VIROTHERAPY INSIDER

Oncolytic Viruses Series PART 1

NEW CANCER TREATMENTS

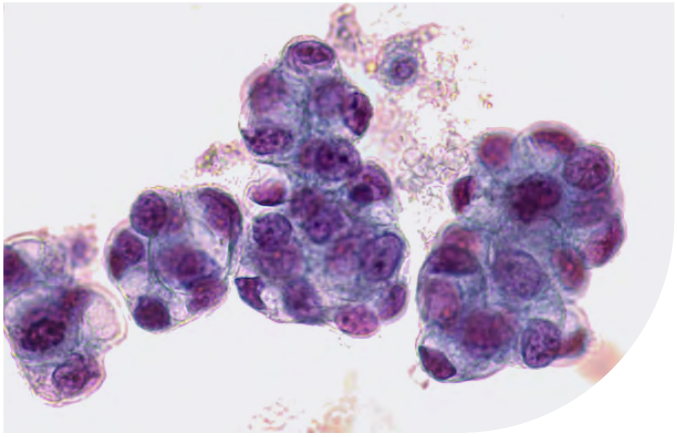
Do oncolytic viruses hold the answer?

In this first part of our oncolytic viruses (OV) series, Kai Lipinski, CSO, Vibalogics reviews cancer treatment and the unique advances seen in the field of drug development including the benefits of OV and also discuss the challenges faced in commercialization and market adoption of these therapies. Kai also explains how expertise of contract service providers can support developers in bringing their innovations to market.

Kai Lipinski, PhD, CSO

Introduction

With an estimated 18 million cancer cases around the world in 2018*, cancer is a leading cause of death and an enormous financial and social burden. Global spending on cancer therapies and supportive care drugs is expected to reach $200 billion by 2022**. With this in mind, it is clear that the prevention of cancer is one of the most significant public health challenges of the 21st century.



Data extracted from https://www.wcrf.org/

***Data extracted from https://bisresearch.com/industry-report*

Traditional treatments for cancers include surgery, chemotherapy, radiation therapy, monoclonal antibody and antibody-drug conjugate treatments, hormone therapy and stem-cell transplantation. All of these have played a major role in significantly improving survival rates over the last 100 years.

However, mortality rates for many cancers remain high. Moreover, many of the standard therapies remain invasive to the patient and, in the case of chemotherapy and radiation therapy, toxic too, negatively affecting the patient's experience and causing long-term health impacts of their own. A number of treatments are also often ineffective or only support a limited extension to the patient's life once they are impacted with this devastating disease.

With this in mind, drug developers are keen to explore new modalities and scientific approaches to revolutionize cancer treatment and deliver on the moonshot-promise of curing the disease. Oncolytic viruses (OVs) are a promising entry in this field, showing exciting potential. However, they remain in their infancy. What is holding them back from truly achieving their full potential, and how can obstacles be overcome?

New promise through advanced treatment options

In recent years, the three traditional first-line approaches to treatment – surgery, radiation and chemotherapy – have been joined by new alternative therapeutic approaches that show great promise in tackling cancer, such as hormone treatments.

As a result of the routine use of one or more of these traditional therapies, the mortality rate of cancer has decreased since 1990 from 142.5 (per 100,000 people) to 121.1 in 2017.

While the current therapies have been successful at improving survival rates, these treatments all have their drawbacks that make them less than ideal and continue to push science to developing new and improved approaches:

Surgery

Is invasive, posing its own risk to the patient, including chronic pain and other post-surgical complications. If intervention doesn't take place early enough, it can be of limited therapeutic effect, as the cancer may have begun to metastasize.

Radiation therapy

Carcinogenic and is highly damaging to the healthy tissue surrounding the tumor.

Chemotherapy

Involves toxic chemicals which have harmful side effects for patients that can be very disabling both in the short and long term.

