

Can we cure cancer?

Cancer, a most notorious disease which has been prevalent for millenia and is currently one of the leading causes of deaths globally, is essentially brought about by the uncontrollable division of cells as a result of a breakdown of the body's normal control mechanism. These cells then have the potential to spread and infiltrate the healthy surrounding tissues. This 'domino effect' may lead to the formation of tumours depending on the type of cancer, and worse still, if not treated in its early stages of development, cancerous cells can spread to different parts of the body other than the area from where it originated via the blood or lymphatic system. It is cancer's expansive and spreadable nature that has forged it to become such a virulent and pestilent disease to this day, leading to the emergence of tumours, the impairing of the immune system, and other harmful alterations which would otherwise prevent normal bodily functions from occurring. Yet, cancers all begin from the same root cause so the question begs why haven't we been able to find a cure. The golden bullet or magical molecule that has yet to be found that can be used for all cancer. If the root cause is the same, surely from the time of Galen in Ancient Athens and Imhotep in Ancient Egyptians in 1600 BC to now, we must have found it. The problem lies in the fact that each cancer is different from one another with varying mortality rates. Exemplifying this is testicular cancer and pancreatic cancer with 5-year survival rates of 95% and 9% respectively.

I don't know if we will be able to find this one magical molecule because the fact is all cancers are different, whether it may be down to it be number of mutations, where the hotspot is, which type of mutation in a gene or collection of genes is more likely to lead to a cancer initiation, epigenetic factors and environmental ones too. But maybe one day we might find it but as of today, I don't think we can fully cure it because we don't totally understand it. We can definitely find treatments and such but to fully cure it is another story especially since humans persist in doing things we know will get tumours going: sunbathing without protection, smoking, eating poor diets and getting fat. On top of this, there's the fact that we're all living longer and cancer being a disease of old age with accumulated mutations (White, M. C et al (2013)) where the incidence of most cancers increases with age, rising more rapidly in midlife once mutations have become to accumulate leading to increased genetic instability. The other part of the answer lies in DNA and its extraordinary flexibility. The random chance of life means that the odds are heavily against a fertilized egg making it into a human being, statistically speaking. When it does so it will have encoded in its DNA millions of variants, not only making each of us different to one another (the basis of DNA 'fingerprinting') but also giving us an individual specific 'fingerprint' upon which the layering of subsequently acquired mutations will inevitably lead to cancer. The cancers that emerge are so highly individual that each is unique. Each tumour has a different genetic make-up and the astonishing individuality and complexity of each tumour is being revealed in molecular detail by current DNA sequencing methods. In Dr Hesketh's book 'Betrayed by Nature' he regrets describing DNA sequencing "the greatest revolution in the history of medicine" in the book. He commented: "I should have substituted 'science' for 'medicine' because the technical advances that have occurred since the human genome was first sequenced in 2003 have already changed how we think about cancer and how we treat it and in the end they will affect everyone on earth."

The persistence of humans in the said activities above correlates to more than 85% of all lung cancers and 30% of all deaths are caused by smoking. Second hand smoke can also increase 5% the risk of cancer. Smokers are more likely than nonsmokers to develop different types of cancers, such as; lung, larynx, mouth, esophagus, bladder, kidney, throat, stomach, pancreas, cervix and acute myeloid leukemia. This is down to the chemicals in smoking which can affect a large number of cell-signaling pathways and some of these chemicals like benzo a pyrene which induces a G (guanine) to T (thymidine) swap in exon hotspots within p53 inactivating the tumour suppressor and allowing cancer (lung cancer) to predominantly happen (M F Denissenko , A Pao, M Tang, G P Pfeifer 1998). Up to 10% of total cancer cases may be induced by radiation , both ionizing and nonionizing, typically from radioactive substances and ultraviolet rays. Furthermore, cancers induced by radiation include some types of leukemia, lymphoma and skin cancers. There are a lot of types of UV radiations - UVA, UVB, UVC- but generally UVR is considered the dangerous ones as it can be a tumour initiator and promoter. UV-induced DNA damage activates mechanisms for removal of DNA damage, delay in cell cycle progression, DNA repair, or apoptosis by transcriptional activation of p53-related genes, such as p21 (Brugarolas et al., 1995) and MDM2 negative feedback loop. UVR specifically has an impact on levels of damage to the DNA and gene mutations to the p53 tumor suppressor genes which as we talked about can lead to uncontrolled proliferation if the cell can no longer control its mitotic cycle phase and then cancer eventually. Both of these environmental factors also relate to telomeres as they shorten telomere length quicker and increase risk of cancer at earlier ages. According to A M Valdes et al (2005), 'the telomere attrition caused by smoking one pack of cigarettes a day for a period of 40 years is equivalent to 7.4 years of life'. So even though treatments will be found, cancer is more likely to happen because of human styles of living and this will impact treatments and also add another layer of complexity to finding a cure- environmental factors add another layer of complexity because cures for which type of cancer are affected by what factors. Example of two twins where one is a smoker and one isn't. They have the same DNA and yet the smoker is more likely to get lung cancer than a non smoker due to environmental epigenetics. Throughout their lives they were exposed to different influences that could have switched normal genes on or off, such as the tumor-suppressor genes responsible for shutting down cancer cells when they begin to grow. Cancer is selective to that individual and so finding a treatment specific to them which would work is hard enough, let alone finding a cure for their circumstance; which is due to a lack of information.

