between DeepChek® and in-house pipelines.

Conclusions

These results highlight the potential and challenges of NGS for CMV-resistance genotyping. Differences in mutation detection between NGS and Sanger sequencing, as well as insufficient sequencing depth, were observed in some samples. Reanalysis on the Ion S5™ platform confirmed most additional variants detected by the DeepChek® assay and demonstrated the reproducibility of NGS variant detection across sequencing and bioinformatics workflows.



P010

Comparative analysis of the human cytomegalovirus helicase-primase complex for the development of a new therapeutic strategy

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Abstract

Introduction

The helicase-primase complex (HPC=pUL70-pUL105-pUL102) of the human cytomegalovirus (HCMV) plays a central role in the initiation of viral DNA replication and therefore represents a potential therapeutic target. Pritelivir and amenamevir are two inhibitors targeting the HPC of alpha-herpesvirus, but they do not have any antiviral activity against HCMV. In this context, this study aims to identify the molecular determinants responsible for the ineffectiveness of these inhibitors, in order to develop potential therapeutic that target the HCMV HPC.

Materials and Methods

A comparative analysis between HSV and HCMV was performed on the residues involved in interactions between inhibitors and HPC. To assess their role in susceptibility to inhibitors, the homologous residues in HCMV were substituted with these conserved HSV-1 residues. Mutants were built in HCMV-BAC (bacterial artificial chromosome containing the HCMV genome) and then transfected in MRC5 to study their impact on replication and sensitivity to antivirals.

Results

Two amino acids of interest were identified: Y882 in HSV-1 helicase and F360 in HSV-1 primase, which are conserved in VZV but not in HCMV. The mutations F956Y in the HCMV helicase and R262F in the HCMV primase were generated and transfected in MRC5. Analysis of the replicative capacity of the mutated viruses showed an impact of the mutations on HCMV replication (increased for F956Y and decreased for R262F). Antiviral assays demonstrated that these substitutions did not confer susceptibility of HCMV to the inhibitors at a concentration up to 100nM.

Conclusion

These results suggest that mutations of residues F956 and R262 alone are not sufficient to restore sensitivity of HCMV to inhibitors of the HPC. Double mutant has to be tested. Further analyses will be necessary to identify the other residues essential for this interaction, in order to optimize the inhibitors so that they target the HCMV helicase-primase complex.



P011

The long-running motivation to discover nuclear egress-directed antiherpesviral prototype drugs - helter skelter stepping forward

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Abstract

(1) Introduction/Aim. The regulation of nucleocytoplasmic capsid egress represents a centrally important rate-limiting step of herpesviral replication and pathogenesis, making it an important novel target for antivirals.

(2) Materials and Methods. Several tools have been generated on the basis of protein expression systems, reporter cells, recombinant herpesviruses, and quantitative methods of antiviral drug assessment.

(3) Results. Experimental impairment of the nuclear egress functionality has demonstrated an intranuclear accumulation of immature A/B-type capsids in HCMV cellular infection. The core nuclear egress complex (NEC) consists of a heterodimer-based assembly of two viral proteins expressed by all known herpesviruses. Crystal structures have been solved for alpha-, beta-, and gamma-herpesviruses, revealing a hook-into-groove binding scaffold that is strictly conserved within the entire virus family. The NEC-association with herpesvirus-encoded kinase activity proved to be highly relevant for the fine-regulation of core NEC and capsid binding. Of note, functional validation of the herpesviral NEC has been achieved by several independent approaches, including mutant viruses, overexpressed constructs, synthetic hook peptides, and inhibitory small molecules. This provides the current basis for defining the NEC as a promising target for antiviral drug discovery. Here, we focus on the consecutive characterization of first generations of NEC-directed prototype drugs. These include (i) initial screening hits that achieved a proof-of-principle (merbromin), (ii) warhead compounds with covalent NEC-binding capacity (ibrutinib, LDC599, and hits reported by others e.g. GK2), (iii) computer-assisted pharmacophore prediction and experimental confirmation of broadly acting antiviral NEC inhibitors (P-004, P-020, a.o.), and (iv) egress-inhibiting small molecules based on indirect mechanisms (maribavir, a.o.).

(4) Conclusions. Our results exemplify that pharmacological interference with NEC functionality is hitting a conserved key point of herpesviral replication, that shows potential for the development of novel antiviral drugs and strategies.



P012

Use of AltoStar® CMV PCR Kit 1.5 in non-blood samples based on validation data and external quality assessment data

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Abstract

Introduction and aim

Plasma, whole blood and urine are routinely used as clinical samples for detection of CMV infection in *e.g.,* immunocompromised patients, but the relevance of testing other non-blood samples is increasing to support the diagnosis, prognosis and management of CMV infection.

We evaluated the off-label performance of the AltoStar® CMV PCR Kit 1.5/ AM16 workflow (altona Diagnostics) for the detection of CMV in in bronchoalveolar lavage fluid (BALF) and participated the CMV Non-Blood Sample EQA Pilot Study CMVNB25 by Quality Control for Molecular Diagnostics (QCMD).

Material

BALF samples (anonymized) were collected and tested for CMV infection. The CMV Non-Blood Sample EQA Pilot Study (QCMD) was used to test amniotic fluid, swabs and urine samples.

Methods

89 BALF samples underwent sample pre-treatment were processed on the AltoStar® CMV PCR Kit 1.5/ AM16 workflow. The results of the BALF samples were compared to the results generated with the artus® CMV/EZ1 workflow (QIAGEN).

10 defined non-blood samples from QCMD were processed on the regular extraction protocol.

Results

84 out of 89 BALF samples tested gave concordant results with the AltoStar® CMV PCR Kit 1.5 and the artus® CMV assay. 5 samples were discordant.

3 out of 4 amniotic fluid samples of the QCMD panel were detected positive for CMV, one sample negative (defined as negative control by QCMD). 3 out of 4 urine samples were detected positive for CMV, one sample negative (defined as negative control by QCMD). 2 out of 2 swab samples were detected positive for CMC DNA correctly.

Conclusion

In conclusion, the AltoStar® CMV PCR Kit 1.5/ AM16 workflow is suitable to detect CMV DNA in bronchoalveolar lavage fluid, amniotic fluid and swabs (both synthetic and off-label use), whereas urine sample testing is a validated sample material for the workflow and CE-IVD approved.



P013

The conundrum in CMV viraemia: To treat or not to treat?

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Abstract

Introduction:

Cytomegalovirus (CMV), a ubiquitous virus, its seroprevalence is 40% to 50% in developed countries. CMV Infection ranges from asymptomatic shedding to non-hepatotropic hepatitis, especially with altered immune status. We highlight three cases with varying CMV antiviral approaches.

Method:

Authors directly involved with the primary clinicians. Data collected, shared and discussed with clinical team and necessary permissions taken.

Results:

First patient had alcoholic hepatitis, seropositive with mild-moderate ascites, jaundice, no cirrhosis, end-organ disease, acutely raised LFTs with liver parenchymal disease. CMV DNA testing performed. Viral load consistently >100,000 IU/ml. Assumption,CMV hepatopathy with local loss of viral control, patient started on PO Valgan. 3-log fall in DNA levels <10 days, with improved LFTs. Viraemia cleared after 21 days of treatment.

Second patient, renal transplant recipient (high-risk), on triple immunosuppression. For regular CMV DNA monitoring, normal LFTs, no signs of end-organ disease. Was started on PO Valgan. Slow response to treatment, 1 log decrease after 14 days. Required further reduction of immunosuppression f/b a sudden drop in CMV viraemia. After 3 months, treatment for 2 months, likely for Maribavir.

Third with Idiopathic Thrombocytopenic Purpura (ITP), seropositive, on prolonged steroids, developed CMV DNAemia of 5-log load. Spontaneous DNA levels dip 1 log, made us believe CMV-specific memory T-cells active. Though not long-lasting; 2nd surge in DNA levels, was started on PO Valgan. Treated with 2 weeks of therapy.

Conclusion:

CMV viral dynamics are an intricate web of functioning host immunity and the viral load. Very little/almost no consensus on the start timing, duration and stop for the treatment with altered immune status. Scenarios outside of published clinical guidance, a nuanced approach to tip the immune-tolerance state into a viral clearance o. Need of the hour is to devise a local/national consensus on treatment of such cases.



P015

Evaluation of CMV IgM Confirmation and IgG Avidity Testing Following High-Volume Automated Screening in a Tertiary Care Hospital

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Abstract

Background: Cytomegalovirus (CMV) is a major cause of congenital infection worldwide. CMV IgG, IgM, and IgG avidity assays are widely used to distinguish primary from past infection. This study evaluated CMV serological screening, confirmatory testing, and prenatal diagnostic results in a tertiary care hospital.

Methods: CMV serological results obtained over a one-year period were retrospectively analyzed. A total of 3,943 CMV IgG and 4,073 CMV IgM tests were performed using the Atellica IM Analyzer (Siemens Healthineers, Erlangen, Germany). To assess reproducibility, 113 CMV IgG-positive samples were retested on the same platform. In addition, 398 CMV IgM-reactive samples were retested using the VIDAS® system (bioMérieux, Marcy-l'Étoile, France). CMV IgG avidity results and CMV DNA real-time PCR (RT-PCR) results from amniotic fluid samples submitted for prenatal diagnosis were also evaluated.

Results: Complete concordance (100%) was observed among the 113 CMV IgG-positive samples retested on the Atellica platform. Of the 398 CMV IgM-reactive samples, only 33 (8.3%) were confirmed positive by VIDAS, including four pregnant women. Among 331 CMV IgG avidity requests, 147 (44.4%) were rejected because of negative CMV IgG results. Of the remaining 184 samples, 173 (94.0%) showed high avidity, 9 (4.9%) low avidity, and 2 (1.1%) borderline avidity. CMV DNA RT-PCR was performed on 14 amniotic fluid samples, and all were negative.

Conclusions: CMV IgG testing showed excellent reproducibility, whereas most CMV IgM-reactive results were not confirmed by an alternative assay, highlighting the importance of confirmatory testing. Most avidity results indicated past infection, and no fetal CMV infection was detected by amniotic fluid RT-PCR. Combined use of CMV IgM confirmation, IgG avidity testing, and molecular prenatal diagnosis may improve the evaluation of suspected maternal CMV infection.



P016

An unusual case of disseminated CMV infection leading to encephalitis driven secondary HLH

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Abstract

Introduction: Cytomegalovirus (CMV), a ubiquitous virus belongs to Herpesviridae. With a seroprevalence of 40-60% in the UK its infection/reactivation presents with a spectrum of diseases depending on factors such as age, immune status, comorbidities and reactivation of virus. Here we present a case of secondary HLH triggered by disseminated CMV encephalitis.

Methods: Patient was managed/followed in real time and data was entered. It was shared with clinicians and appropriate permissions were taken for presentation.

History: Patient was in the hospital for 21 days, being treated for UTI when a drop in GCS (8/15) led to move in ICU. He had significant past medical history of neutropenia, smouldering myeloma under investigation, Stiff-man syndrome for which he was on mycophenolate. As per antimicrobial policy, patient was started on broad-spectrum antibiotics and a lumbar puncture performed. Multiplex PCR testing revealed presence of CMV DNA. Due to past medical history, immunohistochemistry of skin biopsy (4/4 sites, to R/O lymphomas), confirmed 'Owl's Eye Appearance', diagnosing disseminated CMV infection. Blood CMV DNA testing showed a load of 1.5 X 10^6 IU/ml. Quantification of CSF CMV DNA was done. Patient discussed in HLH MDT, a diagnosis of CMV-driven secondary HLH was confirmed. Patient was started on IV Ganciclovir, and at the time of writing this abstract, is being monitored weekly for CMV DNA viral load, with HLH markers.

Conclusion: Herpesviruses, cause lifelong latent infections. Reactivation, defined by patient's altered immune status and chronic co-morbidities ranging from of mononucleosis like syndrome or disseminated disease leading to end-organ diseases such as colitis, hepatitis, encephalitis and syndromes like secondary HLH. Scientific literature on systemic illnesses from these viruses is scarce, forming a lacunae leading to their misdiagnosis/underdiagnosis. The need of the hour is to come up with local/national recommendations to include these viruses in the differential diagnosis.



P017

Evaluating CMV vaccines targeting glycoprotein B and viral Fcγ receptors to prevent congenital CMV transmission in rhesus macaques

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Abstract

Human cytomegalovirus (HCMV) is the leading infectious cause of congenital birth defects worldwide. While infection is asymptomatic in immunocompetent individuals, congenital CMV (cCMV) infection can result in severe neurological sequelae, including hearing loss and neurodevelopmental impairment. Despite decades of research, no licensed CMV vaccine is currently available. The most efficacious vaccine candidate evaluated to date, a glycoprotein B (gB)/MF59 subunit vaccine, demonstrated approximately 50% efficacy in preventing primary CMV infection, highlighting both the promise of gB-based vaccines and the need to develop more efficacious vaccines. Our previous studies identified Fc-mediated antibody functions as correlates of protection against cCMV. Furthermore, we recently demonstrated that rhesus CMV (RhCMV) lacking all three viral Fc gamma receptors (vFcγRs), Rh05, Rh152/151, and Rh173, are cleared more rapidly than wild-type virus in rhesus macaques (RM), suggesting that vFcγRs contribute to immune evasion and represent promising vaccine targets. To exploit this vulnerability, we developed a novel subunit vaccine combining RhCMV gB with all three RhCMV vFcγRs adjuvanted with saponin/monophosphoryl lipid A nanoparticles (SMNP). Initial proof-of-concept studies in RhCMV-seropositive and seronegative male RM demonstrated robust vFcγR-specific IgG responses, confirming vaccine immunogenicity. In addition, dams receiving control vaccines based on Epstein-Barr virus gB, exhibited a 100% cCMV transmission rate, as evidenced by detectable RhCMV DNA in amniotic fluid. Based on these findings, nine dams were immunized with the combined gB-vFcγR vaccine and enrolled in our rhesus model of cCMV to evaluate protection against maternal-fetal transmission following viral challenge. Currently, six animals have achieved pregnancy and are undergoing evaluation. Ongoing analyses include assessment of binding and neutralizing antibodies, as well as Fc-mediated effector functions such as antibody-dependent cellular phagocytosis (ADCP) and cellular cytotoxicity (ADCC). These studies will determine whether targeting both viral entry and immune-evasion mechanisms can enhance protection against cCMV transmission and inform the design of next-generation CMV vaccines.



P018

Non-Canonical HCMV Immediate-Early Expression Patterns in Human Tumors: Biological Insights from a Novel Clinical Cytomegalovirus Isolate

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Abstract

Introduction

Human cytomegalovirus (HCMV) is a ubiquitous herpesvirus with oncomodulatory properties that has been associated with several malignancies. Although HCMV nucleic acids and proteins are frequently detected in tumors, their biological significance remains unclear. Among 140 clinical HCMV isolates analyzed, one isolate, designated C26, displayed atypical molecular and cellular features distinct from those of canonical HCMV strains. Notably, these features closely resembled HCMV-associated characteristics observed in tumor specimens and cancer cell lines. We therefore investigated the relationship between the C26 isolate and HCMV-associated signals detected in cancer.

Materials and Methods

A total of 358 tumor specimens representing diverse malignancies and 55 cancer cell lines were analyzed. HCMV immediate-early (IE) protein expression was assessed by immunodetection and Western blotting. Viral genomic features were examined using nested PCR and highly specific TaqMan PCR assays. Fluorescence in situ hybridization (FISH) was used to determine nucleic acid localization.

Results

HCMV IE immunoreactivity was detected in 98% of tumor specimens and 99% of cancer cell lines despite the absence of canonical HCMV sequences in many samples. Both tumor-derived cells and C26-infected cells exhibited predominantly cytoplasmic IE-related signals and non-canonical IE proteins of approximately 40, 25 and 15 kDa, substantially smaller than canonical IE72 and IE86. Moreover, serum from cancer patients recognized the same 40, 25 and 15 kDa proteins present in primary glioblastoma cell lines from patients that expressed cytoplasmic IE proteins. PCR assays targeting exons 2 and 3 identified a smaller DNA fragment, and sequencing revealed a recurrent IE-region variant lacking intron 2. FISH demonstrated predominantly extranuclear nucleic acid localization.

Conclusions

The C26 clinical isolate shares key molecular and ultrastructural features with HCMV-associated signals detected in tumors and cancer cell lines. Further studies are required to define the potential different molecular identity of this virus and its relevance to cancer biology.



P019

The mCMV antigenic protein m164/gp36.5 is encoded on a polycistronic RNA during the immediate early phase

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Abstract

An essential component in the immune response against cytomegaloviruses (CMV) are CD8 T cells. Through the expression of viral peptides by major histocompatibility complex class I (MHC-I), CD8 T cells terminate productive infection and reactivation during acute infection. It is hypothesized that restricted peptide presentation drives the expansion of CMV-specific CD8 T cells during latency, a phenomenon known as memory inflation (MI). In BALB/c mice, the acute CD8 T-cell response to murine CMV (mCMV) and MI are focused on two epitopes, derived from Immediate Early 1 (IE1/M123; L^d) and m164/gp36.5 (D^d). Although m164/gp36.5 is expressed with E-kinetics, the m164 epitope has been described to be presented in IE- and E-phase. Two distinct mRNAs expressed with IE- or E-kinetics were found after acute infection and during latency. In the E-phase, a 2kb mRNA driven by the m164 promoter dominates. Still, in the IE-phase, a 5kb mRNA initiated at the transcription start site of the recently described ORF m166.5, encompassing the viral ORFs m166.5 to m164, was identified. We hypothesize that the 5kb mRNA is polycistronic and responsible for IE m164 antigen presentation. While overlapping polycistronic mRNAs are common in herpesviruses, evidence for translation of downstream genes is rare. Polycistronic mRNAs contain internal translation initiation sites, such as internal ribosomal entry sites (IRES), to initiate protein translation. To identify a potential IRES within the 5kb mRNA, we screened sequences upstream of the m164 translation start site for translation initiation using a dual reporter vector. We identified 240bp upstream of the m164 ORF that can initiate translation and confirmed the identified sequence as an IRES in a circRNA reporter assay. These results may explain the unconventional m164 peptide presentation in the IE phase and the induction of MI by increasing the m164 antigen presentation during latency.



P020

HCMV Reprograms Host Cell Metabolism to Support Viral Replication

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Abstract

1) Introduction/Aim

Human cytomegalovirus (HCMV) establishes lifelong latency in CD34+ hematopoietic progenitors and cells of the myeloid lineage. HCMV nucleic acids and proteins have been reported in several cancers and inflammatory tissue lesions, supporting the concept that HCMV may act as an oncomodulatory and immunometabolic modifier rather than a classical directly transforming oncogenic virus. HCMV reactivation profoundly rewires host-cell metabolism, including glucose uptake, mitochondrial respiration, and anabolic cofactor metabolism, thereby supporting viral replication and potentially shaping inflammatory signalling. In our study we investigate how HCMV-driven metabolic rewiring contributes to viral replication.

2) Materials and Methods

We investigated mitochondrial changes following HCMV infection. Mitochondrial biogenesis was assessed by immunostaining and western blotting. Electron transport chain (ETC) complex I and II activities were measured using inhibitor-resolved spectrophotometric assays. Mitochondrial respiration and ATP production rates were measured using the Seahorse XF Mito Stress Test.

3) Results

We found that HCMV increased markers of mitochondrial biogenesis and remodelled ETC complex activity. HCMV infection increased complex I activity 2-fold while reducing complex II activity up to 90%. HCMV-induced oxygen consumption was partly (~50%) mediated by the HCMV-encoded long non-coding RNA β-2.7, which has been reported to associate with ETC complex I. Pharmacological disruption of mitochondrial metabolism using pyrvinium pamoate reduced HCMV IE86 and gB expression and impaired viral replication. We further identified that NAD kinase, a key enzyme generating $NADP^+$ for NADPH-dependent anabolic and redox pathways, was induced by HCMV infection.

4) Conclusion

Together, our findings indicate that HCMV replication depends on mitochondrial and metabolic rewiring, including ETC remodelling and NADP(H)-linked anabolic metabolism. These results provide mechanistic insight into HCMV–host metabolic interactions and suggest that targeting virus-induced metabolic dependencies may offer therapeutic opportunities in HCMV-associated pathologies.



P021

Analytical evaluation of pooled urine CMV PCR for neonatal testing

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Abstract

Introduction/Aim: We evaluated the analytical performance of routine urine CMV real-time PCR and assessed the predicted impact of different pool sizes on CMV detection, since evidence on the analytical suitability of pooled urine CMV testing remains limited.

Materials and Methods: A CMV-positive urine control with a previously estimated with a previously estimated in-house viral load was serially diluted in CMV-negative urine up to 1:256. CMV DNA was extracted using the QIAsymphony SP platform and quantified using the GeneProof CMV PCR kit. Agreement between the nominal and measured concentrations was assessed using regression analysis. Repeatability was evaluated using replicate testing, standard deviation, and coefficient of variation. Based on the experimentally derived dilution curve, model-based pooling simulations were performed for total pool sizes of 4, 6, 8, and 10.

Results: The assay showed excellent analytical performance in urine, with strong agreement between nominal and measured concentrations across the tested range (slope 1.014, intercept 0.043, R^2 0.990). CMV DNA remained detectable throughout the dilution series, with acceptable repeatability at low viral loads. Pooling simulations showed that pool size 4 remained within the experimentally supported analytical range up to source dilution 1:64, whereas pool sizes 6, 8, and 10 remained within it up to dilutions 1:32, 1:32, and 1:16, respectively. All pool sizes retained predicted detection down to the lower manufacturer-declared urine LOD range (255.48–745.68 IU/ml), but pool size 4 remained closer to this range across the dilution series, while larger pool sizes reached substantially lower predicted post-pooling concentrations.

Conclusions: This assay-platform combination showed robust analytical performance in urine. Based on our experimental data, 1:4 pooling appears to be the most analytically justified strategy for neonatal urine CMV testing. Larger pool sizes may remain analytically feasible, but should be interpreted cautiously and ideally validated directly with the extraction workflow used.



P022

HCMV driven signaling rewires the mitochondrial metabolism via inhibition of complex II through SP1-PTPMT1 regulation

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Abstract

Introduction: Human cytomegalovirus (HCMV) remodels host signaling networks to create a pro-viral metabolic state. In this study, we investigate how HCMV-driven signaling impacts mitochondrial function and cellular metabolism. We propose that activation of ERK1/2 plays a central role in coordinating downstream signaling events that influence mitochondrial activity and promote metabolic reprogramming. Our findings suggest a functional link between ERK1/2 signaling and an SP1-PTPMT1 regulatory axis, connecting nuclear transcriptional responses to mitochondrial control. Additionally, HCMV infection increased PTPMT1 expression, supporting mitochondrial dephosphorylation events that suppress Complex II activity. In line with the recent work by Purdy, J. G., showing that HCMV supports lipidome remodeling through glutamine-driven reductive carboxylation, our data further indicate that mitochondrial metabolism is actively rewired during infection.

Methods and Results: Building on prior work linking HCMV infection to mitochondrial dysregulation, we observed a 90% reduction in complex II activity in infected fibroblasts. Further, to probe the role of PTPMT1, we treated infected fibroblasts with alexidine, a PTPMT1 inhibitor. Alexidine treatment led to effective inhibition of PTPMT1 and resulted in a significant decrease in HCMV immediate-early (IE) gene expression, indicating that PTPMT1 activity supports early viral transcription.

Conclusion: Together, these signaling nodes establish a regulatory circuit linking SP1-PTPMT1 to mitochondrial dysfunction and metabolic reprogramming. This model provides a mechanistic framework for understanding how HCMV manipulates host kinase, phosphatase, and transcription factor networks to impair Complex II and favor a Warburg-like metabolic state. Defining this pathway identifies new molecular targets for limiting HCMV-induced metabolic reprogramming and associated disease.



P023

Retrospective Evaluation of Cytomegalovirus DNA Positivity in Non-Blood Clinical Specimens

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Abstract

Introduction/aim: Cytomegalovirus (CMV) is an important cause of morbidity and mortality, particularly in immunocompromised patients.Although plasma is commonly used for diagnosis, the clinical significance of CMV DNA detected in non-blood samples remains unclear. This study investigated CMV DNA positivity in non-blood samples and its association with concurrent plasma positivity.

Material and Methods: CMV DNA PCR results from non-blood samples collected between September 2025 and May 2026 were retrospectively analyzed. The study included bronchoalveolar lavage(BAL)/sputum, urine, biopsy, amniotic fluid, and stool samples from 241 patients (61.8% male; age range, 0-97 years). Testing was performed using the CMV ELITe MGB® kit until January 2026 and Bosphore CMV Quantification Kit thereafter. Clinical data and plasma CMV DNA results were evaluated in CMV-positive patients.

Results:CMV DNA was detected in 38.6% (93/241) of patients, with positivity rates of 59.7% in BAL/sputum, 37.2% in biopsy, and 4.5% in urine samples. No positivity was observed in amniotic fluid (n=6) or stool (n=1) specimens. Positive cases were mostly identified in patients from Pulmonology, Gastroenterology, Intensive Care, and Hematology departments, predominantly among patients with pneumonia, malignancies, and inflammatory bowel disease (IBD). Among 39 patients with concurrent plasma CMV DNA results, 24 were plasma-positive and 15 were plasma-negative. BAL viral loads were significantly higher in plasma-positive patients than in plasma-negative patients (med:7,519 vs. 97 IU/mL, $p<0.05$). CMV DNA positivity in biopsy samples was mainly observed in patients with IBD.

Conclusions: CMV DNA positivity in non-blood specimens was predominantly observed in critically ill and immunocompromised patients, and patients with ulcerative colitis and Crohn's disease. The detection of CMV DNA in non-blood specimens despite negative plasma CMV PCR results suggests that localized CMV infection may occur without systemic viremia. These findings indicate that non-blood specimens may provide additional diagnostic value in the evaluation and follow-up of CMV infection in high-risk patients.



P024

A 10-year diagnostic evaluation in Germany: cytomegalovirus as a major human herpesviral pathogen

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Abstract

(1) Introduction. Herpesvirus infections belong to major pathogens in the human population. This study aimed at evaluating diagnostic data for eight human herpesviruses, based on datasets derived from a large European tertiary care center. Specifically, we analyzed 118,692 herpesvirus submittals to the Diagnostic Division of the Virological Institute, University Hospital Erlangen (UKER), Germany, between July 2014 and June 2024. **(2) Materials and Methods.** Our points of focus were the following: (i) the frequencies of herpesvirus diagnostic results with positivity rates, (ii) departments representing main sample submitters, (iii) the specific importance of intensive care units (ICUs), (iv) the COVID-19 pandemic period, and (v) distinct properties of sample types. **(3) Results.** Overall, we are stating the highest frequencies of diagnostic assessment for herpes simplex virus (HSV), human cytomegalovirus (HCMV), and Epstein–Barr virus (EBV) infections, pointing to their dominant relevance for clinical practice. Notably, HCMV submittals (46.6% of total), together with EBV (26.2%) and HSV (15.7%), accounted for almost 90% of all herpesviral diagnostic samples during this period. Within these key groups, HCMV, EBV and HSV showed positivity rates of 14.5%, 35.0%, and 18.5%, respectively. Concerning a main input of sample submittals, two departments were predominant in our center, i.e., the Departments of Haematology–Oncology and Anaesthesiology. These included patients under multifold types of treatment associated with an increased risk of herpesvirus reactivation or primary infection. Furthermore, another high portion of submittals was noted for ICUs and external sources. In addition, a numerical, transient increase in herpesvirus diagnostic submittals, from various sources, was shown for the COVID-19 pandemic years (mostly 2021) as compared to other periods. **(4) Conclusions.** Combined, these data underlined the importance of clinical monitoring of herpesvirus infections, particularly for high-risk patients, and the steady need of improvements in preventive measures, therapeutic options, and safe diagnostic tools.



P025

Latent MCMV infection activates epithelial-mesenchymal transition (EMT) of retinal pigment epithelium (RPE) cells following mitochondrial oxidative stress

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Abstract

Introduction: virus spreads to the eye with subsequent establishment of latency in the choroid following systemic neonatal MCMV infection. Since oxidative stress-induced RPE damage is considered to be a key factor in the development of age-related retinal degeneration (AMD), we wished to determine if oxidative stress in the RPE and MCMV ocular latency synergize to enhance development of AMD-like pathology.

Methods: MCMV or medium were injected intra-peritoneally into RPE-specific, SOD2-depleted ($SOD2^{flox/flox}$, $Tyrosinase^{Cre/ERT2}$+) or control mice at <3 days after birth. At 4 months p.i. tamoxifen was administered. At 4 and 8 months post-tamoxifen treatment, SD-OCT were performed. tissues were collected for further examinations. To trigger MCMV reactivation, latently infected SOD2-depleted and control mice were immunosuppressed with methylprednisolone acetate and T-cell-specific antibodies.

