Molecular Therapy
Oncology
Editorial

The 16th International Oncolytic Virus Conference: Advancing oncolytic virotherapy by balancing anti-tumor and anti-viral immunity

INTRODUCTION

From the 27th until the 30th of October 2024, the 16th International Oncolytic Virotherapy Conference (IOVC) took place in Rotterdam, the Netherlands. International researchers from academia and industry focusing on oncolytic viruses (OVs) gathered in this city of "dreamers and doers." Extensive developments in the OV field from fundamental, pre-clinical, and clinical levels were discussed. Both the oral and poster sessions focused on scientific progress made in clinical trials, combination therapies, mechanisms of action, novel platforms and payloads, tumor microenvironment (TME), and for the first time, biomarkers of response. The meeting also featured for the first time a Young Investigators session, providing a platform for emerging researchers to present their work and engage with experts in the field. A particularly notable moment was a patient's story of their experience with virotherapy, offering a meaningful perspective on the real-world implications of this research. Our sincere appreciation goes to the local and international organizing committee of the IOVC for putting together the scientific content, to the Erasmus Congress Center for the excellent organization, and to all the sponsors for making this event possible. This report highlights the key scientific and translational insights from the meeting.

The meeting opened with a unique welcome to Rotterdam by Catherine Kalamidas (Rotterdam Partners), who introduced the city, with a focus on its historical roots and dynamic, resilient spirit. This was followed by a captivating musical journey by Rotterdam-based percussionist Laura Trompetter, before the meeting officially opened with a keynote lecture by Prof. Guido Kroemer (Université de Paris, Sorbonne Université, and Institute Gustave Roussy), who highlighted the evolving understanding of cancer biology. The field has shifted from a cell-autonomous perspective to recognizing the role of the TME and immune system in cancer progression. He highlighted the role of immunogenic cell death (ICD),[1] a process disrupted by the immune evasion mechanisms of cancer, and discussed how OVs and ICD inducers enhance antigenicity and adjuvanticity to improve cancer immunotherapy. He also delved into innovative approaches advancing the field, including artificial intelligence (AI)-powered tools to predict the immunogenicity of compounds, the impact of genetic factors such as formyl peptide receptor 1 polymorphism on dendritic cell function, and novel strategies such as targeting B cell lymphoma 2 in dendritic cells to enhance their therapeutic potential. These insights underscored the transformative power of leveraging interdisciplinary research and the immune system to advance cancer treatment.

REENGINEERING IMMUNITY: INSIGHTS ON MECHANISMS OF ACTION IN ONCOLYTIC VIROTHERAPY

A central focus of the conference was the intricate interplay between OVs and immune system modulation.[2] Richard Vile (Mayo Clinic) provided insights into how OVs can modulate T cell responses. His lab explored the competitive dynamics between anti-viral and anti-tumor T cell responses, highlighting how innovative engineering approaches can tip the balance toward better therapeutic outcomes. For instance, encoding tumor antigens within OVs was shown to increase the precursor frequency of T cells specific to those antigens, potentially enhancing anti-tumor efficacy.

Other approaches included the discovery of mechanisms by which translation control can influence OV effectiveness. Aida Said (University of Ottawa) investigated how Maraba virus MG1 infection affects host cell translation. Using ribosome profiling, the study identified an R motif, prevalent in 22% of highly translated genes, especially immune response genes. Deleting this motif from glycine decarboxylase, a pro-cancer gene in prostate cancer, significantly reduced translation efficiency, confirming its role in enhancing translation. These findings highlight how translation regulation influences MG1 virus-host interactions. Another significant contribution came from Michael Brown (Duke University), whose studies with poliovirus demonstrated that priming the immune system with either poliovirus or control antigens prior to treatment greatly amplified anti-tumor responses. This enhancement was attributed to the phenomenon of trained immunity, the durable reprogramming of innate immune cells to exhibit long-term memory and heightened functionality. Jennifer Altomonte (Technical University of Munich) created a chimeric OV by fusing vesicular stomatitis virus (VSV) and Newcastle disease virus (NDV) to boost tumor cell killing while reducing neurotoxicity. VSV-NDV induced potent tumor ICD, activated dendritic cells, and improved T cell responses, leading to tumor regression in melanoma and pancreatic cancer models. Additionally, a VSV-NDV-expressing soluble programmed cell death protein 1 (PD-1) offers a promising "all-in-one" immunotherapy for solid tumors. Nitya Mohan (Institute of Cancer Research, London) explored how herpes simplex virus (HSV)-1-based RP1 infection enhanced cytotoxic T cell priming in a model with peripheral blood mononuclear cells (PBMCs) and dendritic cells, focusing on tumor-associated antigens in head and neck cancer and melanoma. RP1 was found to induce type 1 and type 2 interferon

