The Maturing Field of Oncolytic Virotherapies: From Research to Clinic

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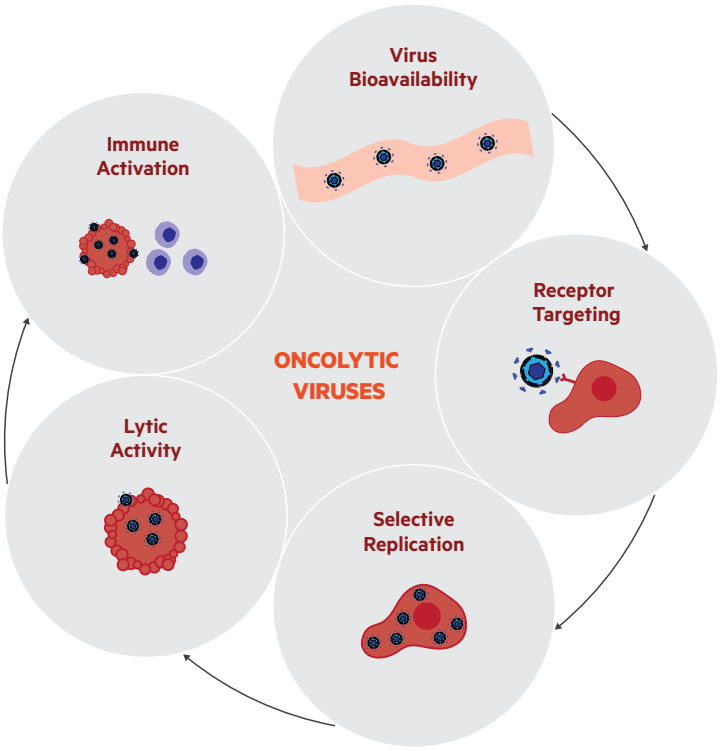
SUMMARY

Oncolytic viruses (OVs) can selectively target and kill cancer cells, and the groundbreaking FDA approval of Amgen's oncolytic virus for melanoma, T-VEC, has poised the field for emergence of next-generation therapies. We outline the scientific background behind the key elements of OV therapeutics that can be modified for greatly improved efficacy—and then use this framework to classify key opinion leaders, map current market landscape, and discuss emerging innovations and opportunities.

HIGHLIGHTS

1. We profile 19 early stage biotech companies exploring this versatility and identify key engineering efforts by each of them.
2. OVs amenable to systemic delivery will significantly expand upon targetable indications and therapeutic opportunity; very few companies have been able to develop such OVs to date.
3. There is substantial opportunity and potential value in combining OV therapies with other immunotherapies, such as checkpoint inhibitors.
4. A handful of late stage therapies in the clinical pipeline will shed light on the efficacy of next-gen engineered OVs.
5. A large deal flow, comprising both, M&A activity and partnerships, underscores significant pharmaceutical industry interest in OV therapeutics.

GRAPHICAL ABSTRACT



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EXECUTIVE SUMMARY

BACKGROUND AND SCOPE

Oncolytic viruses (OVs) can selectively target and lyse cancer cells to provide therapeutic benefits to cancer patients. The field of oncolytic virotherapy is poised for a breakthrough following the groundbreaking FDA approval of T-VEC in 2015. Compared to other immunotherapies, OVs are more modular and could potentially make a significant impact in cancer care. For example, they could provide therapeutic benefit to patients who do not respond to checkpoint inhibitors by initiating a robust anti-tumor immune response. Given these features, there is significant interest in OVs both in biotech startups and larger pharmaceutical companies. We briefly review the science behind OVs and enumerate the companies driving these therapies into the clinic in an attempt to provide insight into potential opportunities for future innovation.

METHODOLOGY

We compiled a comprehensive list of oncolytic virotherapy companies by searching for active clinical trials involving OV therapeutics as well as preclinical OV candidates and platforms in development. We then dissected the oncolytic virus space by identifying the major challenges of engineering effective therapies—namely, bioavailability, selective targeting and replication of OVs, enhanced lytic activity, and activation of systemic immunity – and classified early-stage OV companies into each of these spaces. This allowed us to identify the areas in which most companies are focusing their efforts as well as the areas that represent the greatest opportunities, such as production of OVs amenable to intravenous delivery. We further classified each major cancer indication by presence/absence of OV companies, market size, competitiveness, and demand. This analysis allowed us to identify the most promising indications in which existing OV companies are likely to thrive, as well as key areas of opportunity for OV companies to expand into. Finally, to characterize financial opportunities in the OV space, we tracked OV M&A and partnership deals by categorically searching through biotech news sources. These M&A and partnership deals were compared to the industry average to reveal trends in enthusiasm from larger pharmaceutical companies.

NEW OPPORTUNITIES

After parsing through current advancements in the preclinical and clinical state of OVs, we believe that there is significant room to engineer improved OV therapies. Many clinical stage companies are racing to improve tumor cytotoxicity, the ability to engage a potent anti-tumor immune response, bioavailability during systemic delivery, and selective targeting and replication in cancer cells. We predict that combining all of these approaches in a single therapy will pioneer the next generation of OVs. Though companies currently utilize divergent approaches in selecting oncolytic virus types for specific indications, we anticipate that a single superior virus exhibiting favorable selectivity, cytotoxicity, and bioavailability will emerge for each indication. Moreover, OVs that can be engineered to potently activate anti-tumor responses can be paired with other immunotherapies for increased efficiencies of both treatments. This remains an active area of investigation with many exciting opportunities.

Oncolytic virotherapy is entering into a crowded market, both with competition from numerous OV companies and from other immunotherapies. Nonetheless, the current market climate for OV companies is hospitable. After Amgen's Imlygic's approval in 2015, there has been a huge spike in interest from big pharmaceutical companies in the OV space. This presents great partnership and exit opportunities for startups in the OV space.

ONCOLYTIC VIRUSES— OVERVIEW AND HISTORY

Oncolytic viruses (OVs) are characterized by their ability to specifically infect and replicate within cancer cells. This behavior was first noted among virologists in the 20th century **(Figure 1A – left)**, with wild-type virus clinical trials beginning mid-20th century. Some of the first and widest studied naturally occurring viral strains were myxomavirus, bovine herpes virus 4, reovirus, Newcastle Disease Virus (NDV), and Vesicular Stomatitus Virus (VSV) [1, 2]. In preclinical and clinical trials in the early to mid-20th century, however, the results were less than promising, often causing side effects such as acute liver toxicity and hepatitis [3, 4]; however, excitement remained as the field continued to conduct clinical trials and the concept of genetically engineered viruses began to take hold **(Figure 1A)**.

In 1949, the first clinical trial utilizing a naturally occurring oncolytic virus (Hepatitis B Virus) was launched [1, 5]. While this study marked a landmark in clinical OV therapy and 7 out of 22 patients had clinical benefit, 14/22 patients developed hepatitis from exposure to the hepatitis strain, and one patient died. Between 1949 and 1974, three additional studies were conducted utilizing Egypt 101 virus, APC, and Mumps virus (wild-type), treating over 150 patients **(Figure 1A – middle)** [1, 6], showing varying results of regression, with side effects such as mild encephalitis, fever, and malaise.

As recombinant DNA technology arose in the final quarter of the 20th century, so did viral engineering practices. Through the beginning of the 21st century, a new field for oncolytic virus immunotherapy began to take hold. Immunotherapies utilize the body's immune system to recognize and kill cancerous tissues [7]. Oncolytic virotherapy was recognized as part of this burgeoning field. Easily manipulated and produced viruses, such as HSV and adenoviruses, have been the most commonly studied within the field. Broadly, this approach sought to engineer increased oncolytic functionality into the vectors such as tumor specific growth targeting (via surface receptors) and selective intracellular viral replication within the cancerous cells only [7].

As research progressed, the theoretical ideal vector sought after by many research groups and biotech companies began to take form. While some unmodified oncolytic viruses such as Reolysin have shown clinical success, the holy grail of OV therapy still remains elusive. One such trait would be the ability to substitute most of its genome, allowing a large recombinant genetic "cargo" capacity (the number of recombinant base pairs capable of packaging inside of the virus). This would allow the expression of transgenes such as toxicity or immune-stimulatory agents to be co-expressed during viral replication and life cycle [4, 7]. This was initially achieved by early success with HSV, which has an 130 kilobase payload [7]. In addition, the viral strain would necessitate ease of genetic engineering. With this feature, researchers could impart traits such as cancer cell-specific replication to the viral replication machinery without overburdening the strain itself.

At the same time, the field on oncolytic viruses continued to push forward, the field of virology began to further advance, with the first 3D structure of a virus published in 1985 [1]. In 1994, virology and oncolytics had advanced far enough to propose the concept of genetically engineered oncolytic viruses, and in 1998, the Phase I trial for G207 began in the United States. With gene therapy trials in full swing, the field suffered a tragic occurrence in 1999: during a clinical trial utilizing an adenovirus treatment for a chronic disease, 18-year-old Jesse Gelsinger died due to toxic shock [1]. Waves moved through the field as clinical trials began to come to a slow and eventual halt **(Figure 1B –**

left). Further, in 2002, two healthy volunteers in a French study developed Leukemia as a side effect of a gene therapy trial. This setback negatively impacted the clinical trial outlook as well.

However, through the tragedy came hope for OV therapies. With the first approval of H101 type 5 adenovirus with E1B-55KD (Shanghai Sunway Biotech) taking hold in China in 2005, it seemed the OV world could weather the storm. While companies continued to sprout up to bring new therapies to market, large pharmaceutical companies in the US began to take notice. Finally, in 2015, Amgen received the first approved OV therapy in the United States [7]. Through the storm came hope for OVs, and it seems that this is just beginning.

Further work sought to functionalize the surface of the viral envelope. As many cancers overexpress certain receptors on their cell surface such as prominin-1 and CD133, virus strains expressing corresponding ligands could achieve specific binding and uptake into cancer cells, as well as specific replication/expression within the cells, giving them redundancy in their targeting and leading to a highly sought after behavior in oncolytics, low off-target effects [7, 8]. The infected cancer cells effectively become viral replication factories, also leading to high local concentrations of OVs at the cancer site.