Results: At 4 months post-tamoxifen treatment, no replicating virus were detected in eyes of infected mice. Although MCMV DNA was detected in 4 of 10 RPE samples from infected control mice, it was present in 9 of 10 RPE samples from infected, RPE-specific, SOD2-depleted mice. OCT examinations showed that hyperreflective lesions were present in the majority of infected, RPE-specific, SOD2-depleted mice (16/28 eyes) but were observed only occasionally in infected control mice and uninfected, RPE-specific, SOD2-depleted mice while no lesions were observed in uninfected control mice. EM/H&E staining confirmed the migration of pigmented RPE cells to the inner retina. MCMV was reactivated in RPE cells (but not in migrated RPE cells) of latently infected SOD2-depleted mice (but not in infected control mice) following systemic immunosuppression.. The results of Visium Spatial Gene Expression showed that several signaling pathways (TGF-β, Wnt and NOTCH) related to EMT were activated in RPE cells near hyperreflective lesions.

Conclusions: oxidative stress in the RPE enhances spread of latent ocular MCMV infection, resulting in activation of EMT and intraretinal migration of RPE cells.



P026

Development of an iPSC-based model for latent HCMV infection

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Abstract

Besides the significant improvements of pre- and post-transplant prophylaxis, CMV infections still remain a major threat in the first 6 months after transplantation. Once CMV reactivation occurs, the treatment options are limited leading to severe outcomes. Hence, understanding the mechanism how reactivation is initiated and identifying new prophylactic treatments is of importance.

For that, we established a new induced pluripotent stem cell (iPSC)-based latency model which allows the reliable production of CD34+ hematopoietic progenitor cells (HPCs) commonly used as a model for HCMV latency. Based on a protocol published by Ackermann et al in 2024 **[1]**, we used an iPSC line and differentiated them into so-called hemanoids. We then stimulated them to produce CD34+ HPCs. Contrary to commonly used cell lines to study HCMV latency, which origin from leukemia patients (THP-1, Kasumi-3), iPSCs are derived from healthy, voluntary donors. Moreover, the iPSC/hemanoid approach circumvents the no donor-to-donor variations evident in primary CD34+ HPCs or CD14+ monocytes. Hence, this new model provides a constant genetic background while having culture conditions similar to standard cell lines.

We can demonstrate that the iPSC-derived CD34+ HPCs have a similar phenotype as primary CD34+ HPCs. To distinguish the different infection cycles of HCMV in this model system, we used a double-fluorescent recombinant HCMV which expresses mNeonGreen with immediate early protein 1 kinetics and mScarlet under control of the SV40 promoter. This allowed identification of infected cells based on their red fluorescence, with IE1-mNeonGreen expression marking lytically infected cells, whereas latently infected cells remained IE1-mNeonGreen-negative**.** We used this virus to show that the produced CD34+ HPCs support latency establishment and reactivation which we could show by flow cytometry and in an extreme limiting dilution assay (ELDA).

[1] Ackermann (2024, doi: 10.1186/s13287-024-03785-2)



P027

Conditional-replication models of human cytomegalovirus latency in permissive cell types

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Abstract

Introduction. Human cytomegalovirus (HCMV) reactivates from latency to cause life-threatening infections in immunocompromised patients and may contribute to congenital infections. Numerous studies have characterized HCMV latency in bone marrow progenitors; however, early reports describing latency in fibroblasts when lytic replication was artificially blocked suggest that permissive cells may comprise additional reservoirs i*n vivo*.

Methods. Fibroblasts or ARPE-19 epithelial cells were infected with GFP-tagged HCMVs and maintained in medium containing letermovir, which disrupts HCMV genome packaging. GFP+ cells declined and became rare beyond 42 days post-infection. Cultures infected long-term were trypsinized. Equal aliquots were either sonicated or left intact, then serially diluted and cultured on fibroblasts in the absence of letermovir to detect infectious virions in sonicates or reactivation in intact cells.

Results. GFP+ foci in cultures of intact cells (but not sonicates) were observed with either cell type and four different HCMV strains up to 87 days post-infection. In some experiments one in as few as 27 initially infected cells reactivated. ARPE-19s produced >30-fold more GFP+ foci than fibroblasts, suggesting a greater propensity for supporting latency. However, that reactivations declined significantly following passage suggested that latent cells may fail to propagate. Similar findings were obtained using a conditionally-replicating (Shield-1-dependent) guinea pig cytomegalovirus.

Conclusions. Consistent with recent *in vivo* murine cytomegalovirus studies that detected latency in fibroblasts and endothelial cells (Sitnik, Nat Commun 14:3087; Griessl, Front Immunol 12:668885), our *in vitro* data confirm that permissive cell types can sustain long-term HCMV latency when lytic replication is artificially restricted. If such restrictions occur naturally *in vivo*, then fibroblasts, epithelial cells, and perhaps other cell types may comprise additional reservoirs of HCMV latency in tissues or organs. Models using Shield-1 to regulate HCMV replication instead of letermovir are being developed. Such models may provide novel insights into the molecular basis of cytomegalovirus latency.



P028

Viral modulation of NK cell recognition: MATp1 controls m157–Ly49H interactions

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Abstract

Introduction/Aim

Infection of mice with murine CMV (MCMV) has been instrumental in our understanding of CMV pathogenesis, immune responses and evasion in vivo. Both MCMV and HCMV regulate surface MHC-I expression in order to evade T and NK cells. We have previously shown that MCMV ensures optimal MHC-I expression through immunoevasive proteins such as m04/gp34 and MATp1, balancing evasion of cytotoxic T cells while inhibiting natural killer (NK) cell via Ly49 receptors. We have now uncovered additional, m04-independent role for MATp1 – rheostat-like modulation of m157.

Materials and Methods

BAC-derived Smith strain viruses were used to infect laboratory mice that express receptors recognizing m157. The study combined in vitro Ly49H reporter cell assay with infection and adoptive transfer experiments. Multicolor flow cytometry was employed to quantify receptor–ligand interactions and NK cell activation, while confocal microscopy visualized protein expression and localization. Several novel m157 specific monoclonal antibodies were generated which enabled molecular characterization of m157 and MATp1 interactions.

Results

Cells infected with MCMV lacking functional MATp1 expressed higher m157 level than cells infected with WT MCMV. In vitro, more m157 resulted in stronger engagement of Ly49H receptor which in vivo in C57Bl/6 mice translated into better control of the virus replication, increased proliferation and activation of Ly49H$^+$ NK cells. MATp1-mediated modulation of m157 was independent of MHC I and m04, but may involve m06.

Conclusions

MATp1 is an 11 kDa MCMV protein targeting at least 6 distinct Ly49 receptors. By acting as a rheostat for m157 it ensures the virus' survival in various strains – retaining inhibition in those expressing Ly49I and limiting activation and memory NK cell formation in mice expressing Ly49H. These findings contribute to understanding NK cell regulation, immune evasion mechanisms, and virus–host co-evolution, and provide a novel tool for studying NK cell memory.



P029

Disruption of the m152 Promoter IRFE sequence paradoxically enhances expression of m152 and IE1 during acute mCMV Infection

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Abstract

Introduction:

To elucidate virus-host dynamics, we investigated the transcriptional regulation of mCMV key immunomodulator m152/gp40. m152/gp40 modulates host defences by disrupting MHC-I presentation, NK cell activation, and STING-mediated type-I IFN induction. These interactions results in a dynamic equilibrium where the virus co-opts host machinery for immune evasion, while the host deploys countermeasures to restore immune surveillance. Ultimately, defining these overlapping regulatory networks may reveal novel molecular targets to enhance immune recognition.

Materials and methods:

Transcription factors binding the viral m152 and cellular MHC-I (H2-K1) promoters were identified via DNA pull-down/LC-MS, and confirmed using ChIPseq. Promoter-luciferase reporter constructs were generated to assess transcriptional activation and functional interactions between IRFE and NF-κB elements located in the promoters. Recombinant viruses with targeted promoter mutations were generated for functional validation.

Results:

We localized functional IRFE and NF-κB binding sites in the m152 promoter, and identified its homology with the mouse H2-K1 MHC-I promoter. Our goal is to uncover shared transcriptional regulatory mechanisms for m152 and MHC-I.

Through phishing assay, we found that IRF2, IRF9, and NF-κB bind to both promoters. A luciferase reporter assay confirmed that m152/gp40 expression is stimulated by IFN and NF-κB pathways, and that IRFE element is critical for viral gene expression, as mutations within this region drastically impair basal expression levels compared to other regulatory elements.

The generated viral recombinants carrying loss of function mutations in the IRFE, showed higher expression of m152 and surprisingly, high expression of IE1 during the acute phase.

Conclusions:

The m152 promoter utilizes shared transcriptional regulatory elements with its prey MHC-I, relying heavily on the IRFE sequence for basal expression control. Unexpectedly, mutating this responsive element in viral recombinants drives higher expression of both m152 and IE1 during acute infection. This uncovers a complex, novel regulatory link between host interferon-responsive pathways and immediate early cytomegalovirus gene expression.



P030

HCMV UL98 encodes a unique alkaline nuclease engaging host DNA repair pathways

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Abstract

Introduction/Aim: *Herpesviridae* is a family of double-stranded DNA viruses including human cytomegalovirus (HCMV), herpes simplex virus (HSV), and Kaposi´s sarcoma-associated herpesvirus (KSHV). Among all herpesvirus proteins, alkaline nucleases (ANs) serve as important factors in infection. For instance, UL12, the HSV-1 AN, is implicated in viral homologous recombination and mitochondrial DNA degradation, and SOX, the KSHV AN, promotes mRNA turnover and AIM2 inflammasome suppression. Despite the structural conservation of herpesvirus ANs, the role of HCMV AN UL98 beyond its nuclease activity remains unclear. This project aims to identify the non-canonical functions of UL98 during infection.

Materials and Methods: We generated recombinant HCMV TB40/E strain viruses using *en passant* mutagenesis, replacing UL98 with UL12 or SOX to evaluate AN cross-complementation. In parallel, affinity purification coupled to mass spectrometry was employed to identify UL98-associated host proteins throughout the viral life cycle.

Results: Replacement of UL98 with UL12 or SOX in the TB40/E strain revealed that neither homolog can compensate for its loss, suggesting a distinct and non-redundant role for UL98 during HCMV infection. Given the lack of functional complementation, we performed an interactome analysis of UL98, identifying candidate host factors enriched in DNA damage response pathways, including DNA Ligase IV (LIG4), a key component of the non-homologous end joining (NHEJ) pathway. This interaction was subsequently validated by co-immunoprecipitation, confirming a stable association between UL98 and the host factor through the course of infection.

Conclusions: Our findings suggest that UL98 performs a specialized and non-redundant function during HCMV replication that cannot be efficiently replaced by its viral homologs. Ongoing studies aim to determine whether UL98 exploits host DNA repair machinery to promote viral genome maintenance and replication or to modulate antiviral DNA damage responses during infection.



P031

Transcriptomic signatures of innate immune dysregulation and myeloid activation are associated with hearing loss and neurological injury in congenital cytomegalovirus

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Abstract

Background: Globally congenital cytomegalovirus (cCMV) affects 1.76 million births annually, and a fifth have long-term sequelae. The biological mechanisms determining clinical outcomes remain poorly understood.

Methods: TINI-CC, a prospective cohort study, enrolled infants with cCMV <3 months of age in Greece and UK. Blood was collected at enrolment, and participants followed-up for 2 years. Long-term sequelae included sensorineural hearing loss (SNHL) and/or neurodevelopmental impairment. Healthy infants without cCMV were recruited as controls. Whole-blood RNA sequencing was performed, and differential gene expression (DEG) analysis was conducted, with Gene Ontology and Ingenuity Pathway Analysis. Selected plasma proteins were measured using immunoassays (ELISA, Olink®).

Results: Forty-five cases and 18 matched controls were assessed, median age 45 [IQR 20–75] days. At baseline, 58% of infants were symptomatic (48% SNHL, 65% abnormal brain imaging). By 2 years, 84% had sequelae, including 11% with progressive SNHL.

Compared with controls, infants with cCMV demonstrated 412 DEGs, including upregulated granulocyte-driven inflammatory pathways. Compared with asymptomatic cCMV (n=6), those with isolated SNHL (n=9) exhibited 937 DEGs enriched for interleukin-1β signalling, myeloid and platelet activation. Plasma interleukin-1β concentrations were significantly higher in severe–profound versus mild–moderate hearing loss (p=0.01). Progressive hearing loss (n=5) compared to stable, or no hearing loss was associated with 231 DEGs, with strongest enrichment in neutrophil activation pathways ($p=3.8\times10^{-9}$). There were 440 DEGs between infants with normal (n=15) versus severely abnormal brain imaging (n=7), reflecting pathways for cellular stress response and myeloid activation, with corresponding higher plasma colony stimulating factor 3 in infants with abnormal imaging (p=0.009).

Conclusions: Neonatal responses to cCMV are characterised by persistent immune activation and dysregulated myeloid function. Progressive and severe SNHL were associated with interleukin-1β signalling and neutrophil activation, and neurological injury linked to myeloid and metabolic stress pathways, identifying potential future biomarker and host-directed therapy targets.



P032

Human Cytomegalovirus Reprograms Breast Cancer Cells Toward a Triple-Negative and Metastatic Phenotype

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Abstract

Breast cancer remains a leading cause of cancer-related mortality in women, with triple-negative breast cancer (TNBC) representing the most aggressive subtype due to the absence of effective targeted therapies. Human cytomegalovirus (HCMV) has increasingly been implicated in tumor progression; however, its mechanistic contribution to breast cancer pathogenesis remains poorly understood. Here, we investigated whether HCMV promotes TNBC-associated phenotypic reprogramming through modulation of key prognostic receptors and tumor-associated cellular pathways.

Using transcriptomic, proteomic, molecular, and functional analyses in luminal (MCF7) and HER2-positive (SKBR3) breast cancer models, we demonstrate that HCMV infection induces extensive host-cell reprogramming characterized by suppression of ESR1, PGR, and ERBB2 expression at both transcript and protein levels, thereby promoting a TNBC-like phenotype. Mechanistically, HCMV immediate-early (IE) proteins and the viral miRNAs hcmv-miR-US25-2-3p, hcmv-miR-UL36-3p, and hcmv-miR-UL22A-3p mediated repression of ESR1 and PGR. In contrast, ERBB2 downregulation occurred indirectly through virus-mediated suppression of the EGFR/CyclinD1/CDK4/6 axis, resulting in stabilization of the RB/E2F4 repressor complex at the ERBB2 promoter.

Beyond receptor suppression, HCMV infection induced extensive inflammatory, metabolic, and epithelial-mesenchymal transition (EMT)-associated remodeling consistent with a state of virus-driven phenotypic plasticity. Although infected cells displayed reduced proliferative and metabolic activity, they exhibited enhanced invasion, EMT-associated transcriptional reprogramming, and increased metastatic dissemination in zebrafish xenograft models. Elevated TGFβ signaling and partial EMT-like states likely contributed to this invasive phenotype.

Collectively, our findings identify multiple viral mechanisms through which HCMV promotes TNBC-associated cellular reprogramming and metastatic behavior. These results support a previously unrecognized role for HCMV in driving aggressive breast cancer phenotypes and highlight HCMV-targeted therapeutic strategies as potential approaches for HCMV-positive TNBC.



P033

Opposing Effects of HCMV and Viperin-Derived ddhCTP on Host Protein Synthesis

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Abstract

Human cytomegalovirus (HCMV) profoundly hijacks host cellular machinery to support its replication. A hallmark of this viral takeover is the hyperactivation of host translation, driving an increase in total protein synthesis to fuel viral factory assembly. Conversely, the host innate immune system counters this exploitation through the radical SAM enzyme Viperin (RSAD2), which synthesizes the antiviral nucleotide ddhCTP.

In this study, we investigated the translational consequences of this host-pathogen conflict in MRC5 human lung fibroblasts, uncovering a divergence in translational control. While primary HCMV infection robustly accelerates total cellular protein synthesis, treatment with the nucleoside precursor ddhC elicits the exact opposite phenotype, precipitating drop by 25% in total translation. Crucially, we relate this ddhC-mediated translational arrest to severe elongation stress, which triggers widespread ribosome collisions.

These findings reveal a novel translational checkpoint operating during viral restriction. While HCMV attempts to force host biosynthetic machinery to its maximum capacity, the Viperin-ddhCTP axis effectively intercepts this program. By inducing ribosome stalling and subsequent collisions, this pathway disrupts the translation elongation cycle and shuts down the protein synthesis required to sustain viral replication. This study highlights the therapeutic potential of using next-generation nucleotide analogues to leverage ribosome quality control pathways against viral infections.



P034

IFN-γ compromises glutamatergic synapse development and impairs motor coordination following congenital CMV infection

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Abstract

Introduction/Aim: Congenital human cytomegalovirus (cHCMV) infection of the brain is a leading cause of neurodevelopmental impairment. Using neonatal mouse cytomegalovirus (MCMV) infection as a model of cHCMV, we previously demonstrated that activated NK/ILC1 cells contribute to cerebellar pathology through the production of interferon-gamma (IFN-γ). The aim of this study was to investigate whether MCMV-induced cerebellar abnormalities result in long-term functional deficits.

Materials and Methods: Newborn mice were infected with MCMV and assessed for cerebellar development, motor coordination, immune responses, and synaptic alterations. NK/ILC1 cell frequencies and absolute numbers were analyzed in the brain and spleen, while serum IFN-γ levels were measured in male and female mice. Glutamatergic synapses in the cerebellum were quantified, and motor coordination was evaluated using behavioral testing. To assess the contribution of IFN-γ to neuropathology, infected mice were treated with neutralizing anti–IFN-γ antibodies.

Results: MCMV infection impaired cerebellar development and resulted in deficits in motor coordination. These functional impairments were associated with a marked reduction in cerebellar glutamatergic synapses. Importantly, neutralization of IFN-γ prevented both the loss of glutamatergic synapses and the impairment of motor coordination.

Conclusions: Our findings identify IFN-γ as a critical mediator of synaptic loss and motor dysfunction following congenital CMV infection.



P035

Multi-strain cytomegalovirus infections and viral evolution in children attending daycare

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Abstract

Introduction. Mixed-strain CMV infections in immunocompetent hosts suggest that immunity induced by one strain does not always protect against reinfection by a second strain. Indeed, non-primary congenital infections have been associated with reinfections rather than reactivations. How rapidly new strains or variants evolve remains unclear. To gain further insights into multi-strain infections and CMV evolution, we analyzed CMV isolates cultured from parents and children attending three daycare centers in Richmond Virginia, USA, between 1986 and 1991.

Methods. CMV isolates derived from fibroblast cultures of urine or saliva samples were passaged two to six times and stored frozen. DNAs were extracted from selected isolates and analyzed by amplicon and whole genome sequencing (WGS).

Results. Four of 37 children's isolates analyzed (11%) contained two strains that were shed by other daycare children or their relatives. Longitudinal isolates (n=18) from eight children collected between four and 35 months apart matched exactly in amplicon sequences. WGS of eight of these 18 isolates revealed minimal within- and between-host evolution, with ≤ 11 SNPs along the genome. Notably, two viruses shared by two different hosts each contained identical 13-nt deletions in *RL12* or 38-nt deletions in *US7*. Recent strains (2016-2025) from transplant patients (n=14), congenitally (n=10), or postnatally (n=17) infected children in Austria had high sequence similarity (99-100% identity) to all but two daycare sequences (96% identity).

Conclusions. Mixed infections are common among daycare children, yet strain composition and prevalence can change over time. Viruses with disrupting *RL12* and *US7* mutations can be transmitted between hosts and maintained within a host long-term, further supporting that these are pseudogenes. Interestingly, evolutionary sequence analysis finds little evidence for host-specific adaptation, and suggests neutral evolution. Immunological pressure and the inherent mutation rate appear insufficient to drive rapid variant selection, indicating that a protective vaccine should remain effective over time.



P036

PYCR1 Links HCMV-Induced Metabolic Rewiring to Mitochondrial Respiration and ETC Remodelling

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Abstract

Introduction: The proline biosynthetic enzyme PYCR1 is highly expressed in many human cancers and is associated with poor prognosis. Human cytomegalovirus (HCMV), a ubiquitous herpesvirus linked to inflammatory diseases and several cancers, induces extensive metabolic reprogramming to support viral replication. We previously observed that HCMV protein expression in colon cancer and glioblastoma tissues correlated with elevated PYCR1 expression. This study investigated whether HCMV regulates the proline biosynthetic enzymes PYCR1, PYCR2, and PYCRL and explored their contribution to cellular metabolism.

Material: Human fetal lung fibroblasts (MRC5) infected with HCMV were used to investigate expression of proline biosynthetic enzymes, intracellular proline levels, mitochondrial respiration, and respiratory chain associated proteins. PYCR1 knockdown using siRNA was performed to assess its functional role in HCMV-induced metabolic reprogramming.

Methods: Expression of PYCR1, PYCR2, and PYCRL following HCMV infection was analysed by qPCR, Western blotting, and immunofluorescence. Intracellular proline levels were quantified using the acid ninhydrin assay. Cellular oxygen consumption rate (OCR) was measured using Seahorse analyser. To investigate mechanisms underlying PYCR1 mediated regulation of mitochondrial function, proteins involved in complex IV activity and respiratory chain organisation were analysed by SDS-PAGE, Blue Native PAGE, and immunoblotting.

Results: HCMV infection induced expression of all three enzymes, with PYCR1 showing the strongest increase. Despite this induction, intracellular proline levels remained unchanged, suggesting a function beyond proline biosynthesis. Silencing PYCR1 reduced HCMV-induced OCR by approximately 40%, demonstrating a significant role in enhanced mitochondrial respiration. Increased PYCR1 expression was also associated with elevated levels of COXIV-1, COX17, and COX7A2L, indicating involvement in complex IV regulation and respiratory chain remodelling.

Conclusions: PYCR1 plays a previously unrecognised role in supporting HCMV-induced mitochondrial bioenergetics independent of proline production. By promoting respiratory chain remodelling and mitochondrial respiration, PYCR1 contributes to the metabolic adaptation of infected cells. These findings identify PYCR1 as a potential therapeutic target in virus-associated inflammation and cancer.



P037

Investigation on the interactome of human cytomegalovirus RL11 proteins reveals that pUL6 induces angiogenesis through MERTK

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Abstract

Human cytomegalovirus (HCMV) contains a repertoire of proteins that modulate the host to overcome elimination and establish persistence. As these proteins are virulence factors, they provide targets for therapeutic intervention. HCMV expresses many, mostly uncharacterized, membrane proteins with potential roles in viral tropism, spread, and immunomodulation, such as those of the RL11 family. The aim of this project is to characterize the RL11 proteins to gain further insight into immune evasion strategies and pathogenesis and to identify new therapeutic targets for both antivirals and immunotherapies. We performed an avidity-based extracellular interaction screening with the HCMV RL11 protein family and a platform containing 80% of all human single-transmembrane proteins, previously employed to identify Neuropilin 2 as a HCMV receptor (Martinez-Martin et al., 2018, Cell). This screen identified several novel interactions between RL11 proteins and host receptors involved in immune modulation and angiogenesis. We focused on the novel binding partners for the HCMV pUL6 protein: MER receptor tyrosine kinase (MERTK) and vascular endothelial growth factor receptor 2 (VEGFR2). We validated these interactions by cellular binding assays and determined their binding kinetics by surface plasmon resonance. Both MERTK and VEGFR2 induce angiogenesis, a process involved in several pathologies associated with HCMV. Moreover, MERTK inhibits the inflammatory response and induces efferocytosis. Our results indicate that pUL6 promotes angiogenesis of primary endothelial cells. The use of kinase inhibitors, neutralizing antibodies and endothelial cells lacking VEGFR2 expression showed that this effect was mediated by interaction with MERTK. In addition, pUL6 induced MERTK-dependent signaling via the Akt-Foxo1 pathway that has recently been identified to promote pro-angiogenic gene expression. We are currently investigating the role of pUL6 in the context of infection and whether pUL6 also modulates the effector function of phagocytic cells.



P038

Baseline antibody levels predict the risk of BK polyomavirus associated nephropathy in kidney transplant recipients

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Abstract

Introduction: BK polyomavirus-associated nephropathy (BKVAN) causes up to 15% of kidney allograft losses, with management limited to reduction of immunosuppression, increasing rejection risk. Neutralizing antibodies confer partial protection but perform inconsistently as predictive biomarker of disease risk. The value of non-neutralizing antibodies has not yet been explored.

Material: A retrospective cohort of 173 kidney transplant recipients (KTR) was stratified into 3 groups according to BKV status within one year of KT: negative (n=100), viruric (n=33) and BKVAN (n=40). A systems serology approach was used to characterize the biophysical and functional properties of BKV-specific antibodies before transplantation. We measured the levels of total IgG and IgG subclasses, IgM and IgA, IgG binding to Fcγ receptors, IgG-dependent complement deposition (ADCD), cellular phagocytosis (ADCP) to BK virus proteins (VP1, large T and small t antigens and agnoprotein) and neutralizing antibodies. The predictive value of pre-transplant antibody profiles was evaluated by ROC analysis and multivariate logistic regression.

Results: Viruric and BKVAN groups showed significantly lower pre-transplant levels of IgG, IgG1, IgG3 and FcγR binding IgG to VP1, and not to the other BK virus proteins, as compared to the negative group ($p<0.001$). The negative group also displayed higher levels of ADCP than the Viruric and BKVAN groups ($p<0.001$). In contrast, neutralizing antibody levels were not significantly different between the three groups. In multivariate analysis, VP1 IgG and responsiveness to hepatitis B vaccination were independently associated with both BKV reactivation (OR 0.32 [0.19–0.50]) and BKVAN (OR 0.27 [0.15–0.46], both $p<0.001$).

Conclusions: Pre-transplant humoral immunity to VP1 is associated with the risk of subsequent BKV reactivation and BKVAN. These findings suggest that pre-transplant antibody profiling could contribute to risk stratification of KTR and inform personalized immunosuppression and BKV monitoring strategies.



P039

Evaluation of the VIDAS®-IGRA-CMV assay for monitoring CMV-specific cellular immunity in seropositive kidney transplant recipients

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Abstract

Introduction.

In kidney transplantation, assessing anti-cytomegalovirus (CMV) cellular immunity of CMV-seropositive recipients (R+) could help tailor antiviral prophylaxis strategies, reduce exposure to treatments and their toxicities, and better prevent late-onset infections following prophylaxis. The objective of this study was to evaluate the performance of the VIDAS® IGRA-CMV test (bioMérieux) for monitoring CMV-specific cellular immunity by comparing it to the gold standard QuantiFERON®-CMV test (QIAGEN).

Material and methods.

A prospective study was conducted in 13 R+ kidney transplant recipients, who were followed for the first 6 months post-transplant. The VIDAS® IGRA-CMV and QuantiFERON®-CMV tests were performed 1, 2, and 3 months after transplantation. The concentrations of interferon-γ (IFN-γ) produced following stimulation with various CMV-specific antigens were measured (Lysate, IE-1, and pp65). The diagnostic performance of the VIDAS® IGRA-CMV was evaluated using ROC analyses, in comparison with the results of the QuantiFERON®-CMV, to predict the occurrence of viral replication.

Results.

The VIDAS® IGRA-CMV demonstrated promising diagnostic performance, with a cutoff value of 2.24 IU/mL for the Lysate reagent, which is relevant for identifying patients at risk of viral reactivation with a viral load > 3 $\log_{10}$ IU/mL. The dynamic assessment of the increase in IFN-γ between the 1st and 2nd months post-transplant (threshold ≥ 1.97 IU/mL) appears to be a promising complementary marker, less influenced by the level of circulating lymphocytes. The results obtained with the IE-1 and pp65 antigens are inconsistent with the performance reported for the ELISpot assay.

Conclusion.

The VIDAS® IGRA-CMV test could represent a compromise between the ease of use of the QuantiFERON®-CMV and the high sensitivity of the ELISpot. However, its implementation in clinical practice will require larger multicenter studies to standardize interpretation thresholds and demonstrate its robustness and reproducibility. Finally, its cost-effectiveness must also be evaluated.



P040

The emotional trajectory following maternal cytomegalovirus infection in pregnancy: a longitudinal cohort study from the CMV-preg registry

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Abstract

Introduction: This study aimed to characterise emotional trajectories after maternal CMV diagnosis and to identify clinical factors associated with early and late psychological outcomes.

