Tackling the Complexities of Bringing Oncolytic Viruses to Market

Oncolytic viruses (OVs) have emerged as a remarkable non-to-low-toxic and non-invasive alternative to traditional cancer treatments. These relatively new cancer therapeutics are being increasingly explored by the pharmaceutical industry to benefit from their selectivity and potential to enhance existing medicines. Despite some early clinical trial successes, numerous obstacles impede the progress of this exciting therapeutic area. In this article, Kai Lipinski, Chief Scientific Officer at ReciBioPharm, delves into the challenges that OV developers face in pursuing project success and assesses potential resolutions to bring pioneering new treatments one step closer to launch.

A Need for New Cancer Treatments

Globally, cancer is estimated to cause 10 million deaths a year and accounts for every one in six fatalities.[1] While traditional cancer treatments have improved survival rates, their efficacy and toxicity limitations amplify the need for alternatives or complementing treatment modalities. These include chemotherapy's potentially disabling side effects, radiotherapy's harm to surrounding healthy tissues and the invasive, often painful nature of surgery, underscoring the demand for innovation.

Promising approaches like chimeric antigen receptor T cell (CAR-T) and immune checkpoint blockade (ICB) therapies have limitations due to the immunosuppressive tumour microenvironment and cancer heterogeneity. Although proof-of-concept of CAR-T therapy for blood-related cancers is the reality today (CD19 target: Kymriah, Yescarta, Tecartus, Breyanzi; BCMA target: Abecma, Carvykti), successfully treating solid cancers is still to come. The potential to selectively target, infect and eliminate cancer cells while activating an immune response makes OVs a revolutionary prospect in the world of oncology. The roots of this therapy trace back to successful clinical trials as early as the 1950s.[2]

With an evolving understanding of molecular interactions, OVs are considered ideal candidates for combination therapies, especially when supporting traditional cancer treatments like immunotherapies. This combined approach allows for the targeting of a wider spectrum of tumours while enhancing therapeutic efficacy.[3]

The biopharmaceutical industry is enthusiastic about the transformative potential of OVs and is actively involved in developing new OV technologies to improve treatment outcomes. The burgeoning global OV market is projected to see a compound annual growth rate of 26.2% from 2021 to 2028, ultimately reaching $609.7 billion4. Despite a development pipeline containing over 100 OVs, their potential is yet to fully materialise into widespread commercial success. Currently, only one OV, T-VEC (Imlygic®), is approved for use in the US and there is one conditional approval in Japan (Delytact®; Daiichi Sankyo Company, Limited) for a regenerative medical product for treating malignant glioma – interestingly, both viruses are based on HSV-1.

Tackling OV Development Challenges

The push for more OVs to enter the market comes from various stakeholders. Patients with diverse cancer types would benefit directly from a broader range of potential oncology treatments while healthcare professionals would gain access to a more versatile set of treatment options. Developers, along with their investors, are eager to see OVs achieve success in the market.

However, navigating the path from preclinical development to commercialisation is challenging. OV developers embarking on this mission currently face a multitude of challenges despite the collective determination to make these promising therapies accessible to those in need.

1. Process Optimisation and Scale-up

Meeting expedited clinical readiness deadlines demands rapid progress, and scaling up without losing product quality is essential to meet increasing clinical supply requirements and for further production expansion.

To address these challenges, a multifaceted approach can be beneficial:

- **Expertise in process optimisation,** harnessed through subject matter experts (SMEs) with extensive OV manufacturing experience, can enable the efficient transfer and modification of processes at smaller scales. Having a comprehensive understanding of the intricacies involved enables efficient problem-solving and adaptation at various stages of manufacturing, resulting in a robust process.
- **Effective project and program management** ensures that overall timelines are met, prioritisation is maintained and escalation processes are streamlined.
- **Collaborative management of material supply issues,** including partnering with suppliers to address potential material shortages, guarantees a smooth production flow.

2. Assay Development and Qualification

The development and qualification of assays are pivotal steps in the journey to clinical readiness for OVs. Finalising assay transfer, qualification, verification and validation promptly is crucial to ensure reliable product quality assessment. The challenge of sourcing and qualifying additional outsourced testing labs for certain assays not available in-house adds complexity to the process.

Contract development and manufacturing organisations (CDMOs) represent a key resource for knowledge, providing access to specialised expertise in OV development and

manufacturing. Leveraging SME input from both the sponsor and CDMO can prove invaluable. Their expertise in assay development and qualification streamlines the process, ensuring it aligns with the project's timelines. Establishing a strong partnership with the CDMO and maintaining reliable reaction times from both parties enhances the collaboration and enables efficient assay-related problem-solving.

An in-depth understanding of assays applicable to live viruses and their challenges is critical as each OV product comprises specific properties. On the other hand, many assays can be applied to a platform, and the available set-up from an experienced CDMO enables a plug-and-play strategy for pipeline projects.