Figure 1A

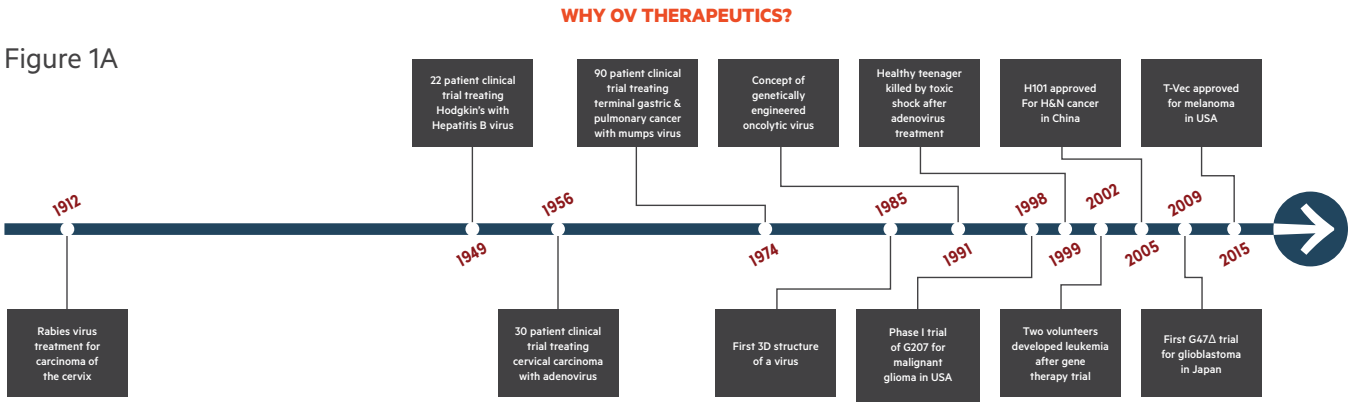

Figure 1B

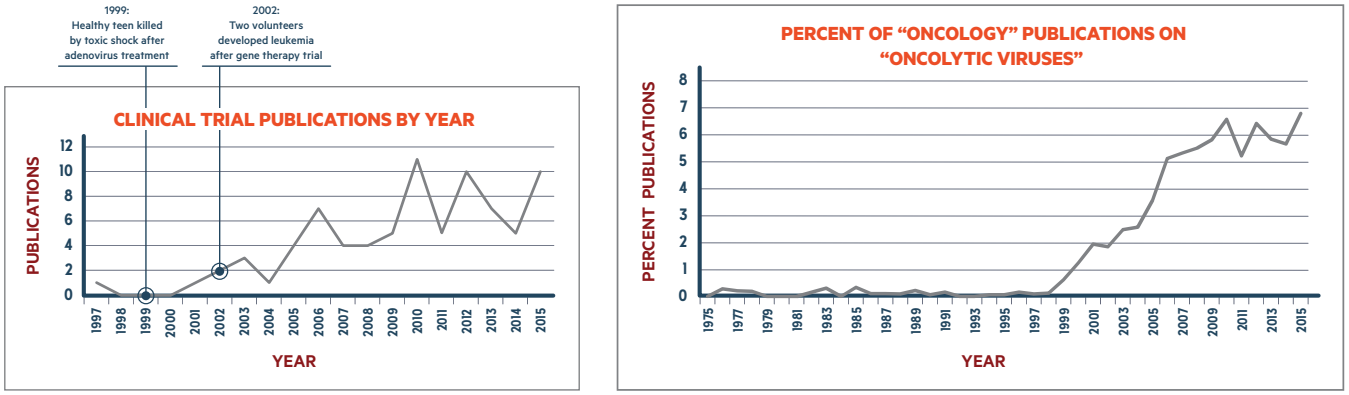

Figure 1. Why OV therapeutics now? Oncolytic viruses have a history reaching back to the early 20th century; however, recent advancements have led to a sharp increase in OV studies and clinical trials over the past decade, despite major setbacks in the gene therapy field around the turn of the century.

The adenovirus platform was targeted by many efforts early on in OV development. Due to its large capacity for foreign DNA, adenovirus was taken as an early workhorse for recombinant exogenous protein expression. In addition to this feature of its genome, it also exhibits low mutagenesis rates and low genotoxicity, thereby protecting its genetic cargo [9]. Moreover, these strains are non-integrative into host chromosomes, making them transiently expressed and reducing the risk of becoming carcinogenic themselves.

As a delivery mechanism, many adenovirus strains have been shown to have efficient intracellular delivery and high viral titers in vivo. Furthermore, some strains have exhibited cancer selective killing properties as well, positioning these as ideal candidates to build upon supplementary oncolytic activity. As discussed, the FDA approved Amgen's T-Vec (Imlygic) in 2016, marking the first approval of an oncolytic virus for unresected melanoma. With the observed increase in OV clinical trials, it stands that many new therapies may be on the rise in the coming years. Even with the recent approval of T-Vec, many of the engineering challenges to OVs still exist. In this report, we discuss the leading players in OV research, pushing the boundaries of OV engineering. Later in the report, we provide a wealth of information and resources on a number of leading companies testing the limits of OV therapeutics in both R&D and the clinic.

SCIENCE & ENGINEERING OF OV THERAPIES

The efficacy of oncolytic viruses is based on a dual mechanism of direct tumor-cell killing and engaging systemic immunity, either through endogenous activation of the immune system or by selective triggering with engineered viruses [7, 10, 11]. Although the concept of oncolytic virotherapy has been around for some time, there have been significant technical and scientific breakthroughs that are beginning to see clinical implementation.

An oncolytic virus should: (1) selectively target or replicate in tumor cells; (2) kill target cells; (3) engage anti-tumor immunity; (4) avoid anti-viral immunity to prevent viral clearance and generation of neutralizing antibodies (e.g., for re-dosing) **(Figure 2)**. Thus, there are numerous decisions in selecting and designing an oncolytic virus. There are an exceptionally large number of viruses that infect mammalian cells, and a large subset of these have been shown to be efficacious in tumor-cell killing. The tumor subtype and patient population will dictate the selection of the virus; certain viruses have defined tropisms for cells with particular signaling defects and cellular receptors, while type of viruses also dictate genetic payload carrying capacity. Subsequent decisions include employing engineered or endogenous receptor-targeting mechanisms as well as other genes to encode functions into oncolytic viruses to either enhance lytic activity or immunotherapy. Lastly, decisions on combination with other therapeutics will dictate the design (e.g., combinations with radiation or existing check-point blockade therapeutics) [7]. A current, somewhat unaddressed, limitation remains in systemic delivery of oncolytic viruses, which will be critical for tumors that are not accessible via intratumoral injections [11]. Below, there is a brief discussion on the science and engineering that enables effective oncolytic virus therapies, as well as key opinion leaders who have contributed to this growing body of research **(Table 1)**. For a more in depth overview of the science of OV therapies, we recommend the reviews cited here [7, 10, 11].

SELECTION OF ONCOLYTIC VIRUS TYPE

RNA and DNA viruses have both been utilized for oncolytic virotherapy. Both clinically approved OVs are DNA viruses: T-VEC, which was recently

approved by the FDA, is a herpes simplex virus (HSV), and H101, the virus developed by Shanghai Sunway Biotech, is an adenovirus. Vaccinia virus is another DNA virus that is being evaluated in several clinical trials. These viruses are interesting to apply towards therapy as they have relatively large transgene capacity and can be used to deliver complex genetic payloads to cancer cells. Examples of RNA viruses include reovirus, poliovirus, measles virus, NDV, and SVV. These viruses are typically harder to modify, but they can have natural tropisms for certain cancers (e.g., reovirus selectively replicates in cells with overactive Ras signaling). Additionally, certain viruses have the ability to cross the blood-brain barrier (BBB) and can be useful for treating brain cancers, such as reovirus, SVV, poliovirus, and NDV [7].