Methods: In this prospective Swiss registry, women with CMV infection completed validated questionnaires one week after diagnosis and maternal–fetal medicine consultation (T1) and at 32 weeks' gestation if the pregnancy continued (T2). Outcomes included well-being (WHO-5), anxiety symptoms (HADS), post-traumatic stress symptoms (PCL-5), depression symptoms (EPDS), and decision regret (DRS). Score evolution was assessed using paired Wilcoxon tests. Emotional trajectories were analysed using multivariable linear regression models at T1, at T2 adjusted for baseline values, and for score changes over time.

Results: At T1, emotional burden was high, with reduced well-being in 52.9%, clinically significant anxiety in 36.2%, and post-traumatic stress symptoms in 31.8%. All scores improved significantly over time ($p<0.001$). Valaciclovir exposure was associated with higher wellbeing at T1, lower anxiety, and lower post-traumatic stress symptoms. Fetal anomalies were associated with lower well-being at T1, higher anxiety at T2, higher depressive symptoms, and worsening anxiety over time. Having an amniocentesis performed (regardless of CMV result) was associated with higher post-traumatic stress symptoms shortly after diagnosis but with lower depressive symptoms at T2. Screening acceptability was high at T1 and T2 (89.4% and 98.6%), while decisional regret decreased from 18.3% to 4.3%.

Conclusion: Emotional distress after CMV diagnosis is frequent but follows distinct, time-dependent trajectories. These findings support CMV screening within structured counselling pathways and help identify women at risk for persistent distress who may benefit from targeted psychological support.



P041

Priority topics in the diagnosis and management of Cytomegalovirus in pregnancy: a targeted guideline from the Belgian Healthcare Knowledge Centre (KCE)

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Abstract

1) Introduction/Aim *Cytomegalovirus* (CMV) is the leading cause of congenital infection in developed countries and a major contributor to childhood hearing loss and neurodevelopmental impairment. Emerging evidence, particularly regarding antenatal antiviral therapy, alongside substantial variability in clinical practice related to CMV diagnosed during pregnancy, led the Belgian Healthcare Knowledge Centre (KCE) to develop an updated clinical practice guideline.

2) Materials and Methods The guideline was developed using GRADE methodology. Targeted priority research questions on diagnosis, treatment, and management were identified through stakeholder consultation. Systematic literature searches were conducted in MEDLINE, Embase, and the Cochrane Library. Recommendations were formulated considering the quality of available evidence, benefits, harms, patient preferences, and resource implications.

3) Results Serological testing (IgM or IgG changes) was found unreliable for diagnosing non-primary maternal infection and is not recommended. High-dose valaciclovir (8 g/day) may be offered as secondary prevention in early primary maternal infection (periconceptional or 1st trimester infections), although there is no sufficient evidence to currently justify its routine use for tertiary prevention. Negative amniocentesis may be reassuring (if performed > 18 weeks and > 8 weeks after maternal infection in untreated patients, or after 21 weeks and at least 7 weeks after maternal infection if treated) and may not justify routine enhanced imaging. Routine earlier amniocentesis with shortening of valaciclovir treatment (at least seven weeks of treatment, at least until 21 weeks) may not be currently justified. The evidence level for all recommendations was found to be generally very low.

4) Conclusions This guideline provides a pragmatic framework for CMV management in pregnancy despite existing evidence gaps. In practice, it supports shared decision-making between clinicians and patients, and it outlines key priorities for future research to strengthen the evidence base and refine recommendations.



P042

Improving the serological staging of CMV infection in pregnant women using an epitope-specific IgM microarray

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Abstract

Introduction First-trimester screening aims to identify pregnant women with CMV primary infection, for whom Valaciclovir treatment is recommended to prevent fetal transmission. According to current guidelines, screening comprises anti-CMV IgG and IgM testing, followed by IgG avidity assessment when IgM testing is reactive. Treatment is indicated for women with low avidity or those with intermediate avidity confirmed by a second assay.

Here, we evaluated whether comprehensive IgM analysis using an epitope-specific (ETS) microarray containing 10 CMV antigens (p38, p130, IE2, gL, p65, p150.XP1, p150.1, p52, and IE1) might improve the identification of recently infected women at risk.

Methods The sample cohort comprised 57 serum samples from pregnant women with positive or borderline-positive CMV IgM ELISA results obtained as part of routine diagnostics (2014–2022), including 16 low-avidity, 11 intermediate-avidity, and 30 randomly selected high-avidity control samples (all assays by Euroimmun).

For the study, samples were retested using the VIDAS CMV IgG avidity assay (bioMérieux) and classified as low risk (at least one test showing high avidity) or high risk (both tests showing low or intermediate avidity). The samples were then tested using the Viramed CMV ViraChip IgM microarray. The discriminatory ability of IgM antibodies against different antigens was evaluated by ROC analysis.

Results IgM antibodies against p130 and p150.1 showed the highest ability to discriminate between high- and low-risk groups, with AUCs of 0.91 and 0.87, respectively (Anti-p130 IgM: sensitivity/specificity: 95%/84%, optimal cutoff: >43 units; Anti-p130 IgM; sensitivity/specificity: 90%/76%, optimal cutoff: >327 units). A conditional tree analysis combining quantitative Euroimmun IgM and Anti-p130-IgM levels increased the AUC to 0.94.

Conclusion IgM antibodies against p130 and p150.1 showed excellent performance in identifying pregnant women with primary CMV infection, suggesting that comprehensive ETS IgM analysis using a microarray could supplement avidity testing to identify pregnant women at risk for fetal transmission.



P043

Retrospective Diagnosis of CMV-Related Hearing Loss: The Experience of Two Portuguese Centers

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Abstract

Introduction: Congenital CMV infection is the leading non-genetic cause of sensorineural hearing loss (SNHL) in children. Retrospective diagnosis of congenital CMV infection in children with hearing loss can be achieved through PCR analysis of neonatal dried blood spots (DBS). Since 2000, this methodology has been used at Centro Hospitalar Cova da Beira (Covilhã, Portugal; Center 1) and, since 2004, at Faculdade de Ciências Médicas (Lisbon, Portugal; Center 2).

The aim of this study was to review the combined experience of these two centers in the retrospective diagnosis of congenital CMV infection in children with hearing loss.

Materials and Methods: The age of the children ranged from 3 weeks to 13 years. Children with unilateral or bilateral hearing loss of previously unexplained etiology were included.

The same laboratory methodology was used in both centers. Briefly, DNA was extracted using a heat-induced extraction method. CMV DNA was then detected by a nested PCR.

Results: A total of 255 DBS cards were analyzed, 109 from Center 1 and 146 from Center 2. Overall, 37 samples were positive for CMV DNA (37/255; 14.5%). Twenty positive cases were identified in Center 1 (20/109; 18.3%) and 17 in Center 2 (17/146; 11.6%).

No statistically significant difference in positivity rates was observed between the two centres (18.3% vs. 11.6%; chi-square test, $p = 0.14$).

Conclusions: The rate of CMV detection among children with SNHL in our study was consistent with that reported in most published series (10–20%), but lower rates have been already described. In our study a higher positivity rate was observed in Center 1, but without statistical significance. If this trend reflects a true difference between centers, it is most likely attributable to differences in patient selection, as the laboratory methodology was identical in both institutions.



P045

Neurodevelopmental Outcomes in Congenital Cytomegalovirus Infection: A Bayesian Model-Averaged Meta-Analysis

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Abstract

Background: Congenital cytomegalovirus (cCMV) infection is the most common congenital infection worldwide and an important cause of long-term neurodevelopmental impairment. However, the magnitude of neurodevelopmental deficits remains uncertain, particularly among children with asymptomatic infection.

Aim: To quantify the association between cCMV infection and neurodevelopmental outcomes using Bayesian model-averaged (BMA) meta-analysis.

Methods: Embase, MEDLINE, PsycInfo, and Scopus were searched for studies evaluating neurodevelopmental outcomes in children with cCMV classified as symptomatic or asymptomatic at birth and assessed using standardized tests. Continuous outcomes were pooled as standardized mean differences (SMD), with negative values indicating worse performance. BMA meta-analysis estimated pooled effects and quantified evidence using Bayes factors (BF10). Results are presented as pooled SMDs with 95% credible intervals (CrI) and posterior probabilities of a neurodevelopmental difference (PPD). PROSPERO: CRD420251065006.

Results: Children with symptomatic cCMV showed substantially poorer neurodevelopmental performance than controls (4 studies; SMD −0.83, 95% CrI −1.31 to −0.22), with strong evidence for an effect (BF10=22.12; PPD=0.96). In contrast, children with asymptomatic cCMV showed little evidence of impairment (18 studies; SMD −0.07, 95% CrI −0.17 to 0.04), with moderate evidence favoring no effect (BF10=0.25; PPD=0.20). Among 6 studies reporting outcomes irrespective of symptom status, the pooled effect suggested a small adverse association (SMD −0.19, 95% CrI −0.31 to 0.03), although evidence for an effect was weak (BF10=1.50; PPD=0.60).

Conclusions: Symptomatic cCMV is associated with clinically meaningful neurodevelopmental impairment, whereas asymptomatic cCMV shows little evidence of adverse effects. Symptom status at birth appears to be a key determinant of risk and should inform follow-up strategies. As universal newborn screening increases the number of diagnosed infants, intensive neurodevelopmental surveillance may be prioritized for children with symptomatic cCMV.



P046

The Australian Congenital CMV Register (ACMVR): measuring developmental outcomes and antiviral therapy use to drive clinical change

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Abstract

Introduction Congenital cytomegalovirus (cCMV) is the leading infectious cause of childhood hearing loss and neurodevelopmental disability. Evidence describing antiviral use and outcomes in affected children is limited. We aimed to describe antiviral therapy use and early developmental outcomes in Australian children with cCMV.

2) Methods The cCMV Register collects prospective data on children diagnosed with cCMV in Australia. We performed descriptive analyses of cases enrolled between 2020 and 2024, including neonatal characteristics, newborn hearing screening (NHS) and audiologic outcomes, antiviral therapy use, and 12-month developmental screening.

3) Results Among 232 children (50% male; 93% singletons; 75% term), 52% (88/170) had signs of infection in the neonatal period, most commonly jaundice, intrauterine growth restriction, and microcephaly. Nearly half (49%, 87/179) did not pass newborn hearing screening (NHS); of these, 63% (55/87) received antiviral therapy. Among those who passed NHS, 38% (35/92) were treated. By 12 months, 11% (10/92) of children who initially passed NHS had developed late-onset hearing loss; six had received antiviral therapy. Developmental data at 12 months were available for 40 children, with parent-reported concerns in gross motor (35%, 14/40), fine motor (20%, 8/40), and communication (17%, 7/40) domains.

4) Conclusions This registry represents an important data platform for tracking cCMV treatment and outcomes. Findings to date demonstrate substantial variability in antiviral prescribing. The data also highlights the progressive nature of hearing loss in cCMV, with late-onset loss observed despite initial screening results. These results illustrate the critical need to determine whether antiviral therapy can halt or modify hearing progression, and to identify which subgroups are most likely to benefit. Ongoing prospective data collection, particularly in asymptomatic cCMV, will be essential to inform future evidence-based clinical pathways.



P047

Neonatal CMV viral load in blood and urine is associated with disease severity at birth and long-term outcome in congenital CMV infection: An international cCMVnet study

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Abstract

Introduction Congenital cytomegalovirus (cCMV) infection is a leading cause of sensorineural hearing loss and neurodevelopmental impairment. The prognostic value of neonatal CMV viral load remains controversial. We evaluated the association between neonatal CMV viral load in blood and urine, disease severity at birth, and long-term outcomes in a large international cCMV cohort.

Materials and Methods This multicenter study included infants with confirmed cCMV infection enrolled in the Congenital CMV Network (cCMVnet) from 91 centers across 12 countries. Inclusion criteria were quantitative viral load measurement in blood and urine within the first 28 days of life and ≥6 months of follow-up. Viral loads were analyzed as continuous variables and according to median, quartile, and ROC-derived thresholds. Associations with symptomatic disease at birth and long-term sequelae, defined as SNHL, epilepsy, visual impairment, and/or neurodevelopmental impairment, were assessed.

Results A total of 1,147 infants were included. Symptomatic infants had higher urinary (median [IQR]: 6.72 [5.79–7.47] vs 6.48 [5.38–7.20] log10 IU/mL, p<0.0001) and blood viral loads (3.67 [3.04–4.34] vs 3.34 [2.70–3.91] log10 IU/mL, p<0.0001) than asymptomatic infants. Higher urinary and blood viral loads were associated with hearing loss and the composite outcome of long-term sequelae. Higher urinary viral load was additionally associated with motor impairment, whereas higher blood viral load was associated with visual impairment. Increasing viral load was associated with a progressively greater risk of long-term sequelae, supporting a dose–response relationship. No clinically useful threshold could be identified.

Conclusions

Higher urinary and blood CMV viral loads were associated with symptomatic disease at birth and long-term sequelae, particularly hearing loss. Neonatal CMV viral load behaved as a continuous marker of disease burden rather than a dichotomous predictor. These findings support the incorporation of viral load into multivariable prognostic models rather than its use as a standalone biomarker.



P048

One-year neurodevelopmental outcomes among children with congenital CMV in New York State, US

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Abstract

Introduction/Aim: Neurodevelopmental outcomes vary widely among children with congenital cytomegalovirus (cCMV). In the United States (US), universal screening for cCMV is infrequently performed. Limited data therefore exist regarding cCMV outcomes among US infants, particularly those with asymptomatic infection. We sought to determine the one-year neurodevelopmental outcomes of infants identified by universal newborn cCMV screening.

Methods: PROACTIVE NYS is a longitudinal study of children with cCMV identified through universal newborn dried blood spot screening or routine clinical care in New York State, US from 2023 – 2024 and enrolled with parental consent. We administered the Ages and Stages Questionnaire-3 (ASQ-3) and ASQ:Social-Emotional-2 (ASQ:SE-2) assessments at 12 months old to screen for neurodevelopmental delays. We defined cCMV disease as having any cCMV-related abnormality within the first month of life and cCMV infection as having no identified abnormalities. We performed descriptive analyses, Wilcoxon rank-sum testing to assess associations between cCMV disease and neurodevelopmental assessment scores, and Fisher's exact testing to assess associations between cCMV disease and neurodevelopmental referral recommendations.

Results: Among 107 participants, 12-month ASQ-3 was completed by 39 (36%), including 19/39 (49%) with cCMV disease, and 12-month ASQ:SE-2 was completed by 40 (37%), including 20/40 (50%) with cCMV disease. Failure rates for the ASQ-3 sub-domains were low (3-5% of respondents). Similarly, overall ASQ-SE:2 scores were within the "low or no risk" zone (score <50), with a mean 18.1 (SD 15.3). No association was found between cCMV disease and ASQ-3 sub-domain or total score or ASQ:SE-2 score. Neurodevelopmental referral rates did not differ significantly by presence of cCMV disease.

Conclusions: Among children with cCMV disease and infection, few had neurodevelopmental delays at one year. Findings may be limited by participant attrition and small sample sizes. Longer follow-up monitoring is needed to better understand cCMV neurodevelopmental outcomes, particularly those deemed asymptomatic at birth.



P050

Cytomegalovirus-based viral vectors elicit robust systemic and tissue-resident immune response against SARS-CoV-2 antigens

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Abstract

1) Introduction

The COVID-19 pandemic highlighted the need for vaccines that provide durable protection. Current COVID-19 vaccines face challenges such as waning immunity and limited mucosal protection, contributing to reinfections and ongoing viral transmission. These limitations underscore the importance of developing next-generation vaccines that can induce tissue-specific and systemic immune responses. Cytomegalovirus (CMV) represents a promising vaccine vector platform due to its ability to elicit robust and long-lasting immunity. The aim of this study was to develop murine CMV (MCMV)-based vaccine vectors expressing the SARS-CoV-2 Spike (S) protein and to evaluate the impact of vector design and immunization route on the quality of the induced immune responses.

2) Materials /Methods

MCMV-based vaccine vectors expressing the S protein were generated using either a wild-type or an immunologically attenuated viral backbone expressing the NKG2D ligand RAE-1γ. Mice were immunized intraperitoneally (IP) or intranasally (IN). Humoral and cellular immune responses were assessed by measuring S-specific antibody titers in serum and S-specific CD8+ T-cell responses in blood, spleen, and lungs.

3) Results

IP administration induced higher titers of long-lasting S-specific antibodies in serum than IN immunization. Both immunization routes elicited systemic S-specific CD8+ T-cell responses; however, their kinetics and phenotypic characteristics differed substantially. Overall, IP immunization with both vectors generated higher frequencies of S-specific CD8+ T cells in blood, spleen, and lungs, with most cells displaying a KLRG1+ CD127− phenotype. Importantly, IN immunization with the recombinant MCMV vector expressing RAE-1γ resulted in robust accumulation of S-specific CD8+ T cells exhibiting markers of tissue residency in the lungs, exceeding levels induced by licensed COVID-19 vaccines.

4) Conclusions

CMV-based vaccines represent a versatile platform for tailoring immune responses through vector engineering and route of administration. These approaches can influence both the magnitude and quality of immunity, supporting the development of next-generation vaccines against respiratory pathogens.



P051

Longitudinal analysis of HCMV-specific T-cell function reveals stable immune profiles but divergent antiviral control in older adults

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Abstract

Human cytomegalovirus (HCMV) is a globally prevalent herpesvirus that establishes lifelong latency, with reactivation usually controlled by $CD4^+$ and $CD8^+$ T-cell responses. In older people, overt HCMV disease is uncommon, yet lifelong carriage is associated with T-cell memory remodelling and increased mortality risk. Evidence from frail older cohorts, together with detection of HCMV genomes in urine, suggests persistent carriage and low-level reactivation may act as co-morbidity factors by altering immune efficacy despite retention of measurable antiviral T-cell function.

In our previous AQUARIA study, we used an in vitro viral dissemination assay to assess antiviral effector capacity of PBMCs, $CD4^+$ T cells, $CD8^+$ T cells and NK cells from young and older HCMV-seropositive donors. Although absolute immune cell numbers and HCMV-specific IFNγ T-cell responses showed no age-related defect, T cells from older donors were less able to control HCMV dissemination in vitro. These findings indicated that cell frequency and cytokine production may not fully capture age-associated changes in antiviral control.

In this follow-up study, we extend these observations using longitudinal sampling, viral dissemination assays and spectral flow cytometry. Some donors have been analysed across multiple time points spanning up to eight years. HCMV-specific IFNγ, IL-10 and TNFα responses to peptide pools, myeloid and lymphoid cell numbers, and T-cell memory subset distributions remain stable within donors. Viral dissemination assays on matched donors in 2022 and 2024 continue to identify impaired T-cell-mediated viral control in older donors, with 2026 analyses underway.

Activation-induced marker analysis indicates enrichment of HCMV-specific $CD4^+$ and $CD8^+$ T cells within central and effector memory subsets. We are investigating whether reduced antiviral function in CMV-specific T cells from older donors reflects altered checkpoint inhibition or insufficient co-stimulation. Preliminary analyses highlight differential inhibitory receptor expression, including PD-1 and TIGIT, on $CD8^+$ T cells, when comparing good and poor HCMV controllers.



P052

Maternal and household predictors of congenital cytomegalovirus (cCMV) in a diverse population undergoing universal neonatal screening

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Abstract

Introduction: Our current knowledge of the protective effectiveness of maternal immunity and of maternal ethnic-demographic characteristics predicting the risk of cCMV is limited by the lack of universal neonatal and maternal CMV screening in most countries. Here, we investigated maternal predictors of cCMV in a diverse population undergoing universal neonatal screening. Our objectives were to: 1) define the effect of maternal preconception immunity, when co-assessed with ethnic-demographic characteristics, on the risk of cCMV; and 2) identify predictors of cCMV in the subgroup of mothers with preconception immunity.

Materials and Methods: A case-control study conducted at two Jerusalem hospitals (April 2022-March 2025). All newborns with parental consent were tested for cCMV in eight-sample pools. Each cCMV-positive infant was matched with cCMV-negative infants tested in the same pools. CMV serostatus and ethnic-demographic characteristics were compared between mothers of cCMV-positive (cases; N=174) and cCMV-negative (controls; N=1003) infants.

Results: Maternal CMV seropositivity rate was higher in the control-group (89.7%; 744/829) compared with the case-group (53.2%; 83/156) ($p<0.001$). In multivariable logistic regression analysis, CMV sero-negativity (adjusted OR [AOR], 7.8; 95% CI, 5.16-11.81) and having a child younger than 24 months of age (AOR, 2.04; 95% CI, 1.17–3.57) were independently associated with increased risk for cCMV, whereas older maternal age (AOR, 0.93; 95% CI, 0.90–0.97) and Ultra-Orthodox (UO) affiliation (AOR, 0.51; 95% CI, 0.35–0.75) were independently associated with reduced risk for cCMV. In seropositive mothers (N=827), older maternal age (AOR, 0.94; 95% CI, 0.90–0.98) and UO affiliation (AOR, 0.55; 95% CI, 0.35–0.88) remained independently associated with reduced risk for cCMV.

Conclusions: The study identifies real-world predictors of cCMV and maternal correlates of protection, highlighting the protective effect of maternal immunity as influenced by demographic and household characteristics. The findings will inform prenatal risk assessment and prevention strategies.



P053

Dual-purpose Dried Blood Spot Workflows: Combining CMV Detection and Proteomics in Support of Future Risk Stratification

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Abstract

Background: Universal newborn screening for congenital cytomegalovirus (CMV) has gained increasing attention in recent years and has been implemented in states in the US. However, more than 90% of infected infants remain asymptomatic and do not require treatment, highlighting the need for biomarkers that can identify those at risk of developing long-term sequelae. Recent advances in high-throughput proteomic technologies have created new opportunities for biomarker discovery using neonatal dried blood spots (DBS). We evaluated whether a protein extraction procedure designed for proteomic analyses affects the performance of subsequent CMV detection using polymerase chain reaction (PCR) from the same DBS.

Methods: DBS were prepared using CMV-positive whole blood at three viral loads (10,000, 5,000 and 2,500 IU/ml). Three independent dilution series were generated, each analysed in triplicate. DNA extraction and PCR-based CMV assays were performed either directly or following a protein elution step. Cycle threshold (Ct) values were compared between workflows. Linear regression analyses were performed separately for each workflow to assess the relationship between CMV viral load and Ct value, and regression equations were compared using Chow test.

Results: Detection rates and Ct values were similar with and without protein elution across all evaluated viral loads. Linear regression analyses demonstrated comparable relationships between CMV viral load and Ct value in both workflows, and the Chow test showed no difference between regression equations (p=0.30).

Conclusions: Protein extraction from neonatal DBS did not substantially impair subsequent CMV PCR, supporting the feasibility of a dual-purpose workflow. By enabling both molecular CMV detection and proteomic biomarker discovery without additional DBS consumption, this approach may maximise the information obtained from newborn screening samples. Such workflows could facilitate future biomarker studies aimed at identifying infants with congenital CMV at greatest risk of long-term sequelae and potentially those most likely to benefit from follow-up and intervention.



P054

CMV-Associated Cytokine Remodeling and IL-17 Signaling in Glioblastoma

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Abstract

1) Introduction

Glioblastoma (GBM) is the most aggressive primary brain tumor in adults, with limited treatment options and poor patient survival. Human cytomegalovirus (HCMV) has been detected in most GBM tumors and has been proposed as an important factor for tumor progression and patient outcome. Because radiotherapy can trigger HCMV reactivation, understanding the immunological consequences of viral activity in GBM is of particular interest.

2) Materials and Methods

In the VIGAS II study, in which GBM patients are treated with Valganciclovir to assess its effect on patient outcome, we investigated the relationship between HCMV status and immune responses in 109 patients with GBM. Patients were stratified according to HCMV serology into seronegative, seropositive non-reactivated, and seropositive reactivated groups. Cytokine profiles were assessed in plasma samples, and the effects of HCMV infection on IL-17 signaling were examined in GBM cell lines.

3) Results

Our analyses revealed that HCMV seropositivity was associated with broad changes in circulating cytokine patterns, while viral reactivation resulted in additional immune alterations. In particular, reactivated patients displayed elevated levels of IL-17D. Furthermore, HCMV infection in vitro of GBM cells increased the expression of IL-17D as well as the IL-17 receptors IL-17RA and IL-17RD in GBM cells. Functional studies showed that both IL-17A and IL-17D enhanced GBM cell proliferation and invasiveness, suggesting a potential role for IL-17 signaling in tumor progression.

4) Conclusion

Together, our findings indicate that HCMV status is linked to distinct cytokine profiles in patients with GBM and identify IL-17 signaling as a pathway potentially involved in HCMV-associated tumor-promoting effects. Ongoing studies will further characterize immune cell populations associated with HCMV control and reactivation to better understand their impact on disease progression and therapeutic response.



P055

The Role of Uterine NK cells in the Control of HCMV

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Abstract

Congenital CMV infection occurs in between 0.5–1% of live births worldwide and is the leading infectious cause of birth defects underpinning the need for the development of an effective CMV vaccine. Consequently, identifying and understanding tissue-specific immune responses that prevent vertical transmission is a major research question.

Natural killer (NK) cells can develop adaptive, memory-like responses to viral exposure, including to human cytomegalovirus (HCMV) and HIV. We have previously shown that human tissue-resident NK cells in the liver (lrNK) control HCMV more effectively than circulating NK (cNK) cells from the same individual. Furthermore, NKG2C and CD2 were expressed by adaptive lrNK cells and higher expression was associated with better viral control.

We aimed to investigate whether, similar to tissue-resident NK cells in the liver, uterine NK (uNK) cells can also respond to and control HCMV and, additionally, whether specific subsets could be better able to control HCMV replication. To do this, NK cells were isolated from the blood and uterine mucosa from donors in their first or third trimesters of pregnancy and characterised by flow cytometry with donors further stratified by HCMV serostatus. Our data show that in the third trimester we observed significant differences in the expression of markers indicative of HCMV NK cell adaptation, e.g. NKG2C, CD2 and KIRs, that correlated with HCMV serostatus of the donors (n>20). Furthermore, initial findings from first-trimester samples suggest that comparable phenotypes associated with HCMV serostatus are observed.

Finally, preliminary data from viral dissemination assays (n=3) suggests that uNK cells are better able to control HCMV replication than paired cNK cell counterparts in vitro.

In summary, we have observed that HCMV infection induces an adaptive phenotype in tissue resident uNK cells and that they potentially have greater anti-viral activity in vitro with clear implications for understanding congenital infection in vivo.



P056

Double Jeopardy: Congenital CMV and Holder Pasteurisation Deplete Breast Milk IgA, with Clinical Consequences for Neonates who are Preterm

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Abstract

Background

For preterm infants, breastmilk is beyond nutrition; it contributes to their immune system. Yet two threats converge against this protection: congenital CMV (cCMV) and Holder pasteurisation (HoP), the very intervention designed to make donor milk safe. We investigated whether cCMV and HIV exposure suppress breast milk humoral immunity, whether this deficit carries clinical cost, and whether pasteurisation diminishes immunological benefits.

Methods

Mother-infant dyads (infants <1.5 kg, <14 days) were enrolled. PCR quantified CMV from paired breastmilk and infant saliva. Total and polyreactive IgA/IgG were measured by Luminex across fresh, HoP, and microwave-pasteurised breastmilk conditions. Clinical progress was recorded weekly.

Results

Twenty-six dyads were enrolled; median gestational age 28 [28–29] weeks, birthweight 1027.5 [913.75–1200] g, maternal age 32.5 [25.75–38] years. Three infants had cCMV and four were HIV-exposed; gestational age and birthweight did not differ between exposure groups ($p=0.63$, $p=0.70$). All IgA levels in unpasteurised breastmilk highly correlated with paired infant salivary levels ($\rho \geq 0.95$; $p<0.001$). Lower total IgA ($p=0.04$) and higher polyreactive IgA ($p=0.02$) levels were observed in breast milk from mother-infant dyads in which the infant had cCMV. Higher CMV viral load inversely correlated with polyreactive IgG ($\rho=-0.738$) and total IgA ($\rho=-0.632$). HIV exposure was similarly associated with lower total IgA ($p=0.05$) and higher polyreactive IgA ($p=0.01$). In turn, lower total IgA in breastmilk was associated with respiratory deterioration ($p=0.016$). HoP significantly reduced total IgA/IgG ($p<0.001$); microwave pasteurisation preserved all antibody measures ($p>0.208$).

Conclusion

Breastmilk composition supports infant mucosal immunity, and antibody-mediated viral suppression can occur at the mucosal interface. CMV/HIV exposure may diminish humoral immunity in breastmilk and contribute to morbidity in preterm infants. Microwave pasteurisation may be preferable over HoP in preserving breastmilk antibodies, and verification in larger studies could inform strategies to reduce morbidity in preterm infants.