responses and activate natural killer (NK) T cells. The fusogenic glycoprotein (GALV)-encoding RP1 variant showed greater immunogenicity than its non-GALV counterpart. Ongoing research aims to further clarify the role of GALV in anti-viral and anti-tumor immune responses to optimize OV-based immunotherapy. This evolving understanding of the mechanism of action of OVs set the stage for in-depth discussions on how OVs interact with and modulate the immune system.

POWER IN PARTNERSHIP: COMBINATORIAL STRATEGIES IN ONCOLYTIC VIROTHERAPY

Building on these mechanistic insights, the conference also highlighted how combining OVs with complementary therapeutic modalities can overcome the limitations of monotherapies and enhance overall treatment efficacy. Stephanie Drymiotou (The Francis Crick Institute) presented strategies to enhance the efficacy of vaccinia virus for ovarian cancer treatment by improving tumor specificity and combining it with therapeutic agents. Through high-throughput screening, a tubulin polymerization inhibitor was identified, significantly prolonging survival in preclinical models. A similar approach was presented by Amarin Wongariyapak (The Institute of Cancer Research, London) that involves combining OVs with targeted molecular therapies. Using phospho-proteomics and large-scale small interfering RNA kinome screens, the study identified key kinases that regulate viral killing activity and inflammatory pathway activation. Preliminary findings suggest that combining RP1 with targeted kinase inhibitors could improve therapeutic outcomes, with ongoing analyses to validate potential drug candidates for cancer treatment.

Benjamin Kendall (Mayo Clinic) investigated how anti-viral immune responses in oncolytic virotherapy can compete with anti-tumor T cell activation, potentially affecting immunotherapy efficacy. Using a melanoma model with modified ovalbumin antigens, he found that high-affinity variants drive strong T cell expansion but also induce autoimmunity, while low-affinity variants elicit weaker responses. His findings highlight a key challenge in integrating OVs with checkpoint inhibitors or chimeric antigen receptor (CAR)-T cell therapy, as viral antigen dominance may limit tumor-specific immune activation. Building on this, Richard Vile's group (Mayo Clinic) explored the addition of oncolytic VSV to improve CAR-T cell therapy for solid tumors. Initial studies revealed that administering VSV before CAR-T cell infusion diminished efficacy due to excessive type 1 cytokine responses. To overcome this, dual-specific CAR-T cells were engineered that express both a CAR targeting epidermal growth factor receptor and a T cell receptor recognizing VSV, enhancing persistence, tumor infiltration, and effector function. Before infusion, these CAR-T cells were exposed to VSV *ex vivo*, selectively enriching dual-specific T cells and reinforcing their ability to recognize viral antigens. This strategy demonstrated significant tumor regression in preclinical models and offers a promising approach to optimizing CAR-T cell therapy, particularly for adult and pediatric brain cancers. Zaid Taha (University of Ottawa) introduced a dual-virus oncolytic strategy to enhance tumor targeting and immune activation. VSV-HER2T delivers a truncated human epidermal growth factor receptor 2 (HER2) antigen to $HER2^{-}$ tumors, enabling elimination by the antibody-drug conjugate (T-DM1), significantly reducing metastatic burden. A T cell engager (TCE)-armed vaccinia virus further enhanced immune response, leading to TME reprogramming and a 40% cure rate in preclinical models. This approach demonstrates the potential of combinatorial virotherapy to overcome antigen limitations and broaden cancer immunotherapy applications.

These approaches underscore the potential of combining diverse therapeutic modalities to enhance the effectiveness of oncolytic virotherapy.

NEXT-GENERATION VIRAL PLATFORMS AND PAYLOADS

Following the exploration of combination therapies, the conference shifted its focus to cutting-edge advancements in engineering viral platforms. A highlight of this session was the work of Stephen Russell (Vyriad) on cytomegalovirus (CMV) engineering, which demonstrated its potential as a delivery vehicle capable of generating CAR-T cells directly within tumors. This cleverly designed approach leverages preexisting anti-CMV immunity, as studies have shown that CMV-specific T cells can effectively promote tumor regression. The proof-of-concept involved constructing CMV vectors encoding CD3-targeted lentiviral components, successfully transducing T cells, and producing CAR-T cells *in situ* within the TME. Preclinical studies demonstrated successful T cell recruitment and tumor cell elimination, highlighting the potential of CMV as both an oncolytic agent and a delivery platform for engineered immunotherapies.

