Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Oncolytic viral immunotherapy in the time of COVID-19

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The 2020 global pandemic of Covid-19 has refocused the entire scientific community towards understanding the SARS coronavirus-2 (SARS-CoV-2) and developing urgently needed therapies and vaccines to halt the spread of this newly emerging virus. By October 2020, all of humankind had witnessed first-hand the medical, social and economic disruptions caused by the global pandemic. With more than 47,000,000 infections globally, in excess of 1,200,000 deaths (November 2020)– and with no end in sight - these pandemic priorities will continue to dominate the scientific landscape for years to come. *Cytokine & Growth Factor Reviews* has responded to the coronavirus pandemic with the publication of two Special Issues of the journal devoted to pre-clinical and clinical studies on Covid-19 immunopathogenesis, clinical management and development of therapeutic options. Going forward, an Elsevier online compendium of articles 'Therapeutic Opportunities in the Management of Covid-19′ has been established. Recent CGFR reviews and future contributions will be located in one place to provide continued coverage of the evolving biomedical knowledge concerning SARS-CoV-2.

Could the current heightened public awareness of viruses and their devastating physiological power result in heightened excitement for virus-based cancer therapies? Development of viral vaccine platforms has already seen a surge of interest, but what about viral immunotherapies for the treatment of cancer? The past fifteen years have already witnessed an exponential growth in the use of viruses as anticancer agents [1–3], culminating in 2015 with the US FDA approval of Talimogene laherparepvec (T-VEC) in the treatment of metastatic melanoma. Will our new 2020 'virological' reality produce a wave of support for the development of oncolytic viruses (OVs) as a means to 'flatten the curve' of one of the leading causes of death worldwide? In this special issue of *Cytokines and Growth Factor Reviews – Oncolytic Viral Immunotherapy 2020*, international experts discuss the innovative approaches developed for OV-based immunotherapies.

The issue begins with an encyclopedic evaluation of the cytokines, chemokines and growth factors that orchestrate the immune response to oncolytic virus immunotherapy, provided by Jonathan Pol and colleagues together with Guido Kroemer in Paris. As a consequence of the expression of an immunosuppressive environment in many types of cancer, an ineffective immune response fails to eliminate malignant targets. However, OVs can profoundly reshape the tumour microenvironment by inducing immunogenic cancer cell death and triggering the release of danger signals and cytotoxic cytokines that facilitate immune cell infiltration to the tumour bed and stimulation of cytotoxic immune activity.

Since the mid-twentieth century, viruses have attracted considerable attention for their potential anti-cancer properties, after several anecdotal case reports demonstrated remarkable tumour regression during naturally acquired viral infections [4]. One such early example is the case of an 8-year old boy with a complete regression of a Burkitt's lymphoma in the right eye while diagnosed with a natural measles virus (MeV) infection [5]. Now close to fifty years later, several groups are currently deploying vaccine strains of MeV, a single-stranded enveloped RNA virus, as a prime OV candidate because of its proven safety and potential for multi-level genetic engineering. Pidelaserra-Marti and Engeland provide a structured summary of the different anti-tumour activities of oncolytic MeV, including induction of immunogenic cell death, activation of antigen-presenting cells and T cell priming following MeV treatment. In addition, the authors discuss recent data related to MeV Phase I clinical trials. A systematic overview of the different genetic modification strategies used to improve MeV as an oncolytic vector is also covered by Leber and colleagues. This review discusses different combinatorial approaches to bolster MeV oncolytic activity and summarizes the current status of the use of MeV as a vaccine-platform for other non-malignant diseases.

Viruses are usually seen as a threat, which is evidenced by the

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pleiotropic anti-viral cellular defences we have evolved to naturally protect our organism from viral pathogens. Interferons (IFNs) are the most potent anti-viral cytokines induced by virus-infected cells and can reduce the efficacy of OVs. However, many types of cancer cells have been shown to be compromised in terms of generating a potent IFN antiviral state, thus making these tumours a particularly sensitive niche population for oncolytic virus replication. IFNs can also positively influence both innate and adaptive anti-tumour immune responses. Thus, a fine-tuned balance is required for OVs to activate an IFN response to potentiate tumour immunity, while limiting the amount produced, so the replicative and oncolytic properties are maintained. Geoffroy and Bourgeois-Daigneault review the diverse functions of IFNs and explore the complex pros and cons of these cytokines in the interplay between oncolytic viruses and anti-tumour immunity. In addition to IFNs, the clinical efficacy of OVs can also be compromised by immunological and physical barriers that limit viral delivery, replication, and spread within tumours. Marotel et al. address the dichotomy of the response of natural killer (NK) cells to OV exposure, while Santry et al., describe how the tumour vasculature can serve as a target for OV-directed vascular shutdown, yet also has an essential function to disseminate viruses within the tumour bed. These reviews also cover how such hurdles can be overcome by genetic or chemical approaches to enhance NK cell activation or facilitate OV penetrance into tumour tissues. Interestingly, many of these cellular processes are mediated by signaling pathways linked to overactivated kinases in cancer. Gilchrist et al. provide a comprehensive review of pharmaco-viral approaches to cancer therapy with a focus on oncogenic kinase inhibitors as a means to bolster OV efficacy. Because many targeted kinase inhibitors are FDA-approved for the treatment of different cancers, their combination with OV platforms can be easily achieved, with the goal to improve tumour cell killing and strengthen the immunological response against cancer.