P057

Strain-specific immunity and cytomegalovirus reinfection in seropositive pregnant women

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Abstract

Introduction

Congenital cytomegalovirus (CMV) infection is a leading cause of childhood hearing loss and neurodevelopmental impairment. Most congenital infections occur in women who are CMV-seropositive before pregnancy, often due to reinfection with a new CMV strain. This study aimed to determine the frequency of CMV reinfections among seropositive pregnant women and to assess the relationship between reinfection and CMV shedding.

Methods

Pregnant women with CMV IgG positivity were enrolled after their first prenatal visit and before 20 weeks' gestation, then followed prospectively. Demographic data were collected, and blood, urine, saliva, and vaginal samples were obtained at enrollment and at scheduled intervals throughout pregnancy and immediately postpartum. Maternal sera were tested for strain-specific anti-CMV antibody responses to four unique epitopes. Reinfection was defined as the development of a new strain-specific antibody during pregnancy. All specimens were tested for CMV DNA using real-time PCR.

Results

Among 277 enrolled women, the mean age was 27.1 years (±5.5), and 78.0% were non-Hispanic Black, 87.7% had public or no health insurance, and 88.9% lived in high-deprivation neighborhoods (Area Deprivation Index, ADI > 60). The majority of women (81.9%) were multigravida. CMV reinfection occurred in 23.4% (95% CI, 18.6–28.9). Reinfection was more common in women lacking baseline strain-specific antibodies (40%) than in those with ≥1 antibody at enrollment (16.5%; OR 3.43, 95% CI, 1.9–6.1). CMV shedding occurred in 41% of participants during follow-up. Shedding rates did not differ between women with reinfection and those without a new strain-specific antibody.

Conclusions

In this urban cohort of CMV-seropositive pregnant women, reinfections were frequent, as was CMV shedding. The presence of ≥1 strain-specific antibody at baseline was associated with reduced reinfection risk, suggesting a protective role for strain-specific immunity.



P058

Risk Factors for Maternal Cytomegalovirus Infection and Shedding: Implications for Prevention in Pregnancy

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Abstract

1) Introduction/Aim

This study aimed to characterize exposures and predictors of cytomegalovirus (CMV) seropositivity among pregnant women and to assess CMV shedding among CMV-seropositive women.

2) Materials and Methods

A total of 561 pregnant women were screened by CMV IgG and CMV IgM using an enzyme-linked immunosorbent assay prior to 20 weeks' gestation as part of a CMV behavioral risk reduction trial. All seropositive women underwent PCR testing of blood, saliva, urine, and vaginal specimens. Maternal demographic characteristics, medical and obstetric history, exposures to young children, and sexual exposures were analyzed by serological status.

3) Results

CMV seroprevalence was 75.9% (95% CI, 72.2 – 79.4%). Among 135 seronegative women, 5 seroconverted during pregnancy (3.7%, 95% CI, 1.2–8.4%). Two infants were diagnosed with cCMV (4.6 per 1000): one following maternal seroconversion, and one born to a seropositive mother. Among seropositive women, 37.6% (95% CI, 32.9 – 42.3%) shed CMV during pregnancy in ≥ 1 compartment. Logistic regression identified independent associations between seropositivity and race/ethnicity (non-Hispanic Black and Hispanic White vs. non-Hispanic White), multigravidity, and longer duration of sexual activity. Direct care of young children (aOR = 1.8, 95% CI, 1.1–3.0) and sexually transmitted infections (STIs) during pregnancy (aOR = 2.4, 95% CI, 1.3–4.2) were also independently associated with seropositivity. Women with both exposures—STIs and childcare—were over four times more likely to be seropositive (aOR = 4.2, 95% CI, 1.9–9.3). CMV-seropositive women with and without viral shedding showed similar exposure patterns during pregnancy.

4) Conclusions

CMV seropositivity was common in this cohort, with substantial rates of viral shedding and measurable risk of congenital infection. Demographic factors, childcare exposures, and STIs were key predictors of seropositivity, underscoring the need for targeted prevention strategies in pregnancy.



P059

Re-evaluation of HHV-6 and EBV Shedding Alongside Cytomegalovirus (CMV) Reactivation in Breast Milk of Healthy CMV-Seropositive Women

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Abstract

Introduction:

Previous studies demonstrated a high rate of CMV reactivation in the lactating breast and subsequent shedding in seropositive mothers' breast milk (BM), leading to CMV-transmission and potentially postpartum symptomatic infection in preterm or very low birthweight infants, causing multi-organ manifestations.

In contrast, earlier BM-studies concerning shedding of other Herpesviruses, found no evidence of HHV6-DNA, challenging the assumption that BM presents a vector for HHV6. In endemic HTLV-areas in Japan was shown that BM is not a significant source of EBV and HHV6 infection. Nevertheless, shedding of EBV in BM was associated with subclinical Mastitis (SCM) and with HIV-shedding of mothers with SCM, whereas higher BM-EBV-loads appeared in mothers with malaria in Kenya.

These observations along with the established knowledge on CMV-shedding suggest that BM may serve a route of EBV-transmission, even though there are doubtful findings in healthy mothers.

Materials- Methods:

A total of 78 samples (BMs) were analyzed using short-term- (18h), long-term- fibroblast microcultures (10d) and Real-Time-qPCR (CMV, HHV6, EBV). 17 were pooled breast milk powder preparations (PBMs; >5 donor samples per pool) provided of a Donor BMs-Bank. The remaining 61 fresh-breast-milk samples (FBMs) derived from 30 mothers (1-346 days postpartum).

Results - Conclusion:

Among the PBMs, 12/17 tested positive for CMV-DNA including 2 that were also HHV6-DNA positive. Among the FBMs, 49/61 tested positive for CMV-DNA and in only 1 one of them was detected HHV-6-DNA 9 days postpartum, exactly as with CMV-DNA. No FBM tested positive for EBV-DNA. Overall, CMV-DNA was detected in 61 samples and HHV-6-DNA in only 3 samples. CMV-specific cytopathic effects were observed in 35 samples in short-term cultures and 36 samples in long-term cultures, reflecting partial viral inactivation in BM, likely attributable short-term pasteurization of BM samples.

CMV shedding was frequent, whereas HHV-6 shedding was rare and EBV DNA was undetectable in BM from healthy CMV-seropositive women.



P060

Primary CMV infection in pregnancy: is there an additional diagnostic or predictive value of immunoblot analysis focusing on gB1 antibodies?

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Abstract

Aim:

To evaluate the utility of gB1 in immunoblot analysis for determining the timing and transmission risk of maternal CMV infection in pregnancy.

Methods:

Observational study including 151 pregnant women referred for suspected primary CMV infection at the University Hospital Tübingen between September 2023 and August 2025. CMV-specific IgG, IgM and IgG avidity were measured and CMV immunoblot assays were carried out. Associations between immunoblot gB1 band reactivity and CLIA IgG avidity were analyzed as well as the maternal–fetal transmission of CMV detected at the time of second-trimester amniocentesis.

Results:

Increasing CLIA IgG avidity was associated with a significantly increasing probability of IgG gB1, gB2 and avidity gB2 band positivity. Among cases with low CLIA IgG avidity (<15 %), absence of IgG avidity gB2 achieved the highest detection rate (>90 %) and absence of IgG gB1 the lowest false-positive rate (<10 %). Maternal–fetal CMV transmission at the time of amniocentesis occurred in women without gB1-specific IgG antibodies in 20 %, while CMV transmission occurred in those with gB1-specific IgG antibodies in only 4.6 %.

Conclusion:

Immunoblot band patterns correlate with CLIA IgG avidity and can help determine the timing of primary CMV infection in pregnancy, particularly when avidity results are inconclusive. Absent IgG gB1 reactivity provides a specific marker for very recent infection, while absent IgG avidity gB2 offers high sensitivity. In women with a primary CMV infection treated with valacyclovir, the presence of gB1-specific IgG antibodies identifies a subgroup with a lower residual risk of maternal - fetal transmission.



P061

Longitudinal Evolution of Brain MRI Abnormalities in Children with Congenital Cytomegalovirus Infection

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Abstract

Background

Congenital cytomegalovirus (cCMV) infection is the most common congenital infection worldwide and a major cause of neurological morbidity. Brain MRI performed during the neonatal period provides valuable information regarding central nervous system involvement and prognosis. However, data on the longitudinal evolution of MRI abnormalities beyond infancy remain limited.

Aim

To characterize the longitudinal evolution of brain MRI abnormalities in children with congenital CMV infection and describe imaging changes over time in treated and untreated patients.

Methods

We conducted a retrospective longitudinal study of children with confirmed cCMV infection who underwent brain MRI during the neonatal period and repeat MRI between 2 and 4 years of age. MRI findings at both time points were categorized according to the Alarcon MRI scoring system to facilitate standardized longitudinal comparison. Changes in white matter (WM) abnormalities, ventriculomegaly, temporal cysts, ventricular adhesions, calcifications, and other structural abnormalities were assessed.

Results

Sixteen children with cCMV infection underwent serial MRI evaluation. Eleven received antiviral treatment during infancy. No child demonstrated radiological deterioration on follow-up MRI. Improvement in MRI findings was observed in 3/16 children, all of whom were treated. Alarcon scores improved from 2 to 1 in two children and from 3 to 2 in one child. The most frequent changes included partial or complete resolution of WM abnormalities and reduction in the degree of ventriculomegaly. In contrast, calcifications, ventricular adhesions, caudothalamic cysts, and paraventricular germinolytic cysts generally remained stable over time. Overall, most structural abnormalities persisted but did not progress.

Conclusions

Brain MRI abnormalities in children with cCMV infection were predominantly stable or showed partial improvement during early childhood, with no evidence of radiological progression in this cohort. Longitudinal MRI assessment may contribute to a better understanding of the natural history of cCMV-related brain abnormalities.



P062

Limit of detection determination of CMV in umbilical cord blood (UCB)

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Abstract

Introduction/Aim UCB has a high concentration of haematopoietic stem cells and can be used as a graft source for patients with malignant or genetic diseases who may be cured by allogeneic hematopoietic cell transplantation (HCT), not having an HLA-matched family member or a volunteer unrelated adult donor. While there is no CE-IVD marked assay for CMV screening of cord blood donors, the commercial AltoStar® CMV PCR Kit 1.5/ AM16 workflow was validated for UCB to reduce the risk of viral transmission by the transplant.

Material UCB was collected and provided by a cord blood bank (Germany) and spiked with defined concentrations of 1st WHO International Standard for Human Cytomegalovirus (NIBSC code: 09/162). Serial dilutions were prepared for the limit of detection analysis, based on requirements described in guidelines by the German Federal Medical Association.

Methods 10 dilutions, ranging between 25 IU/ml and 3200 IU/ml, were tested with 8 replicates per dilution, and this in 5 different runs. The AltoStar® CMV PCR Kit 1.5/ AM16 workflow (altona Diagnostics) was used off-label for processing the UCB samples with the whole blood extraction protocol.

Results Using probit analysis, a specialized regression model of binomial response variables, the limit of detection for UCB was calculated with 338 IU/ml with a confidence interval of 265 IU/ml to 514 IU/ml.

Conclusion CMV screening of umbilical cord blood units is crucial for ensuring recipient safety in UCB transplantation. Off-label use of the AltoStar® CMV PCR Kit 1.5 with appropriate in-house validation for UCB allows reliable identification of potential CMV-infected UCB units.



P063

Is Routine Cerebrospinal Fluid Examination Still Relevant in Congenital Cytomegalovirus Infection?

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Abstract

Background: Current ECCI and Polish recommendations do not advocate routine cerebrospinal fluid (CSF) examination in infants with congenital cytomegalovirus infection (cCMV) and no longer consider CMV PCR positivity in CSF an independent indication for antiviral treatment. This approach may overlook infants whose only evidence of central nervous system (CNS) involvement is detectable CMV DNA in CSF.

Methods: In a predominantly prospective cohort study, neonates with confirmed cCMV who were hospitalised between 2018 and April 2026 were evaluated. Lumbar puncture was performed in 115/137 infants (83.9%) following parental consent. After exclusion of bloody CSF samples, 109 infants were included. Clinical presentation, neuroimaging findings, laboratory abnormalities and CSF results were analyzed. Infants with positive CMV PCR in CSF and confirmed first-trimester maternal infection or unknown timing of infection were offered six months of valganciclovir therapy. Infants whose parents declined treatment were intended to serve as controls.

Results: Abnormal CSF findings were detected in 18/109 (16.5%), all with positive CMV PCR in CSF; pleocytosis was present in 12/109 (11.0%). One infant had concomitant HHV-6 infection. All 18 infants received antiviral treatment.

Among infants with positive CMV PCR in CSF, only 3/18 (16.7%) had findings that would definitely qualify for antiviral treatment according to current recommendations, including sensorineural hearing loss, extensive neuroimaging abnormalities, chorioretinitis or hepatitis with thrombocytopenia. An additional 6/18 (33.3%) had only subtle abnormalities, most commonly mild vasculopathy or small subependymal cysts. Overall, 9/18 infants (50.0%) with positive CMV PCR in CSF would not have met current treatment criteria.

Conclusions: Half of the infants with CMV DNA detected in CSF would not have qualified for antiviral treatment under current recommendations. The clinical significance of isolated CSF CMV positivity and the impact of withholding treatment in these patients remain unknown and warrant further investigation.



P065

Hemophagocytic Lymphohistiocytosis as a Fatal Complication of Congenital Cytomegalovirus Infection: Two Cases from a Single Tertiary Center

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Abstract

Congenital cytomegalovirus (cCMV) infection is the most common congenital infection worldwide and a leading cause of neurodevelopmental impairment and sensorineural hearing loss. Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome resulting from uncontrolled immune activation. While cytomegalovirus is a recognized trigger of secondary HLH, HLH complicating congenital CMV infection is exceptionally rare. A review of the available literature identified only isolated reports of neonatal HLH associated with congenital CMV infection, underscoring the rarity of this entity.

Case presentations: We report two fatal cases of HLH developing during symptomatic cCMV infection despite antiviral therapy.

The first patient was hospitalized in 1997. Symptomatic cCMV was diagnosed at three weeks of age based on hepatomegaly, splenomegaly, thrombocytopenia, petechiae and intracranial calcifications. Intravenous ganciclovir was initiated. Despite treatment, the infant developed bicytopenia, hypofibrinogenemia, hypertriglyceridemia, marked hyperferritinemia and hemophagocytosis, fulfilling diagnostic criteria for HLH. The disease followed a fulminant course and resulted in death at three months of age.

The second patient was hospitalized in 2017. At birth, hepatosplenomegaly, thrombocytopenic purpura and profound sensorineural hearing loss were present. cCMV infection was diagnosed on day 14 of life and valganciclovir therapy was started. Despite early treatment, hepatosplenomegaly persisted and multiple cutaneous angiomatous lesions developed. At eight weeks of age, the infant presented with fever, progressive splenomegaly and disseminated petechiae. Laboratory evaluation demonstrated worsening thrombocytopenia with anemia, hypertriglyceridemia, hyperferritinemia and decreased natural killer cell count, consistent with HLH. Treatment included intravenous ganciclovir, CMV-specific hyperimmune globulin, corticosteroids and HLH-directed therapy; however, the patient died 10 days after HLH diagnosis.

Conclusions: HLH is an exceptionally rare but devastating complication of cCMV infection. Persistent or progressive hepatosplenomegaly, fever, worsening cytopenias and markedly elevated inflammatory markers in infants with cCMV should prompt evaluation for HLH. Early recognition may facilitate timely initiation of targeted therapy and improve outcomes.



P066

Postnatal CMV infection in extremely preterm infants: a single-center cohort study

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Abstract

Introduction: Postnatally acquired cytomegalovirus (CMV) infection has been associated with increased morbidity in preterm infants, including bronchopulmonary dysplasia (BPD) and necrotizing enterocolitis (NEC). However, evidence guiding treatment decisions and data on outcomes in this population remain limited.

Materials and methods: A retrospective single-center cohort study was conducted including neonates born between January 2021 and December 2024 at the Hospital of Lithuanian University of Health Sciences who developed postnatal CMV infection, defined as detection of CMV DNA in blood after 21 days of life. Clinical data were extracted from medical records. Outcomes, including BPD and NEC, were described, and exploratory comparisons between treated and untreated infants were performed using Fisher's exact test.

Results: A total of 33 infants were included with a median birth weight of 850 g (IQR 540-1236) and median gestational age of 26 weeks (IQR 23-29). CMV infection was diagnosed at a median age of 46 days (IQR 37-90). Most infants (90.9%) received breast or donor human milk, and 87.9% underwent red blood cell transfusions prior to diagnosis. At the time of CMV DNA detection, increased respiratory secretions (30.3%) and sepsis-like illness (30.3%) were the most common clinical manifestations, while neutropenia and thrombocytopenia (39.4% and 24.2%, respectively) were common laboratory abnormalities. Antiviral treatment was administered to 28 patients (84.8%), including intravenous ganciclovir (12.1%), oral valganciclovir (24.2%), or sequential intravenous-to-oral therapy (57.1%), with a median treatment duration of 24.5 days (IQR 14-77). BPD was diagnosed in 42.9% and NEC in 35.7% of infants. No deaths were reported.

Conclusions: Postnatally acquired CMV infection in extremely preterm, very low birth weight infants was frequently accompanied by respiratory symptoms and hematological abnormalities. Although antiviral treatment was commonly used, its impact on clinical outcomes could not be assessed due to low numbers of untreated patients.



P067

Current practices in antenatal CMV testing and management in Belgium

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Abstract

Introduction

In Belgium antenatal cytomegalovirus (CMV) screening is currently neither recommended nor reimbursed and antenatal treatment with high dose valaciclovir is currently at the charge of the patient. Our objective is to describe current practices regarding antenatal CMV screening, treatment with valaciclovir, and termination of pregnancy (TOP) in case of CMV maternal infection .

Method

We conducted an online survey of practitioners involved in pregnancy follow up or specialist management of CMV, between September and November 2024. Quantitative data from complete questionnaires were analysed using descriptive statistics, responses to open questions underwent thematic analysis.

Results

We analysed 298 complete responses. Most respondents (89.4%) reported prescribing CMV screening despite the absence of national recommendations or reimbursement. Screening objectives included foetal imaging follow-up, hygiene counselling, and prevention of vertical transmission with valaciclovir, while considering TOP was less frequently cited. TOP was perceived as occurring at all stages after maternal infection, but predominantly in cases of severe foetal involvement. Among foetal medicine specialists, 51.7% prescribed valaciclovir systematically, while others prescribed it non-systematically. Treatment acceptance and adherence were perceived as good, with cost identified as the main barrier.

Conclusion

Antenatal CMV screening is widespread in Belgium, influenced by emerging evidence for valaciclovir, despite heterogeneous use due to cost barriers. TOP may occur even in cases without severe foetal involvement. Our results underscore the need for high quality counselling and updated national guidance.



P068

A multiplexed loop-mediated isothermal amplification assay for the detection of congenital cytomegalovirus infection in newborns

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Abstract

Congenital cytomegalovirus (CMV) infection is a leading cause of sensorineural hearing loss and developmental delay in children. Congenital CMV infection is more often asymptomatic in newborns, with a large percentage (~90%) of newborns showing no signs of infection or clinical abnormalities at birth. With no available vaccines or prevention strategies during pregnancy, timely newborn screening for congenital CMV infection is essential in order to diagnose, evaluate, and determine the best treatment course for infected newborns as early as possible. We developed a multiplexed colorimetric loop-mediated isothermal amplification assay (LAMP) for the detection of multiple CMV gene targets with the goal of detecting CMV in newborn urine. Compared to the conventional method for newborn congenital CMV detection of quantitative polymerase chain reaction (qPCR), which has a 90-minute turnaround time and requires the use of specialized lab equipment, our single target LAMP assay requires only a constant heat source and gives a colorimetric result within 45 minutes. Moreover, the limit of detection of the two assays are not dissimilar. In our study, qPCR detected CMV in a range of $3.88x10^2$ copies/mL to $6.30x10^6$ copies/mL, whereas our single target colorimetric LAMP assay detected CMV in a range of $1x10^3$ copies/mL to $1x10^6$ copies/mL. To address the possibility of genetic variation of CMV in the environment, we multiplexed our colorimetric LAMP assay to achieve simultaneous detection of two highly conserved CMV gene targets in a single reaction tube. The multiplexed assay was able to detect CMV without false positives due to random amplification. Our LAMP assay provides a quicker point-of-care option for CMV detection. This assay could be applied to the large-scale screening of congenital CMV without the need for specialized laboratory equipment or highly trained personnel due to the colorimetric nature of the assay allowing for naked-eye detection.



P069

Universal Cytomegalovirus Antenatal Screening in General Practice - what do Australian general practitioners think?: A Cross-Sectional Survey

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Abstract

Introduction / Aim

Congenital cytomegalovirus (cCMV) is the leading infectious cause of childhood disability in high-income countries. Current Australian guidelines emphasize primary prevention through counselling on hygiene measures and targeted serological testing for women at increased risk of exposure. Some European guidelines recommend universal first-trimester CMV screening, with valaciclovir treatment for confirmed maternal primary CMV infection.(1) We aimed to evaluate GP readiness for universal CMV screening should Australian guidelines change.

Methods

Australian GPs were invited via professional networks and social media to participate in a cross-sectional online survey from May to October 2025. The survey assessed current CMV prevention practices and perspectives on a hypothetical two-stage CMV screening model: CMV IgG at the first antenatal visit, with seronegative women proceeding to CMV IgG and IgM testing at 12 weeks' gestation. Surveys were conducted using REDCapTM.

Results

A total of 263 GPs from all Australian states and territories participated; 56% had more than 10 years' experience. GP CMV risk-reduction practices were variable: 30% of reported counselling all pregnant patients about CMV and 36% reported performing targeted CMV testing in pregnancy. Almost all (98%) supported the proposed universal 2-stage CMV screening model if recommended by health authorities, with > 80% agreeing that it would be "easy" to implement. Metropolitan-based GPs were significantly more likely than non-metropolitan GPs to "strongly agree" that implementation would be easy. However, less than half respondents (47%, 115/243) were confident that specialist review would occur within 10 days of referral for suspected CMV infection.

Conclusions

Australian GPs appear highly supportive of health authority-recommended universal antenatal CMV screening to detect first-trimester maternal primary infection. However, implementation readiness is limited by concerns about timely access to specialist review. Clear referral pathways and service capacity for rapid specialist assessment will be essential before any policy shift towards routine universal screening.

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P070

Implementation of targeted first-trimester cytomegalovirus screening following antenatal risk-reduction counselling in Australia: a pilot study of feasibility, acceptability and psychological impact

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Abstract

Introduction: First trimester CMV serological screening to identify primary maternal infection and facilitate timely antiviral therapy is entering clinical practice in some high-income settings but has not yet been widely adopted in Australia.

Aims: This study evaluated the feasibility, acceptability and psychological impact of a structured CMV education and targeted serological screening pathway in an Australian tertiary hospital.

Methods: We conducted a prospective implementation study at the Mercy Hospital for Women in Melbourne, Australia. Women <12 weeks' gestation who were CMV IgG negative on early pregnancy investigations were offered CMV risk-reduction counselling and repeat CMV testing between 12+0 and 13+6 weeks' gestation. Feasibility outcomes included uptake of education and screening, and acceptability. Psychological impact was assessed using State Trait Anxiety Inventory at baseline and follow-up time points in second trimester and postpartum. Decisional regret was assessed at 3 weeks postpartum.

Results: Of 199 eligible participants, 137 were contactable, 84 received study information, and 66 (78%) consented to participate. After 7 exclusions (6 due to miscarriage), 54/59 participants (92%; 95% CI: 82%–97%) completed repeat CMV serology within the recommended gestational window, demonstrating the feasibility of integrating the pathway into routine antenatal care. No maternal CMV seroconversions were detected (0.0%; 95% CI: 0.0%–6.6%). Acceptability was high, with 93% of participants satisfied with the screening program and 96% indicating they would choose testing again. Anxiety scores were significantly lower at 15–20 weeks' gestation (mean difference 2.41, p=0.02) and postpartum (mean difference 3.1, p=0.04) compared with baseline, with no evidence of sustained screening-related anxiety. No participants reported decisional regret.

Discussion: Implementation of antenatal CMV prevention education and targeted first-trimester screening was feasible, acceptable to pregnant women, and not associated with adverse psychological effects. These results provide implementation evidence to inform future policy, guidelines, and larger effectiveness studies evaluating antenatal CMV screening.



P071

Impact of antenatal cytomegalovirus screening on knowledge and attitudes of postpartum women about congenital cytomegalovirus infection: A nationwide cross-sectional study in Greece

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Abstract

Introduction

Cytomegalovirus (CMV) is the most frequent cause of congenital infection worldwide. In Greece, antenatal CMV screening is recommended and seropositivity may provide a false sense of security leading to an increased risk of nonprimary maternal infections. The aim of this cross-sectional national study was to estimate how antenatal CMV screening affects knowledge, attitudes, and practices of postpartum women in Greece on congenital CMV (cCMV) infection.

Materials and Methods

A questionnaire-based cross-sectional study was conducted using a stratified random sample of postpartum women across Greece. The questionnaire was distributed from October 2022 to May 2024. Self-reported awareness of cCMV infection and attitudes was assessed for participants.

Results

Among 314 participants, 78% of them had undergone serology testing during pregnancy, while 57% of them acknowledged being aware of cCMV infection. Only 24% of CMV-screened women had been informed by their gynecologist about cCMV infection. A statistically significant difference was found between screened and non-screened women regarding both self-reported awareness and knowledge of CMV prevention measures ($p<0.005$). Among mothers, 69% were CMV IgG negative during the first trimester screening while serostatus didn't affect overall CMV awareness ($p>0.13$). Interestingly, 77% of participants expressed willingness to get vaccinated if a licensed vaccine existed. Vaccination willingness was positively associated with prenatal CMV screening ($p=0.023$), but no differences were observed between seropositive and seronegative women ($p=0.283$).

Conclusions

Antenatal CMV screening is associated with increased cCMV awareness of new mothers. Antenatal CMV screening could be used as a way of both timely diagnosing and promoting awareness of cCMV infection among new mothers. Despite the implementation of prenatal CMV serology screening, the risk of cCMV infection remains present. Women of childbearing age should be educated on CMV prevention measures regardless of their serostatus.



P073

Added value of EUROLINE Anti-CMV IgG immunoblot alongside avidity testing for the timing of maternal CMV infection during pregnancy

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Abstract

Introduction: Accurate dating of primary cytomegalovirus (CMV) infection during pregnancy is essential, as fetal risk is highest following maternal primary infection. CMV IgG avidity testing is widely used for this purpose, but borderline or discordant results may complicate interpretation. This study evaluated the added value of the EUROLINE Anti-CMV (IgG) immunoblot, with particular focus on glycoprotein B (gB) reactivity, as a complementary tool to routine CMV serology.

Methods: Sixty serum samples were selected and classified according to CMV IgG avidity measured on the Alinity i platform into low (<50%), intermediate (50–60%) and high (>60%) avidity groups (n=20 each). Additionally, 17 seroconversion sample pairs were analyzed and subdivided into intervals of <100 days (n=9) or >100 days (n=8) between collections. All samples were tested using the EUROLINE Anti-CMV (IgG) immunoblot detecting antibodies against gB, p52, p150 and CMV lysate.

Results: Positive gB reactivity was observed in 17/20 high-avidity samples, 5/20 low-avidity samples and 13/20 intermediate-avidity samples. In seroconversion samples collected within 100 days, gB was positive in 1/9 cases. In seroconversion samples collected after more than 100 days, gB was negative in all cases. Additional control samples with persistently high CMV IgG showed positive gB reactivity on immunoblot.

Conclusions: The EUROLINE Anti-CMV (IgG) immunoblot appears to provide the greatest complementary value in samples with intermediate avidity, where gB reactivity may help to further distinguish recent from past infection. The low gB positivity in early seroconversion samples may reflect delayed anti-gB development. Discordant findings between avidity and gB reactivity, particularly in seroconversion samples, suggest that both methods reflect different stages of humoral immune maturation and that the EUROLINE immunoblot should be interpreted in combination with avidity testing and with clinical context.



P074

Maternal perception of CMV screening during pregnancy: a cross-sectional study of women undergoing enhanced CMV screening

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Abstract

Introduction

Cytomegalovirus (CMV) screening during pregnancy remains controversial, partly because of concerns regarding maternal anxiety. As CMV screening strategies are expanding, data on women's perceptions remain limited. This study aimed to assess the emotional impact and acceptability of enhanced CMV screening during pregnancy.