Hormone therapy

Can lead to unwanted health impacts for patients as treatments disrupt the body's natural hormone balance, leading to potential unpleasant side effects for patients.

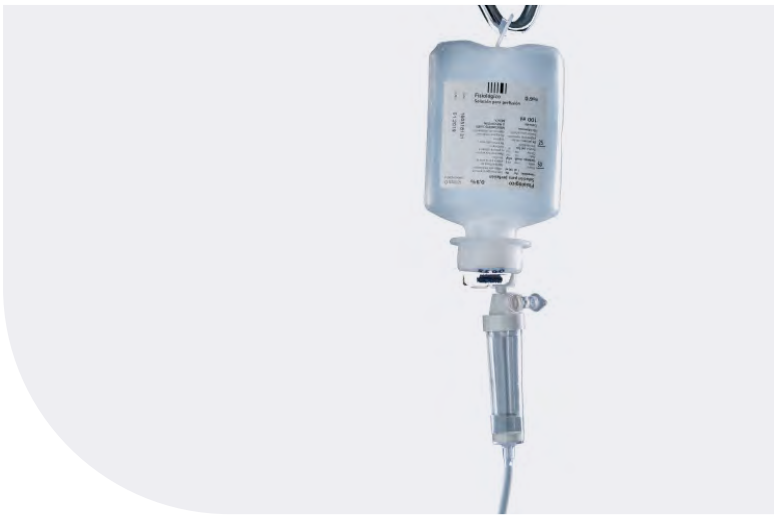
142.5 (1990) → 121.1 (2017)

Advanced treatment options

With this in mind, it is no surprise that work is ongoing to develop alternative cancer treatments that are at least as effective as existing therapies, while eliminating the harmful side effects and enhancing treatment convenience for patients. One of these advances includes the use of immunotherapy which allows for the body's immune system to detect abnormal cells and minimize cancer growth.

Immunotherapy

Including immune checkpoint inhibitors, T-cell transfer therapy, treatment vaccines, and oncolytic viruses are being explored as new advances with positive benefits.

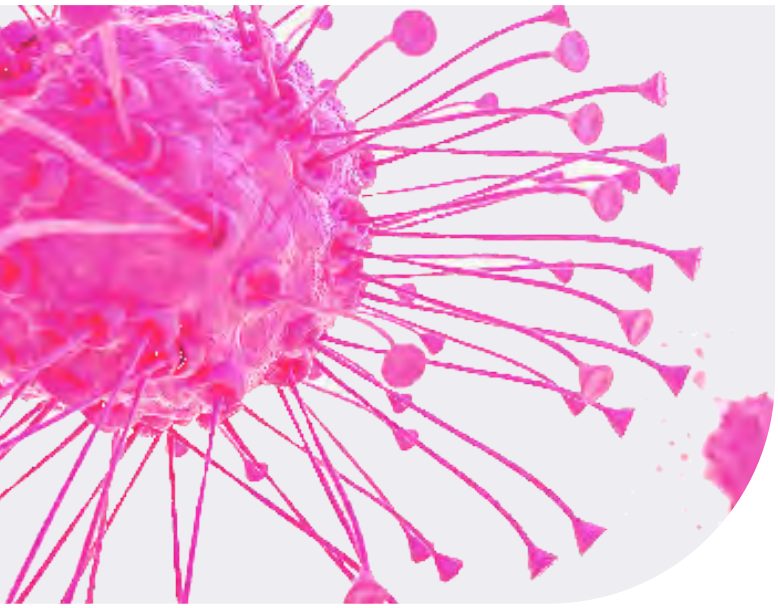


Harnessing the immune system

The central question that has occupied cancer and immunology scientists for many years is, why are cancer cells not rejected by the immune system? We now understand that this is because cancer cells contain genotypic and phenotypic changes affecting its antigen-presentation and immune-suppressive profile, providing their own defense mechanism to the human immune system.

