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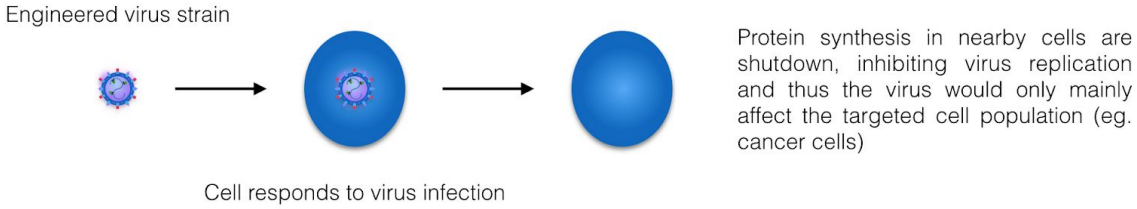
Learning from the past: What do you think has been the most important medical discovery in the last 10 years and why?

There have evidently been myriad medical discoveries in the past decade, which are of the utmost importance due to the constant evolution of pathogens and diseases, for example antibiotic resistant bacteria, in addition to the intention of predicting, diagnosing and suppressing detrimental diseases, such as the recent discovery of liquid biopsies for minimally-invasive cancer diagnosis (Heitzer et al., 2014; Takai et al., 2016) or alternate treatments towards coronary heart disease (CHD). Cancer treatment in the form of oncolytic virotherapy (Foreman et al., 2017), however, is arguably the most important overall, not only due to its adaptability with other treatments, but also in relation to its versatility against multiple forms of cancer and its amenability.

"Immunotherapy uses our immune system to fight cancer... helping the immune system recognise and attack cancer cells" (Cancer Research UK, 2017). Immunotherapy, like all fields of science, is an immense area with multiple applications in cancer treatment. An example of immunotherapy is oncolytic virotherapy (OV). OV engineers viruses to target, infect and break down cancerous cells through multiple means, including being directly cytotoxic to the cancer cells or setting off the immune system of the patient to be cytotoxic and break down the cancer cells (National Cancer Institute; Russell et al., 2012).

The ability to engineer the viruses in an in vitro setting is greatly advantageous because this would allow for highly personalised treatments against varying types of cancer. The targeting methods are inclusive of pro-apoptotic, translational (see figure 1), transcriptional, transductional targeting, and targeting based on the tumour's microenvironment or the use of carrier cells for the virus (Singh et al., 2012). Depending on the virus strain, the virus could be used naturally, for example the Mumps virus, or be engineered, such as measles, to be preferential towards the cancer cells.

Figure 1: Translational Targeting



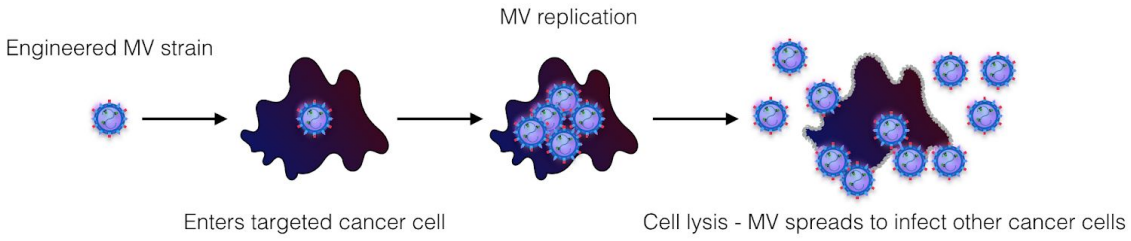
Source: Li, Kelly Ka Lee. "Translational Targeting." 21 February, 2018.

Since OV directly targets the cancer cells, they leave the normal cells unharmed, though there are side effects with the immune system commencing the break down of the cancer cells (Russell et al., 2012). Even though OV was acknowledged as a potential route for cancer treatment in the 20th century, for example in 1905 two chronic leukemia patients improved in condition while being affected by influenza (Dock, 1904), it was only recently that it has started being researched extensively, hence making it one of the medical 'discoveries' of the past decade.

An example of a virus initiating the body's immune mechanism against malignant cells is the intravenous (IV) dose of measles virus (MV) of 10^{11} TCID50. First to be considered is, of course, the safety and risks involved with the strain. More than 80% of patients demonstrate no symptoms after receiving the vaccination strain against measles, as well as the fact that the "MV [strain used for oncolysis] has a non-segmented genome", resulting in the virus not being able to mix and match segments of genomes, such as in influenza, so it is harder for the virus to evolve and mutate. Thus, the risk of the measles virus mutating is low and unlikely to become pathogenic again, rendering it stable (Aref et al., 2016). Moreover, in the early clinical trials conducted with generally older patients, who commonly have weaker immune systems, the patients responded well to the treatment. Therefore, oncolytic MV can be considered as a safe strain of virus to be used in treatment.