Mathieu Crupi (University of Ottawa) highlighted that viral vectors were shown to be effective delivery vehicles for TCEs, turning cold tumors hot, minimizing systemic toxicities, and enabling localized, self-limiting therapies. Preclinical colorectal cancer models demonstrated the efficacy of TCEs expressed from viral vectors such as adenovirus, measles (MeV), HSV, and vaccinia viruses. Similarly, Ahmet Hazini (University of Oxford) developed an oncolytic adenovirus expressing a bispecific macrophage engager that enhances tumor antigen cross-presentation, promoting phagocytosis, macrophage activation, and adaptive T cell responses, thereby offering a potential antigen-agnostic immunotherapy for cancer.

Innovations in nanoparticle-based delivery systems also received attention. Faith Howard (University of Sheffield) developed a bio-inspired nanoparticle-based "Trojan horse" delivery system that encapsulates both enveloped and non-enveloped OVs, improving tumor targeting, protection, and co-delivery with immunotherapies, while ensuring scalable production and stability. In addition, Duong Nguyen (Calidi Biotherapeutics) developed a vaccinia-derived extracellular enveloped virus-based platform designed for systemic delivery to metastatic cancers, enhancing tumor targeting while evading immune clearance.

Katrin Schroër (Witten/Herdecke University) introduced adenovirus-directed evolution, a method that generates enhanced oncolytic adenovirus vectors by modifying the H1 loop of the fiber knob, improving DNA replication and lytic activity in CAR-deficient tumor cells. Another key contribution came from Shradha Khanduja's (University of Massachusetts) research on Salmonella-mediated delivery, which provided an innovative method for transporting OVs to tumor sites. This strategy not only improved delivery efficiency but also reprogrammed the TME to reduce immunosuppression and enhance treatment efficacy.

TRANSFORMING THE TME WITH ONCOLYTIC VIRUSES

A second excellent keynote lecture was presented by Prof. Abhishek D. Garg from KU Leuven, who emphasized the complexity of the TME in shaping immunotherapy outcomes. Prof. Garg emphasized that effective immune responses require not only T cell clonality, specificity, and functionality but also the alignment of multiple hallmark pathways, including immune activation, inflammatory signaling, antigen presentation, and spatial immune cell organization. He highlighted how immune barriers, such as macrophages and wound-healing pathways, contribute to tumor heterogeneity, regulate T cell infiltration, and influence therapeutic efficacy. His lecture underscored the necessity of integrating quantitative, qualitative, spatial, and temporal analyses to dissect the complexities of the TME and laid the foundation for discussions on how OVs can modulate these immune barriers to improve immunotherapy outcomes.

Building on this theme, studies on glioma virotherapy using the adenovirus Delta24-RGD by Candelaria Gomez-Manzano (MD Anderson Cancer Center) unveiled an alternative innate immune sensing mechanism, wherein the NONO protein binds to the viral fiber and cyclic GMP-AMP synthase (cGAS), forming a complex in the nucleus. This NONO-cGAS-fiber complex bypasses conventional Toll-like receptor recognition and does not induce interferon secretion in glioma cells; however, it may activate the cGAS-STING (stimulator of interferon genes) pathway in immune cells, offering a potential strategy to enhance viral persistence and therapeutic efficacy. Liang Deng's team (Memorial Sloan Kettering Cancer Center) engineered modified vaccinia Ankara viruses for cancer immunotherapy by deleting inhibitory genes (E3, E5R, and WR199) and introducing immunostimulatory transgenes (FLT3 ligand, OX40 ligand, interleukin-12 [IL-12]). The first-generation virus (MQ710), in phase 1 trials, enhances cGAS-STING signaling and expands dendritic and T cells by deleting viral gene E5R and expressing FLT3L and OX40L. The second-generation virus (MQ833), in preclinical testing, further deletes E3 and WR199 to boost innate immune activation and introduces extracellular matrix-anchored IL-12, which enhances T and NK cell responses.