Adaptive immune resistance can lead to a "cold" tumor microenvironment, where the tumor goes unnoticed by the body's own immune system. Immunological ignorance, or tolerance, can be changed through the use of OVs, which can find the cancer cells, kill them and yielding a "hot" or active environment and thereby solicit an immune response to the tumor.

Due to this mechanism, OVs can potentially add another effective modality to the treatment mix, in support of the traditional therapies utilized in the treatment of cancer.



$962m

by 2030

Data extracted from Global Oncolytic Virus Therapy Market Outlook 2021

A history of oncolytic viruses

The use of viruses to destroy tumors dates back to the early 1900s, although the field did not readily progress for many years. There was a subsequent resurgence in the 1960s, however, the treatments in these early trials performed below expectation in terms of overall efficacy, and also showed severe toxic side effects. As a result, interest in the use of viruses declined and was not seriously followed up on for several decades.

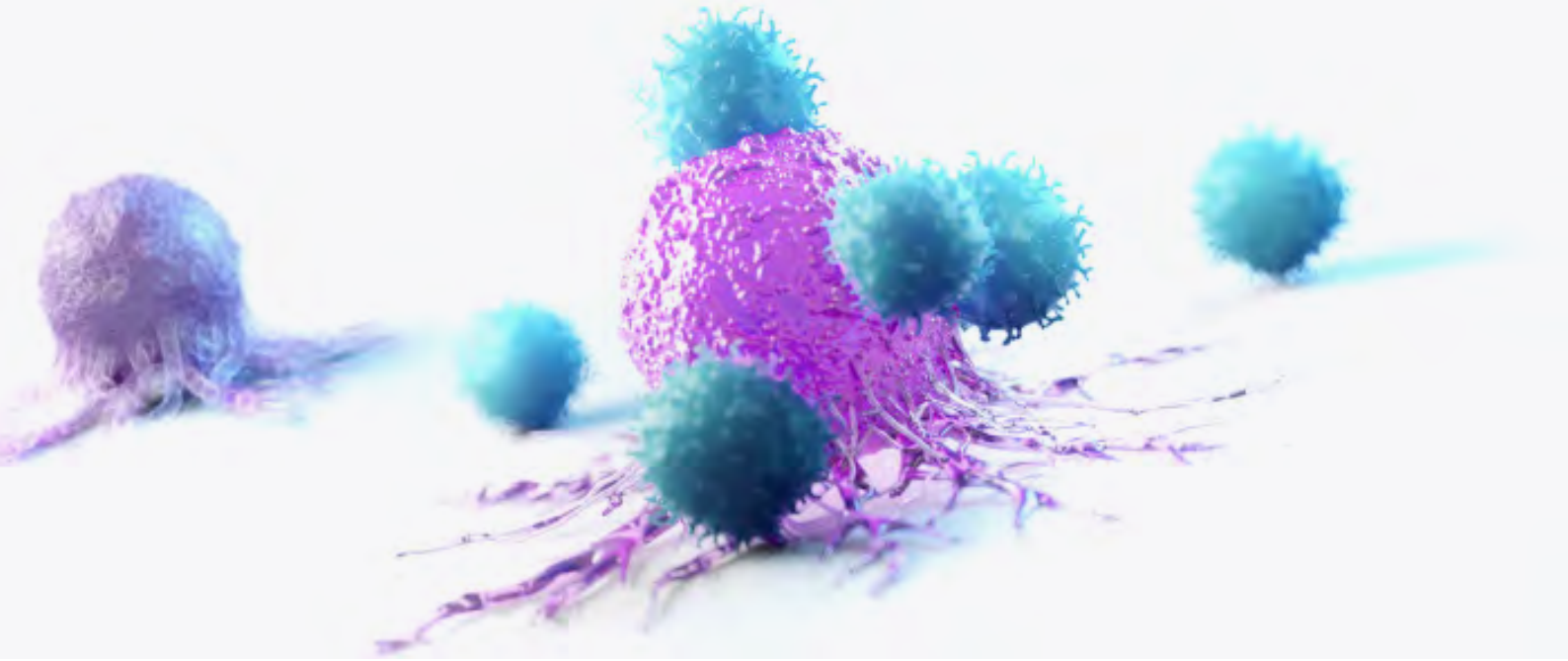
The advancement of molecular biology, molecular virology and reverse-genetics, though, has made possible a new generation of now tailored & engineered oncolytic viruses. These engineered OVs have shown significantly improved efficacy compared to early counterparts, and now hold promise as a new type of cancer immunotherapy.

