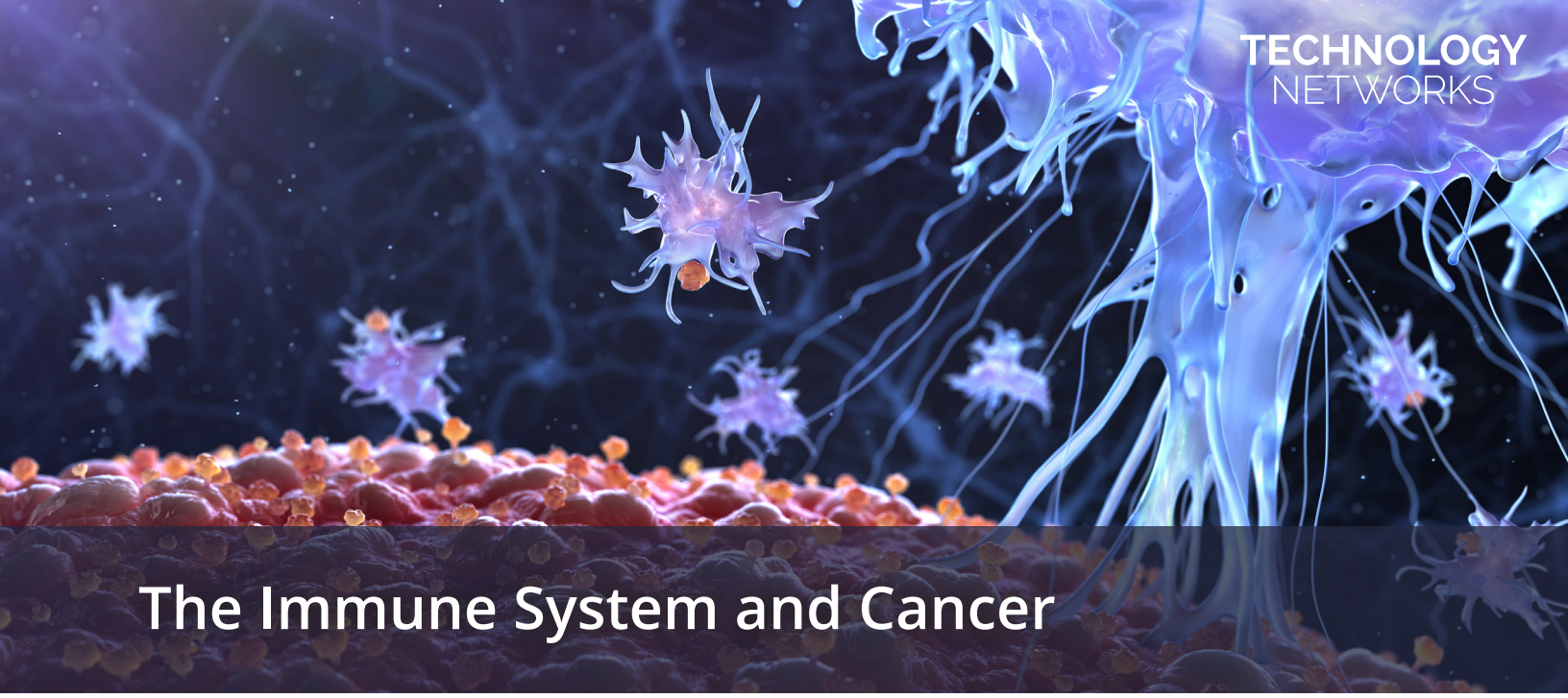


The Immune System and Cancer

When the world-renowned cancer scientists Douglas Hanahan and Robert A. Weinberg published an updated version of their seminal paper "The Hallmarks of Cancer" in 2011, they added two important new characteristics of a tumor: its ability to reprogram energy metabolism and to evade immune destruction.[1] Since then, there has been an acceleration in our understanding of how cancer evades the immune system, and an explosion in new therapeutics that re-configure the immune system to mount a powerful anticancer response. In this list, we highlight some of the latest insights into the immune system and cancer.