Method

A retrospective cross-sectional study was conducted among women who delivered at Limoges University Hospital where monthly CMV screening was already being offered prior to the implementation of the French national CMV screening program. An anonymous questionnaire assessed perceptions of CMV screening, information received, waiting time for results, result disclosure, and CMV-related knowledge. Overall perception was evaluated using the IMPACTAR bipolar score, ranging from anxiety-provoking to reassuring.

Results

Forty-three women completed the questionnaire. Mean age was 31.1 ± 4.7 years. The mean IMPACTAR score was 0.36 ± 1.49, indicating an overall neutral to slightly reassuring perception. Overall, 54% of participants reported feeling reassured, 24% neutral and 22% anxious. Waiting for test results was the main source of anxiety, whereas result disclosure was generally perceived as reassuring. Screening itself was well accepted, and blood sampling was considered easily acceptable by 80% of participants. CMV knowledge (mode of transmission, prevention, fetal consequences) was limited (mean score 5.8/15) and was not associated with overall perception.

Conclusion

In this cohort, enhanced CMV screening during pregnancy was well accepted and generally perceived as reassuring. Anxiety was mainly related to waiting for results rather than to screening itself. These findings support the continuation of CMV screening strategies during pregnancy and highlight the importance of improving information provided to pregnant women regarding CMV infection and preventive measures.



P075

First national data from systematic CMV screening during first trimester of pregnancy in France

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Abstract

Introduction

Routine screening for cytomegalovirus (CMV) during the first trimester of pregnancy was recommended in France since June 2025 for seronegative women or women with no information regarding their CMV serostatus to enable early identification of primary maternal infections at risk of severe congenital infection. The French National reference Center collects the number, characteristics and management of cases and available fetal and neonatal outcomes in the national data base.

Methods

A first descriptive analysis was performed on primary maternal CMV infections occurring during the periconceptional period or the first trimester recorded between 2025 and 2026. CMV exposure factors, maternal management, prenatal diagnostic results, congenital infection status at birth, and symptomatology of infected newborns were collected.

Results

Among a total of 277 cases identified, 207 were reported through the simplified notification form implemented following the national recommendations.

Exposure to young children was reported in 60% of cases with available information (mean age of the youngest child living in the household was 2.9 years) and 92.7% had a child aged 4 years or younger.

Antiviral treatment was initiated in 76.8% of patients mainly using a four-dose daily regimen (96.4%). 77.7% started treatment at or before 14 weeks of gestation. The average time between diagnosis and treatment was 1.9 weeks.

Amniocentesis was performed on 126 patients at a mean gestational age of 19.4 weeks of amenorrhea, with 23.8% positive CMV PCR results.

Among 66 documented infant's cases, 31 congenital CMV infection were reported. Among the 26 infected infants with available clinical data, 24 (92.3%) were asymptomatic, 1 (3.8%) had mild symptoms and 1 (3.8%) had severe disease.

Conclusion

Most patients received management consistent with current recommendations, including early antiviral treatment. Long-term follow-up of this cohort will allow evaluation of the impact of this strategy on maternal-fetal transmission and the burden of congenital CMV infection.



P076

Universal versus selective neonatal screening for congenital cytomegalovirus infection: impact on detection of clinically unrecognized disease

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Abstract

Introduction: The pooled global birth prevalence of congenital cytomegalovirus infection (cCMV) is estimated at 6.7 per 1,000 live births, in Slovenia a rate of 1.4 per 1,000 is reported. Despite this high burden, most countries, including Slovenia, rely on selective screening of newborns, leaving many cases undetected. We evaluated the feasibility and diagnostic yield of universal dried blood spot (DBS)-based screening integrated into the Slovenian national newborn screening program and compared it with selective clinical case detection.

Methods: In this prospective nationwide pilot study, newborns born in all Slovenian maternity hospitals between May and September 2023 underwent universal cCMV screening. DBS samples collected within 48–72 hours of birth were tested for CMV DNA using quantitative PCR. Positive results were confirmed by urine PCR within 21 days of life. Confirmed cases underwent standardized clinical evaluation. Historical registry data from 2003–2022 were used for comparison. Ethical approval was obtained (0120-38/2023/4).

Results: A total of 5,556 newborns were screened. Thirteen newborns tested positive on DBS screening, and cCMV infection was confirmed in 10, corresponding to a lower-bound birth prevalence of 1.80 per 1,000 live births (95% CI 0.98–3.31). None of the confirmed cases had been clinically suspected at birth, and all passed routine newborn hearing screening. The detection rate was significantly higher than the historical rate achieved through selective clinical identification (0.09 per 1,000 live births; $p<0.001$). Standardized evaluation identified symptomatic cCMV in six infants, all of whom received valganciclovir treatment, mainly because of central nervous system abnormalities detected on neuroimaging.

Conclusions: Universal DBS-based screening substantially increased cCMV detection compared with selective clinical identification and revealed a significant burden of clinically unrecognized disease. Standardized evaluation of screen-detected infants identified symptomatic cases that would likely have remained undiagnosed under selective screening, enabling timely antiviral treatment and comprehensive follow-up.



P077

Feasibility and Outcomes of Universal and Targeted Neonatal Screening for Congenital Cytomegalovirus Infection

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Abstract

Background

Congenital cytomegalovirus infection (cCMV) is the most common congenital infection and a major cause of sensorineural hearing loss and neurodevelopmental impairment. There is no consensus on the optimal neonatal screening strategy. We evaluated the feasibility of universal neonatal cCMV screening, and the outcomes of two screening approaches based on saliva CMV DNA detection.

Methods

This prospective single-center cohort study was conducted at Hospital Sant Joan de Déu (Barcelona, Spain), a university tertiary pediatric hospital. Saliva CMV DNA testing was performed in newborns <15 days born or admitted to the Neonatal Unit. Three periods were analyzed: two universal screening phases (February 2021–February 2022, during the COVID-19 pandemic, and September 2022–March 2023) and one targeted screening phase including newborns meeting predefined clinical criteria (April 2023–December 2025). Positive saliva results were confirmed by urine CMV PCR.

Resullts

The number of newborns born or admitted was 3,334, 1,623, and 10,539 in periods 1–3, respectively, of whom 3,091, 1,483, and 1,085 were screened. The universal screening coverage rate was 92.3%, and the parental acceptance rate was 97.1%. In the universal screening phases, mean age at saliva collection was 1.46 days (SD 1.80) and results were available at 3.74 days (SD 1.82). Across all phases, 65% of saliva-positive newborns (34/52) were not confirmed by urine CMV PCR. Confirmed cCMV positivity among screened newborns was 0.06% (2/3,091) and 0.34% (5/1,483) in the first and second universal screening periods (p=0.04). In the targeted screening period,it was 1.01% (11/1,085), compared with 0.15% (7/4,574) for universal screening overall (p<0.001).

Conclusions

Universal neonatal cCMV screening was feasible. The higher yield of targeted screening likely reflects a higher-risk, symptomatic-enriched population but inevitably misses asymptomatic cases. The lower rate in the first universal screening period may reflect reduced CMV circulation under COVID-19 distancing measures.



P078

Assessment of Adherence to the Diagnostic Algorithm for Primary Cytomegalovirus (CMV) Infection During Pregnancy

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Abstract

Introduction

Primary cytomegalovirus (CMV) infection during the preconception period and first trimester of pregnancy carries a risk of vertical transmission. The Hellenic Society of Obstetrics and Gynecology (HSOG) has issued recommendations for the diagnosis of primary CMV infection. This study evaluated adherence to these recommendations.

Materials and Methods

We retrospectively reviewed the medical records of pregnant women referred to an outpatient infectious diseases clinic for evaluation of positive CMV serology. Cases were classified as first-trimester primary or non-primary infections. Primary infections were further categorized as timely or delayed diagnoses according to adherence to the recommended diagnostic algorithm.

Results

Between January 2025 and April 2026, 98 pregnant women were referred for suspected primary CMV infection. Thirty-seven referrals were inappropriate: 14 women had positive CMV IgG with high avidity from early pregnancy, 17 had documented CMV seropositivity from a previous pregnancy, and 6 had negative CMV IgG and IgM at the end of the first trimester followed by seroconversion during the second or third trimester.

Delayed diagnosis of first-trimester primary CMV infection occurred in 26 women: 5 due to delayed CMV IgG avidity testing, 7 because initial screening was performed only during the second trimester, and 14 because an initially negative CMV IgG result was not repeated until the second trimester.

Thirty-five women were diagnosed promptly according to the recommended diagnostic algorithm.

Conclusions

According to national and European recommendations, CMV IgG and IgM screening should be performed as early as possible and no later than 16 weeks' gestation. In our cohort, 37.8% (37/98) of referrals resulted in unnecessary repeat investigations, causing additional anxiety and confusion, while 26.5% (26/98) experienced delayed diagnosis of primary CMV infection. Given the proven benefit of early valacyclovir treatment in reducing vertical transmission, improved awareness and education of healthcare providers are needed to optimize adherence to diagnostic recommendations.



P080

Awareness and practices of perinatal care professionals about congenital cytomegalovirus infection: A nationwide cross-sectional study in Greece

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Abstract

Introduction

Congenital cytomegalovirus infection (cCMV) is the most common congenital infection worldwide and antenatal education has been shown to reduce cCMV risk. However, data regarding awareness and practices related to cCMV infection among perinatal healthcare providers remain limited. The aim of this national cross-sectional study was to assess knowledge, attitudes, and practices among pediatricians and obstetricians in Greece regarding cCMV infection.

Materials and Methods

A nationwide questionnaire-based cross-sectional study was conducted. The questionnaires were randomly distributed via email to pediatricians and obstetricians through local medical associations across Greece between October 2022 and May 2024. Knowledge, attitudes and practices on cCMV infection were assessed for participants.

Results

A total of 198 questionnaires were collected, representing 3.2% of the total population of pediatricians and obstetricians in Greece. Among participants, 66% were pediatricians and 65% were women. The mean age was 43.7 years, and 50% reported more than 10 years of professional experience. Overall, 46.7% reported being satisfied with their level of awareness regarding cCMV infection, and more than 80% demonstrated satisfactory knowledge about the disease. A statistically significant difference was observed between pediatricians and obstetricians regarding knowledge about transmission through urine ($p<0.005$). More than 80% agreed with serological screening and counseling of pregnant women. Furthermore, 76% of pediatricians routinely recommended hearing screening, while 15% of obstetricians would consider suggesting pregnancy termination in cases of primary CMV infection during the first trimester.

Conclusions

Overall, our study indicates a relatively satisfactory level of awareness regarding cCMV infection among perinatal healthcare-professionals in Greece. Nevertheless, certain areas require continuous education to ensure adequate disease management. Promotion of counseling for pregnant women remains the primary strategy for disease prevention. This may represent an important opportunity for education and clinician support through professional organizations.



P081

Promoting Behavioral Strategies for Cytomegalovirus (CMV) Risk Reduction Among Pregnant Women

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Abstract

1) Introduction/Aim

This study aimed to evaluate whether a cognitive-behavioral intervention could decrease self-reported CMV risk behaviors and improve knowledge in pregnant women.

2) Materials and Methods

A total of 513 pregnant women (< 20 weeks' gestation) were randomized to either a CMV risk-reduction intervention (n=257) or an attention-matched control stress-reduction program (n=256). Both groups completed a brief individualized behavioral skills session, viewed a short educational video, received weekly text messages for 12 weeks, and attended 6 and 12-week follow-up visits. The experimental arm focused on avoiding contact with young children's saliva and urine (stopping saliva sharing, modifying kissing practices, and increasing handwashing). Questionnaires assessed pre- and post-intervention outcomes. To account for participant attrition (7.8%) under a Missing at Random (MAR) assumption, pre/post survey metrics were restructured into a longitudinal long format and analyzed using ordinal/binomial mixed-effects models in SAS, with a random intercept per participant.

3) Results

Pre- and post-intervention assessments were completed in 473 women (92.2% retention). The cohort was predominantly non-Hispanic Black (72.9%), and 80.9% regularly cared for young children. Baseline CMV awareness was limited; only 11.1% (95% CI, 8.5 – 14.2%) had ever heard of congenital CMV. Post-CMV intervention, kissing on the child's mouth (>1 day/week) decreased from 27.7% to 12.2% ($p < 0.0001$). Food and item sharing with children decreased substantially (46.2% pre vs. 15.6% post, <0.001), while handwashing frequency increased (25.6% pre vs. 39.5% post, <0.001). In the CMV group, correct CMV knowledge scores also increased significantly following the intervention.

4) Conclusions

Pregnant women lack awareness or accurate knowledge regarding congenital CMV and preventative behavioral measures. This study demonstrates that a structured, cognitive-behavioral, digital, and text-based intervention can effectively reduce CMV risk behaviors among pregnant women.



P082

The right to know about CMV: perspectives of pregnant women and families with lived experience of CMV

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Abstract

Introduction

Congenital cytomegalovirus (CMV) is the leading infectious cause of childhood disability in high-income countries, affecting approximately 1 in 200 newborns. Around 20% of affected children experience long-term sequelae, including sensorineural hearing loss, intellectual impairment, epilepsy, and cerebral palsy. Despite this, awareness of CMV among pregnant women remains low, and most do not receive antenatal counselling about risk reduction strategies. Hygiene-based behaviours are currently the only effective primary prevention strategy.

Methods

This narrative review synthesised published literature examining barriers and enablers to antenatal CMV counselling. A targeted search was conducted using terms related to CMV, pregnancy, awareness, hygiene precautions, and lived experience. Findings were complemented by reflections and written contributions from co-authors with lived experience of congenital CMV to provide additional insight into acceptability, communication, and information needs.

Results

Substantial gaps were identified in health professional knowledge, confidence, and motivation to provide CMV counselling. Common concerns included perceived challenges in implementing hygiene precautions and concerns about causing unnecessary anxiety. In contrast, pregnant women reported a strong desire to receive CMV information early in pregnancy from trusted healthcare providers. Evidence suggests that CMV education does not result in psychological harm and supports behaviour change. Lived experience perspectives highlighted the importance of informed choice and described distress associated with missed opportunities for prevention. Effective communication strategies include framing behaviours as achievable risk reduction, acknowledging and normalising variations in applying these strategies, involving partners, and using clear written and digital resources.

Conclusions

There is a critical need to embed CMV education within routine antenatal care and strengthen clinician confidence to deliver this information. Incorporating lived experience into programme design is essential. Improving awareness of CMV hygiene precautions represents an immediately actionable opportunity to strengthen efforts to prevent CMV infection in pregnancy.



P083

Improving maternal awareness of Cytomegalovirus infection: a controlled educational intervention study

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Abstract

Introduction: Congenital cytomegalovirus (cCMV) infection is the most common congenital infection worldwide and a leading cause of sensorineural hearing loss and neurodevelopmental impairment. Despite its public health impact, awareness of CMV among women of childbearing age remains limited. Educational interventions promoting preventive hygiene measures may reduce maternal primary infection and consequently cCMV.

Methods: Between March and July 2025, women attending pediatric outpatient services were assigned to one of three groups: Group A (control), receiving neither educational material nor information; Group B, receiving printed educational material only; and Group C, receiving the same material with a one-to-one explanation by healthcare professionals. One month later, participants completed an anonymous web-based questionnaire assessing CMV-related knowledge and awareness.

Results: Of 300 eligible women, 216 completed questionnaires were analyzed (72% response rate): 71/110 (65%) in Group A, 82/102 (80%) in Group B, and 63/88 (72%) in Group C. Maternal age was lower in Group C than in Groups A and B (30.6 vs 33.6 and 33.5 years; $p<0.05$), whereas parity and educational level were comparable. General awareness of CMV was reported by 81% of participants, without differences among groups. Knowledge of CMV transmission increased from 52% in Group A to 63% in Group B and 86% in Group C ($p<0.05$). Awareness of CMV-related sequelae increased from 44% in Group A to 63% and 68% in Groups B and C, respectively ($p<0.01$). Knowledge that preventive measures can reduce the risk of congenital infection remained limited but was higher in Group C (29%) than in Groups A (10%) and B (12%) ($p<0.01$).

Conclusions: Personalized counseling combined with printed educational material was more effective than printed information alone in improving CMV knowledge. However, awareness of CMV sequelae and preventive strategies remained suboptimal, highlighting the need for broader educational interventions.



P084

Fetal antiviral treatment decreases the risk of severe neurodevelopmental impairment among children with congenital CMV infection

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Abstract

Introduction/Aim

We aimed to investigate the effect of fetal treatment on neonatal outcomes in congenital CMV (cCMV) infected infants, with a history of first trimester or periconceptual maternal infection.

Materials and Methods

A retrospective cohort study was performed. CCMV infected infants born after confirmed periconceptual/first trimester maternal infection were classified into 3 groups, according to fetal treatment: valaciclovir, hyperimmune immunoglobulin (HIG), or no treatment. Primary outcomes were clinically apparent (CACMV) or inapparent (CICMV) neonatal CMV disease, SNHL (birth or delayed-onset), and neurodevelopmental impairment (NDI).

Results

51 cCMV infants were included: 12 in the valaciclovir, 26 in the HIG, and 13 in the no maternal treatment group. In mothers treated with HIG, treatment initiation was significantly earlier versus the valaciclovir group (median 11.5 versus 22 weeks GA); all valaciclovir mothers had started treatment late, beyond the 14th week GA. CACMV neonatal infection rates were similar among the groups (33.3% valaciclovir, 26.9% HIG, and 36.4% no treatment group). SNHL at birth (3.8%) and total hearing loss at the end of follow up (15.4%) was less prevalent in the group of children whose mother had received HIG; although not statistically significant. Children born to mothers treated with valaciclovir had a significantly (p=0.015) shorter median NDI follow-up (28.0 months) vs the HIG group (54.0 months), and were significantly less likely to develop severe NDI (0 vs 35.0%, p=0.005); this difference remained significant when HIG and no treatment groups were merged together versus the valaciclovir group (39.1% vs 0%, p=0.039). Although, NDI intervention was offered equally between the groups, severe NDI was potentially less frequent in the valaciclovir group also due to earlier intervention initiation, indicating raising NDI awareness in cCMV children.

Conclusions

In this small retrospective cohort study, valaciclovir maternal treatment was associated with a better neurodevelopmental outcome in cCMV infected children.



P085

Awareness and knowledge of congenital cytomegalovirus infection (cCMV) among healthcare professionals and pregnant women: systematic review and meta-analysis

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Abstract

Introduction: Congenital cytomegalovirus (cCMV) contributes significantly to neonatal morbidity and is the leading cause of non-hereditary sensorineural hearing loss. In the absence of CMV vaccination, hygiene practices are key to decreasing cCMV cases. The aim of this study was to determinecCMV awareness among pregnant individuals and healthcare professionals.

Materials and Methods: We systematically searched Pubmed, Scopus, Web of Science, clinicaltrials.com and Cochrane Library from inception to May 2026for studies providing data on awareness of cCMV infection among healthcare professionals and pregnant women. The study protocol was registered in PROSPERO (CRD420251080227). For studies with comparable data, generic inverse variance meta-analysis was performed using random-effects models given the methodological heterogeneity.

Results: A total of 59 observational studies and 2 randomized trials met the inclusion criteria including 19.295 pregnant women and 15.739 healthcare professionals from 17 countries. Low levels of knowledge were noted in both groups regarding route of transmission (18/61, 30%), symptoms in pregnant women (5/61, 8%),symptoms in neonates (9/61, 15%), long term effects (9/61, 15 %) and preventive practices (11/61, 18%).Metanalysis with random effects models showed significantly higher mean knowledge scores after the implementation of educational interventions in HCP [3 studies, 589 participants, pooled MD =6.41, 95%CI (2.84, 9.97), p 0.0004]. A minimum 35-fold increase in healthcare providers' intention to counsel on cCMV prevention was achieved through structured educational interventions[2 studies, 222 participants, p<0.00001, $I^2$0%]. The overall risk of bias was high as most of the included studies were designed as non-randomized.

Conclusions: Low cCMV awareness and knowledge levels were noted among pregnant women and HCP. Our results emphasize the need for targeted educational programs in both healthcare professionals and pregnant women to decrease the burden of cCMV infection.



P086

Automation in Dried Blood Spot testing

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altona Diagnostics GmbH, Hamburg, Germany

Abstract

Background:

Congenital cytomegalovirus infection (cCMV) is a major cause of childhood hearing loss and neurodevelopmental delay. Targeted screening for cCMV is widely recommended as standard of care and dried-blood spots (DBS) are often used as already collected from all newborns in high-income countries.

Aim:

QCMD (Quality Control for Molecular Diagnostics) provides External Quality Assessment (EQA) proficiency samples for testing CMV DNA from Dried Blood Spots (DBS). We retrospectively tested two panel sample sets with the AltoStar® CMV PCR Kit 1.5 to assess the suitability of the assay for CMV testing from DBS.

Material & Methods:

Samples were cut (Whatman Cytivia Protein 903 Saver card, 1x12 mm punch per sample) and 1 ml AltoStar® Dried Blood Spots Pretreatment Buffer 1.5* (RUO, altona Diagnostics GmbH) was added per punch. Incubation was performed at 65 °C for 30 min. After centrifugation the sample was further processed using the AltoStar® workflow including the AltoStar® CMV PCR Kit 1.5 for the detection of CMV DNA.

Results:

The of 2024 panel included 7 core samples (1 negative sample, 6 CMV DNA positive samples) and in addition one educational clinical sample. In the 2025 panel all 8 samples were core samples, one of them was a negative sample. All 16 DBS samples from the EQA schemes were processed successfully. The automated processing of the sample was monitored via the Internal Control and revealed no inhibition or failure during the extraction.

All samples were detected correctly with the AltoStar® CMV PCR Kit 1.5.

Discussion:

Compared to the consensus results of participants using commercial assays, the sensitivity and specificity of the AltoStar® CMV PCR Kit 1.5 was excellent.

Conclusion:

The results showed that the AltoStar® workflow is suitable for automated extraction of CMV DNA from DBS, demonstrated by a high sensitive detection of CMV DNA from DBS samples.



P087

Can digital PCR in amniotic fluid improve the prenatal diagnosis of congenital cytomegalovirus infection?

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Abstract

Introduction: Congenital cytomegalovirus (cCMV) infection despite negative amniocentesis results has been reported in up to 8% of cases and is generally not associated with long-term sequelae. This study evaluated the performance of digital PCR (dPCR) in amniotic fluid (AF) samples, including both untreated women and women receiving valacyclovir.

Materials and Methods: A total of 160 AF samples from pregnancies with primary CMV infection were included. All had previously been tested for CMV DNA by routine real-time PCR. Stored samples were retrospectively re-analyzed by dPCR targeting the CMV UL123 gene. Analytical sensitivity was assessed using a CMV DNA plasmid of known concentration.

Results: The minimum number of positive partitions (out of 26,000) required for reproducible detection was two; therefore, positivity was defined as a mean of ≥2 positive partitions across five replicates. Seventy-two AF samples selected from untreated women were divided into three groups (n=24 each): CMV-positive AF with confirmed cCMV at birth, CMV-negative AF with uninfected neonates, and CMV-negative AF followed by confirmed cCMV infection at birth. dPCR results were concordant with real-time PCR findings in all cases except one from the latter group, which tested positive by dPCR (1/24, 4.2%). An additional cohort of 88 AF samples from valacyclovir-treated women was analyzed. dPCR confirmed all real-time PCR results. Among the 76 CMV-negative AF samples, five newborns (7%) were diagnosed with cCMV at birth; three required postnatal antiviral therapy because of mild MRI brain abnormalities. No sequelae were observed during follow-up.

Conclusions: dPCR identified only one additional CMV-positive AF sample missed by real-time PCR. These findings suggest that false-negative prenatal diagnoses are more likely due to delayed fetal transmission after amniocentesis than to limited analytical sensitivity of real-time PCR. Further studies are needed to assess outcomes in infants with cCMV despite negative prenatal AF testing, particularly following maternal valacyclovir treatment.

YOUNG INVESTIGATORS' ABSTRACTS



Y001

Human cytomegalovirus pentamer engages endothelin B receptor to trigger ERK/CK2-dependent histone lactylation which dictates viral permissiveness

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Abstract

Human cytomegalovirus (HCMV) is a ubiquitous herpesvirus that establishes lifelong persistence and causes severe disease in immunocompromised individuals and congenitally infected infants. Productive infection of endothelial, epithelial, and myeloid cells requires the viral pentameric glycoprotein complex (gH/gL/UL128/UL130/UL131A). Although several host factors involved in pentamer-mediated entry have been described, how HCMV couples entry to the induction of immediate early (IE) gene expression and the establishment of a replication-permissive cellular state remains incompletely understood.

Here, we identify the endothelin B receptor (ETBR) as a critical determinant of pentamer-dependent HCMV permissiveness. Using pharmacological inhibition, genetic silencing, biophysical interaction studies, phosphoproteomics, metabolic flux analysis, and chromatin profiling, we demonstrate that the HCMV pentamer directly engages ETBR through UL128. This interaction promotes caveolin-1–dependent endocytosis and activates an ERK/CSNK2A1/CREB signaling cascade required for IE86 expression and initiation of viral DNA replication.

Mechanistically, ETBR signaling induced profound metabolic rewiring characterized by increased glycolysis and oxidative phosphorylation, accompanied by pyruvate dehydrogenase inhibition and enhanced lactate production. Blocking lactate generation suppressed IE expression and abolished productive infection. Elevated lactate promoted histone lactylation, including H3K18 lactylation enrichment at the HCMV major immediate early promoter and coding regions. Inhibition of ETBR or ERK signaling reduced histone lactylation. Notably, histone delactylase inhibition restored IE expression under ETBR blockade.

Together, these findings establish ETBR as a dual-function receptor that integrates HCMV entry with signaling, metabolic remodeling, and epigenetic regulation required for productive infection. Moreover, our findings highlight the ETBR-ERK-lactylation axis as a potential therapeutic target for HCMV-associated disease.



Y002

CYTOMEGALOVIRUS INFECTION IN HIV-EXPOSED PRETERM INFANTS

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Abstract

Despite the high burden of cytomegalovirus(CMV) infection in sub-Saharan Africa, data on infection rates and CMV-specific immune responses in preterm infants remain limited. We determined the prevalence of congenital and postnatal CMV(cCMV, pCMV) infection in HIV-exposed uninfected(HEU) premature infants and examined CMV-specific immune responses in this cohort.

154 infants <14 days and <1.5 kg (median gestational age 28 weeks[IQR 28.0–30.0]) were enrolled; 30/154(19%) were HEU. Blood and saliva samples were collected at enrolment, with weekly follow-up saliva sampling and clinical data collection. Saliva CMV DNA was detected and quantified by PCR. CMV-specific T-cell responses were assessed using an ELISPOT assay measuring interferon gamma(IFNγ) production following CMV peptide stimulation.

CMV was detected before 21 days of age in 34/154(22%) infants, indicating cCMV. Of these, 25/154(16%) had persistent CMV measured, and 14/25(56%) had clinical features compatible with symptomatic cCMV disease. pCMV was detected in 43/154(28%) infants at a median age of 4.0 weeks [IQR 3.0–5.0]. Persistent pCMV occurred in 23/154(15%) infants, of whom 13/23(57%) were symptomatic. Infants with pCMV had a significantly longer duration of hospital stay compared to CMV-uninfected infants, and peak saliva CMV viral load correlated positively with duration of hospital stay during pCMV infection (r=0.47, p=0.023). Reduced IFNγ responses were observed in infants with symptomatic cCMV infection.

The reported persistent cCMV rate is substantially higher than those reported globally. More than half of CMV-infected infants were symptomatic. Higher postnatal CMV viral loads were associated with prolonged hospitalization. IFNγ-producing T-cell frequencies were lower in HEU infants compared to unexposed; and lower in symptomatic vs asymptomatic infants with cCMV.

These findings suggest that impaired cellular immune responses may be associated with symptomatic CMV disease. To further characterize CMV-specific immune responses, comprehensive immune profiling using high-parameter flow cytometry is currently ongoing.



Y003

Early Cytomegalovirus Screening and Treatment in Pregnancy: First Insights From a Swiss National Register

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Abstract

Introduction: The Swiss Society of Gynecology and Obstetrics issued an expert opinion in 2021 recommending that all pregnant women beinformed about the possibility of serological screening for CMV in early pregnancy and, if infected, the available options for prenatal diagnosis and antiviral treatment.

Methods: Since 2023, the CMV-preg prospective registry has collected data from 12 university hospitals, regional hospitals, and private practices to evaluate outcomes of primary CMV infection and the effectiveness of prenatal antiviral treatment. This interim analysis includes pregnancies with periconceptional infection (–6 weeks before LMP to 6 weeks' gestation) or first-trimester infection (6–14 weeks), enrolled between 2023 and 2025 with known outcomes.