A fast-growing market

With this in mind, it is no surprise that the OV market is growing quickly, with more and more treatments entering development all the time.

In fact, the global OV market is projected to reach $962 million by 2030, with a compound annual growth rate (CAGR) of 26.28% through the forecast period from 2020 to 2030.

It is estimated that, globally, about 150 - 200 companies are currently working on OV products.



How oncolytic viruses work

Key to the effectiveness of OVs is how they support the body's natural immune system to attack cancer cells on its own. The central aim of cancer immunotherapy is to transform "cold" tumor environments into "hot", leading, hopefully to the patient's immune system attacking the tumor and resulting in systemic tumor rejection.

To understand how this works, it is important to remember how "wild" viruses behave naturally. All viruses are parasites and need a cellular environment that favors replication of genetic information (DNA or RNA) and cell division. When infecting a cell, a virus must "buy" itself sufficient time before its host's immune system discovers it and responds to clear the infection.

A cancer tumor, on the other hand, has adapted mechanisms masking its phenotypic changes from immune surveillance and offers in parallel, and in contrast to healthy, normal cells, a selectively replicative environment for viruses.

OVs are designed to selectively infect cancer cells to replicate inside them, producing genetic markers designed to trigger an immune response that not only targets the OV, but the cells it has infected as well.

As simple infectious organisms, viruses are the ideal vectors for conveying targeted information designed to provoke an immune response. With today's knowledge about (a) general and disease-related immunology (b) specific immune reactions against viruses, (c) virus- and host-mediated immune-evasion and -suppression mechanisms, an OV can be designed and created with the ability to infect a cancer cell, program it to alert the immune system to the presence of the tumor and acknowledge/recognize it as "foreign" cell type. In doing so, they offer the possibility for traditional cancer treatments to be supported by the body's own defense mechanisms for the first time.

↑ 26.8%
2020-2030

Data extracted from Global Oncolytic Virus Therapy Market Outlook 2021

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Oncolytic viruses in the clinic

