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Cancer killing virus? It's going viral!



How Oncolytic Viral therapies are becoming the new trend for cancer treatment

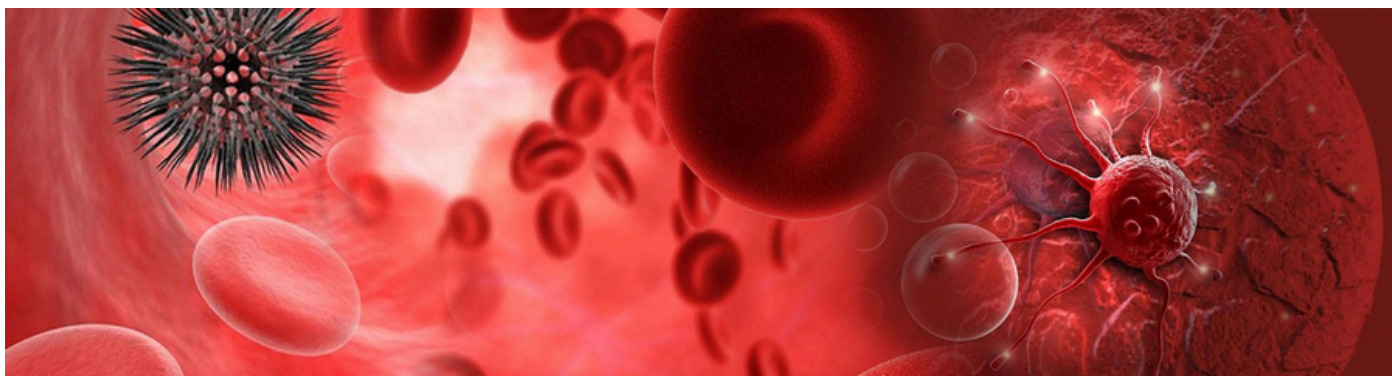


Image source: Lupine Publishers

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Woes of Melanoma (Skin Cancer)

Around the world, the number of people diagnosed with melanoma is rising. In Australia, the statistics showed that the percentage of the population diagnosed with melanoma of the skin has risen from 14,485 cases in 2016, to more than 16,000 new cases in 2020, representing the world's highest incidence rate for melanoma [1].

Melanoma is a type of skin cancer which is caused by overexposure to the sun. Symptoms of melanoma can include change in colour, size and shape of an existing mole or the appearance of a new spot [1]. The growth of the mole can damage blood vessels and cause bleeding, which can be fatal to the patient. The treatments for melanoma are various, including surgery, radiotherapy,

targeted therapy or immunotherapy, which depends on the size and location of the tumour [1]. To date, surgery remains one of the principle mainstay ways to treat localized cancer. However, the use of oncolytic viruses (OVs) has emerged as a promising therapeutic for cancer treatment [2], which several patients have begun to benefit from.



Image source: Malignant Melanoma by GP Online

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Story of Randy Russel

He was told it was the end of the road, and only had 6-7 months to live. As he was leaving the hospital, one of the doctors gave him a gleam of hope of survival, "Try Vanderbilt!"

Ten years ago, Randy Russell found out that he got skin cancer, and a small mole had begun to appear on his skin. He went to get the surgery and got the mole removed, however, more moles appeared on his skin one after another. He had begun to struggle with this cancer, as he could not get rid of the tumour completely no matter his unceasing effort. He was hopeless and aggravated because the tumour had begun to bankrupt his family after more than ten rounds of surgeries. Due to the worsening of his condition, he was told it was the end of the road,

and only had 6-7 months to live. As he was leaving the hospital, one of the doctors gave him a gleam of hope of survival, "Try Vanderbilt!" [4].

Russell was willing to take the risks by taking an experimental drug directly injected into his tumours at Vanderbilt University Medical Center. Surprisingly, the tumours reduced to half the size after each visit. After a few times of the experiment, the doctors said, "Look, there's nothing more we can do for you. It's just gone [4]."

Imlygic
(Talimogene laherparepvec)



Emergence of IMLYGIC as an OV saviour

It is reasonable to speculate that IMLYGIC® is currently the biggest player in the US viral immunotherapy market,

In fact, this experimental drug is called talimogene laherparevec (T-VEC), which is a virus that researchers used to kill Russell's cancer tumours [4]. It is the first ever virus that has been used for the treatment of patients with skin cancer, such as melanoma. Since then, the development of highly potent OV's have come a long way. In recent years, a viral oncolytic company Amgen made a drug called IMLYGIC®, which has

received the U.S. Food and Drug Administration (FDA) approval in October 2015 and since then has made it successfully into the market [5]. The beauty of IMLYGIC® is that this drug uses the virus itself as an active drug reagent, where the virus is genetically engineered so that it could destroy tumours and kill cancer cells without harming the normal cells to the patient [2]. This makes it ideal for treating patients with mela-

noma lesions in the skin and lymph nodes, where the lesions cannot be removed completely by the traditional surgery [5]. It is reasonable to speculate that IMLYGIC® is currently the biggest player in the US viral immunotherapy market, in the fact that IMLYGIC® is the first FDA approved medication for melanoma in 2015, and Amgen is still holding the largest market share [6].