Results: Among 190 pregnancies included (81 periconceptional infections, 99 first-trimester infections, 10 without specific dating), 86 (45%) were treated with valaciclovir 4×2g/d after maternal infection diagnosis; they stopped treatment after a negative amniocentesis (n=62) or at birth (n=24). Treated women presented lower risks of positive amniocentesis (13/75, 17% vs 28/79, 35%; aRR 0.48, 95%CI 0.27–0.85), congenital CMV infection at birth (15/86, 17% vs 35/104, 34%; aRR 0.49, 95%CI 0.29– 0.83), and symptomatic congenital infection (4/86, 5% vs 28/104, 27%; aRR 0.17, 95%CI 0.06–0.45) compared to those untreated. Stratified analyses showed a similar effect to reduce maternal–fetal transmission among first-trimester infections (RR 0.44, 95%CI0.22–0.90 for positive amniocentesis; RR 0.47, 95%CI 0.25–0.87 for congenital CMV infection at birth) and no significant differences among periconceptional infections. Stratified analyses found a significant reduction of symptomatic congenital infection among both first-trimester (RR 0.17, 95%CI 0.05–0.54) and periconceptional infections (RR 0.13, 95%CI 0.02–0.98).

Conclusion: Early CMV screening and prenatal antiviral treatment appear safe and reduce fetal infection and symptomatic disease, particularly when treatment is started soon after maternal infection.



Y004

Neonatal Vδ1 γδ T Cells Balance Antiviral Immunity and Inflammatory Control During Acute CMV Infection

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Abstract

Introduction: Human γδ T cells contribute to antiviral immunity and have been implicated in cytomegalovirus (CMV) infection, with Vδ1 γδ T cells representing a major responsive subset. However, how age shapes Vδ1 T cell responses during acute CMV infection remains incompletely understood, particularly in early life. Here, we investigated age-dependent Vδ1 T cell responses in neonates and adults with acute CMV infection.

Materials and Methods: We performed single-cell transcriptomic analysis of peripheral blood γδ T cells from neonates and immunocompetent adults with acute CMV infection, together with age-matched controls. Vδ1 T cell subsets, activation states, proliferation, cytotoxic programs, and polarization-associated transcriptional signatures were compared between age groups.

Results: Acute CMV infection induced robust activation and expansion of Vδ1 T cells in both neonates and adults. However, neonatal and adult Vδ1 T cells responded through distinct antiviral strategies. In neonates, Vδ1 T cells showed evidence of de novo effector differentiation, accompanied by gradual acquisition of cytotoxic programs and a balanced induction of type 1– and type 2–associated transcriptional features. In contrast, adult Vδ1 T cells displayed pre-existing cytotoxic signatures at baseline and responded predominantly through proliferative expansion, enhanced cytotoxicity, and type 1–skewed inflammatory programs. These findings suggest that early-life Vδ1 T cell responses may balance antiviral defense with controlled inflammation, whereas adult responses rely more strongly on expansion of pre-armed cytotoxic cells.

Conclusions: Our study reveals age-specific antiviral strategies of human Vδ1 T cells during acute CMV infection. These findings provide a framework for further investigation using in vitro CMV infection models to define the molecular mechanisms underlying their antiviral responses.



Y005

Effect of Valaciclovir on Fetal Blood Parameters and Ultrasound in Congenital CMV infections: A Multicentre Case-Cohort Study

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Abstract

Objectives: To identify predictors of moderate-to-severe symptomatic congenital CMV infection among fetal blood and imaging parameters in fetuses treated with valaciclovir.

Methods: Multicentre case-cohort study with matching on gestational age at maternal primary infection. Platelet count, gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), β2-microglobulin, immunoglobulin M, CMV viremia, and ultrasound findings at 20–24 weeks' gestation were compared between fetuses treated or untreated with valaciclovir.

Results: Among 118 included fetuses, 17 received valaciclovir between maternal infection diagnosis and fetal blood sampling (FBS); of these, 13 were treated from the first trimester and 4 from the second trimester. Moderate-to-severe symptomatic infection occurred in 4/17 (24%) fetuses treated before FBS, and in 23/101 (23%) fetuses untreated before FBS.

After matching, fetuses treated after maternal infection showed significantly lower viremia and higher platelet counts compared with untreated fetuses, as well as a significantly lower risk of abnormal ultrasound findings. In contrast, severe ultrasound abnormalities and elevated β2-microglobulin (>11 mg/L) were not significantly reduced by treatment and remained reliable predictors of moderate-to-severe symptomatic infection in treated fetuses.

Among the four fetuses with moderate-to-severe symptomatic infection despite treatment before FBS, three presented severe ultrasound abnormalities, and one showed neurodevelopmental delay in motor and communication domains at 2 years of age without other signs of congenital CMV infection. All four cases were treated after 13 weeks' gestation and with a delay of more than 6 weeks following maternal infection.

Conclusion: Prognostication in CMV-infected fetuses treated with valaciclovir from first-trimester should rely primarily on imaging, as treatment improves viremia and reduces subsequent CMV-cytotoxicity. In fetuses treated late after maternal infection, β2-microglobulin may remain the only informative blood marker, as elevated levels seem to persist in moderate-to-severe symptomatic cases.



Y006

Preliminary Safety and Efficacy of Valganciclovir With and Without Maternal Derived CMV Cytotoxic T-Lymphocytes (CTLs) as Adoptive Cellular Therapy in Neonates with Moderate/ Severe Congenital CMV Infection (cCMV) (IND17449) (NCT05645989)

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Abstract

Background:

Neonates have significant immaturity in viral specific T-cell adaptive immunity, in part secondary to fetal immune maturation skewed toward maternal tolerance in-utero. Furthermore, CMV's large genome facilitates evasion of normal host immune responses. cCMV infection is the most common cause of developmental delay, sensory neural hearing loss and neurological damage during infancy. Current Valganciclovir therapy is limited by bone marrow suppression and persistent CMV viremia. We therefore investigated the safety and efficacy of Valganciclovir with and without maternal donor-derived CMV-CTLs.

Methods:

Term neonate (> 34weeks and > 2500gm (AGA) (>1500gm/m2) (SGA), <21 days of life were eligible for study of Valganciclovir with and without maternal donor-derived CMV-CTLs, which were manufactured utilizing the Cytokine Capture System® (CCS®) on the CliniMACS® Prodigy® device as we reported. A 3-subject safety run in of Valganciclovir + maternal donor-derived CMV-CTLs was followed by a randomization to Valganciclovir + CMV-CTLs. CMV-CTLs were administered at 0.5 x 10^4 CD3/kg q2wks up to 5 infusions. Valganciclovir (16mg/kg dose PO q12hrs). Hearing, brain MRI and neurodevelopment were measured at baseline and 1yr.

Results

Seven neonates have been enrolled. Following the 3-subject safety run-in, 4 were randomized: 2 to valganciclovir alone and 2 to valganciclovir + CMV-CTLs. Five subjects have received CMV-CTLs, with a mean of 3.6 infusions/subject (range, 1–5). CMV-CTLs were well tolerated, with no acute GVHD, CRS, ICANS, infusion-related reactions, neurotoxicity, or other CTL-related toxicities. Five subjects achieved CR, defined as CMV PCR negativity; 2 are not yet evaluable, including 1 receiving active CMV-CTL therapy and 1 crossover subject awaiting CMV-CTL infusion for persistent blood CMV PCR >1000 copies/mL on valganciclovir. Two subjects have completed 1-year follow-up, both with normal hearing and neurodevelopmental findings.

Conclusion

Valganciclovir + maternal donor-derived CMV-CTLs were well tolerated and demonstrated 100% CR rate. Randomization is ongoing to determine long-term safety and efficacy.



Y007

The UK lags behind Southern Europe in the prevention, diagnosis and treatment of Congenital CMV

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Abstract

INTRODUCTION Congenital Cytomegalovirus (cCMV) is a leading non-genetic cause of sensorineural hearing loss in the United Kingdom (UK). Antiviral treatment in early pregnancy or in the neonatal period can improve outcomes for affected infants. Unlike other countries in Europe, there is no routine antenatal or neonatal screening for CMV in the UK.

AIM This study aimed to compare management of congenital CMV in pregnancy and infancy between the UK, Spain (targeted screening) and Greece (universal antenatal screening)

METHODS Within this observational prospective European study (cCMVnet), data on investigations, management and outcomes of congenital CMV in pregnancy and infancy were extracted. Statistical analysis was conducted in SPSS, comparing proportions between the UK, Spain and Greece.

RESULTS 1383 infants were included (198 UK, 951 Spain, 234 Greece). In the UK, investigations for CMV were less frequently performed during pregnancy, including first trimester serological testing (41.9% UK vs 68.7% Spain vs 78.5% Greece) ($p < 0.001$), and amniocentesis (9.6% vs 20.5% vs 57.3%)($p<0.001$) Fewer UK mothers received antiviral treatment during pregnancy (2.9% vs 23.5% vs 45.4%)(($p<0.001$). A larger proportion of UK infants were aged over 29 days at diagnosis (16.5% vs 13.5% vs 4.1%) ($p= 0.002$). Similar proportions of UK and Spanish infants were 'symptomatic' at birth (53.3% vs 53.4% vs 24.4%) and received antivirals (67.2% vs 62.3% vs 31.7%), however more UK infants had hearing loss at 1 year (50% vs 30.8% vs 11.4%) and developmental delay (unable to sit by 12m (20.2% vs 10.5% vs 7.2%).

CONCLUSION These findings suggests that the UK may lag behind Southern Europe in the early treatment and testing of maternal and congenital CMV infection. The observed differences in infant outcomes may reflect this disparity, however they are also likely influenced by the absence of routine maternal and neonatal CMV screening programmes in the UK.



Y008

Screening for congenital cytomegalovirus in infants born to mothers with HIV: An International Survey of Practice

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Abstract

Introduction

The impact of in utero HIV exposure on congenital cytomegalovirus (cCMV) risk remains unclear in the current antiretroviral therapy (ART) era. Understanding cCMV screening practices for infants who are HIV-exposed but uninfected (HEU) is important as guidelines move towards normalising pregnancy for people living with HIV, whilst ensuring infants with cCMV are identified.

Methods

An online survey was disseminated through the Penta ID Network and cCMVnet (April-May 2026), this explored cCMV screening policies, HEU-specific screening practices, availability of CMV diagnostics, and numbers of infants who are HEU diagnosed with cCMV at respondents' institutions. Responses were analysed descriptively overall and by World Bank income group.

Results

In total, 174 responses from 57 countries were received, 80% of respondents worked in tertiary care. 8.6% of respondents reported universal newborn cCMV screening, 55.8% targeted screening, and 35.6% no institutional policy. Over a quarter of respondents (28%) reported screening all infants who are HEU for cCMV, comprising 36% from high-income countries (HICs) and 16% from low-and-middle-income countries (LMICs). Availability of CMV diagnostics varied by income group, with reduced access to urine PCR in LMICs (39% vs 95% in HICs). Among respondents able to estimate the number of infants who are HEU diagnosed with cCMV in the last 5 years, 48.3% reported none and 13.8% reported 1–5. Uncertainty regarding these numbers was more common in LMICs (45.1% vs 17.5% in HICs) and in centres with no cCMV screening policy (41.9% vs 20% with universal screening).

Conclusions

cCMV screening practices for infants who are HEU vary widely, likely reflecting a lack of contemporary evidence to inform practice. In the absence of universal screening, cohort studies of infants who are HEU screened for cCMV and comprehensively assessed for cCMV-associated disease and long-term sequelae are needed to inform whether targeted cCMV screening should be implemented for this cohort.



Y009

The first viral 'deletome': systematic functional characterisation of every HCMV gene using CRISPR and multiomics

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Abstract

Available therapies for HCMV suffer from the potential for drug resistance and significant side effects, and a vaccine is not available. A comprehensive understanding of the functions of viral proteins is therefore critical for the rational design of new antiviral drugs.

We previously found that HCMV manipulates the expression of thousands of host proteins, including downregulation/degradation of known and novel antiviral restriction factors and cell death pathway components. Metabolic and biosynthetic pathways were upregulated to favour productive viral infection. However, a systematic understanding of which viral factor modulates each host protein is currently lacking.

We have developed a systematic CRISPR-Cas9 'deletome' screen to discover the functions of every HCMV protein. We established 180 cell lines, each co-expressing Cas9 and guide RNAs targeting one-or-other of 168 canonical HCMV proteins and 12 novel ORFs, then infected these with HCMV. 18-plex tandem mass tag-based proteomics and RNAseq enabled a systematic comparative analysis of gene function at the level of host protein and transcript, revealing both global and individual insights into viral protein function. In addition to validating the regulation of multiple host proteins known to be downregulated by individual HCMV factors, we have generated a compendium of functions for every HCMV protein, characterising host and viral regulation at both protein and transcript level. A particular benefit of the 'deletome' study is the ability to distinguish where host proteins/transcripts are co-regulated by two or more viral factors, which occurred frequently.

We will also introduce insights into the overlap between this screen and our previous analyses of protein degradation during HCMV infection as well as the HCMV 'interactome', leading to a unified model of HCMV protein function.



Y010

Persistently primed microglia restrict the reactivation of latent cytomegalovirus at the expense of neuronal synaptic connectivity

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Abstract

Introduction: Microglia are the resident immune cells of the central nervous system (CNS), where they maintain tissue homeostasis and respond to pathogenic stimuli, including viral infections. Herpesviruses establish latent infections from which they reactivate intermittently. Congenital infection with human cytomegalovirus, the most common congenital viral infection, is associated with severe and persistent neurological sequelae affecting the CNS. Despite their critical role in immune surveillance, the contribution of microglia to the control of latent viral infections in the brain remains poorly defined. This study aimed to elucidate the role of microglia in immune surveillance and neuropathology associated with latent cytomegalovirus infection in the brain.

Materials/Methods: To investigate the impact of persistent cytomegalovirus infection of the brain on microglia, we employed a mouse model of congenital CMV infection in which neonatal mice were infected with murine cytomegalovirus (MCMV). Wild-type MCMV, wild-type C57BL/6 and BALB/c mice, and transgenic *Sall1Cre*^{ERT2}*Ifngr1*$^{fl/fl}$ mice were used throughout the study. Microglia were depleted using PLX5622, an inhibitor of colony-stimulating factor 1 receptor signaling. In addition to the murine model, brain tissues from HCMV-infected fetuses and human fetal organotypic brain slice cultures (hfOBSCs) were used. Experimental outcomes were assessed using flow cytometry, viral plaque assays, confocal microscopy, bulk and single-cell RNA sequencing, electrophysiological recordings, and Barnes maze test.

Results: MCMV latency in the CNS was associated with persistent microglial priming, including interferon-γ-dependent activation and extensive transcriptional reprogramming at the single-cell level, leading to the expansion of a microglia subset associated with latent infection. Primed microglia exerted enhanced control over latent infection and superior recall responses in an IFN-γ-dependent manner. However, primed microglia also mediated excessive dendritic spine elimination in the hippocampal CA1 region, resulting in impaired synaptic plasticity and spatial learning in latently infected mice.

Conclusion: Taken together, our findings demonstrate that microglia are key drivers of neuropathology during latent viral infection.



Y011

JAK Independent Activation of STAT5 Promotes HCMV Reactivation in Primary Dendritic Cells

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Abstract

Human cytomegalovirus (HCMV) establishes a persistent life-long infection, which is usually asymptomatic, but poses life-threatening risks in immunocompromised patients. HCMV establishes latency in CD34+ haematopoietic progenitor cells, with reactivation occurring upon terminal differentiation to myeloid dendritic cells (DCs) and macrophages. In DCs, IL-6 induced reactivation requires concomitant activation of ERK-MAPK and Src family kinases (SFKs) which promote chromatin remodelling of repressed MIEP (Major Immediate Early Promoter) to an active form. SFK activity has been shown to promote MOZ histone acetyltransferase recruitment to the MIEP. However, SFKs do not bind DNA directly leading us to investigate the mechanism that translates SFK activity into MOZ recruitment to the MIEP. A phosphor-proteomic screen performed in reactivating DCs suggested the STAT5B paralog of the STAT5 family as a candidate. Here we show that the transfected MIEP is responsive to STAT5B over-expression, is enhanced by IL-6, and can be reversed when co-incubated with a gp130 inhibitory peptide. Furthermore, constitutively phosphorylated STAT5B at serine (but not tyrosine) residues activates the MIEP, consistent with STAT5B driven activation occurring in a JAK-independent manner. Consistent with these transfection studies, pharmacological and genetic approaches reveal that IL-6 induced viral reactivation in DCs is STAT5-dependent but similarly independent of upstream JAK activation. However, HCMV reactivation in PMA stimulated macrophages interestingly was observed to be JAK-dependent STAT5 independent. Finally, we demonstrate that in latently infected DCs, STAT5 binding to the MIEP is detectable rapidly post IL-6 stimulation. Thus, these data suggest an intriguing role for STAT5 dependent activity in HCMV reactivation in response to IL-6 which we hypothesise is via a SFK, and not the canonical JAK activation pathway. More generally, the data support the emerging concept that the mechanisms of HCMV reactivation are likely cell type and ligand-specific and reflect multiple escape strategies from latency.



Y012

The assembly of the HCMV IE1 protein into distinct foci on mitotic chromosomes

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Abstract

The HCMV immediate early 1 (IE1) protein is crucial for initiating early viral gene expression and modulating host transcription. In addition to its role in viral lytic cycle, IE1 has also been shown to counteract both intrinsic and innate immune responses. Additonally, recently it has been shown to induce amplification of the centromeric DNA, which also resulted in the induction of innate immune responses. The IE1 is a nuclear protein and was shown to associate with cellular genome in a "**chromosome painting**" pattern. However the functional significance of IE1 chromosome association remains unclear. IE1 associates with chromosomes *via* its C-terminal chromatin tethering domain (CTD), and more specifically through the **nucleosome-binding motif (NBM)** found within CTD. NBM mediates IE1 interaction with histones H2A-H2B. Notably, IE1 has been suggested to participate in viral genome tethering to host chromatin during latency, similar to episome maintenance proteins in other herpesviruses such as KSHV LANA.

In this study, we report a **previously unrecognized localization pattern of HCMV IE1** in the form of **chromosome-associated spots (CAS),** which we detect in part of the cell population in addition to the chromosome painting pattern. We observed this novel IE1 localization pattern in both transfected and HCMV-infected cells, across multiple cancer cell lines. IE1 CAS localize specifically to peri-centromeric regions. Using domain mapping, we identified the IE1 core domain as responsible for CAS localization, independent of the CTD. We further show that expression level of IE1 protein influences which localization pattern predominates. Notably, the IE1 mitotic localization pattern changes upon establishment of latency, indicating that CAS formation might be tied to the switch from lytic to latent state. The novel CAS localization of IE1 suggests a new, possibly cell-type specific function of this protein, distinct from its role in transcriptional regulation.

LATE BREAKING ABSTRACTS



LB(O)001

MAPKAP Kinase 2 Orchestrates Memory T Cell Inflation in Cytomegalovirus Infection

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Abstract

Memory T cell inflation is a unique immunological phenomenon observed during persistent viral infections, such as Cytomegalovirus (CMV). Unlike conventional memory T cell responses, which contract after infection resolution, a subset of CMV-specific T cells undergoes a progressive and sustained expansion, termed “inflation”, which is thought critical for long-term immune surveillance. The mechanisms that govern memory T cell inflation remain incompletely understood, yet they are pivotal for shaping these unique responses and informing therapeutic strategies for chronic viral infections. In this study, we investigate the role of MAP kinase-activated protein kinase 2 (MK2), a critical signaling mediator, in regulating T cell responses during murine CMV (MCMV) infection. Using MK2 knockout (MK2-KO) mice, we reveal that MK2 deficiency leads to alterations in the dynamics of MCMV-specific T cell responses without impairing viral control or tissue replication. Notably, MK2-KO mice display a reduction in non-inflationary MCMV-antigen-specific $CD8^+$ T cells, followed by enhanced inflation of MCMV-antigen-specific $CD8^+$ T cells. These findings suggest that MK2 plays a role in modulating the balance between inflationary and non-inflationary T cell subsets. Moreover, we confirm the importance of MK2 in differentiation of effector and memory T cells, as indicated by diminished expression of Killer Cell Lectin-Like Receptor G1 (KLRG1), a marker of terminal effector differentiation, on MCMV-specific $CD8^+$ T cells in MK2-KO mice. These results suggest MK2 is a pivotal regulator of T cell magnitude, kinetics, and phenotype during both acute and chronic MCMV infection. By elucidating the role of MK2 in the regulation of memory T cell inflation, this study provides critical insights into potential therapeutic strategies targeting MK2 in the management of persistent viral infections, immune aging, or immunocompromised conditions.



LB(O)002

The RL11 family glycoprotein pUL11 Impairs NK Cell Antiviral Activity in HCMV Infection

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Abstract

Introduction Human cytomegalovirus (HCMV) encodes many proteins which modulate the host's immune system. In immunocompetent hosts this results in viral persistence, although generally without acute symptoms. In immunocompromised individuals such as transplant recipients however, diminished T- and NK-cell responses can lead to poorly controlled HCMV replication and severe disease. HCMV-driven immunomodulation is likely to contribute to the loss of T- and NK-cell function in these patients.

Aim The pUL11 protein is expressed on the surface of infected cells and binds and inhibits the CD45 receptor tyrosine phosphatase on neighbouring T cells, resulting in reduced T cell control of infection. CD45 also has essential roles in NK cells; it activates Src-family kinases thus enabling ITAM phosphorylation of activating receptors such as NKp44, NKG2C, and CD16. We therefore determined whether pUL11 also inhibits NK cell activity.

Methods The effects of pUL11 on NK cell cytokine secretion, cytotoxicity, antibody-dependent responses and CD45 phosphatase activity were determined, in the context of HCMV infection and using purified pUL11. NK cell control of HCMV was quantified using a pair of GFP-expressing viruses, one of which contained a deletion of the UL11 ORF.

Results NK cells restrict the spread of ΔUL11-HCMV significantly more effectively than that of the parental strain. Fc receptor engagement by anti-HCMV IgG preparations strongly enhances NK control of infection, with ΔUL11-HCMV again significantly better controlled than WT-HCMV. In both cases, IFNγ production was markedly inhibited when pUL11 was present. pUL11 also reduced TNFα, perforin and granzyme B secretion, and NK cell degranulation. Inhibition of CD45 phosphatase activity by pUL11 was shown in a fluorometric assay.

Conclusions Our findings show that pUL11 impairs NK cell–mediated control of HCMV infection by suppressing cytokine release and cytotoxic function, particularly during ADCC, suggesting a new immunosuppressive role for pUL11.



LB(O)003

Characteristics of cytomegalovirus shedding in household contacts of CMV-seropositive pregnant women: a longitudinal study in a high CMV seroprevalence population

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Abstract

Introduction/Aim: Data regarding CMV shedding prevalence among household contacts in highly CMV-seropositive populations remain scarce. We evaluated CMV shedding prevalence, patterns, and viral load across age groups in household contacts of CMV-seropositive pregnant women.

Methods: A prospective longitudinal study enrolled 423 household contacts categorized into four age groups: <7 years (n=160), 7–15 years (n=91), 16–25 years (n=34), and >25 years (n=121). Participants were followed every 4 weeks over 7 months (from first trimester to delivery), with urine and saliva samples collected a median of 6 times (range 3–7) for CMV-DNA quantification. Prevalence ratios (PR) were calculated across age categories and body fluids.

Results: Overall, 43% (182/423) of participants shed CMV in saliva and/or urine during follow-up. Exclusive detection occurred in urine for 38.7% (164/423) and in saliva for 18% (77/423) of participants. CMV shedding prevalence significantly decreased with increasing age: 68% (113/165; PR=5.92, 95%CI:3.57–9.79) in children <7 years, 45% (41/91; PR=3.54, 95%CI:1.93–6.49) in ages 7–15 years, 14.7% (5/34; PR=1.27, 95% CI:0.49–3.27) in ages 15–25 years, and 11.5% (14/121) in adults >25 years. Younger age strongly correlated with shedding, particularly in saliva (PR=12.00, 95%CI:3.83–37.58) compared to urine (PR=6.56, 95%CI:3.79–11.35). Overall, viral load did not differ significantly across age groups (median CMV-DNA in urine respectively of 3.1, 3.0, 2.4, and 2.9; p=0.053; and in saliva of 3.3, 2.8, 3.1, and 2.3 $\log_{10}$copies/ml; p=0.058), though it peaked in young infants. Continuous shedding occurred exclusively in the urine of children <7 years, whereas adults exhibited intermittent shedding.

Conclusion: Pregnant women in high CMV seroprevalence settings face substantial viral exposure from household contacts, predominantly young children under 7 years who exhibit high shedding prevalence (~70%) and continuous excretion. Preventive hygiene measures should focus on limiting direct contact with bodily fluids from young household members.



LB(O)004

Antenatal CMV Evaluation of Screening (ACES) Study: Preliminary Results of a UK Pilot Implementation

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Abstract

1) Introduction/Aim The Antenatal CMV Evaluation of Screening (ACES) study is the first pilot implementation study in the UK assessing the feasibility, acceptability, and cost of incorporating routine antenatal Cytomegalovirus (CMV) screening into clinical practice. The primary objective is to evaluate a screening pathway for women booking up to 14+0 weeks gestation at University College London Hospitals (UCLH) to inform future national policy.

2) Materials and Methods We initiated a prospective screening cohort targeting 1,000 pregnant women. Eligible women are offered CMV screening utilizing standard serological assays. Screen-positive individuals follow established clinical pathways, including the offer of antiviral therapy. The study features nested sub-studies: ACES-Dx evaluates novel point-of-care diagnostics. ACES-Bio validates predictive protein biomarkers in amniotic fluid, alongside single-cell and spatial transcriptomics of the maternal-fetal interface. To comprehensively assess acceptability, we utilize online participant surveys for women both accepting and declining screening, supplemented by in-depth qualitative interviews with women and healthcare professionals.

3) Results Recruitment commenced this month with excellent uptake; 12 out of 13 eligible women have accepted screening to date. Among the screened women, four demonstrated IgG seropositivity, including one case with IgM present but high avidity; the remainder were seronegative. We have successfully recruited 6 patients into the diagnostics sub-study and 1 into the biomarkers sub-study. Crucially, we have already received numerous responses to our online surveys from women both accepting and declining screening, providing valuable early insights into families' views on CMV testing.

4) Conclusions Early data from the ACES pilot demonstrate high acceptability for first-trimester antenatal CMV screening, indicating excellent uptake among the heterogeneous patient population of a central London tertiary center. As recruitment accelerates, we anticipate gathering a robust cohort. We will present comprehensive preliminary results concerning screening feasibility, qualitative insights into patients' and professionals' views, and initial sub-study progress.



LB(O)005

CMV-Scan, a high-resolution serological assay, distinguishes vaccine-induced responses from wild-type CMV infections among participants of the MSD V160 vaccine trial

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Abstract

Introduction: V160, a replication-deficient whole virus vaccine based on the AD-169 strain, showed 42% efficacy against primary infection in adult women in a recent clinical trial. Because vaccinees are seropositive by conventional tests, CMV qPCR from monthly saliva or urine samples was used as the efficacy endpoint. Many participants had only a single, low-level positive qPCR suggesting false positivity and the possibility that vaccine efficacy was greater than originally estimated.

Methods: CMV-Scan is a phage-display-immunoprecipitation-sequencing assay, consisting of >350,000 peptides representing all known CMV strains spanning the whole viral proteome. CMV-Scan was performed on blinded sera from 28 participants who received either placebo or vaccine, with or without shedding by qPCR during the trial. We compared these results to unvaccinated CMV-uninfected negative controls and known cases of wild-type primary infection controls, before and after seroconversion. Total proteome, peak domain response profiles, and strain-specific responses were used to build a supervised classification framework to distinguish vaccine- from wild-type-induced responses.

Results: Total proteome and number of peak responses after vaccination were weaker than after wild-type infection ($p<0.001$). Peak response to the pp65_aa360-483 domain was highly indicative of vaccine responses, while a set of 15 additional features, including UL139 (which is deleted in V160), were specific for wild-type infections. V160-specific responses were found in all 10 qPCR-negative vaccinees. Among the 15 participants with shedding prior to last serum collection (9 placebo and 6 vaccine recipients), all had wild-type-specific CMV-Scan features, 6 of which also had non-AD169-strain-specific responses. Three participants with shedding beginning after the latest sample tested did not have evidence of WT infection by CMV-Scan.