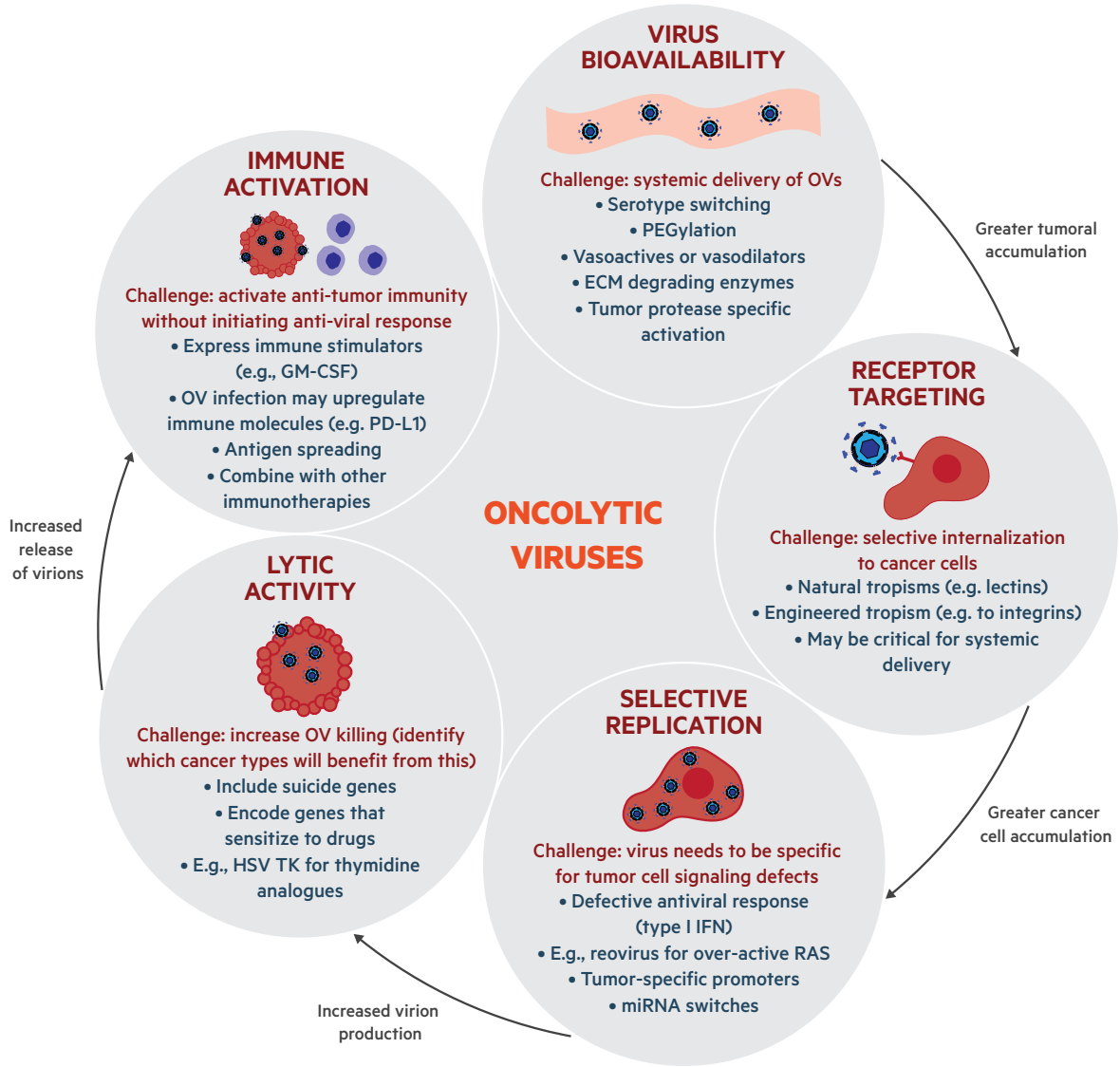

Figure 2. Science behind the efficacy of oncolytic viruses. Many elements of oncolytic viruses can be engineered. These components are interconnected and can build on each other synergistically.

Thus, the selection of virus should be guided by the patient population that is being targeted and will guide the degree of viral engineering required for a potent therapy.

Several baseline considerations should also be taken into account for patient selection. Chief among these is that patients treated with oncolytic viruses should be immunocompetent, so as to not succumb to illness due to the virus. Additionally, testing patients for neutralizing antibodies against the virus being administered is beneficial. As such, the choice of virus for minimizing virulence or knocking out virulence genes has been relatively well defined for several viruses of interest. Furthermore, as more -omic data is available from cancer patients, identifying subpopulations that are most likely to respond to oncolytic viruses might be possible.

CONSIDERATIONS IN MANUFACTURING TO GMP STANDARDS

The choice of oncolytic virus type will necessarily dictate the associated manufacturing challenges. For instance, parvovirus has low natural infectivity and high stability, which translates into low handling risk and ease of obtaining large quantities of high-purity titers. However, its low transgene capacity limits the extent to which OVs involving parvovirus can be augmented with vectors delivering tumor payloads. On the other hand, measles virus offers a larger cargo capacity and displays a natural tropism toward cancer cells via the CD46 membrane protein, but displays exceptional fragility and is difficult to obtain in sufficient purity to satisfy GMP standards. Further, some virus types are difficult to produce in large enough quantities for larger Phase II and Phase III trials, whereas others provide the advantage of production in mammalian cells, eliminating the concern of tracking endotoxin throughout the purification process.

In addition to virus-specific challenges, there is a set of universal challenges with regard to manufacturing OVs. Because the criteria for clinical OV platforms were derived from those defined in GMP specification of viral vaccine drugs, which require much less viral particle titer, OV companies face additional complications in producing large titers to stringent standards of purity. Moreover, deviations in regulation standards across countries represent an additional complication for later stage clinical trials conducted as multi-center studies. For additional information on clinical-grade production of OVs, see reference [12].

ENHANCING ONCOLYTIC VIRUS BIOAVAILABILITY

Most oncolytic viruses have to be delivered intratumorally. This is because there are numerous barriers to systemic delivery, which if adequately addressed, would result in significant opportunities for oncolytic viruses. These barriers include absorption by the liver, neutralization by host immunity in circulation, and various barriers in the tumor microenvironment (e.g., ECM, interstitial pressure, stromal cells) [11]. One approach to decrease neutralization is serotype switching between injections, as is possible in the case for adenoviruses and VSV, which have multiple serotypes. Another strategy to avoid immune cell recognition is PEGylation of the virus, though this often leads to decreased efficacy of viral entry to cells [13]. Additionally, to increase viral delivery within the tumor bed, treatment with vaso-modulators has shown efficacy. Once in the tumor microenvironment, viruses still have significant ECM barriers. To address this issue, some viruses have been engineered to express enzymes such as hyaluronidase to increase tumor delivery [14]. Alternatively, approaches that enable tumor-associated protease activation by modifying the F-protein cleavage site has shown some improvement and may result in improved OV biodistribution

[15]. These approaches might increase efficacy for both systemically and locally delivered therapies.

Mutating the fibre knob of adenoviruses, which binds cell surface coxsackievirus and adenovirus receptors, has been shown to also limit liver uptake and toxicity when administered systemically. Alternatively, targeting the liver

NAME	LOCATION	EXPERTISE/RELEVANT INTERESTING WORK
John C. Bell	Ottawa Hospital Reseach Institute	Oncolytic virus potentiation mechanism; cross-talk of CAFs with tumor cells to increase OV therapy; tumor vasculature sensitization to therapy mediated by VEGF signaling [11, 16, 21]
Yves Boucher	Edwin Steele Lab	Delivery of OV by targeting vasculature and ECM; pre-treatment with chemotherapeutic enhances spreading of OV [22]
Roberto Cattaneo	Mayo	Measles virus and lymphoma; engineering MVs to be activated by cancer-associated proteases [15]
E. Antonio Chiocca	BWH	HSV for glioma; immune response to potentiate or limit therapeutic efficacy/limit therapy [10, 23]
Mark J. Federspiel	Mayo	OV manufacturing; enveloped-viral entry mechanisms [24]
Joseph C. Glorioso	U. of Pittsburgh	HSV oncolytics; retargeting HSV to EGFR; HSV for glioma treatment [25]
Noriyuki Kasahara	U. of Miami	Gene therapy; radio sensitization [26]
Howard L. Kaufman	Rutgers Cancer Inst.	Melanoma, cancer immunology [7]
Angelica Loskog	Uppsala University	OImmuno-oncology therapies; adenovirus; targeting tumor and microenvironment [27]
Robert L. Martuza	MGH	Neurosurgery; combo of OV with chemotherapies for GBM stem cells [28]
Karen Mossman	McMaster University	Virology and immunology; bovine herpes virus OV activity related to KRAS activity [19]
Stephen J. Russell	Mayo	Measles; VSV; engineering tropism; PEGylation to increase systemic availability [13]
Khalid Shah	MGH	Brain tumors; neural stem cells; OV-encapsulated in MSC; hyaluronidase to degrade ECM [29]
Dmitriy Zamarin	MSK	Newcastle disease virus; combinations with checkpoint blockade [30]

Table 1. Key opinion leaders in academia.

with oncolytic viruses is an idea that is being explored given that a large inoculum of viruses end up there after systemic administration. This includes a vaccinia virus developed by Jennerex for hepatocellular carcinoma [16, 17].

RECEPTOR TROPISM OF ONCOLYTIC VIRUS

Once the virus is in the vicinity of the cancer cell, entry to the cells can either rely on endogenous or engineered tropism of the virus. Several oncolytic viruses have an endogenous tropism for receptors and cell surface molecules that are overexpressed by cancer cells; these include nectins for HSV or CD155 for polio virus. However, it is important to confirm that the tumor type of interest strongly expresses these receptors, and stromal cells in the microenvironment do not express them as they may serve as a sink for viruses. Alternatively, adenoviruses have been engineered with an RGD motif to bind to overexpressed integrins on the surface of cancer cells [18]. Several examples of RGD-modified viruses are being evaluated clinically. Additionally, pseudotyping one virus with targeting elements from a second virus is feasible. Modification of tumor cell targeting tropism might be necessary for systemic delivery to decrease accumulation of viruses in non-target cells that also express the viral entry receptor.

SELECTIVE REPLICATION OF ONCOLYTIC VIRUSES IN CANCER CELLS

Many cancer cells have downregulated components of the type I IFN signaling pathway, which is often necessary for cellular antiviral machinery. This makes cancer cells more susceptible to viral infection. Additionally, cancer drivers result in increased specificity for OV by limiting apoptosis that would normally occur soon after viral entry. For example, BCL family of cell survival proteins enable the replication of viruses by preventing immediate apoptosis of infected cells. Similarly, reoviruses, which are being advanced in the clinic now, can selectively replicate in cells with overactive RAS signaling [19].

Additional specificity can be engineered into oncolytic viruses. For example, viral components can be expressed under the control of tumor-specific genes, such as the expression of E1A adenoviral protein under control of the PSA promoter for prostate cancer. Additionally, adenoviruses can be restricted to hypoxic environments transcriptional regulation of HIF-1α for E1A production. However, viruses that are activated by microenvironment-specific signals may also target cancer associated fibroblasts, which are a barrier to effective function. Other examples of control include miRNA regulation, which relies on differentially expressed miRNAs between normal and cancer cells.

LYSIS OF CANCER CELLS

Some cancer cells are resistant to apoptosis from viral mediated killing. Including transgenes such as TNF-related apotosis-induced ligand (TRAIL) has been shown to increase killing efficacy. This expression can be combined with promoter specificity as discussed above.

ACTIVATION OF ANTI-TUMOR IMMUNITY

Initiation of an anti-tumor immune response significantly improves efficacy of oncolytic viruses. A common strategy is the expression of inflammatory cytokines and signaling molecules, such as GM-CSF. This is utilized in the FDA approved oncolytic virus, T-VEC, and also in several other viruses currently under clinical investigation. Additionally, adenoviruses expressing HSP70 have been shown to increase antigen presentation by increasing APC uptake of tumor antigen peptides [20]. As new biology is dissected in anti-tumor immunity, other genes may be encoded into oncolytic viruses to increase their efficacy.