Priscilla Kinderman (Leiden University Medical Center) investigated M8, a modified VSV derivative, as an immunostimulatory oncolytic virus to enhance checkpoint inhibitor therapy responses. In a colorectal carcinoma mouse model, M8 plus anti-PD-1 therapy led to a 60% tumor clearance, significantly remodeling the TME by increasing inflammatory myeloid cells. Finally, David Johnson (University of Oxford) presented a cutting-edge liver perfusion platform designed to study viral therapies for colorectal cancer liver metastases in an *ex vivo* setting. This model can provide detailed insights into viral kinetics and TME interactions, offering a robust tool for optimizing viral therapies. These advancements underscore the critical role of understanding and reprogramming the TME to enhance therapeutic outcomes.

ADVANCES IN CLINICAL ONCOLYTIC VIROTHERAPY

The presentation of clinical trials spanned two sessions, highlighting progress in oncolytic virotherapy and revealing its growing impact on patient outcomes. Robert Coffin (Replimune) highlighted the progress of their clinical program with RP1 in combination with nivolumab for multiple solid tumors, including melanoma, following up on promising results in earlier studies. Building on this success, Replimune has developed RP2, an enhanced version of RP1 expressing a CTLA-4 antibody. Ongoing trials are evaluating RP2 with immune checkpoint inhibitors (nivolumab/atezolizumab) or bevacizumab in solid tumors (this study was registered at ClinicalTrials.gov: NCT04336241), unresectable and advanced hepatocellular carcinoma (this study was registered at ClinicalTrials.gov: NCT05733598), and metastatic uveal melanoma (this study was registered at ClinicalTrials.gov: NCT06581406), with plans to expand into additional tumor types.

Another key highlight was Antonio Chiocca's (Brigham & Women's Hospital) presentation on HSV-1-based CAN-3110 for the treatment of glioblastoma. Longitudinal data from serial biopsies over 120 days following multiple intratumoral injections revealed a progressive increase in inflammation and T cell infiltration at the tumor site, indicating enhanced immune activation with each dose. Notably, pseudoprogression correlated with a trend toward a sustained anti-tumor immune response. This pioneering work underscores the value of longitudinal sampling in identifying biomarkers that inform OV-based immunotherapy and guide optimal dosing strategies for glioblastoma. Furthermore, Victor van Beusechem (ORCA Therapeutics, Amsterdam UMC) demonstrated systemic $CD8^+$ T cell activation following local ORCA-010 administration in prostate cancer, reinforcing the ability of OVs to elicit systemic immune responses. Velia Penza (Mayo Clinic) shared data on MeV (MV-NIS) in bladder cancer patients, linking increased infiltration of $CD4^+$ T cells, $CD20^+$ B cells, and a high number of tertiary lymphoid structures with improved therapeutic efficacy.

Francesca Barone (Candel Therapeutics) presented CAN-2409, reporting a significant increase in median overall survival from less than 12 to 20.6 months in non-small cell lung cancer (NSCLC) stage III/IV patients refractory to PD-1/programmed cell death ligand 1 (PD-L1) inhibitors in a phase 2 clinical trial (this study was registered at ClinicalTrials.gov: NCT04495153). Notably, the injection site influenced treatment response, with direct lung

lesion injections outperforming administration in lymph nodes or metastases. This effect is hypothesized to be due to tumor heterogeneity at the primary site, where initiating an oncolytic effect locally first may induce both local and systemic anti-tumor immune responses against metastases. In addition to NSCLC, CAN-2409 is being evaluated in multiple phase 2 and 3 clinical trials for prostate (this study was registered at ClinicalTrials.gov: NCT01436968), lung (this study was registered at ClinicalTrials.gov: NCT03131037), and pancreatic cancer (this study was registered at ClinicalTrials.gov: NCT02446093), further expanding its potential applications in solid tumors.

Prof. Noriyuki Kasahara (University of California, San Francisco Brain Tumor Center) presented updates on DB107-FC (vocimagene amiretrorepvec, formerly Toca511), previously discussed at IOVC 15.[3] Early phase 3 data showed a promising 26% 3-year survival rate in high-grade glioma (HGG) patients. A new phase 1/2 trial will treat newly diagnosed HGG patients with multiple intratumoral and intravenous doses, shifting from monotherapy to a combination approach with radiation and/or temozolomide, with biomarker analysis guiding efficacy evaluation (this study was registered at ClinicalTrials.gov: NCT06504381). Moreover, on behalf of Sabine Mueller, Dr. Kasahara also discussed advances made in pediatric oncology, with a first trial of intratumoral or intrathecal administration of oncolytic MV-NIS in recurrent medulloblastoma and atypical teratoid rhabdoid tumor in children and young adults. With limited adverse events and a short duration of viral shedding, this treatment was considered safe and well tolerated.