In simple terms, the way oncolytic MV works is the targeting, infection and finally the disintegration of the cell wall or membrane (lysis) as seen in figure 2 (Plemper et al.).

Figure 2: The integration and disintegration of cancer cells by an engineered MV strain



Source: Li, Kelly Ka Lee. "The Integration and Disintegration of Cancer Cells by an Engineered MV Strain." 21 February, 2018.

Due to the lysis of the cancer cell, the MV can then spread to the other cancer cells and in turn cause them to lyse. This chain reaction would optimally result in the breakdown of all the cancer cells in the body. On the one hand, it needs to be acknowledged that there is still the long term possibility of the replicating MV becoming pathogenic. On the other hand, the potential in OV could possibly be one of the personalised outlooks that the medical community has been searching for. Naturally, any of the replicating viruses used in OV should go through appropriate testing (pre-clinical studies), for example "immunodeficient mice reconstituted with human bone marrow" to trial the virus, before it is placed in human subjects (clinical studies) as per medical research guidelines (Chernajovsky et al., 2006).

Oncolytic virotherapy has also been seen to increase the synergy of immunomodulation when used in combination with chemotherapy (Simpson et al.). In other words, it promotes the immune response of the body in addition to the chemotherapy and hence amplifies the mechanisms of the immune system. This is proven in table 1, where the majority of the data on the rightmost column under "Oncolytic virus-chemo synergy" is greater than the "Immunomodulation reference [caused by chemo alone]" (Pandha et al., 2016).

Table 1

Mechanisms of immunomodulation caused by chemotherapy (chemo) alone, and synergy seen when combined with oncolytic virus

Chemotherapy drug	Mechanism of immunomodulation caused by chemo alone	Immunomodulation reference	Oncolytic virus–chemo synergy
Cyclophosphamide	Triggers TRAIL $CD8^+$ T cell-mediated apoptosis	3	
	Induces proinflammatory production/induction of ICD marker calreticulin/HMGB1	4–6	
	Decreased T_{reg} function	7–9	10,11
	$CD8^+$ T cell-specific tumor activity	7	
	Induces T-helper type 1 or 17 immunity	12	11
	Decreases complement function		13
	Suppression of immune cell types		14,15
	Inhibits or delays viral neutralization response		14–23
	Increases MDSCs	24,25	
	Enhances DC function	26	
	Synergy, but unknown immune function, if any		27,28
Gemcitabine	Decreases MDSCs	29	29–31
	Decreases neutralizing antibodies	29	29
	Induces ICD marker calreticulin	4	
	Induces ICD marker HMGB1		32,33
	Depletes B cells	34	35
	Synergy, but unknown immune function, if any		32,36–45
Bortezomib	Enhances DC function	46	
	ICD and DAMP release	14	
	Antitumoral immunity		47
	$CD8^+$ T cell-mediated inhibition of tumor growth	46	
	Synergy, but undefined immune function, if any		48,49
Doxorubicin	Induces ICD marker calreticulin	4	50
	Granzyme B released by CTLs	51	
	Induces type I IFN response	52	
	Increases T_{reg} cells and significantly decreases NK cells	53	
	Decreases B7-H1/PD-L1 from cell surface	54	
	Synergy, but undefined immune function, if any		55–59
Mitoxantrone	Induces DC/T-cell tumor infiltrate	60	
	Releases ATP	60	
	Ecto-CRT, ecto-HSP70, and HMGB1	61,62	
	Tumor antigen-specific $CD8^+$ and $CD4^+$ T-cell activity	60,63,64	65
	Enhances DC function	66	
Temozolomide	Decreases T_{reg} function	67	
	Tumor-specific T-cell responses	68	68
	Synergy, but undefined immune function, if any		69–74
Docetaxel	Decreases MDSCs, increases $CD8^+$ T cells	75	
	Enhances DC function	75	
	Synergy, but unknown immune function, if any		76–82
Paclitaxel	Granzyme B released by CTLs	83	
	Induces ICD marker calreticulin	4	
	Induces MHC	84	
	Decreases T_{reg} function	85–87	
	Induces T-helper type 1 immunity	12	
	Type I IFN and HMGB1 release in vitro		88
	NK cells essential for strong synergy		10
	Slows neutralizing antibodies (with carboplatin)		89
	Synergy, but unknown immune function, if any		90–99
5-Fluorouracil	$CD8^+$ T cell-mediated apoptosis	100	
	Induces carcinoembryonic antigen (CEA)	101	
	Decreases MDSCs	102	
	Synergy, but unknown immune function, if any		103–105
Cisplatin	Decreases T_{reg} function	106	
	$CD8^+$ T cell-specific tumor activity	106	
	Granzyme B released by CTL	50	
	Enhances DC function, cytokine release, and cytotoxic T-cell activation		107
	Synergy, but unknown immune function, if any		108–118
Mitomycin C	Enhances DC function	71,119	
	Synergy, but unknown immune function, if any		120–124
Azadeoxycytidine Irinotecan	Enhances DC function	71	
	Decreases T_{reg} function	125	
	NK cells essential	126	126
	Synergy, but unknown immune function, if any		126–129
Rapamycin/everolimus	Inhibition of T-cell proliferation	130	131
	Decreases DC maturation	130	
	Increases T_{reg} cells	130	
	Decreases cellular IFN		132
	Decreases cytokine release		131
	Decreases antiviral antibody production		131,133
	Synergy, but unknown immune function, if any		132–136
5-Aza	Induces cancer testis antigen	137	
	Induces MHC	137	