Beyond initiating the immune response through genetic expression, the presence of the virus itself is inflammatory. For example,

the upregulation of PD-L1 on tumor cells after infection by reovirus has been observed. This bodes well for combination therapies with checkpoint blockades. The general phenomenon may be valuable in converting tumors that are considered 'immunologically cold' to a state that is more receptive to other forms of immunotherapies. A key concern, however, is being able to initiate a potent anti-tumor immune response while minimizing the anti-viral response.

COMBINATION WITH OTHER THERAPIES

Immunotherapies are increasingly making a push in the clinic. Oncolytic viruses certainly have some advantages over other immunotherapy modalities but will also largely make an impact through combinations. As mentioned above, the combination with checkpoint inhibitors has shown promise and is being explored in several clinical trials. There is significant need for further evaluation, especially in terms of identifying the dosing, timing, and biology of the immune response. Additionally, combinations with other modalities such as radiation or chemotherapies are being actively explored.

Checkpoint inhibitors have become a mainstay in immunotherapies, especially for solid cancers. They have strong efficacy in tumors that already have some level of tumor infiltrates and are thought to be high mutational burden, such as melanoma. In comparison, chimeric antigen receptor (CAR) T cells have had limited success in solid tumors, and are susceptible to high toxicity. CAR-T cells, however, can be genetically engineered, like oncolytic viruses, to encode additional functionality. Oncolytic viruses may have a competitive advantage compared to other modalities due to their modularity, ability to engage both arms of the immune response, and ability to have efficacy without an endogenous immune response prior to treatment. Beyond the challenges discussed above, production of oncolytic viruses is also a large challenge. They, however, may have an advantage compared to adoptive cell transfer in the ability for oncolytic viruses to multiply and spread within the tumor.

INNOVATION & DEVELOPMENT IN NEW BIOTECH

The recent FDA approval of T-VEC sets a precedent for early stage biotech companies to push their products through clinical trials and obtain FDA approval. Oncolytic viruses have much versatility as therapies, with numerous virus types that can be engineered to fine-tune properties such as tumor cell targeting, intracellular replication, and immunomodulation. Consequently, OV therapies have the potential to be applied to many indications either as monotherapies or in combination with other drugs. However, companies attempting to get an oncolytic virus therapy to market will have to face numerous challenges, among which are navigating pre-existing immunity toward viruses in patients, manufacturing therapies to GMP standards, choosing the optimal method of delivery, ensuring biosafety, accurately characterizing the pharmacodynamics of viral delivery, and optimally assessing clinical response. Below are the major players involved in the early stage development of various oncolytic virus immunotherapies.

LANDSCAPE IN ADVANCED BIO-TECH & PHARMA PARTNERS

APPROVED ONCOLYTIC VIROTHERAPIES

The field of oncolytic viruses has become exciting since the first FDA approval of an OV therapy in 2015. However, the journey of this new modality of treatment started back in the late 1990's with the first engineered oncolytic adenovirus by Onyx Pharmaceutical. However, after acquiring Onyx's development partner, Warner-Lambert, Pfizer halted the

COMPANY	THERAPIES & PLATFORMS	DESCRIPTION
Ascend Biopharmaceuticals *Australia* http://www.ascendbiopharma.com/	ASN-002 ASN-008	ASN-002 is an oncolytic immunotherapy modified from **adenovirus**. It contains a gene encoding interferon, intended to increase immune system stimulation, and is delivered as an intratumoral injection. The product is currently in a **Phasel/IIa** monotherapy trial for **nodular basal cell carcinoma**. Ascend Biopharma is also optimizing a lead candidate, ASN-008, for a chemo-immunotherapy combination trial.
BeneVir *Maryland* http://www.benvir.com/	T-Stealth™ oncolytic virus platform	BeneVir is a **preclinical** stage company developing oncolytic viruses using their T-Stealth™ technology, which makes the virus "invisible" to the immune system and prevents it from being destroyed before it can be effective. They will target **advanced solid tumors**.
DNAtrix http://www.dnatrix.com/	DNX-2401 DNX-2440 DNX-2450 MYX-135 Armed DNX platform	The DNX pipeline consists of modified adenovirus oncolytic immunotherapies that replicate in retinoblastoma-deficient cells and infect cells expressing RGD-binding integrins more effectively. Their Armed DNX platform consists of oncolytic viruses with genes encoding T-cell stimulators. DNX-2440 and DNX-2450 are Armed DNX products in the preclinical and discovery phase, respectively, for solid tumors. DNX-2401 is undergoing multiple **glioblastoma** trials, with a planned **Phase III** monotherapy trial and various combination therapies in the **Phase I and II** stages. The company also has an engineered **myxoma** virus for **hematological malignancies** in the discovery phase.
Genelux *California* http://www.genelux.com/	GL-ONC1 GL-ONC2 GL-ONC3 GL-ONC4	Genelux's leading candidate is GL-ONC1, an oncolytic modified **vaccinia virus**. Preclinical testing indicates that the treatment is effective against least against 40 types of **solid human tumors** as both a monotherapy and in combination therapies, and the product is currently entering **Phase II** trials. A unique feature of GL-ONC1 is that it includes a gene encoding for GFP, making it possible to image infected cells. Other candidates in the company's **preclinical** pipeline include GL-ONC2 (**pancreatic** and **thyroid** cancers), GL-ONC3 (**pancreatic** and **vascular** cancers), and GL-ONC4 (**prostate** cancer).
Nouscom *Switzerland* http://www.nouscom.com/	Endovax/ Exovax	Nouscom is a **preclinical** stage company. Their approach to immunoncology involves combining Endovax, a targeted oncolytic virus encoding immunomodulators, with Exovax, an adenovirus vector encoding many cancer neoantigens. The combination of these two therapies infects and destroys cancer cells while triggering the cancer-specific immune response and subsequently boosts the response to achieve sustained immunity. The ability to package over 100 neoantigens into Exovax constitutes a platform for designing personalized cancer vaccines. The team behind Nouscom is the same team that led Okairos, a company developing T-cell based vaccines, which was bought out by GlaxoSmithKline for $325M.
Oncolytics *Canada* http://www.oncolytics biotech.com/	REOLYSIN®	Oncolytics has developed an engineered **reovirus** that replicates in Ras-activated tumor cells. REOLYSIN is applicable to a diverse set of cancers, and is currently undergoing clinical trials in the US, Canada, and Europe for many indications. It is furthest along in its completed **Phase II** combination trials in the US for **lung cancer, melanoma, pancreatic cancer, head and neck cancer, and advanced malignancies**.

Table 2. Early stage OV companies, lead candidates and platforms, and progress in clinical development.

Oncorus *Massachusetts* http://www.oncorus.com/	ONCR-001	Oncorus's lead candidate, ONCR-001, is an engineered **herpes simplex virus** oncolytic immunotherapy. The therapy is currently in **preclinical** development for **glioblastoma**. The company is also developing a platform to design a second generation of viruses that will contain therapeutic payloads to increase potency.
ORYX *Germany* http://www.oryx-medicine.com/	ParvOryx	ORYX's technology, ParvOryx, utilizes an oncolytic **parvovirus** that infects tumor cells and triggers a tumor-specific immune response upon oncolysis. The virus encodes a protein that enhances cytotoxicity by inhibiting cell division, transcription, and replication while inducing cell death. ParvOryx has recently completed a **Phase I/II** trial in **glioblastoma**.
PsiOxus *United Kingdom* http://psioxus.com/	Enadenotucirev T-SIGn viruses (NG-348, NG-350a, NG-347, NG-345)	Enadenotucirev is an engineered oncolytic **adenovirus** that can be administered intravenously and still retain activity, making it active toward primary and metastatic cancer cells. It is currently in **Phase I** combination trials for **ovarian cancer** and **carcinomas** (the latter in collaboration with Bristol-Myers Squibb). T-SIGn is a platform that modifies enadenotucirev with gene delivery vectors to deliver tumor payloads that can modify the tumor microenvironment to enhance the immune response. Four products generated from this platform are in the **preclinical** stage.
Replimmune *United Kingdom* http://replimmune.com/		Replimmune closed a series A round of $30M one year ago. Little is known about this company or its pipeline, except that they are in the **preclinical** stage. The CEO of Replimmune is the former CSO of BioVex, which was acquired by Amgen in 2011 for $1B.
Targovax *Norway* http://www.targovax.com/	ONCOS-102	ONCOS-102 is Targovax's lead product, an **adenovirus**-derived oncolytic immunotherapy. It has completed **Phase I** and will undergo subsequent combination trials in **mesothelioma, melanoma, ovarian cancer,** and **prostate cancer**. Targovax also has a pipeline for producing viruses with unique characteristics by incorporating different transgenes.
TILT Biotherapeutics *Finland* http://tiltbio.com/	TILT-123 TILT-234 TILIT-321	TILT is a **preclinical**-stage company developing an oncolytic **adenovirus** with transgenes encoding cytokines for use in enhancing tumor T-cell therapies. Initial applications of the technology will be focused on enhancing tumor infiltrating lymphocyte, chimeric antigen receptor, and checkpoint inhibiting antibody therapy. Their first Phase I will likely be in **metastatic melanoma**.
Turnstone Biologics *Canada* http://www.turnstonebio.com/	Maraba oncolytic viral immunotherapy platform	Turnstone's product is a heavily engineered **rhabdovirus** that replicates only in cancer cells. It is an oncolytic immunotherapy that evades immune recognition in humans. The company's lead drug is underdoing a **Phase I/II melanoma** trial funded by a series A round. They also plan to use this product in a combination trial for **non-small cell lung cancer**. Turnstone recently closed a $41.4M series B to complete the melanoma Phase I/II trial as well as begin three additional clinical programs.
VCN Biosciences *Spain* http://www.vcnbiosciences.com/index.html	VCN-01	VCN-01 is a tumor-selective oncolytic **adenovirus**. It expresses PH20 hyaluronidase, an enzyme that breaks down tumor extracellular matrix and allows the virus to access tumor tissue more easily, thereby increasing bioavailability. The therapy is undergoing combination **Phase I** trials for intratumoral injections for **advanced pancreatic cancer** and intravenous injections for **advanced solid tumors**.