Safety and signs of efficacy of OVs encoding immunostimulating transgenes was demonstrated in five clinical trials, including a total of 70 patients treated with TILT-123 (these studies were registered at ClinicalTrials.gov: NCT04695327, NCT04217473, NCT05271318, NCT05222932, and NCT06125197), a 5/3 chimeric adenovirus encoding tumor necrosis factor-α and IL-2, as presented by Akseli Hemminki (University of Helsinki and Tilt Biotherapeutics). Patients showed increased tumor-infiltrating T cells, which resulted in tumor shrinkage and increased overall survival after a single intravenous injection of TILT-123. The combination of TILT-123 with tumor-infiltrating lymphocytes led to complete responses in several mucosal melanoma patients, and the combination with pembrolizumab treatment in refractory ovarian cancer patients resulted in 64% disease control and systemic immune response.[4] Likewise, William Jia (Virogin Biotech) reported that VG161, an HSV-1 engineered to express IL-12, IL-15/IL-15Ra, and a PD-L1 blocking peptide, restored immune checkpoint inhibitor therapy responsiveness in hepatocellular carcinoma. This resulted in an abscopal effect, characterized by increased infiltration of T and NK cells beyond the injection site.

Liang Deng (Memorial Sloan Kettering Cancer Center) presented data on a phase 1 trial of MQ710 (a modified vaccinia virus) for Kaposi sarcoma, where multiple *in situ* doses in combination with pembrolizumab led to complete clinical and tumor pathological responses (this study was registered at ClinicalTrials.gov: NCT05859074). Richard Trauger (Oncolytic Biotech) presented the GOBLET study, showing a 2.5-fold increase in objective response rates in pancreatic ductal adenocarcinoma (PDAC) patients treated with pelareorep (oncolytic reovirus) plus atezolizumab.

Francesca Barone (Candel Therapeutics) also introduced the state-of-art EnLIGHTEN discovery platform, combining AI-driven multigenic payload selection with an advanced HSV engineering technology to enhance OV and CAR-T cell therapy for solid tumors. Additionally, new delivery approaches, such as endoscopic ultrasound-guided oncolytic adenovirus RGDCOX2CRAdF local injection for pancreatic tumors, were highlighted by Masato Yamamoto (University of Minnesota).

PREDICTING SUCCESS: BIOMARKERS AND MOLECULAR INSIGHTS IN ONCOLYTIC VIROTHERAPY

While the clinical trials presented demonstrate the promising potential of oncolytic virotherapy, the need for strategies to enhance response rates remains evident, emphasizing the importance of identifying reliable biomarkers to optimize patient-specific treatments. Christine Engeland (Witten/Herdecke University) highlighted unique response patterns to OV treatments in PDAC, observed in patient-derived cell cultures, driven by the induction of ICD. While no single biomarker reliably predicted outcomes, specific activations of metabolic and signaling pathways emerged as promising indicators for OV selection. Jonny Hertzog (German Cancer Research Center) underscored the influence of molecular subtypes, such as basal-like or classical-like PDAC, in determining responses to adenovirus therapies. He proposed that incorporating multiple classifiers, including genetic and molecular features, could improve patient stratification, although stromal and immune components remain underexplored. Addressing the challenges of preclinical-to-clinical translation, Guido Wollmann (Medicine University Innsbruck) introduced a bioinformatics-driven epitope prediction approach combined with ELISpot assays. This strategy enabled precise monitoring of $CD8^+$ T cell responses to VSV-glycoprotein across diverse major histocompatibility complex class I alleles, providing a robust framework to refine preclinical modeling and enhance therapeutic efficacy. Eftychia Stavrakaki (Erasmus MC) presented an innovative autologous *ex vivo* coculture platform of OV-infected patients' glioma cells with autologous PBMCs. The findings revealed that robust oncolysis alone was insufficient to ensure immune activation, as failure to elicit immune responses was linked to persistent expression of type I/II interferon pathway transcription factors and a myeloid-rich microenvironment. Retrospective analysis of clinical trial samples validated the predictive value of biomarkers identified in the *ex vivo* model.