History of Oncolytic Viral Therapy

Oncolytic viral therapy began over a century ago as an observational science. It was observed early on that there is notable cancer regression occasionally after a viral infection.[7] But the viral oncolytics has been in the backseat due to greater developments in the fields of radiation and chemotherapy since 1930s [8]

As we might think by the flashy name 'cancer killing virus,' that the virus

infects and actually kills every single cancer cell in the tumour is not true. Most oncolytic viral therapies for cancer cells work on increasing the response of the immune system of the human body to tackle the cancer cells, as viral therapies are not effective by themselves as a complete treatment. These work best as complementary agents to existing therapies like antineoplastic therapy, chemotherapy, and radiotherapy.[9]



Image: Oncorine by Shanghai Sunway Biotech

Oncolytic Virus immunotherapy market overview

According to the report published by Persistence Market Research in 2019, the viral immunotherapy for cancer global market is predicted to have a value of about 214M US dollars by 2029. The high market value of the viral immunotherapy is predicted based on the market growth since 2018, as shown in the below figure, in the scenario where this approach of cancer and tumour treatment presented a significant promise of high efficacy and improved quality of life. In addition, the growth of market value is also projected by the increasing number of clinical trials,

such as Transgene and Oncolytics Biotech. The opportunity in the viral immunotherapy market has been increased and reached to a number of \$50M USD. However, there are only very few players in the recent market, including Amgen and Shanghai Sunway Biotech. In other words, the very segmented market of viral immunotherapy allows new entrants to share the big cake, depending on the progress in their pipeline. It is shown in the figure that the Shanghai Sunway Biotech (Oncorine®), a Chinese based company, is the major competitor of Amgen in the current global market. Oncorine was the first ever OV drug to be approved (2005 China) Amgen is still holding its big share mainly in North America, but also trying to increase its influences on this particular field globally.

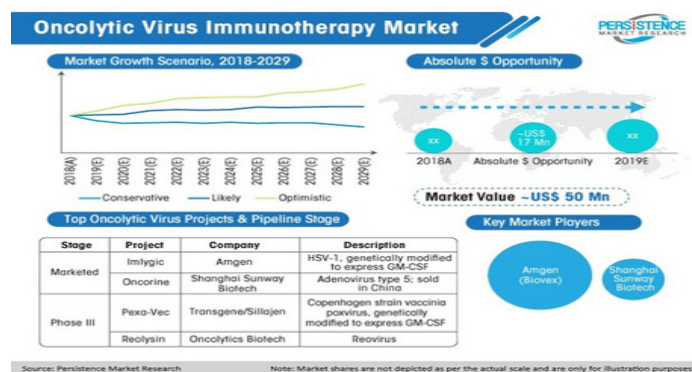


Figure 1: Summary of oncolytic virus immunotherapy market analysis [10].

Science behind the scene

The genetically modified virus, when enters the cancer cells, replicates and triggers an immune response which was initially inhibited by the body because of the ability of tumour cells to hide from the T-Cells using the immune checkpoints and instigating an immunosuppressive tumour microenvironment (TME) response [11]. The viral cells benefit from the already deregulated pathways of malignant tumours and thrive in the

host body. Since, the extent of the viral attack on tumours is regulated and specific, the risk of the virus going rampant in the body is highly minimised. With that said, the real problem lies in the application of viral therapy itself because there is no one 'magic' virus which can be used for all cancers. It all depends on the metabolomic pathways and markers of the specific cancer and the attack mechanism of the virus.

[12]. Oncorine was a major leap in viral oncolytics but didn't see much success as it was only approved for usage in China. The major leap has come in the form of a drug called IMLYGIC® (a.k.a T-VEC) by Amgen which was approved for usage by the FDA in 2015 and hit the market in 2018. It uses a genetically modified Herpes Simplex Virus and is used in treating metastatic melanoma (skin cancer).

It was the first viral oncolytic therapy drug to be approved by the FDA [13] and has set the precedent for other players in the market to follow suit. IMLYGIC® is injected directly into the skin lesions and works by increasing the activity of the immune cells, even those distant to the tumour, to kill the tumour cells [13]. It works best with GM-CSF, an immune stimulant to help cancer patients recover faster [14].