Table 2 (continued). Early stage OV companies, lead candidates and platforms, and progress in clinical development.

Viralytics *Australia* https://www.viralytics.com/	CAVATAK™	CAVATAK is an engineered **coxsackievirus** that specifically targets and replicates in cancer cells. It is an oncolytic immunotherapy that works by targeting the ICAM-1 surface protein. Currently, CAVATAK is being evaluated in **Phase I and II** clinical trials for **melanoma, prostate cancer, lung cancer,** and **bladder cancer**. The Phase II trial for melanoma has recently been completed and looks favorable.
ViraTherapeutics *Austria* http://www.virathera peutics.com/		ViraTherapeutics is collaborating with Boehringer Ingelheim to develop its platform. Its lead candidate, **vesicular stomatitis virus glycoprotein** (VSV-GP), is **preclinical**. The company is private and has yet to disclose which indications it will go after, though they claim that VSV-GP is effective against a broad range of cancers.
Virttu *United Kingdom* http://www.virttu.com/	SEPREHVIR® SEPREHVEC platform	SEPREHVIR is an oncolytic immunotherapy derived from **human herpes virus**. It is in **Phase II** trials for **mesothelioma**, has completed **Phase I** trials for **head and neck cancer** and **adult glioma**, and in an ongoing **Phase I** for **pediatric non-CNS solid tumors**. Virttu also has developed a platform to produce viruses that will localize specifically at tumors and load them with therapeutic transgenes to enhance destruction of tumor cells and activation of the immune response.
Vyriad *Minnesota* http://www.vyriad.com/	MV-NIS VSV-IFNb-NIS VSV-IFNb	Vyriad is developing a portfolio of oncolytic immunotherapies based on **vesicular stomatitis virus** (VSV) and **measles virus** (MV). Their lead candidates are MV-NIS, in **Phase II** for **myeloma** and **ovarian cancer**, VSV-IFNb-NIS, a **preclinical** therapy for **endometrial cancer**, **multiple myeloma, acute myeloid leukemia,** and **T-cell lymphoma.** Both of these therapies are distributed intravenously. In addition, Vyriad is performing a partnered **Phase I** trial with AstraZeneca and MedImmune for intratumoral injections of VSV-IFNb into **solid tumors**. Multiple other candidates are in the preclinical stage. A unique property of Vyriad therapies is that they contain a gene that allows noninvasive monitoring for virus spread via imaging.
Western Oncolytics *Ohio* http://westernoncoly tics.com/	WO-12	WO-12 is a **preclinical** oncolytic immunotherapy engineered from **vaccinia virus**. Western Oncolytics claims that their product can work across a wide range of **solid tumor** types, up to 85% of all cancers, and has partnered with Pfizer to develop the therapy through the preclinical stage until Phase I trials, after which Pfizer has exclusive rights to acquire WO-12.

Table 2 (continued). Early stage OV companies, lead candidates and platforms, and progress in clinical development.

drug development process before the Phase III trial could begin. Shanghai Sunway Biotech's slightly modified adenovirus, H101, became the world's first approved oncolytic virus in 2005 after receiving SFDA approval in China for nasopharyngeal cancer with an objective response rate and no survival data in their Phase III trial. Even though Sunway Biotech bought rights to Onyx's virus to expand into global market outside of China, they didn't get far [31, 32].

The path for the future of oncolytic viruses was paved after the FDA approved Imlygic (T-VEC), a genetically modified herpes simplex virus type 1 carrying a transgene for GM-CSF (an immunostimulant), in 2015 for "local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery" [33]. The approval was based on therapeutic benefit and not overall survival benefit. Amgen had bought Imlygic from BioVex in 2011 for $425 million upfront, plus another $575 million in milestones [34]. Analysts predicted that oncolytic virotherapies' sales will be modest compared to other modalities and would reach

$6.4 billion by 2023 [35]. Consistent with this, sales of Imlygic have been meager and were not even listed in Amgen's financial reports for 2016 [36]. To push the use of Imlygic, Amgen is collaborating on combination therapy trials of Imlygic with Merck's anti-PD1, Keytruda, in head and neck cancer and advanced melanoma [37, 38]. Imlygic has set the tone for the oncolytic virotherapy field for years to come, with many biotechs trying to either mimic strategy of use or build upon the limitations.

LATE STAGE DEVELOPMENT VIROTHERAPIES

Hard on the heels of Amgen for FDA approval is SillaJen, with a comprehensive oncolytic virotherapy history. With previous experience in developing Onyx-15 oncolytic adenovirus, David Kirn founded Jennerex Biotherapeutics to develop genetically modified vaccinia viruses as oncolytic virotherapies [32]. In 2010, Jennerex negotiated a $116 million deal from Transgene in exchange for European commercialization rights of Pexa-Vec (JX-594) [39]. Pexa-Vec is an engineered vaccinia virus expressing GM-CSF that can be administered both intratumorally and intravenously by leveraging the specialized characteristic of escaping neutralizing antibodies. However, after failing the primary endpoint of overall survival benefit in an advanced hepatocellular carcinoma (HCC) Phase IIb trial, Jennerex was acquired by SillaJen in 2014 in a deal worth $150 million at the high end [40, 41]. At the beginning of 2016, SillaJen announced the initiation of a multinational Phase III trial of Pexa-Vec for first line therapy in advanced HCC, where the only approved drug is sorafenib, stemming from the Onyx-Bayer partnership [42].

Similarly, Cold Genesys is at the Phase III stage with CG0070 for bladder cancer. The journey began with Genetic Therapy Inc., a subsidiary of Novartis, developing an oncolytic adenovirus expressing GM-CSF. In 2003, Cell Genesys Inc. acquired exclusive rights and IP of the oncolytic virotherapies in addition to $28.5 million for further development on the condition that Novartis retains certain options in future. Concurrently, Cell Genesys entered into a research collaboration with VectorLogics to enhance the cell-targeting abilities of their viruses. After failing in Phase III for their prostate cancer vaccine GVAX, Cell Genesys got acquired by BioSante in 2009 through a $38 million all-stock merger. The oncolytic virotherapies worldwide rights were then passed on to Cold Genesys in 2010 in exchange for 19.9% ownership, $95,000 in cash, and future milestone and royalty payments [43]. Cold Genesys CG0070 further to bring the therapy to Phase III trials. The study is ongoing but not recruiting more participants.

INCOMING COMPANIES WITH DEALS/ PARTNERSHIPS

With the playing field for oncolytic virotherapies wide open after FDA's approval of Imlygic, many emerging biotech companies are jumping on board with their version of the next-generation oncolytic virus. The level of excitement in the field has also attracted significant big pharma attention. Below is a list of happenings:

1. PsiOxus has gained attention with its systemically delivered "unarmed" adenovirus, enadenotucirev, amongst big pharma who want to address tumors that are currently resistant to their checkpoint inhibitors. Between Merck and Briston-Myers Squibb, PsiOxus chose to go with BMS's offering of $10 million upfront and shared development costs [44].

BMS came back 6 months later to obtain exclusive worldwide license agreement with 2. PsiOxus for NG-348, an "armed" oncolytic virus in preclinical stage. BMS is paying $50 million upfront as well as up to $886 million in milestones. BMS is responsible for global clinical development and commercialization activities related to NG-348 [45].

3. Even though GSK isn't involved in the oncolytic virus development space, GSK's VC unit SR One in combination with the Woodford Fund contributed $39 million in series C round to PsiOxus Therapeutics [46].
4. Pfizer is back in the game by becoming a strategic collaborative partner and lead investor in Ignite Immunotherapy, which will focus on discovery and development of next-gen intravenous oncolytic virotherapies. Pfizer holds 50% equity investment, will fund research and development for 3 years, has 2 seats in the BoD, and has an exclusive option to acquire Ignite after initial research program is completed [47].
5. Boehringer Ingelheim is on board as well after entering a long-term collaboration with ViraTherapeutics, where Boehringer Ingelheim Venture Fund is a core investor. With a deal valued at up to $236 million, Boehringer is receiving joint development rights to the lead candidate VSV-GP and the right to acquire ViraTherapeutics after conclusion of Phase I clinical trials [48, 49].
6. Even though Bayer Healthcare hasn't entered a collaboration with any biotech, it has shown signs of interest in the oncolytic virus space by funding research studies and publishing a presentation that mentions the oncolytic virus asset as a "specific strategic need/gap of the business within Bayer" [50].
7. Celgene has backed Oncorus as an active strategic investor in their $57 million series A. Oncorus is going after aggressive cancers including glioblastoma multiforme (GBM) [51].
8. In order to tap into patient populations unresponsive to checkpoint inhibitors, Merck has collaborated with multiple oncolytic virotherapy biotechs including DNAtrix and Oncolytics (in addition to Amgen) for combination therapy with Keytruda [52, 53].
9. Similarly, AstraZeneca's global biologics research and development arm, MedImmune, has entered into a licensing agreement with Omnis Pharmaceuticals to develop and commercialize Omnis' lead oncolytic virus program. The main incentive of AstraZeneca here is to rapidly progress combination studies with MedImmune's immunotherapies [54].
10. In order to stay relevant with critical mass, Targovax and Oncos Therapeutics merged in 2015 with Oncos' shareholders getting 50% of stock of the combined company. Their lead candidate in their portfolio include engineered human serotype 5 adenovirus ONCOS-102 and RAS mutation targeting vaccine TG01 [55].
11. Similarly, Omnis and Magnis have merged together to form Vyriad with 8 oncolytic virotherapies in clinical phases and 7 in the preclinical stage. Their oncolytic virotherapies are based on engineered vesicular stomatitus virus (VSV) and measles virus [56].