3. Product Yield and Dosage Requirements

Product yield and meeting dosage requirements are critical when developing OVs and any other product for clinical use. Designing processes to consistently produce high yields, with a high titer, low total particle: infectious particle ratio, high process recovery and a compliant process residual profile are paramount to ensuring a reliable and high-quality product, and subsequently, robust clinical supply. Moreover, modifying scaled-up processes to enable high-drug product titers is necessary to meet the dosage demands of clinical trials, particularly when targeting the intravenous administration route.

To tackle these challenges effectively, a streamlined process development approach is imperative. Conducting multiple process development studies optimises both upstream and downstream parameters, ensuring the development of a robust process capable of meeting product yield and quality requirements. High flexibility, from both the CDMO and sponsor, is key in swiftly implementing necessary process adaptations to meet dosage requirements and aligning the production process with the clinical trial needs.

This comprehensive approach ensures that OV developers can successfully address these challenges and advance their products from the research and development to clinical phases, offering promising new treatments to patients in need.

Having access to extensive process data for specific OV types allows a platform approach to be extended to future clients with minimal development activities before commencing GMP manufacture.

4. The Role of Collaboration in OV Development

Overcoming the hurdles on an OV's journey to clinical phases – including expedited process development, limited access to expertise, scaling production, optimising product yield and addressing complex technical intricacies – demands specialised solutions. These challenges underscore the multifaceted nature of OV development, requiring tailored strategies and expertise to surmount.

The success of innovative OV therapies heavily relies on a joint effort, not just between researchers and developers but also across different entities involved in the process, such as preclinical development (PD), quality control (QC), production, project management and quality assurance/qualified person (QA/QP).

- **Mutual dependence for progress:** A symbiotic relationship between shareholders with shared responsibilities forms the cornerstone for a united approach in tackling the multifaceted hurdles of OV development.
- **Transparent and constructive exchange:** Open and transparent communication channels from all stakeholders foster an environment of constructive problem-solving. This allows for the swift identification of challenges and enables a proactive approach towards finding a resolution.
- **Specialised, expert and diverse collaborators:** Active collaboration between SMEs from various backgrounds is essential in deciphering and resolving the technical intricacies that come with OV development, driving innovative solutions in this complex area.

Ultimately, the success of OV development relies not just on scientific breakthroughs but on a unified commitment to addressing challenges. This involves collaborative efforts driven by a shared goal of bringing potentially life-changing treatments to fruition.

The Measurable Impact of Overcoming OV Development Challenges

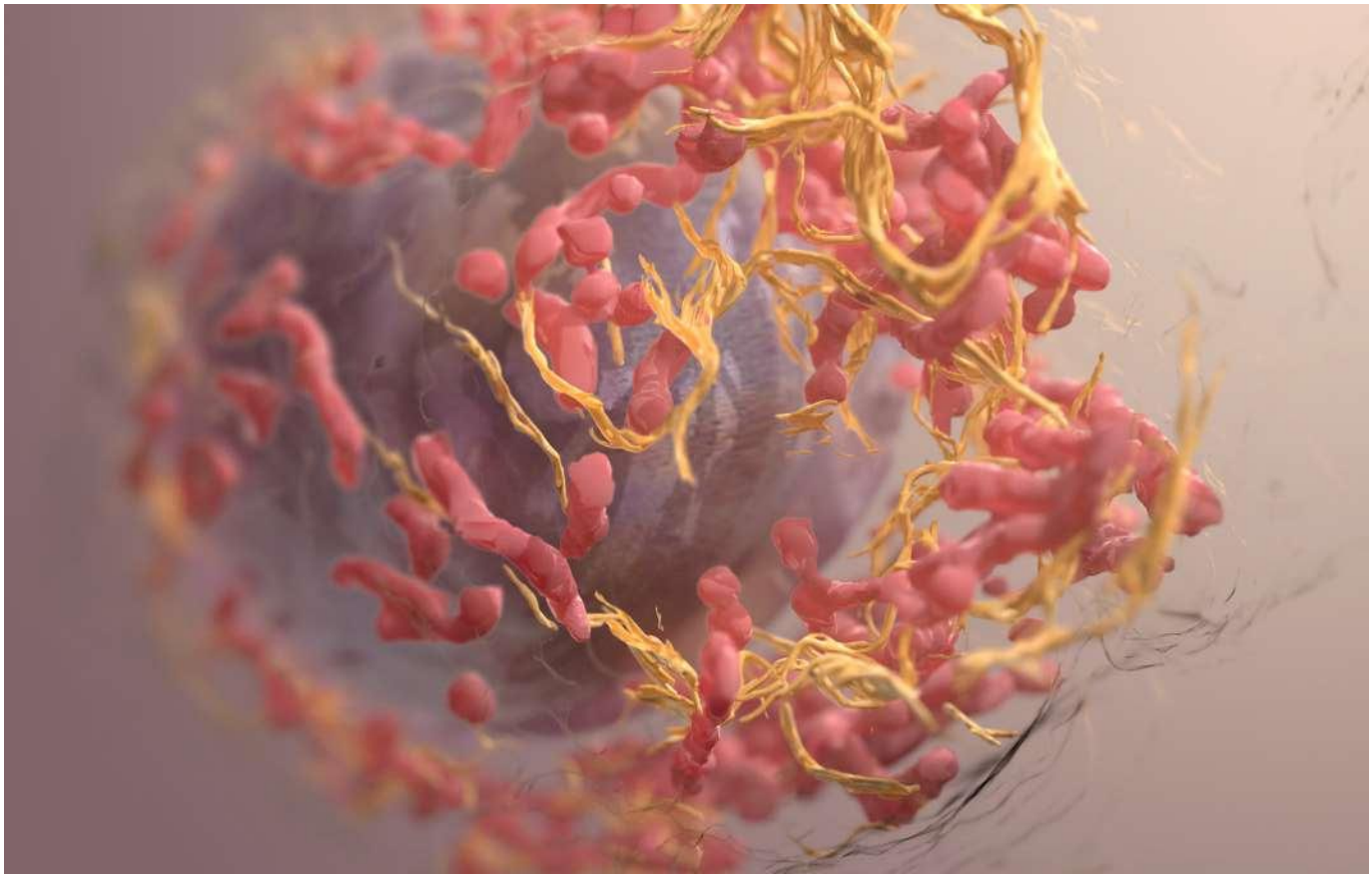
Overcoming the hurdles that can arise in process optimisation, assay development and qualification, and ensuring product yield, has significantly advanced the OV field. This has led to meaningful progress and benefits for both research and potential patient outcomes.