YOUNG INVESTIGATORS SESSION: NEXT-GENERATION INNOVATORS IN ONCOLYTIC VIROTHERAPY

The conference concluded with a session showcasing research and perspectives from young investigators in the field. Highlights

included Marjan van de Merbel (Leiden University Medical Center) who presented a three-dimensional co-culture model integrating prostate cancer cells and immune cells to evaluate the effects of virotherapy and immunotherapy. Nicole Dam (Leiden University Medical Center) identified Zeb1 as a key negative regulator of reovirus-induced oncolysis in PDAC-associated fibroblasts, and Richard Baugh (University of Leeds) discussed the role of intercellular adhesion molecule-1 as a biomarker of coxsackievirus A-21 efficacy in patient-derived Ewing sarcoma models.

Anne Everts (Erasmus MC) demonstrated the safety and efficacy of intravenously administered NDV in a technically challenging orthotopic PDAC syngeneic mouse model. Maria Davola (McMaster University) shared preclinical insights into bovine herpesvirus type 1 virotherapy using a humanized PDAC mouse model with an human leukocyte antigen class I match revealing its immune dependency to exert anti-tumor activity. Linus Kloker (Virotherapy Center Tübingen) explored combination treatment with repeated intratumoral T-VEC injections and anti-PD1 immunotherapy in a clinical setting in three patients with aggressive NUT carcinomas. Safety of the treatment was demonstrated, and partial responses on CT imaging as well as enhanced intratumoral $CD8^+$ T cell infiltration were observed.

Other important advancements include strategies to regulate transgene expression from oncolytic viruses. Laura Kayser (DKFZ) showcased optimized RNA switches enabling dynamic, drug-dependent therapeutic protein expression by OVs, and Taha Azad (Université de Sherbrooke) introduced a novel approach leveraging antibiotics for high-throughput insertional mutagenesis to create oncolytic virus libraries expressing immunomodulatory genes. The innovative studies presented in this session underscored the diverse strategies being developed by the next generation of researchers to enhance the effectiveness of oncolytic virotherapy.

GOLDEN VIRUS AWARD

During the memorable dinner at the historic Hotel New York, Prof. Juan Fueyo (Director of Neuro-Oncology Experimental Research, MD Anderson Cancer Center), a distinguished leader and pioneer in OV research, was announced as the 9th winner of the prestigious Golden Virus Award. This honor recognized his groundbreaking contributions to oncolytic virotherapy, particularly his innovative work with delta-24-RGD to combat brain tumor malignancies. In his keynote lecture, Prof. Fueyo highlighted critical challenges facing the field, with a particular focus on the complex interplay between anti-viral and anti-tumor immune responses. This balance is critical to prevent OV clearance and optimize anti-tumor efficacy. In his address, Prof. Fueyo noted that increased lymphocyte infiltration does not necessarily correlate with improved survival outcomes. He discussed the phenomenon of immunodominance, wherein T cells predominantly target viral antigens rather than tumor antigens, potentially diminishing therapeutic efficacy. Strategies such as inducing immune tolerance to viral epitopes, microbiome modulation, and leveraging molecular mimicry were proposed to enhance anti-tumor immunity. Furthermore, Prof. Fueyo cautioned that combination therapeutic approaches may inadvertently amplify anti-viral responses, accelerating viral clearance and thereby reducing the overall effectiveness of oncolytic virotherapy.

A PATIENT'S STORY: A CLINICAL CASE STUDY HIGHLIGHTING THE POTENTIAL OF VIROTHERAPY

One of the most compelling moments of the conference was the story of Dr. Beata Halassy, a Croatian virologist and immunologist, who shared a remarkable story about turning her scientific expertise into a lifesaving treatment.[5,6] Diagnosed with triple-negative breast cancer in 2016, she underwent standard treatment, including mastectomy and adjuvant treatment. Her cancer recurred 2 years later as aggressive carcinoma infiltrating her skin and pectoral muscle. With limited options, Dr. Halassy turned to her expertise, identifying two non-pathogenic viruses as potential treatments: the vaccine strain of MeV, in a phase 1 trial for metastatic breast cancer at the time, and VSV, a mild animal pathogen with promising preclinical data. Over 8 weeks, she self-administered high-titer intratumoral injections, leading to initial tumor enlargement before reduction, while triggering mild self-resolving side effects such as fever. Post-surgery pathological analysis and follow-up imaging confirmed complete remission, and she has remained cancer-free for over 4 years, without serious side effects.