OUTLOOK

JOURNEY TOWARD THE IDEAL OV THERAPY

As noted throughout the report, various aspects must be considered during the process of viral selection and engineering for oncolytic therapies. To address these points, existing companies in the OV space are taking a multifaceted approach to developing their lead candidates **(Figure 3)**. Some companies looking to enter multiple indications are building up portfolios with multiple viruses, such as DNAtrix, which is hedging their bets on adenoviral therapies for solid tumors and glioblastoma and on myxoma virus for hematological malignancies. Indeed, viruses are not of equal utility and efficacy with regard to every indication, and characteristics such as natural tropisms or differential ability to cross the blood brain barrier present the possibility that there may emerge a single optimally effective viral platform per indication. Furthermore, companies such as DNAtrix, Oncorus, PsiOxus, and several others **(Table 2)** are strategically building up platforms to customize viral vectors that deliver tumor payloads including immune stimulators, suicide

genes, ECM modulators, and other factors that modulate lytic activity, bioavailability, and anti-tumor immunity. While many companies are taking steps toward producing the ideal OV therapy, a major challenge that remains is expanding the delivery mode from intratumoral injection to intravenous delivery. Although the latter is subject to additional challenges, developing an OV amenable to this mode of delivery represents an opportunity to treat additional indications that cannot be treated by intratumoral injection, thereby expanding the applicability of OV therapies as a whole. However, relatively few companies—PsiOxus, Vyriad, and Viralytics among them—have been able to develop such OVs to date **(Figure 3)**. We anticipate the path toward increased success and efficacy rate of OV therapeutics will necessarily involve more sophisticated and comprehensive engineering efforts. The biggest engineering effort will be geared towards increasing virus bioavailability during systemic delivery, selective targeting and lysis of cancer cells to increase the therapeutic window, and more potent engagement of the anti-tumor immune response.

MARKET CROWDEDNESS AND OPPORTUNITIES

OV therapies are currently mostly restricted to solid tumors that are accessible to intratumoral injections. As such, most OV companies have pursued similar indications and the landscape competitiveness is fairly uniform **(Figure 4)**. Acute myeloid leukemia stands out as an exception with very low intra-OV competition. This is because OV companies need to optimize intravenous delivery to target any type of liquid

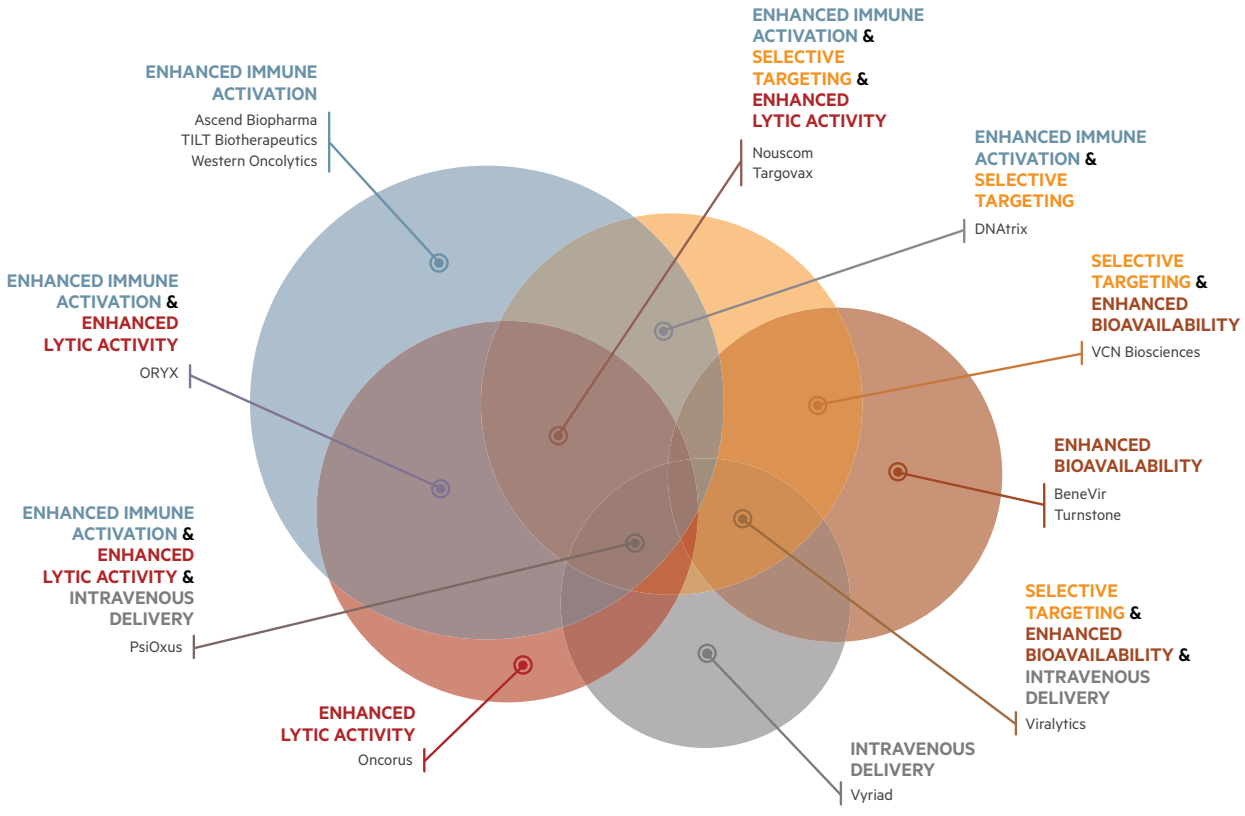

Figure 3. A breakdown of the early stage oncolytic virus companies based on five key areas of improvement.

cancer, and as we have mentioned, systemic delivery of OV is a major challenge. Therefore, any OV technology with an improved systemic delivery platform for targeting liquid tumor or solid tumors not amenable to intratumoral injections represent a huge opportunity in the field.

Some benchmarks for assessing competitiveness from other modalities are the number of approved therapies for the indication, especially in the last 5 years, and 5-year survival rate for the indication. Low 5-year survival rate and limited number of approved therapies indicate unmet need. In terms of these benchmarks, the indications currently explored by OV that present the most opportunity are mesothelioma, hepatocellular carcinoma, glioma, and pancreatic cancer **(Figure 4)**.

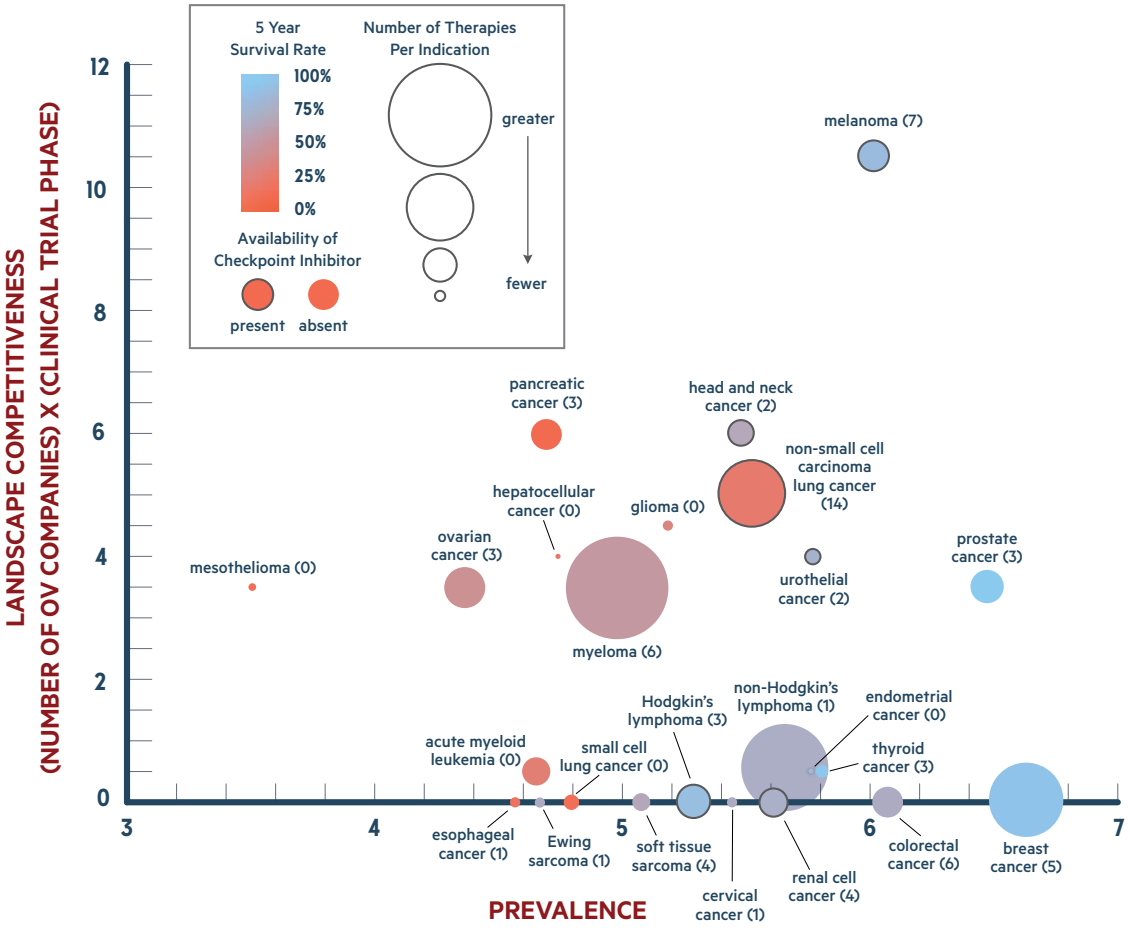

Figure 4. Market competitiveness of the major oncological indications. Indications are mapped via their prevalence, a proxy for market barrier (the number of drugs available per indication), and the landscape competitiveness (the sum of OV companies in the space multiplied by clinical trial stage of their lead therapies). Indications mapped onto the x-axis represent spaces that OV companies have yet to enter. Circle size represents the number of non-OV FDA-approved therapies for each indication, indicating competition from non-OV therapeutics, and circle color indicates the 5-year survival rate. Of all available therapies indicated by the size of the circle, the number approved in the last 5 years is indicated parenthetically next to the name of the indication. Presence of a dark outline on the circle indicates the availability of an FDA-approved checkpoint inhibitor in the space.