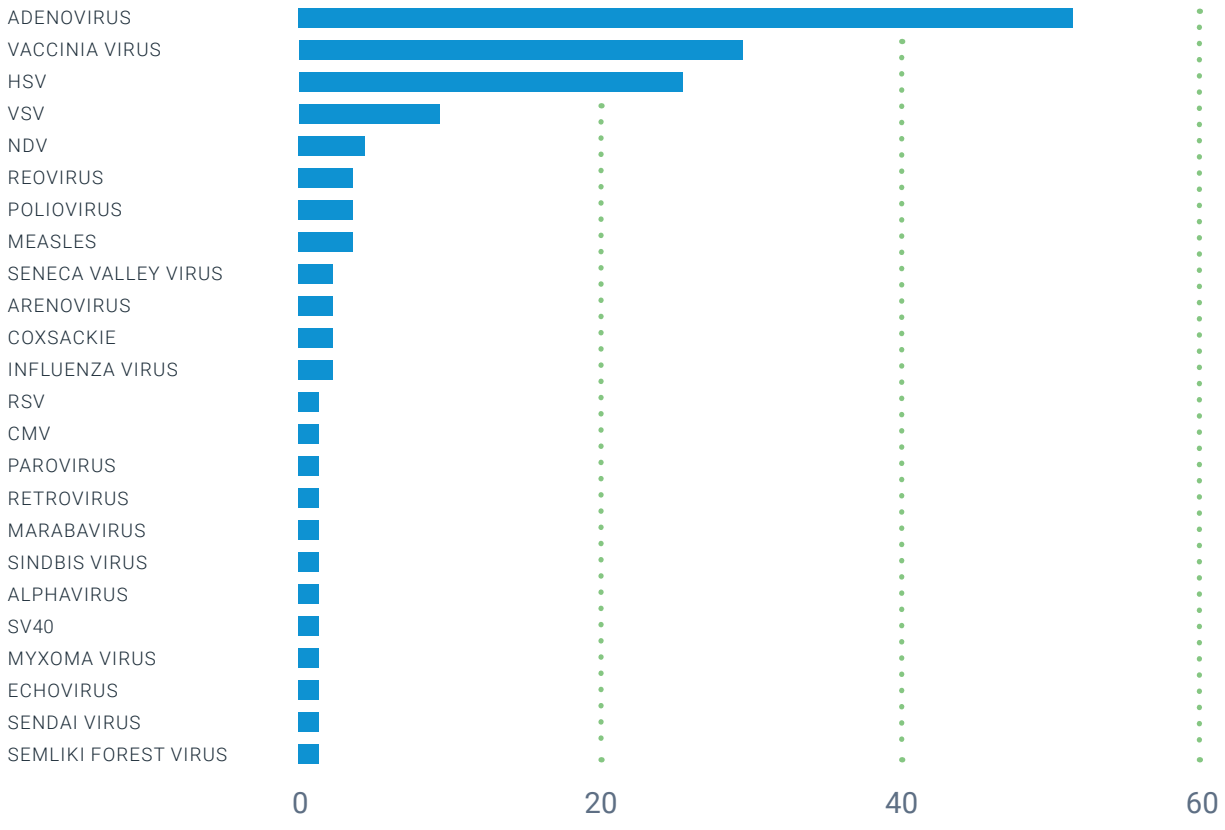
To date there is only one US FDA Marketed OV (Amgen Inc., Imlygic, HSV-based) Additionally, there many clinical OVs in development, utilizing a range of naturally occurring viruses as viral platforms.

The viral vector systems used in the most advanced treatments in phase III clinical trials are:

- **Reovirus**
  used in Reolysin; Oncolytics Biotech; NCT01166542
- **Adenovirus**
  used in CG0070; CG Oncology; NCT04452591

A number of other viral platforms are also being used as the basis of treatments in earlier pre-clinical development and clinical phase trials. Examples include:

- **Herpes Simplex Virus**
- **Vaccinia Virus**
- **Vesicular Stomatitis Virus (VSV)**
- **Newcastle Disease Virus (NDV)**
- **Measles**
- **Retrovirus**
- **Poliovirus**
- **Influenza Virus**



Data extracted from https://www.clinicaltrials.gov/

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The perfect oncolytic virus

The perfect oncolytic virus represents the holy grail of current cancer innovation but has yet to be found.

So, what exactly does the perfect OV look like? What makes the ideal "magic bullet"? The profile of an ideal necessarily includes the following characteristics:

Effective at infecting the target site and doing its job

- It replicates in and selectively kills tumor cells, including cancer stem cells, while sparing all or most other cells.
- Has a low ratio between total and infectious viral particles (to maximize therapeutic effect and reduce risk of unwanted immunological side effects).
- It hides long enough from the host's immune system so that it can deploy its oncolytic and immunogenic properties.
- Pre-existing immunity is not present or is not a hurdle for therapy, or even beneficial.
- It is effective on multiple tumor types.
- Works also on far progressed, non-infected metastatic disease.
- It directly kills the cancer cell – known as "oncolysis" – and induces a long-lasting adaptive anti-tumor immune response, meaning the immune system can fight distant metastases on its own.