Although self-experimentation in medicine has been a subject of ethical debate, historical and professional discourse suggest that it has played a valuable role in scientific progress and should not be dismissed outright. Ethical reviews and regulations have generally recognized that self-experimenters, when acting as true investigators, are not subject to the same ethical concerns as experiments involving external participants.[7] Dr. Halassy's courageous journey not only underscores the potential of virus-based cancer therapies but also highlights the evolving discussion surrounding the ethics and regulatory frameworks of self-experimentation in biomedical research.

CONCLUSIONS

The 16th International Oncolytic Virus Conference showcased significant progress in oncolytic virotherapy, with a notable shift toward promising clinical trials. A key focus was balancing robust anti-tumor immune responses with anti-viral immunity to maximize efficacy while minimizing premature viral clearance. Strategies to achieve this included encapsulated OVs for enhanced systemic delivery and TME modulation to optimize immune priming. Additionally, AI-driven modeling, accelerated viral engineering, and real-time immune monitoring were highlighted as key factors for next-generation personalized therapies. Beyond the promising clinical trial data, Dr. Beata Halassy's compelling personal story underscored the real-world impact of oncolytic virotherapy, inspiring further innovation.

To close the event, Prof. Clemens Dirven (Erasmus MC) and Prof. Rob Hoeben (LUMC Leiden) reflected on the meeting. Prof. Hoeben provided a virologist's perspective, questioning the necessity of viral replication and emphasizing the need for biomarkers to predict

treatment response, while Prof. Dirven highlighted the clinical implications, including promising data on multiple virus injections and the urgent need for accelerated GMP production. Their insights underscored both the progress achieved and the challenges ahead in translating oncolytic virotherapy into effective treatments. As discussions wrapped up, anticipation grew for the next IOVC, set to take place in Reykjavik, Iceland, an inspiring setting for new breakthroughs and continued progress in the field.

Eftychia Stavrakaki,[1,3] Anne Everts,[2,3] Bernadette G. van den Hoogen,[2] and Martine L.M. Lamfers[1]

[1]Department of Neurosurgery, Erasmus Medical Center, Rotterdam, the Netherlands; [2]Department of Viroscience, Erasmus Medical Center, Rotterdam, the Netherlands
[3]These authors contributed equally

Correspondence: Martine L.M. Lamfers, Department of Neurosurgery, Erasmus Medical Center, Rotterdam, the Netherlands.
E-mail: m.lamfers@erasmusmc.nl

https://doi.org/10.1016/j.omton.2025.200950

REFERENCES

1. Kroemer, G., Galassi, C., Zitvogel, L., and Galluzzi, L. (2022). Immunogenic cell stress and death. Nat. Immunol. *23*, 487–500.

2. Lemos de Matos, A., Franco, L.S., and McFadden, G. (2020). Oncolytic Viruses and the Immune System: The Dynamic Duo. Mol. Ther. Methods Clin. Dev. *17*, 349–358.

3. Rajwani, J., Evseev, D., Kaul, E.S., and Mahoney, D.J. (2024). The 15th International Oncolytic Virotherapy Conference: Clinical successes point to a brighter future for cancer treatment. Mol. Ther. Oncol. *32*, 200774.

4. Block, M.S., Clubb, J.H.A., Mäenpää, J., Pakola, S., Quixabeira, D.C.A., Kudling, T., Jirovec, E., Haybout, L., van der Heijden, M., Zahraoui, S., et al. (2025). The oncolytic adenovirus TILT-123 with pembrolizumab in platinum resistant or refractory ovarian cancer: the phase 1a PROTA trial. Nat. Commun. *16*, 1381.

5. Corbyn, Z. (2024). This scientist treated her own cancer with viruses she grew in the lab. Nature *635*, 529–530.

6. Forcic, D., Mrsic, K., Peric-Balja, M., Kurtovic, T., Ramic, S., Silovski, T., Pedišić, I., Milas, I., and Halassy, B. (2024). An Unconventional Case Study of Neoadjuvant Oncolytic Virotherapy for Recurrent Breast Cancer. Vaccines (Basel) *12*, 958.

7. Hanley, B.P., Bains, W., and Church, G. (2019). Review of Scientific Self-Experimentation: Ethics History, Regulation, Scenarios, and Views Among Ethics Committees and Prominent Scientists. Rejuvenation Res. *22*, 31–42.