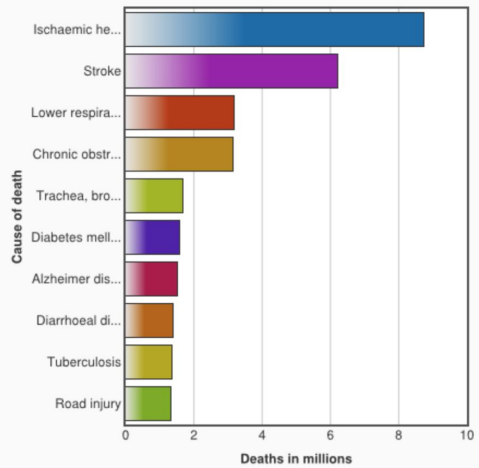
Abbreviations: ICD, immunogenic cell death; T_{reg}, regulatory T cell; MDSCs, myeloid-derived suppressor cells; DC, dendritic cell; DAMP, danger-associated molecular pattern; CTLs, cytotoxic T lymphocytes; NK, natural killer; MHC, major histocompatib complex; TRAIL, TNF-related apoptosis inducing ligand; Ecto-CRT, ecto calreticulin.

Source: Pandha, Hardev, et al. "Cancer Immunotherapy via Combining Oncolytic Virotherapy with Chemotherapy: Recent Advances." *Oncolytic Virotherapy*, 2016, p. 1., doi:10.2147/ov.s66083.

Another medical discovery of the past decade is the use of liquid biopsies to diagnose cancer. The problem for circumstances like pancreatic cancer is that affected patients are generally only diagnosed in the advanced stages of the cancer, where the cancer has metastasized. The reason for this delayed diagnosis is due to "the lack of an efficient method for detection of early-stage lesions", such as the lack of specific indicative biomarkers (Takai et al., 2016). Henceforth, if the cancer cells have started to circulate in the blood, earlier diagnosis may be possible and thus limit the cancer's spread. Nonetheless, though it is difficult to compare the significance between oncolytic virotherapy and liquid biopsies due to the contrasting areas of medicine they are located in: diagnosis and treatment, it is debatable that oncolytic virotherapy would be more consequential due to the higher number of people who would be affected should the relative discovery be successful (effective and efficient). Needless to say, a large number of patients would benefit as well if liquid biopsies were in their most ideal state.

Additionally, statistics from the World Health Organisation have shown that the top cause of death globally in 2015 was CHD at around 15.5% in contrast to trachea, lung and bronchus cancers at around 5% (see figure 3). Thus the advancement of another CHD treatment discovery, such as Dronedarone - used for the treatment of CHD patients with paroxysmal or persistent atrial fibrillation (AF), instead of soltalol and amidarone, could be controversially more important than cellular immunotherapy for cancer treatment (Pisters et al., 2013). Despite that, it has

Figure 3: Top 10 causes of death globally 2015



Source: *"Top 10 Causes of Death Globally." World Health Organization, WHO, Jan. 2017, www.who.int/mediacentre/factsheets/fs310/en/. Accessed 23 Feb. 2018.*

been interpreted that “most cancers were associated with an increased risk of CHD during the first 6 months after diagnosis” (Zöller et al., 2012). Hence, cancer treatment in all forms could possibly be considered as a priority ahead of CHD treatment due to the potential consequence of CHD in association with the cancer.

Furthermore, research has now estimated that in the United Kingdom (UK) 1 in 2 people will be diagnosed with cancer in their lifetime, conceivably as a result of the increased life-expectancy in relation to cancer, which affects more of the aging population (Ahmad et al., 2015). Consequentially, not only would the diagnosis and minimizing the risks of getting cancer be important, but also the ability to treat the cancer. Therefore, cancer treatment in the form of cellular immunotherapy would perhaps be more beneficial percentage-wise to the general population than CHD treatment, though CHD treatment is vital in its own context as well.

Though it has to be noted that every medical discovery has the capacity to be fully beneficial, including liquid biopsies and alternate CHD treatments, the progression in oncolytic virotherapy is debatably the most important medical discovery since it offers an exceptional way to treat cancer, and potentially other cellular diseases as well if researchers can successfully target the diseased cells with the re-engineered viruses and induce immunomodulation against the disease.

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