How does the immune system recognize cancerous cells at the earliest stage?

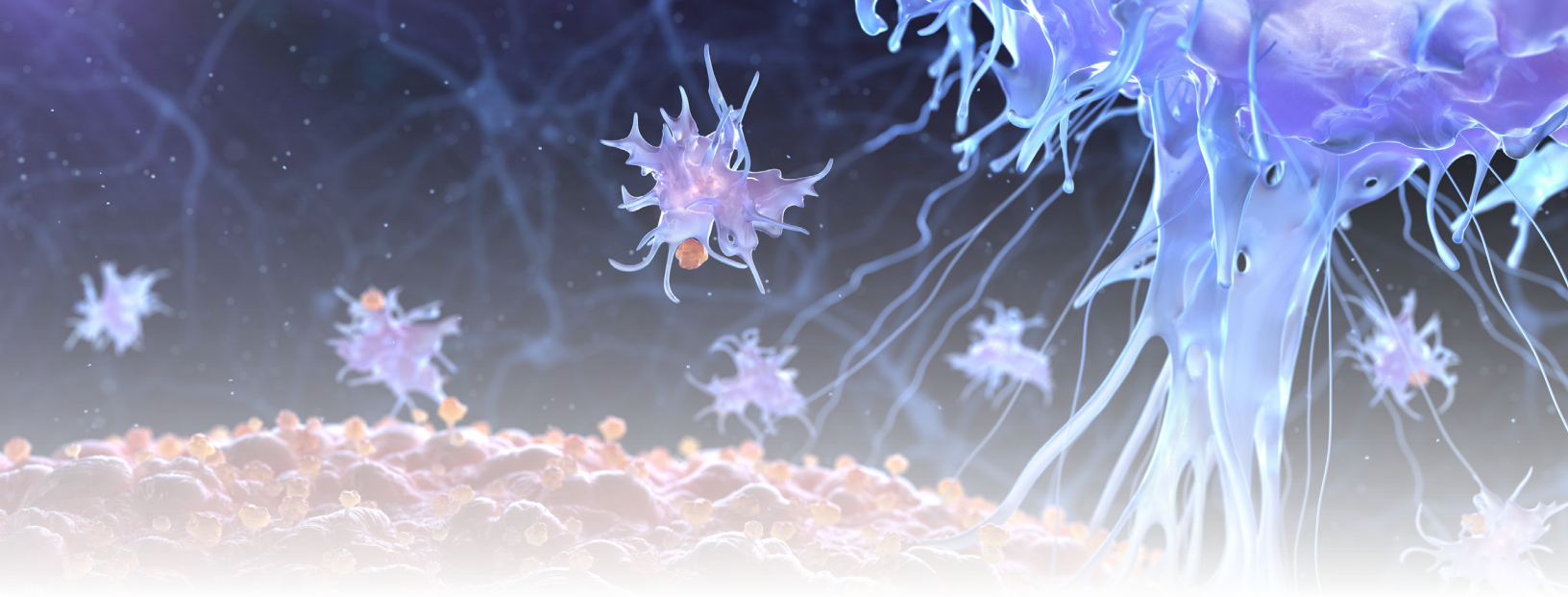
Scientists have long been puzzled by the inability of the immune system to detect cancer.[2] On the one hand, it is known that inappropriate inflammation can cause cancer, but on the other hand immunosurveillance is thought to be a critical mechanism for inhibiting cancer development and progression. According to Elizabeth Jaffee, the body's immune system is capable of intercepting pre-malignancies and preventing cancer, and does so countless times every day in all of us. The key to understanding how, lies in characterizing the "premalignant antigenic repertoire", that is the driver of mutations and nonmutated self-proteins that are expressed at abnormal levels on tumor cells and detected by immune cells.[2] It is more complex than just the category of antigen, however, and also includes post-translational modifications such as glycosylation.[2] Some studies have suggested that it is the presence of structures such as micronuclei resulting from DNA damage that flags the initiation of cancer to the immune system and triggers inflammation.[3]

The aging immune system and cancer incidence

A recent study suggests that an aging immune system plays a larger role in cancer incidence than previously thought.[4] Researchers studied two million cases of cancer in people aged 18–70 years and developed a mathematical model to predict how cancer incidence might rise in relation to a declining immune system. The aging immunity model fitted the increasing incidence of cancer better than the conventional model where cancer risk is proportional to the accumulation of mutations (the multiple mutation model). Because immunity declines more slowly in women than men, the results may explain the higher likelihood of men developing cancer than women.