One of the most significant impacts lies in the initiation of clinical trials. Overcoming developmental hurdles ensures timely access for patients to potentially groundbreaking therapies, enhancing the potential for positive health outcomes. These advancements in clinical trial readiness stem from the more efficient and quality-assured manufacturing process. This enhancement significantly reduces the risk of batch failures, ensuring consistent product quality and meeting rigorous regulatory standards.

Furthermore, resolving scalability challenges has secured a sustainable and scalable supply chain for OVs, accommodating both current clinical dosing requirements and potential dose escalation for future medical needs. These improvements in manufacturing processes have directly contributed to ensuring a reliable and consistent supply of OVs for advancing clinical needs. In particular, shifting from adherent to suspension cell line conditions has catapulted the scalability and robustness of OV production. Such cell line options comprise currently mostly HEK293, HeLa and A549, and proprietary cell lines like CAP®, EB66® and AGE1.CR®.

Moreover, optimising process efficiency and enhancing assay development has significantly increased product yield, meeting stringent dosage requirements and fostering the qualification of advanced assays. These improvements highlight a key aspect of OV development, ensuring not only higher product yields but also the necessary tools to gauge their efficacy accurately.

Additionally, collaborative efforts have played a pivotal role, encouraging synergy between stakeholders, researchers and developers, contributing to overcoming key obstacles and achieving milestones in the OV development journey.



Collaboration has been instrumental in navigating challenges, emphasising the importance of collective efforts in driving OV development forward.

The combined impact of overcoming these challenges marks a transformative stride in OV development, showcasing advancements across multiple fronts and paving the way for more promising OV therapies.

The Future Outlook

The increase of OV therapies in the pipeline has the potential to help many people living with cancer. However, traversing the pathway to clinical approval requires developers to understand the obstacles and decide how they can be overcome.

The numerous challenges facing OV developers encompass a spectrum of complexities, ranging from expediting process development to limited access to those with the required expertise, and beyond. These obstacles can appear formidable, but they are not insurmountable. Those equipped with the right blend of efficient project management, collaborative partnerships, expertise and flexibility, can successfully address these barriers.

The proficiency and expertise held by dedicated professionals and institutions are instrumental in charting a path through the hurdles, offering novel insights and solutions to intricate problems. Flexibility, outstanding willingness and a high level of project/product identification serve as cornerstones in adapting to dynamic situations and addressing evolving requirements, ensuring adaptability in the face of unforeseen challenges.

Through these concerted and combined efforts, OVs are poised to offer promising new treatments to cancer patients. Further development in this area holds the potential to usher in a brighter future for oncology.

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Kai Lipinski

Kai Lipinski has a wealth of experience in viral vector manufacturing from a variety of roles before he joined ReciBioPharm. He served as Principal Scientist at Cobra Biologics, focusing on upstream process development for virus and mammalian protein expression projects. Prior to that, Kai worked as Senior & Principal Scientist at ML Laboratories, where he was responsible for the development of targeted adenoviral vectors for cancer gene therapy approaches. At Vibalogics, Kai is central to the establishment of virus Process Development and Manufacturing capabilities, technical developments and the acquisition of many key clients. Kai has a PhD in Transcriptional Regulation by Adenoviral E1A Proteins, and a Post-Doc, also on Transcriptional Regulation, from the University of Duisburg-Essen.