Aging also plays a huge role in cancer because as we get older, two things happen: less efficient DNA repair systems and as a result more mutations. In Vera Gorbunova, Andrei Seluanov, Zhiyong Mao, and Christopher Hine (2007), there is a proven link between increasing age and less effective DNA repair systems that lead to an increased number of mutations though more studies are needed to clearly establish this link. One example of this is telomeres. Telomeres are specific DNA protein structures found at both ends of each chromosome where a small portion of telomeric DNA is lost with each cell division. When telomere length reaches a critical limit, the cell undergoes senescence and/or apoptosis - a death clock for cells. With age, telomeres shorten and this increases the risk of diseases such as cancer. Several studies indicate that shorter telomeres are a risk factor for cancer. Individuals with shorter telomeres seem to have a greater risk for development of lung, bladder, renal cell, gastrointestinal, and head and neck cancers (Monica McGrath et al 2007). Certain individuals may also be born with shorter telomeres or may have genetic disorders leading to shorter telomeres - everyone's DNA fingerprint is different. In Patrick J.

Killela et al (2013) paper, TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. In their observations, Pediatric primary GBMs rarely contained TERT mutations (11%), whereas adult primary GBMs frequently did (83%). This suggests that GBMs more frequently occur in adults as adult cells do not need to renew while younger cells are still growing and are constantly renewing and 'there is no selective advantage conferred by activating telomerase through a genetic mutation'- also showing the grave differences between adult cancers and those of childrens which makes finding a magical molecule so hard and making finding treatments so hard as they're selectively different. What does this suggest for finding a cure theoretically? Of course, we cannot stop aging but could it be possible to target telomerase. Since uncontrolled proliferation is one of the 6 hallmarks of cancer as dictated by cancer cells being able to add more telomeres via transcription of the switched on telomerase enzyme, could it be possible to target increased activity of telomerase. According to Hanna Holysz, Natalia Lipinska, Anna Paszel-Jaworska, and Blazej Rubis (2013), specifically for breast cancer - another example where the cure and treatment varies-, expression of telomerase in various human cancers and its diminished expression in most normal cells suggest that the enzyme might serve as a good target for anticancer drugs. Due to telomerase inhibition, activity, or expression, these drugs might kill tumor cells by allowing telomeres to shrink or by provoking apoptosis. Since telomerase seems to be a universal cancer marker, the agents targeting the enzyme might work against a broad spectrum of tumors. Nevertheless, a number of questions must be answered. For instance, researchers need to determine which normal cells reveal telomerase expression/activity and to what extent. They also need to assess the importance of the enzyme to those cells. Telomerase-inhibiting agents might cause cancer cells to lose their telomeres and die well before normal cells, with their much longer telomeres, lose enough of their telomeres to suffer any ill effects. It should be unquestionably demonstrated that inhibition of telomerase can destroy telomerase-producing tumors as expected. Another problem might be the delivery of telomerase-targeting agents in a way that would provide high efficiency and specificity. Therapeutic potential of vaccination has been explored in many clinical trials involving patients with breast cancer. A large variety of cancer immunogens have been tested. The majority of clinical vaccination studies have been carried out in patients with metastatic breast cancer, characterized by extremely aggressive malignant tumors, resistant to all standard cytotoxic treatments, and with longest-lasting disease.