Immune cell profile and cancer risk

Researchers from the Mayo Clinic have shown that women who went on to develop breast cancer had different immune cells in their breast tissue compared to those who didn't.[5] They quantified the numbers of



various types of immune cells in breast tissue from four groups of women: those with normal tissue, benign breast disease, benign lump or thickened breast tissue. They found that compared with normal tissue, women with benign breast disease had greater numbers of several types of immune cell, and those who later developed cancer had lower numbers of antibody-producing cells, suggesting that the immune system plays a role in early breast cancer development.

Weakening of the immune system as a sign of cancer

Changes in immune activity have also been suggested as a potential signal for the presence of cancer. In one study, scientists evaluated blood samples in 974 people, half of whom several years later went on to receive a brain cancer diagnosis. They found that interactions between cytokines – molecules than enable immune cells to communicate with one another – were much weaker in the blood of people who subsequently developed the most common type of brain tumor, glioma. The authors speculate that this may happen with other tumors and could be a general sign of tumor development.[6]

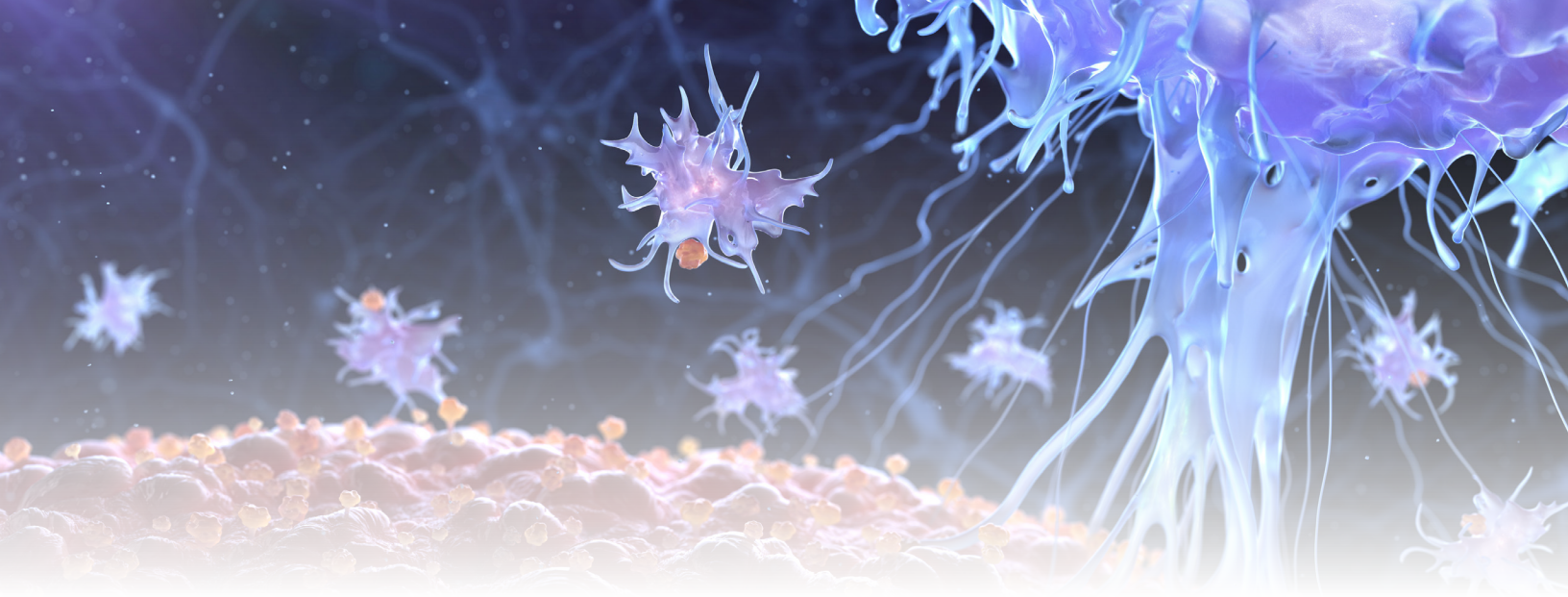
Bacteria, the immune system and cancer

One intriguing aspect of the relationship between the immune system and cancer is that there may be a significant third player involved – our body's bacteria. In one study, researchers found that the bacterial signatures present within pancreatic tumors either stimulate or suppress the immune response. The authors speculate that this could be a key difference between the few people with pancreatic cancer who survive and the many for whom there are no effective treatment options.