Moreover, across all cancer types, esophageal cancer and small cell lung cancer also have a very low 5-year survival rate along with few approved therapies, and should be amenable to intratumoral injection, therefore representing an excellent opportunity for the OV modality to expand into **(Figure 4)**. Generally, low 5-year survival rate and few approved therapies as options for patient also represent a huge opportunity for OVs to compete for first-line therapy status and also have significant pricing power. Furthermore, 5-year survival rate for a particular indication may not always be the best predictor, as other factors such as the stage of the cancer greatly influence the prognosis. Thus, a possible strategic route is to selectively go after a subset of the cancer population, similar to Imlygic's strategy in melanoma.

Another big opportunity is combining OV therapies with checkpoint inhibitors. Early insight on OV's ability to engage the anti-tumor immune response came from Imlygic's clinical trial where 34% of non-injected non-visceral tumors and 15% of visceral tumors had greater than 50% reduction in size [57]. This suggested that OVs could boost anti-tumor immune response, which presented a tremendous opportunity for OVs to pursue combination therapy with checkpoint inhibitors, especially in immunologically cold tumors. Today, numerous clinical trials investigating combinations of OV therapies with checkpoint inhibitors are underway and

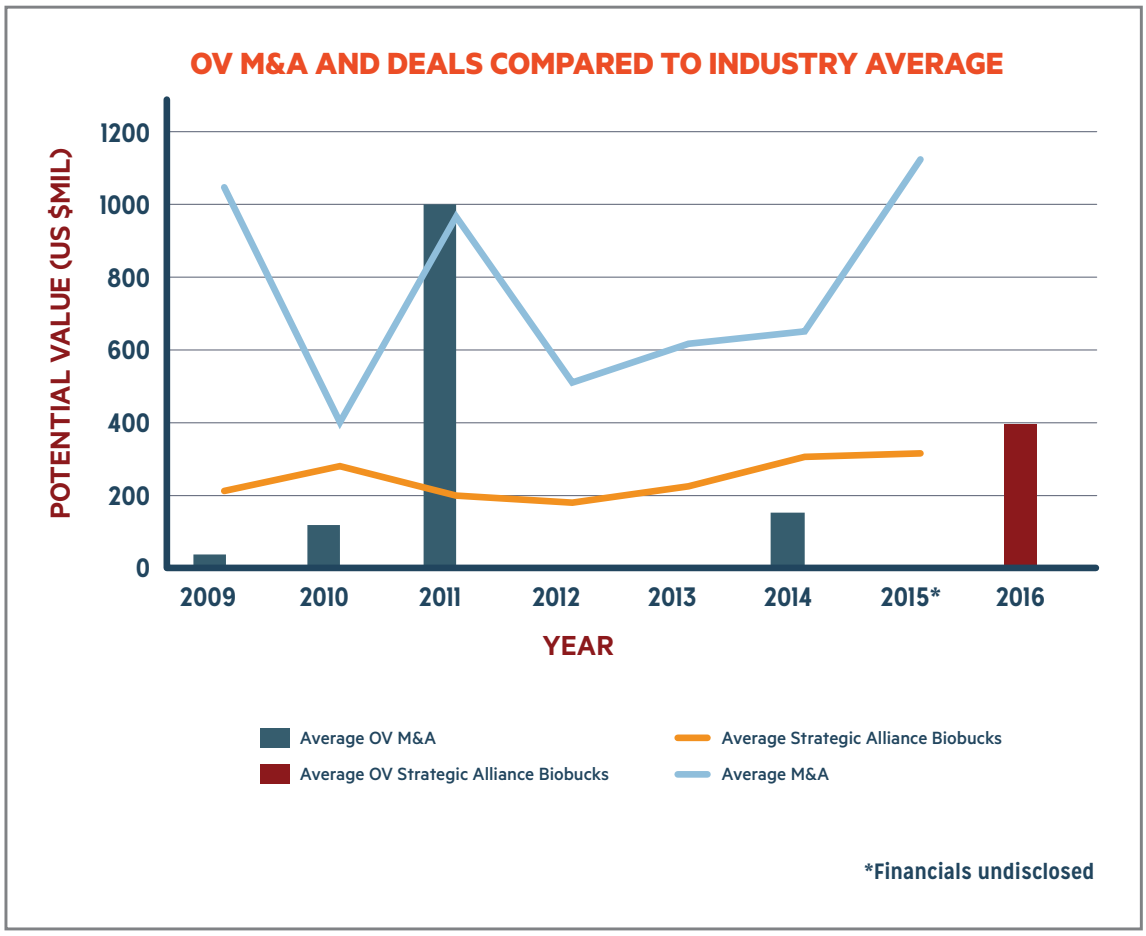

Figure 5. Comparison of OV M&A and strategic alliance deals with the industry average from 2009-2016.

preliminary results look favorable. For instance, the Phase Ib trial of Imlygic with anti-CTLA4 showed an objective response rate of 50% and durable response rate of 44% in patients with advanced melanoma [58]. Similarly, Viralytics' Cavatek showed 100% disease control rate in combination with Keytruda, and 50% response rate in combination with Opdivo in melanoma patients [59]. These promising results indicate the huge opportunity for OV therapies to boost the efficacy of checkpoint inhibitors and become more competitive compared to other modalities.

TRENDS AND EXIT OPPORTUNITIES IN THE OV SPACE

Although big pharma had shown interest in OV, the M&A and deal trends demonstrate that they had been waiting for the field to prove itself. Average OV M&A potential value was much lower for the last 7 years compared to the industry average, and strategic alliances did not exist until 2015 **(Figure 5)**. Following the approval of Imlygic in the US in 2015, there has been much more activity from big pharma. Even though Imlygic's sales have been subpar, FDA approval of an OV modality has generated significant excitement in the field. Since Imlygic's approval, we have seen four big pharma jump on board with big investments in OV, and a few more actively expressing interest, foreshadowing great exit opportunities for upcoming OV companies. With regard to deal valuations, there have been two close-to-billion dollar M&A and deals in OV space – one of these was Amgen's acquisition of Imlygic [34]. Following the FDA approval of Imlygic, BMS offered a close-to-billion dollar deal to PsiOxus [45]. It is likely that this trend will continue as even more promising OVs demonstrate efficacy in clinical trials. In order to predict the future of OV, we will have to carefully watch current OVs in Phase III clinical trials as well as OV/checkpoint inhibitor combination trials.

TEAM MEMBER BIOGRAPHIES

JAKE BECRAFT is a fourth year PhD candidate in the Biological Engineering Department at MIT in the lab of Professor Ron Weiss. While his thesis research focuses around synthetic regulation of next generation RNA vaccines, his broader research interests encapsulate synthetic biology and self-regulating stem cell therapies. In addition to strict scientific research, Jake is also involved in the MIT Biotech Group's Investment Due Diligence team, exploring his interest in startups, venture capital, and venture creation. He is also active in the MIT Science Policy Initiative, serving as a member and coordinator for multiple science advocacy trips to DC. In addition, Jake serves as a Science and Technology advisor to a freshman legislator in the Massachusetts State House. In his free time, he is an avid snowboarder and loves to attend live stand-up comedy shows around the city.

JAIDEEP DUDANI is a fourth-year PhD candidate in Biological Engineering at MIT, working in the lab of Sangeeta Bhatia at the Koch Institute for Integrative Cancer Research. He is currently an NSF fellow and Ludwig Center for Molecular Oncology fellow. He is broadly interested in the development and translation of innovative scientific concepts to useful technologies. His research is focused on developing functional biomarkers of disease that can be therapeutically targeted using injectable nanotechnologies that probe and perturb proteolytic enzymes aberrantly expressed in numerous cancers and during bacterial infection. He collaborates closely with industry, clinicians, and academic groups. He holds an undergraduate degree in Bioengineering from UCLA, where he developed microfluidic technologies for high-throughput single-cell phenotyping in the lab of Dino Di Carlo. He has published over ten peer-reviewed papers (including 7 first-author publications) and has several patent filings.

OLESYA LEVSH is a fourth-year PhD candidate in the biology department at Massachusetts Institute of Technology. Her research focuses on elucidating specialized metabolic pathways in diverse plant species and understanding the role of enzyme evolution in the emergence of specialized metabolism, as well as utilizing synthetic biology to produce commercially valuable plant metabolites. Outside of science, Olesya is interested in venture capital and healthcare innovation. She takes healthcare-oriented courses at MIT Sloan School of Management and is involved with MIT Biotech Group's Investment Due Diligence group. Her ambition is to be able to impact healthcare by combining her scientific background with an expanding knowledge of concepts in market strategy and the biotech industry in order to push innovation. In her free time, Olesya enjoys discovering and cooking new recipes. She spends her summers hiking in the White Mountains and her winters skiing in the Northeast.

RACHIT NEUPANE is a fourth-year PhD candidate advised by Professor Jacqueline Lees at the MIT Koch Institute for Cancer Research. He currently holds a David H. Koch Graduate Fellowship and was previously a Praecis Presidential Graduate Fellow at MIT. As a researcher, Rachit examines the role of epigenetic regulators in tumor maintenance in the context of lung and colon cancer. He has also actively forged collaborations to develop better preclinical models, utilize mRNA delivery systems, and translate non-invasive imaging particles for biological applications. Rachit's active interest in entrepreneurship and healthcare innovation has led him to serve as an executive member in MIT Biotech Group as the Director of Events, as well as a project leader in the Investment Due Diligence group. He is also enrolled in the MIT Sloan Healthcare Certificate Program to explore business development and strategy in biotech. Outside of MIT, Rachit develops product and commercial strategy with Avir Technologies, a start-up developing mobile-based diagnostics and management solutions for chronic diseases.