Conclusion: Using high-resolution strain-specific serology, responses to WT infections were readily distinguishable from those to V160. This approach will be used to support re-estimation of vaccine efficacy in the V160 trial and could be incorporated into endpoint determination for future trials.



LB(O)006

Viral shedding in CMV-seropositive pregnant women receiving hygiene-based behavioral education in a highly seropositive population

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Abstract

Introduction/aim: Detecting CMV in bodily fluids signals viral replication driven by reactivation or reinfection in seropositive women. This study evaluated whether hygiene-based behavioral counseling throughout pregnancy impacts maternal reinfection as estimated by viral shedding.

Materials and Methods: An exploratory cohort study was conducted with CMV-seropositive pregnant women receiving public prenatal care in Brazil. Participants were enrolled at <18 weeks' gestational age, lived in households with >=2 people per bedroom, and at least one child <=7 years old. Two cohorts were compared: the pre-intervention group (G1), who received standard care; and the Intervention group (G2) who were provided structured guidance through educational sessions, short videos, biweekly electronic messages, and hygiene/sexual supplies. Participants were followed monthly until delivery, with urine, saliva, and vaginal swab samples tested at each visit for CMV-DNA to assess the prevalence of viral shedding between the two groups.

Results: The study evaluated 101 women in G1 and 80 women in G2, with both groups showing comparable demographic profiles, household contacts (2.3 vs. 2.5 per woman), and proportions of young children (47% vs. 43%). Specimens were collected a median of 6 times (range 3–7) during pregnancy. A proportion of 32.7% (33/101) of G1 mothers shed CMV-DNA in at least one body fluid, compared with 21.3% (17/80) in G2 (p=0.09). Shedding was reduced in saliva in the intervention group (0% in G2 vs. 8.9% in G1, p<0.01) and in urine (6.3% in G2 vs. 12.9% in G1) and vaginal secretions (21.3% in G2 vs. 32.7% in G1), although these later differences were not statistically significant.

Conclusions: Overall, the trend towards decreased shedding in the intervention group suggests hygiene education could reduce viral acquisition during pregnancy. This pilot evidence justifies a larger randomized controlled trial testing hygiene interventions against gestational CMV reinfection in this high-risk population.



LB(P)001

Targeting the HCMV glycoprotein pUL11 restores T cell control of infection

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Abstract

Introduction Human Cytomegalovirus (HCMV) modulates the host´s immune system in many complex ways. Immune surveillance of infected cells is impaired and, by less well studied mechanisms, antiviral functions of uninfected lymphocytes are also suppressed by the virus. In immunocompromised patients such as haematopoietic stem cell transplant (HSCT) recipients, an insufficiency of functional antiviral T cells can lead to uncontrolled HCMV replication and disease. As HCMV immunomodulation contributes to T cell inhibition, preventing these effects may improve T cell control of the virus. The viral glycoprotein pUL11 is expressed on the surface of infected cells and binds and inhibits the tyrosine phosphatase CD45 on neighbouring T cells. CD45 phosphatase activity is essential for T cell receptor signalling and the interaction with pUL11 impairs both $CD4^+$ and $CD8^+$ T cell effector functions, suppressing pro-inflammatory cytokine secretion and cytotoxic responses.

Aim To disrupt the interaction between pUL11 and its ligand, CD45, with the goal of improving T cell control of HCMV infection.

Methods We have made use of a monoclonal antibody (mAb) targeting pUL11 that blocks its interaction with CD45. The effects of this antibody on T cell control of infection, cytokine production and cytotoxicity were measured in in vitro infection control assays. CD45 phosphatase activity was determined using a fluorometric assay.

Results Blocking pUL11 binding to CD45 improves T cell responses, restores CD45 phosphatase activity and significantly limits viral spread in our co-culture assays. We see these effects with T cells from healthy CMV seropositive blood donors and from recently transplanted HSCT patients, and also with T cell preparations used therapeutically to control HCMV reactivation in HSCT patients.

Conclusions Our findings suggest that a therapeutic antibody targeting pUL11 could enhance endogenous or adoptively transferred T cell responses in high-risk patients, offering a novel immunotherapeutic strategy for HCMV control.



LB(P)002

Functional Inhibition of the Human Cytomegalovirus Immunoevasin pUL11

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Abstract

HCMV has a seroprevalence of 83% globally; immunocompromised individuals suffer from increased morbidity and mortality caused by poorly controlled active HCMV infections. HCMV encodes many immunomodulatory proteins, which contribute to this loss of immune control, and disrupting HCMV-driven immunomodulation may be therapeutically useful. pUL11, from the HCMV RL11 family, is expressed on the surface of infected cells and binds and inhibits the receptor tyrosine phosphatase CD45 on neighbouring lymphocytes. This leads to hyperphosphorylation of Lck and therefore to impaired TCR signalling and reduced T cell control of HCMV. A monoclonal antibody targeting pUL11 from the Merlin strain of HCMV blocks the CD45-pUL11 interaction and restores T cell functions. However, pUL11 is a highly variable protein and antibodies that we have generated appear to be specific for the strain of pUL11 used for immunization.

Therefore, we aim to develop a broadly-specific antibody that can recognize pUL11 from multiple strains of HCMV by performing structural studies of the interaction interface to identify potential epitopes of pUL11 for antibody generation.

pUL11 constructs derived from several clinical strains of HCMV were expressed, purified and characterized in terms of their ability to bind and inhibit CD45, glycan composition and position using mass spectrometry and CGE-LIF, dimerization state using Bio-SAXS and predicted structures using in silico methods.

The predicted N-terminal globular domain of pUL11 was identified as the minimal functional region. A model of this region was developed, incorporating glycosylation and SAXS data. pUL11 is multiply glycosylated with oligomannose glycans and forms dimers, which may underly its ability to inhibit CD45. A predicted binding site of the anti-pUL11 Merlin mAb was identified.

pUL11 is a potential therapeutic target, as disrupting its interaction with CD45 leads to enhanced immune control of HCMV. Structural studies into the pUL11-CD45 interface may allow the design of clinically useful blocking antibodies.



LB(P)003

Evaluation of Cytomegalovirus IgG, IgM, IgG Avidity, and PCR Findings by Gender and Pregnancy Status at a Tertiary Care Center in Istanbul Over a 2.5-Year Period

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Abstract

Introduction & Aim: Cytomegalovirus (CMV) is a leading pathogen of congenital infections. IgM is prone to non-specific positivity in antenatal screening, complicating the serological diagnosis of primary infection. We evaluated CMV IgG seroprevalence, IgM positivity, reflex IgG-avidity and PCR by sex and pregnancy status at a tertiary centre, benchmarking practice against international guidelines.

Material & Methods: Retrospective laboratory serosurveillance (January 2024–June 2026): Anti-CMV IgG, IgM were measured on the Abbott Alinity i analyser(CMIA) and IgG-avidity on VIDAS analyzer(ELFA). CMV DNA was tested by RT-PCR(CMV ELITe MGB-EliTECH Be Genius). Pregnant requests were defined by perinatology, antenatal or obstetric clinics with pregnancy-related indications. IgG, IgM, avidity and PCR results were matched by sample number. Proportions were compared with chi-square or Fisher tests.

Results: 6,922 IgG and 12,504 IgM tests were analysed (Tables 1–2). Overall IgG seroprevalence was 95.6%, higher in women (96.4% vs 94.0%; $p<0.001$) and in pregnant women (98.7% vs 94.0%; $p<0.001$); only 1.3% of pregnant women were seronegative. IgM positivity was 4.7% (equivocal 1.0%), lower in pregnancy (3.5% vs 6.2%; $p<0.001$) and higher in men (6.3% vs 4.3%; $p<0.001$). Among 131 IgM-positive samples with a same-sample avidity result, 98.5% showed high avidity (median index 0.88); all pregnant cases (80/80, 100%) were high-avidity. CMV PCR (n=941) was requested almost exclusively outside pregnancy (only two pregnancy-related requests, both negative) and predominantly in men, and did not track IgM (Table 3).

Conclusions: Our study demonstrated that IgM positivity during pregnancy almost always reflects a past infection, as revealed by the results of the reflex IgG avidity test. CMV PCR, on the other hand, has been frequently used for patients with compromised immune systems and for non-pregnancy-related indications. Consistent with the recommendations of ACOG and SMFM, which do not recommend routine maternal IgM screening, these data support indication-based testing, confirmatory avidity testing for positive IgM results.



LB(P)004

Modulation of cellular microRNA-219a-5p expression during Human Cytomegalovirus (HCMV) infection in the U373MG cell line

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Abstract

Introduction: Human Cytomegalovirus (HCMV) extensively manipulates host cell environment in order to establish optimal conditions for viral replication and persistence. Host cell microRNAs (miRNAs) are frequently dysregulated during this process and play a crucial role in virus-host interactions. MiR-219a-5p is a brain-enriched miRNA that functions as a tumor suppressor and is typically found down-regulated in glioma tissues and cell lines. However, its potential regulation during HCMV infection has not been investigated yet. This study explores the impact of HCMV infection on the temporal expression dynamics of host miR-219a-5p in a glioblastoma cell line model.

Methods: U373MG cells were infected with HCMV at different multiplicities of infection alongside mock-infected controls. The temporal expression profile of miR-219a-5p relative to control miR-16 was quantified by digital PCR across seven time points, from 15 min to 96 hpi. Statistical evaluation of miRNA expression was performed using two-way ANOVA.

Results: Time-course analysis of relative miR-219a-5p expression revealed that mock-infected U373MG cells exhibited a notable decline in miR-219a-5p levels, with a sharp downregulation occurring at 48 hours. Conversely, HCMV-infected cells maintained higher and more stable expression levels of miR-219a-5p throughout the 96-hour observation period, showing a significant divergence from the mock group at 48 hpi ($p=0.0322$). The overall status of HCMV infection had a significant effect on maintaining miR-219a-5p expression ($p = 0.0004$).

Conclusions: HCMV infection effectively outweighs the basal downregulation of host miR-219a-5p in U373MG cells, maintaining its stable expression throughout the viral cycle. This sustained miR-219a-5p profile indicates a specific viral manipulation of the host miRNA landscape. Further investigation is warranted to determine whether this stabilization is a deliberate viral strategy to support the viral life cycle or an indirect consequence of the altered cellular environment during prolonged infection.



LB(P)005

High-throughput Epitope Screening of Human Cytomegalovirus Immediate Early Protein 2 Reveals an Immunodominant $CD4^+$ T-cell Hotspot

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Abstract

Human Cytomegalovirus (HCMV) is an omnipresent pathogen that is associated with increased morbidity and mortality of immunocompromised individuals. Studies of T-cell immunity to HCMV primarily reflect anti-CMV pp65 or immediate early antigen 1 (IE1) activity. Recent evidence highlights the importance of the major immediate-early 2 (IE2) protein, which is expressed early after HCMV infection and reactivation, for regulating the lytic HCMV replication cycle. In this study, we designed a comprehensive screening approach to assess T cell responses against the IE2 HCMV protein in the peripheral blood of 15 HCMV-seropositive and 6 HCMV-seronegative healthy adults using IE2 synthetic long peptide (SLP) pools and cytokine flow cytometry. The T cell response against the IE2 protein was dominated by $CD4^+$ T cells whereas IE2-specific $CD8^+$ T-cell reactivity was measured in only 3 donors. Numerous novel HLA class I- and II-restricted IE2 T-cell epitopes were identified. Most of the donors recognized chiefly the $IE2_{351-434}$ residues, revealing a remarkably immunogenic area of the protein. Functional characterization of the IE2 $CD4^+$ and $CD8^+$ T cell responses uncovered 5 highly antigenic SLPs, which induced polyfunctional Th1 cytokine ($IFN\text{-}\gamma^+$/ TNF^+/ $IL\text{-}2^+$) response and could serve as candidate vaccine antigens. These findings support the evaluation of the five highly immunogenic IE2-derived SLPs as T cell-inducing vaccine candidates targeting immediate-early HCMV gene expression.



LB(P)006

One program, different clocks: cell type sets the pace and endpoint of HCMV infection

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Abstract

HCMV pathogenesis depends on its ability to infect diverse host cell types, enabling dissemination, persistence, reactivation, and transmission. Yet most insights into productive infection comes from fibroblasts, and it remains unclear whether HCMV infection follows distinct or common trajectories in different cell types and what are the barriers imposed on infection in distinct cellular environments. We profiled host and viral transcriptomes across five permissive or semipermissive human cell types, primary and BJ5a fibroblasts, microvascular endothelial cells (TIME), retinal pigment epithelial cells (ARPE 19), and THP 1 derived macrophages, integrating these measurements with reporter virus flow cytometry and single cell live imaging.

Despite profound differences in infection kinetics, HCMV followed a common transcriptional trajectory across all five cell types. Viral transcriptomes progressed along a single path in principal component space and preserved canonical temporal class progression. Cell types differed mainly in where they entered this trajectory, how rapidly they progressed, and where infection slowed or halted. HCMV also drove a shared host rewiring architecture, including repression of interferon, inflammatory, and antigen presentation programs, activation of mTORC1, proteasome, and cholesterol biosynthesis pathways, and suppression of cell cycle and adhesion programs. Cell identity instead imposed distinct stage specific barriers. ARPE 19 cells showed delayed immediate early onset associated with high intrinsic interferon stimulated gene expression, whereas TIME cells showed accelerated immediate early accumulation and an early burst of viral transcription. BJ5a fibroblasts tracked primary fibroblasts through 72 hpi but later diverged, revealing an unexpected late barrier associated with reduced viral DNA replication. Macrophages progressively diverged from the fibroblast trajectory and reached a replication ceiling, with stalled viral progression.

Together, these results reveal that HCMV executes a conserved, rate adjustable program whose pace and endpoint are set by host barriers acting at distinct stages.



LB(P)007

Fortification of breast milk with anti-CMV antibodies to prevent postnatal cytomegalovirus acquisition in preterm infants

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Abstract

Background: Breast milk is the most common route of postnatal cytomegalovirus (pCMV) transmission from CMV-seropositive mothers to preterm infants, who are at high risk of pCMV acquisition because of their immature immune systems. While recognizing the importance of breast milk for preterm infant health, little is known about effective strategies to eliminate pCMV transmission risk while maintaining the benefits of unpasteurized breast milk in this high-risk population. We hypothesize that the exogenous addition of a potent and safe antibody to neutralize CMV shedding in breast milk can eliminate pCMV acquisition for preterm infants.

Methods: We consented and collected breast milk from mothers of preterm infants (born <32 weeks gestation, n = 30). We tested the safety and neutralization potency of varying doses (1 – 500 µg/mL) of the polyclonal anti-CMV hyperimmune globulin product, Cytogam, diluted in breast milk spiked with increasing levels of infectious CMV, in a relevant fetal gut epithelial cell line (HIEC-6) as well as human fibroblast and epithelial cell lines.

Results: We found that fortifying delipidized breast milk with Cytogam did not inhibit its neutralization potency and was not cytotoxic to HIEC-6 cells at experimental concentrations. In fibroblasts, we identified 500 µg/mL Cytogam as the optimal dose for reducing exogenous CMV in breast milk. On HIEC-6 cells, we confirmed that breast milk fortification with 500 µg/mL of Cytogam could eliminate detection of exogenously added CMV up to 33 pfu (1 x 10^5 genome copies) and could reduce CMV infectivity to <10% in breast milk even at high virus doses (4000 pfu/4 X 10^6 genome copies).

Conclusions: The CMV-neutralizing potency and lack of cytotoxicity of breast milk fortified with a clinically approved anti-CMV product, Cytogam, presents a unique opportunity to safely and effectively prevent pCMV acquisition in preterm infants while maintaining optimal early enteral nutrition for this vulnerable population.



LB(P)008

Limited-Sampling AUC-Guided Therapeutic Drug Monitoring Reveals High Variability in Ganciclovir Exposure in Infants Treated for Cytomegalovirus Infection

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Abstract

Introduction: Valganciclovir is used for the treatment of CMV infection in infants. Rapid developmental changes in renal function, body composition, and drug disposition may result in variability of valganciclovir (VGCV) exposure.

Aim: To assess VGCV exposure and the clinical utility of limited-sampling, AUC-guided therapeutic drug monitoring (TDM) using microsampling for dose individualization in infants with CMV infection.

Methods: GCV concentrations were measured during routine TDM in infants receiving valganciclovir. Capillary blood samples were obtained by heel prick at 2, 4, and 8 h after drug administration and collected using a volumetric absorptive microsampling (VAMS) device (Mitra®, 10 µL). GCV was quantified by liquid chromatography–tandem mass spectrometry (LC–MS/MS). $AUC_{0–12}$ was estimated using the limited-sampling equation: $AUC_{0–12} = 0.373 + 1.885 \times C_2 + 2.927 \times C_4 + 5.674 \times C_8$. $AUC_{0–12}$ of 27–40 mg·h/L was used as the target exposure range. Dose recommendations incorporated measured exposure, clinical response, and hematological toxicity.

Results: Forty-eight pharmacokinetic profiles from 23 infants were evaluated. $AUC_{0–12}$ ranged from 1.28 to 101.91 mg·h/L, with a median of 27.49 mg·h/L (IQR 20.20–40.89). Only 11/48 profiles (22.9%) were within the target range; 24/48 (50.0%) were below and 13/48 (27.1%) above target. Overall, 77.1% of assessments demonstrated off-target exposure. Available weight-normalized doses ranged from approximately 8.6 to 17.8 mg/kg, with only a weak association between dose and AUC. Serial assessments in individual infants demonstrated substantial changes in exposure during treatment despite relatively small changes in weight-based dosing.

Conclusions: VGCV exposure in infants with CMV infection is highly variable and poorly predicted by weight-based dosing alone. Heel-prick VAMS sampling using only 10 µL of capillary blood combined with LC–MS/MS provides a minimally invasive and practical approach to limited-sampling AUC estimation. This strategy frequently identifies clinically relevant under- or overexposure and may support dynamic valganciclovir dose individualization during infancy.



LB(P)010

Prenatal Valganciclovir Therapy in Congenital Cytomegalovirus Infection: Pregnancy Outcomes and Neonatal Results - A Single-Centre Retrospective Analysis

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Abstract

Introduction / Aim

Congenital cytomegalovirus (cCMV) infection is the most common congenital viral infection worldwide, affecting approximately 0.2–0.7% of live births and representing a leading cause of sensorineural hearing loss and neurodevelopmental disability. Prenatal valganciclovir (VGCV) therapy to suppress intrauterine viral replication is used off-label, with limited evidence on safety and efficacy. This study evaluated pregnancy courses and neonatal outcomes in women receiving prenatal VGCV for confirmed fetal CMV infection at a tertiary referral centre.

Materials and Methods

This monocentric retrospective analysis included pregnant women treated with VGCV (3×450 mg/day) for confirmed fetal CMV infection (positive PCR in amniotic fluid) between January 2015 and December 2022 at the Charité - Universitätsmedizin Berlin, CVK. Data were extracted from medical records and a prospective questionnaire (CRF VGCV2022). Primary endpoints were neonatal AABR outcome and mode of delivery; secondary endpoints included neonatal anthropometrics, cerebral imaging, ophthalmological findings, and neurodevelopmental follow-up. Statistical analysis was performed using Microsoft Excel.

Results

Of approximately 40 cases identified, 9 had complete follow-up data (lost-to-follow-up >70%). All 9 deliveries were spontaneous vaginal births. Apgar scores were normal in 8/9 neonates; one showed transient depression (1/5/10). Umbilical artery pH ranged from 7.17 to 7.34. Birth weight ranged from 3,280 to 4,010 g (mean 3,626 g). AABR was normal in 8/9 neonates (one inconclusive). Cerebral imaging was unremarkable in 6/7 assessed neonates; one showed periventricular signal changes. Two children (22%) required neuropaediatric follow-up. No severe maternal haematological toxicity was documented.

Conclusions

Prenatal VGCV therapy was well tolerated in this small cohort, with reassuring perinatal outcomes. The high rate of loss to follow-up severely limits interpretation. Prospective multicentre trials are urgently needed to establish the efficacy and safety of prenatal VGCV therapy in fetal CMV infection.



LB(P)011

In utero battlefield: modelling congenital CMV in trophoblast organoids

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Abstract

Introduction

Conventional 2D models for investigating congenital cytomegalovirus (cCMV) infection are utilizing trophoblast cell lines that are used for antiviral screening, receptor studies and basic replication kinetics. These models lack the complex cellular architecture found at maternal-fetal interface that would allow understanding the transmission of the virus, immune consequences and developmental timing. Fundamental placental CMV research is hampered by the lack of a validated 3D human trophoblast model; unfeasible CMV replication outside its natural host; placental complexity comprising of trophoblast stem cells (TSC), extravillous trophoblasts (EVT) and syncytiotrophoblasts (STB); barriers in obtaining the tissue and ethical considerations. Nonetheless, understanding the placental susceptibility for CMV infection and the development of a suitable 3D model are necessary for understanding the mechanism of cCMV disease and generation of effective preventive and therapeutic cCMV interventions.

Materials and Methods

We aim to develop a human trophoblast organoid model resembling the maternal-fetal interface in-vivo to enable investigation of cCMV infection. For this we use a combination of 2D and 3D models comprising TSC, EVT and STB. Lastly, we aim at looking at changes in gene expression and immune response in the host.

Results

To assess the primary target of infection we infected 2D monocultures of individual placental cells. Our results show STB exhibited the most IE1-positive nuclei, followed by EVT and TSC. Next, we generated 3D trophoblast organoid system from first-trimester placental tissue that mimics the interaction between TSC or EVT and STB.

Conclusions

Further research is needed to validate the infection in model organoids. Studies should examine the impact of co-culture between infected placental organoids with brain organoids, as human CMV virus affects neurogenesis during embryonic development. With the successful development of a complex co-cultured 3D system, treatment strategies could be revisited, aiming to find a better approach directed at earlier detection and mitigation of the adverse effects.

AUTHORS' INDEX



Author name	Abstract number
Abanoz, Fahrunnisa	LB(P)003
Abdelkawy, Yara S.	O038, Y001
Abdul Khaliq, Sana	P022
Abdul-Sater, Ali	O008
Abouguendia, Hatem	P020, P036, Y001
Adler, Stuart	P035
Adley, Amity	P082
Afink, Gijs	LB(P)011
Agacinska-Odroniec, Marta	P029
Agrofoglio, Luigi	O035
Airenne, Tomi T.	Y001
Alain, Sophie	O034, O035, P007, P008, P009, P039, P074, P075
Alarcón, Ana	P077
Albanese, Andrea Salvatore	P030
Alchin, Haley	LB(O)004
Aleman Navarro, Adriana	LB(P)007
Alexander, Ellie	O013
Alfi, Or	P002
Algarotti, Alessandra	O031
Alipour, Maedeh	P036, P054, Y001
Almeida, Sofia	P043
Alonso-Ojembarrena, Almudena	O023, P005, P047, Y007
Alshamandi, Waleed	LB(P)010
Altfeld, Marcus	O029
Álvarez-Vallejo, Beatriz	O023, O024, P005, P047, Y007
Amenitsch, Lena	O008
Anam Khawaja, Iqra	P036
Andacic, Laura	P030
Anderson-Carnage, Morgan	O016
Andree-Busch, Nicole	O028
Andrei, Graciela	P008
Ang, Ching-Seng	O015
Ansarizadeh, Mohammadhassan	P018, P033
Antoniadi, Marina	O047
Antoniadou, Anastasia	O012, P078, P084
Antrobus, Robin	O003, Y009
Ara, Fatima	Y007
Ara, María	P047
Arabaci, Cigdem	LB(P)003



Aragon, Davi	LB(O)003, LB(O)006
Arossa, Alessia	O007, Y010
Artsen, Michael	P041
Asafa, Olayinka	P056
Asbach-Nitzsche, Alexandra	O027
Ashraf, Awais Muhammad	LB(P)002
Ashurov, Anna	O042
Ashurov, Artem	O042
Attilakos, George	LB(O)004
Atukorala, Ishara	O015
Awobajo, Funmileyi O.	P056
Ayello, Janet	O016, O017, Y006
Babl, Verena	O008
Badeau, Thomas	P018
Bagley, Matthew	O043
Baiesi Pillastrini, Federico	P087
Bailey, Heather	LB(O)004
Bakar, Asrar Abu	P006
Balachandran, Harikrishnan	O002
Balboni, Alice	P087
Baldanti, Fausto	O007, O018, O031, O044
Baldassarre, Mariella	O011
Bamford, Alasdair	Y008
Baquero-Artigao, Fernando	O024, P005, P047, Y007
Baquero-Artigao, Francesco	O023
Barnett, Sarah	O022, P031
Barnowska, Agnieszka	P063
Bartek, Jiri	Y001
Baud, David	P040, Y003, Y005
Bayda, Nader	O035
Bayer, Christof	O039
Beard, Sally	O015
Beck, Marine	O035
Becker, Sara	P029
Bedir Demirdag, Tugba	P023
Behbehani, Gregory	O016
Bekker, Adrie	P006, P056, Y002
Beltrami, Anna	O011
Bennett, Amelia	LB(O)004, Y008
Benou, Sofia	P071, P080



Berthelot, Océane	O009
Bertović, Ivana	P028
Bestard, Oriol	O032
Bhugra, Arjun	P013, P016
Bianchessi, Antonio	O018
Bianchi, Leila	O014
Bianco-Wilhelmi, Vanessa	P018
Bilev, Eleni	O029
Bissinger, Alfred Lennart	P059, P060
Blanchet, Clement	LB(P)002
Blázquez-Gamero, Daniel	O023, O024, P005, P006, P031, P047, Y007, Y008
Bocchini, Benedetta	O025
Bonifazi, Francesca	O031
Boonyaratanakornkit, Jim	O037
Boppana, Suresh	O026, P057, P058, P081
Borgatti, Eva Caterina	P008, P087
Borsodi, Christian	P042
Boucoiran, Isabelle	LB(O)005
Bourgon, Nicolas	O009, Y005
Boussata, Souad	LB(P)011
Boutolleau, David	O034
Bouyrigu, Chaïma	P009
Bouza, Eleni	O047
Bowen, Asha	P046
Bozdayi, Gulendam	P004, P023
Bošnjak, Berislav	O045
Bradley, Eleanor	P055
Brannen, Sydney	Y006
Brasiene, Vykinta	P066
Bressolette-Bodin, Céline	O034
Breuer, Judith	O013, O041
Briganti, Domenica Federica	O044
Brinkmann, Melanie M.	O028, P026
Britt, Bill	P057
Britt, William J.	LB(O)003, LB(O)006, O026, P058, P081, Y010
Britton, Philip N	O010, P046
Brizić, Ilija	O030, P028, P034, P050, Y010
Brown, Richard	P031
Brune, Wolfram	O046, P030
Bulsiewicz, Dorota	LB(P)008



Bunin, Nancy	O017
Buonsenso, Danilo	O023, P005, P047
Burback, Peter	P035
Busam, Amelie	O013
Buxmann, Horst	O023, P005, P047
Bybjerg-Grauholm, Jonas	P053
Bækvad-Hansen, Marie	P053
Büttner, Falk F. R.	LB(P)002
Cader, Agnieszka	O019
Caggana, Michele	O021, P048
Caillard, Sophie	P038
Cairo, Mitchell	O016, O017, Y006
Calò Carducci, Francesca	O011
Cantiani, Alessia	P087
Capasso, Letizia	O024
Capoccia-Brugger, Romina	Y003
Capretti, Maria Grazia	O011, P087
Caproni, Anna	P018
Cassaniti, Irene	O018, O031, O044
Cauquot, Maxime	P007
Cavallaro, Giacomo	P045
Cecere, Gaetano	P083
Ceulemans, Michael	P041
Chali, Tolina	O001
Champion, Jesse	Y009
Chandrasekaran, Preethi	O048
Chasqueira, Maria	P043
Chegou, Novel N.	P056
Chen, Jingyi	O027
Chen, Xiaohan	O039
Chernoske, Willow	O036
Chiappini, Elena	O014
Chielens, Laura	P041
Chiusolo, Patrizia	O018, O031
Christaki, Irene	P085
Čičin-Šain, Luka	O030, Y010
Clark, Julia	P046
Classen, Nica	O042
Cokarić Brdovčak, Maja	P028, P050
Comolli, Giuditta	O044