As I mentioned before, cancers very much differ from one another and this is connected to mutations in different places and via a result of lifestyle which can encourage mutations in certain areas - like smoking encourages more lung cancer related mutations. This makes finding treatments hard, let alone finding a cure because even similar classed cancers differ: Breast Cancers- like the drug Herceptin for Her2 specific cancers where there is an overexpression of the gene. Generally, they stimulate the cell to grow and multiply but breast cancer cells with too many HER2 receptors can pick up too many growth signals and cause them to start growing and multiplying too much and too fast. Specifically targeted therapies like with the use of Herceptin are common for complications relating to the HER2 gene and even the success rates are not 100%, 93% for 7 disease free years (OHC specialists in cancer and blood disorders). Furthermore, heterogeneity plays a significant role and if we compare Lung cancer and Acute Myeloid Leukemia in Figure 1 in Cyriac Kandath et al (2016), not only are there fewer average mutations per MB in AML (0.8) as compared to (30) in Lung cancer, the type of mutations differs hugely too. There is a greater chance of a C>T

mutation in AML and a greater chance of a C>A in Lung cancers. Furthermore, in Cyriac Kandoth et al (2016) Figure 2, if we compare percentages of samples mutated in individual tumour types between Lung Cancers and AML for histone mutations in MLL2 and MLL3 gene sections, there is a much higher mutation rate in Lung Cancer of 20.1%, 15.5% as compared to 0.5% and 0.5% in AMLs. If we look at just a section of a gene for all 12 cancers, they are all very different which suggests that the cancers are very much different genetically as there are different things going on (e.g. SETD2 where all the % vary). Moreover, a mutation in the FLT3 gene which provides instructions for making a protein called fms-like tyrosine kinase 3 (FLT3), which is part of a family of proteins called receptor tyrosine kinases (RTKs). Receptor tyrosine kinases transmit signals from the cell surface into the cell through a process called signal transduction. In AML, 26.5% of all cases have this mutation in their gene vs just the 4% in lung cancer which suggests that FLT3 is a common driver mutation that presents with a high leukemic burden and confers a poor prognosis in patients with AML (Naval Daver, Richard F. Schlenk, Nigel H. Russell & Mark J. Levis, 2019).

As we can see, cancer isn't just affected by one thing or one factor but an accumulation of many different factors that self amplify. The factors are all related to one another but some cancers have different factors affecting them like lung cancer having way more mutations and also different epigenetic ones than AML. Each cancer is different which is why it is so hard to cure as each one has to be tackled separately. However, what is similar in 10 out of the 12 cases is a mutation in TP53 - at very high levels to- which suggests that in most cancers, there needs to be a faulty p53 gene. When cell signalling goes wrong, crucial genes may be switched on or off incorrectly, such as the gene coding for the protein p53 which prevents apoptosis from occurring which in turn leads to uncontrollable cell division and growth and it's this coupled with epigenetic factors, environmental factors and lifestyle choices that gives way to a huge array of cancers that are all different to each other. Potentially, a way to unmutate or get p53 back to full functionality would be a major cornerstone in the fight against one of the world's oldest diseases. Recently however, Researchers have shown in mice that designer antibodies can curb the growth of tumors by targeting RAS and p53- the most well known proto-oncogene and tumour suppressor- which are mutated in many tumors but have largely defied drug development efforts (Johns Hopkins Medicine 2021). Antibodies are generally 'Y' shaped with two same 'arms' but researchers at John Hopkins engineered "bispecific" antibodies that bind to a different target with each arm. In lab experiments, the p53- and RAS-specific diabodies attached to their respective neoantigen-mutated antigens specifically expressed by tumor tissue- targets but not to fragments from normal p53 and RAS proteins or from other, closely related proteins. The newly designed antibodies act like a bridge, grabbing onto immune cells with one end and cancer cells with the other. By pulling them close together, the antibodies help immune cells find and kill the cancer cells. This is a huge step in treating cancers in a very broad spectrum and although tests have yet to be done on humans, bispecific antibodies detecting receptors or fragments only on cancer cells is a huge step towards finding that magical molecule.

Overall, I don't think we can cure cancer with the information we have right now and even with some of our treatments, cancer can become resistant to certain treatments such as chemotherapy. This is due to the fact that cancers exhibit Darwinism and their genes can mutate inside these cancerous cells, where some gene mutations may be advantageous to the cancer cells and lead to them becoming resistant. Recurrences are possible where

cancer comes back after being treated. This happens if all of the cancer cells are not destroyed because then, the surviving cells can grow and divide to form another tumour, allowing for metastasis to occur. Statistically speaking, recurrence rates vary widely between cancer types, and within cancer types according to stage, histology, genetic factors, patient-related factors, and treatments (Cancer Recurrence Statistics- 2018). However, with new treatments coming out and with technological advancements, I remain optimistic that one day we will win the battle against this age-old disease whether that's through finding one single cure for all or many different cures for each cancer.

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