Safe to use

- Shows genetic stability and cannot recombine easily to a wild-type virus that can pose a potential threat to patient health.
- It does not integrate into host genome (no genotoxicity, insertional oncogenesis) and does not pose any risk to the germline.
- It does not induce auto-immune disease.
- A relatively low dose is required.
- It can be cleared from the body's system quickly and safely.
- Good animal models for pre-clinical toxicity are available to demonstrate safety.

Simple to administer in the real world

- Flexible routes of administration including both systemic and intra-tumoral delivery dependent on treatment approach and patient benefit (intra-tumoral, as a general rule, will utilize a lower dose and reduce the cost per dose).
- Single dose administration, with lifetime benefit.
- Product storage at 2-8°c, making transport and storage more feasible, particularly in emerging markets that lack necessary cold-chain management capability.

Straightforward to develop and manufacture

- Genetic engineering is (relatively) easy and fast.
- Ample packaging capacity for therapeutic cargo genes.
- Efficient to manufacture with high titers for reduced cost of goods and a cost-effective price to payer and patient dose.
- Stable during purification process.
- Ability to be terminally sterile-filtered (0.2 µm) to reduce need for aseptic processing conditions and process validation.

The perfect oncolytic virus - *continued*

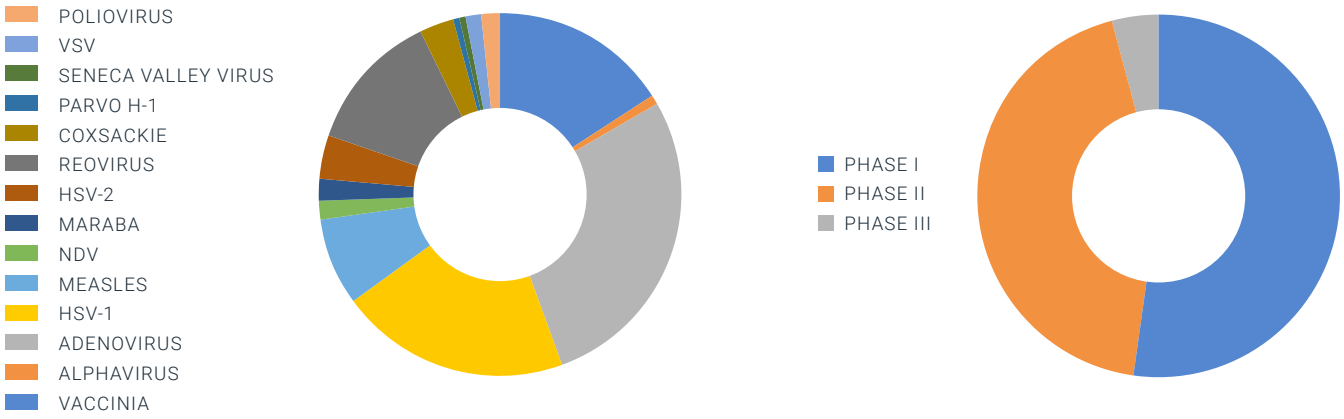
However, in reality, it is very difficult to create an OV which meets the ideal profile as outlined above. Cancers each have a unique genetic profile, which makes finding a single OV capable of attacking more than one, or even all cancer types, immensely challenging.

Moreover, immune responses can differ between patients. This means that, even if the OV is successful in making the tumor environment hot, the immune system itself may not be strong enough to attack the tumor effectively. Some patients may also have pre-existing immunity to some OVs – a particular issue when using common viruses or vectors, such as influenza virus or measles, due to prior exposure or vaccination to the virus type.

In addition to all of this, there are production and product stability issues with the virus that need to be overcome. Not all viruses are easy to manipulate to create potential therapies, and some are not suitable enough to manufacture, transport or store to successfully scale up for commercialization.