[7] In another study, researchers uncovered a mechanism that may explain how oral hygiene – or more specifically the bacterium that cause periodontitis – may play a part in the onset of pancreatic cancer. They found that the main virulence factor of the bacterium, a proteinase enzyme, also occurs in malignant tumors of the gastrointestinal tract. It is thought that this virulence factor can activate other enzymes that facilitate tumor invasion.[8]

How tumors evade the immune response

Tumors are master manipulators that disguise themselves from immune cells and switch on signals that dampen down the immune response. For example, scientists recently identified a subpopulation of fibroblasts called antigen-presenting cancer-associated fibroblasts (apCAFs) that can interact with the immune system to help pancreatic cancer cells avoid detection.[9] These apCAFs have the capacity to present antigens to T cells and could therefore be exploited therapeutically to redirect the immune response towards pancreatic tumors.

Another study looked at how tumors exploit important immune cells called regulatory T cells (Tregs). Tregs are important controllers of the immune system – one of the main checkpoints that prevents an inappropriate



immune response. This study reveals that tumors take advantage of Tregs by controlling their ability to release certain cytokines. Tregs within mouse and human tumors were able to make either cytokine IL-10 or IL-35, but not both cytokines at the same time. The team were able to demonstrate that for a tumor to suppress the immune system, it requires both types of cytokine, which then act together to switch on another molecule that disables killer T cells. This raises the possibility of designing drugs to block either cytokine, blocking activation of killer T cells, and consequently preventing the tumor from dampening down the immune system.[10]