Why OV's are a better cell therapeutic agent than conventional cancer therapies

Even in the current early phases of viral immunotherapy of cancer, the side effects are much less severe than conventional cancer therapies. It doesn't destroy the body and compromise the immunity of the patient. It is selective in its action and can turn the cold tumours to hot hence making treatment much more effective. [15]

IMLYGIC® has also proven that tumour lysing OV's can impart long

lasting immunity against tumour cells due to their ability to overcome the immune checkpoints which deter the immune activity against tumour cells.

To take the most advantage of these immune checkpoint inhibitors (ICI), IMLYGIC® has partnered up with Keytruda by Merck, an ICI drug for melanoma, for a combined trial which they claim can be even less toxic than either of them standalone.

The results showed an improved ORR (Objective response rate) of 56%. Recent partnership with the drug ipilimumab has also shown increased ORR [16]. It should provide a second revival of viral immunotherapies and their combination with novel drugs for more efficacy. [17]

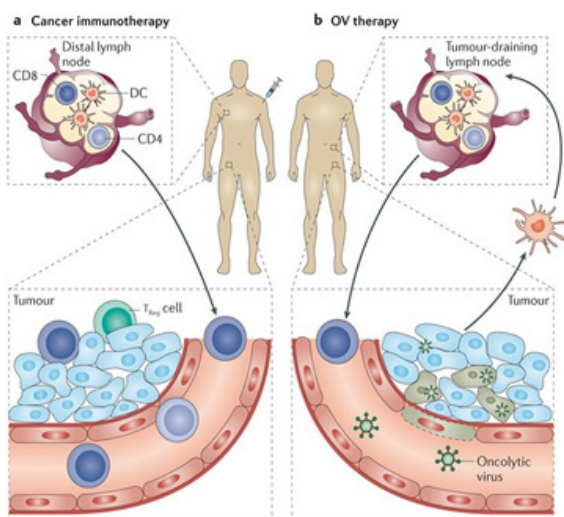


Figure2: a) Cancer immunotherapy. b) OV therapy. [18]

Regulatory hurdles

The regulatory process for a medical product in one nation requires the approval of the medical administration agency of this nation. FDA of US is one of the most authoritative medical administration agencies in the world. Due to the scientific authority, rigidity and impartiality of the FDA certification system, drug administration agencies in many countries regard enterprises' passing the FDA certification as an important reference for declaring the registration of domestic products. Therefore, to accept and pass the FDA certification will help one product to apply for EU CEP and Australia TGA certification, so as to open the global market.

Many small countries even do not have their own drug agencies but directly admit FDA certification. As the national drug agency, FDA certification focuses on the safety and curative effect of drugs.

The regulatory environment for OV drugs is tougher and more complicated than other drugs. As a virus

based biological agent, OV drugs are very aggressive to the human body. Drug agency must collect evidence to prove that the virus will accurately attack tumor tissues without harming health organs of patients, which requires larger scale of clinical test and more careful argumentation.[19]

There is a long process before IM-LYGIC® to get FDA certification, including Investigational New Drug (IND), which evaluates the safety and effect of this drug initially, the data and material of IMLYGIC® are reviewed by professionals in medicine, pharmacy and chemistry. Once IND is passed, IMLYGIC® was applied to 3 stages of clinical test in contrast with the placebo group. The final step is New Drug Application (NDA) which summarizes all political, social and scientific information collected about the drug and apply for final approval before appearing in the market. Even after IMLYGIC® can be sold in the market, a more general stage 4 clinical test to more than 1000 cases for reviewing on safety and curative effect of this drug were still continu-

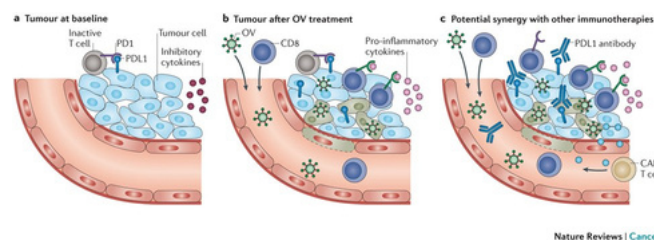


Figure3: a) Cold Tumour cell. b) Hot tumour cell after OV therapy. c) Synergy with ICI [18]

ing for 4 to 10 years.[20] IMLYGIC® was approved by European Medicine Agency in 2015 [21] and by Australia TGA in 2016.[22] Where both assessment reports mentioned that they consider FDA certification as one of the most important reference.

Conclusion

The Oncolytic Viral therapy market is unsaturated and has immense potential for growth. The combination with ICI drugs provides a novel and stronger approach for cancer treatment with relatively less side-effects compared to conventional cancer treatments. The scope and extent of the market is yet to be analysed as it's an emerging market but the harsh regulatory environment makes it tougher for new oncolytic viral drugs to prosper. The high cost of treatment will also be an issue moving forward.

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