Finally, there is the challenge of navigating regulatory approval during the trial stage and in commercial. Each market has its own regulatory pathway and requirements. North America and Europe have particularly high regulatory requirements that must be secured to deliver a new treatment to the clinical trial stage or as a commercially-marketed product.

With all of this in mind, it is no surprise that few oncolytic viruses have been approved for treatment. However, the segment remains an exciting and emerging technology set to accelerate over the coming years. Particularly, the combination of OVs with traditional therapies (radiation, chemotherapy) and/or innovative immune checkpoint inhibitors is currently leading the way for very promising, effective and long-lasting treatment in some patients.



Data extracted from 2021: https://www.clinicaltrials.gov/

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Considerations for development of oncolytic viruses

There are several measures that OV developers can take to maximize their treatment's chances of reaching clinical trial successfully.

These include:

Selecting a suitable virus candidate

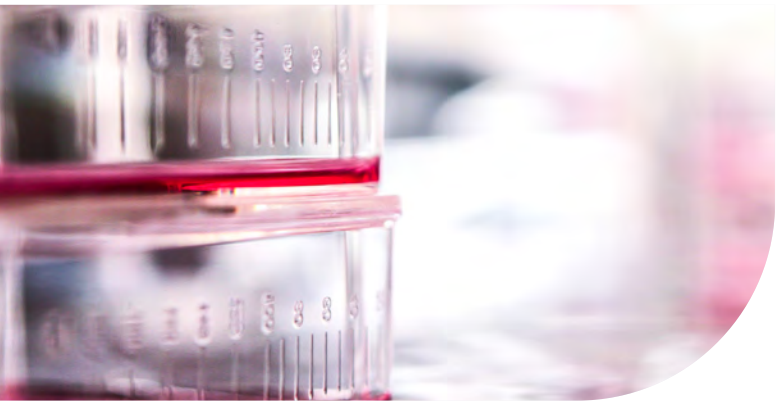
Every virus platform offers unique strengths and weaknesses, in terms of its ability to be genetically modified, the kinds of cells it prefers to infect and the way it reproduces within the cell. Choosing the candidate with the right profile for the needs of your treatment is key.

Choosing the right cell line

There are a number of cell lines already approved for OV development, which can help streamline development and make the OV product commercially viable. Each cell line has its own compatibility requirements depending on factors, such as which OV is being developed, whether the OV is enveloped, productivity for the virus in question, suspension versus adherent, etc.

Take care of your seed materials and understand your scale-up options

Whatever cell line you select for your innovation, it is important to look after the seed materials for it and, as soon as its feasibility is confirmed, to take steps to source and store sufficient material to achieve the required manufacturing scale when you are ready to commercialize.



Analytical development Is key

As live viruses are highly complex molecules, any testing and analysis program should reflect this complexity. Expert support should be sought to develop and carry out the appropriate assays needed to ensure GMP release of raw materials, cell and virus banks, and finally Drug Substance & Drug Product. Paying due consideration to appropriate bioanalytical assays and post-treatment patient monitoring is also important.

Rigorous development is critical in linking product and process

The processes required for drug substance and drug product development for oncolytic viruses are very different from those needed for other treatments. With this in mind, you should carefully think out your development roadmap from the very beginning of your project, and take the time to devise and refine discovery, analysis, trial and scaling processes well before embarking on any development work.

Leverage infrastructure and expertise through CDMO partners

To develop the appropriate processes and analytical protocols, as well as to prepare, manufacture and store the seed materials safely, it is vital to have access to the right equipment and specialist team. It is possible to build this capability in-house, but that can take time and considerable capital expenditure to achieve. Working with an expert partner, on the other hand, can provide access to this resource.

Considerations for development of oncolytic viruses - *continued*

Drug developers are advancing science through the incredible work performed in research and discovery of exciting new OV treatments to fight cancer. By following the above top tips, they can go a long way towards ensuring their treatments successfully reach trial. However, many of these measures require a team of experts and dedicated equipment.