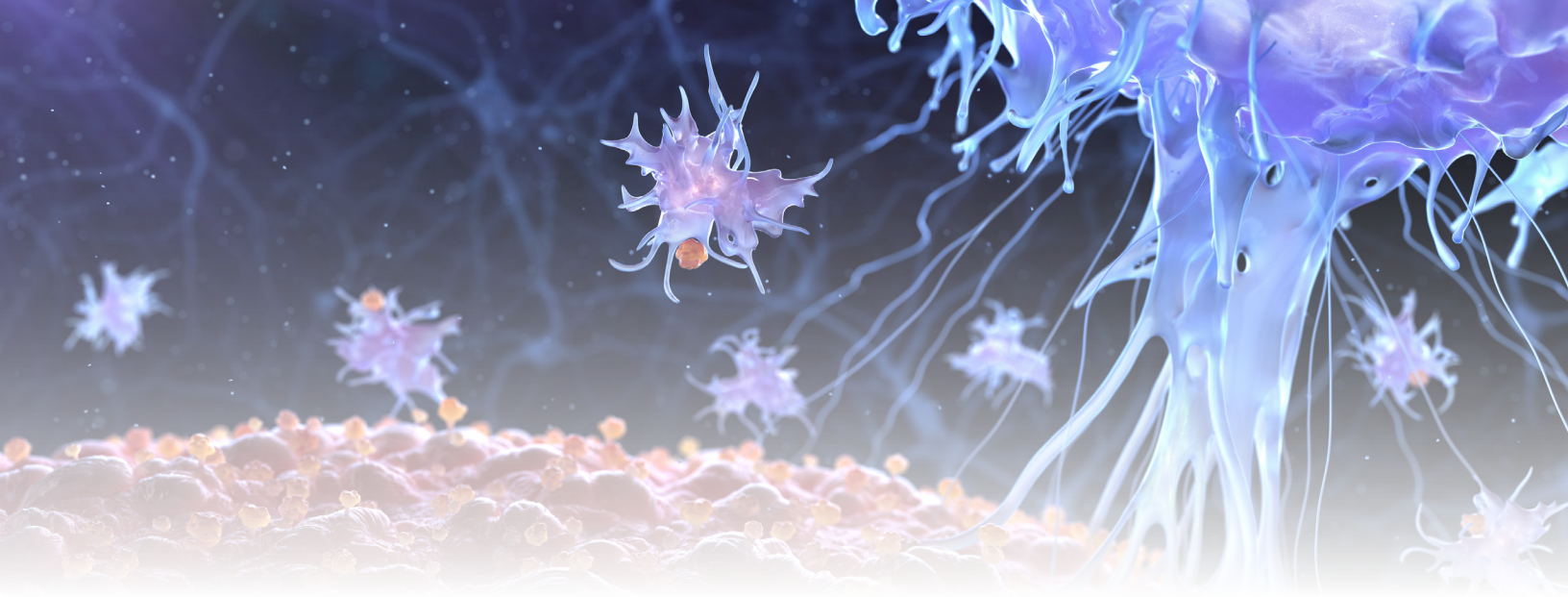
Researchers are also keen to understand why breast tumors in particular seem to be intractable to immunotherapy treatment. A recent study analyzed more than 1,000 breast cancer patients who had been treated with immunotherapy. They were able to group breast cancer patients into seven clusters based on the different immune evasion mechanisms that their cancer uses. Moreover, they identified two molecules – transforming growth factor beta and decoy receptor 3 – that were heavily relied upon by breast tumors trying to escape the immune response.[11]

Current types of cancer immunotherapies

There are a wide range of "immunotherapy" cancer treatments both in development and already approved. These include monoclonal antibodies that target molecules on the surface of cancer cells, such as the drug trastuzumab (Herceptin), vaccines that prevent cancer and those with potential therapeutic benefit.[12] Then there are checkpoint inhibitors, a newer type of immunotherapy that works by releasing the immune system's brakes,[13] which have shown remarkable efficacy in a small subset of patients. Finally, there are the chimeric antibody receptor (CAR) T-cell therapies, which involve taking immune cells from a patient and genetically engineering them to recognize and respond to their cancer cells. The first CAR T-cell therapy approach was approved recently to treat a childhood blood and bone marrow cancer and is referred to as "the first gene therapy in the US".

The future

As quickly as new immunotherapy breakthroughs come through the pipeline, tumors are evolving to make life harder. For example, recent research has shown that tumors can "change their spots" to evade the bispecific immunotherapy antibody cibisatamab. They do so by switching off a key molecule called carcinoembryonic antigen on the surface of cells that is otherwise recognized by the treatment.[14] Therefore, finding novel approaches to harness the immune system is still a priority and a range of new strategies are being pursued. For example, a combination immunotherapy treatment that targets both innate and adaptive immunity has shown important proof-of-principle efficacy in a preclinical study of liver cancer, for which there are currently few treatment options.[15] Another study identified a gene that could make checkpoint inhibitors work for a



a wider variety of cancer patients. The study found that when the *DUX4* gene is expressed in cancer cells, it can prevent the cancer from being recognized and destroyed by the immune system. Blocking its activity might therefore increase the success of immune checkpoint inhibitors in people who are currently non-responders.[16]