Connors, Megan	LB(P)007
Cook, Charles	LB(O)001
Cooke, Kenneth	O017
Coote, Dominic	P031
Corbett, Jason	O027
Cormano, Daniela	P083
Costa, Bibiana	O045
Costa, Elena	P041, P067
Coste-Mazeau, Perrine	P075
Coucke, Wim	O033
Coutinho, Conrado	LB(O)003, LB(O)006
Coyne, Carolyn	O002
Crevits, Luna	P073
Croker, Hannah	P082
Cui, Leah	P020
Cunnington, Aubrey	O022, P031
Čuvalo, Berislav	O045
Czajkowska, Agnieszka	LB(P)008
Czech-Kowalska, Justyna	LB(P)008, O019
D'Acunzo, Ida	P045
D'Adamo, Federica	P087
D'Angelo, Piera	O007, O018, O044
Dall'Armi, Blandine	P039
Damatopoulou, Anna	P085
Damour, Alexia	P010
Dang, Xindi	O006
Daniel, Jency	O021, P048
Daniels, Danielle	O021, P048
David Mehaber, Stav	P052
Davis, Jordann	P046
De Angelis, Morena	P087
De Catte, Luc	O015
De Conninck, Caroline	P041
De Marco, Giulio	P083
De Muynck, Emilie	O033
Deb, Anasua	O027
Decker, Thomas	O008
Del Valle, Rut	O024
DeLaMora, Patricia	O021, P048
Delforge, Marie-Luce	P041



Desimpelaere, Astrid	P073
Desravines, Rudie	O021, P048
Desta, Silas	O001
Dhital, Ravi	O006
Dhotre, Kishore	P011
Di Meo, Florent	O035
Diaz-Decaro, John	P052
Diaz-Gonzalez, Daniel	O035, P008
Dimitriou, Gabriel	P071, P080
Dinopoulos, Argirios	P061
Distler, Ute	P029
Dominguez, Sara	P005
Doorly, Robert	O043
Dos Santos, Aline	LB(O)006
Dougherty, Sonia	P046
Drongovskij, Anastazija	LB(P)011
Drysdale, Simon	P031
Dungu, Kia Hee Schultz	P053
Dunican, Claire	O022, P031
Dvorak, Christopher	O017
Dzikiene, Renata	P066
Dölken, Lars	P019, P028
Ebah, Diane	O034
Eiben, Maike	P086
Eichhorn, Raphael	P035
Eichler, Jutta	P011
Einsiedler, Christina Sandra	O028
Eisen, Sarah	LB(O)004, P031
Eiz-Vesper, Britta	O045
Elgarten, Caitlin	O017
Engelhardt, Anna	O029
Erdem, Kubra	LB(P)003
Eržen, Nika	P076
Esteva Afonso, Cristina	P077
Eventov Friedman, Smadar	P052
Evren, Kubra	P004, P023
Fairclough, Rosie	O043
Fakhroo, Aisha	Y011
Falk, Christine	O045
Farlik, Matthias	O008



Farmaki, Evangelia	O005
Farrell, Maura	P017
Fatafta, Mohammd Amr	P017
Fedorov, Roman	LB(P)002
Ferris, Elizabeth	O004, Y009
Fidan, Isil	P023, P004
Fidler, Katy	O022, P031, Y007
Fielding, Ceri	O004, O029
Figlerowicz, Magdalena	P065
Filip, Thomas	O008
Filis, Christos	O012, P078, P084
Fiorenza, Maryse	P074
Fiori, Simona	O014
Fontalvo Acosta, Melissa	P077
Forer, Boaz	P002
Fortelny, Lucio	P011, P024
Fortuny, Claudia	O024
Fougère, Yves	O023, O024, P005, P047
Foulon, Ina	O023, P005, P041
Fourgeaud, Jacques	O009, Y005
Fowler, Karen	O026, P057, P058, P081
Friedlich, Phillipe	Y006
Frigati, Lisa	Y002
Fritz, Lea	O045
Frobert, Emilie	O034
Frugier, Tony	O048
Fryganas, Andreas	O012, O020, P061, P084
Full, Florian	O002
Furione, Milena	Y010
Förster, Reinhold	O045
Gabrielli, Liliana	P087
Gacina, Lydia	P050
Galli, Luisa	O011, O014
Gallmann, Dalia	Y003
Gampawar, Piyush	P031
Ganbat, Gantulga	LB(O)002, LB(P)001, LB(P)002
Gantt, Soren	LB(O)005
Ganzenmüller, Tina	O002, P059
Garcia, Erica	P017
Garnier-Geoffroy, Françoise	O034



Garofoli, Francesca	O011, O024
Garrigue, Isabelle	O034
Garrote, Elisa	O023, P005, Y007
Geiger, Pia	P011
Georgiev, Hristo	O045
Germi, Raphaelle	O034
Ghirardello, Stefano	O007, O011
Giapros, Vasileios	P071, P085
Gifford, Saffron	O027
Gillespie, Alanna N	O048, P046
Giménez, Noemí	O024
Ginossar, Noam	LB(P)006
Giorgi, Melpomeni	O012, O020, P061
Gkentzi, Despoina	O005, O023, O047, P005, P031, P071, P080
Gkioule, Charikleia	P059, P060
Glad, Mette Trantel	P053
Goebel, W. Scott	O017
Goldsmith, Jory A.	O042
Golemac, Mijo	Y010
Gopal, Aiswarya	P019
Goswami, Ria	LB(P)007
Gozdur, Aleksandra	O019
Grammenoudi, Sofia	O005
Gravina, Assunta	P083
Gray, Clive M.	P056, Y002
Gregorini, Marilena	O044
Griffiths, Hannah	O022, P031
Griffiths, Paul	O041
Grivea, Ioanna	P071
Grosek, Štefan	P001
Grošelj, Urh	P076
Grzybowska, Karolina	LB(P)008, O019
Gualtieri, Renato	P003
Guenin, Anne-Laure	P007
Guilleminot, Tiffany	O009
Gupta, Tejasv	Y012
Gutierrez Jauregui, Rodrigo	O029
Guzel Tunccan, Ozlem	P004, P023
Guérin, Emilie	P009
Görzer, Irene	O039, P035



Göttler, Rebecca	O002
Gül, Gülseven	Y003
Haack, Isabell	Y010
Haegele, Sandra	O002
Hahn, Friedrich	O028
Hamilton, Stuart	P008
Hammer, Quirin	O029
Hamon, Magali	P074
Handel, Andrew	O021, P048
Hannan, Natalie	O015
Hantz, Sébastien	O034, P007, P009, P010, P039, P074, P075
Hargreaves, Alexander	O041
Harmsze, Ankie	P006
Harrison, Lauren	O017, Y006
Hasanpour, Shaghayegh	P032, P036, Y001
Hassan, Ahmed	O045
Hatterschide, Joshua	O002
Hatzidaki, Eleftheria	P071
Haug, Yara	P060
Hefter, Yosefa	P052
Hengel, Hartmut	O002, O042
Hepca, Oana	O018
Hicar, Mark	O021, P048
Hicks, Kate	LB(O)005
Hoffmann, Katja	O002, O042
Holder, Beth	P055
Holmes, Natasha	P070
Hoopmann, Markus	P060
Horsch, Antje	P040
Hosseini, Shirin	Y010
Hribljan, Valentina	Y010
Hu, Jing	LB(O)005
Hua, Xinyang	O048
Hui, Lisa	O010, O015, O048, P069, P070, P082
Husain, Bushra	O029, P037
Hymes, Saul	O021, P048
Iro, Mildred	P031
Iskandar, Elizabeth	O018, O031
Jackson, Sarah	O043, P051
Jacobs, Roland	LB(O)002



Jacobs, Tom	P006
Jacobsen, Carina	O029
Jaki, Lena	P008
Jan, Wajanat	O022, P031
Jarck, Jan	P086
Jenne, Silja	P011
Jiang, Xuan	O001
Johannesson, Nina	LB(P)011
John, Minnie	O021, P048
Jones, Cheryl	O048, P046
Jones, Christine E.	O049
Jones, Lauren	O040
Jonjić, Stipan	O030, P028, P034, P050, Y010
Jump, Pamela	O049
Jurado, Angeles	P062
Juranić Lisnić, Vanda	P028, Y010
Jürgens, Carina	P037
Kachramanoglou, Carolina	O022, P031
Kadambari, Seilesh	O048, P031
Kaforou, Myrsini	P031
Kagan, Karl Oliver	O002, P060
Kakkar, Fatima	LB(O)005
Kali, Gugu T.J.	P056, Y002, Y008
Kalidindi, Manasa	O026
Kalimeris, Stylianos	Y003
Kalinke, Ulrich	O045
Kao, Carol	Y006
Kapoor, Neena	O017, Y006
Karagiannidou, Sofia	O005, O012, O020, O023, O024, P005, P031, P061, P078, P084, Y007
Karagoz, Dilan	P004, P023
Karatas, Aysel	LB(P)003
Karavana, Georgia	O047
Karofylakis, Emmanouil	P078
Karthigeyan, Krithika	LB(P)007
Kasztelewicz, Beata	O019
Katechi, Konstantina	O047
Katsarou, Angeliki	P078
Kaufmann, Maren	P026
Kavvatha, Dimitra	O012, P078, P084
Kay, Denise	O021, P048



Kay-Fedorov, Penelope C.	LB(O)002, LB(P)001, LB(P)002, O029, P037
Kenea, Abera	O001
Kervella, Delphine	O032
Khawaja, Iqra Anam	P033, Y001
Kiefmann, Julia	P056
Klein, Florian	O042
Kliavdianou, Maria	O047
Knibbe, Catherijne A. J.	P006
Koch, Manuel	O042
Kocur, Arkadiusz	LB(P)008
Kohl, Ann-Kathrin	O002
Kokkinaki, Chrysanthi	LB(P)004
Kolb, Philipp	O002
Kong, Yi Wen	LB(O)001
Kornhauser Cerar, Lilijana	P001
Korres, George	O012
Korte, Martin	Y010
Kossi Gota, Ghislain	O035
Kourlaba, Georgia	P071
Kovač, Jernej	P076
Krmpotic, Astrid	P050
Kropff, Barbara	O039, O041
Krstanović, Fran	O030, Y010
Kumar, Abhinav	P016
Kunze, Mirjam	O002
Kunzweiler, Colin	P052
Kuthubutheen, Jafri	O048
Kveštak, Daria	P034, Y010
Kyriakopoulou, Aikaterini	O047
L'Huillier, Arnaud	P003
Lachmann, Nico	P026
Lacourt, Sonia	O009
Ladomenou, Fani	P085
LaGamma, Edmund	Y006
Laketa, Vibor	O042
Lankina, Anastasia	O041
Lanna, Federica	P087
Larouche, Ariane	LB(O)005
Lassnig, Caroline	O008
Laval, Lucie	O035, P009



Lawler, Sean E.	LB(O)001
Lazarczyk, Marzena	O038
Lazzarotto, Tiziana	O011, O018, O031, P087
Le Goff, Jerome	O034
Le Moine, Alain	O032, P038
Le Prevost, Marthe	LB(O)004
Lee, Dean	O016, O017, Y006
Lefevre, Camille	P010
Lek, Elizabeth	P031
Lemmermann, Niels A.	P019, P029
Leppek, Kathrin	P019
Leruez-Ville, Marianne	O009, P075, Y005
Leuzinger, Karoline	P008
Levin, Mike	P031
Lewis, Hannah	O037
Li, Hanqi	O004
Li, Yimei	O017
Liao, Yanling	O016
Liao, Yi	P025
Liberatore, Andrea	P087
Ligat, Gaëtan	P007
Lilleri, Daniele	O007, O011, O018, O031, O044
Lin, Yuchen	Y009
Lischka, Peter	P011
Lisnić, Berislav	P028, Y010
Liu, Peng	O006
Liu, Siqing	O001
Liu, Tong	P020
Liu, Xuanlin	P006
Liuzzi, Giuseppina	O011
Liñan, Nerea	P077
Loizou, Chrysanthi Eleni	O005, O020, P084
Longbottom, Katherine	O022, P031
Lorenzetti, Giulia	O011
Lui, Nicole	O041
Luo, Minhua	O001
Lyall, Hermione	O022, O023, O024, P005, P006, P031, P047, Y007, Y008
Lösing, Josephine	P011
Mace, Emily	O040
Mackenzie, Charlene	O048



Maeki, Takahiro	O028
Mafi, Sarah	P007, P009, P039
Mahanama, Adhyana	O049
Maier, Oliver	P026
Majeti, Saketh	P027
Malagola, Michele	O018, O031
Male, Victoria	P055
Malee, Kathleen	O021, P048
Mamatsi, Eleftheria	O047
Mancino, Giuseppina	O025
Mandzhukova, Ivet	O040
Mania, Anna	P065
Marchant, Arnaud	O032, P038
Marcos, M. Angeles	P008
Maria Borst, Eva	Y012
Marques, Augusta	P043
Marschall, Manfred	P011, P024
Marshall, Brendan	P025
Marsico, Concetta	P087
Martin, Camilia	LB(P)007
Martinez de Tejada, Begoña	Y003
Martinez-Martin, Nadia	O029, P037
Maruotti, Giuseppe	O011
Marzan, Melvin	P069
Materljan Franki, Jelena	P028, P050
Matteoli, Michela	P034
Mavroeidi, Stamata	O047
Mayeras, Melissa	O035
Mazioti, Argyro	O012, P061
Mazor, Marija	P028
Mazur-Melewska, Katarzyna	P065
Mazzarelli, Laura Letizia	O011
McArdle, Andrew	O022, P031
McCoy, Jacqui	P070
McIntyre, Sarah	O010
McLellan, Jason S.	O042
McNally, Jane	P046
McVoy, Michael	P027, P035
Medved, Magdalena	P028, P050
Mele, Dalila	O018, O031, O044



Menna, Elisabetta	P034
Mercado, Noe B.	LB(O)001
Merelli, Maria	O011
Messerle, Martin	Y012
Mevorach Zussman, Noa	LB(O)004
Mihalić, Andrea	O030, P034, Y010
Miklic, Karmela	P050
Miller, Katherine	O006
Miranda-Sole, Carlota	P031
Mo, Xiaokui	Y006
Molakalapalli, Akshay	P027
Moliner Cladерón, Elisanda	O023, P005, Y007
Mollik, Madlen	O039, P035
Montagnani, Carlotta	O014
Montagner, Francesco	O028
Montague, Amy	O049
Moreno, María	P077
Moreno-Betancur, Margarita	O048
Morris, Erin	Y006
Moschopoulos, Charalampos	P078
Moses, Samuel	P013
Mosimann, Beatrice	Y003
Muga, Oihana	P047
Muller, Yves	P011
Mura, Omar	O044
Mussi-Pinhata, Marisa	LB(O)003, LB(O)006
Muñoz Almagro, Carmen	P077
Märtson, Anne-Grete	P006
Müller, Mathias	O008
Müller, Regina	P011
Nachman, Sharon	O021, P048
Narayan, Priyanka	LB(P)007
Nastouli, Eleni	LB(O)004
Naucler, Cecilia	P033
Navarro, David	P008
Nayak, Jennifer	O021, P048
Negrini, Silvia	LB(O)003, LB(O)006
Nessali, Abel	P012, P062, P086
Nevels, Michael	O027
Nichols, Samuel	P031



Nika, Angeliki	O047
Noguera-Julián, Antoni	O023m P005, P047, P077, Y007
Nolan, Sheila	O021, P048
Nosan, Gregor	P076
Ntshinka, Awanda	Y002
Nurbekova, Assel	P029
Nyegaard, Mette	P053
Nygaard, Ulrikka	P053
Näther, Laura	O002
Obergfäll, Debora	P011
Ocak, Kerem	LB(P)003
Oiknine-Djian, Esther	P052
Okecha, Georgina	O043, P051
Ọlánrewájú, Ayọ̀kúnlé	O036
Op de Beeck, Anne	P038
Orange, Jordan	O040
Ornaghi, Sara	O011
Osanyinlusi, Samuel A.	O029, P037
Oschwald, Ricarda	O002
Ostermann, Eleonore	O046
Otero, Claire E.	P017
Paciorkowska-Świder, Wanessa	O019
Padalko, Elizaveta	O033, P073
Paeschke, Katrin	P029
Paixão, Paulo	P043
Pajkrt, Dasja	LB(P)011
Palasanthiran, Pamela	P046
Palmetti, Matteo	O011, O014
Paltiel, Ora	P052
Palyvou, Maria	O047
Panagioti, Eleni	LB(O)001, LB(P)005
Panet, Amos	P002
Pang, Ying	O002
Panisoi, Georgia	O047
Panning, Marcus	P008
Pantalone, Mattia	P036
Papachatzi, Eleni	O023, P031
Papadakis, Georgina	O048
Papaevangelou, Vana	O005, O012, O020, O023, O024, O047, P005, P006, P021, P031, P047, P061, P071, P078, P080, P084, Y007, Y008



Papakonstantinou, Maria Eleni	O047, P021
Parabere, Solene	O034
Paulus, Christina	O027
Payne, Helen	O022, P006, P031, P056, Y002, Y008
Pedrero-Tomé, Roberto	O024, P047
Pellegrini, Carlo	O044
Pelosi, Emanuela	O049
Penner, Justin	O022, P031, Y007, Y008
Permar, Sallie R.	P017, LB(P)007
Petropoulou, Chrysoula	O047
Petrovec, Miroslav	P001
Phelan, Peter	P068
Piccini, Stefania	O007
Piccirilli, Giulia	O018
Piccirillo, Priscilla	P029
Pichon, Christine	O009
Pietrzyk, Aleksandra	LB(P)008, O019
Pinninti, Swetha	O026
Pinto, Ana	O046
Pirouzfar, Mohammad	P018, P020, P036, Y001
Pittet, Laure	P003
Piwoz, Julia	O021, P048
Ploil, Claudia	O028
Plückebaum, Nina	O029, P037
Pokalyuk, Cornelia	P035
Poliankou-Zannaki, Despoina	O047
Polverelli, Nicola	O018, O031
Pomar, Léo	P040, Y003, Y005
Poole, Emma	O027, Y011
Posfay-Barbe, Klara	P003
Poulakis, Zeffie	O048
Pournaras, Spyridon	P021
Powell, Kim	O048
Poyet, Jean-Luc	P007
Poznanski, Piotr	O038
Preston, Hannah	O040
Primus de Jong, Célia	P041, P067
Prins, Nicole	P056, Y002
Pritchett, Cedric	P068
Privato, Roberto	O014



Pronier, Charlotte	O034, P008
Puchhammer, Elisabeth	O039
Quinn, Michael	O021, P048
Rabie, Helena	P006, P056, Y002, Y008
Radan, Anda-Petronela	Y003
Rahbar, Afsar	P018, P054
Raimondi, Francesco	O023, O024, O025, P005, P045, P047, P083
Ramani, Ramya	O028
Ramirez G, Maria Camila	LB(P)001
Ramsperger, Marc	O048
Rantho, Lesego	P056
Rashidi, Ahmad S.	O030, Y010
Ravens, Sarina	Y004
Rawlinson, William	P011
Rayner, Simon	O001
Rebello, Gitanjali	O021, P048
Reeves, Keith	O002
Reeves, Matthew	O041, O043, P055, Y011
Reiche, Myrthe	P056
Reichlin, Amy	Y006
Religa, Piotr	O038
Remita, Amine	LB(O)005
Repič Lampret, Barbka	P076
Retzlaff, Silke	P012
Reuberger, Elisabeth	P042
Ribot, Elodie	P074, P075
Ricci, Erica	O011
Riemann, Lennart	O045
Rio, Ines	P069
Rios Barnes, Maria	O023, O024, P005, P047, P077, Y007
Ritter, Birgit	O029, P037
Rivera, Rafael	O036
Roberts, Jeffrey	LB(O)005
Rode, Natalia	P069, P082
Rodrigues, Lucia	P043
Rodriguez-Molino, Fernanda	O023
Rodríguez-Molino, Paula	O024, P005, Y007
Roesner, Lennart M.	O045
Rogers, Pam	O010
Rohrer, Lino	O002



Romashova, Veronika	P051
Ross, Shannon	O026, P057, P058, P081
Rottengatter, Karin	P012, P062, P086
Roy, Vincent	O035
Rubina, Anzelika	O003, O004
Russel Pantalone, Mattia	P054
Russo, Domenico	O031
Ruzsics, Zsolt	O030
Saavedra-Lozano, Jesús	O023, O024, P005, P047, Y007
Sack, Virginia	O021, P048
Saffery, Richard	O048
Saffioti, Carloina	O011
Saidi, Zahra	O042
Salih, Semiha	O001
Salker, Madhuri	O002
Salomè, Serena	O011, O023, O024, O025, P005, P045, P047, P083
Salonidi, Eleni	O047
Salvanos, Iraklis	O047
Salvatore, Christine	O021, P048
Sanchez Bas, Sergio	O029
Sanchez, Pablo	O006
Sanchez-Clemente, Nuria	Y007
Santos, Aline	LB(O)003
Saoudi, Thanina	P074
Sarafidis, Kosmas	P071
Sartori, Pauline	P040
Saud, Zack	O040
Sauer, Andrea	P062
Savanagouder, Mamata	Y012
Scaturro, Pietro	P030
Schaefer, Edo	O017, Y006
Scherer, Myriam	O028
Schindler, Christian	O008
Schlachter, Linda	O042
Schmid, Lara	P060
Schmidt, Florian	O046
Schroeder, Kristen	P036
Schulte, Tim	Y001
Schulz, Thomas	LB(P)002
Schweintzger, Nina	P031



Scialò, Martina	O025, P083
Seidenari, Anna	P087
Seminari, Elena	O044
Senaldi, Liana	LB(P)007
Serra, Ilenia	LB(P)002
Seskute, Milda	P066
Shackley, Fiona	P031
Shand, Antonia	P082
Shasha, Einav	P002
Shears, Annalie	Y007
Shenoy, Shalini	O017, Y006
Shepherd, Daisy	O048
Shestopal, Danylo	O042
Shillitoe, Benjamin	P031
Shimamura, Masako	O006, Y006
Shukla, Vivek	O026
Siafakas, Nikolaos	O012, O047, P021
Sichitiu, Joanna	Y005
Siddhi, Pooja	P031
Sido, Tal	P052
Siedentopf, Jan-Peter	LB(P)010
Siemes, Anna Rebecca	P019
Simonazzi, Giuliana	P087
Sinelli, Maria Teresa	O011
Singh, Avinash Kumar	O026
Siomou, Ekaterini	P085
Sitnik, Katarzyna M.	O030, Y010
Skordala, Marianna	P071
Skremm, Leonard Alfred	O029, LB(O)002, LB(P)001, LB(P)002
Smithers-Sheedy, Hayley	O010, O048, P046, P069, P082
Socher, Eileen	P011
Sohrabi-Mollayousefi, Peri	P015
Solis, Morgane	P038
Soltirovska Šalamon, Aneta	P076
Sood, Sunil	O021, P048
Soudeyns, Hugo	LB(O)005
Sourvinos, George	LB(P)004
Spalding, Reid	P035
Speirs, Lynne	P031
Spinillo, Arsenio	O007



Spinoni, Vania	O011
Springer, David Niklas	P042
Stamminger, Thomas	O028
Stanley, Taylor	P068
Stanton, Richard J	O003, O004, O029, O040, Y009
Steenpass, Laura	P026
Stegmann, Cora	O028
Sticht, Heinrich	P011
Stopyra, Lidia	P063
Stott, Daniel	LB(O)004
Stratiki, Evangelia	O047
Strawser, Corinne	O006
Strobl, Birgit	O008
Stulgiene, Beatrice	P066
Stump, Hanako	P070
Sturgeon, Jonathan	P031
Stévart, Oriane	P041
Sultan-Beyer, Leila	Y003
Sung, Valerie	O048, P046
Sustic, Marko	P050
Swinburn, Katherine	O010, P069, P082
Syridou, Garyfallia	O005, O012, O020, O023, P061, P078, P084
Szczypka-Stempak, Edyta	P063
Sänger, Katja	P062
Söderberg-Nauclér, Cecilia	O038, P018, P020, P022, P036, P054, Y001
Sütterle, Miriam	O002
Tagarro, Alfredo	O023, P005, P047, Y007
Taguran, Christian	O039
Taher, Husam	P017
Talano, Julie	O017
Tamborino, Agnese Maria	O014
Taormina, Gillian	O021, P048
Tavakoli, Norma	O021, P048
Tavanti, Matilde	O011
Taylor, Myles	LB(P)007
Tency, Inge	P041
Terhune, Scott	O027
Tezer, Hasan	P004
Theodoraki, Martha	O047
Thomaidou, Arsinoe Chrysovalanti	LB(P)004



Thomas, Marco	O039, O041
Tillmanns, Julia	P011
Tilloy, Valentin	P008, P009
Tomaiuolo, Miriam	P087
Torti, Carlo	O011
Traxler, Peter	O008
Trdan, Matevž	P001
Trecarichi, Enrico	O011
Trinca, Terrence	O004
Tripathi, Tanya	P069, P070, P082
Trotta, Michele	O011
Truffot, Aurelie	P008
Tseliou, Melpomeni	LB(P)004
Tsiatsiou, Olga	O023, O024, P005, P047, Y007
Tsiodras, Sotirios	P078
Tsioulos, Georgios	P078
Tsirigotaki, Maria	P085
Turlure, Pascal	O034
Tzani, Aimilia	P003
Ungar, Stephanie	O021, P048
Uršič, Tina	P001
Valdivia Malqui, Emilio	P026
Valimehr, Sepideh	O015
Valoup-Fellous, Christelle	P075
Van Acker, Jos	O033
Van der Veeken, Lennart	P041
Van Hasselt, Coen	P006
Van Laethem, Nika	P073
Van Linthout, Christine	P041
Van Rensburg, Gertrude	Y002
Van Rompay, Koen	P017
Van Zyl, Netta	Y002
Van-Leer, Coretta	P008
Vandrevala, Tushna	O049
Vanhomwegen, Charlotte	O032, P038
Vella, Laura	O016
Venturini, Cristina	O013
Venturini, Elisabetta	O011, O014
Verbanck, Sylvain	O032, P038
Verhagen, Lilly M.	P056



Verjans, Georges M.G.M.	Y010
Verleye, Leen	P041, P067
Vernelen, Kris	O033
Verneris, Michael	O017
Veyrenche, Nicolas	O009
Vidmar Šimic, Marijana	P001
Vieira da Sá, Renata	LB(P)011
Viejo-Borbolla, Abel	O029, P037
Villamor, Eduardo	P045
Villaverde, Serena	O023, O024, P005, P047, Y007
Ville, Yves	O009, P075, Y005
Vimercati, Antonella	O011
Viola, Odette	Y002
Vives-Oñós, Isabel	O024
Vladić, Iva	P034
Vlahava, Virginia-Maria	O040
Vogel, Thore	P005
von Wilmowski, Theo	O003
Vuotto, Fanny	O034
Waegemans, Alexandra	O032
Wagner, Sabrina	P011
Wahl, Clément	O035
Wahlsen, Olov	Y001
Waight, Emma	P046
Wake, Melissa	O048
Wan, Jessica	O023, O024, P005, Y007
Wang, Dai	LB(O)005
Wang, Eddie	O003, O004, O040, Y009
Wang, Jian Ben	P027
Wang, Yongping	O017
Wangen, Christina	P011
Watson, Jotara	P070
Webber, Tariq	Y002
Wedderburn, Catherine	Y008
Weekes, Michael P.	O003, O004, Y009
Weelden, Geert	P056
Wei, Andi	O041
Weidner-Glunde, Magdalena	Y012
Weinberg, Geoffrey	O021, P048
Weiner, Leonard	O021, P048



Weissinger, Eva M.	LB(P)001
Werfel, Thomas	O045
Weseslindtner, Lukas	P042
White, Rob	O041
Whittaker, Elizabeth	P031
Wieland, Britta	O045
Williams, Eleri	O022, P031
Wills, Mark	O043, P051
Wolf, Dana G.	P002, P052
Wood, Kenneth	O021, P048
Woodward, Maggie	LB(P)007
Wright, Victoria	P031
Wübben, Thomas	P019
Xing, David	P017
Xu, Jinxian	P025
Yaffe, Michael B.	LB(O)001
Yaiw, Koon-Chu	Y001
Yamamoto, Aparecida	LB(O)003, LB(O)006
Yang, Tao	Y004
Ylä-Anttila, Päivi	P036
Yu, Zeyi	O042
Yves, Fougère	P003
Zakay-Rones, Zichria	P002
Zammarchi, Lorenzo	O011
Zampolo, Alessandra	LB(O)003
Zandotti, Christine	O034
Zanette, Simona	O023, P005, P047
Zaragkoulias, Andreas	O040
Zavaglio, Federica	O007, O018, O031, O044
Zeevaert, Renate	P041, P067
Zehner, Matthias	O042
Železnjak, Jelena	P028
Zelini, Paola	O007
Zenz, Werner	P031
Zhang, Lihui	O040
Zhang, Ming	P025
Zhang, Tianyu	P030
Zoboli, Valentina	O018

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