As noted several times during the current pandemic, SARS-CoV-2 needs to replicate to high levels within its host to ultimately be able to spread and infect others. Fascinatingly, SARS-CoV-2 exhibits all the features that allows it to do so, in a very efficient manner, and often without the knowledge of the asymptomatic carrier. These replicative features are also important when considering oncolytic viral immunotherapies, as defining the critical characteristics that can promote viral persistence within tumour tissues and concurrently invoke the cytokine and anti-tumour immune response needed for cancer regression, are essential steps to the success of oncolytic viral immunotherapy. Three reviews in this issue describe our current understanding of the factors that can contribute to a successful super-spreading oncolytic and immune stimulating event within tumours. Muscolini et al., delve deeper into our understanding on how OVs can convert a non-immunogenic or “cold” tumour into an inflamed, immunogenic “hot” tumour, and discuss combination strategies using small molecule therapeutics to augment virus multiplication in tumours resistant to oncolysis. Jamieson et al., review the opportunities to engineer and redirect OVs to reprogram the restrictive tumour microenvironment. In addition, Dyer et al., address how metabolic stress and metabolites within tumour tissues can directly affect the host response to OVs and their immunostimulatory capabilities. These reviews provide valuable insights into the design of combinational approaches that are specific for each cancer type and/or individual patient.

SARS-CoV-2 forced many countries to realize that their health care systems were not prepared to handle the large influx of very sick Covid-19 patients. Overcrowding of emergency rooms was initially feared and became a reality in many communities. However, it is the broad range of symptoms and the long-term complications of infection that have been difficult to predict. The coronavirus pandemic has also raised awareness of the need for social distancing and mask policies to prevent person-to-person transmission. Regarding OV immunotherapy, safety has always been the absolute priority in the clinical setting. Fortunately, most OVs developed for clinical use are extensively attenuated, and early phase one clinical trials have unequivocally demonstrated the safety profile of several single viral agents. Unfortunately, the responses obtained with OVs, particularly in early stage clinical trials, has often been suboptimal. de Graaf et al. describe some of the ongoing and completed OV clinical trials and address some strategies to improve efficacy of OV immunotherapy. One of many remaining questions concerns the best OV platform for use against a particular cancer; there is no clear answer here, since most OVs have not been compared head to head in either pre- or clinical settings. Kemp et al., discuss the development of an oncolytic virus consortium that collaborates on the development of different OV platforms, with the goal to comparatively evaluate these against distinct cancers. The authors define the different viruses and tumour types to be examined in a collaborative and open approach between three Dutch Universities. Another important avenue of focus for OV therapies are hard-to-treat cancers, for instance pancreatic ductal adenocarcinoma. Tassone et al. address the poor prognosis of pancreatic cancer and explore how OV combination strategies may be used to improve survival. Finally, Burchett et al. review the unique and important attributes of OVs to be used as vaccines to stimulate T-cell mediated immune responses. While the authors address the details of this particular combination therapy, the use of OVs to focus highly targeted adoptive T-cell therapies will likely have a high potential for success in future clinical settings.

While the world is waiting for life to return to something akin to normal, the global health community is working to reign in the Covid-19 pandemic with the development of novel antivirals and the design of safe protective vaccines. Although this work is of vital importance, one may wonder whether the current focus on SARS-CoV-2 and the massive reallocation of resources risks pushing aside the research and development of therapies on other global health issues. Every year, nearly 9 million people die from cancer and many of these deaths could be prevented with better detection, treatment and prevention programs. Urgent action is thus needed to raise awareness about the “global cancer pandemic”. Hopefully, the current media frenzy surrounding Covid-19 will continue to showcase the importance of improving our knowledge of viral immunology and their potential to contribute novel virus-based immunotherapies to defeat the largest non-infectious pandemic of our modern world.

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