Finally, the future may lie in priming the cancer cells themselves to flag their presence to the immune system. To this end, researchers at Massachusetts Institute of Technology have developed a synthetic gene circuit encoded in DNA that is designed to distinguish cancer cells from non-cancer cells. The circuit is delivered to cells in the affected area of the body using a virus and will bind to molecules that are only active in the cancer cells – completing the circuit. Once the circuit is activated, it produces proteins that will direct the immune system towards the tumor, as well as a checkpoint inhibitor, to remove the brakes on the subsequent immune response. When tested in mice implanted with ovarian cancer cells, the gene circuit triggered T cells to seek out and kill the cancer cells, leaving surrounding healthy cells unharmed.[17]

In summary

There is a complex and intricate relationship between the immune system and cancer. Understanding the process of immunosurveillance and what early signs of cancer are detectable by the immune system offers huge promise as a way to prevent cancer or detect it at its earliest stage. In the meantime, we are continually advancing our understanding of cancer and the mechanisms used to evade the immune response. As more immune targets are discovered, immunotherapies will continue to be an important new weapon in the war against cancer.

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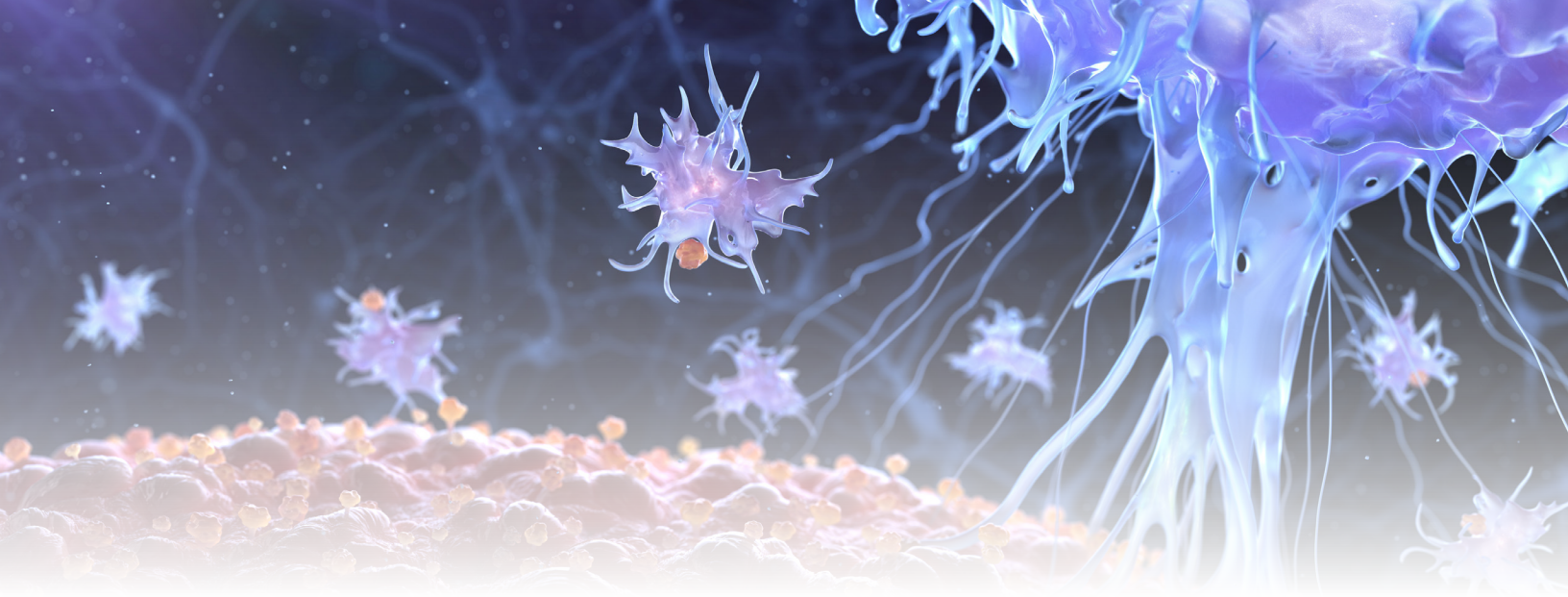

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