Many lack the in-house expertise and resources to develop their innovations alone. There are contract development and manufacturing organizations with dedicated and specialist expertise and capabilities in the development in OV. They are uniquely placed to support developers in bringing their product to clinical trials and beyond.

Benefits to working with capable OV-focused CDMO

Specialist infrastructure

They have the equipment and facilities already in place to quickly scale up production with minimal delay.

Access to manufacturing platforms

OV specialist CDMOs will have their own flexible manufacturing platforms capable of manufacturing a diverse array of OVs quickly and efficiently, representing a plug & play approach.

Experienced teams

Expert teams are in place with the specialist experience needed to support developers in navigating the complexities and unforeseen challenges of OV development.

Drug Substance and Drug Product

Your preferred CDMO will offer drug substance and drug product services, reducing risks, minimizing timelines and number of outsourcing partners.

Support beyond development

In addition, they will have the in-depth knowledge in-house of the regulatory environments in developers' key markets. With this they can provide support to developers in overcoming potential regulatory hurdles as they proceed through clinical trials and enter commercialization.

Working with a partner experienced in developing OVs can help overcome many of the practical obstacles that hinder progress when innovating in this area. Such collaboration can play a vital role in maximizing the chances of a project succeeding.

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How Vibalogics can help?

Vibalogics has extensive experience supporting drug developers of all sizes, and stages, specializing in process development, manufacturing, quality control analytical service for virotherapies, and batch QP release, with a particular focus on OVs.

The company provides a comprehensive service offering at the cutting edge of OV market need to support drug developers in advancing their revolutionary cancer therapies to market.

Vibalogics has GMP accredited, BSL-2/GMO S2 classified facilities in the United States and Germany, providing comprehensive services ranging from process development to GMP seed materials, drug substance and drug product manufacturing, including aseptic processing (class B suites) capabilities, and a full range of quality control services.

The company's team of experts has an excellent track record working with various cell lines relevant for oncolytic viruses, including VERO, A549, HEK293, HeLa, and primary Chicken Embryonic Fibroblasts (CEFs). It also has the capabilities to develop both cell-based (adherent and suspension) and egg-based oncolytic virus products.

In addition, Vibalogics has in-depth knowledge of the global regulatory landscape and can support developers in navigating compliance requirements.

As a result, Vibalogics is well positioned to support drug developers not only at the clinical trial stage, but at the commercial stage too, providing them with expert regulatory and late-phase guidance for bringing OVs successfully to market.

Vital Expertise in Virotherapy.

We are only just beginning to tap into the potential of OV therapies as an effective cancer treatment.

By working with OV specialist CDMOs like Vibalogics, developers of new treatments can be confident they have the support and expertise they need to effectively bring their OV treatment to trial, and to commercialize it when it is time to do so.

To find out more about how Vibalogics can support your new OV therapy:

www.vibalogics.com

Or contact our experts:
www.vibalogics.com/contact

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About the author

Kai Lipinski PhD,
CSO

Kai Lipinski PhD, is CSO at Vibalogics, a full-service contract development & manufacturing organization. Kai has spent the past 23 years working in the virotherapay industry and joined Vibalogics in 2010 holding positions as Head of Cell Culture and Virus Production, Head of Production - Veterinary Products, Head of Process Development, and now currently resides as the companies global Chief Scientific Officer (CSO). At Vibalogics, Kai is central to the establishment of virus process development and manufacturing capabilities, new technology development and evaluation, the company's public scientific representation, and supporting overall strategy and new customer onboarding.

Kai has a wealth of experience in viral vector manufacturing , and has held prior positions as Principal Scientist at Cobra Biologics, with a focused on upstream process development for virus and mammalian protein expression programs, as well as Senior Scientist at ML Laboratories, where he was responsible for the development of targeted adenoviral vectors for cancer gene therapies. 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. He is inventor of several patents and author of peer-reviewed articles.

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