REFERENCES

1. Kelly, E. and S.J. Russell, *History of oncolytic viruses: genesis to genetic engineering*. Mol Ther, 2007. **15**(4): p. 651-9.
2. Russell, S.J., K.W. Peng, and J.C. Bell, *Oncolytic virotherapy*. Nat Biotechnol, 2012. **30**(7): p. 658-70.
3. Aref, S., K. Bailey, and A. Fielding, *Measles to the Rescue: A Review of Oncolytic Measles Virus*. Viruses, 2016. **8**(10).
4. Lichty, B.D., et al., *Going viral with cancer immunotherapy*. Nat Rev Cancer, 2014. **14**(8): p. 559-67.
5. Lawler, S.E., et al., *Oncolytic Viruses in Cancer Treatment: A Review*. JAMA Oncol, 2016.
6. Fukuhara, H., Y. Ino, and T. Todo, *Oncolytic virus therapy: A new era of cancer treatment at dawn*. Cancer Sci, 2016. **107**(10): p. 1373-1379.
7. Kaufman, H.L., F.J. Kohlhapp, and A. Zloza, *Oncolytic viruses: a new class of immunotherapy drugs*. Nat Rev Drug Discov, 2015. **14**(9): p. 642-62.
8. Zeyaullah, M., et al., *Oncolytic viruses in the treatment of cancer: a review of current strategies*. Pathol Oncol Res, 2012. **18**(4): p. 771-81.
9. Tan, K.X., et al., *Towards targeted cancer therapy: Aptamer or oncolytic virus?* Eur J Pharm Sci, 2017. **96**: p. 8-19.
10. Chiocca, E.A., *Oncolytic viruses*. Nat Rev Cancer, 2002. **2**(12): p. 938-50.
11. Parato, K.A., et al., *Recent progress in the battle between oncolytic viruses and tumours*. Nat Rev Cancer, 2005. **5**(12): p.

965-76.
12. Ungerechts, G., et al., *Moving oncolytic viruses into the clinic: clinical-grade production, purification, and characterization of diverse oncolytic viruses*. Mol Ther Methods Clin Dev, 2016. **3**: p. 16018.
13. Tesfay, M.Z., et al., *PEGylation of vesicular stomatitis virus extends virus persistence in blood circulation of passively immunized mice*. J Virol, 2013. **87**(7): p. 3752-9.
14. Ganesh, S., et al., *Intratumoral coadministration of hyaluronidase enzyme and oncolytic adenoviruses enhances virus potency in metastatic tumor models*. Clin Cancer Res, 2008. **14**(12): p. 3933-41.
15. Springfeld, C., et al., *Oncolytic efficacy and enhanced safety of measles virus activated by tumor-secreted matrix metalloproteinases*. Cancer Res, 2006. **66**(15): p. 7694-700.
16. Breitbach, C.J., et al., *Intravenous delivery of a multi-mechanistic cancer-targeted oncolytic poxvirus in humans*. Nature, 2011. **477**(7362): p. 99-102.
17. Parato, K.A., et al., *The oncolytic poxvirus JX-594 selectively replicates in and destroys cancer cells driven by genetic pathways commonly activated in cancers*. Mol Ther, 2012. **20**(4): p. 749-58.
18. Puig-Saus, C., et al., *iRGD tumor-penetrating peptide-modified oncolytic adenovirus shows enhanced tumor transduction, intratumoral dissemination and antitumor efficacy*. Gene Ther, 2014. **21**(8): p. 767-74.
19. Cuddington, B.P. and K.L. Mossman, *Permissiveness of human cancer cells to oncolytic bovine herpesvirus 1 is mediated in part by KRAS activity*. J Virol, 2014. **88**(12): p. 6885-95.
20. Li, J.L., et al., *A phase I trial of intratumoral administration of recombinant oncolytic adenovirus overexpressing HSP70 in advanced solid tumor patients*. Gene Ther, 2009. **16**(3): p. 376-82.
21. Ilkow, C.S., et al., *Reciprocal cellular cross-talk within the tumor microenvironment promotes oncolytic virus activity*. Nat Med, 2015. **21**(5): p. 530-6.
22. Nagano, S., et al., *Cancer cell death enhances the penetration and efficacy of oncolytic herpes simplex virus in tumors*. Cancer Res, 2008. **68**(10): p. 3795-802.
23. Alvarez-Breckenridge, C.A., et al., NK cells impede glioblastoma virotherapy through NKp30 and NKp46 natural cy*totoxicity receptors*. Nat Med, 2012. **18**(12): p. 1827-34.
24. Clinic, M. *Viral Vector Production Laboratory*. Centers and Programs - Mayo Clinic Cancer Center - Research 2017 [cited 2017; Available from: http://www.mayo.edu/research/centers-programs/cancer-research/shared-resources-core-facilities-services/gene-virus-therapy/viral-vector-production-laboratory.
25. Grandi, P., et al., *Design and application of oncolytic HSV vectors for glioblastoma therapy*. Expert Rev Neurother, 2009. **9**(4): p. 505-17.
26. Takahashi, M., et al., *Radiosensitization of gliomas by intracellular generation of 5-fluorouracil potentiates prodrug activator gene therapy with a retroviral replicating vector*. Cancer Gene Ther, 2014. **21**(10): p. 405-10.
27. Diaconu, I., et al., *Immune response is an important aspect of the antitumor effect produced by a CD40L-encoding oncolytic adenovirus*. Cancer Res, 2012. **72**(9): p. 2327-38.
28. Kanai, R., et al., *Oncolytic virus-mediated manipulation of DNA damage responses: synergy with chemotherapy in killing glioblastoma stem cells*. J Natl Cancer Inst, 2012. **104**(1): p. 42-55.
29. Duebgen, M., et al., *Stem cells loaded with*

multimechanistic oncolytic herpes simplex virus variants for brain tumor therapy. J Natl Cancer Inst, 2014. **106**(6): p. dju090.
30. Zamarin, D., et al., *Localized oncolytic virotherapy overcomes systemic tumor resistance to immune checkpoint blockade immunotherapy.* Sci Transl Med, 2014. **6**(226): p. 226ra32.
31. BIOWIRE2K, *First Oncolytic Viral Therapy Approved for Head and Neck Cancer* 2005, BusinessWire: Online.
32. Garber, K., *China approves world's first oncolytic virus therapy for cancer treatment.* J Natl Cancer Inst, 2006. **98**(5): p. 298-300.
33. *FDA Approves IMLYGIC™ (Talimogene Laherparepvec) As First Oncolytic Viral Therapy In The US.* 2015.
34. Timmerman, L., *Amgen to Acquire BioVex for Up To $1B, to Obtain Cancer-Killing Virus Therapy,* in Xconomy 2011: Xconomy Boston Online.
35. Dolgin, E., *Oncolytic viruses get a boost with first FDA-approval recommendation.* Nat Rev Drug Discov, 2015. **14**(6): p. 369-71.
36. *Amgen Reports Third Quarter 2016 Financial Results*, 2016, Amgen: Amgen News Release.
37. Lederman, L., T-*VEC/Pembrolizumab Combo Shows Early Promise in Advanced Melanoma*, in OncLive 2016.
38. Barber, J., *Merck & Co., Amgen expand Keytruda, T-Vec collaboration to include head and neck cancer,* in First World Pharma 2015.
39. Carroll, J., T*ransgene, Jennerex ponder fate of tumor-fighting virus after PhIIb failure*, in Fierce Biotech 2013.
40. Carroll, J., *Korean CRO grabs failed cancer vaccine in $150M-max Jennerex buyout,* in Fierce Biotech 2013.
41. SillaJen, *SillaJen Announces Completion of Jennerex, Inc. Acquisition*, in PR Newswire 2014.
42. *SillaJen reports initiation of multinational randomized Phase 3 study of Pexa-Vec in HCC patients*, in News Medical Life Sciences 2016.
43. *Cold Genesys Buys BioSante's Oncolytic Virus Technology, in Genetic Engineering & Biotechnology News* 2010.
44. *Bristol-Myers Squibb and PsiOxus Therapeutics Announce Immuno-Oncology Clinical Collaboration to Evaluate the Combination of Opdivo and Enadenotucirev, in Business Wire* 2016.
45. *Bristol-Myers Squibb Signs Exclusive Worldwide License Agreement with PsiOxus Therapeutics for NG-348, an "Armed" Oncolytic Virus to Address Solid Tumors, in Business Wire* 2016.
46. Taylor, N.P., *PsiOxus bags $39M from Woodford, GSK for checkpoint inhibitor combo trial,* in *Fierce Biotech* 2015.
47. *Pioneers in Oncolytic Virus and Gene Therapy Fields Announce Formation of IGNITE Immunotherapy Inc., a Company Focused on Oncolytic Cancer Vaccine Discovery and Development*, in *Business Wire* 2016.
48. *Boehringer Ingelheim Boosts Immune-Oncology Pipeline Through Collaboration with ViraTherapeutics,* in *Business Wire* 2016.
49. *Boehringer buys into oncolytic viruses via €210m ViraTherapeutics deal*, in *PMLiVE* 2016.
50. Kuhn, I., et al., *Directed evolution generates a novel oncolytic virus for the treatment of colon cancer.* PLoS One, 2008. **3**(6): p. e2409.
51. Lawrence, S., *Celgene backs next-gen oncolytic virus startup in $57M Series A.* Fierce Biotech, 2016.
52. Carroll, J., *Merck adds oncolytics combo study to its huge Keytruda effort,* in *Fierce Biotech* 2015.
53. House, D.W., *Oncolytics Bio poised to*

begin early-stage study of REOLYSIN with Keytruda and chemo in pancreatic cancer, in *Seeking Alpha* 2015.
54. *MedImmune enters licensing agreement with Omnis Pharmaceuticals for oncolytic viruses in immuno-oncology,* in *AstraZeneca Media Centre* 2015.
55. Taylor, N.P., *Targovax to merge with Oncos then IPO in push for immuno-oncology mainstream*. Fierce Biotech, 2015.
56. *Omnis, Magnis Merge into Vyriad, with Focus on Cancer Immunotherapies*. Genetic Engineering & Biotechnology News, 2016.
57. Andtbacka, R.H., et al., *Patterns of Clinical Response with Talimogene Laherparepvec (T-VEC) in Patients with Melanoma Treated in the OPTiM Phase III Clinical Trial*. Ann Surg Oncol, 2016. **23**(13): p. 4169-4177.
58. Puzanov, I., et al., *Talimogene Laherparepvec in Combination With Ipilimumab in Previously Untreated, Unresectable Stage IIIB-IV Melanoma*. J Clin Oncol, 2016. **34**(22): p. 2619-26.
59. Taylor, P., *Viralytics' anticancer virus aces checkpoint inhibitor combo trials*, in *Fierce Biotech* 2016.